

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-430

PHARMACOLOGY REVIEW(S)

MEMO

FOOD AND DRUG ADMINISTRATION

**Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research**

Date: October 27, 2009

From: Kimberly Hatfield, Ph.D.
Toxicologist

To: NDA 22-430

Subject: Changes to labeling for NDA 22-430

Nonclinical recommendations for labeling were made for NDA 22-430 in my review submitted to the NDA and signed on 6-22-2009. Subsequent changes that were made during label negotiation to Sections 8.1, 8.2, 8.3, 13.1 and 13.2 are all appropriate, and I concur with the final label submitted to the Sponsor on 10-26-2009.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY P HATFIELD
10/27/2009

LYNNDA L REID
10/27/2009
I concur with final labeling submitted on 10/26/09.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22-430
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 01/30/09
PRODUCT: **Lysteda (tranexamic acid modified-release tablets)**
INTENDED CLINICAL POPULATION: **Women with heavy menstrual bleeding (menorrhagia)**
SPONSOR: **Xanodyne Pharmaceuticals, Inc.**
DOCUMENTS REVIEWED: **Module 4: Nonclinical study reports and literature**
REVIEW DIVISION: **Division of Reproductive and Urologic Drug Products
(HFD-580)**
PHARM/TOX REVIEWER: **Kimberly Hatfield, Ph.D.**
PHARM/TOX SUPERVISOR: **Lynnda Reid, Ph.D.**
DIVISION DIRECTOR: **Scott Monroe, M.D.**
PROJECT MANAGER: **Nenita Crisostomo**

Date of review submission to Division File System (DFS): June 22, 2009

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

Nonclinical data support approval of tranexamic acid (Lysteda), 1.3g (2 x 650mg tablets) three times daily, for treatment of heavy menstrual bleeding.

B. Recommendation for nonclinical studies

No additional nonclinical studies are required.

C. Recommendations on labeling

The Sponsor's submitted labeling for Sections 8.1, 8.3, 13.1 and 13.2 are acceptable with minor changes. The recommended labeling is shown below. Annotated labeling can be found on page 48 of the review.

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b(4)

1 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 ✓ § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

b(4)

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Pharmacology. Tranexamic acid is an antifibrinolytic agent and has been investigated to treat heavy menstrual bleeding, which is a hyperfibrinolytic condition. The antifibrinolytic action of tranexamic acid was demonstrated through nonclinical literature studies which showed that tranexamic acid caused hemostatic effects in vivo and in vitro in rats, and inhibited fibrinolysis in rabbits, but did not alter hemostasis.

Pharmacokinetics / Toxicokinetics. In the dog, C_{max} and AUC increase with dose, but less proportionally at higher doses. The same is true for plasma concentrations in the rat. The 600 mg/kg/d dose in dogs (middle dose examined) was found to have an AUC only 5 times higher than that in humans following the proposed clinical dose of 3.9 g/d. Tranexamic acid has two known metabolites, but >95% of the dose is excreted in the urine (primary mechanism of elimination) as unchanged drug product. Fetal plasma concentrations were also detected at each dose of tranexamic acid used in the reproductive toxicity study, indicating in utero exposure of drug during maternal dosing. The label for the reference drug, Cyklokapron, indicates that tranexamic acid crosses the placenta, with concentrations in cord blood equivalent to that in maternal blood. Tranexamic acid has also been detected in breast milk at concentrations one hundredth of the serum peak concentration, and detected in semen, though it only affects fibrinolytic activity and not migration.

General Toxicology. The Sponsor is relying on previous findings of safety for the drug Cyklokapron, but also conducted a chronic 39-week toxicity study in male and female dogs. Treatment-related transient ocular toxicity was observed mainly at doses 6 times the recommended human dose of 3.9 g/day based on AUC (highest dose tested of 1200 mg/kg/d). Observations included reddening and discharge in the eyes, changes in the nictitating membrane/conjunctiva, altered reflectivity in the fundus of the eye, conjunctival inflammation, and inflammatory exudate in the eye. In previous studies with tranexamic acid and Cyklokapron, dose- and time-related ophthalmological changes have been observed in the rat, cat, and dog at doses 6-40 times the recommended human dose based on mg/m² (250-1600mg/kg/d) at durations of 6 days to 1 year, with an incidence of 25-100% of animals treated. Ocular changes that were noted in the tapetum of the eye in dogs are not clinically relevant, as humans do not have a tapetum. However, other noted ocular changes in the dog could be a potential risk in human populations. The NOAEL determined in the chronic toxicity study in the dog was primarily based on ocular toxicity, and was only 5 times the proposed clinical dose, based on AUC. While this is a

low margin of exposure, there was low systemic toxicity at all doses, and ocular changes are a known possible adverse event that will be addressed in labeling.

Genotoxicity. A literature study was submitted that concluded that tranexamic acid is negative for genotoxicity based on the rec-assay on *Bacillus subtilis*, the Ames test, in vitro and in vivo chromosomal aberration assays, and the dominant lethal test.

Carcinogenicity. The current labeling for Cyklokapron indicates an increased incidence of leukemia in male mice that is likely related to tranexamic acid treatment, as well as hyperplasia of the biliary tract and cholangioma and adenocarcinoma of the intrahepatic biliary system in rats at doses exceeding the MTD. Hyperplastic, but not neoplastic changes were noted at lower doses, while the use of a different strain of rat did not show similar hyperplastic/neoplastic changes in the liver as noted above. Carcinogenicity in the rat could be strain specific, and limited to exceedingly high doses.

Reproductive Toxicity. The embryofetal and pre/postnatal development studies show no dose-related toxicity of tranexamic acid in the rat in regards to maternal and fetal health.

Special Toxicity. Published articles submitted by the Sponsor primarily investigate ocular toxicity in dogs, mice and rabbits. These studies implicate that ocular toxicities (exudate and conjunctivitis) are the result of exaggerated pharmacology of tranexamic acid due to its antifibrinolytic mechanism of action. As mentioned above, nonclinical findings of ocular toxicity are noted in the Cyklokapron label, specifically in regards to focal areas of retinal degeneration, and general retinal changes that were all dose-related.

B. Pharmacologic activity

Tranexamic acid is a synthetic lysine derivative and an antifibrinolytic agent that is able to form a reversible complex with plasminogen. Through binding to plasminogen, tranexamic acid prevents the binding of plasminogen to the surface of fibrin, thus retarding fibrinolysis. Under certain conditions such as hemophilia, where there is defective formation or rapid dissolution of fibrin, excessive or recurrent bleeding can occur in patients. As such, antifibrinolytic agents are administered in order to control the excessive bleeding that could occur.

Heavy menstrual bleeding is a hyperfibrinolytic condition, characterized as cyclic, normal intervals of menstruation with excessive volume, and is mechanistically associated with increased fibrinolytic activity in the endometrium, increased production of prostaglandins, and higher concentrations of plasminogen activators in the uterus and menstrual fluid. It has been reported that 10% of gynecological patients report heavy menstrual bleeding to their doctors in a given year (3 million women in the U.S. population).

C. Nonclinical safety issues relevant to clinical use

The following items are safety concerns identified both in nonclinical studies submitted with this application, and from the literature:

- Ocular toxicity (reddening, discharge, changes in the nictitating membrane/conjunctiva, inflammatory exudate were present in dogs at doses 6 times the proposed clinical dose based on AUC)
 - This is a relevant clinical concern. An instance of reversible conjunctivitis was noted in literature in a patient treated with tranexamic acid. After treatment with Cyklokapron, visual abnormalities represent the most frequently reported postmarketing adverse reaction in Swedish patients. Previous labeling recommends ophthalmological examinations in patients treated continually for more than several days.
- Tranexamic acid crosses the placenta, and is present in cord blood at equal concentrations to maternal plasma
 - This is of low concern. There is potential that a woman could use Lysteda in anticipation of a heavy menstrual bleed if she does not know she is pregnant and has breakthrough bleeding during her first cycle. However, reproductive studies have not revealed any adverse effects of treatment with tranexamic acid during pregnancy.
- Central nervous system effects
 - This is of low concern. Literature studies have indicated that tranexamic acid treatment in rats causes hyperexcitability and convulsion through the blocking of GABA-driven inhibition of the CNS. This is at a dose 0.002 times the proposed clinical dose based on mg/m². Clinical doses have only shown adverse nervous system effects of headache, dizziness, and migraine.
- Cardiovascular events
 - Tranexamic acid is contraindicated in patients with active thromboembolic disease, likely based on the mechanism of action. There is no known nonclinical data to support this safety issue.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-430

Review number: 1

Sequence number/date/type of submission: 000 / January 30, 2009 / original

Information to sponsor: Yes () No (X)

Sponsor and/or agent: Xandoyne Pharmaceuticals, Inc.

One Riverfront Place, Newport, KY 41071-4563

Manufacturer for drug substance: 

b(4)

Reviewer name: Kimberly Hatfield, Ph.D.

Division name: Division of Reproductive and Urologic Products

HFD #: 580

Review completion date: June 18, 2009

Drug:

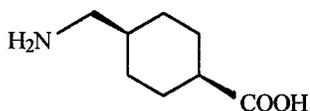
Trade name: Lysteda (tranexamic acid)

Chemical name: trans-4-(aminomethyl)cyclohexanecarboxylic acid

CAS registry number: 1197-18-8

Molecular formula/molecular weight: C₈H₁₅NO₂, 157.21 g/mol

Structure:



Relevant INDs/NDAs/DMFs: IND 68,096: tranexamic acid

NDA 19-280: Cyklokapron (500 mg tablets)

NDA 19-281: Cyklokapron (100 mg/ml injectable)

Drug class: antifibrinolytic

Intended clinical population: women with menorrhagia (heavy menstrual bleeding)

Clinical formulation: 650mg tranexamic acid modified-release tablets

Component	Code #	Reference	Pharmaceutical Function	Quantity Per Tablet
Tranexamic Acid			Active	650.00 mg
Microcrystalline Cellulose NF		NF		
Colloidal Silicon Dioxide		NF		
Pregelatinized Corn Starch		NF		
Povidone		USP		
Hyperomellose		USP		
Stearic Acid		NF		
Magnesium Stearate		NF		
Total				

b(4)

b(4)

***taken from current NDA submission Module 2.3.P*

The Sponsor has developed a 'modified-release tablet' that was designed and formulated to minimize the dose-limiting gastrointestinal adverse effects associated with immediate-release tablet formulations. However, there is discussion at this time between the Agency and the Sponsor on whether the product can be labeled as 'modified-release'. As such, the final release characteristics of the tablet are still to be determined by CMC.

The Sponsor notes that the impurity profile of tranexamic acid identified 4 process impurities, with total impurities in the active material present at not more than _____ of the active pharmaceutical ingredient. The expected daily exposure from the 3900 mg/d dose of tranexamic acid would result in impurity exposure at _____. While this appeared to be a high level, the CMC reviewer determined that the impurity profile was acceptable. The drug substance meets the requirements of EP and JP monographs, and total impurities ranged from _____, over 6 lots of material (as listed in the certificates of analysis). b(4)

b(4)

Route of administration: oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of 22-430 are owned by Xanodyne Pharmaceuticals or are data for which Xanodyne Pharmaceuticals has obtained a written right of reference. Any information or data necessary for approval of 22-430 that Xanodyne Pharmaceuticals does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Xanodyne Pharmaceuticals does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of 22-430.

Background: Lysteda (tranexamic acid) is indicated for the treatment of heavy menstrual bleeding (menorrhagia) and the amelioration of symptoms associated with heavy menstrual

bleeding, including limitations on social, leisure, and physical activities. The recommended dose is two 650 mg tablets taken 3 times daily (3.9 g/day) during menstruation. Patients are advised to start the treatment regimen once their period has started, and not to take Lysteda when they do not have their period. During Phase 3 development, the average duration of exposure was 3 days per menstrual cycle.

Tranexamic acid is a synthetic lysine derivative and antifibrinolytic agent that inhibits the breakdown of fibrin clots. In its currently marketed form in the U.S., Canada and Europe, tranexamic acid is an immediate release formulation. The two goals identified by the Sponsors in their development program were: 1) to develop a modified-release formulation of tranexamic acid that would be a safe, efficacious, fast-acting, non-hormonal treatment for heavy menstrual bleeding that is administered only during menstruation, does not interfere with fertility and addresses the excessive fibrinolysis implicated in many causes of menorrhagia; and 2) to develop a modified-release formulation with improved tolerability over the current immediate-release formulations that cause a high level of gastrointestinal side effects.

In the U.S., tranexamic acid is an approved drug product labeled as Cyklokapron®, and is indicated as an intravenous injection in patients with hemophilia for short-term use (2-8 days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction. At one time, it was also approved for short-term use by oral administration for the same indication, however the oral formulation was discontinued, but not for reasons of safety. The approved i.v. dose is 10 mg/kg body weight 3-4 times daily for 2-8 days, and the previously approved (discontinued) oral dose was 25 mg/kg body weight 3-4 times daily up to 6000 mg/day for 2-8 days. According to the Sponsor, tranexamic acid is approved for use in Europe and Canada for the treatment of menorrhagia, the treatment and prophylaxis of hemorrhage associated with excessive fibrinolysis, and the prophylaxis of hereditary angioedema. The approved dosage is between 1000 mg twice daily (2000 mg/day) and 1500 mg four times daily (6000 mg/day) (Martindale, 2008).

The current Sponsor is submitting NDA 22-430 as a **505(b)(2) application, relying on FDA's** previous finding of safety for Cyklokapron as reflected in the approved labeling. The most current labeling for Cyklokapron was approved on December 22, 2008. For the nonclinical portion of this NDA, the Sponsor will also be relying on literature studies published since 1963, and three of their own conducted nonclinical studies.

Studies reviewed within this submission:

TUS0001	39 week oral dog toxicity study	Module 4.2.3.2.1
TUS0002	Embryo-fetal rat development study	Module 4.2.3.5.2.1
TUS0003	Pre and post-natal rat development study	Module 4.2.3.5.3.1

Relevant peer-reviewed literature submitted for support as per 505(b)(2)

Studies not reviewed within this submission:r
l3
b(4)**2.6.2 PHARMACOLOGY****2.6.2.1 Brief summary**

The Sponsor is relying on published literature on tranexamic acid and previous findings of safety for Cyklokapron to support the pharmacology of their product.

Tranexamic acid is a synthetic lysine derivative and antifibrinolytic agent that acts by reversibly binding to plasminogen to prevent the binding of fibrin, which would lead to fibrinolysis. Since heavy menstrual bleeding is a hyperfibrinolytic condition in the endometrium, an antifibrinolytic agent like tranexamic acid may offer a treatment.

