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APPLICATION NUMBER:

22-430

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY ADDENDUM

NDA: 22-430	Submission Dates: 1/30/2009, 4/24/2009, 9/4/2009, 9/15/2009, 10/27/2009, 11/06/2009
Brand Name	Lysteda
Generic Name	Tranexamic acid
Reviewer	Hyunjin Kim, Pharm.D., M.S.
Team Leader	Myong-Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products
Sponsor	Xanodyne Pharmaceuticals, Inc.
Relevant IND, NDA	IND 68,096, NDA 19-281
Submission Type	Priority
Formulation; Strength(s)	Tablet; tranexamic acid 650 mg
Indication	Treatment of cyclic heavy menstrual bleeding

This addendum is to revise the original Clinical Pharmacology review of NDA 22-430 (DARRTS, 10/15/2009) which contains the following section 2.2.5.4:

2.2.5.4 What are the characteristics of drug metabolism?

Tranexamic acid is eliminated intact by urinary excretion via glomerular filtration. Only a small fraction of the drug is metabolized. 1 and 0.5% of the oral dose are excreted as a dicarboxylic acid and acetylated metabolite, respectively.

NDA 22-430 was filed as a 505(b)(2) application and made a reference to the nonclinical and human safety information of Cyklokapron IV (NDA 19-281, approval, December 30, 1986, Pfizer). However, the third sentence from the section 2.2.5.4. of the review, "1 and 0.5% of the oral dose are excreted as a dicarboxylic acid and acetylated metabolite, respectively", was relied upon the labeling of Cyklokapron 500 mg tablet (NDA 19-280, approval, December 30, 1986, Pfizer). Therefore, the aforementioned sentence should be removed from the review and the section 2.2.5.4 of the review should be read as following:

2.2.5.4 What are the characteristics of drug metabolism?

Tranexamic acid is eliminated intact by urinary excretion via glomerular filtration. Only a small fraction of the drug is metabolized.

1.1 Recommendation

The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds NDA 22-430 acceptable from a Clinical Pharmacology perspective.

1.2 Phase IV Commitments

None

1.3 Revised label

See next page.

19 Page(s) Withheld

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

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22430	ORIG-1	XANODYNE PHARMACEUTICS INC	Lysteda
NDA-22430	TRIAGE-1	XANODYNE PHARMACEUTICS INC	Lysteda

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/s/

HYUNJIN KIM
11/09/2009

MYONG JIN KIM
11/09/2009

OFFICE OF CLINICAL PHARMACOLOGY ADDENDUM

NDA: 22-430	Submission Dates: 1/30/2009, 4/24/2009, 9/4/2009, 9/15/2009, 10/27/2009
Brand Name	Lysteda
Generic Name	Tranexamic acid
Reviewer	Hyunjin Kim, Pharm.D., M.S.
Team Leader	Myong-Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products
Sponsor	Xanodyne Pharmaceuticals, Inc.
Relevant IND, NDA	IND 68,096, NDA 19-281
Submission Type	Priority
Formulation; Strength(s)	Tablet; tranexamic acid 650 mg
Indication	Treatment of cyclic heavy menstrual bleeding

The original Clinical Pharmacology review of NDA 22-430 (DARRTS, 10/15/2009) stated that the clinical pharmacology information submitted in NDA 22-430 was acceptable provided that agreement is reached between the sponsor and the Division regarding the language in the package insert. The agreement on language in the package insert was reached on 10/27/2009. The final agreed label is included in section 1.3 of this review.

1.1 Recommendation

The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds NDA 22-430 acceptable from a Clinical Pharmacology perspective.

1.2 Phase IV Commitments

None

1.3 Final agreed label

The final agreed label is attached.

18 Page(s) Withheld

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

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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/s/

HYUNJIN KIM
10/27/2009

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10/27/2009

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-430	Submission Dates: 1/30/2009, 4/24/2009, 9/4/2009, 9/15/2009
Brand Name	Lysteda
Generic Name	Tranexamic acid
Reviewer	Hyunjin Kim, Pharm.D., M.S.
Team Leader	Myong-Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products
Sponsor	Xanodyne Pharmaceuticals, Inc.
Relevant IND, NDA	IND 68,096, NDA 19-281
Submission Type	Priority
Formulation; Strength(s)	Tablet; tranexamic acid 650 mg
Indication	Treatment of heavy menstrual bleeding (HMB, menorrhagia) and the amelioration of symptoms associated with heavy menstrual bleeding, including limitations on social, leisure, and physical activities

An Optional Inter-Division Level Clinical Pharmacology Briefing was held on June 9, 2009 in conference room 3300 of White Oak Bldg 51. Attendees included Drs' Edward D. Bashaw, Hae-Young Ahn, Myong-Jin Kim, Doanh Tran, Seongeun Cho, Ting E Ong, Kris E Estes, Nitin Mehrotra, Jiang Liu, Lisa Soule and Hyunjin Kim.

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1 Executive Summary

Tranexamic acid is an antifibrinolytic agent which diminishes the dissolution of fibrin by plasmin. In U.S., intravenous (IV) and tablet formulations of tranexamic acid are currently approved for short-term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction in patients with hemophilia. The approved tranexamic acid products are as follows:

- Cyklokapron IV: 10 mg/kg, 3-4 times daily for 2-8 days (NDA 19-281, approval, December 30, 1986, Pfizer).
- Cyklokapron 500 mg tablet: 25 mg/kg, 3-4 times daily for 2-8 days (NDA 19-280, approval, December 30, 1986, Pfizer).

However, only the IV formulation (NDA 19-281) is currently available in U.S. The tablet formulation (NDA 19-280) was never marketed after its approval.

In this NDA, the sponsor is seeking approval of a new tablet formulation (650 mg) of tranexamic acid for the treatment of heavy menstrual bleeding (HMB, menorrhagia). The current submission is filed as a 505(b)(2) application and made a reference to the nonclinical and human safety information of Cyklokapron IV (NDA 19-281). Currently, there is no FDA approved drug for this indication. The proposed dosage regimen is two 650 mg tablets administered 3 times daily, a total of 3,900 mg daily, during menstruation up to five days.

The sponsor submitted four phase 1 trials to characterize the single and multiple dose pharmacokinetics (PK) and absolute bioavailability, and to assess the QT prolongation and the food effect on the exposure of tranexamic acid. In addition, two pivotal phase 3 safety and efficacy trials and the interim analysis of two ongoing phase 3 safety trials were submitted. The primary endpoint of these phase 3 trials was a reduction in Menstrual Blood Loss (MBL) during the entire menstrual period.

1.1 Recommendation

The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the clinical pharmacology information submitted in NDA 22-430 acceptable provided that agreement is reached between the sponsor and the Division regarding the language in the package insert.

1.2 Phase IV Requirements

A pediatric study is required under section 2 of the Pediatric Research Equity Act (PREA). The sponsor agreed to conduct a PK study with healthy female subjects, 12 – 17 years old, with heavy menstrual bleeding.

- Timeline (NDA 22-430, Response to Clinical Information Request #5, September 15, 2009)
 - Protocol submission to FDA: February 2010
 - Initiation of study: September 2010
 - Final study report submission to FDA: March 2012

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Tranexamic acid is a synthetic lysine derivative with antifibrinolytic activity. In the presence of tranexamic acid, the lysine receptor binding sites of plasmin for fibrin are occupied, thus preserve and stabilize fibrin's structure.

Pharmacokinetics of tranexamic acid

- Tranexamic acid was absorbed with a median (range) t_{max} of 3 (2 - 4) hours following a single administration of two Lysteda 650 mg tablets under fasting state.
- The absolute bioavailability (F) of Lysteda was 43.9%.
- Single and multiple dose trial was conducted to assess the PK linearity of Lysteda following a single oral dose (Day 1) and multiple dose administrations (2 x 650 mg every 8 hours, Days 2 to 7) under fasting state. Steady state was reached within 32 hours after the first dose.
- The PK linearity of Lysteda was calculated by comparing the ratio of least square means of AUC_{τ} (Day 7) to AUC_{inf} (Day 1). The ratio of least square means of AUC_{τ} (Day 7) to AUC_{inf} (Day 1) was 0.973 with 90% Confidence Interval (CI) between 86.5 and 109.5%.
- Lysteda exhibited linear PK independent of time following repeated administration (three times daily) of a 1,300 mg (2 x 650 mg) dose under fasting state. The ratio of AUC_{τ} (Day 7) to AUC_{inf} (Day 1) was close to 1.
- The plasma binding of tranexamic acid is about 3% and is mostly accounted for by its binding to plasminogen¹.
- Urinary excretion via glomerular filtration is the main route of elimination. More than 95% of the dose is excreted in the urine as the unchanged drug, which suggests that there is less than 5% of metabolism².
- The mean (coefficient of variation, CV) terminal half-life of tranexamic acid following a single dose administration of Lysteda was 11.4 hours (17.6%). Following an IV injection of Cyklokapron, the mean terminal half-life was 10.2 hours (13.0%). Most elimination occurred in 10 hours for both Lysteda and Cyklokapron IV.

