N19280

APRVL

LTR

NDA 19-280
19-281

DEC 30 1986

Kabivitrum Inc.
Attention: Ronald G. Leonard, Ph.D.
1311 Harbor Bay Parkway
Alameda - CA 94501

Dear Dr. Leonard:

Please refer to your May 7, 1986 new drug applications submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Cyclokapron (tranexamic acid) Tablets and Injection.

We also acknowledge receipt of your amendments dated January 14, February 3, March 14, May 13, July 16, October 9, November 14, 25, and 26, 1985, January 29, July 24, and August 1, 1986 to both NDAs and of your amendments dated July 22 and 23, and September 17, 1985 and July 3, 1986 to NDA 19-280 only.

We have completed the review of these applications including the submitted draft labeling 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 enclosed draft labeling. Accordingly, the applications are approved effective on the date of this letter.

Please submit twelve copies of the FPL to each new drug application as soon as available. Please individually mount seven of the copies on heavy weight paper or similar material. For administrative purposes these submissions should be designated "FPL Supplements" to the approved NDAs 19-200 and 19-201. Approval of these supplements by FDA is not required before the labeling is used.

The final printed labeling (FPL) must be identical to the enclosed draft labeling. Marketing the products with FPL that is not identical to this draft labeling may render the products misbranded and unapproved new drugs.

Should additional information relating to the safety and effectiveness of the drugs become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

Please submit one market package for each of these drug products when they are available.

In addition, we would appreciate your submitting copies of the introductory promotional material that you propose to use for these products. Please submit one copy to the Division of Cardio-Renal Drug Products and a second, along with a copy of the package insert, directly to:

Division of Drug Advertising and Labeling, HFN-240
Room 16B-04
5600 Fishers Lane
Rockville, Maryland 20857

Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

While these applications are approved for the indication specified in the marked-up draft labeling, the required validation of the analytical methods has not been completed, but is ongoing in our laboratories. In such cases the policy of the Center for Drugs and Biologics is to proceed with approval. We expect your continued cooperation to resolve any problems that may arise.

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, please contact:

Ms. Gwyn Reis
Consumer Safety Officer
(301) 443-4730

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

Enclosure

cc:
Original NDA
HFN-[illegible]
HFN-110/CSO
HFN-713/CCHI
HFN-83
HFN-100/Dr. Temple
HFN-232 (with labeling)
HFN-110/GRuis/12/24/86
gr/12/23/86/4693s

APPROVAL

FPL

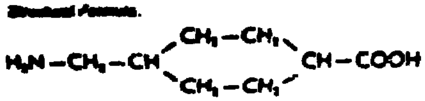
Cyklokapron® Tablets and Injection
(Tranexamic acid)

APPROVED

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-(amino methyl) 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 – 7.5.

CLINICAL PHARMACOLOGY
Tranexamic acid is a competitive inhibitor of plasminogen activation, and at much higher concentrations, a noncompetitive inhibitor of plasmin, 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 – 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 – 12 liters. Urinary excretion is the main route of elimination via glomerular filtration. Overall renal clearance is equal to overall plasma clearance (110 – 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 – 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 obtained. Tranexamic acid concentration in cerebrospinal fluid is about one tenth of that of the plasma. The drug passes into the aqueous humour, 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.

INDICATIONS AND USAGE
Cyklokapron® is 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® is 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 cerebral infarction may be caused by Cyklokapron in such patients.

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® should be reduced in patients with renal insufficiency because of the risk of accumulation.
See DOSAGE AND ADMINISTRATION.

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.

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 children, principally in connection with tooth extraction. The limited data suggest that dosing instructions for adults can be used for children 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.

OVERDOSAGE
There is no known case of overdosage of Cyklokapron®. Symptoms of overdosage may be nausea, vomiting, orthostatic symptoms and/or hypotension.

DOSAGE AND ADMINISTRATION
For dental extraction in patients with hemophilia: Immediately before surgery, substitution therapy is given together with tranexamic acid, 10 mg per kg body weight I.V. After surgery, 25 mg per kg body weight are given orally three to four times daily for two to eight 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. Dose	Tablets
120 – 250 (1.36 – 2.83 mg/dL)	10 mg/kg BID	15 mg/kg BID
250 – 500 (2.83 – 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
Tablets 500 mg (flat, white, round with bevelled edges, arcs above and below the letters CY), 100 tablets.

Ampoules 100 mg/mL, 10 x 10 mL.

STORAGE
Store Cyklokapron tablets and injection at room temperature (15 - 30°C).

Manufactured by
KabiVitrum AB
S - 112 87 Stockholm, Sweden

Distributor
KabiVitrum Inc
Alameda, CA [illegible]501 USA

Revised January 1987

457 127

Tom E 7/20/87

Cyklokapron® Tablets and Injection
(Tranexamic acid)

6 mg

Antifibrinolytic agent

APPROVED

DESCRIPTION

Each tablet contains 500 mg of tranexamic acid
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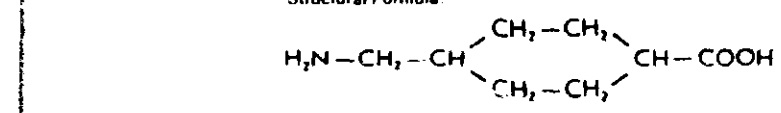

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Parenteral therapy, 10 mg per kg body weight 3 to 4 times daily can be used for patients unable to take oral medication.

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

Serum Creatinine (μmol/L)	Tranexamic Acid Dosage I.V. Dose	*Tablets*
120 – 250 (1.36 – 2.82 mg/dL)	10 mg/kg BID	15 mg/kg BID
250 – 500 (2.83 – 5.65 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

Tablets 500 mg (flat, white, round with bevelled edges, scored above and below the letters CY) 100 tablets.

Ampoules 100 mg/mL, 10 x 10 mL.

STORAGE

Store Cyklokapron *tablets and* injection at room temperature (15 – 30°C).

Manufactured by
KabiVitrum AB
S – 112 87 Stockholm, Sweden

Distributor:
KabiVitrum Inc.
Alameda, CA 94501 USA

Revised January, 1987

457-127

For intravenous infusion, Cyklokapron® solution for 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® solution for injection. Cyklokapron® solutions for 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

Tablets 500 mg (flat, white round with bevelled edges, arcs above and below the letters CY): 50 tablets, 100 tablets.

Manufactured by
KabiVitrum AB
S-112 87 Stockholm

Distributor:
KabiVitrum, Inc.
Alameda, CA 94501 USA

Add Storage Statement

Revised December 22, 1986

PHARM

REV

NDA: (a) 19280
(b) 19281

Kabi Vitrum, Inc.
Greenwich, CT

NOR 3

Submission Date: May 7, 1984

Receipt (FDA) Date: May 7, 1984

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Drug: (a) Cyklokapron (Tranexamic acid) 500 mg tablets
(b) Cyklokapron (tranexamic acid) 100 mg/ml, I.V. Solution

Category: Antifibrinolytic (a competitive inhibitor of plasminogen activation and at higher concentrations a noncompetitive inhibitor of plasmin).

Indication: _____

Dose:
1. Local fibrinolysis or prostatectomy: 5 to 10 ml i.v. at a rate of 1 ml/min. or 2 or 3 tablets b.i.d. or t.i.d.
2. Dental extraction in patients with coagulopathies: Immediate, , 10 mg/Kg, i.v. After Surgery, 25 mg/Kg, t.i.d. or q.i.d., orally for 6 to 8 days (100 mg/Kg/ day).
3. Hereditary angioneurotic oedema: 2 to 3 tablets, 2 to 3 times daily, for a few days (to 90 mg/Kg/day).

Contents of Submission: References submitted for pharmacology section.

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OKAMOTO S & OKAMOTO U: Amino-methyl-cyclohexane-carboxylic acid-AMCHA. A new potent inhibitor of the fibrinolysis. Keio J Med, 1962, 11, 103-114.

OKAMOTO S, OSHIBA S, MIHARA H & OKAMOTO U: Synthetic inhibitors of fibrinolysis: In vitro and in vivo mode of action. Ann N Y Acad Sci 1968, 146, 414-429.

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LANDMANN H: Comparative studies of antifibrinolytic agents. Folia Haematol 1967, 87, 106-112

LANDMANN H: Studies on the mechanism of action of synthetic antifibrinolytics. A comparison with the action of derivatives of benzamidine on the fibrinolytic process. Thrombos Diathes haemorrh (Stuttgart) 1973, 29, 253-275.

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Table 1 TOXICITY AFTER SINGLE ADMINISTRATION OF TRANEXAMIC ACID TO MICE, RATS, RABBITS, CHICKENS AND DOGS

Route of administration	Species	Strain	Sex	No of animals per dose level	LD_{50} (g/kg)	Observation period (days)	Ref
Oral	Mouse	NMRI	M, F	10	>12.5	1 and 7	Sirén,1966b
	Mouse	ddy	M, F	10	>10	3	Takayama et al.,1971
	Rat	Sprague-Dawley	M, F	10	>11.3	1 and 7	Sirén,1966c
	Rat	Wistar	M, F	10	>10	3	Takayama et al.,1971
	Rabbit		M	6	>3	2 and 7	Sirén,1967
	Chicken			10	>10	3	Takayama et al.,1971
	Dog	Mongrel	M		>5	3	Takayama et al.,1971
Subcutaneous	Mouse	NMRI	M, F	10	3.9 (M) 3.8 (F)	1 and 7	Sirén,1966b
	Mouse	ddy	M, F	10	5.3 (M) 6.4 (F)	3	Takayama et al.,1971
	Rat	Sprague-Dawley	M, F	10	4.9 (M) 6.3 (F)	1 and 7	Sirén,1966c
	Rat	Wistar	M, F	10	4.6 (M) 4.7 (F)	3	Takayama et al.,1971
	Rabbit		M	6	4.0	2 and 7	Sirén,1967
Intraperitoneal	Mouse	NMRI	M, F	10	2.7 (M) 2.4 (F)	1 and 7	Sirén,1966b
	Rat	Sprague-Dawley	M, F	10	2.2 (M) 2.1 (F)	1 and 7	Sirén,1966c
	Rabbit		M	6	3.4	2 and 7	Sirén,1967
Intravenous	Mouse	NMRI	M, F	10	1.3 (M) 1.4 (F)	1 and 7	Sirén,1966b
	Mouse	ddy	M, F	10	1.4 (M) 1.5 (F)	3	Takayama et al.,1971
	Rat	Sprague-Dawley	M, F	10	0.9	1 and 7	Sirén,1966c
	Rat	Wistar	M, F	10	1.4 (M) 1.1 (F)	3	Takayama et al.,1971
	Rabbit		M	6	1.4	2 and 7	Sirén,1967
	Dog	Mongrel	M		1.1	3	Takayama et al.,1971

Table II TOXICITY AFTER REPEATED ADMINISTRATION OF TRANEXAMIC ACID TO RATS, RABBITS, CATS, DOGS AND MONKEYS

Species	Duration of treatment	Route of adm	No of animals/ dose group	Dose levels (mg/kg/day)	Dosing schedule	Parameters studied*	Ref
Rat	14 days	i.p.	10♂ + 10♀	0, 250, 500, 1,000	7 days/week	CS, BW, H, BC, GP	Sirén, 1967-1
Rat	14 days	p.o. (in the diet)	6♂ + 6♀	0, 1, 2.5, 5, 7.5% drug diet	Test diet ad libitum	CS, BW, FC, H, U	Devitto & Gordon, 1971
Rat	16 weeks	p.o.	6♂ + 6♀	0, 1,000, 2,500 5,000	5 days/week	CS, BW, H, BC, GP, MP	Sirén, 1967-1
	17 weeks	p.o.	10♂	5,000, 7,500	5 days/week	CS, BW, H, GP	
Rat	6 months	p.o.	20♂ + 20♀	0, 750, 1,500, 3,000, 4,000	5 days/week	CS, BW, FC, WC, H, BC, U, GP, MP	Takayama et 1971
Rat	18 months	p.o.	51-54♂ 51-54♀	0, 4.8% drug diet	Test diet ad libitum	CS, BW, FC, H, BC, U, GP, MP	Johansson & Jönsson, 1980
Rat	22 months	p.o. (in the diet)	54♂ + 54♀ 72♂ + 72♀ (controls)	0, 0.3, 1.2, 4.8% drug diet	Test diet ad libitum	CS, BW, FC, H, BC, U, O, GP, MP	Gordon, 1971a 1972; Kopenh & Sparano, 19 Sparano, 1972
Rabbit	13 days	i.v.	4♂	0, 60, 120, 180	Daily	CS, BW	Palmer & Bradshaw 7
Rabbit	1-10 months	p.o. (in the drinking water)	3-6	0, 500 mg/day	Daily	EEG, electron microscopy of eyes	Johnson et al., 1977

* CS = clinical signs; BW = body weight; FC = food consumption; WC = water consumption; BC = blood chemistry; U = urinalysis; O = ophthalmology; EEG = electroencephalography; GP = gross pathology; MP = microscopic pathology

11 cont.

Species	Duration of treatment	Route of adm	No of animals/ dose group	Dose levels (mg/kg/day)	Dosing schedule	Parameters studied*	Ref
Cat	4-14 days	i.v.	4-6	125, 250, 2x250	Daily	Clinical and histological examination of eyes	Kleinsorge & Schnitzlein, 1976
Cat	6 days	i.v.	?	125, 250, 500	Daily	Clinical and histological examination of eyes	Luckhaus, 1976
Dog	3 days	i.v.	3	0, 1,000	Daily	BC, ECG, GP, MP	Guzman, 1965a,
Dog	1-7 days	i.v.	2	0, 2,000	Daily	Clinical and histological examination of eyes	Gordon & Spurano, 1971
Dog	1 month	i.v.	2♂ + 2♀	0, 2x10, 2x50, 2x250	Twice daily 5 days/week	CS, BW, FC, WC, H, BC, U, ECG, BP, GP, MP	Balazs & Porpora, 1969; Ohtake & Kepenis, 1968
Dog	18 weeks	p.o.	2♂ + 2♀	0, 2x50, 2x250, 2x500	Twice daily 5 days/week	CS, BW, H, BC, U, ECG, O, GP, MP	Sirén, 1966a
Dog	12 months + 13 months recovery	p.o.	3♂ + 3♀	0, 2x100, 2x200, 2x400, 2x800	Twice daily 7 days/week	CS, BW, FC, WC, H, BC, U, ECG, BP, O, GP, MP	Brecher & Spurano, 1972; Spurano, 1972c Tuveli, 1972a
Dog	12 months	p.o.	3-4♂ + 3-4♀	0, 2x400, 2x600	Twice daily 7 days/week	CS, BW, FC, H, BC, O, ECG, GP, MP including electron microscopy of eyes	Ekvärn et al. 1979; Johnsson 1979
Monkey	7-14 days	i.v.	1-3	0, 2,000	Daily	CS, O, MP	[illegible] & Bodhart, 1973

* CS = clinical signs BW = body weight FC = food consumption WC = water consumption
BC = blood chemistry U = urinalysis O = ophthalmology ECG = electrocardiography
BP = blood pressure EEG = electroencephalography MP = microscopic pathology GP = gross pathology

Table III STUDIES ON CARCINOGENIC POTENTIAL OF TRANEXAMIC ACID IN MICE AND RATS

Species	Duration of study	Route of adm	No of animals/ dose group	Dose levels	Dosing schedule	Refs
Mouse	20 months	p.o. (in the diet)	60-61	0, 4.8%	Test diet ad libitum	Takayama, 1976a
Rat	22 months (interim sacrifices at 3 & 12 months)	p.o. (in the diet)	108-144	0, 0.3, 1.2 4.8%	Test diet ad libitum	Gordon, 1971a,b, 1972; Kepenis & Sparano, 1972; Sparano, 1972a,b
Rat	24 months	p.o. or s.c.	60	0, 1, 10 g/kg (p.o.) 0, 0.35, 3.5 g/kg (s.c.)	Once a week for five consecutive weeks	Ogawa & Ono, 1976a,b
Rat	20 months	p.o. (in the diet)	49-79	0, 4.8%	Test diet ad libitum	Takayama, 1976b
Rat	18 months (interim sacrifices at 3, 6, 9, 12 and 15 months)	p.o. (in the diet)	102-108	0, 4.8%	Test diet ad libitum	Johansson & Jönsson, 1980

Table IV MUTAGENICITY TESTS - in vitro

Compound	Type of test	Test system	With and without metab.act.	Negative controls	Positive controls	Refs
Tranexamic acid (Kabi)	Gene mutation	Salmonella typhimurium (strains TA1535, TA1537 and TA1538)	Yes	Yes	Yes	Hossack, Richol Jones&Bellamy,
Tranexamic acid (Daiichi)	Gene mutation	Salmonella typhimurium (strains TA1535, TA1537 and TA1538)	Yes	Yes	Yes	-"-
Tranexamic acid	Gene mutation	Salmonella typhimurium (strains TA1535, TA1537, TA1538, TA100 and TA98	Yes	Yes	Yes	Shimada, Nagai, Morita&Akimoto,
Tranexamic acid	Primary DNA damage	Bacillus subtilis (strains H17(rec$^+$) and M45(rec$^-$)	No	No	Yes	-"-
Tranexamic acid	Cytogenetic	Chinese hamster cells (D6)	No	Yes	Yes	-"-

Table IV cont. MUTAGENICITY TESTS with tranexamic acid - in vivo (i.p. adm.)