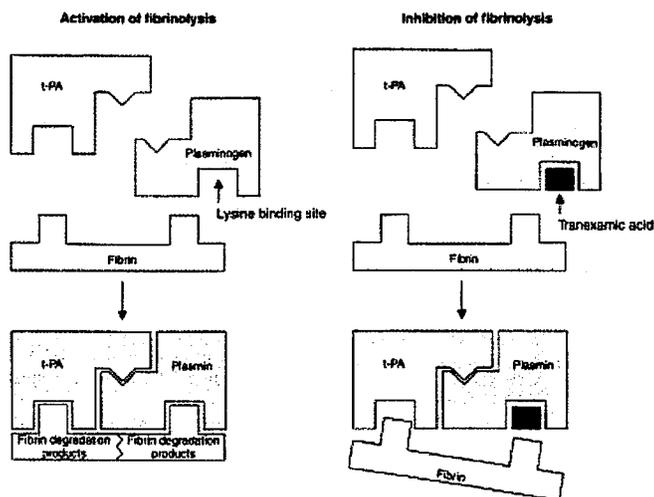
In the central nervous system, tranexamic acid may cause hyperexcitability and convulsion by blocking GABA-driven inhibition of the CNS. In the Cyklokapron label, tranexamic acid is contraindicated in patients with subarachnoid hemorrhage, active intravascular clotting, and acquired defective color vision. In the warnings section, the potential ocular toxicity of Cyklokapron is noted based on nonclinical studies of retinal changes and degeneration. Cardiovascular events, the potential for ureteral obstruction and recommendation for alternate doses in patients with renal insufficiency are noted under precautions. Finally, gastrointestinal disturbances are noted as potential adverse events with Cyklokapron administration.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Under certain conditions such as hemophilia, where there is defective formation or rapid dissolution of fibrin, excessive or recurrent bleeding can occur in patients. Normally, a highly coordinated blood coagulation cascade is activated in an injured vessel that ultimately results in the formation of covalent bonds between fibrin molecules, forming an initial clot to inhibit blood loss. The fibrinolytic system is activated by the deposition of fibrin during wound repair, and establishes a balance between the formation and lysis of fibrin to maintain a hemostatic seal while the injured vessel wall is repaired. Fibrinolysis is mediated by the activation of plasminogen, the plasma precursor of the proteolytic enzyme plasmin, and through the coordinated efforts of tissue plasminogen activator, plasminogen activator inhibitors, and antiplasmin, excessive fibrinolysis is inhibited. In hemophilia patients, the balance of fibrin formation and dissolution is defective. As such, antifibrinolytic agents are administered in order to control the excessive bleeding that could occur.

Tranexamic acid is a synthetic lysine derivative and an antifibrinolytic agent that is able to form a reversible complex with plasminogen. Through binding to plasminogen, tranexamic acid blocks the interaction of plasminogen and the heavy chain of plasmin with lysine residues of fibrin, preventing the binding of plasminogen to the surface of fibrin, thus

retarding fibrinolysis. Plasmin is still formed from plasminogen, but is unable to bind to fibrinogen or fibrin monomer (background and figure taken from Dunn and Goa, 1999).



Heavy menstrual bleeding is a hyperfibrinolytic condition and is characterized as cyclic, normal intervals of menstruation with excessive volume (>80mL menstrual blood loss per cycle) (Gleeson et al., 1994). Mechanistically, heavy menstrual bleeding is associated with increased fibrinolytic activity in the endometrium, and higher concentrations of plasminogen activators are found in the uterus and menstrual fluid in women with heavy menstrual bleeding than their normal cyclic blood loss counterparts (Albrechtsen, 1956; Lethaby et al., 2002). While for most women the cause is unknown, the CDC reports that 10% of gynecological patients report heavy menstrual bleeding to their doctors in a given year, which equates to about 3 million women in the U.S. population (Dilley, 2003).

Three literature studies were provided by the Sponsor to demonstrate the antifibrinolytic action of tranexamic acid. The first (Sperzel and Huetter, 2007) evaluated the hemostatic effects of tranexamic acid in in vivo and in vitro models. Tranexamic acid was shown to inhibit tissue plasminogen activator-induced fibrinolysis in vitro ($IC_{50}=24.1 \mu\text{M}$), reduce rat tail bleeding time in vivo (3 mg/kg bolus plus mg/kg/h infusion), and dose-dependently increase thrombus formation and weight (100 mg/kg/h infusion), but had no effect on coagulation time at concentrations up to 3 mM. The second study by Bergqvist and Arfors (1974) showed that in rabbits, fibrinolysis was inhibited with tranexamic acid, but initial hemostasis was not altered, nor was the normal rebleeding pattern altered. Tranexamic acid also did not affect platelet function or clot formation and stability. Finally, the third study by Hoylaerts et al. (1981) showed that tranexamic acid caused a dose-dependent retardation of fibrinolysis. Examination of the binding of plasminogen to fibrin clots showed that tranexamic acid displaced plasminogen from the fibrin surface (50% displacement at $1.3 \mu\text{M}$ for Glu-plasminogen and $5 \mu\text{M}$ for Lys-plasminogen). Tranexamic acid did not modify the fibrinolytic activity of plasmin, and at concentrations of 0-10 μM , tranexamic acid had no influence on the activation of plasminogen by tissue plasminogen activators in the absence of fibrin. Therefore, the inhibitory action of tranexamic acid in the presence of fibrin is due to

dissociation of plasminogen from the fibrin surface by saturating the high affinity lysine binding sites of plasminogen.

2.6.2.3 Secondary pharmacodynamics

Effects on cancer: Pharmacological studies have examined the effects of tranexamic acid on cancer, since fibrinolysis is involved in the growth and spread of neoplasms, and an antifibrinolytic agent such as tranexamic acid could be an effective cancer agent. Studies examining the anticancer properties of tranexamic acid have primarily been in animal models of cancer. The following summarizes results that have been observed with tranexamic acid treatment:

- Prolonged survival of mice inoculated with Lewis lung adenocarcinoma cells (HED=2400 mg/d; drinking water) (Astedt and Tropé, 1980)
- Reduced mean tumor weight in mice inoculated with C3H breast carcinoma cells (HED=480 mg/d; drinking water) (Astedt and Tropé, 1980)
- Reduced ascitis fluid recovered from rats inoculated with AH130 rat hepatoma cells (HED=4800 mg/d; oral or i.p.) (Astedt and Tropé, 1980)
- No effects on DNA synthesis in Lewis lung adenocarcinoma cells, C3H breast carcinoma cells, or AH130 rat hepatoma cells in vitro (Astedt and Tropé, 1980)
- No effect on growth of tumor cell lines QG-56, OC-1 and PC-12, but inhibited the growth of these tumor cells in nude mice (HED≈17,300 mg/d; diet) (Ogawa et al., 1982)
- Minimal effects on ovarian cancer cell growth in vitro (IC50 between 5500 and 11,000 µg/mL) (Kikuchi et al., 1986, 1987)
- No effect on tumor growth, but an increase in the efficacy of radiation treatment on tumor growth in rats injected with lung carcinoma cells or prostate tumor cells (HED=28,800 mg/d; s.c.) (Kal et al., 2004)
- Reduced tumor weight by ~50% after 7-8 days treatment in rats with implanted sarcomas. Decreased angiogenesis in rats was also observed in this study (HED=19,200 mg/d; s.c.) (Sundbeck et al., 1981)
- Decreased the number of lung metastatic foci in mice inoculated with Lewis lung carcinoma cells in their footpads (HED=28,800 mg/d; diet) (Tanaka et al., 1981, 1982).
 - The authors conclude that the inhibition of fibrinolysis may decrease the potential for distant metastases.
- Decreased blood flow around sarcoma tumors implanted in rats after 10 days treatment, but not 3 days (HED=19,200 mg/d s.c.) (Sundbeck et al., 1981)

As a result, the literature suggests that tranexamic acid may have anticancer properties, anti-angiogenic properties and the potential to inhibit cancer cell metastasis at doses in animals (480-28,800 mg/d) that are in the range of the proposed clinical dose in this NDA (3900 mg/d).

2.6.2.4 Safety pharmacology

Neurological effects:

Effects on the central nervous system

Tranexamic acid may cause hyperexcitability and convulsion by blocking GABA-driven inhibition of CNS (Furtmüller et al., 2002). In vitro, tranexamic acid was found to bind the GABA binding site of GABA_A receptors in membranes from rat cerebral cortex, but in patch clamp studies with human embryonic kidney cells transfected with recombinant GABA_A receptors, tranexamic acid dose dependently blocked GABA-induced chloride ion flux instead of activating the receptors directly. Furthermore, direct application of tranexamic acid (0.8 mg/kg; 0.002 times the recommended clinical dose based on mg/m²) to the lumbar spinal cord of rats caused hyperexcitability that was blocked by cotreatment with a GABA_A receptor agonist. In a separate study, i.v. administration (~40 mg/kg; 0.2 times the recommended clinical dose based on mg/m²) and intracisternal administration (1-5 mg/kg; up to 0.03 times the recommended clinical dose based on mg/m²) of tranexamic acid caused epileptic seizures in cats (Yamaura et al., 1980). Intracisternal dosing caused the seizures much more rapidly than by i.v. dosing.

Information from the Cyklokapron label

In the contraindications section of the reference label, Cyklokapron is contraindicated

- **“in patients with subarachnoid hemorrhage.** Anecdotal experience indicates that cerebral edema and cerebral infarction may be caused by Cyklokapron in such patients.”

Cardiovascular effects:

In the contraindications section of the reference label, Cyklokapron is contraindicated

- **“in patients with active intravascular clotting.”**

In the precautions section of the reference label, it is noted that

- **“Venous and arterial thrombosis or thromboembolism has been reported in patients treated with Cyklokapron. In addition, cases of central retinal artery and central retinal vein obstruction have been reported.”**
- **“Patients with a previous history of thromboembolic disease may be at increased risk for venous or arterial thrombosis.”**
- **“Cyklokapron should not be administered concomitantly with Factor IX Complex concentrates or Anti-inhibitor Coagulant concentrates, as the risk of thrombosis may be increased.”**
- **“Patients with disseminated intravascular coagulation (DIC), who require treatment with Cyklokapron, must be under strict supervision of a physician experienced in treating this disorder.”**

Renal effects:

In the precautions section of the reference label, it is noted that

- **“The dose of Cyklokapron injection should be reduced in patients with renal insufficiency because of the risk of accumulation.”**
- **“Ureteral obstruction due to clot formation in patients with upper urinary tract bleeding has been reported in patients treated with Cyklokapron.”**

In the geriatric use section of the reference label, it is noted that

- **“This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.”**

Alternate doses for patients with moderate to severe impaired renal function are included in the reference label for Cyklokapron.

Gastrointestinal effects:

In the adverse reactions section of the reference label, it is noted that

- **“Gastrointestinal disturbances (nausea, vomiting, diarrhea) may occur but disappear when the dosage is reduced.”**

Other:

Ophthalmology

In the contraindications section of the reference label, Cyklokapron is contraindicated

- **“in patients with acquired defective color vision, since this prohibits measuring one endpoint that should be followed as a measure of toxicity (see Warnings).”**

In the warnings section of the reference label, the following nonclinical toxicity is noted:

- **“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.”**

Due to these previous findings of ocular toxicity in animals, the current 39-week oral toxicity study in the dog, conducted by the Sponsor, investigated ocular health in dogs, and included one arm of the study using atapetal dogs. Treatment-related transient ocular toxicity was observed mainly at a high dose of 600 mg/kg/bid (6 times the recommended human dose based on AUC), with observations including reddening and discharge in the eyes, changes in the nictitating membrane/conjunctiva, altered reflectivity in the fundus of the eye, conjunctival inflammation, and inflammatory exudate in the eye. The complete study report can be found in Section 2.6.6.3.

2.6.2.5 Pharmacodynamic drug interactions

In the dosage and administration section of the reference label, it is noted that Cyklokapron

- “is a synthetic amino acid, and should not be mixed with solutions containing penicillin.”

2.6.3 PHARMACOLOGY TABULATED SUMMARY

No tabulated summaries were available in the NDA submission.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

In the dog, C_{max} and AUC increase with dose, but less proportionally at higher doses. The same is true for plasma concentrations in the rat. The 600 mg/kg/d dose in dogs (middle dose examined and the NOAEL) was found to have an AUC only 5 times higher than that in humans following the proposed clinical dose of 3.9 g/d. Tranexamic acid has two known metabolites, but >95% of the dose is excreted in the urine (primary mechanism of elimination) as unchanged drug product. Fetal plasma concentrations of tranexamic acid were also detected at each dose used in the reproductive toxicity study, indicating in utero exposure of drug during maternal dosing. The Cyklokapron label indicates that tranexamic acid crosses the placenta, with concentrations in cord blood equivalent to that in maternal blood. Tranexamic acid has also been detected in breast milk at concentrations one hundredth of the serum peak concentration, and detected in semen, though it only affects fibrinolytic activity and not migration.

2.6.4.2 Methods of Analysis

[see under individual study reviews]

2.6.4.3 Absorption

In clinical study XP12B-101 in healthy adult females, a 1.0 g i.v. dose of tranexamic acid resulted in a 3 phase monoexponential decay. This 3 phase decay was also observed in a literature study with 3 healthy volunteers administered the same dose, with most elimination occurring in the first 8 hours, and an elimination half-life of 2 hrs (Pilbrant et al., 1981). This is also confirmed in the current Cyklokapron labeling. While Pilbrant noted that absorption of the immediate-release tablet was not affected by food, studies with the modified-release tablet by the Sponsor concluded that after a single 1.3 g oral dose of modified-release formulation, the C_{max} and AUC are increased by 7% and 15% after food intake compared to fasting. They concluded that the modified-release formulation can be taken with food. Comparison of an immediate release tablet dose (Cyklokapron) to the proposed modified-release tablet in this NDA showed that the AUC and C_{max} ratios were 115% and 107% respectively, and that male subjects receiving the immediate-release tablets had slightly greater C_{max} values than the single dose C_{max} values in females administered the modified-release tablet. The oral bioavailability of tranexamic acid, as determined in clinical study XP12B-101 and calculated from serum concentration analyses after oral and i.v. administration, was 44.9% of the oral dose administered in healthy female volunteers. After a

single dose (1.3 g) of the modified-release tablet proposed in this NDA, the T_{max} was 3 hrs, with a C_{max} of 13.2 mg/L, an AUC of 74.6 µg*h/L and terminal t_{1/2} of 11 hrs. These values did not change significantly upon dosing 1.3 g tid for 5 days (T_{max}=2.6 hrs; C_{max}=15.8 mg/L; AUC=74.8 µg*h/L; t_{1/2}=na).