Intrinsic factors

- Renal impairment
 - No pharmacokinetic study was conducted in patients with renal impairments.
 - Tranexamic acid is primarily eliminated via the kidney by glomerular filtration with more than 95% excreted as unchanged drug in urine³. Therefore, the increased exposure in renally impaired patients is expected with possibly higher incidence of adverse events associated with Lysteda.

¹ Prescribing information of Cyklokapron IV (NDA 19-281)

² *Id.*

³ *Id.*

- Therefore, dosage adjustment is recommended for patients with reduced renal function based on the renal dosage adjustment available in the prescribing information of Cyklokapron IV⁴.
- Hepatic impairment
 - No pharmacokinetic study was conducted in patients with hepatic impairments.
 - A small fraction of tranexamic acid is metabolized. 1 and 0.5% of the oral dose are excreted as a dicarboxylic acid and acetylated metabolite, respectively⁵.
 - No dosage adjustment is needed for patients with hepatic impairment.
- Pregnancy and lactation⁶
 - No studies were conducted in pregnant women. However, tranexamic acid is known to pass the placenta and appear in cord blood at concentrations approximately equal to maternal concentration.
 - **Tranexamic acid is present in the mother's milk at a concentration of about a hundredth of the corresponding serum concentrations. Caution should be exercised when tranexamic acid is administered to a nursing woman.**

Extrinsic factors

- Food effect
 - Lysteda may be administered without regard to meals. There were approximately 7% increases in C_{max} and $AUC_{0-t_{1/2c}}$ in subjects under fed compared to fasting state. In the phase 3 clinical trials, patients were instructed to take Lysteda without regards to meals.

Biopharmaceutics

- In the drug development phase, three tablet formulations (to-be-marketed formulation (TBM), delayed release (DR), and immediate release (IR)) of tranexamic acid were developed. Following absolute bioavailability, food effect, and multiple dose PK trials, TBM formulation was chosen to be used in the subsequent phase 3 trials. Therefore, Lysteda, the brand name of tranexamic acid tablet, in this review will represent the TBM formulation.
- Lysteda is not expected to show dose dumping in the presence of alcohol because its release profile in 0.1 N HCl containing 5, 10, 20 and 40% alcohol did not show significant increase of dissolution rate at any given time points from 15 to 90 minutes compared to its release profile in distilled water.

QT prolongation:

- In a trial to assess the effect of Lysteda on ventricular repolarization, the largest upper bound of the two-sided 90% CI for the mean difference between Lysteda (1,300 mg (2 x 650 mg) and 3,900 mg (6 x 650 mg)) and placebo were 7.4 and 6.9 ms, both below 10 ms, the threshold for the regulatory concern. Therefore, Lysteda did not exhibit significant QT prolongation effect. (QT review by Dr. Nitin Mehrotra DFSed on May 15, 2009)

⁴ *Id.*

⁵ *Id.*

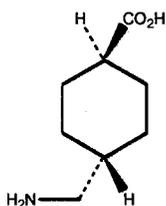
⁶ *Id.*

2 Question Based Review

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug?

- Tranexamic acid is the trans-stereo-isomer of 4-(aminomethyl)-cyclohexane carboxylic acid. It has a molecular weight of 157.2 and the following structure:



- Tranexamic acid is a competitive inhibitor of plasminogen activation.
- The formulation of Lysteda is provided in Table 1.

Table 1. Composition of Lysteda

Material	Amount (mg)
Tranexamic acid	650.00
Microcrystalline Cellulose NF	
Colloidal Silicon Dioxide NF	
Pregelatinized Corn Starch	
Povidone USP	
Hypromellose USP	
Stearic Acid NF	
Magnesium Stearate NF	
Total	

b(4)

b(4)

b(4)

2.1.2 What are the proposed mechanism of action and therapeutic indications?

Tranexamic acid is a synthetic, lysine amino acid derivative, which diminishes the dissolution of hemostatic fibrin by plasmin. In the presence of tranexamic acid, the lysine receptor binding sites of plasmin for fibrin are occupied, preventing bindings to fibrin monomers, thus preventing and stabilizing fibrin's matrix structure.

The proposed therapeutic indications of tranexamic acids is the treatment of HMB and the amelioration of symptoms associated with heavy menstrual bleeding, including limitations on social, leisure, and physical activities.

2.1.3 What are the proposed dosage and route of administration?

Each Lysteda is available as a 650 mg tablet. The recommended dose is two 650 mg tablets (1,300 mg) of Lysteda taken three times daily (1,300 mg three times daily) up to 5 consecutive days during menstruation without regards to meals.

2.1.4 What are HMB and its current pharmacological treatments?

HMB is a hyperfibrinolytic condition as cyclic, normal intervals of menstruation with excessive blood loss. The normal menstruation cycle lasts between 21 and 35 days, with bleeding usually lasting between 2 and 6 days, **and an average of approximately 30 – 40 mL of blood loss per cycle**⁷. Excessive blood loss has been defined as blood loss of more than 80 mL in the clinical trials for the current submission.

- HMB is often associated with a disruption in daily routines, work, and sexual activity leading to significant decrease in health-related quality of life. While HMB is rarely life threatening, it may cause iron deficiency anemia, fatigue, hospitalization, and the need for red blood cell transfusions. According to the Centers for Disease Control and Prevention (CDC), 3 million women of reproductive age report HMB yearly.

Currently, there are no US approved drugs for the treatment of HMB.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical trials used to support dosing or claims?

Trial XP12B-101: A randomized single dose absolute bioavailability and bioequivalence crossover trial with healthy non-smoking female volunteers.

- to assess bioequivalence of TBM and DR formulations compared to IR formulation, and to determine the absolute bioavailability of the tablet formulations (TBM, DR, and IR formulations) to the IV formulation, Cyklokapron IV.

Trial XP12B-102: A randomized single dose comparative bioavailability 4-way crossover trial with healthy nonsmoking adult female volunteers under fasting and fed states.

- to assess the single dose relative bioavailability of TBM and DR formulations, following a 1,300 mg (2 x 650 mg) dose, under fasting and fed states.

Trial XP12B-103: A randomized single and multiple dose PK assessment in healthy nonsmoking adult female volunteers under fasting state.

- to assess the PK linearity of TBM and DR formulations, after a single oral dose (Day 1) compared to a daily (1,300 mg (2 x 650 mg) every 8 hours) dosage

⁷ Apgar BS, Kaufman AH, George-Nwogu U, Kittendorf, A. Treatment of menorrhagia. Am Fam Physician 2007;75(12):1813-19.

regimen (Days 2 to 7), under fasting state.

Trial XP12B-104: A randomized, single dose, double blind, placebo- and positive-controlled, 4 way crossover trial of the electrocardiographic QT interval prolongation effect of Lysteda, TBM formulation, in healthy young adult females.

- to evaluate the effect of Lysteda on ventricular repolarization in healthy female subjects. In particular, to assess the effects of two dose levels of Lysteda, 1,300 mg (2 x 650 mg) and 3,900 mg (6 x 650 mg) administered as single doses.

Trial XP12B-MR-301: A phase 3, randomized, double blinded, placebo controlled, parallel group, multicenter trial to evaluate efficacy and safety of 650 and 1,300 mg (2 x 650 mg) oral doses of TBM formulation, Lysteda, three times daily administered during menstruation for the treatment of menorrhagia.

- to assess the efficacy and safety of Lysteda with two different doses to reduce MBL in women with menorrhagia when administered during menstruation compared to placebo over 3 treatments periods or menstrual cycles.

Trial XP12B-MR-302: A phase 3, long term, multicenter, open label extension trial to evaluate the safety of a 1,300 mg (2 x 650 mg) oral dose of TBM formulation, Lysteda, three times daily administered during menstruation for the treatment of menorrhagia (ongoing).

- to assess the 1,300 mg (2 x 650 mg) oral dose of Lysteda three times daily administered during menstrual period in women with menorrhagia.

Trial XP12B-MR-303: A phase 3, randomized, double blinded, placebo controlled, parallel group, multicenter trial to evaluate efficacy and safety of a 1,300 mg (2 x 650 mg) TBM formulation, Lysteda, three times daily administered during menstruation for the treatment of menorrhagia.

- to assess the efficacy and safety of Lysteda to reduce MBL in women with menorrhagia when administered during menstruation compared to placebo over 6 treatment periods or menstrual cycles.

Trial XP12B-MR-304: A phase 3, multicenter, open label extension trial to evaluate the safety of a 1,300 mg (2 x 650 mg) TBM formulation, Lysteda, three times daily administered during menstruation for the treatment of menorrhagia (ongoing).

- to assess the 1,300 mg (2 x 650 mg) oral dose of tranexamic acid three times daily administered during menstrual period in women with menorrhagia who had completed either trial XP12B-MR-301 or XP12B-MR-303.

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical trials?

HMB is a hyperfibrinolytic condition with excessive blood loss which has been defined as blood loss of more than 80 mL in clinical trials for the current submission. During the clinical trials, MBL was assessed by the alkaline hematin test (AHT) method. The

Menorrhagia Impact Questionnaire (MIQ) was also administered immediately after each menstrual period under investigation.

