CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-281/S008/S009

APPROVAL LETTER

DIV

NDA 19-280/S-008
NDA 19-281/S-009

SEP 9 1999

Pharmacia & Upjohn Company
Attention: Daniel Chirby
7000 Portage Road
Kalamazoo, MI 49001

Dear Mr. Chirby:

Please refer to your supplemental new drug applications dated March 15, 1999, received March 16, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cyklokapron® (tranexamic acid) Tablets and Injection.

We acknowledge receipt of your submission dated August 18, 1999, in which you provided immediate container and carton labels for the injectable product.

These supplemental new drug applications provide for changes to the CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections of the package insert.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text and with the minor editorial revision listed below. Accordingly, these supplemental applications are approved effective on the date of this letter.

In the HOW SUPPLIED section of the package insert, please delete the line "NDC 0013-1114-01 10 mL ampule".

The final printed labeling (FPL) must be identical, and include the minor editorial revision indicated, to the submitted draft labeling (package insert submitted March 15, 1999, immediate container and carton labels submitted August 18, 1999).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplements NDA 19-280/S-008, 19-281/S-009." Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we

request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

(S) 9-9-99

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDAs 19-280/S-008, 19-281/S-009
HFD-180/Div. Files
HFD-180/J.DuBeau
HFD-180/Duffy
HFD-180/Adams
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-103/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-21/ACS (with labeling) - for drug discussed at advisory committee meeting.
HFD-095/DDMS-IMT (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE
JD/September 9, 1999 (drafted)
JD/9/9/99/c:\mydocs\nda\19280 & 1-slr-action-ltr.doc
APPROVAL (AP)

(S) 9/9/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-281/S008/S009

FINAL PRINTED LABELING

2 A

Cyklokapron®

tranexamic acid tablets and tranexamic acid injection

Pharmacia &Upjohn

Antifibrinolytic agent

DESCRIPTION

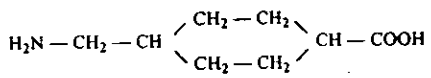
Each tablet contains 500 mg of tranexamic acid.

Each mL of the sterile solution for intravenous injection contains 100 mg tranexamic acid and Water for Injection to 1 mL.

FORMULATION

Chemical Name: trans-4-(aminomethyl) cyclohexanecarboxylic acid.

Structural Formula:



Empirical Formula: $C_8H_{15}NO_2$ Molecular Weight: 157.2

Tranexamic acid is a white crystalline powder. Inert ingredients in the tablets are microcrystalline cellulose, talc, magnesium stearate, silicon dioxide and povidone. The aqueous solution for injection has a pH of 6.5 to 8.0.

CLINICAL PHARMACOLOGY

Tranexamic acid is a competitive inhibitor of plasminogen activation, and at much higher concentrations, a noncompetitive inhibitor of plasmin, i.e., actions similar to aminocaproic acid. Tranexamic acid is about 10 times more potent *in vitro* than aminocaproic acid.

Tranexamic acid binds more strongly than aminocaproic acid to both the strong and weak receptor sites of the plasminogen molecule in a ratio corresponding to the difference in potency between the compounds. Tranexamic acid in a concentration of 1 mg per mL does not aggregate platelets *in vitro*.

Tranexamic acid in concentrations up to 10 mg per mL blood has no influence on the platelet count, the coagulation time or various coagulation factors in whole blood or citrated blood from normal subjects. On the other hand, tranexamic acid in concentrations of 10 mg and 1 mg per mL blood prolongs the thrombin time.

The plasma protein binding of tranexamic acid is about 3% at therapeutic plasma levels and seems to be fully accounted for by its binding to plasminogen. Tranexamic acid does not bind to serum albumin.

Absorption of tranexamic acid after oral administration in humans represents approximately 30 to 50% of the ingested dose and bioavailability is not affected by food intake.