2.6.4.4 Distribution

The following information is found in the current label for Cyklokapron:

- **“After an intravenous dose of 1 g, the plasma concentration time curve shows triexponential decay with a half-life of about 2 hours for the terminal elimination phase. The initial volume of distribution is about 9 to 12 liters.”**
- **“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.”**
- **“Tranexamic acid passes through the placenta. The concentration in cord blood after an intravenous injection of 10 mg/kg to pregnant women is about 30 mg/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 3 hours.”**
- **“The concentration of tranexamic acid in a number of other tissues is lower than in blood. In breast milk the concentration is about one hundredth of the serum peak concentration. Tranexamic acid concentration in cerebrospinal fluid is about one tenth of that of the plasma. The drug passes into the aqueous humor, the concentration being about one tenth of the plasma concentration.”**
- **“Tranexamic acid has been detected in semen where it inhibits fibrinolytic activity but does not influence sperm migration.”**

Additional literature information indicates that tranexamic acid crosses the blood-brain barrier when administered to patients at 1000 mg i.v. six times per day for 8 days (~2 times the recommended daily clinical dose) (Tovi et al., 1972). Also, salivary concentrations of tranexamic acid could not be detected after single oral doses of tranexamic acid (1 g), though plasma concentrations reached their max at 7 µg/mL. After using a mouth rinse of a 5% aqueous solution of tranexamic acid, salivary concentrations of 200 µg/mL were observed 30 minutes post dose, but plasma concentrations were below 2 µg/mL (Sindet-Pedersen, 1987).

2.6.4.5 Metabolism

No information was available in the current Cyklokapron label regarding the metabolism of tranexamic acid. As referenced in Dollery (1999), little metabolism of tranexamic acid occurs as 30% of an i.v. administered dose in humans (10 mg/kg) is recovered in urine 1 hr post dose, followed by 45% during the first 3 hrs post dose, and 90% after 24 hrs post dose. Unchanged compound is primarily excreted in the urine, along with small amounts of an N-acetylated derivative (0.5%), and a deaminated dicarboxylic acid (1%).

2.6.4.6 Excretion

The following information is found in the current label for Cyklokapron:

- **“Urinary excretion is the main route of elimination via glomerular filtration. Overall renal clearance is equal to overall plasma clearance (110 to 116 mL/min) and more than 95% of the dose is excreted in the urine as the unchanged drug. Excretion of tranexamic acid is about 90% at 24 hours after intravenous administration of 10 mg/kg body weight.”**
- **“In breast milk the concentration is about one hundredth of the serum peak concentration”. This indicates some excretion into breast milk.”**

As referenced in Dollery (1999), the elimination half-life of tranexamic acid ranges from 80-120 min. In addition, when comparing the renal clearance of tranexamic acid with the glomerular filtration rate, it suggests that glomerular filtration without either tubular excretion or absorption occurs.

2.6.4.7 Pharmacokinetic drug interactions

The following information is found in the current label for Cyklokapron:

- **“Cyklokapron should not be administered concomitantly with Factor IX Complex concentrates or Anti-inhibitor Coagulant concentrates, as the risk of thrombosis may be increased.”**
- **“The drug [Cyklokapron] is a synthetic amino acid, and should NOT be mixed with solutions containing penicillin.”**

Since metabolism of tranexamic acid is minimal and glomerular filtration is not a saturable process for excretion, the Sponsor concluded that there would be low potential for other drugs to interfere with the metabolism of tranexamic acid, and that it was unlikely that any drug interaction would occur with other renally eliminated drugs. Per agreements with the Agency, no drug-drug interaction studies were performed.

2.6.4.8 Other Pharmacokinetic Studies

A toxicokinetic study was included in the 39-week oral repeat dose study conducted in dogs, which is included in this review (see section 2.6.6.3.1). In addition, some toxicokinetic data was collected in the reproductive toxicology studies to support this submission (see section 2.6.6.6). Tabulated summaries of key toxicokinetic parameters in these studies can be found below in section 2.6.5.

2.6.4.9 Discussion and Conclusions

In human subjects, tranexamic acid undergoes triexponential decay with a half-life of approximately 2 hrs for the terminal elimination phase. Dosing in the presence of food does not have an effect on absorption. The currently proposed modified-release tablet of tranexamic acid has comparable AUC and C_{max} ratios to the immediate-release tablets used previously. The overall bioavailability of tranexamic acid is 45% following either oral or i.v. administration. Tranexamic acid has two known metabolites, but >95% of the dose is excreted in the urine as unchanged drug product. Urinary excretion is the primary mechanism of elimination via glomerular filtration.

In reproductive tissues of concern, tranexamic acid does pass through the placenta, with a concentration observed in cord blood to be equivalent to that in maternal blood. In addition,

tranexamic acid has been detected in semen, but only affects fibrinolytic activity and not migration. Finally, tranexamic acid has been detected in breast milk at concentrations one hundredth of the serum peak concentration, so elimination of the drug does occur in breast milk.

Toxicokinetic data in the dog indicate that AUC and Cmax increase dose proportionally up to 300 mg/kg/bid, with Tmax between 1.5 and 3 hrs, and t_{1/2} between 1.7 and 3.2 hrs. Analysis of plasma concentrations in the dog indicate no accumulation between Day 1 and Week 8 of dosing (up to 300 mg/kg/bid), however a slight increase in plasma concentration was observed at Week 34. The 300 mg/kg/bid (600 mg/kg/d) dose in dogs was found to have an AUC 5 times that in humans following the proposed clinical dose of 3.9 g/d (358 µg*h/mL in dogs versus 74.8 µg*h/mL in humans).

2.6.4.10 Tables and figures to include comparative TK summary

None included.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

2.6.7.3 Toxicology: Overview of Toxicokinetics Data for Tranexamic Acid

Species	Study Location	Dose (mg/kg/day)	Sex	Day 1				Week 8		Week 34		
				Cmax (ug/ml)	AUC(0-12) (ug-hr/ml)	T _{1/2} (hr)	C3 (ug/ml)	C12 (ug/ml)	C3 (ug/ml)	C12 (ug/ml)	C3 (ug/ml)	C12 (ug/ml)
Dog	4.2.3.2 TUS0001	200	Male	27.8	127	2.3	21.0	3.01	25.4	5.78	36.0	5.75
			Female	22.7	121	3.2	23.4	3.30	19.9	4.94	45.5	7.15
		600	Male	71.0	316	2.9	63.9	14.3	54.8	16.1	72.5	5.42
			Female	80.2	359	1.7	54.5	11.4	63.6	13.2	132	17.4
		1200	Male	111	689	3.2	93.1	13.2	120	33.8	203	15.7
			Female	120	467	2.6	67.2	7.66	128	19.0	130	16.2
		1200 (atrapetal)	Male	65.3	358	2.4	47.4	9.73	65.8	20.8	82.4	16.4
			Female	63.8	336	2.7	57.4	8.98	69.8	27.1	97.2	6.31

Cmax = maximum plasma concentration
 AUC(0-12) = area under the curve between dosing and 12 hours post-dose
 T_{1/2} = half life
 C3 = plasma concentration 3 hours post-dose
 C12 = plasma concentration 12 hours post-dose

***taken from current NDA submission Module 2.6.7 – Toxicology Tabulated Summary*

2.6.7.3 Toxicology: Overview of Toxicokinetics Data for Tranexamic Acid (Continued)

Species	Study Location	Dose (mg/kg/day)	Status	Dosing Day 15 ^a C(pre-dose) (ug/ml)	Dosing Day 15 ^a C3 (ug/ml)
Rat	4.2.3.5.2 TUS0002	300 mg/kg/day	Non-pregnant	0.639	6.88
			Pregnant	0.46	11.1
			Fetus	-	1.45
		750 mg/kg/day	Non-pregnant	1.81	14.0
			Pregnant	1.21	32.8
			Fetus	-	4.28
		1500 mg/kg/day	Non-pregnant	3.64	25.4
			Pregnant	2.34	35.5
			Fetus	-	5.6

C (pre-dose) = plasma concentration prior to dosing
 C3 = plasma concentration 3 hours post-dose
^a Dosing day 15 was gestation day 20 for pregnant rats

***taken from current NDA submission Module 2.6.7 – Toxicology Tabulated Summary*

Table 3: Pharmacokinetic Parameters of the Modified-Release Formulation After Oral Dosing 1 Day Compared to 5 Days

Parameter	1 day	5 days
Dose	1.3 g	1.3 g TID ^a
AUC (mcg*h/L)	74.6 ^b	74.8 ^c
Coefficient of variation	33%	30%
C _{max} (mg/L)	13.2	15.8 (5.2 ^d)
T _{max} (h)	3.1	2.6
t _{1/2} (h) ^e	11.1	NA

Source: Moore, 2008a, Moore, 2008b

Note: Values represent geometric means, except T_{max} which is the arithmetic mean.^a Dosed every 8 hours (3.9g/day)^b AUC₀₋₄^c AUC_∞^d C_{min} corresponding steady-state concentration^e Reflects terminal half-life***taken from current NDA submission Module 2.5 – Clinical Overview**The pharmacokinetic profile of tranexamic acid was determined in 39 healthy women following a single 1.3 g oral dose of the modified-release formulation compared to repeated oral doses of 1.3 g three times a day for 5 days.*

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

The Sponsor is relying on a 39-week repeat oral dose toxicity study in the dog, published literature on tranexamic acid, and previous findings of safety for Cyklokapron to support the general toxicity of their product. The major nonclinical findings in the 39-week study were ocular toxicities, primarily noted at the high dose of 600 mg/kg/bid (1200 mg/kg/day), and included reddening, discharge, conjunctival inflammation, altered reflectivity of the fundus, inflammatory exudate, and changes in the nictitating membrane/conjunctiva. Atapetal dogs were included in this study as comparators to show that reflectivity changes were associated with the tapetum of the eye. Humans do not have a tapetum, so these reflectivity changes are species specific and not clinically relevant. The NOAEL for this study was 300 mg/kg/bid (600 mg/kg/d), and is 5 times the recommended daily dose based on AUC.

Published literature on the general toxicity of tranexamic acid was submitted including a 6-month study in rats performed in Japan. However, due to limited translation and only a summary from the Sponsor, this study is of limited use. The only major findings noted were dose-related diarrhea, catarrhal gastritis and epithelial necrosis in the caecum of males. The NOAEL was reported to be 750 mg/kg/d, and is 2 times the recommended daily dose based on mg/m².

Genetic toxicology:

The label for Cyklokapron indicates that “no mutagenic activity has been demonstrated in several in vitro and in vivo test systems.” The Sponsor has submitted a literature study by Shimada et al. (1979) that concludes that tranexamic acid is negative for genotoxicity based

on the rec-assay on *Bacillus subtilis*, the Ames test, in vitro and in vivo chromosomal aberration assays, and the dominant lethal test.

Carcinogenicity:

The Sponsor is relying on the current labeling for Cyklokapron in regards to carcinogenicity. The label notes an increased incidence of leukemia in male mice that is likely related to tranexamic acid treatment (~5 g/kg/d in food), as well as hyperplasia of the biliary tract and cholangioma and adenocarcinoma of the intrahepatic biliary system in rats treated by diet at doses exceeding the MTD for 22 months. Hyperplastic, but not neoplastic changes were noted at lower doses, while the use of a different strain of rat did not show similar hyperplastic/neoplastic changes in the liver as noted above. It appears that carcinogenicity in the rat could be strain specific, and limited to exceedingly high doses.

Reproductive toxicology:

The label for Cyklokapron indicates that tranexamic acid is a Pregnancy Category B drug. It also states that:

- **“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.”**
- **“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.”**
- **“Tranexamic acid is present in the mother’s milk at a concentration of about a hundredth of the corresponding serum levels.”**

The Sponsor has conducted two nonclinical reproductive toxicity studies. The embryofetal development study showed only slight changes in fertility parameters and minor/variant fetal abnormalities that were not treatment-related. Fetal plasma concentrations were detected indicating in utero exposure to tranexamic acid. The pre/postnatal development study showed only slight changes in maternal and fetal body weight during gestation and lactation that were not treatment-related. No significant findings were observed in the F0 or F1 generation. The maternal and fetal NOAEL for rats in these studies was established at 750 mg/kg/bid (1500 mg/kg/d), which is equivalent to 14.6 g/day in humans (4 times the recommended daily dose based on mg/m²). No changes to the current Pregnancy Category (Category B) are recommended.

Special toxicology:

Published articles submitted by the Sponsor primarily investigate ocular toxicity in dogs, mice and rabbits. These studies indicate that ocular toxicity (exudate and conjunctivitis) is the result of exaggerated pharmacology of tranexamic acid due to its antifibrinolytic mechanism of action.

The label for Cyklokapron notes the nonclinical ocular toxicity of tranexamic acid in the warnings section:

- **“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.”**

2.6.6.2 Single-dose toxicity

Single dose toxicity can be evaluated based on clinical pharmacokinetics. The current labeling for Cyklokapron prescribes a dosage of 10 mg/kg i.v. three to four times daily following tooth extraction. The current NDA proposes a 1300 mg oral dose three times daily. In a 70 kg female, this equates to a 18.6 mg/kg dose three times daily. In clinical study XP12B-101, single dose administration of tranexamic acid by i.v. (1 g, or ~14 mg/kg) or oral (1.3 g modified release tablets) gave the following comparative PK:

Parameter	Tranexamic acid 1 g (i.v.)	Tranexamic acid 1.3 g (oral)
C _{max} (µg/mL)	95.24	11.70
AUC _{0-tdc} (µg*h/mL)	121.43	68.97
AUC _{inf} (µg*h/mL)	122.96	71.30
T _{max} (h)	0.08	3
t _{1/2} (h)	10.22	11.37

Data presented are arithmetic means, except for T_{max} which is presented as median.

It appears that the proposed clinical oral dose has a lower exposure than a clinical i.v. dose which is similar to the currently prescribed dose. Since a 10 mg/kg i.v. dose 3-4 times daily has been approved for use, and is considered relatively safe, then a single 1.3 g (18.6 mg/kg) dose should also be considered relatively safe.

2.6.6.3 Repeat-dose toxicity

2.6.6.3.1 Study title: 39 week oral (capsule) toxicity study in the dog

Key study findings: The objective of this study was to evaluate the toxicity of tranexamic acid when administered to male and female dogs twice a day for 39 weeks. One main focus of this study was to evaluate ocular health due to previous findings of retinal atrophy in dogs receiving similar high doses of tranexamic acid (600 mg/kg/bid) for one year. Atapetal dogs were included in this study as a comparator. Key findings in this study were mainly at the high dose of 600 mg/kg/bid (unless otherwise noted), and included:

- reddening and discharge in the eyes;
- changes in the nictitating membrane/conjunctiva and altered reflectivity in the fundus of the eyes (100-600 mg/kg/bid; no dose related severity)
- conjunctival inflammation

- loose/liquid feces
- excessive salivation (600 mg/kg/bid; 1 female at 100mg/kg/bid, but minimal)
- inflammatory exudate in the eye (600 mg/kg/bid; 1 female at 100 mg/kg/bid)
- toxicokinetics: dose-related increases of C_{max} and AUC, with T_{max} of 1.5-3 hrs and t_{1/2} of 1.7-3.2 hrs
- ocular changes were treatment related and occurred in both males and females
- atapetal dogs did not show altered reflectivity of the fundus, indicating that reflectivity changes are associated with the tapetum of the eye
 - humans do not have a tapetum, therefore changes are not considered clinically relevant
- NOAEL for male and female dogs in this study was established at 300 mg/kg/bid (600 mg/kg/day), based on ocular changes, and is 5 times the recommended human dose of 3.9 g/day based on AUC.