The following primary endpoint was used in phase 3 clinical trials (XP12B-MR-301 and XP12B-MR-303):

Primary endpoint

- The reduction in MBL during the entire menstrual period as assessed by the AHT Method.
 - At least 50 mL difference of the reduction of MBL from baseline to treatment groups
 - The mean reduction in MBL must be greater than or equal to the reduction in MBL identified as meaningful to women through Receiver Operating Characteristic (ROC) analysis

2.2.3 Are the active moieties in the plasma appropriately identified and measured to assess PK parameters and exposure response relationship?

Yes. Blood samples were collected during each trial period at pre dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 10, 14, 24, 28, 32, and 36 hours post-dose for female subjects who were given Lysteda. The details of analytical procedures to measure the tranexamic acids in the plasma are described in section 2.6, analytical section.

2.2.4 Dose-response

Trial XP12B-MR-301

- This is a phase 3, randomized, double blinded, placebo controlled, parallel group, multicenter trial to evaluate efficacy and safety of 650 and 1,300 mg (2 x 650 mg) Lysteda three times daily administered up to 5 days during menstruation for the treatment of menorrhagia over 3 treatments periods or menstrual cycles.
- Based on this phase 3 trial, a dosage regimen of 1,300 mg (2 x 650 mg) three times daily was selected as an efficacious and safe regimen.

2.2.4.1 What are the characteristics of the dose-response relationship for efficacy?

Primary endpoint

- Subjects in the 650 and 1,300 mg (2 x 650 mg) three time daily active treatment groups experienced significant reductions from baseline in mean MBL per month of 46.5 and 65.3 mL, respectively. These were significantly greater reductions in mean MBL compared with the reduction of 3.0 mL experienced by subjects in the placebo group (Table 2). In addition, these were greater than the MBL reduction of 36 mL identified as meaningful to women through the ROC analysis.
- However, the mean reduction in MBL on treatment of the 650 mg three times daily active treatment group was not greater than or equal to 50 mL.

Table 2. Mean reduction from baseline MBL using the alkaline hematin method

Treatment Group	n	Mean (SD) Reduction	Percent Reduction (a)	Least Square Means Change (b)	Within- Treatment P-value	Between- Treatment P-value (c)
3.9 g/day XP12B-MR	112	65.31 (51.136)	38.6	65.32	<0.0001	<0.0001
1.95 g/day XP12B-MR	115	46.45 (57.142)	26.1	44.07	<0.0001	<0.0001
Placebo	67	2.98 (45.947)	1.9	7.06	0.5968	

a The percent reduction from baseline was calculated by dividing the overall group mean change in MBL post-baseline by the overall group mean MBL at baseline.

b Least square means were computed at the mean baseline level.

c Between-treatment comparison of active treatment group (1,300 mg (2 x 650 mg) or 650 mg three times daily) versus placebo group.

2.2.4.2 What are the characteristics of the exposure-response (dose-response) relationship for safety?

- Based on sponsor's report of adverse events, the numbers of subjects experiencing treatment related (possibly, probably, and definitely altogether) adverse events that occurred in at least 5% of subjects in any active treatment groups and corresponding adverse events in placebo group are presented in Table 3.
- Overall, the most frequent treatment related adverse events were viral respiratory tract infection, fatigue, and musculoskeletal pain.

Table 3. Treatment related adverse events

	XP12B-MR 3.9 g/day N = 115 n (%)	XP12B-MR 1.95 g/day N = 115 n (%)	Placebo N = 67 n (%)	Overall N = 297 n (%)
Total number of AEs	495	656	297	1448
Number of subjects with at least 1 AE	97 (84.35)	104 (90.43)	56 (83.58)	257 (86.53)
Blood and lymphatic system disorders	1 (0.87)	7 (6.09)	2 (2.99)	10 (3.37)
Anemia	1 (0.87)	6 (5.22)	1 (1.49)	8 (2.69)
General disorders and administration site conditions	11 (9.57)	19 (16.52)	8 (11.94)	38 (12.79)
Fatigue	4 (3.48)	13 (11.30)	3 (4.48)	20 (6.73)
Immune system disorders	6 (5.22)	8 (6.96)	2 (2.99)	16 (5.39)
Multiple allergies	4 (3.48)	6 (5.22)	0	10 (3.37)
Infections and infestations	20 (17.39)	34 (29.57)	11 (16.42)	65 (21.89)
Sinusitis	3 (2.61)	7 (6.09)	1 (1.49)	11 (3.70)
Viral upper respiratory tract infection	8 (6.96)	12 (10.43)	3 (4.48)	23 (7.74)
Musculoskeletal and connective tissue disorders	39 (33.91)	40 (34.78)	16 (23.88)	95 (31.99)
Arthralgia	5 (4.35)	7 (6.09)	1 (1.49)	13 (4.38)
Musculoskeletal pain	6 (5.22)	10 (8.70)	2 (2.99)	18 (6.06)
Myalgia	6 (5.22)	5 (4.35)	0	11 (3.70)
Respiratory, thoracic and mediastinal disorders	12 (10.43)	20 (17.39)	4 (5.97)	36 (12.12)
Nasal congestion	3 (2.61)	8 (6.96)	0	11 (3.70)
Throat irritation	0	7 (6.09)	2 (2.99)	9 (3.03)

2.2.4.3 Does this drug prolong the QT or QTc interval?

No significant QT prolongation effect of tranexamic acid with the single doses of 1,300 mg (2 x 650 mg) and 3,900 mg (6 x 650 mg) was detected in the QT trial. The largest upper bound of the two-sided 90% CI for the mean difference between Lysteda (1,300 mg (2 x 650 mg) and 3,900 mg (6 x 650 mg) as single doses) and placebo were 7.4 and 6.9 ms, both below 10 ms, the threshold for the regulatory concern. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms indicating that the assay sensitivity of the trial was established. (QT review by Dr. Nitin Mehrotra, DARRTS, May 15, 2009)

2.2.5 Pharmacokinetics

2.2.5.1 What are the single and multiple dose PK parameters?

Single and multiple dose PK of tranexamic acid were characterized in the trials XP12B-101 and XP12B-103, respectively.

Single dose PK trial was conducted to determine the absolute bioavailability of Lysteda to Cyklokapron IV. The doses used in this trial were 1,300 mg (2 x 650 mg) and 1,000 mg for Lysteda and Cyklokapron IV, respectively (Trial XP12B-101).

- Figure 1 shows the concentration time profiles following single administration of Lysteda and Cyklokapron IV.

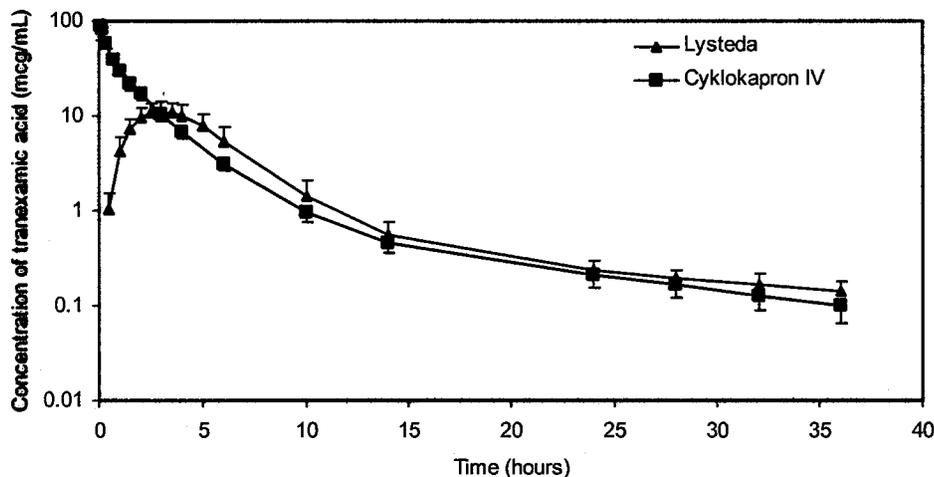


Figure 1. Mean (\pm SD) tranexamic acid concentration-time profiles following single administration of Lysteda 1,300 mg (2 x 650 mg) and Cyklokapron IV 1,000 mg under fasting state (n=26) in a semi-logarithmic scale; Trial XP12B-101

- Concentration-time profiles of Lysteda and Cyklokapron IV were similar in the elimination phase.
- Most elimination occurred within 10 hours.
- The mean terminal half life values (CV) of tranexamic acid were 11.4 (17.6%) and 10.2 (13.0%) hours following single administration of Lysteda and Cyklokapron IV, respectively.
- There was higher variability of PK values associated with Lysteda than Cyklokapron IV.
- The absolute bioavailability (F) of Lysteda was 43.9%.