After an intravenous dose of 1 g, the plasma concentration time curve shows a triexponential decay with a half-life of about 2 hours for the terminal elimination phase. The initial volume of distribution is about 9 to 12 liters. Urinary excretion is the main route of elimination via glomerular filtration. Overall renal clearance is equal to overall plasma clearance (110 to 116 mL/min) and more than 95% of the dose is excreted in the urine as the unchanged drug. Excretion of tranexamic acid is about 90% at 24 hours after intravenous administration of 10 mg per kg body weight. After oral administration of 10 to 15 mg per kg body weight, the cumulative urinary excretion at 24 hours is 39% and at 48 hours, 41% of the ingested dose or 78% and 82% of the absorbed material. Only a small fraction of the drug is metabolized. After oral administration, 1% of the dicarboxylic acid and 0.5% of the acetylated compound are excreted.

The plasma peak level after 1 g orally is 8 mg per L and after 2 g, 15 mg per L, both obtained three hours after dosing.

An antifibrinolytic concentration of tranexamic acid remains in different tissues for about 17 hours, and in the serum, up to seven or eight hours.

Tranexamic acid passes through the placenta. The concentration in cord blood after an intravenous injection of 10 mg per kg to pregnant women is about 30 mg per L, as high as in the maternal blood. Tranexamic acid diffuses rapidly into joint fluid and the synovial membrane. In the joint fluid the same concentration is obtained as in the serum. The biological half-life of tranexamic acid in the joint fluid is about three hours.

The concentration of tranexamic acid in a number of other tissues is lower than in blood. In breast milk the concentration is about one hundredth of the serum peak concentration. Tranexamic acid concentration in cerebrospinal fluid is about one tenth of that of the plasma. The drug passes into the aqueous humor, the concentration being about one tenth of the plasma concentration.

Tranexamic acid has been detected in semen where it inhibits fibrinolytic activity but does not influence sperm migration.

Cyklokapron

brand of tranexamic acid tablets and tranexamic acid injection

INDICATIONS AND USAGE

CYKLOKAPRON Tablets and Injection are indicated in patients with hemophilia for short term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction.

CONTRAINDICATIONS

CYKLOKAPRON Tablets and Injection are contraindicated:

1. In patients with acquired defective color vision, since this prohibits measuring one endpoint that should be followed as a measure of toxicity (see WARNINGS).
2. In patients with subarachnoid hemorrhage. Anecdotal experience indicates that cerebral edema and cerebal infarction may be caused by CYKLOKAPRON in such patients.
3. In patients with active intravascular clotting.

WARNINGS

Focal areas of retinal degeneration have developed in cats, dogs and rats following oral or intravenous tranexamic acid at doses between 250 to 1600 mg/kg/day (6 to 40 times the recommended usual human dose) from 6 days to 1 year. The incidence of such lesions has varied from 25% to 100% of animals treated and was dose-related. At lower doses some lesions have appeared to be reversible.

Limited data in cats and rabbits showed retinal changes in some animals with doses as low as 126 mg/kg/day (only about 3 times the recommended human dose) administered for several days to two weeks.

No retinal changes have been reported or noted in eye examinations in patients treated with tranexamic acid for weeks to months in clinical trials.

However, visual abnormalities, often poorly characterized, represent the most frequently reported postmarketing adverse reaction in Sweden. For patients who are to be treated continually for longer than several days, an ophthalmological examination, including visual acuity, color vision, eye-ground and visual fields, is advised, before commencing and at regular intervals during the course of treatment. Tranexamic acid should be discontinued if changes in examination results are found.

PRECAUTIONS

General

The dose of CYKLOKAPRON Tablets and Injection should be reduced in patients with renal insufficiency because of the risk of accumulation. (See DOSAGE AND ADMINISTRATION.)

Ureteral obstruction due to clot formation in patients with upper urinary tract bleeding has been reported in patients treated with CYKLOKAPRON.

Venous and arterial thrombosis or thromboembolism has been reported in patients treated with CYKLOKAPRON. In addition, cases of central retinal artery and central retinal vein obstruction have been reported.

Patients with a previous history of thromboembolic disease may be at increased risk for venous or arterial thrombosis.