Type of test	Species (strain)	Dose levels (mg/kg)	No of animals/ dose group	Dosing schedule	Negative control	Positive control	Refs
Cytogenetic	Mouse (ddY)	100, 1500, 3500	15	Once	Yes	Yes	Shimada, Nagai, Morita&Akimoto 1979
Cytogenetic	Mouse (ddY)	100, 1500, 3500	5	5 times	Yes	Yes	-"-
Cytogenetic	Rat (Sprague-Dawley	100, 1500, 3000	15-18	Once	Yes	Yes	-"-
Cytogenetic	Rat (Sprague-Dawley)	100, 1500, 3000	5	5 times	Yes	Yes	-"-
Cytogenetic	Rat (Sherman)	100, 1500, 3000	10	Once	Yes	Yes	-"-
Cytogenetic	Rat (Sherman)	100, 1500, 2500	6	5 times	Yes	Yes	-"-
Dominant lethal test	Mouse (ddY)	100, 3000	10 (males)	Once	Yes	Yes	-"-

Table V REPRODUCTION AND TERATOLOGY STUDIES PERFORMED WITH TRANEXAMIC ACID

Type of study	Species	Route adm	Treatment period	No of animals/ dose group	Dose levels mg/kg/day	Ref
Teratology	Mouse	p.o.	7-12 of gestation	15	0, 300, 1,500	Morita al., 19
Teratology	Rat	p.o.	9-14 of gestation	15	0, 300, 1,500	Morita al., 19
Teratology	Rabbit	p.o.	6-18 of gestation	10-13	0, 100, 200, 400	Palmer Readshu
Teratology	Rabbit	i.v.	6-18 of gestation	12-13	0, 50, 100, 200	Palmer Readshu 1971b
Peri- and postnatal action	Rat	p.o.	From day 16 of gestation to 21 days postpartum	13-33	0, 100, 300, 1,000	Strippo Jackson 1971b
Male fertility	Rat	p.o.	126 days premating	10	0, 222 (0.3% in the diet), 856 (1.2% in the diet)	Strippo 1971
Fertility and general reproductive performance	Rat	p.o.	Females: 2 weeks premating; throughout mating to day 11 of gestation or throughout mating, gestation and lactation to day 21 postpartum	20-40	0, 201-437 (0.3% in the diet), 792-1,160 (1.2% in the diet)	Strippo Jackson 1971a

I. Pharmacology.

(Sponsor, edited)

Tranexamic acid (trans AMCA, Cyklokapron) is an antifibrinolytic drug. It is the trans-stereo-isomer of 4-aminomethylcyclohexane carboxylic acid.

A. Mode of action

Tranexamic acid has a mechanism of action similar to that of E-amino caproic acid (EACA), but is about 10 x as potent, according to sponsor.

Both drugs form reversible complexes with plasmin and plasminogen at sites of the heavy chain of plasmin and at corresponding sites of plasminogen, which leads to a dissociation of the complex between fibrin and specific substrate binding sites on plasmin and plasminogen. The therapeutic plasma concentrations of tranexamic acid (3×10^{-5} - 10^{-4} moles/L; or 5-15 mg/L) is about the same as the dissociation constants for plasminogen-Tranexamic acid and plasmin-tranexamic acid complexes. The esterolytic and caseinolytic effects of plasmin are inhibited at more than 100 times higher concentrations. Dissociation of the complex between fibrin and specific substrate binding sites on plasminogen and appears to prevent the functional interaction between plasminogen and tissue activator which is mainly located on the fibrin. EACA and tranexamic acid bind to 5-6 different sites in the plasminogen molecule (Marcus et al and 1979).

	Tranexamic acid	EACA
Native plasminogen (NH_2-terminus-Glu)	1 strong binding site $K_{diss} = 1.1 \times 10^{-6}M$ Site 2-5, 4 weak sites $K_{diss} = 8 \quad 10^{-4}M$	1 strong binding site $K_{diss} = 9 \times 10^{-6}M$ Site 2-6, 5 weak sites $K_{diss} = 5 \times 10^{-3}M$
Proteolytically modified (NH_2-terminus-Lys)	Site 1 = $2 \times 10^{-6}M$ Site 2 = $3.6 \times 10^{-5}M$ Site 3-5 = $1 \times 10^{-3}M$	

B. Influence on other enzymes

Tranexamic acid ($5 \times 10^{-2}M$) competitively inhibits the activation of trypsinogen by enterokinase and non competitively inhibits the proteolytic activity of trypsin at 4-fold greater concentration. The Tranexamic acid has been found to decrease the tumor growth rate significantly in mice inoculated intramuscularly into one hindleg with a mouse mammary carcinoma. The growth rate of a 20-methyl-chloranthrene induced sarcoma was, however, not influenced by tranexamic acid.

Tranexamic acid was found to enhance metastasis formation when tumor cells were given by intravenous injection (for reference see Peterson, 1977).

Interaction with the cardiovascular system

Tranexamic acid administered by i.v. infusion in the anaesthetized cat at doses of 0.4 to 2 mg/kg/min for 60 minutes (120 mg/kg) and i.m. in the rabbit, cat and dog at doses of 170 mg/kg did not cause significant changes in arterial blood pressure, respiration, or ECG. An intravenous dose of 250 mg/kg in the cat, infused during 60 minutes, increased carotid blood pressure by about 15%.

Tranexamic acid did not contract the nictitating membrance in anethetized cats at doses of 5-500 mg/kg, intravenously, injected over 2 minutes. Contrary to tranexamic acid, EACA at an intravenous dose of 150 mg/kg caused a marked contraction of the nictitating membrane, which was prevented by pretreatment with reserpine.

C. Thrombosis inducing conditions

According to the sponsor, in long term oral toxicity tests, fibrin deposits or thrombi have not been observed. However, in an oral dog study (below), 1/3 F at 1200 mg/kg exhibited a meningeal artery thrombus. When tranexamic acid was given twice daily for 1 month by intravenous infusion (with 0.9% benzylalcohol) thromboembolism in the peripheral pulmonary arteries was found in two out of eight dogs. Findings of thrombi were also observed in four dogs both at the high dose (500 mg/kg) and at the intermediate dose (100 mg/kg) at necroscopy. The event was not noticed clinically and the dogs were in good physical condition. Sponsor believes that the histopathological alterations were the consequence of the repeated intravenous infusions, but does not provide substantiation.

Pulmonary thrombosis induced in the rat by lactic acid is not affected by tranexamic acid at an intravenous dose of 100 mg/kg. The drug (50 mg/kg, i.v.) does not alter ellagic acid induced hypercoagulable state in dogs.

Thrombin, which given alone to dogs caused oedematous lungs, caused fibrin thrombi in 2 of 7 dogs simultaneously administered tranexamic acid (50 mg/kg i.v.). A dose of 100 mg/kg tranexamic acid administered concurrently with thrombin and followed by infusion of the same dose of tranexamic acid for 6 hrs, resulted in fibrin thrombi in all the dogs. At this dose, fibrin was also observed in the kidney and liver. On the other hand, no thrombi were found in dogs treated with tranexamic acid alone at the same doses. A deposition of fibrin in the lungs and kidneys of dogs has also been found when thrombin is given simultaneously with tranexamic acid (100 mg/kg every second hour). In rabbits, more capillary microthrombi, fibrin deposits in the lungs and kidneys, were found when they were treated with thrombin and tranexamic acid (50 mg/kg/hour i.v.)

compared to treatment with thrombin alone. In the rat, tranexamic acid (100 mg/kg i.p.) has been shown to accelerate the deposition of ^{125}I-labeled fibrinogen in the liver in which necrosis has been induced by carbon tetrachloride. A higher, almost lethal dose (600 mg/kg i.v.) seems to affect the alteration in the fibrinolytic activity of the pulmonary tissue following femoral crush injury.

In arterial haemorrhagic shock produced by extensive blood loss (45-50%) in dogs, tranexamic acid has been found to cause major thrombi and emboli in systemic and portal veins as well as in arteries. The dose used was high, 100 mg/kg i.v. every second hour. Contrary to this finding Avikainen and Eklund, 1974, found no macroscopic thrombi in rabbits with traumatic and haemorrhagic shock (about 20% blood loss) when they were given i.v. 100 mg/kg of tranexamic acid before and 300 mg/kg during the experiment. Histologically some fibrin with erythrocyte, leucocyte and platelet aggregations and in addition, perivasular edema, were observed in the lung in a few cases. In this study radioactive fibrinogen was used to demonstrate fibrin thrombi, but no increased radioactivity could be observed in the lung, liver, kidney or spleen.

D. Metabolism

1. Absorption

Tranexamic acid has amphoteric properties with two pKAs, 4.3 and 10.6. Its solubility in water is about 13 percent (w/w) at physiological pH and 40% (w/w) at pH 4.2. The material produced by Kabi contains less than 0.1 percent of the cis-isomer and less than 0.5 percent of BCA (bis-trans-4-carboxycyclohexanemethyl amine). Tranexamic acid is determined in biological fluids by electro capture gas chromatography developed at Kabi by Vessman, 1977.

Absorption from the gastrointestinal tract is about 20% in the rat in the dose range 0.4 to 4 g/kg. Following a single oral dose of 0.4g/kg by gavage, absorption is still taking place 24 hours later, but food intake markedly decreases the bioavailability in the rat.

In man no effect of food on gastrointestinal absorption of the drug following a dose of 2 gm (40 mg/kg) has been observed and there is no influence of the food on the maximum plasma concentration obtained. The plasma concentrations following tranexamic acid given by gavage (4g/kg) and in the feed (4.8 g/kg) to rats are in the range of 20-50 mg/L during the 24 hours with both methods of administration. In the dogs, the gastrointestinal absorption decreases with increased dosage. The gastrointestinal absorption in the dog is 60-70%, in man 50%, rabbit 50%, mouse 30% and rat 20% at reasonably low oral doses.

The maximal plasma concentrations are about 50-60 mg/L in dogs after an oral dose of 100 mg/kg and in rats about 10-30 mg/L after an oral dose of 400 mg/kg.

2. Tissue distribution

Tranexamic acid does not bind to serum albumin. The plasma protein binding seems to be fully accounted for by its binding to plasminogen which is saturated at very low concentration. 50 percent of the drug is bound at 50 ug/L and only 10 percent at 2 mg/L. The plasma protein binding appears to be negligible at therapeutic plasma levels of 5-10 mg/L.

Autoradiographic studies of tranexamic-methylene-^{14}C administered i.v. in the cat resulted in the highest concentration in the kidney followed, in order, by the blood, lung, liver, gastrointestinal tract. The cerebral cortex level was very low, as were levels in cornea, iris, ciliary body and retina. No activity was seen in the vitrous body and lens.

3. Detoxification

Possible routes of biotransformation are acetylation or deamination followed by oxidation or reduction. Using ^{14}C-labeled drug, four different metabolites can be traced in the urine.

Man appears to produce more of the DCA than of the acetylated compound (2 and 0.5%) while the rabbit produces more of the acetylated compound (0.5 and 4%).

4. Excretion

From the plasma concentration time curve in rats following oral and intravenous administration, it has been shown that the half-life is about 2 hours.

An insignificant fraction of the dose is cleared via the bile, (of the order 0.1 - 0.2%) and there is no apparent effect on bile flow or biliary clearance (0.7-1.5 $ml/kg^{-1}.h^{-1}$) with increasing plasma concentrations of tranexamic acid.

In the dog, half-life of the drug is about 2 hours following intravenous injection. The plasma clearance is comparable to the glomerular filtration rate. The dog, similar to the rat, excreted very small amounts of tranexamic acid in the bile.

II. Toxicology

A. Current Submission

1. Chronic Rat Study.

Rats, SD, Control, 51/sex; Treated (4.8 % in diet), 54/sex/18 months. (Kabi A B, R&D, Dept. Tox., Stockholm, Sweden April 3, 1978 to October 9, 1979). (Johansson & Jönsson.)

Average dosage, first month, 4403± 496 mg/kg (M) and 4572± 463 mg/Kg (F); and from 3rd or 4th month until end of study, 2243± 121 (M) and 2807± 187 mg/Kg (F) (Chemical batches 5422 - 01, 54525-51, and 54530-51).

Schedule for sacrifice was as follows:

3 and 6 months, 6/group; 9 months, 4/group;
12 months, 6 group; 15 months, 4/group; terminal, all survivors.

Observations included clinical signs (CS), body weight (BW), food consumption(FC), blood components(H), blood chemistry(BC), urinalysis (U), Gross pathology (GP), and microscopic pathology (MP).

Because a dose dependent bile duct hyperplasia was observed in the Lederle carcinogenicity study, (to be summarized later in the review) this study was designed to follow the sequential development of the expected hyperplasia. Because it was a repeat experiment, only the maximum tolerated dose level was used.

Results:

Marked diarrhea was the main drug-related sign to be observed. Body weight gain reduction in the last 3 months was attributed to this diarrhaea.

Tabulation of Results:

Groups	Control		Treated	
Sex	M	F	M	F
Original numbers/group	51	51	54	54
Deaths or moribund sac.(MS)	(MS=2)	(MS=2)	(MS=5)	(MS=1)
(From lab Table I) Total	2(4%)	2(4%)	13(24%)	5(9%)
During 10 to 18 mo. period	2/35(6%)	1/34(3%)	12/37(32%)	3/36(8%)
From Summary Page 21, mortality for 2nd half of study	4%	4%	41%	8%
Renal lesions as cause of death	0	0	10	2
Feed Intake		Comparable to Controls		
Body Weight gains (% of controls)	-	-	-11%	-23%
Red Blood cells		.....not counted.....		
Average plasma concentration (9a.m.)		(M&F,46)		
mg/L(from Table VIII and p20) (3:30p.m.)		(M&F,33)		
Creatinine, micromals/L (n=6)				
12 mo., as presented in table VI	52.2	52.9	152.7	52.8
minus one outlier(650.0)	"	"	53.3	"
18 mo.,	104.4	53.5	144.1	59.4
Cholesterol, m mol/L	6.6	3.8	5.1	3.2

(No)	Control		Treated	
	M	F	M	F
TERMINAL SACRIFICE	(23)	(22)	(15)	(23)
Kidney Weight	4.8	2.6	9.7	2.6
Ren. Pel. Concrement	3(minor)/45(M&F)		(15/15)100%	(16/23)70%
epithelium			(most of those with concretions)	
Testicular atrophy	(4/23)17%	0	(9/15)60%	0
Vascular lesions	2/23 9%	0	(9/15)60%	0
Testicular	0	0	6/9 with atrophy(above)	
(13/11 rats: 6, testis; 4, pancreas.; 1, carotid Art.; and 2, epididymis. (relationship to treatment unknown, but higher than controls).				
Myocardial fibrosis	13%	0	7%	0
Hyperplasias				
Biliary (early)	1/8(15mo)	0	1/8(16mo)	0
(T.Sac., 18 mo)	1/23(4%)	0	1/15(7%)	1/23(4%)
Adrenocortical	0	2/22	0	1/23
Thyroid	2/23(8%)	0	2/15(13%)	0
Parathyroid	2/23	0	2/15*	0
*No. 7:1 Exhibited Both.			1/15	
Pancreas	1/23(4%)	0	2/15(13%)	0
Adenohypophyseal	1/23	0	0	0
Hepatocellular alterations	7/45(M&F)	-	2/38	
Mammary fibroadenoma	0	15/51(29%)	0	8/54(15%)

Additional Data

Listed tumors, Scheduled Sacrifices

	Control		Treated	
	M	F	M	F
Mammary tumors (6 and 9 mo.)(6+4)	0/10	3/10	0/10	0/10
(12 and 15 mo.)(6+4)	1/10	7/11	0/10	2/12
(18 mo.)all survivors	1/23	9/22	0/15	8/23
Pituitary Tumors (15 mo.)(4)	0/4	0/4	2/4	0/4
(not seen earlier) (18 mo.)	13/23	0/22	0/15	0/23
Pancreatic tumors (18 mo.)	13/23	0/22	10/15	0/23
(not seen earlier)				
Overall Tumor Incidence (6-15 mo.)	2/20	11/21	3/20	3/22
(18 mo.)	24/23	16/22	12/15	11/23

Death was attributed to renal pelvic concrement causing either renal insufficiency or lethal bleeding from the atropic renal parenchyma. Death totals from various sources do not seem to be in agreement.

Liver weights as well as growth and histopathology were unremarkable.

The higher average creatinine value in the treated males at 12 months is the result of a single high value with a 10-fold increase over control values. (Possibly a decimal error in data entry?)

At 18 months one control male also had such an unusually high value while lesser elevations were seen in 2 more control males, 3 treated females, and most of the treated males. These elevations seem to be a definite effect of treatment influenced by sex and age.