Study no.: TUS0001

Volume #, and page #: Volume 1, page 1

Conducting laboratory and location: 7 } b(4)
 3 }

Date of study initiation: November 16, 2004

GLP compliance: Yes

QA report: yes (X) no ()

Drug, lot #, and % purity: Tranexamic Acid (TA)

Batch # 04R0170/0404013M, purity 100%

Batch # 04R0315, purity 99.4%

Batch # TSAAJ96, purity 99.6%

Methods

Doses: 0, 200, 600, 1200 mg/kg/day (0, 100, 300, 600 mg/kg/bid)

Species/strain: Beagle dogs

Number/sex/group or time point (main study):

Group 1: 0 mg/kg/d: 5M, 5F

Group 2: 200 mg/kg/d: 4M, 4F

Group 3: 600 mg/kg/d: 4M, 4F

Group 4: 1200 mg/kg/d: 5M, 5F

Group 5: 1200 mg/kg/d: 3M, 3F (Atapetal dogs obtained from alternative supplier)

Route, formulation, volume, and infusion rate: Oral capsule, bid (12 hr interval)

Satellite groups used for toxicokinetics or recovery: n/a

Age: 4-6 months (Atapetal dogs were ages 9-15 months)

Weight: Males: 9.2 – 11.8 kg; Females: 6.4 – 9.7 kg

Sampling times: before treatment start and at necropsy

Unique study design or methodology (if any):

Atapetal dogs were included in this study to compare the development of anticipated ophthalmic lesions in dogs with a normal tapetum against those which are classified as atapetal.

Atapetal = lacking a clinically apparent ocular tapetum. The tapetum lucidum is a reflecting layer immediately behind, and sometimes within, the retina of the eye of many vertebrates that serves to reflect light back to the retina, increasing the quantity of light caught by the retina. This improves vision in low light conditions, but can cause the perceived image to be blurry from the interference of the reflected light. It is therefore primarily found in nocturnal animals with good night vision, such as cats, bottlenose dolphins, dogs, and deer. The tapetum lucidum is not present in the human eye, which is why humans have poor night vision. (From www.wikipedia.org; search term: tapetum)

Observation and Times:

Clinical signs: twice daily, detailed exam once per week

Body weights: on arrival, at weekly intervals during acclimatization and treatment periods, and on day of necropsy

Food consumption: daily throughout acclimatization and treatment

Ophthalmoscopy: before start of treatment and during weeks 13, 26 and 39. High dose and control animals were also examined after 1 and 2 months of treatment.

EKG: once during acclimatization, after 4 months treatment, and at end of study

Hematology: before start of treatment, at 4 months, and week 39

Parameters: hemoglobin (Hb), red blood cell count (RBC), packed cell volume (PCV), mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), platelet count, total leukocyte count (WBC) and leukocyte differential count (neutrophils, lymphocytes, monocytes, eosinophils, basophils, large unstained cells), cell morphology, reticulocytes, prothrombin time, activated partial thromboplastin time (APTT).

Clinical chemistry: before start of treatment, at 4 months, and week 39

Parameters: urea, creatinine (Creat), glucose (Gluc), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein (T. Prot), albumin (Alb), globulin (Glob), albumin/globulin ratio (A/G), bilirubin (Bili), cholesterol (Chol), calcium (Ca), sodium (Na), potassium (K).

Urinalysis: before start of treatment, at 4 months, and week 39

Parameters: volume, specific gravity (SG), glucose, pH, protein, color and appearance.

Gross pathology: at necropsy

Organ weights: at necropsy

Histopathology: Adequate Battery: yes (X), no ()

Peer review: yes (), no (X)

Toxicokinetics: 1 mL blood samples were obtained from cephalic or saphenous veins, or if required by jugular venipuncture at the following times:

Day 1: 0.75, 1.5, 3, 6, 9, 12 (pre 2nd sub-dose), 15 and 24 hrs after 1st sub-dose

After 2 months: Pre-dose, 0.75, 1.5, 3, 6, 9, 12 (pre 2nd sub-dose), 15 and 24 hrs after 1st sub-dose.

After 8 months: Pre-dose, 0.75, 1.5, 3, 6, 9, 12 (pre 2nd sub-dose), 15 and 24 hrs after 1st sub-dose.

Analysis was performed by GC/MS using negative ion chemical ionization (NICI) and selected reaction monitoring after extraction and derivatization. The assay standard curve was linear (0.500-500 µg/mL) and the LLOQ was 0.500 µg/mL.

Results:

Mortality: One female (300 mg/kg/bid) was euthanized on Day 3 due to deteriorating clinical condition. The animal had decreased activity, slow breathing, cold body surface, abnormally dark colored extremities, and at necropsy was found to have an intussusception. No further deaths occurred at this dose, or the higher dose, therefore this death was not considered treatment-related.

Clinical signs: Clinical observations were mainly noted in the 600 mg/kg/bid groups. They included the following:

- Excessive salivation pre- and post-dose in M and F at 600 mg/kg/bid. Duration for males was Week 1 or 2 up to Week 39, and for females was Week 10-Week 39. One female at 300 mg/kg/bid experienced this as well.
- Resistance to dosing procedure from Week 5 on in 600 mg/kg/bid groups.
- Loose and liquid feces from Week 1 or 2 on in M and F at 600 mg/kg/bid.
- Abnormal coloration (reddening) and gelatinous discharge of the eyes were sporadically noted in M and F at 600 mg/kg/bid. This finding was treatment-related as antibiotic treatment did not clear the effect, though once animals were taken off treatment for 1-2 weeks, the condition cleared. In two dogs, this finding recurred a number of times.

Body weights: No significant findings related to administration of test article.

The atapetal dogs did not gain as much weight as dogs in other groups in the study. These dogs were older and from a different supplier, so this was not unexpected.

Food consumption: No significant findings related to administration of test article.

The atapetal dogs generally consumed less than the other groups, but this did not change with treatment.

Ophthalmoscopy: Ocular changes occurred in the nictitating membrane/conjunctiva and fundus regions of the eye in both males and females, predominantly at the 600 mg/kg/bid dose. **One male (Group 4 – 600 mg/kg/bid) was observed to have a third eyelid protrusion at month 1 of treatment.** This was characterized by a thickening of the deep surface of the third eyelid, and a fibrinous, gelatinous, purulent exudate adherent to the deep third eyelid and the globe. This observation could be attributed to trauma due to a history of fighting; however at month 2, two atapetal dogs (1M and 1F – 600 mg/kg/bid) **exhibited the same changes.** **All lesions resolved by the time of the final exam.** At the final exam, one additional male (Group 4 – 600 mg/kg/bid) showed a similar lesion, though it appeared to be a milder form.

Also at various times during treatment, 4 males (Groups 1-3, 100-600 mg/kg/bid) and 2 females (300 mg/kg/bid) showed a fundus change which was recorded as subtle

hyperreflectivity, areas of dullness/darkening, areas of graying, and altered reflectivity. These were subtle changes and were reported to occur dorsal to the optic disc in islands or poorly defined geographic areas, and only detected by indirect ophthalmoscopy. Some lesions were sporadic, and were not detectable in subsequent exams, though they were specifically looked for. No cumulative or permanent damage was seen in any animal. No fundus changes were observed in the atapetal dogs.

In timed examinations at the end of the study, the fundi of all dogs were normal at pre-dose with no visible lesions. At 3 hr post first sub-dose exam, 2M and 1F (600 mg/kg/bid) and 2F (300 mg/kg/bid) showed the same greying change in the tapetal fundus as seen previously. At 6 hrs post dose, all dogs returned to the pre-dose appearance. All other animals showed normal reflectivity. As a result, some ocular changes occur following dosing, but do not persist, and resolve quickly.

EKG: No significant findings related to administration of test article.

Hematology: No significant findings related to administration of test article. Some changes in WBC and PCV at Week 17 and Week 39 were also observed pre-dose, so no correlation with treatment could be made.

Clinical chemistry: No significant findings related to administration of test article. Urea levels were slightly higher in both males and females at 300 and 600 mg/kg/bid at Week 39 compared to controls. These changes were not clearly dose-response related and similar trends were observed at pre-dose. Therefore, these were determined not to be treatment-related.

Urinalysis: No significant findings related to administration of test article.

Gross pathology: No significant findings related to administration of test article.

Organ weights: No significant findings related to administration of test article. The Sponsor notes that some individual male animals (300-600 mg/kg/bid) and female **animals (atapetal – 600 mg/kg/bid) had higher** bodyweight-related adrenal weights. Some values were outside the normal background range. These changes were not associated with histological change, and were not considered toxicologically significant.

Histopathology:

Finding	Males (mg/kg/bid)				
	0	100	300	600	#600
Eyelid ^a	5	4	4	5	3
Slight epithelial hyperplasia, palberal conjunctiva ^b	0	0	0	1	0
Larynx ^a	5	4	4	5	3
Slight ulceration, vocal folds ^b	0	0	2	0	0
Mesenteric lymph nodes ^a	5	4	4	5	3
Slight erythrocytosis/ erythrophagocytosis ^b	0	1	1	1	1
Nictitating membrane ^a	5	4	4	5	3
Prominent mucosal assoc. lymphoid tissue present ^b	0	0	0	1	0

a: number examined

b: number of instances

indicates atapetal animals

Finding	Females (mg/kg/bid)				
	0	100	300	600	#600
Eyes ^a	5	4	4	5	3
Slight reduced tapetal layer ^b	0	0	0	4	0
Nictitating membrane ^a	5	4	4	5	3
Minim. mucosal/submucosal neutrophils ^b	0	2	0	0	1
Slight mucosal/submucosal neutrophils ^b	0	0	0	1	0
Minim. inflamm. exudate, bulbar aspect ^b	0	1	0	1	0
Slight inflamm. exudate, bulbar aspect ^b	0	0	0	1	0
Moder. inflamm. exudate, bulbar aspect ^b	0	0	0	0	1
Slight conjunctivitis, bulbar ^b	0	0	0	1	1

a: number examined

b: number of instances

indicates atapetal animals

Histopathology of the eye was the predominantly noted finding in this study. All other findings were minimal and considered incidental.

The focus on ocular health is due to previous findings of retinal atrophy in dogs (unknown breed) receiving similar high doses of tranexamic acid (600 mg/kg/bid) for one year. No treatment related retinal changes were found in any dogs in this current study. In the nictitating membrane of females, inflammatory exudate was present in 2 high dose females and one high dose atapetal female, along with some conjunctivitis. Minimal inflammatory exudate was also observed in 1 low dose female as well. These observations were not seen in males. In addition, mucosal associated lymphoid tissue was observed in one high dose male, and the Sponsor noted that there was considerable inter-animal variation in the degree of this finding. Overall, it was not

considered toxicologically significant, as it was only one case. Many of the changes in the nictitating membrane showed considerable variation, however findings were considered treatment related.

The reduced tapetal layer in the eyes of high dose females was investigated further in the alternate eyes of control and high dose females as there is normally minor morphological variation in tapetal thickness in dogs in this region of the eye. Interanimal variation at the level of the tapetum was observed, and there was similar variation in both control and treated females. The initial finding was attributed to variability in these structures and variation in the sectional plane, and was therefore considered not treatment related, and not toxicologically significant.

Toxicokinetics:

Mean Toxicokinetic ratios on Day 1 (Males and Females)

(Values were derived from the full concentration-time profiles on Day 1 only following the first sub-dose)

Parameter	Day 1							
	100 mg/kg/bid		300 mg/kg/bid		600 mg/kg/bid		#600 mg/kg/bid	
	M	F	M	F	M	F	M	F
Dose ratio	1	1	3	3	6	6	6	6
C _{max} (µg/mL)	27.8	22.7	71.0	80.2	111	120	65.3	63.8
T _{max} (h)	2.3	3.0	2.3	2.3	2.3	1.5	2.3	1.5
AUC (h*µg/mL)	137	121	316	358	689	467	358	336
t _{1/2} (h)	2.3	3.2	2.9	1.7	3.2	2.6	2.4	2.7
AUC ratio	1	1	2.3	3.0	5.0	3.9	2.6	2.8
AUC/dose	1.4	1.2	1.1	1.2	1.1	0.8	0.6	0.6

indicates atapetal animals

For ease of comparison – human PK at the recommended human dose (1.3 g tid; 3.9 g/day) has a C_{max} of 15.8 mg/L and an AUC of 74.8 µg*h/mL.

AUC and C_{max} increased relatively dose proportionally in tapetal animals, but AUC was less than dose-proportional at 600 mg/kg/bid. Group 5 atapetal animals did not show a dose proportional increase in exposure. T_{max} was generally between 1.5 and 3 hrs at all doses, and t_{1/2} ranged between 1.7 and 3.2 hrs.

No C_{max} or AUC data was available for Weeks 8 and 34. However, plasma concentrations were obtained at 3 and 12 hrs at Day 1, and Weeks 8 and 34. Analysis of this data showed that at the 100 and 300 mg/kg/bid doses, there were generally no differences between Day 1 and Week 8 concentrations, while Week 34 concentrations were increased slightly compared to Day 1 and Week 8. At 600 mg/kg/bid, 3 hr concentrations increased at Weeks 8 and 34, although these effects were not marked. The 12 hr concentrations were more variable with Week 8 and 34 concentrations slightly higher than Day 1.

Plasma concentrations were measurable at all dose levels up to 24 hrs. There was no evidence of sex differences in TK parameters between male and female dogs. Based

on AUC, the exposure multiples for each dose in females (compared with human female AUC at 3.9 g/d) are 2, 5 and 6 times the clinical dose. The dose multiples are slightly different at 2, 5 and 10 times the clinical dose.

2.6.6.3.2 Study title: Evaluation of the safety of tranexamic acid: Chronic oral toxicity in rats. (*Takayama et al., 1971*)

Background: This literature study was submitted by the Sponsor to support the repeat dose toxicity of tranexamic acid. However, the report is provided only in Japanese, with only an abstract and figures translated to English. Since there was insufficient data submitted to do an independent review of the study, only a summary of study results based on the reviewer analysis of figures and summary of study provided by the Sponsor will be provided here.