Table 4. Tranexamic acid PK Values following single administration of Lysteda 1,300 mg (2 x 650 mg) and Cyklokapron IV 1,000 mg under fasting state (n=26); Trial XP12B-101

Parameter	Arithmetic Mean [CV]	
	Lysteda	Cyklokapron IV
C _{max} (mcg/mL)	11.70 [28.7%]	95.24 [22.8 %]
AUC _{0-t_{ldc}} (mcg·h/mL)	68.97 [26.7%]	121.43 [11.7 %]
AUC _{inf} (mcg·h/mL)	71.30 [26.0%]	122.96 [11.7 %]
t _{max} (h) ^a	3 [2 - 4]	0.08 [0.08 – 0.17]
t _{1/2} (h)	11.37 [17.6%]	10.22 [13.0 %]

^aData presented as median [range]

Single and multiple dose trial was conducted to assess the PK linearity of Lysteda, after a single oral dose (Day 1) compared to a daily (1,300 mg (2 x 650 mg) every 8 hours) dosage regimen (starting at 11 pm on Day 2 to 7am on Day 7), under fasting state (Trial XP12B-103).

- Concentration-time profiles following single and multiple dose administration of Lysteda are provided in Figure 2.

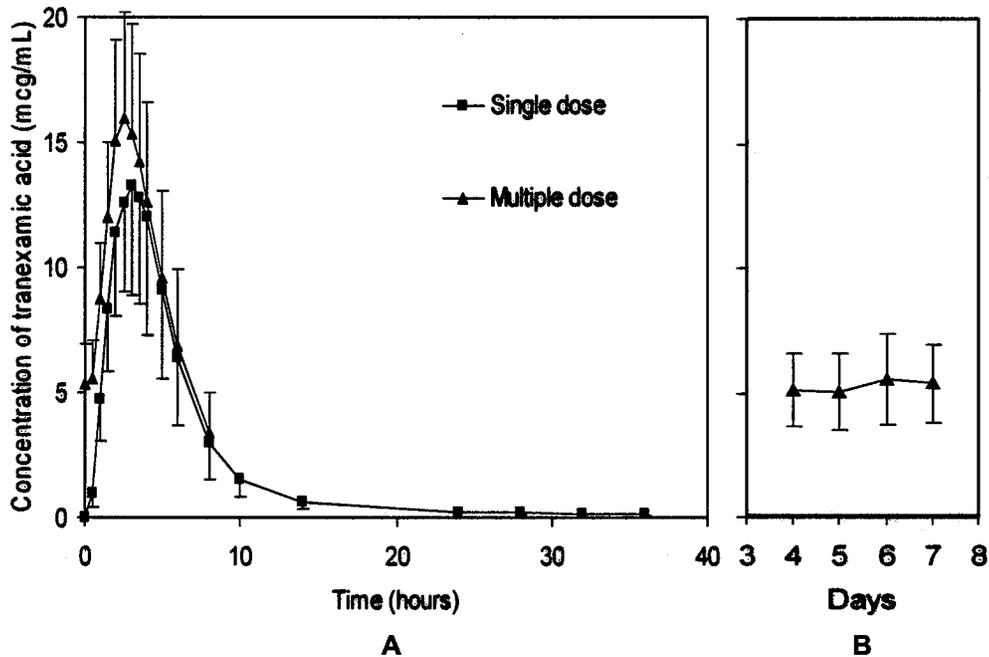


Figure 2. A: Mean (\pm SD) tranexamic acid concentration-time profiles following single (Day 1) and multiple dose (Day 7) administration of Lysteda 1,300 mg (2 x 650 mg) under fasting state (n=19) in a linear scale; B: Mean (\pm SD) tranexamic acid trough concentrations on Day 4 to 7 following multiple dose (Day 2 to 7) administration of Lysteda 1,300 mg (2 x 650 mg) under fasting state (n=19) in a linear scale; Trial XP12B-103

- The PK characteristics of tranexamic acid following single and multiple dose administration of Lysteda are presented in Table 5.

Table 5. Tranexamic acid PK values following single and multiple dose administration (Day 7) of Lysteda under fasting state (n=19); Trial XP12B-103

Parameter	Arithmetic Mean [CV]	
	Single dose	Multiple dose
C_{max} (mcg/mL)	13.83 [32.14 %]	16.41 [26.19 %]
$AUC_{0-t_{1/2}}$ (mcg·h/mL)	77.96 [31.14 %]	77.67 ^b [29.39 %]
AUC_{inf} (mcg·h/mL)	80.19 [30.43 %]	-
t_{max} (h) ^a	2.5 [1 - 5]	2.5 [2 - 3.5]
$t_{1/2}$ (h)	11.08 [16.94 %]	-

^a Data presented as median [range]; ^b $AUC_{0-\tau}$ (mcg·h/mL)

- Mean (\pm SD) trough concentrations of tranexamic acid following administration of Lysteda from Day 4 to 7 are presented in Table 6. Steady state was reached by

Day 4 (Figure 2B and Table 6). The time to reach the steady state was less than 32 hours because the three times daily dosing started at 11 pm on Day 2 and trough concentration of Day 4 was measured at 7 am.

Table 6. Mean (\pm SD) trough concentrations of tranexamic acid following multiple dose administration of Lysteda from Day 4 to 7

Day	Arithmetic Mean [CV] of trough concentrations
4	5.10 [28.35 %]
5	5.06 [30.03 %]
6	5.54 [33.02 %]
7	5.38 [29.21 %]

- The time-dependent PK linearity of Lysteda was calculated by comparing the ratio of least square means of AUC_{τ} (Day 7) to AUC_{inf} (Day 1).
- The ratio of least square means of AUC_{τ} (Day 7) to AUC_{inf} (Day 1) was 0.973 with 90% CI between 86.5 and 109.5.
- Lysteda exhibited linear PK independent of time following repeated administration (three times daily) of a 1,300 mg (2 x 650 mg) dose under fasting state because the ratio of AUC_{τ} (Day 7) to AUC_{inf} (Day 1) was close to 1.

2.2.5.2 What are the characteristics of drug absorption?

After oral administration of Lysteda, C_{max} occurs at approximately at 3 hours. The absolute bioavailability of tranexamic acid following administration of Lysteda in women aged 18-49 is approximately 43.9%. The steady state was achieved within four doses (32 hours) of Lysteda administration.

2.2.5.3 What are the characteristics of drug distribution?

Tranexamic acid is 3% bound to plasma proteins with no apparent binding to albumin. Tranexamic acid is rapidly distributed with an initial distribution volume of distribution of 0.18 L/kg and steady-state apparent volume of distribution of 0.39 L/kg⁸.

2.2.5.4 What are the characteristics of drug metabolism?

Tranexamic acid is eliminated intact by urinary excretion via glomerular filtration. Only a small fraction of the drug is metabolized. 1 and 0.5% of the oral dose are excreted as a dicarboxylic acid and acetylated metabolite, respectively⁹.

2.2.5.5 What are the characteristics of drug excretion?

⁸ *Id. at 1.*

⁹ *Id.*

Tranexamic acid is eliminated primarily via the urine with more than 95% of the dose excreted unchanged. Excretion of tranexamic acid is about 90% at 24 hours after intravenous administration of 10 mg per kg body weight. Most elimination post intravenous administration occurred during the first 10 hours, giving an apparent elimination half-life of approximately 2 hours. The mean (CV) terminal half-life of Lysteda is approximately 11 (18%) hours. Overall renal clearance of tranexamic acid is equal to overall plasma clearance (110-116 mL/min)¹⁰.

2.2.5.6 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

There is only one dose, 1,300 mg (2 x 650 mg) Lysteda, studied in the phase 1 trials. Therefore, the degree of PK linearity can not be assessed.

2.2.5.7 What is the inter-subject variability of PK parameters in volunteers?

The PK trials were conducted with young (ages 18 – 45) healthy female volunteers. The inter-subject variability (% CV) in steady state tranexamic acid PK (C_{max} and $AUC_{0-t_{1dc}}$) from Lysteda was approximately 30% (Table 5).

2.3 Intrinsic factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure of efficacy or safety response? What dosage regimen adjustments, if any, are recommended for each of these groups?

2.3.1.1 Elderly

Lysteda is indicated for women of reproductive age and is not intended for geriatric use.

2.3.1.2 Pediatric

Safety and efficacy of Lysteda have not been established in pediatric patients.

The sponsor requested a waiver of pediatric trial in children < 12 years and a deferral of the pediatric PK trial in children between 12 and 17 years old at the time of the original NDA submission. A PK study with healthy female subjects, 12– 17 years old, with heavy menstrual bleeding will be conducted as a post marketing requirement.

2.3.1.3 Sex

Lysteda is indicated for women and is not intended for men

2.3.1.4 Race

¹⁰ *Id.*

The effect of race on the PK of Lysteda has not been evaluated.

2.3.1.5 Renal impairment

There were no trials conducted with renally impaired patients by the current sponsor. However, there is a renal dosage adjustment recommendation in the prescribing information of Cyklokapron IV (tranexamic acid for IV injection, NDA 19-281, approval on 12/30/1986).