The testicular atrophy and vascular lesions were said to be the usual old-age degenerations; however, the treatment vs control differences were quite marked and only the terminal sacrifices were considered. Such testicular effects may have been present in the animals that died, too.

Sponsor made a distinction between the hyperplasias of renal pelvic epithelium and hyperplasias of other organs. The first listed (epithelium) is prepondrantly in male treated rats, the rest although approximately equivalent in number are slightly more frequent in the treated group when expressed as percentages. The incidence differences for other types lack significance because of the small numbers involved. The epithelial hyperplasias are said to be the result of irritation. The danger of hyperplasia appears to be low and possibly irritation related for the epithelial type; however, these data do not rule out a higher rate of treatment occurrance in a susceptable strain, or with longer exposure such as was seen in the Lederle study (22 months), which will be described later in this review.

2. Reevaluation of the tranexamic acid - induced retinotoxicity in dogs.

Focal anterior retinal atrophy with loss of rods and cones was seen in dogs (1/4) orally administered 800 or (3/3) given 1600 mg tranexamic acid/Kg/day, (div. b.i.d.) for 1 year (Lederle, 1972; pharm review, IND 6406, 1/21/72. M.M.H.).

This one year study was repeated by Kabi AB with oral doses of 800 and 1200 mg/Kg/day, (div. b.i.d.) (Report 79-99-014, 1979). A light-microscope examination of the left eye of each dog had revealed* anterior retinal atrophy in 4/6 high dose and 3/5 low dose dogs, high dose and posterior retinal atrophy in 5/6 high dose and 1/5 low dose dogs. Thus, retinotoxicity was confirmed in a repeat study.

*See under II B, previously reviewed studies

In order to study the morphogenesis of the retinal atrophy, the (preserved, stored) right eyes (of the above Kabi Study) were examined by electron microscopy in order to reevaluate the etiology of the original findings.

According to the sponsor, the developing stages to be retrospectively deduced from observations of this material are as follows:

Stages

1. Reduction of the length of the photoreceptor outer segments. No changes were seen in the retinal pigment epithelium (RPE).

2. Apical filaments were seen on the RPE surfaces as long as remnants of photoreceptor outer segments were present.

3. With diminishing size of the photoreceptor inner segments, the apical filaments decreased in size and number.

4. In intermediate stages of atrophy they lost their normal orientation and became clustered along the RPE surface.

5. When the retinal atrophy comprised the entire photoreceptor layer and parts of the outer nuclear layer, changes also occurred in the RPE. The epithelial changes at the central retina and at the peripheral retina differed at this stage.

6. With progressing retinal atrophy, the peripheral RPE became condenced with melanin granules occupying the major part of the cytoplasm and sparse other organelles visible. The basal infoldings were retained until advanced stages of atrophy.

7. No evidence of total loss of the RPE at the periphery of the retina was found; however, the RPE was severely affected by the atrophy in the central part.

Degenerative changes were frequently seen in the form of absence of apical filiments and basal infoldings, vesiculation of the endoplasmic reticulum, margination of the nuclear chromatin, an irregular nuclear outline and a varying reduction of the REP thickness. In places the RPE was totally lost and the remaining retinal cells rested directly on Burch's membrane. In these instances, collapsed capillaries were seen in the choriocapillaries. Bruch's membrane did not show any morphologic changes.

The conclusion of Sponsor's report states:

"It is suggested that the difference in the severity of the atrophy of the central and peripheral RPE might be due to the differences in the microcirculation at the 2 sites."

Sponsor attributes these effects to a high dose sympathomimetic impairment of the blood supply.

3. Mutagenicity.

No mutagenicity was observed in the following tests according to Shimada, H., Et al., Oyoo Yakuri (Pharmacometrics) 18 (1): 165-197, 1979.

1. Rec-assay on Bacillus subtilis
2. Salmonella microsome test
3. Chinese hamster cytogenic test
4. Chromosomal aberrations in bone marrow cells of mice and rats.
5. Dominant lethal test in mice.

B. Material from previously reviewed IND's.

Toxicology.

1. Acute Toxicity. Orally, the drug volume exceeds the animals test capacity and a median toxicity value is not determinable. The oral median toxicity value exceeds 10g/Kg/ in mice, rats, and chickens; exceeds 5g/kg in dogs; and 3g/Kg in rabbits.

In mice, rats, rabbits and dogs the I.V. median lethal values were all between 1.0 and 1.6 g/Kg, the i.p., 2.1 to 3.4 gm/Kg.

In mice, rats, and rabbits the S.C. median toxicity values were between 3.8 to 6.4 g/Kg.

Following oral administration of high single doses of tranexamic acid, the main clinical signs are diarrhea in mice and rats, and vomiting in dogs. After i.v. administration of high single doses, the main symptoms are convulsions in mice and rats, and emesis and convulsions in dogs.

2. Subchronic Toxicity:

Table TOXICITY AFTER REPEATED ADMINISTRATION OF TRANEXAMIC ACID TO RATS, RABBITS, CATS, DOGS AND MONKEYS

Species	Duration Schedule	Route	N/group	Dose levels (mg/kg/day)	Parameters studied	Ref
Rat	14 days (7/week)	i.p.	10M+10F	0,250,500,1.000	CS,BW,H,BC,GP	Siren, 1967-1969

A notation "blood coagulated" appeared in 7/60 treated, but 0/20 control rat records. Also noted were (H-D) hyperemia of G-I tract mucosa with slight blood-mixed contents and watery stomach.

This study indicates that the blood of treated animals can become coagulated under normal observation procedures.

Rat 34 days	in diet	6M+6F/GP	0,1,2.5,5,7.5% (0,1000,2500,5000 and 7500) mg/Kg	CS,BW,FC,H,U Devitto&Gordon, 1971

Deaths: 3/6M, 1/6F in 7.5% group; 1/6M, 5%; and 2/12 (1 accidental) in Control group. Body weight reduced: markedly at 7.5%, moderately at 5%.

Rat 16 weeks (5 days/week)	p.o.	6M+6F/GP	0,1,2.5,5gm/kg	CS,BW,H,BC,GP
17 weeks (5 days/week.	p.o.	10M/GP	5 & 7.5gm/kg	CS,BW,H,GP Siren 1967-1968. KABI.

Results:

a. 16 weeks.

Deaths: Not clear. Apparently (6/6)M, 1/6 1F, H-D(5,000 mg/kg); 4/6M, (2.5gm/kg), 2/6M, (1gm/kg) and 1/6M, control. Most deaths reportedly were accidental intubation deaths without reason given for dose relationship.

Drowsiness was seen (especially H-D); loose stools "quite often seen in treated rats".

Blood counts were unremarkable, some plasma protein values were low in H-D rats which, according to author, corresponded well with microscopical observations. Organ weights were unremarkable. Sex organs were not reported.

Gross pathology: G-I hyperemia was seen.

Histopathology: Author reports "most interesting" lesions in the salivary glands of treated animals. Acidophilic substance was seen in the lumina and dilated ductuli of the glands. Cytoplasm of glandular epithelium was partly degenerated and loose; however, the slightly enlarged nuclei did not exhibit signs of degeneration.

An atrophy of all layers of the cecum and colon acendens was seen in some animals.

b. 17 weeks.

Deaths, 7500 mg/kg, 2/10 (M) (days 22 and 33). Some weight gain depression at 7500 mg/kg. Drowsy rats. Laboratory findings unremarkable. No histopathology reported. No deaths were seen at 5,000 mg/kg, in contrast to the deaths seen in part a, above, where 6/6M, 1/6F (5,000mg/kg), 4/6 M (2,500 mg/kg), 2/6 M (1000mg/kg), and 1/6M (control) were lost.

Rat 6 months 5 D/W	p.o. 20M + 20F/GP	0, 750, 1,500, 3,000 4,000 mg/Kg	CS, BW, FC, WC, H, BC, U GP, MP	Takayama et al., 1971

Deaths: 25 (21 intubation errors). Diarrhea, dose related, 1500 to 4000 mg/kg. Occult blood in stools increased in severity with time at the higher dosages. Weight gains were depressed in H-D males. Cholesterol values decreased in M at 2 highest doses. Catarrhal gastritis was dose and time related at the 3 highest doses; epithelial necrosis was seen in the cecum of males at the 2 highest doses at 3 months, but was not noticed at 6 months. This was also seen in the 16 week study (above). The authors considered tranexamic acid to be of low toxicity. This is another study with excessive intubation losses. Whether these deaths were also dose related is no longer easily determinable because the original IND is in storage. It is obvious that treated animals are more difficult to work with.

Rabbit	13 days	i.v. 4M/GP	0, 60, 120, 180 mg/kg	CS, BW	Palmer & Readshaw, Lederle, 1969

Results: No mortality; post-injection tachypnoea, dose related; variable weight changes; Serum concentrations fell rapidly first 30 minutes, post-injection; Higher serum values at all periods (10, 30, 180 min.) after 13 days. This study indicates that drug blood levels decrease rapidly after i.v. administration.

Dog 3 days		i.v. 3/GP	C, 1,000 mg/Kg	BC, ECG, GP, MP	Guzman, Cutter Labs, 1965

(Infusion time, 2 hrs. and 10 min.) One Amikapron treated (tranexamic acid) dog struggled against the restraint during the first infusion, convulsed and died. Original EKG read as possibly indicating myocardial damage. Autopsy revealed cardiac hemorrhage. Only this one (of 4) treated dogs exhibited cardiac petechia

Dog 1 month bid, 5D/W	i.v.	2M+2F/GP	0, 2x10, 2x50 2x250mg/kg	CS, BW, FC, WC, H, BC, U ECG, BP, GP, MP	Balazs & Porpora, Porpora, Ohtake & Kepenis (Lederle Labs, 1969)

Injection rate was 20 mg/kg/minute
Results: Emesis and salivation frequently seen in M-D and H-D dogs, dose related. Urinary output reduced with respect to water intake. Inhibition of fibrinolysis was found at all dose levels. Toxicity not evident in the standard blood, clinical tests and physical examinations.
Focal enlargement of acini and dilation of ducts was found in 2 HD and 1 MD dog. Pulmonary thromboembolism was seen in 1 HD, M and 1 M-D, F.

Dog 18 weeks bid 5D/W	p.o.	2M+2F/GP	0, 2x50, 2x250 2x500mg/kg	CS, BW, H, BC, U, ECG, O, GP, MP	Siren, 1966 (KAB1-AB)

Results: No mortality. Weight gains lower in H-D dogs. Emesis and diarrhea dose-related in incidence and severity. Ophthalmology unremarkable. EKG's not submitted but reported unremarkable by veterinarian. Blood and serum unremarkable. Gross and histopathology unremarkable except for female sex organs which were larger (or more mature) in 2 control dogs, not in 6 treated dogs, as follows:

Dose mg/kg	Dog Number	Body Wts. Before to after 18 weeks	Uterine Wt.
Controls	9	6.9 to 8.1	11.55
	24	7.7 to 8.6	17.49
100	15	7.8 to 9.3	2.97
	7	6.1 to 7.6	3.63
500	22	7.0 to 8.8	2.36
	1	6.2 to 7.4	3.14
1000	6	5.9 to 7.3	2.92
	10	6.1 to 6.8	------

Dog 12 months + 13 months bid 7D/W	p.o.	3M+3F/GP 1/3 reserved for recovery	0, 2x100, 2x200 2x400, 2x800 mg/kg	CS, BW, FC, WC, H, BC, U, ECG, BP, O, GP, MP Brecher, Sparano Tonelli (Lederle, 1972)

Results: Deaths 1 HD F on day 277, no apparent cause. High dose compound intolerance included salivation, lacrimation, emesis, loose stools and reduced body weights.

Laboratory parameters, gross and histopathology, were unremarkable except for optical findings such as hyperreflectivity of the tapetum lucidum and the peripapillary area and atrophy of the rod and cone layer in the anterior retina. These findings were dose and time dependent and occurred only in the 2 highest dosage groups.

One third of the dogs were allowed to recover for 1 additional year, but the H-D eye changes remained uncorrected. Recovery was to be seen in the 800 mg/kg/day dose group

Dog 12 months bid, 7D/W	p.o.	3/sex, C & LD 4/sex, HD	0, 2x400, 2x600	CS, BW, FC, H, BC, O, ERG, GP, MP Ekvärn, et al Johansson including Kabi-AB, 1979 electron microscopy of eyes

Results: Vomiting and loose stools, diarrhea.

Deaths: 1 H-D, F, 30 weeks, convulsive state and pathology, meningeal artery thrombus. The relationship of these findings to the treatment remains unknown. Hyperreflective areas were seen on ophthalmological examination.

Body weights, food consumption, hematological, biochemical, gross and histological observations were unremarkable.

Peak plasma concentrations of drug were reached about 2-3.5 hours after each dosage.

Ophthalmoscopy revealed a changed reflectivity in the tapetal fundus, appearing within the first two months of treatment in all dogs from both dose groups. The effect occurred throughout the study. Repeated ophthalmoscopy during one day after 50 weeks of treatment confirmed that these changes were transient and were observed in connection with the peak plasma levels.

Persistent lesions (hyperreflective areas around the disc and localized hyperreflective areas elsewhere in the tapetal fundus) were observed in six out of eight dogs given 2 x 600 mg/kg/day. These changes appeared after 5-14 weeks in five out of the six dogs.

Microscopical examination of the retina revealed atrophy at two distinct zones in tranexamic acid treated dogs: at the anterior retina (ora ciliaris retinae) and the posterior retina (around the optic disc).

Anterior retinal atrophy was found in 4 of 6 dogs after one year in the highest dose group and in 3 of 5 dogs in the 2 x 400 mg/kg/day dose group. Posterior retinal atrophy was observed in 5 of 6 dogs given 2 x 600 mg/kg/day and in one of 5 dogs given 2 x 400 mg/kg/day for one year. The atrophic areas of the posterior retina corresponded to the hyperreflective areas observed clinically. The dogs with the largest hyperreflective areas also had the most advanced posterior retinal atrophy. The animals with retinal atrophy also had higher peak plasma levels and larger AUC values as compared to those of the unaffected dogs.

Tranexamic acid did not seem to cause an impaired retinal function as judged by electroretinography (ERG). At nine months no ERG changes were observed (tested before dosage). At twelve months the electroretinograms (recorded 2-3.5 hours after dosage) were altered in tranexamic acid treated dogs, but the threshold for the ERG response was normal. The alterations, which consisted of increased amplitudes and outstretched b waves, were postulated to be the functional equivalent to the transient ophthalmoscopical changes. Similar ERG changes have been observed in dogs given single high doses (250-500 mg/kg) of tranexamic acid intravenously.

The mechanism for the development of the retinal atrophy is not known. The atrophic changes observed in the retina are similar to those seen at senescence in dogs as well as in man. No morphologic changes were observed in the blood vessels in the retina and the choroid. Sponsor has submitted an electron-microspcopic study of the preserved right eyes and a reevaluation. See II, A, current submissions.

Sponsor notes that tranexamic acid is known to produce sympathomimetic effects in cats, and considers it possible the the retinal lesion might be caused by ischemia due to transient impairment of blood supply at plasma levels (200-300 mg/l) obtained in this study. (In man, peak plasma levels are in the range of 10-20 mg/l after a therapeutic oral dose of about 30 mg/kg body weight.)

Sponsor is therefore claiming that the eye toxicity will not be a problem clinically, because it is a high dose exaggerated pharmacological effect.

This claim should be referred to an ophthalmologist.

* CS = clinical signs
FC = food consumption
BC = blood chemistry
O = ophthalmology
BP = blood pressure
MP = microscopic pathology
BW = body weight
WC = water consumption
U=ur lysis
ECG = electrocardiography
ERG = electroretinography
GP = gross pathology

3. (a) OPTHALMOLOGICAL STUDIES

Rabbit	1-10 months Daily	drinking water 3c, 6T	0, 500 mg/day	ERG, electron microscopy of eyes	Johnsson et a Tox & Appl. Pharm. 40: 59- (1977)-Glasgc

Weights not given, dose probably 125 to 250 mg/kg/day.

Results: Retinal architecture appeared normal by both light and electron microscopy and fully dark adopted electroretinograms were similar for control and treated rabbits.
This dose is considered by sponsor to be sub-threshold for retinal damage.

Cat 4-6/GP 4-6 days,HD 14 days (LD&MD)	Daily I.V. Dose, Mg/Kg 2x250 125,250,	Clinical and histo-logical examination of eyes		Kleinsorge & Schnitzlein 1976
Cat 6 days(?/GP) daily, i.v.	125, 250, 500	Clinical and histo-logical examination of eyes		Luckhaus, Knoll, A.G. 1976

Cats, two hour continuous i.v. infusion. In preliminary range finding studies, doses above 500 mg/kg usually killed the cat, but one survived 1250 mg/kg which had been discontinued because of tonic clonic convulsions. Survivors included 500 mg/kg/day, divided dose/2 cats, 6 days; 4 cats, 4 days; and 250 mg/kg, div., 4 cats, 14 days.