Results: Male and female Sprague Dawley rats (20/sex/dose) were treated by oral gavage with tranexamic acid at doses of 0, 750, 1500, 3000, 4000 mg/kg. From the tabular results included in the manuscript, there do not appear to be any significant body weight changes in males or females, and no difference in water or food intake. Hematology changes were noted in males and females with non-dose responsive increases in neutrophils at 3 months in males (up to 51%) and 6 months in females (up to 128%), and decreases in lymphocytes at 3 months in males (9%) and 6 months in females (21%). In addition, increased plasma euglobulin clot lysis time was increased at 6 months in males (52%; 4000 mg/kg) and females (25% and 46%; 3000 and 4000 mg/kg). No significant or dose responsive changes in organ weight or **histopathology were noted.** In the Sponsor's summary of findings, they note that a total of 25 deaths occurred in this study, with 21 due to intubation error (no information provided on the remaining 4 deaths). Incidence of diarrhea was noted at the 3 highest dose levels, and occult blood was observed in stools with increased severity over time at higher doses. In addition, catarrhal gastritis was dose and time related at 1500, 3000 and 4000 mg/kg and epithelial necrosis was observed in the caecum of males at 3000 and 4000 mg/kg at 3 months, but not 6 months. The Sponsor determined that the NOAEL for this study was 750 mg/kg, which equates to an HED of ~7300 mg/day. Compared to the proposed clinical dose of 3900 mg/day, the dose multiple is only 2 (based on mg/m²).

2.6.6.4 Genetic toxicology

As part of this 505(b)(2) application, Xanodyne Pharmaceuticals is relying on published literature and FDA's finding of safety for Cyklokapron in regards to genetic toxicology and mutagenicity as reflected in labeling. The current labeling (12-22-2008) states:

"No mutagenic activity has been demonstrated in several in vitro and in vivo test systems."

The Sponsor has submitted published literature that documents the lack of mutagenicity for tranexamic acid as tested in the rec-assay on *Bacillus subtilis*, the Ames test, in vitro and in

vivo chromosomal aberration assays, and the dominant lethal test (Shimada et al., 1979). Summaries of the results of each of those tests are found below. Overall, these studies indicate that tranexamic acid is not mutagenic under the conditions tested.

Rec-assay

Wild-type H17(rec+) and recombination repair-deficient mutant M45(rec-) of *Bacillus subtilis* was used as the test system, with treatments of tranexamic acid and positive controls kanamycin (protein synthesis inhibitor) and mitomycin C (DNA crosslinker). M45 strain is sensitive to frameshift mutagens and base-pair substitution mutagens. Tranexamic acid did not cause growth inhibition of either M45 or H17 strains at any concentration. Kanamycin inhibited growth of M45 and H17 to a similar degree, while mitomycin C induced growth inhibition in M45 more strongly than in H17. As a result, tranexamic acid did not appear to have any direct effect on DNA damage.

Salmonella/microsome test (Ames test)

The Ames test was performed using five mutant bacterial strains (TA1535, TA1537, TA1538, TA100 and TA98). Compounds used for analysis were tranexamic acid (0.3-3000 µg/plate), 2-aminoanthracene (5 µg/plate), 9-aminoacridine (5 µg/plate) and MNNG (5 µg/plate), and were examined for the generation of histidine revertants with or without S9. The numbers of histidine revertants in any of the 5 bacterial strains were not increased by tranexamic acid (0.3-300 µg/plate) more than controls, with or without S9. The highest concentration of tranexamic acid used (3000 µg/plate) was toxic to all strains (with and without S9). In the other compounds examined, 2-aminoanthracene, with S9, increased revertants in all tester strains, while 9-aminoacridine (minus S9) only increased revertants in TA1537, and MNNG (without S9) only increased revertants in TA1535 and TA100. These results indicate that tranexamic acid did not have a mutational effect on any of the investigated bacterial strains either with or without S9 metabolic activation.

In vitro and in vivo cytogenetic assays

In vitro cytogenetic studies were conducted with a Chinese hamster ovary cell line (D-6) treated for 17 hrs with either control, tranexamic acid (100, 1000 or 6000 µg/mL) or mitomycin C (positive control) (0.01, 0.05 or 0.10 µg/mL). Cells were examined for chromatid/iso-chromatid breaks, chromosome exchange, multiple chromosomes or fragments. The positive control mitomycin C showed a dose response increase of the number of cells affected (13-60.5%), with predominant effects being chromatid breaks at all doses, and iso-chromatid breaks, chromosome exchange, and multiple chromosomes occurring primarily at the high dose. Fragments occurred at all doses of mitomycin C. Tranexamic acid did not induce any chromosome changes at any dose more than controls. As a result, in an in vitro test, tranexamic acid did not induce chromosomal aberrations.

In vivo cytogenetic studies were conducted in nine-week old ddY strain male mice, and Sprague-Dawley and Sherman strain male rats. In an acute study, a single i.p. injection of saline control, tranexamic acid (100, 1500 or 3500 mg/kg (3000 mg/kg for rats)) or mitomycin C (mice 5 mg/kg, rats 2 mg/kg) was given, and chromosomes from bone marrow cells were examined. In a subacute study, animals were treated for 5 days with i.p. injections of saline control, tranexamic acid (100, 1500 or 3500 mg/kg (3000 mg/kg

for SD rats and 2500 mg/kg for Sherman rats)) or mitomycin C (mice 3 mg/kg, rats 1.5 mg/kg), and chromosomes from bone marrow cells were examined. Mitomycin C increased the percentage of cells with chromosomal aberrations in ddY mice, Sprague-Dawley rats and Sherman rats, with the highest percentage at 24 hr after injection. Tranexamic acid did not induce any increased chromosomal aberrations at any dose over control levels. As a result, in an in vivo test, tranexamic acid did not induce chromosomal aberrations.

Dominant lethal assay

In the dominant lethal assay, 10-week old virgin male and female ddY mice were used in an 8-week mating schedule. Males were treated with a single i.p. injection of either control, tranexamic acid (100 or 3000 mg/kg), or EMS (positive control) (350 mg/kg), and mated for 1 week with 3 females that were replaced weekly with 3 new virgin females for 8 weeks. Each female was examined for pregnancy, and total number of living implantations and fetal deaths. The rate of dominant lethal mutations was calculated. In the first 4 weeks, EMS significantly decreased the number of living embryos and increased the number of dead implants in females compared to both controls and historical background. Tranexamic acid did not have any effect on number of live or dead implants in females compared to controls or historical background at either dose at any week during the 8 weeks. EMS also increased the frequency of dominant lethal mutations, specifically during weeks 1 and 2, indicating damage to spermatozoa and spermatids. Tranexamic acid did not increase the frequency of dominant lethal mutations at any time point, and subsequently at no specific stages of spermatogenesis. As a result, tranexamic acid did not induce dominant lethal mutations in mice or rats.

2.6.6.5 Carcinogenicity

As part of this 505(b)(2) application, Xanodyne Pharmaceuticals is relying on FDA's finding of safety for Cyklokapron in regards to carcinogenicity as reflected in the labeling. The current labeling (12-22-2008) states:

- **“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.”**

2.6.6.6 Reproductive and developmental toxicology

Fertility and early embryonic development

As part of this 505(b)(2) application, Xanodyne Pharmaceuticals is relying on FDA's finding of safety for Cyklokapron in regards to fertility and early embryonic development as reflected in the labeling. The current labeling (12-22-2008) states in the pregnancy section:

- "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."
- "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."

Embryofetal development

2.6.6.6.1 Study title: Oral (gavage) twice daily dosing developmental toxicity study in the rat

Key study findings: The objective of this study was to evaluate the maternal and fetal toxicity of tranexamic acid when administered to female rats twice a day during GD6-17. Key findings in this study were minimal and consisted of slight changes in fertility parameters and minor/variant fetal abnormalities that were determined not treatment-related. Toxicokinetics showed that plasma concentrations increase dose-proportionally at 375 mg/kg/bid, but less so at 750 mg/kg/bid. Fetal plasma concentrations of tranexamic acid were detected; therefore fetuses are exposed to tranexamic acid in utero. There were no other significant observations with this treatment. The maternal and fetal NOAEL for rats in this study was established at 750 mg/kg/bid or 1500 mg/kg/day. This dose is equivalent to approximately 15 g/day in humans, and is approximately 4 times the highest proposed clinical dose based on body surface area (mg/m²).

Study no.: TUS0002

Volume #, and page #: Volume 3, page 1

Conducting laboratory and location: 7 b(4)

Date of study initiation: January 18, 2005

GLP compliance: Yes

QA reports: yes (X) no ()

Drug, lot #, and % purity: Tranexamic Acid

Batch # 0311011M, purity 100%

Batch # 0404013M, purity 100%

Methods

Doses: 0, 300, 750, 1500 mg/kg/day (0, 150, 375, 750 mg/kg/bid)

Species/strain: Rats, Crl:CD (SD) IGS BR VAF PLUS strain

Number/sex/group: 111 females; 24 per dosing group (main study)

Route, formulation, volume, and infusion rate: oral gavage, dissolved in UHP water vehicle, 10mL/kg

Satellite groups used for toxicokinetics:

Pregnant satellite group: 5 per dosing group (300, 750, 1500 mg/kg/day)

Non-pregnant satellite group: 5 per dosing group (300, 750, 1500 mg/kg/day)

Study design: Females were dosed twice daily (12hrs apart) by oral gavage. Main study females were dosed from GD6 to GD17. Pregnant satellite females were dosed from GD6 to GD20. Non-pregnant satellite females were dosed from Day 1 to Day 15 of the study (equivalent to GD6 to GD20). Control animals in the main study received vehicle only (UHP water) and followed the same dosing regimen as the other groups. Females were approximately 10 weeks old, and were time-mated prior to delivery to the laboratory.

Parameters and endpoints evaluated: Mortality, clinical observations, body weight, food consumption, number of corpora lutea, number and distribution of implantations, gravid uterine weight, fetal body weight, fetal external abnormalities and visceral abnormalities, plasma concentrations in pregnant and non-pregnant satellite groups.

Results

Mortality (dams): No deaths reported.

Clinical signs (dams): No significant findings related to administration of test article on main study females, or pregnant and non-pregnant satellite females.

Body weight (dams): No significant findings related to administration of test article on main study females, or pregnant and non-pregnant satellite females.

Food consumption (dams): No significant findings related to administration of test article on main study females, or pregnant and non-pregnant satellite females.

Toxicokinetics: The only TK parameter provided was C₃, the 3 hour post dose sample, which was derived from the mean plasma concentration-time profiles. Some dose proportionality of C_{min} and C₃ values were evaluated by calculation of appropriate ratios.

Mean plasma concentrations ($\mu\text{g/mL}$) and basic parameters of tranexamic acid
in non-pregnant rats on Day 15 of treatment

Time Group	Day 15 of Treatment		
	150 mg/kg/bid	375 mg/kg/bid	750 mg/kg/bid
Predose ($\mu\text{g/mL}$)	0.639	1.81	3.64
3 hrs post dose ($\mu\text{g/mL}$)	6.88	14.0	25.4
Dose ratio	1	2.5	5.0
Dose proportionality ratios (C_{min})		2.8	5.7
Dose proportionality ratios (C_3)		2.0	3.7

Mean plasma concentrations ($\mu\text{g/mL}$) and basic parameters of tranexamic acid
in pregnant rats on GD20

Time Group	Gestational Day 20		
	150 mg/kg/bid	375 mg/kg/bid	750 mg/kg/bid
Predose ($\mu\text{g/mL}$)	0.460	1.21	2.34
3 hrs post dose ($\mu\text{g/mL}$)	11.1	32.8	35.5
Fetal plasma ($\mu\text{g/mL}$)	1.45	4.28	5.6
Dose ratio	1	2.5	5.0
Dose proportionality ratios (C_{min})		2.6	5.1
Dose proportionality ratios (C_3)		3.0	3.2
Dose proportionality ratios: Average fetal plasma / average maternal plasma C_3	0.13	0.14	0.15

TK results indicate that tranexamic acid is present in the plasma prior to the second dose of tranexamic acid (pre-dose) in both pregnant and non-pregnant rats. The Sponsor noted that considerable fluctuation between C_{min} and C_3 was observed. Higher C_3 levels of tranexamic acid were observed in pregnant rats versus non-pregnant rats (1.4 – 2.3 fold increase), while C_{min} levels were lower in pregnant rats versus non-pregnant rats. Overall, systemic exposure (shown as C_{min} and C_3 ratios) in both pregnant and non-pregnant rats increased in a dose proportional manner at 375 mg/kg/bid, but in a less than dose-proportional manner at 750 mg/kg/bid. Of note is that fetal plasma concentrations of tranexamic acid were detectable at each dose, indicating in utero exposure to tranexamic acid.

Terminal and necroscopic evaluations: C-section data (implantation sites, pre- and post-implantation loss, etc.):

At start of treatment, 24 females were assigned per group, and were assumed to be pregnant as they were mated off-site. At necropsy, 4-7 animals per group were found not to be pregnant. Overall, there were no changes with dose in number of CL, CL per litter, number of implantations or number of implantations per litter. A slight increase was found for number of early embryo/fetal deaths, but was within range. In addition, the number of live fetuses showed a slight decrease, which correlated with a slight drop in % implantations that become a live fetus. However, the number of live

fetuses per litter was not different among treatment groups. On the whole, these changes were small and did not indicate any treatment-related effects. The chart below is mainly included as reference.

Parameter	Number of incidences			
	0 mg/kg/bid	150 mg/kg/bid	375 mg/kg/bid	750 mg/kg/bid
# females at start of treatment	24	24	24	24
# females with implantations	20	18	18	17
# corpora lutea (total)	272	255	239	251
# corpora lutea per litter	13.6	14.2	13.3	14.8
# implantations	224	228	219	218
# implantations per litter	11.2	12.7	12.2	12.8
# early embryo/fetal deaths	7	7	12	14
# live fetuses	217	221	207	204
# live fetuses per litter	10.9	12.3	11.5	12.0
% implantations	97.3	97.1	94.0	94.0

* p≤0.05; ** p≤0.01; *** p≤0.001

Offspring (malformations, variations, etc.):

No differences in number of male vs. female offspring were observed, and there were no differences in mean litter weight, mean fetal weight, mean placental weight, or mean gravid uterus weight.