Renal dosage adjustment of Lysteda by the reviewer

- The proposed recommended dose of Lysteda is two 650 mg tablets taken three times daily during menstruation up to five days.
- Tranexamic acid is primarily eliminated via the kidney by glomerular filtration with more than 95% excreted as unchanged drug in urine. Therefore, the increased exposure in renally impaired patients is expected with possibly higher incidence of adverse events associated with Lysteda.
- Therefore, dosage adjustment is recommended for patients with reduced renal function.
- The Table 7 is the reviewer recommended dosage adjustment for patients with renal impairments.

Table 7. Dosage adjustment for renal impairment; proposed by the reviewer

Serum Creatinine (mg/dL)	LYSTEDA	
	Adjusted Dose	Total Daily Dose
1.4 to 2.8	1,300 mg (two 650 mg tablets) two times a day for a maximum of 5 days during menstruation	2,600 mg
2.8 to 5.7	1,300 mg (two 650 mg tablets) once a day for a maximum of 5 days during menstruation	1,300 mg
>5.7	650 mg (one 650 mg tablet) once a day for a maximum of 5 days during menstruation	650 mg

- The above dosage adjustment reflected four modifications recommended by this reviewer from the dosage adjustment proposed by the sponsor (Table 8).
 1. Removal of estimated Glomerular Filtration Rate (GFR).
 - There are three unknown variables incorporated in calculating estimated GFR by Cockcroft-Gault formula from the sponsor. These are gender, age, and body weight, which were assumed to be males, 45 years, and 65 kg by the sponsor.
 - These assumptions resulted in inaccurate estimation of GFR. **Therefore, it is recommended to remove “estimated GFR” from the dosage adjustment.**
 2. Removal of “1,300 mg every 48 hours” from adjusted dose for patients with serum creatinine concentration > 5.7 mg/dL
 - Oral dose can be easily taken daily. In addition, 650 mg once every day dose would yield more stable concentration with less fluctuation than 1,300 mg (2 x 650 mg) every 48 hours dose.

Therefore, it is recommended to remove the option of taking “1,300 mg every 48 hours” from adjusted dose for patients with serum creatinine concentration > 5.7 mg/dL.

3. **Change of unit for total daily dose of Lysteda from “gram” to “milligram”** in order to use consistent unit of mass.
4. **Change of abbreviation, “QD” and “BID” to “once every day” and “two times every day”**
5. **Addition of “for a maximum of 5 days during menstruation”** after the dosing regimen to reassure the maximum duration of the use of Lysteda

Renal dosage adjustment of Lysteda by the sponsor

- Table 8 provides the dosage adjustment for patients with renal impairments proposed by the sponsor. The adjusted doses were based on proportional dose reduction as Cyklokapron IV (Table 9).

Table 8. Dosage adjustment for renal impairment; proposed by the sponsor

Serum Creatinine (mg/dL)	Estimated GFR* (mL/min)	LYSTEDA	
		Adjusted Dose	Total Daily Dose
1.4 to 2.8	30 - 60	1.3 g (two 650 mg tablets) BID	2.6 g
2.8 to 5.7	15 – 30	1.3 g (two 650 mg tablets) QD	1.3 g
>5.7	< 15	1.3 g (two 650mg tablets) every 48 hours or 650 mg (one tablet) every 24 hours	0.65 g

* GFR was estimated assuming average age of 45 years and body weight of 65 kg.

- Based on the absolute bioavailability of Lysteda, 43.9%, the exposure from 10 mg/kg of Cyklokapron IV is expected to be similar to the exposure from 22.8 mg/kg Lysteda. Assuming body weight of 60 kg, this leads to the Lysteda dose of 1,368 mg.
- Therefore, proposed single dose of Lysteda, 1,300 mg (2 x 650 mg), is expected to give similar exposure to the 10 mg/kg of Cyklokapron IV dose.

Renal dosage adjustment of approved Cyklokapron IV

- There is a dosage adjustment for patients with renal impairments as shown in Table 9 in the prescribing information of Cyklokapron IV.
- The dosing regimen of Cyklokapron in healthy subjects is 10 mg/kg three to four times daily (may be used for 2 to 8 days).

Table 9. Dosage adjustment for patients with renal impairment; Cyklokapron IV (NDA 19-281)

Serum creatinine (umol/L)	Tranexamic acid IV dosage
120 to 250 (1.36 to 2.83 mg/dL)	10 mg/kg BID
250 to 500 (2.83 to 5.66 mg/dL)	10 mg/kg daily
>500 (>5.66 mg/dL)	10 mg/kg every 48 hours or 5 mg/kg every 24 hours

- This dosage adjustment was based on the trial by Andersson et al¹¹. The trial was conducted in 28 patients with chronic renal disease who were divided into three different groups by the serum creatinine concentrations. Tranexamic acids in a dose of 10 mg/kg were administered intravenously to all patients. Blood samples were collected at predose, 0.5, 1, 3, 5, 8, and 24 hours after the injection.
- The percents dose excreted (mean \pm SD) up to 24 hours were 50.6 (SD not reported), 38.6 ± 13.1 , and 19.2 ± 5.5 for patients with serum creatinine concentrations of 120-249, 250-500, and >500, respectively. In addition, excretions of tranexamic acid in healthy subjects are reported as approximately 90% at 24 hours after IV administration of 10 mg/kg¹². These results were used to support the dose adjustment in Table 9.
- In order to compare the concentration-time profile of tranexamic acids in healthy subjects with renally impaired patients, the results from healthy subjects following Cyklokapron IV 1,000 mg administration in trial XP12B-101 are incorporated into the results from the trial by Andersson et al¹³ (Figure 3).
- Figure 3 shows that there is a trend of increasing exposure of tranexamic acid from healthy subjects to patients with higher serum creatinine concentrations.
- Quantitative exposure comparison between four groups (Cr>500, 250-500, 120-249 umol/L, and Healthy) was not made because these results were from two different trials.

¹¹ Andersson L, Nilsson IM, Colleen S, et al. Role of urokinase and tissue activator in sustaining bleeding and the management thereof with EACA and AMCA. Ann N Y Acad of Sci 1968; 146:642-658

¹² *Id. at 1.*

¹³ *Id. at 11.*

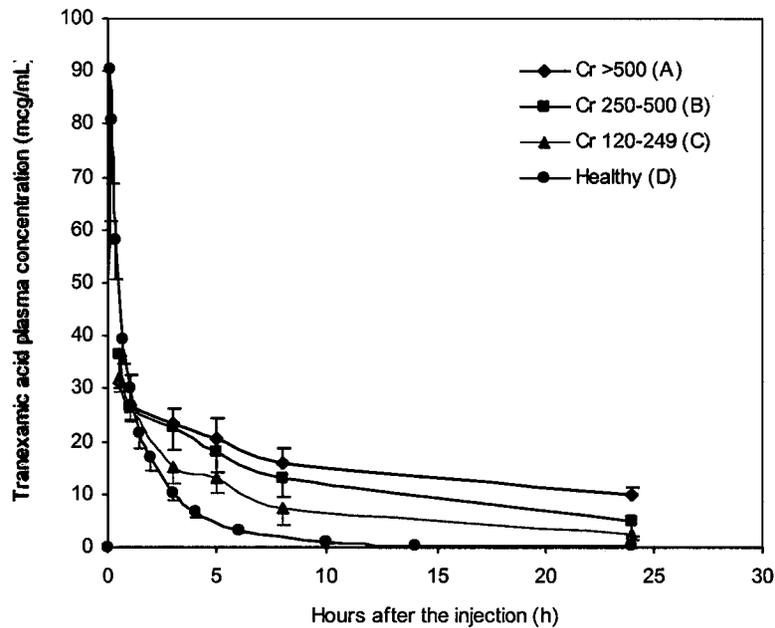


Figure 3. Mean (\pm SD) tranexamic acid concentration-time profiles following single administration of Cyklokapron IV in a linear scale; A, B, C from Andersson et al¹⁴; D from trial XP12B-101

Abbreviation: Cr=serum creatinine concentration

2.3.1.6 Hepatic impairment¹⁵

The effect of hepatic impairment on the disposition of tranexamic acid has not been evaluated. A small fraction of the drug is metabolized. A dicarboxylic acid and acetylated metabolite are excreted, 1% and 0.5% after the administration of an oral dose, respectively.

2.3.1.7 What pregnancy and lactation use information is there in the application¹⁶?

There are no adequate and well-controlled trials in pregnant women. However, tranexamic acid is known to pass the placenta and appears in cord blood at concentrations approximately equal to maternal concentration.

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 tranexamic acid is administered to a nursing woman.

¹⁴ *Id.*

¹⁵ *Id. at 1.*

¹⁶ *Id.*

2.4 Extrinsic factors

2.4.1 What extrinsic factors influence dose-exposure and what is the impact of any differences in exposure on response?

Food intake

Single dose comparative bioavailability crossover trial was conducted to assess the single dose relative bioavailability of Lysteda following a 1,300 mg (2 x 650 mg) dose, under fasting and fed states (Trial XP12B-102). Subjects in fed state were given high fat meals 30 minutes prior to dosing. The meals consisted of 2 slices of buttered toast, 2 fried eggs, 2 strips of bacon, 1 serving of hash brown potatoes, and 240 mL of whole milk.