CYKLOKAPRON should not be administered concomitantly with Factor IX Complex concentrates or Anti-inhibitor Coagulant concentrates, as the risk of thrombosis may be increased.

Patients with disseminated intravascular coagulation (DIC), who require treatment with CYKLOKAPRON, must be under strict supervision of a physician experienced in treating this disorder.

Carcinogenesis, mutagenesis, impairment of fertility

An increased incidence of leukemia in male mice receiving tranexamic acid in food at a concentration of 4.8% (equivalent to doses as high as 5 g/kg/day) may have been related to treatment. Female mice were not included in this experiment.

Hyperplasia of the biliary tract and cholangioma and adenocarcinoma of the intrahepatic biliary system have been reported in one strain of rats after dietary administration of doses exceeding the maximum tolerated dose for 22 months. Hyperplastic, but not neoplastic, lesions were reported at lower doses. Subsequent long term dietary administration studies in a different strain of rat, each with an exposure level equal to the maximum level employed in the earlier experiment, have failed to show such hyperplastic/neoplastic changes in the liver. No mutagenic activity has been demonstrated in several *in vitro* and *in vivo* test systems.

Pregnancy (Category B)

Reproduction studies performed in mice, rats, and rabbits have not revealed any evidence of impaired fertility or adverse effects on the fetus due to tranexamic acid.

There are no adequate and well-controlled studies in pregnant women. However, tranexamic acid is known to pass the placenta and appears in cord blood at concentrations approximately equal to maternal concentration. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Cyklokapron
brand of tranexamic acid tablets and tranexamic acid injection

Labor and Delivery

See above under Pregnancy.

Nursing Mothers

Tranexamic acid is present in the mother's milk at a concentration of about a hundredth of the corresponding serum levels. Caution should be exercised when CYKLOKAPRON is administered to a nursing woman.

Pediatric Use

The drug has had limited use in pediatric patients, principally in connection with tooth extraction. The limited data suggest that dosing instructions for adults can be used for pediatric patients needing CYKLOKAPRON therapy.

ADVERSE REACTIONS

Gastrointestinal disturbances (nausea, vomiting, diarrhea) may occur but disappear when the dosage is reduced. Giddiness and hypotension have been reported occasionally. Hypotension has been observed when intravenous injection is too rapid. To avoid this response, the solution should not be injected more rapidly than 1 mL per minute. This adverse reaction has not been reported with oral administration.

Worldwide Postmarketing Reports: Thromboembolic events (eg, deep vein thrombosis, pulmonary embolism, cerebral thrombosis, and central retinal artery and vein obstruction) have been rarely reported in patients receiving CYKLOKAPRON for indications other than hemorrhage prevention in patients with hemophilia. However, due to the spontaneous nature of the reporting of medical events and the lack of controls, the actual incidence and causal relationship of drug and event cannot be determined.

OVERDOSAGE

There is no known case of overdosage of CYKLOKAPRON Tablets and Injection. Symptoms of overdosage may be nausea, vomiting, orthostatic symptoms and/or hypotension.

DOSAGE AND ADMINISTRATION

Immediately before dental extraction in patients with hemophilia, administer 10 mg per kg body weight of CYKLOKAPRON intravenously together with replacement therapy (see PRECAUTIONS). Following surgery, a dose of 25 mg per kg body weight may be given orally three or four times daily for 2 to 8 days.

Alternatively, tranexamic acid can be administered entirely orally, 25 mg per kg body weight 3 to 4 times a day beginning one day prior to surgery.

Parenteral therapy, 10 mg per kg body weight 3 to 4 times daily can be used for patients unable to take oral medication.