Results: Opthalmological changes were observed which had a dose and time related incidence and severity. Histologically the dose related findings included folding of the outer retinal layers, proliferation of pigmented ephithelium and atrophy of outer nuclear layers in 5 of 6 given 500 mg/kg/day.

At 125 mg/kg there was seen only a mild pigmentation on the 7th day in 1/4 cats with no histological differences from controls. Claimed as no-effect level.

Monkey 7-14 days i.v. 1-3 daily 0, 2,000 CS, 0, MP Knezevich & Boshart, 1972

Cynomolgus monkeys, given 20 mg/ml at rate of 1 ml/kg/min/100 minutes/7 or 14 days to 1 (F) control, 3 (F) treated/7 days; 2M, 1F/group, control and treated/14 days. (2000 mg/kg)

Deaths: 1, treated, day 13; cause unknown. Treated weight losses up to 10% or more. Negative ophthalmoscopic findings, and peripheral retinal atrophy, seen in treated and control alike, led author to conclude no treatment effect from the drug.

(Bayer Institute for toxikologie, 1976).

Dog, 11 days, orally 1000 mg/kg/day.
Cat, 16 days orally 500, 1000, 1500 mg/kg/day.
Cat, 6 days i.v. 125, 250 and 500 mg/kg/day.

Results: Short term i.v. administration (250 and 500 mg/kg) to the cat was associated with partial detachment and atrophy of the central retina, in conjunction with proliferative and degenerative epithelial changes of the stratum pigmenti retinae.

3. (b) EVALUATION OF OPHTHALMOLOGICAL EFFECTS

In the Lederle 22 mo. rat study, retinal atrophy and lenticular lesions, especially both conditions together, were more prevalent in treated than in control animals but the incidence at the 0.3% diet level (150 to 300 mg/kg) appears to be little different than the control incidence.

In cats 125 mg/kg, i.v. apparently is a minimal-effect level for 6 to 14 day exposures.

In the dog studies, exposure for 1 year to 800 and 1200 mg/kg revealed a marked dose dependence.

Bilateral changes in the reflectivity of the tapetum lucidum were seen in 5/5 H-D and 2/6 L-D dogs, while 3/3 H-D dogs and 1/4 L-D dogs examined had anterior retinal atrophy.

After a year for recovery with 1/sex/dose, the 2 H-D dogs still exhibited the fundic changes, as well as histological anterior retinal atrophy and retinal atrophy near the optic disc. The L-D dogs were without changes. (However, it is not clear which 2 L-D dogs were saved for recovery, Considering the low incidence of reported effects, unaffected dogs could have been chosen from this dose level).

In general it can be said that the eye effects are dose and time related and only a high dose effect, but clear cut no effect levels are not always available because of the tendency to run only very high dosage studies.

Sponsor's contention that the dose relationship and time related pathological progression rule these effects out as a clinical concern has merit, but there is more theory than hard data supporting this concept.

Because sympathomimetic side effects of the drug are postulated to be the basis of this pathology, sponsor should especially reference such studies or publications that might support the concept of sympathomimetic eye damage of this nature.

4. CARCINOGENIC POTENTIAL OF TRANEXAMIC ACID IN MICE AND RATS

Species	Duration Schedule	Route	No/Group	Dose levels	Parameters	Refs
Mouse (CDF)	20 months ad lib	diet	60-61 males	0, 4.8%		

Takayama Cancer Institute, Kami Ikebukuro, Toshima-Ku, Tokyo, 1976.

English summary only.

Results: Survival; Control, 50%; Treated, 41%; average weight gain (based on average weights of survivors) of treated mice was 30% that of controls. (4.3 grams, controls; 1.3 grams, treated). Diarrhea was seen in all treated mice for the first 2 months.

The incidence of tumors was as follows:

	No. Examined	Lung tumors	Liver adenoma	Leukemia and/or lymphoma
Control	59	7	1	5 (8%)
TS-79	57	3	1	12* (21%)

*one with reticulum cell carcinoma of spleen.

The incidence of leukemia was statistically insignificant at the 5% level using the chi ^{2} test; therefore, sponsor drew the conclusion that the drug was not carcinogenic. Statistical significance would be influenced by category groupings and the higher survival rate in controls. This male only study is not suitable for carcinogenesis determination.

Rat, 22 months Control 72/sx, treated 54/sx, 0,0.3, 1.2 and 4.8% of diet*
(Sherman-Wychoff) CS,BW,FC,H,BC,U,O,GP,MP,
Interim sacrifices at 3 & 12 months) LEDERLE LABORATORIES, 1971.

(*approximate dose: 1st month; 300, 1200 and 5,000 mg/kg, respectively, intake declined 30 to 40% for next 2 months, then remained constant in ranges of 145 to 185, 600 to 720, and 2600 to 3200 mg/kg).

Histopathology included liver, kidneys, eyes, and gross pathologies in contr l and H-D rats, and grossly observable changes in L, and M-D animals.

Results: High dose weight-gain decline, diarrhea, and adrenal weight changes (at 1 year, no 2-year weights provided) in which male adrenals were larger, the female's smaller. Other differences in the examined parameters include:

Dose:	0	0.3%	1.2%	4.8%
Died, 0-3 months	3/144	1/108	2/108	12/108
Necropsied 3 mo.	12/141	12/107	12/106	12/96
Died 4-12 mo.	5/129	1/95	8/94	6/90
Necropsied 12 mo.	12/124	12/94	12/86	12/78
Died 13-21 mo.	37/112	30/82	27/74	33/66
Necropsied 22 mo.	75	52	47	33
Biliary Hyperplasia at necropsy:				
3 mo.	0/12	0/12	0/12	3/12(1M,2F)
12 mo.	1/12(8%)(M)	0/12	0/12	8/12(3M,5F)
22 mo.	18/75(24%) (10/41M,8/34F)	17/52(33%) (11/29M,6/23F)	40/47(85%) (22/28M,18/19F)	33/33(100%) (16M,17F)
Pyelolithiasis:				
3 mo.	0	0	0	4/12(33%)
12 mo.	0	0	0	2/12(17%)
22 mo.	0	3/23(F)(15%)	3/28(M)(11%)	13/33(39%)
Neoplasms, 22 mo. (partial list)				
hepatomas	3/75(4%)	2/52(4%)	3/47(6%)	3/33(9%)
Cholangioma (adenoma)	0/75	0/52	0/47	4/33
adenocarcinoma of the intrahepatic biliary system.	0/75	0/52	0/47	5/33(15%)
Retinal atrophy	9%	14%	20%	19%
Lenticular lesions	28%	29%	24%	28%
Both ophthalmic lesions(above)	4%	6%	9%	13%

Rats, female, (SD -SLC,) about 60 F/group, Ogawa & Ono, (Daiichi Seiyaku, Japan, 1976), 0.35 and 3.5 g/kg, S.C., or 1.0 and 10 g/kg, orally. Drug was given once a week for 5 consecutive weeks; animals were sacrificed after 1 and after 2 years. (a total of 5 exposures).

Results: Neoplasm type and incidence did not essentially differ between controls and treated groups with respect to the many examined tissues.

Group incidence of bile duct hyperplasia (data not provided) ranged from 30-50%. Some of the animals showed foci of parenchymal cell hyperplasia, but these findings were not considered to be treatment or dose related by sponsor. There was a possible increase in subcutaneous nodules in S.C. treated rats.

This study, using females only, is not suitable as a carcinogenesis study.

Rats,SD 20 months diet Controls (24M, 25F), 4.8% (46M, 33F)
Takayama, Cancer Institute, Kami Ikebukuro, Toshima-Ku, Tokyo, 1976.

Deaths for females 60% C, 58%-TS were comparable, treated vs control, but deaths 50% (C), 74% (TS) were higher for treated males. Average body weight gains were less for treated rats, especially females. Severe diarrhaea was seen, especially during the 1st month.

Treated rat adrenals were slightly heavier than controls.

No report on uterus.

Tumor incidence at 20 months was not different between the groups; however, we note that the base line for histopathological comparison may suffer from a lack of comparative carcinogenic incubation time information, because only 59 to 70% of the treated and 75 to 92 % of the control rats had a pathology work-up.

Sex	Dose	Start	% of original Path Observations	% of Original Sacrificed Survivors
Male	0	24	18(75%)	12(50%)
	4.8%	46	27(59%)	12(26%)
Female	0	25	18(92%)	10(40%)
	4.8%	33	23(70%)	14(42%)

Neither neoplastic lesions in the liver nor biliary hyperplasia were seen.

Yamada, et al (Summary only), 1979 Daiichi Seiyaku Co., Japan.

Rats (Sherman Strain), 54 to 56/sex/dose (0,2.5 and 5.0%) in diet/19 months/sacrified 1 month later. "Histopathological investigations were carried out on organs from all animals". Organ weights were not provided.

Mortality was higher in treated rats than in controls. High dose differences included an increase in deaths the first year and an augmented female death rate over the two years.

Mortality, dead or sacrified moribund.

Dose(diet)	Control		2.5%		5%	
Months	M	F	M	F	M	F
0-12	20	13		22/15	29	23
13-20	19	14		28/17	16	20
No.# of Deaths/treated	39/56	27/55	50/55	32/54	45/56	43/55
Survival	30%	51%	9%	41%	20%	22%

Loose stools, dose related, were observed for all treated rats. High dose males exhibited body weight gain retardation.

The following (incomplete) table from a table which originally summarized the incidence of all proliferative lesions, does not indicate which of the lesions were found at terminal sacrifice, and which were from animals that secumbed earlier; therefore, there is no way to interpret this data because the appearance of the lesions is age related.

Sex	Male			Female		
Dose (% of diet)	0	2.5	5.0	0	2.5	5.0
No. of Rats Reported:						
a. Start	56	55	56	55	54	55
b. Deaths	39	50	45	32	45	43
c. No. Rats with prolif. lesions	31	32	28	40	38	28
d. Terminal Sacrifice	17	5	9	28	22	12
b+d, above	56	55	54	60	67	55

There are probably errors in the terminal sacrifice line as the number of rats with "proliferative lesions" exceeds the number of rats on the terminal sacrifice line.

Pathologies (incomplete listing).

Liver bile duct proliferation

a. focal	17(55%)	13(41%)	10(36%)	20(50%)	25(66%)	15(54%)
b. diffuse	7(23%)	6(19%)	8(29%)	14(35%)	4(11%)	4(14%)
Cystic hyperplasia, liver	0	1(3%)	0	0	3(8%)	4(14%)
Cholangioma or cholangiohepatoma	0	0	0	0	1	1
adrenal adenoma, cortical	0	1	2	0	0	0
medullary hyperplastic foci	2	8	5	3	3	8
pheochromocytoma	8	4	7	0	0	2

Sex	Male			Female		
Dose, mg/kg	0	2.5	5.0	0	2.5	5.0
THYROID adenoma	1	1	0	0	0	0
carcinoma	0	0	0	0	0	1
solid adenoma	0	3	4	3	0	1
Total, thyroid	1	4	4	3	0	2
testis, cell tumor, interst.	0	2	1	-	-	-
Uterus, adenocarcinoma or sarcoma	-	-	-	0	1	3(11%)
Pancreas, nodular hyperplasia	1(3%)	3(9%)	4(14%)	0	0	1(4%)
Lukemia	0	0	0	1(3%)	1(3%)	3(11%)

In spite of the baseline problem, there appears to be an increase in proliferative observations with treatment and dose. Interpretation is limited without additional data.

II(5.) EVALUATION OF CHRONIC STUDIES

Evaluation: In general, there can be seen dose related reduced weight gains, reduced survival, diarrhea, occult stool blood, G-I hyperemia, drowsiness, in all species and, in dogs, salivation and emesis. Accidental intubation deaths tend to be dose related.

The Lederle studies revealed bile and cystic duct hyperplasia and hyperplasia of duct-like structures, opthalmalogical problems and hepatomas, adenomas and carcinomas in the H-D rats.

Sponsor claims that the bile duct and cystic duct hyperplasias are strain specific to the extinct Lederle Sherman Wychoff strain and are not reproduceable in other strains of laboratory animals.

It is to be noted that the later studies which are supposed to establish the aberrancy of the original study differ in many ways from the original experiment and are not exactly comparable. There are also other problems in each of the cited studies which raise more questions than answers, for example:

A rough comparison between experiments can be expressed as follows.

a.a. Hyperplasia

Species	Control	0.3%	1.2%	4.8%
Rats 22 mo., Lederle	Biliary hyperplasia is dose and time related.			
Sherman Wychoff at 22 mo. Sacrifice	18/75(24%)	17/52(33%)	40/47(85%)	33/33(100%)

Rats, SD,F 24 months once/week/5 weeks*, S.C., *i.e., drug only given 5 times, total.	1 and 10 gms/oral 0.35 and 3.5 gms/Kg.

Summary only. Differences claimed by the sponsor to be not statistically significant; however, data was not provided. Group incidence of Biliary Hyperplasia ranged from 30 to 50%. Note that biliary hyperplasia was observed.

Rats, SD 20 months 0 4.8% in diet.	No Biliary hyperplasia seen in either control or treated animals. This is in contrast to other chronic studies.

Rats, Sherman, 19 months, in diet, Daiichi.

Dose (%)	(M) 0	2.5	5.0%	(F)0	2.5	5.0
Bile duct proliferation.						
Focal	17(55%)	13(41%)	10(36%)	20(50%)	25(66%)	15(54%)
Diffuse	7(21%)	6(19%)	8(29%)	14(35%)	4(10.5%)	4(14%)
Cystic Hyperplasia	0	1	0	0	3(8%)	4(14%)

Rats, SD,18 months, 4.8% in diet, Kabi A B.	Hyperplasia of renal pelvic epithelium was exhibited with an incidence to 100 % of rats with pyelolithias. Biliary Hyperplasia 2% Control, 5% Treated.

a.b. Evaluation of the Biliary Hyperplasia (BH) observations.

b.1. The 22 month Lederle study revealed a dose related and a time-related incidence of Biliary Hyperplasia. The L-D difference may not be statistically different from the controls, but the dose relationship is evident.

b.2. There is a rough time-order relationship between the studies, as follows:

	Incidence
Rats, 24 months	30 to 50%
Rats, 22 months	24 to 100%
Rats, 20 months	zero
Rats, 19 months	10 to 66%
Rats, 18 months	2 to 5%

b.3. The 24 month study with only 5 exposures is based upon the premis that a true carcinogen does not require a lifetime of exposure. On that basis, any dose related difference might be taken as evidence of carcinogenic potential with limited exposure. An alternative hypothesis would be to consider 5 exposures to be inadequate for toxic expression, leaving the whole study a study of controls.

Here the data submitted is inadequate. We only know that there was a 30 to 50% incidence of biliary hyperplasia in the groups and that sponsor found no statistical difference in incidence between the groups. Should the Control value be the lowest value, then FDA statisticians should be asked to review the data. Certainly it shows that 24 months of age can produce BHP in all groups. An alternative concept is that limited exposure of this type does not have universal application and/or acceptance, and that the experiment can be considered to indicate that limited exposure does not lead to toxic potential.

b.4. The 20 month Takayama study seems to be out of place in the various possible sequence alignments, but a steep BH incidence curve with time could explain the values. (i.e. 18 to 20 months, 0 to 5%; 19 to 24 months 10 to 100%).

Taken as presented, it indicates a zero boundary for BHP which is possibly consistant with Lederle data. Lederle found a 25% incidence in treated H-D males at 3-months, thus time of appearance could be strain-specific. Other alternatives can be considered because only a summary was provided.

> The zero incidence of BH could also be explained by missing or ungenerated data, by a translator oversight or error, (because scientific translators are not always available), or the summarizer might have considered the information unimportant and deleted it.

b.5. Rats, Daiichi, 19 months.

Except for liver cystic hyperplasia in the Female, the data is not dose related.

This study, however, poses many questions because of the method of data presentation. There is a lack of specific information that can be compared. The tumor incidence table cannot be related to either the terminal sacrifices or to the intercurrent deaths. Considering the time-related increase to be observed with BH in the Lederle Study, this is a serious deficiency.

Information that might be helpful would include the relationship of the Sherman strain of rat to the Lederle Sherman-Wychoff and the generally used S-D rats.

Another question would involve the reliability of such small numbers of survivors. This survival problem was the reported reason for cutting off the proposed 22 months repeat study at 18 months - A procedure which may have solved one problem, but raised others.

At the least, a considerable incidence of BH can be observed in many strains.

b.6. Rats, Kabi AB 18 months. This study is in line with the 20 month S-D study because of the very low incidence of BH in these animals.

Whether this low incidence is related to the shorter length of time of the study, to the strain or to a lack of effect in this strain is not readily determinable. There is only one dose and it is toxic to the organism. One can assume that the shortening of the experiment was related to the progressing die-off of the treated rats. It is possible that a longer experiment might have revealed biliary hyperplasia.

The kidney duct hyperplasia was reportedly related to the renal pelvic concrement and occurred in an increasingly large (dose related) percentage of surviving rats in the treatment groups. The relationship of kidney duct hyperplasia in the other groups is not available from the accessable data; however, in the Lederle report pyelolithiasis was dose and time related.