- Figure 4 shows the concentration-time profiles following single administration of Lysteda under fasting vs. fed states.

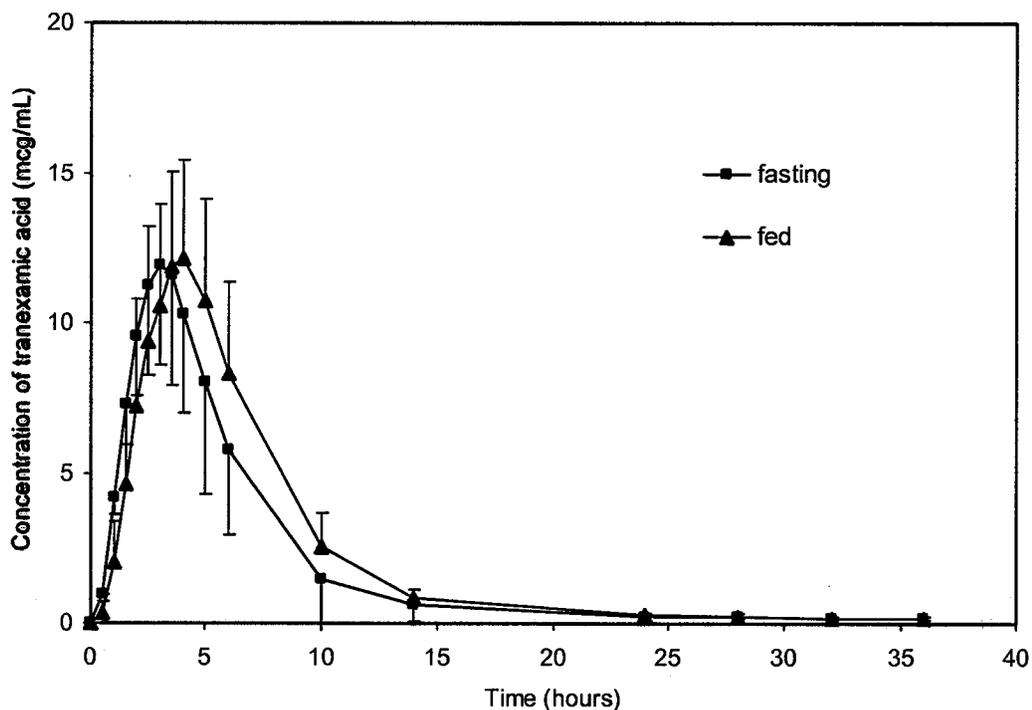


Figure 4. Mean (\pm SD) tranexamic acid concentration-time profiles following single administration of Lysteda 1,300 mg (2 x 650 mg) under fasting vs. fed states (n=26) in a linear scale; Trial XP12B-102

- A single dose administration (two 650 mg tablets) of LYSTEDA with food increased both C_{max} and AUC_{inf} by 7% and 16%, respectively. The 90% CI following administration of Lysteda fell within the range of 80-125% for AUC_{inf} and C_{max} indicating that Lysteda is bioequivalent under fasting and fed states

(Table 10). Therefore, Lysteda may be administered without regard to meals. In the phase 3 clinical trials, patients were instructed to take Lysteda without regards to meals.

Table 10. Tranexamic acid PK Values and relative bioavailability following single administration of Lysteda 1,300 mg (2 x 650 mg) under fed vs. fasting state (n=26); Trial XP12B-102

Parameter	Arithmetic Mean [CV]		Least Square Mean Ratio (Test : Ref)	90% Confidence Interval
	Lysteda - fed (Test)	Lysteda – fasting (Reference)		
C _{max} (mcg/mL)	13.47 [25.2 %]	12.80 [30.3 %]	106.8 %	97.2 – 117.3
AUC _{0-t_{ldc}} (mcg·h/mL)	83.44 [23.1 %]	72.08 [24.8 %]	116.5 %	107.8 – 126.0
AUC _{inf} (mcg·h/mL)	85.53 [23.0 %]	75.11 [23.4 %]	115.4 %	106.5 – 124.9
t _{max} (h) ^a	3.5 [2.5 - 5]	3 [2 - 4]	-	-
t _{1/2} (h)	10.62 [27.5 %]	13.07 [38.2 %]	-	-

^a Data presented as median [range]

Alcohol interaction: In vitro testing

The TBM formulation was proposed to be the MR formulation by the sponsor. Therefore, the sponsor was asked to address the robustness of the MR formulation in presence of alcohol (Clinical Pharmacology review by Dr. Sandhya Apparaju, DARRTSed under IND 68,096 on November 05, 2008).

During the NDA review cycle, the proposed MR formulation was found not to exhibit the characteristics of MR by Dr. Patrick Marroum (Biopharmaceutics review, DARRTS, May 14, 2009).

- The impact of different ratios of alcohol in the dissolution medium on the drug release from the dosage was studied.
- Lysteda was used to compare the drug release profile of tablets in 0.1 N HCl containing 5, 10, 20 and 40% alcohol vs. the release profile in distilled water.
- The dissolution profiles in the different media are shown in Figure 5.
- The f₂ values comparing the dissolution in different ratios of alcohol in 0.1 N HCl vs. the dissolution in distilled water were 76.98, 73.02, 54.56, and 26.74 for 5, 10, 20, and 40% alcohol medium.
- The dissolution profiles in 5, 10, and 20% alcohol were similar to the dissolution profile in distilled water. However, the dissolution profile in 40% alcohol was dissimilar from the dissolution profile in distilled water.
- There was a trend showing a reduction in the dissolution rate as the amount of alcohol in the dissolution medium increases with dissolution in 40% alcohol being the slowest.
- Therefore, Lysteda is not expected to show dose dumping in the presence of alcohol.

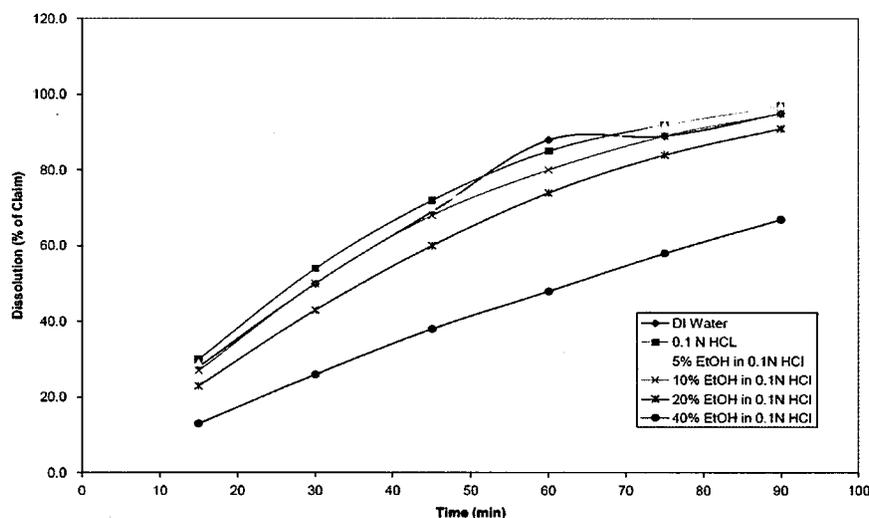


Figure 5. Dissolution profile of Lysteda in different ratios of alcohol

2.4.2 Drug-Drug interaction

No drug-drug interaction trials with Lysteda were submitted.

All-Trans Retinoic Acids

In a study involving 28 patients with acute promyelocytic leukemia who were given either all-trans retinoic acid plus tranexamic acid, all-trans retinoic acid plus chemotherapy, or all-trans retinoic acid plus tranexamic acid plus chemotherapy, all 4 patients who were given all-trans retinoic acid plus tranexamic acid died, with 3 of the 4 deaths due to thrombotic complications.

Factor IX Complex Concentrates or Anti-Inhibitor Coagulant Concentrates¹⁷

A risk of thrombosis may be increased if Lysteda is co-administered with Factor IX complex concentrates or with anti-inhibitor coagulant concentrates.

Combination Hormonal Contraceptives

Concomitant therapy with combination hormonal contraceptives may increase a risk of thrombosis, stroke or myocardial infarction.

Tissue Plasminogen Activators

Concomitant therapy with tissue plasminogen activators may decrease the efficacy of both Lysteda and tissue plasminogen activators.

Metabolism

- Less than 5% of the tranexamic is metabolized. Therefore, there is a low potential for PK interactions through metabolism with other drug on the PK of Lysteda.

¹⁷ *Id.*

Renal excretion

- Tranexamic acid is renally excreted via glomerular filtration. There is no competition for elimination via glomerular filtration and this process is not saturable.
- Glomerular filtration is dependent on renal blood flow and unbound fraction of drug.
- Unless renal blood flow is affected, the interactions with other drugs are possible only through any drug which can bind tranexamic acid and affect the filtration.
- However, given the fact that the plasma protein binding of tranexamic acid is about 3% at therapeutic plasma concentration and it is fully accounted for by its binding to plasminogen, there is low potential for drug interaction through binding with other drugs and affecting the glomerular filtration.
- Therefore, there is low potential for tranexamic acid to have drug interaction with other drugs which are renally eliminated.