Note: For patients with moderate to severe impaired renal function, the following dosages are recommended:

Tranexamic Acid Dosage

Serum Creatinine (μmol/L)	I.V. Dosage	Tablets
120 to 250 (1.36 to 2.83 mg/dL)	10 mg/kg BID	15 mg/kg BID
250 to 500 (2.83 to 5.66 mg/dL)	10 mg/kg daily	15 mg/kg daily
>500 (>5.66 mg/dL)	10 mg/kg every 48 hours or 5 mg/kg every 24 hours	15 mg/kg every 48 hours or 7.5 mg/kg every 24 hours

For intravenous infusion, CYKLOKAPRON Injection may be mixed with most solutions for infusion such as electrolyte solutions, carbohydrate solutions, amino acid solutions and Dextran solutions. The mixture should be prepared the same day the solution is to be used. Heparin may be added to CYKLOKAPRON Injection. CYKLOKAPRON Injection should NOT be mixed with blood. The drug is a synthetic amino acid, and should NOT be mixed with solutions containing penicillin.

HOW SUPPLIED

CYKLOKAPRON Tablets 500 mg (flat, white, round with beveled edges, arcs above and below the letters CY)
NDC 0013-0114-00 100 tablets.

CYKLOKAPRON Injection 100 mg/mL
NDC 0013-1114-10 10 x 10 mL ampules

STORAGE

Store CYKLOKAPRON Tablets and Injection at room temperature, 15° to 30°C (59° to 86°F).

℞ only

Manufactured for:
Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA

Revised October 1999

By:
Pharmacia & Upjohn AB
Stockholm, Sweden

115011099

420-685

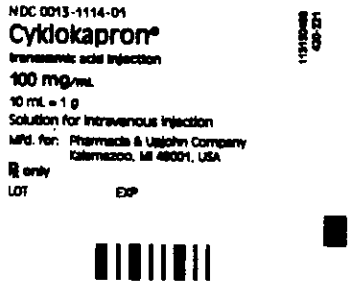
[redacted]

Cyklokapron Injection
(tranexamic acid injection)

Final Printed Ampoule Label

Code 115150498

AP on draft 9/9/99
FPL
Sb: 4/26/00
Rec: 4/27/00



[redacted] 281/S-009

Cyklokapron Injection
(tranexamic acid injection)

Final Printed Carton

Code 115171099

APon draft 9/9/99
FPL
Sub: 4/26/00
rec: 4/27/00

420-686

NDC 0013-1114-10
Contains ten NDC 0013-1114-01

Cyklokapron®

tranexamic acid injection

100 mg/mL

Manufactured for:
Pharmacia & Upjohn
Company
Kalamazoo, MI 49001, USA

By:
Pharmacia & Upjohn AB
Stockholm, Sweden

For intravenous injection
10 x 10 mL ampules

Pharmacia
&Upjohn

160

6 **Page(s) Redacted**

Draft

Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-281/S008/S009

CHEMISTRY REVIEW(S)

7.1

CHEMISTRY REVIEW 3	ORGANIZATION HFD-180	2. NDA Number: 19-281	
3. Named & Address of Applicant: Pharmacia, Inc. P.O. Box 16529 Columbus, OH 43216-6529		4. AF Number: JUL 26 1996	
		5. Supplement	
		Number	Date
6. Drug Name: Cyklokapron® Injection	7. Nonproprietary: Tranexamic Acid	SCM-001 SCS-003 SCS-004 SCM-005 SCS-007 SCM-008	02/25/93 " " " " "
8. Supplement Provides For:		9. Amendments & Reports: AC 01/23/96	
10. Category: anticoagulant	11. Dispensed: Rx XX OTC __	12. Related Docs: NDA 19-280 DMFs [redacted]	
13. Dosage Form: IV injection	14. Potency: 100 mg/mL		
15. Chemical Name & Structure: **APPEARS THIS WAY ON ORIGINAL**		16. Records & Reports: Current: Yes __ No __ Reviewed: Yes __ No __	

17. Comments:

c/c: NDA 19-281/S-001 thru 008
HFD-180/Div File
HFD-181/CSO
HFD-180/SFredd
HFD-180/MAdams
R/D init: EDuffy/7-26-96
MA/dob **F/T 7-26-96/WP:** /S/ 7/26/96

18. Conclusions and Recommendations:

Supplements 001,004,005,007,008 should be APPROVED (AP). S-003 is APPROVABLE pending submission of further CMC information. DMF [redacted] has been reviewed and found acceptable to support approval of these supplements.