Parameter	Type	Number of incidences - visceral			
		0 mg/kg/bid	150 mg/kg/bid	375 mg/kg/bid	750 mg/kg/bid
Total number of litters examined		20	18	18	17
Total number of fetuses examined		113	114	108	105
# w/ major abnormalities		0	0	1 (1)	0
# w/ minor abnormalities		0	0	3 (2)	1 (1)
# w/ variations		6 (4)	7 (4)	5 (2)	4 (2)
Thoracic cavity					
Aortic arch: right sided	major	0	0	1 (1)	0
Descending aorta: right sided	major	0	0	1 (1)	0
Both lungs: single lobe ^a	major	1 (1)	0	1 (1)	0
Innominate artery	minor	0	0	2 (2)	1 (1)
Post caval lung lobe: absent ^a	minor	1 (1)	0	1 (1)	0
Abdominal cavity					
Kidney- uni- or bilateral: increased pelvic cavitation ^a	variant	5 (4)	4 (2)	6 (4)	3 (3)

* p≤0.05; ** p≤0.01; *** p≤0.001

a, b, c: there is a discrepancy in some of the values for this parameter in the table of fetal incidences provided by the Sponsor and the actual individual fetal examination data analysis. Values represent data from individual fetal examination.

Upon external examination, only one fetus (375 mg/kg/bid) had a minor abnormality of short snout and bilateral naris. This was not significant. Upon visceral examination, the table above details the observations made and their severity. All

variants were not listed as they were not different from control. Only the kidney finding was highlighted. Upon Bouin's examination of fetuses, there were no significant abnormalities that were dose-related or different from control. On the whole these observations were very few compared to the number of fetuses examined (105-114 per dosing group), and were not considered significant.

Parameter	Type	Number of incidences - skeletal			
		0 mg/kg/bid	150 mg/kg/bid	375 mg/kg/bid	750 mg/kg/bid
Total number of litters examined		20	18	18	17
Total number of fetuses examined		113	114	108	105
# w/ major abnormalities		2 (2)	0	0	1 (1)
# w/ minor abnormalities		37 (15)	32 (14)	36 (15)	27 (13)
# w/ variations		101 (20)	98 (18)	99 (18)	88 (17)
Skull					
Frontal: incomplete ossification	minor	0	1 (1)	2 (2)	4 (1)
Zygomatic arch: incomp. ossif.	minor	1 (1)	0	1 (1)	3 (3)
Cervical vertebra					
One or more centra: ossified	variant	23 (14)	33 (14)	39 (14)	37 (15)
Rib					
One or more: wavy	minor	2 (2)	2 (2)	1 (1)	7 (4)
14 th - uni- or bilateral: malformed	variant	3 (3)	15** (6)	3 (3)	9 (6)

() indicates the number of litters

* p≤0.05; ** p≤0.01; *** p≤0.001

Skeletal malformations were slight, and on the whole not considered significant. While not dose-related, a significant finding of malformed rib was observed in 15 of 114 fetuses at 150 mg/kg/bid, but the litter incidence did not appear to be significantly different. In addition, the number of fetuses (but not number of litters) with ossified centra in the cervical vertebra increased with dose, but was not significantly different from controls.

Prenatal and postnatal development

2.6.6.6.2 Study title: Oral (gavage) twice daily dosing pre- and post-natal developmental toxicity study in the rat

Key study findings: The objective of this study was to evaluate the effects of tranexamic acid on embryonic, fetal and postnatal development of the rat after twice daily administration of tranexamic acid during maternal GD6-20. Key findings in this study were minimal and consisted only of slight changes in maternal and fetal body weight during gestation and lactation that were determined not to be treatment-related. There were no other significant observations with this treatment in either the F0 or F1 generation. The maternal and fetal NOAEL for rats in this study was established at 750 mg/kg/bid or 1500 mg/kg/day. This dose is equivalent to

approximately 15 g/day in humans, and is approximately 4 times the highest proposed clinical dose based on body surface area (mg/m²).

Study no.: TUS0003

Volume #, and page #: Volume 4, page 1

Conducting laboratory and location: [REDACTED] b(4)

Date of study initiation: March 21, 2005

GLP compliance: Yes

QA reports: yes (X) no ()

Drug, lot #, and % purity: Tranexamic Acid, Batch # 0404013M, purity 100%

Methods

Doses:

- Group 1: 0 mg/kg/day (0 mg/kg/bid)
- Group 2: 300 mg/kg/day (150 mg/kg/bid)
- Group 3: 750 mg/kg/day (375 mg/kg/bid)
- Group 4: 1500 mg/kg/day (750 mg/kg/bid)

Species/strain: Rats, Crl:CD (SD) IGS BR VAF PLUS strain

Number/sex/group: 25 females per dosing group

Route, formulation, volume, and infusion rate: oral gavage, dissolved in UHP water vehicle, 10mL/kg

Satellite groups used for toxicokinetics: n/a

Study design: Females were dosed twice daily (12hrs apart) by oral gavage from GD6 to Day 20 of lactation. Control animals in the main study received vehicle only (UHP water) and followed the same dosing regimen as the other groups. Females were approximately 10 weeks old, and were time-mated prior to delivery to the laboratory. Five female sentinels were also used, caged as F0 females, were allowed to litter, but were not dosed. Only limited clinical observations and litter data were recorded for the sentinels. Offspring (F1) of sentinels were reared to weaning and then discarded without necropsy.

Parameters and endpoints evaluated:

- F0 generation: Mortality, clinical observations, body weight, food consumption, parturition observations, day 7 lactation milk sampling, observations of littering females (nesting, nursing)
- F1 generation during lactation: Litter size, sex, culling, clinical observations, mortalities, body weight, development (ears open, eyes open, static righting reflex, startle response, papillary light reflex).
- F1 generation post-weaning: Mortality, body weight, development and behavior (learning test, water-filled E-maze), locomotor activity, auditory function, sexual development, reproductive capacity, and necropsy on Day 13 gestation (pregnancy status, number of corpora lutea, number and distribution of implantations).

Results

F0 in-life:

Mortality: One female in Group 2 was electively euthanized due to prolonged parturition (day 24). She was found to have one large live male fetus (9.5g) in the right uterine horn, but no implantation sites in the left uterine horn. No external abnormalities of the fetus were noticed. Two other females were sacrificed prematurely during the lactation period: one Group 1 female and one Group 4 female were sacrificed due to the death of their litters.

Clinical signs: There were no clinical observations that were significantly different in treated vs. control animals.

Body Weight and Food Consumption: F0 females in Groups 3 and 4 had 10% and 15% increases in body weight gain over controls at GD20. Food consumption on GD20 was increased in these groups, but not largely. On postpartum day (PPD) 0-4, all F0 females (treated or control) had equivalent weight gain, while at PPD14, all treated groups had higher weight gain than controls (53%, 76% and 38%, respectively). Food consumption for these groups was also elevated (9-15%). The differences in body weight gain dissipated by PPD21.

Mating/Fertility: Out of 25 females in each treatment group at the start of the study, there were 24, 22, 23 and 24 (Groups 1-4, respectively) that were pregnant. Not included is the one pregnant female in Group 2 that was terminated due to prolonged parturition. No remarkable changes from controls were observed in regards to gestation duration, number of pups born, live birth index, viability index, lactation index, cumulative survival index, or sex ratio at birth.

F0 necropsy: There were no observations that were significantly different in treated vs. control animals.

F1 physical development:

Mortality: An increased number of pup deaths and pups terminated due to poor condition were noted by the Sponsor as greater than that normally seen in this laboratory. No cause was determined. The incidence was slightly higher than usual in all groups (control and treated) and was highest in controls than in treated groups, so the increase was determined not to be treatment-related.

Body weight: Slight increases in body weight and body weight gain were observed in Group 4 male and female pups (5-7%) over controls. This was considered slight, but statistically significant. There were no significant body weight differences in F1 males up to week 10, or in F1 females (pre-pairing) up to week 6.

Development observations: There were no differences in treated vs. control pups in regards to percent with righting reflex, percent with startle response, percent with

eyes open, or percent with papillary light reflex. The percentage of pups with ears open was lower in Groups 3 and 4 than controls (6-7%) but was not a statistically significant change. Sexual development was not different in treated vs. control males in regards to preputial separation. However, the Sponsor noted a slight incidence of early onset of mean day of vaginal perforation in F1 females in Group 4 vs. controls (34.3 days vs. 35.8 days), and attributes this slight acceleration in development to the slight increase in bodyweight of the F1 females at PPD21. While the early onset of perforation was a statistically significant change from controls, Group 4 was not significantly different from the other treated groups. Overall, this change is minimal, and likely not treatment related.

Necropsy: There were no noted significant findings that were different from control, and there were a large number of litters and pups with no abnormalities.

F1 behavioral evaluation: There were no noted significant findings that were different from control in regards to the E-maze learning test, auditory acuity, or locomotor coordination.

F1 reproduction:

Body weight: There were no significant differences in body weight change in treated vs. control F1 females during their gestation period (GD0-13).

Mating time course: There were no significant differences in time to mate in treated vs. control F1 females. They ranged from 2.4 to 3.3 days after pairing.

Fertility data: All males and females in Groups 1-4 mated and were fertile except for one male in Group 3. All F1 females in Groups 1-4 were pregnant upon necropsy at GD13. One F1 female in Group 3 was sacrificed due to poor clinical condition on GD11, but was pregnant. All pregnant F1 females were sacrificed on GD13 according to schedule. There were no significant differences in treated vs. control groups for number of corpora lutea, number of implantations, % pre- or post-implantation loss, number of live embryos or % of implantations.

F2 findings: The F2 generation was not examined. F1 females were sacrificed on GD13, and only fertility parameters in regards to F2 were noted. See results above for F1 reproduction.

2.6.6.7 Local tolerance

Local tolerance of tranexamic acid was addressed in the 39-week repeat dose toxicity study in dogs. Oral capsules were administered twice per day (every 12 hours). Resistance to the dosing procedure was noted starting at Week 5 and on in the high dose (600 mg/kg/bid) groups. As such, capsules were coated with tinned dog food immediately prior to dosing in order to help alleviate the resistance to dosing.

The route of administration for Cyklokapron (reference drug) is by intravenous infusion, and there is no information in the most current labeling regarding local tolerance toxicity.

2.6.6.8 Special toxicology studies

The label for Cyklokapron notes the nonclinical ocular toxicity of tranexamic acid in the warnings section:

- **“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.”**

Due to the nonclinical ocular toxicity noted in the label, the Sponsor has provided literature studies to support the safety of tranexamic acid. The first study by Johnson et al. (1977) contradicts the ocular findings noted in the rabbit in the current Cyklokapron label, and documents that no retinal changes (via electroretinography or light and electron microscopy) were observed in New Zealand white rabbits dosed with 0-500 mg/d tranexamic acid for 1-10 months. The high dose equates to an HED of 2400 mg/d.

The Sponsor notes that more recent studies (since the approval of Cyklokapron) implicate that the ocular toxicity observed is a result of the exaggerated pharmacological action of tranexamic acid, mainly due to the excessive inhibition of fibrinolysis. They note that **“similar effects are observed in dogs, mice and humans with genetic plasminogen deficiencies resulting in impaired fibrinolysis.”** Johnstone McLean et al. (2008) have observed dogs with a genetic deficiency of plasminogen having thick mucoid eye discharge, with normal papillary light reflexes, palpebral reflexes, eye motility, drainage, and intraocular pressure. Drew et al. (1998) have also observed that plasminogen-deficient mice have fibrin-rich conjunctival lesions, with secondary effects on the cornea. Kao et al. (1998) have observed that mice deficient in both plasminogen and fibrinogen do not develop these lesions. Human patients with a genetic deficiency of plasminogen have been observed to have liginous conjunctivitis of the eye, which is a fibrin rich thick eye exudate. While other mucosal surfaces can be affected as well, the eye appears to be the most sensitive organ for chronic fibrinolysis inhibition (Schuster and Seregard, 2003). However, it has been shown in a patient treated with tranexamic acid who developed conjunctivitis, that it is reversible after discontinuing medication (Diamond et al., 1991).

The Sponsor concludes that the eye exudates in the 39-week dog study reviewed above are similar to those found in dogs with genetic plasminogen deficiency. In addition, they suggest that the findings in mice are due to an excessive build up of fibrin which could not be removed due to the lack of functional plasminogen. As such, the ocular toxicity findings are likely the result of exaggerated pharmacology of tranexamic acid.

2.6.6.9 Discussion and Conclusions

In chronic 39-week toxicity study in male and female dogs, treatment-related transient ocular toxicity was observed mainly at a high dose of 600 mg/kg/bid. Observations included reddening and discharge in the eyes, changes in the nictitating membrane/conjunctiva, altered reflectivity in the fundus of the eye, conjunctival inflammation, and inflammatory exudate in the eye. In previous studies with tranexamic acid that are documented in the literature and provided in the current Cyklokapron label, dose- and time-related ophthalmological changes were also observed in the rat, cat, and dog at doses between 250-1600 mg/kg/d at durations of 6 days to 1 year, with an incidence of 25-100% of animals treated. Some of the ocular changes that occurred in the 39-week study in the tapetum of the eye are not relevant to human administration of tranexamic acid, as humans do not have a tapetum. However, other ocular changes, e.g., inflammation of the nictitating membrane and conjunctivitis, which occur upon administration of tranexamic acid to female dogs should be identified as a potential risk in human populations.

The embryofetal and pre/postnatal development studies conducted by the Sponsor show no dose-related toxicity of tranexamic acid in the rat in regards to maternal and fetal health. Slight maternal and fetal changes in body weight occur during gestation and lactation, but resolve themselves over time.

Of note is that no ocular changes were noted in either rat reproductive toxicity study.

Toxicokinetics in the chronic dog study showed dose-related increases of C_{max} and AUC, with a less proportional increase of AUC in female dogs at 600 mg/kg/bid. T_{max} was found to occur at 1.5-3 hrs and t_{1/2} ranged from 1.7-3.2 hrs. In the reproductive study with rats, while AUC was not determined, plasma concentrations of tranexamic acid were also shown to increase dose-proportionally at the mid-dose, but not at the high dose (750 mg/kg/bid). Also in the rats, fetal plasma concentrations of tranexamic acid were detectable at each dose, indicating in utero exposure to tranexamic acid.

NOAELs were determined for the three Sponsor conducted studies. Due to ocular effects in the dog, the NOAEL for male and female dogs was established at 300 mg/kg/bid (600 mg/kg/d). In both of the reproductive studies, the maternal and fetal NOAEL for rats was established at 750 mg/kg/bid (1500 mg/kg/d). Human exposure to tranexamic acid in clinical studies results in the following PK parameters. Single dose values are from Phase 1 protocol XP12B-101, while multi-dose values are from a Sponsor conducted study outside of the IND.