Conclusions:

Sponsor's contention that the Lederle experience is strain specific for BHP is not established by the data as presented.

6. Tumors.

Mice, CDF M (only), 4,8% in diet; 20 mo. Tokyo.	Control	Treated
lukemia and lymphoma	5(8%)	12(21%)
liver adenoma	1	1

Rat, Sherman Wychoff 22 months, Lederle, diet.	Control	0.3%	1.2%	4.8%
Hepatoma	3/75(4%)	3/52(6%)	3/47(6%)	3/33(9%)
Cholangioma	0/75	0/52	0/47	4/33(12%)
Adenocarcinoma	0/75	0/52	0/47	5/33(15%)

Rat, SD, F only, 5 dosings (only), 24 months.	neoplasms not essentially different from controls according to sponsor, but possible increase in S.C. nodules after S.C. admin.
Rat, S.D. Takayama. 20 months summary only.	No liver neoplastic (cholangioma or cholangiocarcinoma) lesions were seen. Incidence of other tumors not different between groups. Because data is not differentiated between sacrificed and those that died, these data are of little value as submitted.

Rat, Sherman, Daiichi 19 months, 1979

	Control		2.5%		5%	
	M	F	M	F	M	F
Survival	30%	51%	9%	41%	20%	22%
Uterus, adenocarcinoma or sarcoma	(-)	0	(-)	1	(-)	3(11%)
Pancreas nodules hyperplasia	1	0	3	1	4(14%)	1(4%)
Leukemia	0	1	0	1	0	3(11%)

Rat, S.D., Kabi AB
18 mo.,4.8% in diet

	Control		Treated	
	M	F	M	F
Mammary Fibioadenoma	0	15/51(29%)	0	8/54(15%)
Pituitary tumors	13/27	0/26	2/29	0/27
Pancreatic tumors	13/23(56%)	0/22	10/15(66%)	0/23

COMMENTS ON ABOVE INFORMATION

The 8% control and 21% treated group incidence of leukemia and lymphoma in mice fed for 20 months were not considered to be statistically significant by sponsor.

NOTE: Leukemia was also seen, H-D, 11% in the Sherman Rats.

The Lederle rat study included complete data. The marked increases in cholangiomas and adenocarcinomas were seen only at the highest dose.

The Takayama 20 month study reported a zero incidence of hepatic tumors and BH. This can also be viewed as an error of reporting or translation.

The shortcommings of this study have been covered in the BHP (biliary hyperplasia) discussion.

In the Kabi 18 month study, the incidence of tumors was apparently reduced by the drug. This is in contrast to the other studies.

In summmary. In spite of a shortage of comparable data, the general impression is that high doses of tranexamic acid are associated with an increased incidence of bile duct hyperplasia, leukemia, and uterine tumors in animals.

Other questions that remain are as follows:

INCOMPLETE SUBMISSIONS

Was the histopathology ever submitted for report 90; AB KABI, 1967? Their report 89 noted interesting salivary gland lesions and atrophy of layers of cecum and colon ascendens, but does not seem to be a complete report.

REPRODUCTIVE ORGANS:

Uterine weights are rarely mentioned; however, in 2 studies there are treatment differences in weight. Such differences should have alerted research attention.

a. Dog (88, KABI, 1966, 18 weeks/5 days/week) noted markedly lighter uterine weights in 6 treated dogs but not in 2 control Dc (Previously discussed).

b. Dog, Lederle 1 year. One Dog (1/3) given 400 mg/kg had a heavy uterus. (opposite to the above (a) findings)

c. Rat (Yamada, et al, 1979, 19 mo. Daiichi study, summary only) notes interstital cell tumors of testis and adenocarcinomas or sarcomas of uterus in treated rats. Relevance remains unknown because of inadequate data base in that there is no time-related separation of the data.

2. Lukemias and lymphomas are slightly increased in treated male mice (95, Kami Ikebukuro 1976), and lukemias slightly increased in rats (Yamada, 1979, Daiichi). Is lukemia ruled out in the other studies or unobserved?

Submitted summaries do not provide a time-related data base for lesion comparisons in mice (20 months, Kami Ikebukuro), Both rat and mouse studies need to have results of death separated from results of terminal sacrifices in histopathological reports, because there is a possible dose related increase in proliferative changes, lukemias, and tumors, the incidence of which can be influenced by survival time. The reported bile-duct hyperplasia in the Daiichi study has a high control value as it did in the Lederle report, but comparison are difficult because the apparent dose related cystic duct hyperplasia is not separately reported by Lederle. However, the reported (Lederle) pyelolithiasis may be similar.

Data, as presented, do not permit an evaluation of possible sex-related drug effects of this product.

III. REPRODUCTION AND TERATOLOGY STUDIES PERFORMED WITH TRANEXAMIC ACID

Species, No./group	Route adm.	Treatment period (days)	Dose levels mg/kg/day	Ref
Mouse, 15 1 CR-JCL	p.o.	7-12 of gestation	0,300,1,500	(Daiichi Morita et al., 1971)
10		C-Section, day 18		
5		to weaning.		

Results: Normal parameters unremarkable except treated fetuses were heavier than controls, and survival rate of H-D weanlings was slightly reduced.

Rat, 15/GP Wistar	p.o.	9-14 of gestation	0,300,1,500mg/kg/day	(Morita et al., 1971)
10		C-section, day 20		
5		to weaning-		

Results: Essentially unremarkable.

Rabbit, 10-13/GP Huntingdon, (Palmer & Readshaw, 1971)	p.o.	6-18 of gestation	0,100,200,400mg/kg/day	
		C-section, day 29		

Results: Deaths, 2 at 400; sl. retardation of weight gains in treated, significantly at 400. Slight increase in resorptions and foetal loss of treated M-D and H-D groups.

Rabbit, 12-13, i.v.		6-18 of gestation C-section, day 29	0,50,100,200mg/kg b.i.d.	Huntingdon, (Palmer & Readshaw 1971.)

Results: Slight reduction in weight gain, at H-D. Foetal losses low in control, higher in treated groups. Extensive data not remarkable.

Rat, 13-33/GP (Strippoli & Jackson, 1971)	p.o.	day 16 of gestation to day 21, postpartum	0,100,300,1,000mg/kg/day

Rat (M) 20 Control, 10/Treated GP(diet) 126 days premating (Strippoli Lederle (Sherman-Wychoff.) mg/kg/da 1971, 79)
0,222,(0.3%)
856,(1.2%)

Results: No effect on copulation, spermatogenesis or fertility.

Rat, 20-40/GP in diet.	Females: 2 weeks pre mating; throughout mating to day 13 of gestation and lactation to day 21 postpartum	792-1,160 (1.2%) 201-437(0.3%) mg/kg/day	(Strippoli & Jackson, Lederle, 1971

Results: Deaths, 1 H-D rat (congested lungs); 3 litters died, one control (1/18)(5.5%) and 2/9 H-D (22%). Pups surviving to weaning = 68,65 and 44% (C, L-D, & H-D), respectively. Enlargement of renal pelvis and underdevelopment of renal papilae seen in 7 of 20 H-D pups (35%).

Sponsor considered this study to be unremarkable, but there appears to be a H-D Toxicity.

Rat, Control 40; Treated, 20/GP, gavage, Pregnant females, 0, 100, 300 and 1,000mg/kg Lederle, 1971

20,40c Treated from gestation day 16 thru weaning

Results: Treated rats exhibited a higher incidence of respiratory and middle ear infections; otherwise, study was unremarkable.

IV Mutagenicity Tests in vitro.

Compounds tested included 2 batches of Tranexamic acid (Kabi 1411) and (Daiichi) and tranexamic acid analogue (Kabi 2017), in a gene mutation system, with and without rat liver microsomal metabolic activation with Salmonella typhimurium Strains TA1535,TA1537 and TA1538. Compound concentrations ranged from 10 to 10,000 micrograms/plate.

None of the 3 compounds tested provided evidence of mutagenic potential with strains TA1537 or TA1538.

With strain TA 1535, a large increase in the number of reverted colonies was observed with Tranexamic acid (Daiichi) in the absence of metabolic activation, and with tranexamic acid analogue (Kabi 2017) in the presence of metabolic activation.

With tranexamic acid (Kabi 1411) there was a small increase in the number of revertant colonies in the presence of metabolic activation.

These responses were not dose-related and the sponsor considers the results spurious. These tests were repeated using testor strain TA1535 in 2 separate experiments and no clear evidence of mutagenic potential was observed.

Other test systems were universally negative for the test compounds (alongside effective positive controls) and include the following:

MUTAGENICITY TESTS in vitro

Compound	Type of test	Test system	With and without (WO) metab. act.
Tranexamic acid 0.3 - 3,000 mcg/ mcg/plate	Gene mutation	Salmonella typhimurium (strains TA1535,TA1537 TA1538,TA100 and TA98.	with (Rat)
Tranexamic acid 100, 1000 or 6,000 mcg/ml	Primary DNA damage	Bacillus subtilis (strains H17(rec+) and M45(rec-)	W.O.
Tranexamic acid	Cytogenetic	Chinese hamster cells (D6)	W.O.

In vivo tests were universally negative and included the following.

V MUTAGENICITY TESTS with tranexamic acid - in vivo (i.p. adm.)

Type of Test	Species (strain)	Dose levels (mg/kg)	No of animals/ dose group	Dosing Schedule
Cytogenetic	Mouse (ddY)	100,1500,3500	15	Once (Single, I.P)
Cytogenetic	Mouse (ddY)	100,1500,3500	5	daily for 5 days
Cytogenetic	Rat(Spraque-Dawley)	100,1500,3000	15-18	Once
Cytogenetic	Rat(S-D)	100,1500,3000	5	daily for 5 days
Cytogenetic	Rat (Sherman)	100,1500,3000	18	Once

Cytogenetic	Rat (Sherman)	100,1500,2500	6	daily for 5 days
Dominant lethal test	Mouse (ddY)	100,3000	10 (males)	Once

Conclusion: The review has revealed the following

In the cover letter for the NDA submission, the company dwells on an FDA general approval of their preclinical data. It is my recollection that our only comment to the firm was that everything submitted would be reviewed.

There are gaps in the data base which make a determination of safety projection from non-clinical data difficult. Sponsor's contention that other studies establish a lack of the generally deleterious effects seen in the Lederle study is not supported by the submitted data.

The drug is toxic to the eye with increased dosage and duration of treatment.

1. Ophthalmoscopic Lesions

Retinal lesions are to be seen in rats, dogs, cats, and rabbits in a dose related manner for both incidence and severity. The length of treatment is an important consideration. In the original Lederle study, using Sherman Wychoff rats, a no-effect level was not clearly demonstrated. Sponsor considered minor lesions in 1/4 cats given 125 mg/kg/day/7 days, i.v. to represent a no-effect threshold. Certainly higher dosages did produce retinal lesions which became progressively worse with increasing duration of treatment. Such lesions have been shown to be reversible at all but the highest doses at which levels a one year recovery period does not change atrophy. The threshold for this lesion remains undefined because most long term studies were repeat studies which used only the highest clearly toxic dosages.

The human dose for several indications will be near 100 mg/kg/day which is not far from the 125 mg/kg, i.v., in cats or the 145 mg/kg p.o. in the Lederle rat study, but sponsor is persuasive in emphasizing that this is a dose and time related lesion which will not be a problem in short term clinical use. This may well be, but the labeling should clearly indicate the narrow safety margin between the effective dose in man and toxic levels in animals.

II Carcinogenic potential and hyperplasias.

A. Biliary hyperplasia has been demonstrated by the Lederle study to be dose and time related. The Lederle report is more complete than the purported refutation studies.

Sponsor contends that the effect is strain specific and not shown to be treatment related by other studies, but we cannot completely evaluate this contention because of the lack of basic data in the submissions.

Available data do not support these claims.

Biliary hyperplasias are not strain specific, because they are reported in high percentage in many of the studies (carried out in rat strains other than the one employed by Lederle) that sponsor cites for refutation. However, only summaries of those studies are available with an unevaluable "not significantly different" statement. The reported incidence in these studies does appear to increase with increasing duration of the study. This is also demonstrated by the progressive increase in the treated Lederle rats and possibly with other studies which have the following duration progression. The lack of identification of control values limits evaluation.

18 months,	2%(c) to 5% (treated)
19 months,	10% to 66% (summary data)
20 months,	zero (summary only)
22 months,	24%(c), L-D 33%, M-D, 85%-H-D 100%
24 months,	30 to 50% (No data and only 5 exposures to drug, 1 week apart, Possibly all of the groups can be considered control groups.)

There are also other hyperplasias and/or lesions which may or may not be related to the drug or to the bile duct stimulation, such as kidney duct hyperplasia which was dose related; the "most interesting lesions of the salivary gland", reported in only one study; and hyperplasia of renal pelvic epithelium and vascular lesions. Parallels in other studies are not evaluable because of a lack of submitted data.

B. Tumors are to be seen in increased numbers at the highest dosages for most studies where data is available except for the Kabi 18 mo. S-D rat study which was more enigmatic with apparent treatment reductions in mammary fibroademomas and pituitary tumors (two conditions which are quite variable in their usual appearances, anyway).

The lack of comparative data between groups and studies could be due to poor reporting. The lack of lower or intermediate dosages in these chronic non-Lederle studies prevents non-toxic dose level comparisons.

From the data available, the drug, at least at high dosages, has demonstrated tumorigenic and hyperplastic effects as well as a potential for ophthalmoligical toxicity.

Labeling proposal,

Comments,

1. Under Toxicology, the first paragraph notes that a study in an extinct strain is not considered relevant at maximum tolerated doses and repeated studies in other species and strains failed to reproduce these toxiciti s. This needs changing.

   a. All doses in the original study revealed toxicity. There was no "no-effect" dose level.

   b. The studies submitted do not refute the extinct strain studies because adequate data has not been submitted to establish such a conclusion. To the contrary, the studies while incomplete, tend to support the earlier findings with perhaps a difference in sensitivity.

2. Under Pregnancy there is a statement that there is no evidence of impaired fertility or adverse effect on the foetus.

   a. This is not quite true.

      At 1.2% in diet (H-D), 22 % of the litters died and pups revealed a reduced survival to weaning. Enlargement of the renal pelvis was reported in 35% of the pups.

   b. There is no mention that giving 10mg/kg to the dam will provide a cord blood drug level of 30 mg/L.

Recommendations.

These submissions, NDA 19780
and NDA 19781,

are to be considered non approvable because of incomplete preclinical data which does not, as claimed, refute the Lederle S-W rat findings of toxic potential.

The maximum recommended clinical dosage of 90 to 100 mg/kg/day for short periods of time needs to be compared to apparent no-effect animal dose levels from a time relationship perspective.

Intravenous administration in the cat produced a dose related ophthalmic effects with 1/4 L-D (125mg/kg) animals still exhibiting a minor effect after 7 days. Sponsor claims this to be a no-effect level, but it would be more accurate to call it a minimal-effect level.

Apparent no-effect dose levels, oral

Species	Route	Duration	Manifestation	Dose
Rat	diet	34 days	Reduced weight gain persistent diarrhea accidental deaths.	2500 mg/kg
Rat	p.o. 5D/week	16 weeks	Salivary gland lesions atrophy in cecum and colon ascendens	1000 mg/kg
Rat	p.o intubation	6 months	diarrhea, blood in stools catarrhal gastritis Cecal epithelial necrosis	750mg/kg
Rat	p.o.	(Lederle) 22 months diet	Biliary hyperplasia cholangioma and adenocarcinoma Retinal atrophy	None* 1.2% none
Dog	orally, 1 year		ophthalmological	400

*Sponsor claims the L-D of 150 to 300 mg/kg to be a no-effect level, because the increased incidence over control is not statistically significant.

If clinical experience is adequate to support the safety claim, at least the narrow safety margin of preclinical data should be emphasized in the labeling.

Wm. C. VanArsdel, 3rd, Ph.D.

cc: Original NDA: 19280
NDA: 19281
HFN-110
HFN-110/CSO
HFN-110/W.VanArsdel3rd/10-16-85
klb/11/18/85;3/31/86/03211

MED

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MEDICAL OFFICER'S REVIEW OF ORIGINAL NDAs

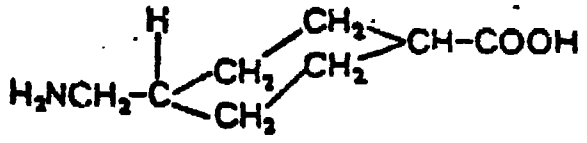
NDA: 19-280

SPONSOR: KabiVitrum

DRUG NAME: Cyklokapron (Tranexamic Acid)

OTHER NAMES: AMCA, AMCHA

Structural Formula:



Empirical Formula: $C_8H_{15}NO_2$

mol weight: 157

The drug is chemically and pharmacologically related to ε-aminocaproic acid (EACA). It is claimed to be 10 times more active *in vitro* and 5-10 times more active *in vivo*. It has been licensed in Europe.