19. Reviewer

Name:	Signature: 7/26/96 /S/	Date Completed:
MIKE ADAMS		07/24/96

Distribution //Original Jacket //Reviewer //Division File

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-281/S008/S009

ADMINISTRATIVE DOCUMENTS

NDA 19-281/S-001,004,005,007,008 JUL 24 1996

Pharmacia and Upjohn Company
Attention: Susan M. Mondabaugh, Ph.D.
7000 Portage Road
Kalamazoo, Michigan 49001

Dear Dr. Mondabaugh:

Please refer to your February 25, 1993, supplemental new drug applications submitted under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for Cyklokapron® (tranexamic acid, USP) Injection.

We also acknowledge receipt of your amendment dated January 23, 1996.

The supplemental applications provide for the following:

S-001: To change the manufacturing site for drug substance to [redacted]

S-004: To delete the [redacted]

S-005: To revise the method for drug substance manufacture and controls to the [redacted] process described in [redacted]

S-007: To change the drug product regulatory methods for the cis-AMCA Limit and for the trans-AMCA Assay; and to replace the USP Pyrogen test with the USP Bacterial Endotoxin test with a specification [redacted]

S-008: For a series of revisions to the locations where the various manufacturing processes and testing are performed: Pharmacia AB (Lindhagensgatan, Stockholm); for the chemical and microbiological testing of raw materials and finished product for release and stability; and for the manufacture of finished drug product. To provide for Pharmacia AB (Kraftvagen, Building 6, Kungsagen) for Bacterial Endotoxin testing of finished drug product; and Pharmacia AB (Rapsgatan, Uppsala) for stability testing of raw materials, active ingredient and finished drug product. Also to provide for revisions to the ampules, to the procedures and

in-process controls for ampule preparation, and to the procedure and parameters for the terminal sterilization process.

We have completed our review of these supplemental applications and they are approved.

We remind you that you must comply with the requirements for an approved new drug application set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Julieann DuBeau
Consumer Safety Officer
(301) 443-0487

Sincerely Yours,

/S/ 7/24/96

Eric P. Duffy, Ph.D.
Acting Chemistry Team Leader
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
NDA 19-281
HFD-180/div file
DISTRICT OFFICE
HFD-80/DDIR
HFD-181/CSO/JDuBeau
HFD-180/SFredd
HFD-820/YYChiu
HFD-180/MAdams/7-24-96
R/D init/EDuffy/7-24-96
MA/dob **F/T 7-24-96**

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-281/S008/S009

CORRESPONDENCE

NOV - 7

NDA 19-281/S-001, 003, 004, 005, 007, 008

Kabi Pharmacia, Incorporated
Attention: Betsy J. Waldheim
800 Centennial Avenue
P.O. Box 1327
Piscataway, New Jersey 08855-1327

Dear Ms. Waldheim:

Please refer to your February 25, 1993 supplemental new drug applications submitted under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for Cyklokapron (tranexamic acid) Injection.

We also acknowledge receipt of your amendments dated July 27, 1994.

The supplemental applications provide for:

S-001: to change the manufacturing site for drug substance from Kabi Pharmacia AB, Strangnas, Sweden to

S-003: to change the drug substance regulatory methods for cis-4-carboxycyclohexylmethyl)amine [cis-AMCA] Limit from and for trans-4-carboxycyclohexyl-methyl)amine [trans-AMCA] Assay from and to replace the USP Pyrogen test with the USP Bacterial Endotoxin test;

S-004: to delete the

S-005: to revise the method for drug substance manufacture (from the Kabi Pharmacia process to the process described in DMF ; and

S-007: to change the drug product regulatory methods for cis-AMCA Limit from and for trans-AMCA Assay from and to replace the USP Pyrogen test with the USP Bacterial Endotoxin test.