	Dose	C _{max} (µg/mL)	AUC _{0-inf} (µg*h/mL)	T _{max} (h)	t _{1/2} (h)	Systemic bioavail (F) (%)
MR tablet	single 1.3g	11.25	69.1	2.94	11.37	44.7
MR tablet	1.3g tid, 5days ^a	15.8	74.8 ^b	2.6	n/a	--

a: Moore et al., 2008.

b: AUC_τ

The intended clinical dose is a TID regimen of 1.3 g tranexamic acid (2x650 mg MR tablets) for a total dose of 3.9 g/d. Comparison of dog PK to human PK now gives the following dose and exposure multiples for the NOAELs of these studies:

Species	NOAEL (Dose)	HED	AUC ($\mu\text{g}\cdot\text{h/mL}$)	Dose multiple (based on mg/m^2)	Exposure multiple (based on AUC)
Dog (chronic)	600mg/kg/d	19.4g/d	358	5	4.8
Rat (Seg 2 and Seg 2/3)	1500mg/kg/d	14.6g/d	*	3.7	*
Human (tid)	3.9g/d	--	74.8		

*: Rat AUC was not available in the studies provided

The NOAEL for tranexamic acid in dogs (600 mg/kg/d), based on both exposure and dose, is 5 times the clinical dose. There was low systemic toxicity, and the observed ocular findings were the primary reason for setting the NOAEL. While some of the ocular findings are not clinically relevant due to the absence of a tapetum in human subjects, there are still ocular effects noted in clinical studies with tranexamic acid. According to the clinical overview, the number of ophthalmic adverse events was low (<1%), but those that led to discontinuation, and were considered possibly related to tranexamic acid included **4 eye disorders – optic disc drusen, visual acuity reduced, vision blurred, and visual field defect**. However, the overview does note that the ocular events noted in study XP12B-MR-302 were reversed after withdrawal of treatment. Overall, ocular toxicity due to tranexamic acid is potentially a related effect of drug administration, and should be communicated to patients, and noted in labeling.

2.6.6.10 Tables and Figures

None.

2.6.7 TOXICOLOGY TABULATED SUMMARY

The following tables were submitted by the Sponsor (found in Module 2.6.7):

2.6.7.1 Toxicology: Overview for Tranexamic Acid

Type of Study	Species and Strain	Route	Duration of Dosing	Doses (mg/kg) ^{a,b}	GLP	Testing Facility	Study Number	Location
Repeat-Dose Toxicity (Pivotal)	Dog, Beagle	Oral	9 Months	0, 200, <u>600</u> , 1200 mg/kg/day (0, 100, <u>300</u> , 600 mg/kg BID)	Yes	T	US0001	4.2.3.2
Reproduction Toxicity	Rat, Sprague-Dawley	Oral	11 Days (GD6-GD17)	0, 300, 750, <u>1500</u> mg/kg/day (0, 150, 375, 750 mg/kg BID)	Yes		TUS0002	4.2.3.5.2
	Rat, Sprague-Dawley	Oral	35 Days (GD6-PND20)	0, 300, 750, <u>1500</u> mg/kg/day (0, 150, 375, 750 mg/kg BID)	Yes	L	US0003	4.2.3.5.3

b(4)

^a For pivotal Repeat-Dose Toxicity, the highest No Observed Adverse Effect Level (NOAEL) is underlined.
^b For Reproduction Toxicity, the highest No Observed Effect Level (NOEL) is underlined.
 GD = Gestation Day; PND = Post Natal Day

2.6.7.7 Repeat-Dose Toxicity: Pivotal Studies for Tranexamic Acid

Species/Strain:	Dog, Beagle	Duration of Dosing:	39 Weeks	Study No.	TUS0001					
Initial Age:	5-7 Months	Duration of Postdose:	None	Location in CTD:	4.2.3.2					
Date of First Dose:	November 16, 2004	Method of Administration:	Oral	GLP Compliance:	Yes					
Vehicle/Formulation:	Gelatin Capsules									
Special Features:	Group 5 dogs were Atapetal									
No Observed Adverse Effect Level: 600 mg/kg/day (300 mg/kg BID)										
Daily Dose (mg/kg)	Group 1 0 (Control) (0 mg/kg BID, 12 hours apart)		Group 2 200 mg/kg/day (100 mg/kg BID, 12 hours apart)		Group 3 600 mg/kg/day (300 mg/kg BID, 12 hours apart)		Group 4 1200 mg/kg/day (600 mg/kg BID, 12 hours apart)		Group 5 1200 mg/kg/day (600 mg/kg BID, 12 hours apart)	
Number of Animals	5M:	5F:	4M:	4F:	4M:	4F:	5M:	5F:	3M:	3F:
Toxicokinetics: AUC(0-12) (µg·hr/ml) - Day 1			137	121	316	358	689	467	358	336
Noteworthy Findings										
Died or Sacrificed Moribund	0/5	0/5	0/4	0/4	0/4	1/4 (Day 3)	0/5	0/5	0/3	0/3
Body Weight (%) ^a	-	-	-	-	-	-	-	-	-	-
Food Consumption (%) ^a	-	-	-	-	-	-	-	-	-	-
Water Consumption (%)										

- No noteworthy findings. + Mild ++ Moderate +++ Marked* p<0.05 ** p<0.01
a At end of dosing period. For controls, group means are shown. For treated groups, percent of control is shown. Statistical significance based on actual data.

2.6.7.7 Repeat-Dose Toxicity: Pivotal Studies for Tranexamic Acid (Continued)

Daily Dose (mg/kg)	Group 1 0 (Control) (0 mg/kg BID, 12 hours apart)		Group 2 200 mg/kg/day (100 mg/kg BID, 12 hours apart)		Group 3 600 mg/kg/day (300 mg/kg BID, 12 hours apart)		Group 4 1200 mg/kg/day (600 mg/kg BID, 12 hours apart)		Group 5 1200 mg/kg/day (600 mg/kg BID, 12 hours apart)	
Number of Animals	5M:	5F:	4M:	4F:	4M:	4F:	5M:	5F:	3M:	3F:
Clinical Observations	Abnormal eye color - (1/5) Eye Discharge - (1/5)				Salivation - (1/4)	Salivation + (1/4)	Abnormal eye color +++ (4/5); Eye discharge +++ (4/5) Partially closed eye - (1/5) Swollen eye - (1/5) Salivation - (3/5)	Abnormal eye color -- (4/5); Eye discharge +++ (3/5) Salivation - (3/5)	Abnormal eye color +++ (3/3) Eye discharge +++ (2/3) Salivation - (3/3)	Abnormal eye color +++ (4/5); Eye discharge +++ (1/5) Salivation - (3/3)
Ophthalmoscopy					Altered tapetal fundus reflectivity (2/3)	Altered tapetal fundus reflectivity (2/5)	Nititating membrane purulent exudates (2/5) Altered tapetal fundus reflectivity (2/5)	Altered tapetal fundus reflectivity (1/5)	Nititating membrane purulent exudates (1/3)	Nititating membrane purulent exudates (1/3)

- No noteworthy findings. + Mild ++ Moderate +++ Marked
* p<0.05 ** p<0.01
a At end of dosing period. For controls, group means are shown. For treated groups, percent of control is shown. Statistical significance is based on actual data.

2.6.7.7 Repeat-Dose Toxicity: Pivotal Studies for Tranexamic Acid (Continued)

Daily Dose (mg/kg)	Group 1 0 (Control) (0 mg/kg BID, 12 hours apart)		Group 2 200 mg/kg/day (100 mg/kg BID, 12 hours apart)		Group 3 600 mg/kg/day (300 mg/kg BID, 12 hours apart)		Group 4 1200 mg/kg/day (600 mg/kg BID, 12 hours apart)		Group 5 1200 mg/kg/day (600 mg/kg BID, 12 hours apart)	
	5M:	5F:	4M:	4F:	4M:	4F:	5M:	5F:	3M:	3F:
Number of Animals										
Electrocardiography	-	-	-	-	-	-	-	-	-	-
Hematology/ Number evaluated	5	5	4	4	4	3	5	5	3	3
Week 17	-	-	-	-	-	-	-	-	-	-
Week 39	-	-	-	-	-	-	-	-	-	-
Serum Chemistry/ Number examined	5	5	4	4	4	3	5	5	3	3
Week 17	-	-	-	-	-	-	-	-	-	-
Week 39	-	-	-	-	-	-	-	-	-	-
Urinalysis	5	5	4	4	4	3	5	5	3	3
Week 17	-	-	-	-	-	-	-	-	-	-
Week 39	-	-	-	-	-	-	-	-	-	-
Organ Weights (%) ^a	-	-	-	-	-	-	-	-	-	-
Gross Pathology	-	-	-	-	-	-	-	-	-	-
Early Descendant	-	-	-	-	-	-	-	-	-	-

- No noteworthy findings. + Mild ++ Moderate +++ Marked
 * p<0.05 ** p<0.01
 a At end of dosing period. For controls, group means are shown. For treated groups, percent of control is shown. Statistical significance based on actual data.

2.6.7.7 Repeat-Dose Toxicity: Pivotal Studies for Tranexamic Acid (Continued)

Daily Dose (mg/kg)	Group 1 0 (Control) (0 mg/kg BID, 12 hours apart)		Group 2 200 mg/kg/day (100 mg/kg BID, 12 hours apart)		Group 3 600 mg/kg/day (300 mg/kg BID, 12 hours apart)		Group 4 1200 mg/kg/day (600 mg/kg BID, 12 hours apart)		Group 5 1200 mg/kg/day (600 mg/kg BID, 12 hours apart)	
	5M:	5F:	4M:	4F:	4M:	4F:	5M:	5F:	3M:	3F:
Number of Animals										
Histopathology										
Eye Finding	-	-	-	Conjunctival inflammatory exudate (1/4)	-	-	-	Conjunctival inflammatory exudates (2/5) Conjunctivitis (1/5)	-	Conjunctival inflammatory exudates (1/3) Conjunctivitis (1/3)
Urinary Bladder	Cystitis (1/5)	-	-	-	-	-	Cystitis (1/5) Ulceration (1/5)	Cystitis (2/5)	-	-

- No noteworthy findings.
 a Absolute and relative weights differed from controls in the same direction. For controls, group means are shown. For treated groups, percent of control is shown.

2.6.7.13 Reproductive and Developmental Toxicity: Segment 2 for Tranexamic Acid

Design similar to ICH 4.1.3	Yes	Duration of Dosing:	GD6-GD17	Study No.	TUS0002
Species/Strain:	Rat, Sprague-Dawley	Day of Mating:	Time mated (G0)		
Initial Age:	10 weeks	Day of C-Section:	GD20	Location in CTD:	4.2.3.5.2
Date of First Dose:	January 18, 2005	Method of Administration:	Oral gavage	GLP Compliance:	Yes
No Observed Adverse Effect Level:	F ₀ Females: 1500 mg/kg/day F ₁ Litters: 1500 mg/kg/day	Vehicle/Formulation:	Water	Special Features: Satellite group of 5/dose (dosed GD6-GD20) used for TK analysis on GD20; dam and fetal blood sampled at 3 hours post dose	
Daily Dose (mg/kg)		0 (Control)	300 mg/kg/day (150 mg/kg BID)	750 mg/kg/day (375 mg/kg BID)	1500 mg/kg/day (750 mg/kg BID)
Dams/Does:	Toxicokinetics: C3 GD20 dam (µg/ml)	NT	11.1	32.8	35.5
	Toxicokinetics: C3 GD20 fetus (µg/ml) (%maternal)	NT	1.45 (13%)	4.28 (13%)	5.60 (16%)
	No. Pregnant	20/24	18/24	18/24	17/24
	No. Died or Sacrificed Moribund	0	0	0	0
	No. Aborted or with Total Resorption of Litter	0	0	0	0
	Clinical Observations	-	-	-	-
	Necropsy Observations	-	-	-	-
	Body Weight (%) ^a	-	-	-	-
	Food Consumption (%) ^a	-	-	-	-
	Mean No. Corpora Lutea	13.6	14.2	13.3	14.8
	Mean No. Implantations	11.2	12.7	12.2	12.8
Mean % Preimplantation Loss	17.8%	10.4%	8.0%	13.1%	

- No noteworthy findings. +Mild +-Moderate +++Marked (6) GD = Gestation day NT = not tested
* p<0.05 ** - p<0.01

a At end of dosing period. For controls, group means are shown. For treated groups, percent of controls are shown. Statistical significance based on actual data

2.6.7.13 Reproductive and Developmental Toxicity: Segment 2 for Tranexamic Acid

Daily Dose (mg/kg)		0 (Control)	300 mg/kg/day (150 mg/kg BID)	750 mg/kg/day (375 mg/kg BID)	1500 mg/kg/day (750 mg/kg BID)	
Litters:	No. Litters Evaluated:	20	18	18	17	
	No. Live Fetuses	217	221	207	204	
	Mean No. Resorptions	0.3	0.4	0.7	0.8	
	No. of Litters with Dead Fetuses	0	0	0	0	
	Mean % Postimplantation Loss	2.7	2.9	6.0	6.0	
	Mean Fetal Body Weight (g)	3.74	3.81	3.70	3.82	
	Fetal Sex Ratios (% male fetuses)	45.1	48.4	50.6	49.6	
	Fetal Anomalies:					
	Gross External (Litters)	0/217 (0/20)	0/221 (0/18)	0/207 (0/18)	0/204 (0/17)	
	Visceral Anomalies (Litters)	1/113 (1/20) ^a	0/114 (0/18)	1/108 (1/18) ^b	0/105 (0/17)	
	Skeletal Anomalies (Litters)	2/104 (2/20) ^c	0/107 (0/18)	0/99 (0/18)	1/99 (1/17)	
	Total Affected Fetuses (Litters)	3/217 (3/20)	0/221 (0/18)	1/207 (1/18)	1/204 (1/17)	

- No noteworthy findings.