FORMULATION: Tablets of 500 mg

CATEGORY: Antifibrinolytic agent

PROPOSED INDICATIONS: hemorrhage or risk of hemorrhage due to

dental extractions in patients with coagulopathies.

DATE OF SUBMISSION: May 7, 1984

DATE OF RECEIPT by Medical Officer: May 2[illegible], 1984

DATE REVIEW COMPLETED: November 16, 1984

INDEX

NDA: 19-280
(TRANEXAMIC ACID IN TABLETS)

NDA 19-280

ADDENDUM TO MEDICAL OFFICER'S
REVIEW OF ORIGINAL NDA

NDA: 19-280 and 19-281

Tranexamic Acid, Cyklokapron

DATE OF SUBMISSION: February 8, 1985

This submission is a response to my telephone requests of December 20, 1984.

It contains:

1. An enlargement of the table on p. 293, vol 1.6 of the original NDA 19-280, where the adverse reactions (AR) which were reported in the clinical studies for tranexamic acid, were summarized. The table is now readable. It appears that the only ARs which were judged as definitely related to the administration of tranexamic acid were cerebral edema/infarction and diarrhea. The cerebral edema according to the sponsor was observed only when the drug was administered to patients suffering from aneurismal subarachnoid hemorrhage which is an indication that we should not approve. The diarrhea was found to be dose dependent and could be avoided by reducing the dose.

   Kabi has reported, in addition, that a fall in blood pressure may result, if the drug is injected (IV) fast. They recommend a rate of 1 ml/min to avoid the pressure fall. We should remind them to include this recommendation in the insert.

2. A statement about the number of tablets and ampoules which were sold in Sweden in 1983 and 1984. From these amounts and the recommended dosage and length of treatment the sponsor calculated that about 205 thousand patients must have used tranexamic acid per year and a total of about 4.5 million since 1969, the year the drug was approved in Sweden.

3. An analysis of the ARs which were reported to the Swedish Drug Information System (Swedis) since 1969. This analysis shows that in-all 48 AR reports were made. According to the sponsor 26 of these reports described 33 reactions which were judged to be due to the use of tranexamic acid i.e. the incidence was approximately 1 reaction in 170,000 patients. According to the analysis there were 11-cardiovascular side effects, 5 skin reactions, 3 neurologic, 2 ophthalmalogic, 1 respiratory and 1 psychiatric and one death. One elderly patient being treated for hematuria with 1.5 g of tranexamic acid for 10 days died from pulmonary embolism.

4. A list of the countries where tranexamic acid is marketed: 13 European countries including England, W. Germany and Austria besides Sweden and Canada.

EVALUATION: I looked through the copy of the SWEDIS (Swedish Drug Information System) report which is included in vol 1.6 p. 296-305 of the original NDA and I was surprised to see several reports of vision abnormalities and hypotension. No such reactions were reported in the clinical trials. My analysis of the AR is as follows:

		drug taken for
Vision abnormalities	10	(a few days - 2 years)
Acute hypotension	5	
Thrombophlebitis, thrombosis	9	
Embolism	3	(all died)
Neurological manifestations (including anxiety, paresthesias etc.)	6	
Rash, anaphylaxis	3	
Pancytopenia	1	
Eosinophilia	1	
	38	

Some of the vision abnormalities were characterized as "not possible or not assessable" by Swedis. However, in view of the animal data and the frequency of these abnormalities (they are the most frequent complaint) we should consider them as drug related. Another point which we should pay attention to is that 5 of the cases of thrombophlebitis or thrombosis involved cerebral veins although none of the involved patients was treated with TA because of aneurismal subarachnoid hemorrhage. The recorded diagnoses were epistaxis hematuria or "disease not specified." There is also the possibility that the neurological manifestations may have been due to cerebral vascular abnormalities. It is true that some of the patients were elderly and had previously vascular problems and/or received several other drugs concurrently.

RECOMMENDATIONS:

1. Instructions should be given to the Division of Scientific Investigations that the inspectors pay particular attention to vision abnormalities, cerebral thrombosis, neurological abnormalities etc. recorded in the patients' records during the clinical trials and also in the Swedis records.

2. Appropriate warnings should be included in the insert.

PHARMACOLOGY:

Mode of Action: Tranexamic acid, like EACA, is a competitive inhibitor of plasminogen activation and a non-competitive inhibitor of plasmin. It forms reversible complexes with plasmin and plasminogen by binding with 5-6 sites of the heavy chain of plasmin and the corresponding sites of plasminogen. This binding leads to the dissociation of fibrin-plasminogen and fibrin-plasmin complexes and thus to inhibition of fibrinolysis. The therapeutic plasma concentration of tranexamic acid (3×10^{-5} to 10^{-4} moles/L or 5-15 mg/L) is about the same as the dissociation constants of plasminogen-tranexamic and plasmin-tranexamic complexes. Concentrations more than 100 times greater than these are required to inhibit the esterolytic and caseinolytic activities of plasmin.

Tranexamic acid has been shown to potentiate the effect of the natural inhibitors of plasmin.

Tranexamic acid can also inhibit other enzymes: enterokinase (trypsinogen activation) trypsin, pepsin, thrombin and C1-esterase but at concentrations higher than 5×10^{-3} or 10^{-2} M i.e. 100-1000 times greater than those required for the inhibition of fibrinolysis. Thus at therapeutic dosages it does not affect the action of these enzymes.

Effect on the Cardiovascular System: IV administration of Tranexamic acid into cats at dosages greater than 50-100 mg/kg increased blood pressure (by about 50%) and heart rate. Unlike with what happens with EACA, the increase in blood pressure was not followed by a decrease. Tranexamic acid is less potent (about 10 times) than EACA on blood pressure and in depleting catecholamines from the heart. On the other hand, as mentioned earlier, its antifibrinolytic effect is about 10 times greater than that of EACA.

Chronic oral toxicity studies have shown that tranexamic acid does not cause thromboembolism. Thromboembolism was induced only after reprated IV administration of large doses, 100 mg/kg/day or more, in a local irritant vehicle (benzylalcohol) or when tranexamic acid was injected at 50 or 100 mg/kg during hypercoagulable states created by injection of thrombin or after hemorrhagic shock induced by large blood volume loss (45-50%). Less extensive blood loss ($\simeq$20%) was not followed by formation of thrombi after tranexamic acid administration. Similary, tranexamic acid did not increase pulmonary thrombosis induced by lactic or ellagic acid.

Absorption: The amount of tranexamic acid which can be absorbed after oral administration varies with the species. The amount absorbed by the dog is 60-70%, by the man and rabbit 50%, the mouse 30% and by the rat 20%. Most of the absorbed drug becomes bound to plasmin and plasminogen and only 3% binds to other plasma proteins. Autoradiographic studies have shown that tranexamic acid does not accumulate in the tissues. The distribution volume in the rat and dog is about 1-2 L/kg. Only a very small amount of tranexamic acid is metabolized (acetylation or deamination). Its half-life is 2 hrs (rat, dog) and is excreted mainly in the urine. An insignificant fraction is cleared through the bile.

Toxicology

Acute Toxicity: very low:

LD50

g/L

	Oral	I.V.
mouse	>10	1.3,1.4
rat	>10	0.9
rabbit	>10	1.4
dog	> 5	1.1
chicken	>10	

Oral administration of sublethal doses causes diarrhea (mice, rats) and vomiting (dogs). I.V. administration of single sublethal doses causes convulsions in the former and convulsions and emesis in the latter.

The Subacute and Chronic Toxicity of tranexamic acid was studied in rats, cats, dogs, rabbits, and monkeys. Tranexamic acid was administered IP into rats for 2 weeks at dosages of 250-1,000 mg/kg/day and orally for 5 and 16 weeks or for 6 months at dosages of 1,000-5,000 mg/kg/day by incorporating it into the food. Salivation, diarrhea, poor grooming and reduced body weight gain were observed at the higher dosages (500 mg/kg/day). The symptoms were dose dependant. Two animals given 7,500 mg/kg/day died during the treatment period. Autopsy revealed marked chronic colitis, and cecitis. Catarrhal gastritis and submucosal edema was observed in the stomach of rats receiving 3,000-5,000 mg/kg/day.

In cats I.V. administration of tranexamic acid at 250-500 mg/kg/day for 6 days induced proliferation of the pigmented epithelium at the tapetum lucidum (around the optic disc) and partial detachment of the retina resulting in folding of the outer nuclear layer and incipient atrophy. These changes were irreversible. Lower dosages induced mild pigmentation which was reversible after drug withdrawal. Oral administration of 500-1,500 mg/kg/day to rats and dogs for 16 days showed no evidence of eye damage but longer administration, up to a year, at dosages 800 mg/kg/day in dogs induced changes in the reflectivity of the tapetum lucidum and sometimes along the major retinal vessels and also at the anterior eye (ora ciliaris retinae). These changes were similar to those observed after I.V. administration into cats.

I.V. administration of tranexamic acid in 3 dogs at 1 g/kg/day as a 5% solution for 3 days caused salivation, frequent vomiting and less frequently tremors. In addition myocardial petechiae and necrosis were seen in 1 of these dogs who died in convulsions. Eye changes were not observed. Such changes, ("focal accumulation of pigment-laden as well as non-pigment-laden mononuclear cells in the pigmented epithelium projecting into and somewhat compressing the underlying layers of the retina. Also in one eye, there was focal disruption and atrophy of the layer of rodes and cones and the inner nuclear layer"), however, were observed in dogs given 2 g/kg/day for 7 days.

Eye changes were not observed in monkeys given tranexamic acid I.V. at 2 g/kg/day for 7 or 14 days.

A dose related tachypnea was observed in rabbits (N.Zealand) after I.V. administration of 60-180 mg/kg/day.

No significant changes were reported regarding laboratory parameters (hematology or clinical chemistry) except in SGPT and SGOT which were increased in some occasions in dogs given 1,000 mg/kg/day for 18 weeks or longer. Urinalyses revealed traces or larger amounts of protein in the urine of animals who received 1,000 mg/kg/day for 18 weeks. No drug-related changes were observed in EKG or blood pressure.

Small thrombi were found in the lungs of 2/8 dogs after repeated iv administration of 100 and 500 mg/kg/day for a month. It was concluded that these thrombi had originated from the venipucture sites and were carried as emboli to the lungs. The vehicle, benzyl alcohol, may have contributed to the formation of the thrombi.

Neoplastic Potential. Effect on Reproduction

Carcinogenicity: The incidence of leukemia in CDF_1, mice fed tranexamic acid for 20 months at about 5 g/kg/day was found to be increased to 21% compared to 8% in control mice (Takayama 1976). This difference, however, was not statistically significant.

A dose related increase in the incidence of bile duct hyperplasia and adenofibrosis was observed in Sherman-Wyckoff rats fed tranexamic acid at 160-3,400 mg/kg/day for 22 months in a study conducted at the Lederle Laboratories. In addition, high dose rats showed an increased incidence in hemangiomas and adenocarcinomas. Increased tumorogenicity or higher incidence of leukemia however, was not found in 2 subsequent studies using Sprague-Dawley rats fed tranexamic acid at 3 g/kg/day for 18 months, and 20 months respectively.

The sponsor claims that the Lederle findings are not relevant to the safety evaluation of tranexamic acid because:

a) Several subsequent carcinogenicity studies have failed to reproduce the neoplastic changes in the liver.

b) The dose-dependent biliary hyperplasia observed in the Lederle study has not been reproduced in subsequent studies. The historical incidence of biliary hyperplasia in Sherman-Wyckoff rats at Lederle Laboratories was (3%). The high incidence (24%) in the control group in the tranexamic acid study may therefore indicate that an environmental factor or contaminant in the diet may have influenced the results of that particular study. The strain of rats used in this study has been exterminated and the study cannot be repeated using the same strain. Also, no samples from the food are available for analysis.

c) No mutagenic acitivity of tranexamic acid has been demonstrated in several in vitro and in vivo test systems.

Mutagenicity: Mutagenic activity was studied in cytogenetic tests in vitro (chinese hamster cells) or ex vivo (bone marrow from Sprague-Dawley and Sherman rats and from mice), dominant lethal test in mice, and tests using bacterial systems (bacillus subtilis and salmonella typhimurium with or without metabolic activation). The results were negative.

Teratogenicity: negative (mice, rats, rabbits)

Effect on Fertility: negative (rats)
Peri- and postnatal effects: negative (rats)

CLINICAL PHARMACOLOGY

Bioavailability and Pharmacokinetics: KabiVitrum has summarized 9 bioavailability studies but has submitted a copy of only one of these studies (Pilbrant et al, Eur. J. Clin. Pharmacol. 20 65, 1981). These studies apparently have shown that after oral administration to normal volunteers 34-54% of the dose is absorbed. Peak plasma concentration is reached within 2-4 hrs and almost all of the absorbed quantity is eliminated in the urine within 24 hrs. Food was found to have no significant influence on the absorption as judged by comparison of the peak plasma concentration, the time required to reach the peak, the AUC from zero to 6 hrs and the urinary excretion data.

After IV administration 30% of the dose is excreted in the urine within one hr, 45-50% within 2-3 hrs and 90-95% within 24 hrs. Complete elimination was found to occur after 144 hrs. The $T_{1/2}$ is about 2 hrs and the plasma clearance 105-135 ml/min. IV administration of tranexamic acid into patients with renal disease showed that the half-life becomes prolonged as renal function decreases. Consequently, patients with renal disease should be given lower dosages based on their serum creatinine levels.

Tranexamic acid diffuses rapidly into joint fluids and synovial membranes where it has been detected at the same concentration as in the plasma. Its half-life in the joints is about 3 hrs. It crosses the placenta and the blood-brain barrier. Its concentration in the cord blood after IV administration to pregnant women was as high as in the maternal blood. In another study, its concentration in the CSF was about 1/10 of that of the plasma. Tranexamic acid has been found in the milk of lactating women but at concentrations 1/100 of that of the plasma. It has also been detected in the semen, however, it does not affect sperm motility. Tests in tissues removed during operations (large intestine, kidney, prostate) have shown that tranexamic acid remains longer than EACA. Values have not been quoted by the sponsor neither copies of the original articles have been submitted.

B. USE OF TRANEXAMIC ACID IN PATIENTS WITH CONGENITAL COAGULOPATHIES FOR THE CONTROL OF HEMORRHAGE AFTER TOOTH EXTRACTIONS.

Tooth extractions in hemophiliacs and other patients with congenital coagulopathies, even in those with mild deficiencies, are a very serious matter. The patient can bleed profusely and may die, if adequate hemostatic therapy is not provided. Usually a concentrate of the deficient factor is infused before the extraction(s) to bring the serum level to at least 20% of normal (in severe cases from ≤1%). Additional infusions are then required to keep this level to about 15-20% for several days after the extraction(s) in

order to prevent postoperative bleeding. Coagulation factor concentrates are very expensive and in limited supply. In addition, they have to be infused, ideally, continuously, which is very inconvenient and also dangerous because the preparations may transmit serum hepatitis, AIDS and/or other viral diseases. They may also induce allergies and the production of antibodies (circulating anticoagulants) and thus create a hemorrhagic condition much more difficult to treat than the original deficiency.

Several investigators in Europe have introduced the use of antifibrinolytic agents, EACA and tranexamic acid, in order to prevent the early dissolution of the fragile clots which are formed in the sockets of patients suffering from congenital coagulopathies and thus reduce the need for replacement therapy. KabiVitrum has submitted reports from 6 such studies, which I have summarized in Table 5. All of these studies were performed during the late sixties and early seventies.

One of the studies (Forbes) was placebo-controlled, randomized and double-blind. Two others (Ramström-Blombäck, Pell) were open and retrospective and the remaining 3 (Bjorlin-Nilsson, Tavenner, Creveld) were uncontrolled.

The Forbes study was adequate and well controlled. It showed that significantly less blood was lost and significantly fewer units of substitution therapy were required to control hemorrhage in the patients who received tranexamic acid compared to the patients who had received placebo.

The Ramström-Blombäck study, although not double-blind but retrospective, seems also reliable. It had a good number of patients (55 with hemophilia A, 14 with hemophilia B and 19 with V. Willebrand's disease), the treatment regimens were well-defined and adhered to, and the results were expressed per tooth removed according to the severity of the deficiency. Thus imbalances in the severity of the disease among the treatment groups were eliminated. The groups represented 3 treatment modalities which were used successively at the Karolinska Hospital in Stockholm, Sweden during the period of 1965-73 as the state of the art for the treatment of hemophilia evolved. The first group represented patients treated with substitution therapy alone, the second group included patients treated with substitution therapy plus tranexamic acid and the third had patients treated with local therapy (thrombin, gelatinous sponge and splints) in addition to substitution therapy and tranexamic acid. The results were clear-cut: Inclusion of tranexamic acid reduced the need for substitution therapy to about 1/2. Further, addition of local therapy reduced this need to approximately 1/8 - 1/9. Similar reductions were observed regarding bleeding episodes and the days of hospitalization (when the severity of the deficiencies was taken into consideration, Table 9).

The Pell study, which was also open and retrospective, was not very well controlled. Treatment modalities and disease severity were not well differentiated. Nevertheless, properly analyzed this study showed results similar to those of the Ramström-Blombäck study.

