Product Authorisation Application
for

KOATE
Dried Factor VIII Fraction

Part I - Summary

MILES LABORATORIES LIMITED,
STOKE COURT,
STOKE POGES,
SLOUGH, SL2 4LY,
BERKSHIRE,
ENGLAND.

NOVEMBER, 1983.

PART I SUMMARY

1. Name and address of applicant

Miles Laboratories Limited,
Stoke Court,
Stoke Poges,
Slough,
SL2 4LY,
Berkshire,
England.

2. a) Name and address of proposed holder

Miles Laboratories Limited,
Stoke Court,
Stoke Poges,
Slough,
SL2 4LY,
Berkshire,
England.

b) Name and address of trading company as will appear on the label

Cutter,
Division of Miles Laboratories Limited,
Stoke Court,
Stoke Poges,
Slough,
SL2 4LY,
Berkshire,
England.

3. Name and address of person resident in Ireland

Not applicable. Miles Laboratories Limited will be responsible for initiation of action and assurance of compliance with any directions given by the Minister or the National Drugs Advisory Board on his behalf.

4. Role of proposed holder of the authorisation

a) as person responsible for the composition of the product in Ireland.

b) as person who imports or procures its importation.

5. Name and address of the actual importer

Accu-Science (Ireland) Limited,
8, South Main Street,
Naas,
Co. Kildare,
Eire.

6. Activities for which the authorisation is required

a) selling and supplying the product in Ireland.

b) procuring the manufacture of the product for sale or supply in Ireland.

c) importing or procuring the importation of the product.

7. Proprietary name of the product

KOATE

8. Product form

30ml, 50ml or 100ml glass vial, with 20mm rubber stopper and aluminium seal containing a white, lyophilised powder for reconstitution with Water for Injection for intravenous administration to human beings. The product is supplied with Water for Injection (10ml, 20ml or 40ml), a sterile double-ended transfer needle and a sterile filter needle.

9. Active constituents

Dried Factor VIII Fraction (approximately 250, 500, 1,000 or 1,500iu/vial. The actual potency will be printed on the label).

10. Clinical use

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

b) Intravenous injection.

c) To be diluted with 10ml (20ml)(40ml) Water for Injection. Allow to warm to 20° - 30°C before administration.

11. Recommended dosage schedules

The following formulae provide a guide for dosage calculations:-

Expected Factor VIII increase (in % of normal) =

$$\frac{\text{I.U. administered x 2.0}}{\text{body weight (in kg)}}$$

I.U. required = body weight (kg) x desired Factor VIII (% normal) x 0.5.

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.

12. Side-effects, contraindications, warnings and precautions

Contraindications

There are no specific contraindications to the use of Dried Factor VIII Fraction.

Warnings

1. Allergic reactions may result from the administration of Factor VIII preparations including chills, fever and hypersensitivity reactions.

2. When large or frequently repeated doses are required in patients of blood groups A, B or AB, there is a possibility of intravascular haemolysis. Should this condition occur leading to progressive anaemia, administration of serologically compatible type O packed red blood cells should be considered. Also, the administration of type specific cryoprecipitate has been recommended for maintaining adequate Factor VIII levels.

3. Massive doses of Factor VIII preparations may result in hyperfibrinogenaemia.

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

Precautions

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

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. Koate, in the vial unopened, is sterile. It 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 always be used for transfer to syringe prior to administering.

5. Koate 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 the onset of intravascular haemolysis should be considered.

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

13. Method of retail sale or supply

c) Through pharmacies, hospitals and other specified outlets for prescription only use.

14. Method of sales promotion

a) Via the professions as a prescription item.

15. Manufacturer of dosage form

a) Cutter,
Division of Miles Laboratories Incorporated,
Berkeley,
California 94710,
U.S.A.

Cutter,
Division of Miles Laboratories Incorporated,
Clayton,
North Carolina,
U.S.A.

b) Production of final product from frozen plasma and all assembly operations.

c) None.

d) The product will be stored at 2^{o} - 8^{o}C, segregated from all other materials at Miles Laboratories Limited.

16. Quality control

a) The manufacturers, Cutter, Division of Miles Laboratories Incorporated, U.S.A., will be responsible for the quality control of the raw materials and the finished product to the extent indicated in Part II of this application.

b) Cutter, Division of Miles Laboratories Incorporated, will be responsible for deciding whether any batch of the product is acceptable for release. Miles Laboratories Limited, U.K. will maintain the necessary documentation and verify that each batch of the product is of an acceptable quality for marketing in Ireland.

17. Containers

Type I, clear glass vials with 20mm grey rubber stopper and aluminium seal with plastic flip-off cap. To be stored at 2^{o} - 8^{o}C.