* p<0.05 ** p<0.01

a = enlarged ventricle, single lobe lungs, microphthalmia

b = right sided aortic arch, right sided descending aorta, single lobe lungs

c = reduced in size orbital cavity, malformed neural arch, malformed scapula

2.6.7.14 Reproductive and Developmental Toxicity: Segment 3 for Tramexamic Acid

Oral (Gavage) Twice Daily Pre- and Postnatal Developmental Toxicity Study in the Rat (TUS0003)

Design similar to ICH 4.1.2:	Yes	Duration of Dosing:	GD6 to PND 20	Study Number:	TUS0003
Species/Strain:	Rat/Sprague-Dawley	Day of Mating:	GD0		
Initial Age:	10 weeks	Method of Administration:	Oral Gavage	Location in CTD:	4.2.3.5.3
Date of First Dose:	March 21, 2005			GLP Compliance:	Yes
No Observed Adverse-Effect Level:	F ₀ Males: NA F ₀ Females: 1500 mg/kg/day F ₁ Litters: 1500 mg/kg/day	Vehicle/Formulation:	UHP Water	Milk samples (3 dams/group) collected on PND7 (samples stored but not analyzed; TK analysis was not performed 20 rats/group) were used to assess effects on reproduction; F1 females sacrificed on GD13	
Daily Dose (mg/kg)		0 (Control)	300 mg/kg/day (150 mg/kg BID)	750 mg/kg/day (375 mg/kg BID)	1500 mg/kg/day (750 mg/kg BID)
F ₀ Females:	No. Pregnant	24	23	23	24
	No. Died/Sacrificed Moribund	0	1	0	0
	No. Aborted or with Total Resorption of Litter	0	0	0	0
	Clinical Observations	-	-	-	-
	Necropsy Observations	-	-	-	-
	Gestation Body Weight (%) ^a	100% (366 g)	98%	104%*	106%*
	Lactation Body Weight (%) ^a	100% (319 g)	101%	103%*	107%*
	Gestation Food Consumption (%) ^a	100% (29 g/rat/day)	97%	107%*	107%*
	Lactation Food Consumption (%) ^a	100% (54 g/rat/day)	111%*	109%*	115%**
	Mean Duration of Gestation (days)	24.4	22.5b	22.5	22.3
No. with Abnormal Parturition	0	1	0	0	

- No noteworthy findings GD Gestation Day PND Post-Natal Day
 * p<0.05 ** p<0.01
 a At end of period. For controls, group means are shown within parentheses. Statistical significance is based on actual data.
 b includes one female euthanized due to prolonged parturition

2.6.7.14 Reproductive and Developmental Toxicity: Segment 3 for Tramexamic Acid (Continued)

Daily Dose (mg/kg)		0 (Control)	300 mg/kg/day (150 mg/kg BID)	750 mg/kg/day (375 mg/kg BID)	1500 mg/kg/day (750 mg/kg BID)
F ₁ Litters: (Prewean)	No. Litters Evaluated	24	23	23	24
	Mean No. of Implantations	11.6	12.1	12.9	13.4*
	Mean No. Pups/Litter	11.1	11.8	12.1	12.5
	Live Births (%)	100%	98.1%	99.7%	99.7%
	No. Litters with Stillborn Pups	0	2	1	1
	Postnatal Survival from birth to Day 4 (compared to Day 0 or 1??)	98.5%	99.7%	99.3%	98.1%
	Postnatal Survival to Weaning	74.3%	85.8%	79.9%	81.3%
	No. of Total Litter Losses	1	0	0	1
	Change in Pup Body Weights-Males (%) ^a	100% (44.1 g)	101%	100%	106%*
	Change in Pup Body Weights-Females (%) ^a	100% (43.2 g)	100%	101%	106%*
	Pup Sex Ratios (%Males)	49.5	52.2	53.4	44.8
	Pup Clinical Signs	-	-	-	-
	Developmental Milestones ^c	-	-	-	-
	Pup Necropsy Observations	-	-	-	-

- No noteworthy findings. +Mild ++Moderate +++Marked
 * p<0.05 ** p<0.01
 a From birth to weaning expressed as % of control absolute change in body weight. For controls, the group means are shown within parentheses. Statistics are based on actual data.
 b Before (and after) culling
 c Ear opening (Day 3), eye opening (Day 15), righting reflex (Day 5), startle response (Day 15), pupillary light reflex (Day 21)

2.6.7.14 Reproductive and Developmental Toxicity: Segment 3 for Tranexamic Acid (Continued)

Daily Dose (mg/kg)		0 (Control)	300 mg/kg/day (150 mg/kg BID)	750 mg/kg/day (375 mg/kg BID)	1500 mg/kg/day (750 mg/kg BID)
F ₁ Males (Postweaning)	Total No. Evaluated Postweaning	20	20	20	20
	Mean No. Evaluated/Litter	0.83	0.91	0.87	0.83
	No. Died or Sacrificed Moribund	0	0	0	0
	Clinical Observations	-	-	-	-
	Necropsy Observations	-	-	-	-
	Body Weight Change (%) ^a	100% (465 g)	102%	103%	106%
	Preputial Separation	44.0	43.9	44.1	42.7
	Sensory Function- Preyer's Reflex	-	-	-	-
	Motor Activity - Rotarod time (sec)	92.3	93.8	106.5	98.9
	Learning and Memory E-maze	-	-	-	-
	Mean No. Days Before Mating	2.6	2.4	3.3	2.4
	No. of Males that Mated	20	20	19	20
No. of Fertile Males	20	20	19	20	

- No noteworthy findings. +Mild ++Moderate +++Marked
 * p<0.05 ** p<0.01
 a From weaning to mating. For controls, group means are shown within parentheses. Statistical significance is based on actual data.
 b At end of postweaning period. For controls, group means are shown. For treated groups, percent of control is shown. Statistics are based on actual data

2.6.7.14 Reproductive and Developmental Toxicity: Segment 3 for Tranexamic Acid (Continued)

Daily Dose (mg/kg)		0 (Control)	300 mg/kg/day (150 mg/kg BID)	750 mg/kg/day (375 mg/kg BID)	1500 mg/kg/day (750 mg/kg BID)
F ₁ Females: (Postweaning, Caesarean Sections)	No. Evaluated Postweaning	20	20	20	20
	No. Died or Sacrificed Moribund				
	Clinical Observations				
	Necropsy Observations				
	Body Weight Change (%) ^a	100% (224 g)	101%	102%	100%
	Gestation (G)	100% (316 g)	101%	103%	101%
	Mean Age of Vaginal Patency (days)	35.8	34.7	34.8	34.3
	Sensory Function- Preyer Reflex	-	-	-	-
	Motor Activity- Rotarod Time (sec)	89.4	87.2	101.4	109.9
	Learning and Memory- E-maze	-	-	-	-
	Mean No. Days Before Mating	2.6	2.4	3.3	2.4
	No. of Females Sperm-Positive	20	20	20	20
	No. of Pregnant Females	20	20	20 ^c	20
	Mean No. Corpora Lutea	15.2	16.5	15.3	16.6*
	Mean No. Implantations	14.5	15.7	14.9	15.6
Mean % Preimplantation Loss	4.6	5.0	2.2	6.0	

- No noteworthy findings.
 * p<0.05 ** p<0.01
 a For controls, group means are shown within parentheses. Statistical significance is based on actual data.
 b From birth to mating
 c One female (#238) was sacrificed on GD11 due to poor clinical condition. Necropsy found broken upper palate with bone protruding into the oral cavity with upper incisors off center. The perinasal area was swollen, abnormal shape and the surrounding soft tissue was dark red and gelatinous. There was periorbital red staining. Although the report did not provide details, these findings are consistent with traumatic injury. The rat was confirmed pregnant, but litter data were not included in group means

2.6.7.14 Reproductive and Developmental Toxicity: Segment 3 for Tranexamic Acid (Continued)

Daily Dose (mg/kg)		0 (Control)	300 mg/kg/day (150 mg/kg BID)	750 mg/kg/day (375 mg/kg BID)	1500 mg/kg/day (750 mg/kg BID)
F ₂ Litters: (examined on GD13)	Mean No. Implantations/Litter	14.5	15.7	14.9	15.6
	Mean No. Resorptions	1.5	1.9	1.2	1.6
	No. of Litters with Dead Embryos	1	0	1	0
	No. of Dead Embryos	1	0	1	0
	Mean % Postimplantation Loss	5.4	7.2	5.5	3.4
	Mean No. Live Embryos	13.7	14.6	14.1	15.0

-No noteworthy findings
 * p<0.05 ** p<0.01

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Pharmacology/Toxicology recommends approval for tranexamic acid (Lysteda) for the treatment of heavy menstrual bleeding.

Unresolved toxicology issues (if any): none

Recommendations: none

Suggested labeling: Submitted labeling is acceptable with the following modifications (additions are underlined, deletions are crossed through).

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2 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

APPENDIX/ATTACHMENTS**REFERENCES:**

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this page is the manifestation of the electronic signature.**

/s/

Kimberly P Hatfield
6/22/2009 02:06:26 PM
PHARMACOLOGIST

Lynnda Reid
6/22/2009 02:18:17 PM
PHARMACOLOGIST

I concur with the Conclusions and Recommendations of the
Primary Reviewer, Dr. Hatfield. The nonclinical data support
approval of this NDA. I also concur with
the proposed labeling.

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA OR SUPPLEMENT**

NDA/BLA Number: 22-430

Applicant: Xanodyne
Pharmaceuticals

Stamp Date: 1-30-2009

Drug Name: Lysteda (tranexamic acid
modified-release tablets)

NDA/BLA Type: 505(b)(2)

On **initial** overview of the BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	Y		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	Y		
3	Is the pharmacology/toxicology section of the NDA legible so that substantive review can begin?	Y		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility, juvenile studies, acute and repeat dose adult animal studies*, animal ADME studies, safety pharmacology, etc)?	Y		The Sponsor has conducted three nonclinical studies: a 9-mo repeat dose study in dogs, an embryo-fetal development study in rats, and a pre/postnatal reproductive study in rats. For all other studies, they are relying on published literature or FDA's finding of safety for Cyklokapron® as reflected in labeling. See additional comments below for further details on what the Sponsor is relying on for nonclinical safety for each type of study.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	Y		Studies in dogs and rats were conducted with tranexamic acid only (minus excipients for clinical tablet formulation) either as a powder in capsules (dogs) or dissolved in UHP water for oral gavage (rats). As such the formulations are not the same as the tablet formulation for clinical use, but are acceptable based on the dosing regimen.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	Y		Clinical route of administration is via modified-release tablet. Both dog and rat studies were conducted via oral capsule or oral gavage.
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	Y		All 3 nonclinical studies were conducted in compliance with GLP as required by the United Kingdom GLP regulations 1999.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	Y		The Agency requested that the Sponsor conduct a chronic dose animal study, and Segment 2 and 3 reproductive toxicity studies. All have been completed, submitted and reviewed under the IND prior to NDA submission.

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA OR SUPPLEMENT**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?		N	Human dose multiples have been included. At this time, the accuracy of the dose multiples have not been confirmed. The Cyklokapron label does contain additional information concerning carcinogenicity that is not included in the current label. Since the Sponsor is relying on the previous label for carcinogenicity findings, they should have the same information.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	Y		4 process impurities have been identified, and total impurities in the active material are present at not more than <u> </u> . This equal <u> </u> impurity exposure with <u> </u> dose of active material.
11	Has the applicant addressed any abuse potential issues in the submission?	Y		The proposed label contains similar information as the Cyklokapron label. There are no known cases of overdosage with either product, and no subject took > twice the daily dosage in a 24-hr period (7.8 g/day).
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable

b(4)

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? YES

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Additional notes:

Nonclinical studies submitted to the NDA:

Pharmacokinetics	
Study #	Title
OA497	Development/validation of a GC/MS method for the determination of tranexamic acid in rat plasma
OA496	Development/validation of a GC/MS method for the determination of tranexamic acid in dog plasma

Toxicology	
Study #	Title
TUS0001	39 week oral (capsule) toxicity study in the dog
TUS0002	Oral (gavage) twice daily dosing developmental toxicity study in the rat
TUS0003	Oral (gavage) twice daily dosing pre and post-natal developmental toxicity study in the rat

Additional comments:

Since this is a 505(b)(2) application, the Sponsor will be relying on published literature, and on FDA's previous finding of safety for Cyklokapron® (Tranexamic acid – tablets and/or injection indicated in patients with hemophilia for short term use (2-8days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction). NDA 19-280 is for Cyklokapron tablets (withdrawn – not for safety reasons), and NDA 19-281 is for Cyklokapron injection (approved and active). The following is a list of what the current Sponsor will rely on in terms of nonclinical safety for their application:

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA OR SUPPLEMENT**

- Pharmacology
 - Relying on published literature for primary/secondary pharmacodynamics and safety pharmacology (central nervous system).
- Pharmacokinetics and ADME
 - Relying on published literature of available data in humans.
 - Nonclinical TK studies were included in submitted toxicology study TUS0001.
 - The Sponsor has not identified relevant literature for nonclinical PK studies published since 1986.
- Single-dose toxicity
 - Relying on FDA's finding of safety for Cyklokapron as reflected in labeling.
 - The Sponsor has not conducted any single-dose studies.
 - The Sponsor has not identified relevant literature for single-dose studies published since 1986.
- Repeat-dose toxicity
 - Relying on their own 9-month chronic dog study (TUS0001) and FDA's finding of safety for Cyklokapron as reflected in labeling.
- Genotoxicity
 - Relying on published literature (bacterial reverse mutation assays, in vitro mammalian cell systems and in vivo mammalian assay) and FDA's finding of safety for Cyklokapron as reflected in labeling.
 - The Sponsor has not conducted any genetic toxicity studies.
- Carcinogenicity
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 - The Sponsor has not identified relevant literature for carcinogenicity studies published since 1986.
- Reproductive and developmental toxicity
 - Fertility and early embryonic development
 - Relying on FDA's finding of safety for Cyklokapron as reflected in labeling to address potential effects on fertility and, in part, on the developing embryo/fetus.
 - The Sponsor has not conducted any fertility studies or non-rodent embryo-fetal developmental toxicity studies.
 - The Sponsor has not identified relevant literature for reproductive toxicity studies published since 1986.
 - Embryo-fetal development
 - Relying on their own embryo-fetal developmental toxicity study (TUS0002).
 - Prenatal and postnatal development
 - Relying on their own prenatal and postnatal developmental toxicity study (TUS0003).
- Local tolerance
 - Relying on FDA's finding of safety for Cyklokapron as reflected in labeling.
 - The Sponsor has not conducted any local tolerance studies.
 - The Sponsor has not identified relevant literature for local tolerance toxicity studies published since 1986.
- Other toxicity
 - Relying on FDA's finding of safety for Cyklokapron as reflected in labeling.
 - The Sponsor has not conducted any other toxicity studies (i.e. immunotoxicity, dependence potential, metabolite toxicity).
 - The Sponsor has not identified relevant literature for other toxicity studies published since 1986.

Reviewing Toxicologist – Kimberly Hatfield, Ph.D.

Date

Team Leader/Supervisor – Lynnda Reid, Ph.D.

Date

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this page is the manifestation of the electronic signature.**

/s/

Kimberly P Hatfield
5/13/2009 03:49:46 PM
PHARMACOLOGIST

Lynnda Reid
5/14/2009 04:35:44 PM
PHARMACOLOGIST

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA OR SUPPLEMENT**

NDA/BLA Number: 22-430

Applicant: Xanodyne
Pharmaceuticals

Stamp Date: 1-30-2009

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modified-release tablets)

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b(4)

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 - The Sponsor has not identified relevant literature for other toxicity studies published since 1986.

Reviewing Toxicologist – Kimberly Hatfield, Ph.D.

Date

Team Leader/Supervisor – Lynnda Reid, Ph.D.

Date

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Kimberly P Hatfield
4/3/2009 04:19:51 PM
PHARMACOLOGIST

Lynnda Reid
4/3/2009 04:26:39 PM
PHARMACOLOGIST