The results of the uncontrolled studies corroborated the findings of the controlled studies.

TABLE [illegible] 5
Clinical Studies submitted by KabiVitrum in Support of the Effectiveness of Tranexamic Acid as Adjunctive Therapy to the Control of Hemorrhage after Tooth Extractions in Patients with Congenital Coagulopathies

Clinical Investigator Affiliation	No of Patients with Coagulopathy A	B	VW	Treatment with AMCA Dosage (g tid)	Duration (days)	Route of administration	No of teeth or roots extr./patient	Bleeding Episodes	days/pt	Blood loss ml per Teeth	Pt	Days of Hospital. per Teeth	Pt	Post-Operative Replacement Therapy units per Teeth	Pt	Year Study Perform or publ.	Study Design Comments	Side Ef- fects
[illegible] et al University of Glasgow Royal Infirmary, England	32 9	3 5		1 placebo	5 5	oral oral	4.9r 5.1r			8.9r 15.3x	18.2* 60.1			9.9 5772	6 3,480	1977	Placebo controlled randomized, double-blind	None
[illegible] and [illegible] N. [illegible] [illegible], Sweden	19 21 16	5 4 5	7 6 7	0 1 1+local**		 oral oral, iv local	3.6 2.9 7.3	23 10 6				2.5 2.4 0.9	8.8 6.9 2.1	(1,100 795 137	3,440 2,370 312)	1966-9 1969-71 1971-3	Retrospective, 1975 Group 2 had more pts with several [illegible] A than groups 1 or 3 (1)(2)(4)	None
[illegible] Guy's College Hospital London, England	6 2	2 1 4	 3 1	0.5-1 0.5-2 0 (splint, paste)	7	iv, oral iv, oral	4.8 (1-20) 5 (2-15) 3.8 (1-7)	1	0.07 0.33 4.4			1.4 0.07 4.2	10 4.5 14	0.06 0.1 0.8	6 6.5 2.8	1973	Retrospective	None
[illegible] [illegible] Hospital [illegible], Sweden	7	5	5	1-2	5-7	iv, oral	9.9 (1-11)	2							917	1973	Uncontrolled Surgical [illegible] applied to all sockets, which were then sutured.	Diar. after to [illegible] dist. Diarrhea (2)
[illegible] University of Birmingham Birmingham, England	19	9	1	1.5	0.28	oral										1972	Uncontrolled	
[illegible] Haemophilia Clinic [illegible], Finland	9	3		0.5-1.5	6	oral	1-7						3-15			1971	13 case reports [illegible] infusions needed [illegible] sign. Reduced [illegible] doubtful [illegible] effect	None
[illegible]	102	42		29														

VW = Von Willebrand's disease
[illegible] = not stated
( ) = Figures in brackets are calculated means of all relevant values

*p < 0.005
** Tranexamic acid + surgical + acrylic splint

Review of Individual Studies

1. FORBES et al (University of Glasgow, Royal Infirmary) studied the effect of AMCA as adjunctive therapy in preventing hemorrhage in patients with hemophilia after tooth extractions (Brit. Med. J. 2:311, 1972). The study was placebo-controlled, randomized and double-blind. Twenty of the patients had hemophilia A while 8 had hemophilia B (Christmas disease). The number of extraction sessions, number of patients with hemophilia A or B and the severity of the deficiencies per group are shown in Table 6. It is obvious that there were no significant differences regarding these parameters between the groups.

[illegible]—Clinical Data on Patients receiving Tranexamic Acid and Placebo

	Placebo	Tranexamic Acid
[illegible]	[illegible]	[illegible]

Each patient received only one dose of factor VIII or factor IX concentrate, equivalent to 1000 ml of blood, I.V. one hour before an extraction session. At the same time he received orally 1 g of AMCA or placebo and 250 mg of tetracycline and these oral dosages were repeated every 6 hours for 5 days.

All extractions were carried out under local anesthesia and inferior dental block (if appropriate). Blood loss was estimated by labeling the red cells with ^{51}Cr. The results are shown in Table 7:

[illegible]—Comparison of Treated and Placebo Groups after Tooth Extraction

	Placebo	Tranexamic Acid
[illegible]	[illegible]	[illegible]

A rank sum test (Mann-Witney U test) indicated that the difference in blood loss between the placebo and the AMCA group was significant ($0.01 < p < 0.025$).

Replacement Therapy: In only two patients it was clinically necessary to transfuse plasma or plasma concentrate in the tranexamic acid group after the initial dose. One of these patients had extraction of 22 roots, the largest number in this series. In the placebo group multiple infusions were required for 11 of the extraction sessions during the five-day trial period and only five patients did not require replacement therapy; all these had a mild or moderate degree of defect. The patient who required the greatest amount of replacement therapy in this study had only a moderate degree of hemophilia and had six roots extracted. He was in the placebo group.

Side Effects were not reported.

Evaluation: This study was adequate and well controlled and clearly indicated that AMCA administered daily for a few days to hemophilic patients after an initial boost of factor VIII or IX levels by the use of a respective concentrate, can control hemorrhage after tooth extractions. Thus it can reduce significantly the need for factor concentrates which are less plentiful, more expensive and more dangerous (possible transmission of hepatitis or AIDS, induction of antibodies).

2. RAMSTRÖM and BLOMBÄCK (Karolinska Sjukhuset, Stockholm, Sweden) treated 67 patients with hemophilia A, or B, or Von Willebrand's disease, after the extraction of 264 teeth and root stumps in 118 treatment sessions during 1965 - 1973 (Int. J. Oral Surg. 4:1, 1975). The distribution of the patients according to disease, sex and age was as follows:

Table 8 Patient distribution in coagulation disorders, sex and age

Disease	No. of patients	M	F	Age range
Hemophilia A				
severe	15	15	0	15-51
moderate	9	9	0	20-42
mild	18	14	4	9-56
Hemophilia B				
severe (1.4 %)	6	6	0	28-48
mild	4	3	1	8-57
v. Willebrand's disease				
severe	2	0	2	29-31
mild	13	2	11	4-81
Total	67	49	18	4-81

In 16 cases it was necessary to prepare mucoperiosteal flaps and in another case to enucleate a radicular cyst. In all cases, except one where intubation anesthesia was used, the extractions and/or operations were carried out under local anesthesia.

The investigators classified the patients in 3 groups representing changes in the method of treatment during the study years. Group 1 consisted of patients who received substitution therapy only, which was the standard treatment at the Karolinska Hospital during 1965-9. Group 2 included patients treated with infusion therapy supported by fibrinolytic inhibitors and antibiotics. This took place during 1969-1971. In Group 3, the Group 2 treatment was supported by local hemostatic means in the extraction alveolus and an acrylic splint attached to the surrounding teeth in order to protect the coagulum in the alveolus.

Group 1. Substitution Therapy

The patient was admitted to hospital the day before the tooth extraction. Patients suffering from hemophilia A and B received substitution therapy with plasma or factor concentrate immediately before the extraction was performed. The infused quantity for patients with hemophilia A was calculated so that the patient's factor level would rise to 30-50% of the normal value. The next 2-3 days following the extraction the level was permitted to fall to 25-30%, and kept at about half this value for 6-10 days. For patients with hemophilia B there was no Swedish factor concentrate available during the first years, which is why only substitution treatment with plasma could be offered. In consideration of the risk of hypervolemia, the level in these patients on the day of extraction could not be raised to more than 10-20%. The patient was discharged from the hospital when he had been free from bleeding, without substitution treatment, for 3-5 days.

In patients suffering from von Willebrand's disease, the substitution treatment was begun the day before the extraction, as these patients show also a slower secondary factor rise, in addition to the primary rise.

On several occasions postoperative bleedings of long duration occurred in this group, which necessitated renewed substitution treatment. In some of these cases the "old" bleeding coagulum was removed under local anesthesia. The alveolus was plugged with Spongostan and the tampon retained in position by suturing. On the few occasions when severe postoperative infections occurred, penicillin was administered.

Group 2. Substitution Therapy Supported By Fibrinolytic Inhibitor and Antibiotics

All the patients in this group were routinely treated with Cyklokapron and penicillin. The treatment with Cyklokapron (1 g t.i.d. orally) was begun the day before the extraction, as a rule on the same day as the patient was admitted to the hospital. The required quantity of plasma and/or factor concentrate was calculated and administered during the extraction

day, in accordance with what has been said above for Group 1. The factor content in the following phase was, however, kept at a lower level and the treatment concluded earlier. In many patients, though, the factor level was raised on the extraction day only to 20-30% (in Group 1 it was raised to 30-50%). This applies mainly to patients treated during the latter half of 1970, and 1971, as the experience gained from the combined method of substitution therapy, fibrinolytic inhibitors and antibiotics was considered to justify also an initial lowering of the level.

Group 3. Substitution Therapy Supported by Fibrinolytic Inhibitor, Antibiotics, Local Treatment of Alveolus and Acrylic Splint

Fibrinolytic inhibitor and antibiotics were administered as in Group 2. Six patients on 13 extraction occasions were not given penicillin, however. One of those patients reported an oversensitivity to penicillin. In the remaining cases, the risk of infectious complications in extraction was assessed as minimal so the administration of penicillin was not considered indicated. Cyklokapron was given perorally at 1 g t.i.d., but in two of the cases intravenously 10 ml at 0.1 g/ml also t.i.d. The quantity of factor concentrate given on the extraction occasion was calculated as increasing the patient's factor level to 5-10% of the normal value.

On the day after the extraction either the same quantity was given, or half or none at all, depending upon previous experience of the patient's - or corresponding patient's - respective response to treatment.

The tooth was extracted with as little trauma as possible and the alveolus was filled with Thrombase 500 and Thrombase dentaire. A piece of Surgicel was then placed over the alveolus as a shield. An acrylic splint was then attached to the surrounding teeth with phosphate cement. The acrylic splint remained in place for 8-10 days.

The distribution of the patients in the various groups and the number of patients treated in more than one group are shown below. Group 2 had the largest number of patients with severe deficiencies (16) compared to group 3 (10 patients) or group 1 (5 patients). The ratio was 3:2:1

Groups	No. of patients			No. of patients	No. of patients in combinations			
	1	2	3		1+2	1+3	2+3	1+2+3
Hemophilia A								
severe	3	11	6	15	2	1	2	
moderate	7	2	2	9	1	1		
mild	9	8	7	18	4		2	
Hemophilia B								
severe (1.4 %)	2	3	4	6	1		1	1
mild	3	1	1	4	1			
v. Willebrand's disease								
severe		2		2				
mild	7	5	7	13	3	1		1
Total	31	30	27	67	11	3	5	2

Results Table 9 shows the amounts of factor VIII or IX or plasma which were used to control the bleeding of the patients and the days of hospitalization for each group. The results are expressed as total amounts and total days and as amount and days per tooth extracted. The results are also classified according to the severity of the hemophilias. It is obvious that the units of replacement therapy required were decreased to about 1/2 when tranexamic acid was added and further to 1/8 or 1/9 when local therapy was also included. Moreover, when the coagulation deficiency was mild no replacement therapy was required when both tranexamic acid and local therapy were used. Considerable decreases were also observed regarding the days of hospitalization. These were reduced to 1/2 (AMCA added) and to 1/3 to 0 (AMCA and local therapy added).

A summary of the number of bleeding complications in the different groups is given in Table 10. In Group 1, postoperative bleedings occurred in 59% of the treatment sessions. In Group 2, the bleeding frequency decreased to 28%, and in Group 3 it was reduced to 10%. It should also be pointed out that the bleedings in Group 1 were far more severe and prolonged than those occurring in Groups 2 and 3. Nine of the bleedings in Group 1 were described as severe and prolonged, but in Groups 2 and 3 there was no such bleeding. Patients with moderate forms of hemophilia A were found to be relatively difficult to treat according to the method used for Group 1. Many of the postoperative bleedings registered were particularly prolonged and complicated. This patient category responded very well to Cyklokapron and antibiotic therapy and no bleedings were registered in Group 2.

Table 10. Bleeding complications in different groups and diseases

Disease	Group 1		Group 2		Group 3	
	No. of treatm. sessions	No. of bleeding compl.	No. of treatm. sessions	No. of bleeding compl.	No. of treatm. sessions	No. of bleeding compl.
Hemophilia A						
severe	3	3	13	5	6	2
moderate	9	7	5	0	2	0
mild	11	8	9	4	11	1
Hemophilia B						
severe	2	2	3	0	3	1
mild	2	1	2	0	3	0
v. Willebrand's disease	12	3	6	1	13	0
Total	39	25	36	10	40	4

Several patients with mild forms and even moderate forms of hemophilia and mild forms of von Willebrand's disease could be treated as outpatients when changed over to treatment according to Group 2, and later to Group 3. This has lighteded the hospital's burden considerably.

Table 9. Difference in substitution therapy and hospitalization days in different groups

Disease	Group	No. of patients	No. of extracted teeth		Hospitalization days	AHF ml	Plasma ml	No. of units*
Hemophilia A severe <1% VIII	1	5	6	Total:	45	6,300	7,800	19,550
				Per tooth:	7.5	1,050	1,260	3,250
	2	11	26	Total:	95	15,600	4,800	41,400
				Per tooth:	3.7	600	185	1,592
	3	6	12	Total:	32	2,100	0	5,250
				Per tooth:	2.6	175	0	438
Hemophilia A moderate 1–4% VIII	1	7	37	Total:	11	3,200	36,100	36,050
				Per tooth:	3	86	1,516	974
	2	2	18	Total:	29	2,800	2,400	8,200
				Per tooth:	1.6	156	133	456
	3	2	5	Total:	3	200	0	500
				Per tooth:	0.6	40	0	100
Hemophilia A mild >5% VIII	1	9	31	Total:	92	1,700	41,200	24,850
				Per tooth:	3	55	1,330	802
	2	8	22	Total:	17	700	600	2,850
				Per tooth:	0.8	32	27	93
	3	8	20	Total:	3	0	0	0
				Per tooth:	–	0	0	0
v. Willebrand's disease	1	7	25	Total:	70	1,500	29,400	18,450
				Per tooth:	2.8	60	1,176	738
	2	5	12	Total:	24	900	5,250	5,375
				Per tooth:	2	75	520	475
	3	7	18	Total:	0	0	0	0
				Per tooth:	0	0	0	0
						Pers. IX conc.		
Hemophilia B <1.4% IX	1	2	3	Total:	27	200	10,800	13,100
				Per tooth:	9	67	3,600	4,366
	2	3	7	Total:	34	100	9,300	11,350
				Per tooth:	4.9	22	1,400	1,621
	3	4	8	Total:	21	120	0	3,000
				Per tooth:	3.5	20	0	500
Hemophilia B >2% IX	1	3	8	Total:	27	0	15,450	11,610
				Per tooth:	3.4	0	1,930	1,460
	2	1	2	Total:	8	0	1,000	750
				Per tooth:	4	0	500	375
	3	1	3	Total:	0	0	0	0
				Per tooth:	0	0	0	0

* *In vivo* value

Extractions have also been performed on patients with rare coagulation defects. Two patients with a mild Factor X deficiency and two patients with a mild Factor XI deficiency have thus been treated. The patients were first given large quantities of plasma. Later, following the administration of fibrinolytic inhibitors and antibiotics, the plasma treatment could be discontinued. One patient developed hepatitis after plasma treatment in 1967.

Contid on p. 27

Side Effects: None was reported

Evaluation. This study had not been planned in advance. It was a retrospective effort to evaluate the new treatment which had been introduced in Europe in 1969-73 for patients with congenital coagulopathies. As a result of the lack of planning the patients in the 3 groups were not comparable regarding the severity of their disease. However, the groups were clearly defined regarding treatment without overlapping of the various modalities and the results were expressed (as units of substitution therapy or days of hospitalization) per tooth extracted according to the severity of the disease. Thus any imbalances in disease severity between the groups were eliminated. It was clearly demonstrated that the introduction of AMCA in the treatment of hemophiliacs requiring tooth extractions reduced the need for postoperative replacement therapy to about 1/2. When combined with local therapy such treatment reduced this need further to 1/8 or 1/9 and in mild cases it completely eliminated replacement therapy. This is not a small gain, because besides reducing expenses (coagulation factor preparations and hospitalization are expensive) the new treatment also reduced the danger of transmitting hepatitis and/or AIDS and of inducing the production of antibodies. The fact that 3 times as many patients with severe hemophilia A decided to have tooth extractions within the first 2 years (1969-71) that tranexamic acid was introduced in the perioperative treatment of hemophilia than they had during the preceding 4 years (1965-9) when such treatment was not available, is perhaps one of the best arguments in favor of the drug. The difference was really 6 fold/year.