2.5 General Biopharmaceutics

- The sponsor developed the three oral tranexamic acid formulations (Table 11) as MR, DR, and IR.
- The *in vitro* drug release profiles of these formulations are shown in Figure 6.
- This comparative dissolution profiles show that the dissolution profile of MR formulation is relatively slower than the dissolution of the formulations DR and IR.
- However, complete dissolution of MR formulation is occurring within 90 minutes, a time frame clearly shorter than what is usually seen for a modified formulation.
- Therefore, the Office of New Drug Quality Assessment (ONDQA) found that MR formulation which was used in phase 3 trials did not exhibit release characteristics of a MR formulation as the sponsor proposed. (Biopharmaceutics review by Dr. Patrick Marroum, DARRTS, May 14, 2009).

Table 11. Formulations of three oral tranexamic acid

Raw material name	Immediate Release	Delayed Release	Modified-Immediate Release
Tranexamic Acid	650.00 mg	650.00 mg	650.00 mg
Microcrystalline Cellulose NF			
Colloidal Silicon Dioxide NF			
Pregelatinized Corn Starch NF			
Povidone USP			
Hypromellose USP			
Croscarmellose Sodium NF			
Microcrystalline Cellulose NF			
Stearic Acid NF			
Magnesium Stearate NF			

b(4)

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Dissolution Profiles of Prototypes

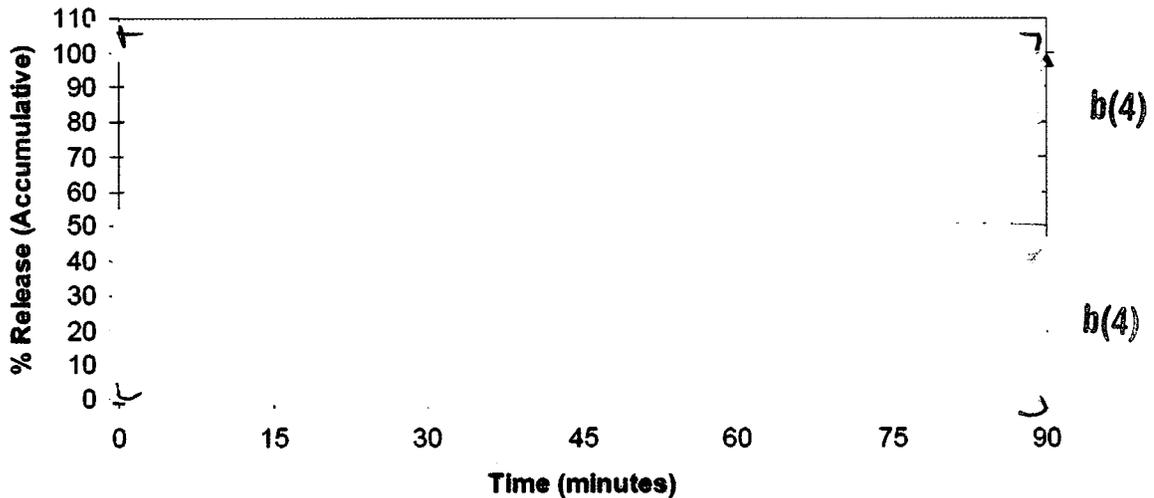


Figure 6. Dissolution profiles of three tablet formulations of tranexamic acid

2.5.1 Are the clinical trial and to-be-marketed formulations the same?

Yes. The tranexamic acid formulation studied in the phase 3 trials (XP12B-MR-301, 302, 303 and 304) is the same as the TBM formulation.

2.6 Analytical Section

Plasma tranexamic acid was separated from heparinized plasma by liquid/liquid extraction. All tranexamic acid samples were derivatized using Methyl iodide. The concentrations of tranexamic acid samples were determined by GC/MS method using Negative Chemical Ionization and Selected Ion Monitoring. The method validation report, “quantitative determination of tranexamic acid in human plasma by GC-MS - Trial NA438”, satisfied the requirements of Bioanalytical Method Validation (Guidance for industry – Bioanalytical method validation, FDA, May 2001).

Type of Biological Fluid		Human Heparinized Plasma
Range of Standard Curve		0.05 – 250 mcg/mL
Linearity (r^2 ; mean \pm SD)		0.99425 \pm 0.00252
Selectivity (difference of the mean concentration from the nominal concentration of the LLOQ)		8.5 %
QC Sample Accuracy (bias)	Intra-assay	-11.7 – 6.9 %
	Inter-assay	-8.7 – 7.1 %
QC Sample Precision (CV)	Intra-assay	2.8 – 3.4 %
	Inter-assay	3.6 – 5.6 %

Recovery		75.8 – 106 % (CV < 15 %)
Stability	-20 ± 5 °C (in the freezer)	9 days
	Number of freezing/thawing cycle tested	3
	5°C ± 3°C (in the refrigerator with extraction solvent)	9 days
	5°C ± 3°C (in the refrigerator as derivatized samples)	9 days
	10°C (in the autosampler as derivatized samples)	7 days
	Room temperature	24 hours

All human plasma samples of following trials were analyzed for the content of tranexamic acid according to the validated method validation report, Trial NA438.

- Bioanalytical trial OA161 for a phase I trial XP-12B-101
- Bioanalytical trial OA162 for a phase I trial XP-12B-102
- Bioanalytical trial OA163 for a phase I trial XP-12B-103

6 Page(s) Withheld

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

✓ § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

4 Appendix

4.1 Individual Clinical Study Review

4.1.1 Trial XP12B-101: A randomized single dose absolute bioavailability and bioequivalence crossover trial with healthy non-smoking female volunteers.

This was a randomized, single dose, 4-way crossover absolute bioavailability and bioequivalence trial performed on 28 healthy non-smoking female with age ranges from 18 to 45 under fasting state. The objective of this trial was to assess bioequivalence of two tablet formulations of tranexamic acid (DR [A] and TBM [B]) compared to the reference tablet formulation of tranexamic acid (IR [C]), and to determine the absolute bioavailability of the tablet formulations (A, B, C) to the IV formulation [D].

There are four treatment groups; tranexamic acid DR, TBM, IR, and tranexamic acid IV injection. On the morning of each period, subjects received a single oral 1,300 mg (2 x 650 mg) dose with 240 mL of water or a single 1,000 mg (10 mL) dose by IV infusion at a rate of 200 mg/min over a period of approximately 5 minutes, of their assigned formulation of tranexamic acid. Blood samples were collected during each trial period at pre dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 10, 14, 24, 28, 32, and 36 hours post dose for subjects who were given tranexamic acid DR, TBM, and IR, whereas they were collected at pre dose, 0.083, 0.17, 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 10, 14, 24, 28, 32, and 36 hours post dose for subjects who were given tranexamic acid IV. No medications or herbal products were permitted for the 7 days prior to the first dose, during the time of sample collection and during the washout period between drug administrations.

In each period, subjects were housed from at least 10 hours before dosing until after 36-hour post dose events. The tranexamic acid dose administration (1,300 mg (2 x 650 mg) for oral formulations and 1,000 mg for IV formulation) were separated by a washout period of 7 days.

A total of 26 out of 28 subjects completed the trial. Subject No. 18 was withdrawn by the investigator in period 1, due to her ECG findings. This was reported as a pre-existing condition. Subject No. 20 did not return for period 4 for personal reason.

The tranexamic acid 650 mg TBM and IR formulations are bioequivalent under fasting states, whereas tranexamic acid 650 mg DR and IR formulations are not bioequivalent (Tables 1 and 2). The absolute bioavailability (F) of the DR, TBM, and IR were 31.4, 43.9, and 45.8 %, respectively (Table 3). F was calculated by the following equation: (geometric mean of $AUC_{inf-oral} \times Dose_{IV}$) / (geometric mean of $AUC_{inf-IV} \times Dose_{oral}$) x 100. The PK characteristics of tranexamic acid following single administration of tranexamic acid 1,000 mg IV are described in Table 4. Figure 1 shows the time concentration profiles following single administration of tranexamic acid DR, TBM, IR, and IV.