We also note that the submission describes the following changes to the drug product manufacturing process and to the sites for drug product manufacture, release testing, stability testing and stability sample storage.

S-008: For a series of revisions to the locations where the various manufacturing processes and tests are performed at Kabi Pharmacia (Kraftragen 1, Kungsangen), at Kabi Pharmacia (Kungholmen, Stockholm), and at Kabi Pharmacia Therapeutics Uppsala (Rapsgatan 7, Uppsala), and for revisions to the ampules, to the procedures and in-process controls for ampule preparation, and to the procedure and parameters for the terminal sterilization process.

We have completed our review and find the information presented is inadequate and the supplemental applications are not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

Within 10 days after the date of this letter, you are required to amend these supplemental applications, notify us of your intent to file an amendment, or follow on of your options under 21 CFR 314.120. In the absence of such action FDA may take action to withdraw the supplemental applications. Any amendment that does not respond to all of the deficiencies listed above will be processed as a minor amendment. The review clock will be reactivated only after all deficiencies have been addressed.

Should you have any questions, please contact:

Ms. Bronwyn Collier
Consumer Safety Officer
Telephone: (301) 443-0487

Sincerely Yours,

John J. Gibbs, Ph.D.
Supervisory Chemist
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

/S/ 11/4/94

19281 SEP - 9 1999

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Numbers: NDA 19-280/SLR-008; NDA 19-281/SLR-009

Name of Drug: Cyklokapron® (tranexamic acid) Tablets and Injection

Sponsor: Pharmacia & Upjohn Company

Material Reviewed

Submission Dates: March 15, 1999 (package insert)
August 18, 1999 (immediate container and carton labels for the injection)

Receipt Dates: March 16, 1999 (package insert)
August 19, 1999 (immediate container and carton labels for the injection)

Background and Summary Description: Pharmacia & Upjohn Company submitted these two labeling supplements in response to a May 11, 1998, telephone call requesting a search on the incidence of thrombosis and to a July 2, 1998, letter requesting revised labeling (see attached letter). These two prior approval labeling supplements provide for revisions to the CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections of the package insert. On August 5, 1999, the firm was requested to submit immediate container and carton labels for the injectable product. Note that Cyklokapron® Tablets (NDA 19-280) and Cyklokapron® Injection (NDA 19-281) share one package insert; therefore, the combined review of both labeling supplements.

Review

I. Package Insert

The revised package insert, which both dosage forms share, (no identifier) submitted March 15, 1999, received March 16, 1999, was compared to the currently approved package insert identified as "115010496, Revised April 12, 1996", submitted March 2, 1998, in Y-011 under NDA 19-281. The package inserts are identical except for the following:

A. In the CONTRAINDICATIONS section:

The following sentence has been added as item #3 at the end of this section: "3. In patients with active intravascular clotting."

This addition, reviewed by the Medical Officer, Dr. Lilia Talarico, is ACCEPTABLE.

B. In the PRECAUTIONS section:

1. In the "General" subsection, the following sentences have been added at the end of this subsection: "Ureteral obstruction due to clot formation in patients with upper urinary tract bleeding has been reported in patients treated with CYKLOKAPRON. Venous and arterial thrombosis or thromboembolism has been reported in patients treated with CYKLOKAPRON. In addition, cases of central retinal artery and central retinal vein obstruction have been reported. Patients with a previous history of thromboembolic disease may be at increased risk for venous or arterial thrombosis. CYKLOKAPRON should not be administered concomitantly with Factor IX Complex concentrates or Anti-inhibitor Coagulant concentrates, as the risk of thrombosis may be increased. Patients with disseminated intravascular coagulation (DIC), who require treatment with CYKLOKAPRON, must be under strict supervision of a physician experienced in treating this disorder."

   These additions, reviewed by the Medical Officer, Dr. Lilia Talarico, are ACCEPTABLE.

2. In the "Pediatric Use" subsection, the word [redacted] has been replaced with "pediatric patients".

   This revision is in accordance with 21 CFR 201.57(f)(9)(i)-(iv) and is ACCEPTABLE.