3. PELL in another retrospective study (Brit. J. Oral Surg 11:155(1973) dealing with tooth extractions, compared the results observed in 14 hemophilic or von Willebrand patients where tranexamic acid was used with 5 cases of mild bleeders, who were managed without antifibrinolytic drugs, at the King's College Hospital in London, England. He divided the patients in 3 groups (Tables 11, 12, and 13):

Group I, Table 11: Eight patients with severe or mild hemophilia A or B (f. VIII or IX levels of 0-15%). These patients had a mean of 6.5 teeth removed (1-26) in one session. Seven of the 8 received AMCA 0.5-2 g every 6 hours preoperatively and/or postoperatively. Five of these 7 patients received in addition cryoprecipitate or fresh frozen plasma (FFP). Moreover, 2 of them had their sockets treated with Surgicel.

Two of the five patients received the coagulation supplements preoperatively (4 units FFP or 10 units of cryoprecipitate), two received them postoperatively (4 units FFP or 3 bags of cryoprecipitate) and one received cryoprecipitate both before (10 units) and after the extractions (18 units). These patients bled for 0-3 days (mean 1 day) and remained at the hospital for an average of 10 days (2-22 days). The eighth patient, a 5 year old hemophiliac boy with a 15% level of f. VIII, had 3 teeth extracted but received neither AMCA nor factor VIII preparations. His wounds were packed with Surgicel and he did not bleed. He remained at the hospital for only 2 days.

Group II, Table 12: Six patients with mild hemophilia, factor VIII or IX levels of 20-26% or with von Willebrand's disease (f. VIII levels of 18%, 29% and 37%). These patients had 2-15 teeth extracted (mean 5). All received AMCA pre- and postoperatively at about the same dosage as the patients in group I. Two of these 6 patients received in addition FFP, one 2 units preoperatively and the other 1 unit postoperatively, while 3 other patients had their wounds treated with Surgicel instead of receiving plasmas. One, 11 year old patient with 20% of f. IX, received no additional hemostatic treatment. He received only AMCA, 1 g/6 hours (starting before the extraction). Only one of the 6 patients bled and for this reason he was treated with the unit of FFP postoperatively mentioned above. This patient remained at the hospital for 10 days. The other 5 patients remained for only 0-5 days (mean 3.4 days) and none of them bled.

Group III, Table 13: Five patients, 4 with hemophilia A (f. VIII levels of 14%-20%) and 1 with von Willebrand's D. (f. VIII levels of 20%). These patients had 1-7 (mean 3.4) teeth extracted in one session. Three of these patients received 1 unit of fresh plasma or FFP preoperatively and 1 unit of plasma or 4 units of FFP postoperatively. The 4th patient received only 2 units of FFP postoperatively. None of these patients received AMCA. All of them bled for 3-6 days (mean 4.5 days) and remained at the hospital for 10-18 days (mean 14 days).

Pell in his publication included in addition the case of a patient with 0% factor VIII activity who developed allergy to cryoprecipitate (vesicular erythematous rash in abdomen, back, shoulders and arms) after the extraction of 1 tooth and was treated succesfully with tranexamic acid pre- and postoperatively.

Side Effects: None was reported.

Evaluation: The classification of the patients in the 3 groups is rather messy. It is not clear why patients with severe bleeding disorders were classified in the same group (Group I) with patients with mild disorders or why patients who received coagulation factor supplements in addition to AMCA were included in the same group with patients who did not receive such supplements or with patients who received neither supplements nor AMCA but were only treated with surgicel locally. Moreover, some of the patients were treated with surgicel in addition to AMCA or in addition to AMCA and FFP or cryoprecipitate. If we confine the comparison between mild bleeders, those who received AMCA and some supplements or surgicel and those who received only supplements but not AMCA i.e. between Group II and III, then it appears that the addition of AMCA reduced both the incidence and the duration of bleeding significantly (one patient bled for 2 days versus all 5 patients who bled for 3-6 days) and thus reduced the days of hospitalization also significantly (from 14 to 4.5 days). It should, however, be pointed out that 3 of the 6 patients who received AMCA had also been treated locally with surgicel while none of the patients of group III (who did not receive AMCA) had been treated with surgicel.

TABLE II

Patient	Age at operation	Sex	Diagnosis	No. of teeth extracted	Days in hospital	Factor VIII or IX assay	Cryo-precipitate or FFP pre-operative	Pre-operative AMCA	Days bleeding	Post-operative AMCA
P. K.	35	M	Christmas Disease	26	22	0%	—	1 g stat. 2 g 6-hourly in drip	2 (F/F splints)	4 units FFP 2 g AMCA 6-hourly in drip
A. T.	44	M	Haemophilia	8	7	0%	10 units cryo-precipitate	1 g I/V 2 g stat. 1 g 6-hourly	1	8 units cryo-precipitate 8 days later, clot removed, bleeding—20 units cryo-precipitate
P. R.	2	M	Haemophilia	1	15	1%	—	—	1	0·5 g AMCA 6-hourly
N. P.	15	M	Haemophilia	1	13	5%	—	0·5 g AMCA I/V Tabs 0·5 g 6-hourly	3	1·0 g 6-hourly
J. T.	29	F	Haemophilia	1	2	9%	10 units cryo-precipitate	2 g 6-hourly	—	No bleeding. Tablets prod. 1 g 6-hourly.
G. D.	4	M	Haemophilia	3	3	15%	Nil	0·5 g 6-hourly 24 hours	—	0·5 g AMCA/3 bags of cryo-precipitate plus I/V AMCA
R. G.	3	M	Haemophilia	3	2	15%	—	—	(Surgical)	—
A. N.	18	M	Christmas Disease	6	3	15%	4 units FFP	1 g 6-hourly	(Surgical)	1 g AMCA 6-hourly

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TABLE 12.

Patient	Age at operation	Sex	Diagnosis	No. of teeth extracted	Days in hospital	Factor VIII or IX assay	Cryo-precipitate or FFP pre-operative	Pre-operative AMCA	Days bleeding	Post-operative AMCA
J. B.	26	F	Von Willebrand's Disease	3	5	18%	5 units FFP	1·5 g AMCA I/V	—	1·5 g AMCA 6-hourly
P. C.	11	M	Christmas Disease	2	4	20%	—	1 g 6-hourly 1 g AMCA I/V	—	1 g 6-hourly
T. R.	16	M	Haemophilia	4	4	20%	Nil	1 g 6-hourly 1 g I/V with anaesthetic	(Surgical to each socket)	0·5 g AMCA 6-hourly 7 days
M. V.	19	M	Haemophilia	3	10	24%	—	0·5 g AMCA 6-hourly	2	1 g AMCA 6-hourly 1 unit FFP after blood post-operation
M. H.	12	F	Von Willebrand's Disease	4	6	29%	—	2 g stat. 1 g 6-hourly	(Surgical)	0·5 g AMCA 6-hourly
M. H.	36	F	Von Willebrand's Disease	15	4	37%	—	2 g AMCA 6-hourly 0·5 g AMCA I/V	(Surgical)	1 g AMCA 6-hourly 7 days Allergic to ZACA

P.11

TABLE 13

Patient	Age at operation	Sex	Diagnosis	No. of teeth extracted	Days in hospital	Factor VIII or IX assay	Cryo-precipitate or FFP pre-operative	Pre-operative AMCA	Days bleeding	Post-operative
R. O.	7	M	Haemophilia	7	17	15%	1 unit FFP	—	6	4 units FFP
N. K.	4	M	Haemophilia	5	18	15%	—	—	6	2 units FFP
T. R.	9	M	Haemophilia	3	16	20%	1 unit Plasma	—	3	1 unit Plasma
A. F.	9	M	Haemophilia	1	11	14%	1 unit FFP	—	4	4 units FFP
B. G.	16	M	Von Willebrand's Disease	1	10	20%	—	—	3	—

4. BJÖRLIN and NILSSON I.M. (General Hospital, Malmo, Sweden) treated 7 patients with hemophilia A, 5 patients with hemophilia B and 5 patients with von Willebrand's disease (17 patients in all) with a combination of the respective coagulation factor concentrate and tranexamic acid in order to prevent bleeding after tooth extractions (Oral Surgery 36:482, 1973) The study was uncontrolled. The concentrates were given only once immediately before the extractions: factor VIII at dosages of 40-60 units/kg and factor IX at 50 units/kg of body weight. Cyklokapron was administered at about 25 mg/kg qid for an average of 7 days following the extractions. The first dose was administered IV together with the concentrate but all the other dosages were given orally.

The severity of the disease in the various groups is shown in Tables 14, 15, and 16. Altogether 37 permanent teeth and 8 deciduous teeth were extracted. Other surgical procedures were root resection with evacuation of a granuloma, removal of an impacted lower right molar, and incision of an abscess (Table 17). Surgicel was applied to all sockets.

Results: No bleeding complications were observed in 15 of the 17 patients. Bleeding was observed in one patient with severe hemophilia B from whom 11 teeth had been extracted in one session and in another patient with severe hemophilia A from whom 5 teeth had been extracted in 2 sessions (both had blood levels of the respective factor <0.5%). For these patients it became necessary to give additional infusions of factor VIII or f. IX concentrate to secure hemostasis.

Side Effects due to AMCA were very few: transient dizziness after the IV administration and GI disturbances after the oral administration. None, however, was serious enough to necessitate withdrawal of the drug. Only the dose was reduced in some patients.

Evaluation. This study was uncontrolled. However, the levels of the deficient factor in many of the patients were very low (5 of the patients with hemophilia A had factor VIII levels at ≤0.5% and the other 2 had levels at 2% and 3%. The patients with hemophilia B had factor IX levels of ≤0.5% (2 pts), 1% (1 pt) and the other 4 patients between 4-7%). Historic evidence and the results of the previously reviewed studies have shown that such patients need infusions of the respective factor concentrates for several days to avoid hemorrhage after tooth extractions. The results of the Björlin-Nilsson study (that AMCA together with local application of surgicel can be quite effective as adjunctive therapy to prevent hemorrhage after tooth extractions even in patients with severe hemophilia) have been confirmed by the studies of Ramström and Blombäck and Pell.

TAVENNER (University of Birmingham Dental School, Birmingham, England) treated 19 patients with hemophilia A, 9 patients with hemophilia B, and 1 patient with VW disease with tranexamic acid starting 1/2 an hour before the tooth extractions at 1.5 g t.i.d. till the patients were discharged from the hospital. The submission contains only the first page of the publication

Table 14 Hemophilia A

Patient	Age (yr.)	Weight (Kg.)	Type of Hemophilia A	Factor VIII (units given)
A. P.	49	70	Mild	1,000
R. R.	37	70	Severe	2,000
L. G. G.	5	22	Severe	2,400
A. P.	27	75 After 6 days	Severe	3,000, after 6 days 600 = 3,600
K. K.	7	20	Moderate	1,500
L. L.	43	68	Severe	3,500
B. C.	24	61	Severe	3,000

Mean: 3,886

Table 15 Hemophilia B

Patient	Age (yr.)	Weight (Kg.)	Type of hemophilia B	Factor IX (units given)
S. P.	14	30	Severe	1,500
G. G.	28	55	Severe	4,000
	23	60	Severe	3,000
M. A.		After 4 days		3,000
E. L.	54	85	Severe	3,000
		After 4 days		3,000
C. S.	7	27	Severe	2,000

Mean: 3,900

Table 16. Von Willebrand's disease

Patient	Age (yr.)	Weight (Kg.)	Type of von Willebrand's disease	Factor VIII (units given)
M. V.	28	50	Mild	1,200
A. P.	14	32	Severe	1,200
J. O.	22	64	Mild	200
J. K.	4	20	Severe	600
A. P.	23	50	Severe	2,700

Mean 1260

All Means: 3,576

TABLE 17 Björlin & Nilsson

Factor VIII activity Before (%)	Factor VIII activity After (%)	ΔMCA total (Gm.)	Dental treatment
7	—	151	Root resection 2 Extracted 16, 14, 26
< 0.5	72	81	Extracted 17, 14, 12, 27, 48
0.5	80	40	Extracted 64
0.5	60	81	Extracted 46, 48 (radix rel), 15
3	37	101	Extracted 36, 75 (radix rel)
2	70	40	Extracted 74
< 0.5	55	64	Extracted 28
< 0.5	62	64	Extracted 38

Factor IX activity Before (%)	Factor IX activity After (%)	ΔMCA total (Gm.)	Dental treatment
7	43	80	Extracted 45, 46
< 0.5	86	120	Extracted 12, 11, 21
0.5	81	210	Extracted 15, 17, 16, 15, 25, 26, 27, 36, 37, 46, 47
8	29	—	
1	62	120	Extracted 24, 26, 27
7	23	—	Extracted 18
4	62	40	Extracted 82, 81, 74

Factor VIII activity Before (%)	Factor VIII activity After (%)	ΔMCA total (Gm.)	Dental treatment
48	—	81	Incision of abscess. Extracted 44
20	87	81	Extracted 48
24	80	81	Removal of an impacted 48
—	—	40	Extracted 32
			Extracted 17, 18

(Brit. Med. J. 2, 314, 1972). From the sponsor's report, it appears that the study was uncontrolled. The results were compared historically with results obtained with EACA from other studies and was concluded that the results obtained with tranexamic acid were "slightly better than those obtained with EACA, the dose used was smaller, and side effects were few." Mild diarrhea was observed in 2 patients.

CREVELD et al (Hemophilia Clinic, Huizen Holland; Ned. T. Tandheelk 78:90, 1971; case report publication) described 10 cases of hemophilia A (9 patients) and 3 cases of hemophilia B who received AMCA, 0.5-1.5 g t.i.d. for 6 days after the extraction of 1-7 teeth. All patients had received cryoprecipitate or a prothrombin complex concentrate before the extractions. Twelve of the patients had severe deficiencies, factor VIII or IX levels were <1%. The investigators concluded that in 8 of the patients AMCA had good to very good results in that it significantly reduced or completely eliminated the postoperative need for cryoprecipitate or prothrombin complex concentrate. In two patients AMCA had no effect, while for 2 other patinets with mild and moderate deficiencies the results were doubltful. On 8 occasions no postoperative infusions were needed.

C. USE OF TRANEXAMIC ACID IN HEREDITARY ANGIONEUROTIC EDEMA (HANE)

Hereditary angioneurotic edema is characterized by recurrent, circumscribed, transient and non-itching edema of the skin and edema of the mucosa of the gastrointestinal and upper respiratory tracts. Involvement of bowel mucous membranes leads to acute attacks of abdominal pain with associated vomiting and occasionally diarrhea. When the edema affects the upper respiratory tract there is a great risk of death by asphyxiation.

Hereditary angioneurotic edema is an autosomal dominant disease. The onset of symptoms commonly occurs in infancy or childhood. Acute attacks usually last from one to about four days and may be separated by periods of remission ranging from days to years. Prodromal symptoms are sometimes reported and vary from patient to patient and from site to site. Triggering factors are not clearly understood. Edema of allergic origin has to be distinguished from this entity.

Hereditary angioneurotic edema has been shown to be due to an inherited deficiency of the functional plasma inhibitor of the activated first component (C1) of the complement system. The episodic swellings are secondary to a deficiency of this C1-esterase inhibitor. C1 is normally found in the serum in an inactive state but under certain conditions becomes activated and then triggers the complement cascade. C1-esterase inhibitor closely regulates the initial reaction of the cascade. A deficiency of this enzyme may thus lead to an uncontrolled activation of ——————→

CHEM

REV

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
REVIEW AND EVALUATION OF MANUFACTURING CONTROLS DATA

Chemist Review #4

Date Completed: December 8, 1986

A. 1. NDA #: 19-280, 19-281

Applicant: Kabi Vitrum Inc.
Address: 1311 Harbor Bay Parkway
Alameda, CA 94501
Tel (415) 769-4650

AF#: Not loacater on microfiche in Records (will check computer when up.)

2. Product Name(s):

Proprietary: Cyklokapron Tablets

Nonproprietary: Tranexamic acid

USAN: Tranexamic Acid

Compendium: None

Code Name and/or Number: Trans AMCA is the code name for tranexamic acid (USAN).

3. Dosage form(s) and Route(s) of Administration:

Oral tablets, 500mg

4. Pharmacological Catgory and/or Principal Indication:

To be used as an antifibrinolytic agent. the mechanism is considered to be an inhibition of the plasminogen activation.

5. Structural Formula and Chemical Name: Refer to Chemist's Review #1 for NDA 19-280.

B. 1. Initial Submission: 5/7/84

Receipt (BD) May 9, 1984
Receipt: Center, May 23, 1984
Assigned: 5/25/85

2. Amendments:

C. Remarks:

The two NDAs 19-280 and 19-281 have been dealt with together in terms of the validation of the analytical methods owing to their similarity of principle and practice. Questions that are currently outstanding are noted to apply to both.
Issues is possible at thi

D. Conclusions:

This application continues to be approvable from the standpoint of chemistry and manufacturing control matters.

Stuart Zimmerman 12/19/86
Stuart Zimmerman, Ph.D.

cc:
ORIG for NDA 19-280
HFN-110
HFN-110/CSO
HFN-110/SZimmerman/12/12/86; 12/17/86
cb/12/12/86/1112v
R/D init: RWolters/12/9/86

12-19-86

cc:
ORIG for NDA 19-281
HFN-110
HFN-110/CSO
HFN-110/S Zimmerman/12/12/86; 12/17/86