18. Labelling

The following text will appear on the labels:-

A. Vial Label - 250, 500, 1000, 1500 Unit Packs

K O A T E(R)

Dried Factor VIII Fraction

For intravenous administration only
Contains no preservative
Sterile - non-pyrogenic

To be diluted with 10ml (20ml) (40ml) Water for Injection

HEPATITIS DANGER - SEE INSERT LEAFLET

Store at 2° to 8°C
Allow to warm to 20°-30°C before reconstitution

If a gel forms on reconstitution, do not use.

Electrolyte Concentration

Citrate	Not more than 55 mmol/l
Sodium	Not more than 200 mmol/l
Chloride	Not more than 200 mmol/l
Fibrinogen	Not more than 0.25g/10ml

PL 0055/0065
PA XXXX

POM

Cutter, Division of Miles Laboratories Limited, Stoke Court, Stoke Poges, Slough, SL2 4LY, England.

Mfd. by : Cutter, Division of Miles Laboratories Inc., Berkeley, C.A., U.S.A.

Batch No. XXXX XXX I.U.

Expiry Date XXXX XXX Grams Protein

Date Removed From Refrigerator _____

B. Carton Label - 250, 500, 1000, 1500 Unit Packs

K O A T E(R)

Dried Factor VIII Fraction

Dosage - See Insert Leaflet

Store at 2° to 8°C

BAYP0000002_206_0006

Contents:

One bottle of Koate
10ml (20ml) (40ml) Sterile Water for Injection
One sterile filter needle for reconstitution
One sterile transfer needle

Contains no preservative
For intravenous administration only
Sterile - non-pyrogenic

Electrolyte Concentration

Citrate ..... Not more than 55 mmol/l
Sodium ..... Not more than 200 mmol/l
Chloride ..... Not more than 200 mmol/l

Fibrinogen ..... Not more than 0.25g/10ml

PL 0055/0065
PA XXXX

POM

Batch No. XXXX

XXX I.U.

Expiry Date XXXX

XXX Grams Protein

Date Removed From Refrigerator _____

HEPATITIS DANGER - SEE INSERT LEAFLET

Instruction - Reconstitution

1. Transfer 10ml of diluent to bottle of lyophilised 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 Insert Leaflet for detailed instructions.

When reconstituted with 10ml (20ml) (40ml) Sterile Water for Injection the solution contains 1% Dextrose and is slightly hypertonic.

This product is prepared from human venous plasma. Each individual unit of plasma has been found nonreactive for hepatitis B surface antigen using a U.S. Federally approved test.

WARNING : KOATE(R) CONCENTRATE IS A PURIFIED DRIED FRACTION OF POOLED PLASMA OBTAINED FROM MANY DONORS. THE PRESENCE OF HEPATITIS VIRUS SHOULD BE ASSUMED AND THE HAZARD OF ADMINISTERING KOATE(R) CONCENTRATE SHOULD BE WEIGHED AGAINST THE MEDICAL CONSEQUENCE OF WITHHOLDING IT, PARTICULARLY IN PERSONS WITH FEW PREVIOUS TRANSFUSIONS OF BLOOD AND PLASMA PRODUCTS.

Cutter, Division of Miles Laboratories Limited, Stoke Court, Stoke Poges, Slough, SL2 4LY, England.

Mfd. by: Cutter, Division of Miles Laboratories Inc., Berkeley, C.A., U.S.A.

C. Sterile Water for Injection

Sterile Water for Injection

Provided as a solvent or diluent for injectables

Sterile - non-pyrogenic

10ml (20ml) (40ml)

Not for Multiple Dose Use

Warning : Because there is no preservative present, unused amount should be discarded immediately following withdrawal of any portion of the content.

POM

Batch No. XXXX

Expiry Date XXXX

Cutter, Division of Miles Laboratories Limited, Stoke Court, Stoke Poges, Slough, SL2 4LY, England.

Mfd. by: Invenex Laboratories Gibco Division, The Dexter Corporation, Chagrin Falls, OH 44022, U.S.A.

19. Sample of packaged product

A fully packaged sample will be provided later.

20. Manufacturing authorisation

A copy of the U.S. product licence authorising the manufacture of the product by Cutter is enclosed.

21. The product is authorised for marketing in the U.K.

ATTACHMENT 1

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Washington

Product License

This is to certify that Cutter Laboratories, Inc. Berkeley, California *through the establishment identified as* Cutter Laboratories, Inc. *located at* Berkeley, California *is hereby authorized to propagate or manufacture and prepare for sale the following:*

Antihemophilic Factor (Human).

this Department having been satisfied that the requirements of the Public Health Service Act, approved July 1, 1944 (58 Stat. 682), for the regulation of biological products and of the regulations thereunder have been met with respect to the product(s) specified above.

Establishment License No. 8

Date: JAN 24 1974

GRO-C

Director, Bureau of Biologics
Food and Drug Administration

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