C. In the ADVERSE REACTIONS section:

The following paragraph has been added at the end of this section: "Worldwide Postmarketing Reports: Thromboembolic events (e.g. deep vein thrombosis, pulmonary embolism, cerebral thrombosis, and central retinal artery and vein obstruction) have been rarely reported in patients receiving CYKLOKAPRON for indications other than hemorrhage prevention in patients with hemophilia. However, due to the spontaneous nature of the reporting of medical events and the lack of controls, the actual incidence and causal relationship of drug and event cannot be determined."

This addition, reviewed by the Medical Officer, Dr. Lilia Talarico, is ACCEPTABLE.

D. In the DOSAGE AND ADMINISTRATION section:

The following first paragraph has been changed from: [redacted]

To: "Immediately before dental extraction in patients with hemophilia, administer 10 mg per kg body weight of CYKLOKAPRON intravenously together with replacement therapy (see PRECAUTIONS). Following surgery, a dose of 25 mg per kg body weight may be given orally three or four times daily for 2 to 8 days."

These revisions, reviewed by the Medical Officer, Dr. Lilia Talarico, are ACCEPTABLE.

E. In the HOW SUPPLIED section:

1. The following has been added: "[redacted]

   In an 8/11/99 telephone conversation with Mr. Daniel Chirby, regulatory affairs, he stated that this addition is an error and should be deleted. The firm is not distributing [redacted] The firm agreed to delete this line in the HOW SUPPLIED section as stated in the cover letter of their 8/18/99 submission.

2. The following NDC number for the 10 x 10 mL ampules has been changed from: [redacted] to: "0013-1114-10".

   In an 8/27/99 telephone conversation with Mr. Daniel Chirby, regulatory affairs, he stated that the NDC number has been changed due to reimbursement purposes (see firm's 8/18/99 submission). He verified that the drug formulation and trade package size and type have not been changed. This revision is ACCEPTABLE.

F. Other revisions:

1. The type size is smaller.

   This editorial revision is ACCEPTABLE.

2. The company logo has been changed from "Pharmacia" to "Pharmacia & Upjohn" and moved from the end to the beginning of the package insert.

This revision is in accordance with 21 CFR 201.1 and is ACCEPTABLE.

3. "℞ Only" has been added at the end of the package insert.

   This addition is in accordance with Section 126 of the Food and Drug Administration Modernization Act of 1997 and is ACCEPTABLE.

4. At the end of the package insert the "manufactured for" statement has been changed from: "Pharmacia Inc." to: "Pharmacia & Upjohn Company". The "manufactured by" statement has been changed from: "Pharmacia AB" to: "Pharmacia & Upjohn AB".

   This is in accordance with 21 CFR 201.1 and is ACCEPTABLE.

5. Minor editorial revisions have been made throughout the package insert.

   These minor editorial revisions are ACCEPTABLE.

II. Immediate Container Label (Injectable product)

The immediate container label, identified as "420-221" (submitted August 18, 1999. received August 19, 1999) was compared to the currently approved immediate container label identified as "429-540" (submitted March 2, 1998, received March 3, 1998, in Y-011 under NDA 19-281). The immediate container labels are identical except for the following:

A. The NDC number has been changed from: [redacted] to: "0013-1114-01".

   This change occurred to correspond with the carton label NDC number change and is ACCEPTABLE.

B. The word "injection" has been added after the established name.

   This addition provides clarifying information and is ACCEPTABLE.

C. The "manufactured by" statement: "Pharmacia AB, Stockholm, Sweden" has been replaced by the "manufactured for" statement: "Pharmacia & Upjohn Company Kalamazoo, MI 49001, USA".

   This is in accordance with 21 CFR 201.1 and is ACCEPTABLE.

D. "℞ Only" has been added.

This addition is in accordance with Section 126 of the Food and Drug Administration Modernization Act of 1997 and is ACCEPTABLE.

E. Minor editorial revisions have been made throughout the immediate container label.

These minor editorial revisions are ACCEPTABLE.

III. Carton Label (Injectable product)

The carton label, identified as "420-223" (submitted August 18, 1999, received August 19, 1999) was compared to the currently approved carton label identified as "435-493" (submitted March 2, 1998, received March 3, 1998, in Y-011 under NDA 19-281). The carton labels are identical except for the following:

A. The NDC number has been changed from: [redacted] to: "0013-1114-10".

In an 8/27/99 telephone conversation with Mr. Daniel Chirby, regulatory affairs, he stated that the NDC number has been changed due to reimbursement purposes (see firm's 8/18/99 submission). He verified that the drug formulation and trade package size and type have not been changed. This revision is ACCEPTABLE.

B. The following words and numbers have been added at the top, front panel of the carton: "Contains ten NDC 0013-1114-01".

This addition provides clarifying information and is ACCEPTABLE.

C. The "stick on" label for the carton has been replaced by a "cardboard" carton.

This change is ACCEPTABLE.

D. The word "injection" has been added after the established name.

This addition provides clarifying information and is ACCEPTABLE.

E. The "manufactured for" statement has been changed from: "Pharmacia Inc." to: "Pharmacia & Upjohn Company." The "manufactured by" statement has been

changed from "Pharmacia AB" to: "Pharmacia & Upjohn AB."

This is in accordance with 21 CFR 201.1 and is ACCEPTABLE.

F. "℞ Only" has been added.

This addition is in accordance with Section 126 of the Food and Drug Administration Modernization Act of 1997 and is ACCEPTABLE.

G. The company logo has been changed from "Pharmacia" to "Pharmacia & Upjohn" and moved from the lower left to the upper right front panel.

This revision is in accordance with 21 CFR 201.1 and is ACCEPTABLE.

H. Minor editorial revisions have been made throughout the immediate container label.

These minor editorial revisions are ACCEPTABLE.

Conclusions

1. The Medical Officer, Dr. Lilia Talarico, finds the following items acceptable: IA, IB1, IC, and ID.

2. These supplements should be approved on draft labeling with the following revision: Delete the line [redacted] from the HOW SUPPLIED section of the package insert. The firm should be requested to submit FPL identical to that submitted on March 15 and August 18, 1999, with the above deletion.

/S/ 9/9/99
Julieann DuBeau, RN, MSN
Regulatory Health Project Manager

/S/ 9-9-99

Attachment: (1) July 2, 1998 Agency letter

cc:
Original NDA 19-280/S-008, NDA 19-281/S-009
HFD-180/Div. Files
HFD-180/DuBeau

NDA 19-280, (19-281)

Pharmacia & Upjohn Company
Attention: James H. Chambers
7000 Portage Road
Kalamazoo, MI 49001

JUL - 2 1998

Dear Mr. Chambers:

Please refer to your approved new drug applications for Cyklokapron® (tranexamic acid) Tablets and Injection and to your annual reports dated March 2, 1998, that we received on March 3, 1998.

At the next printing, please revise your labeling as follows:

A. In the PRECAUTIONS section of the package insert, "Pediatric Use" subsection, replace the word [redacted] with "pediatric patients" or "pediatric populations" in accordance with 21 CFR 201.57(f)(9)(I)-(iv).

B. In the ADVERSE REACTIONS and WARNINGS sections of the package insert, incorporate "central retinal artery obstruction".

C. In the PRECAUTIONS section of the package insert, the following sentence should be added to conform with professional labeling for Factor IX Complex concentrates and Anti-Inhibitor Coagulant concentrates: "Tranexamic acid should not be administered with Factor IX Complex concentrates or Anti-Inhibitor Coagulant concentrates, as the risk of thrombosis may be increased."

D. In the package insert, immediate container labels, and carton labels, change the logo to "Pharmacia & Upjohn Company" in accordance with 21 CFR 201.1.

If you have any questions, contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 443-0487.

Sincerely,

/S/ 7-2-98

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research