Table 1. Tranexamic acid PK Values and relative bioavailability following single administration of tranexamic acid 1,300 mg (2 x 650 mg) DR vs. IR under fasting state (n=26); Trial XP12B-101

Parameter	Arithmetic Mean [CV]		Least Square Mean Ratio (Test : Ref)	90% Confidence Interval
	Tranexamic acid DR (Test)	Tranexamic acid IR (Reference)		
C _{max} (mcg/mL)	8.70 [37.5 %]	12.57 [23.2 %]	66.4 %	60.4 – 73.0
AUC _{0-t_{ldc}} (mcg·h/mL)	48.19 [36.7 %]	71.06 [16.8 %]	64.8 %	59.5 – 70.5
AUC _{inf} (mcg·h/mL)	52.33 [33.3 %]	73.61 [16.9 %]	67.8 %	62.2 – 73.9
t _{max} (h) ^a	4 [2.5 - 6]	3 [1.5 - 4]	-	-
t _{1/2} (h)	12.47 [26.1 %]	11.01 [15.5 %]	-	-

^aData presented as median [range]

Table 2. Tranexamic acid PK Values and relative bioavailability following single administration of tranexamic acid 1,300 mg (2 x 650 mg) TBM vs. IR under fasting state (n=26); Trial XP12B-101

Parameter	Arithmetic Mean [CV]		Least Square Mean Ratio (Test : Ref)	90% Confidence Interval
	Tranexamic acid TBM (Test)	Tranexamic acid IR (Reference)		
C _{max} (mcg/mL)	11.70 [28.7%]	12.57 [23.2 %]	92.4 %	84.0 – 101.6
AUC _{0-t_{ldc}} (mcg·h/mL)	68.97 [26.7%]	71.06 [16.8 %]	95.6 %	87.8 – 104.0
AUC _{inf} (mcg·h/mL)	71.30 [26.0%]	73.61 [16.9 %]	95.1 %	87.4 – 103.5
t _{max} (h) ^a	3 [2 - 4]	3 [1.5 - 4]	-	-
t _{1/2} (h)	11.37 [17.6%]	11.01 [15.5 %]	-	-

^aData presented as median [range]

Table 3. Absolute bioavailability (F) of the tranexamic acid tablet formulations

Formulations	F (%)
DR	31.4
TBM	43.9
IR	45.8

Table 4. Tranexamic acid PK Values following single administration of tranexamic acid 1,000 mg IV under fasting state (n=26); Trial XP12B-101

Parameter	Arithmetic Mean [CV] - Tranexamic acid IV
C _{max} (mcg/mL)	95.24 [22.8 %]
AUC _{0-t_{ldc}} (mcg·h/mL)	121.43 [11.7 %]
AUC _{inf} (mcg·h/mL)	122.96 [11.7 %]
t _{max} (h) ^a	0.08 [0.08 – 0.17]
t _{1/2} (h)	10.22 [13.0 %]

^aData presented as median [range]

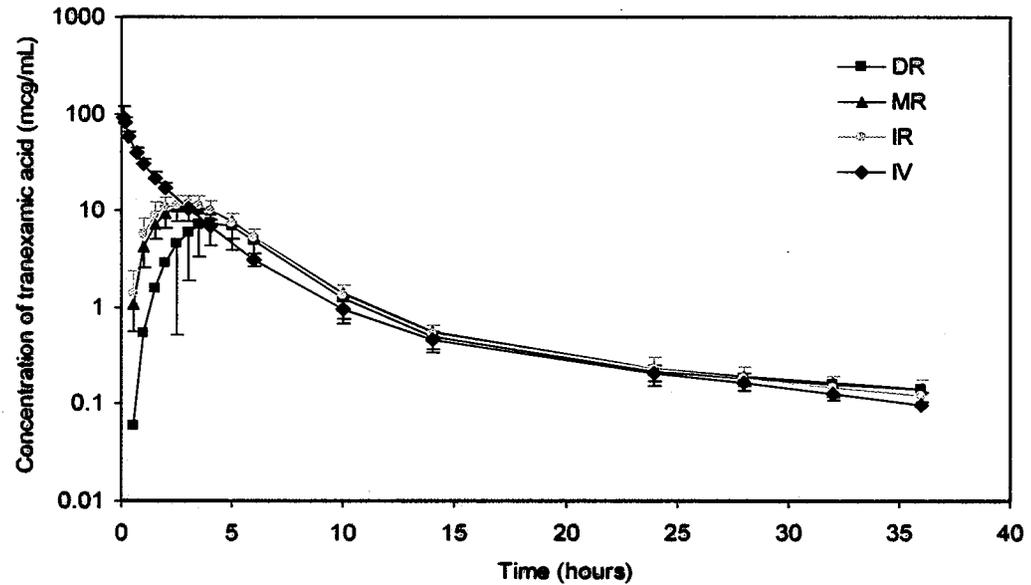
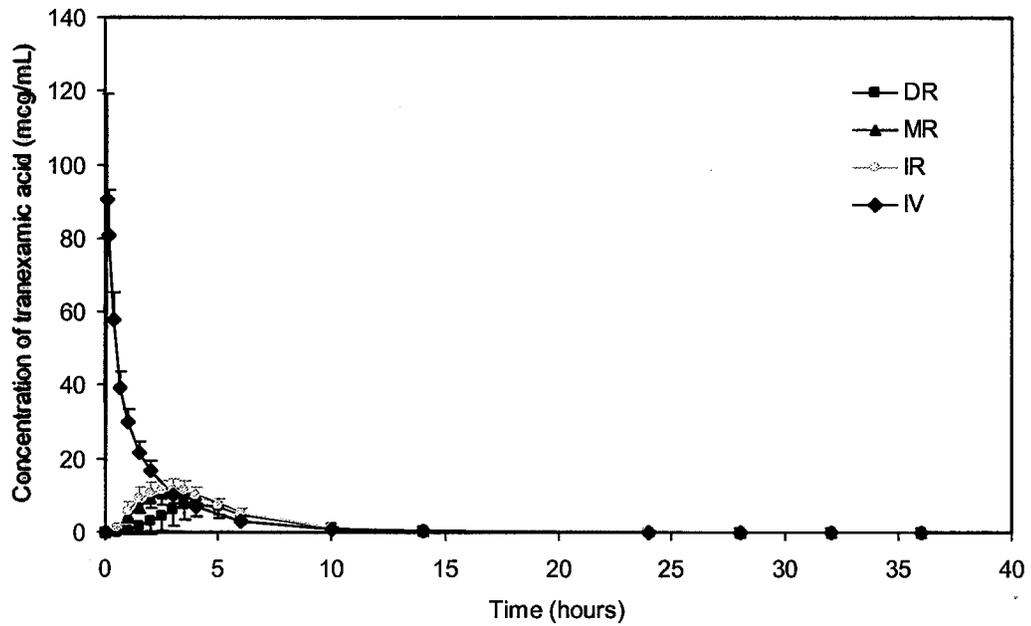


Figure 1. Mean (\pm SD) tranexamic acid concentration-time profiles following single administration of tranexamic acid 1,300 mg (2 x 650 mg) DR, TBM, IR, and 1,000 mg IV under fasting state (n=26) in linear and semi-logarithmic scales; Trial XP12B-101

4.1.2 Trial XP12B-102: A randomized single dose comparative bioavailability 4-way crossover trial with healthy nonsmoking adult female volunteers under fed to fasting states

This was a randomized, single dose, 4-way crossover comparative bioavailability trial, under fasting and fed states, performed on 32 healthy non-smoking adult females with age between 18 to 45. The objective of this trial was to assess the single dose relative bioavailability of two formulations of 650 mg tranexamic acid (TBM and DR), following a 1,300 mg (2 x 650 mg) dose, under fasting and fed states.

An evening dinner was served at 19:00, after which subjects observed a 10-hour overnight fast. On the morning, subjects received a single oral 1,300 (2 x 650 mg) g dose of the assigned formulation, with 240 mL of water. Subjects randomized to treatments A (DR) and B (TBM) were in fasted state prior to dosing and subjects randomized to treatments C (DR) and D (TBM) were in a fed state after receiving a standard high fat breakfast, 30 minutes prior to dosing. Food was restricted for 4 hours after the trial medication was administered. No medications or herbal products were permitted for the 7 days prior to the first dose, during the time of sample collection and during the washout period between drug administrations.

In each period, subjects were housed from at least 10 hours before dosing until after 36 hours post dose. The tranexamic acid dose administrations were separated by a washout period of 7 days. Blood samples were collected during each trial period at pre dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 10, 14, 24, 28, 32, and 36 hours post dose.

A total of 26 subjects completed the clinical phase of the trial. Subject No. 3 withdrew for personal reasons following period 3. Subject Nos. 6 and 30 were dropped out because blood samples could not be obtained at the pre dose blood draw in period 3. Subject Nos. 11 and 23 were removed by the investigator due to the PR interval by electrocardiogram not within the range at pre dose in period 2 and adverse events (vaginal infection, loose stools, vomiting, and nausea) at pre dose in period 4, respectively. Subject No. 17 was removed due to the cocaine testing positive at check-in of period 2. Therefore, 26 subjects were included in the PK comparison of tranexamic acid under fasting vs. fed states for tranexamic acid TBM. Although subject 3 and 23 did not complete the trial, their PK values of tranexamic acid following administration of tranexamic acid DR under fasting vs. fed states were available; hence a total of 28 subjects including subjects 3 and 23 were included in the PK comparison following administration of tranexamic acid DR.

The 90% CI fell within the range of 80-125% for AUC_{inf} and C_{max} indicating that the tranexamic acid TBM is bioequivalent under fasting and fed states (Table 5). The upper limit of the 90% CI for $AUC_{0-t_{1/2c}}$ was above 125%. Following administration of the tranexamic acid DR formulation under fasting vs. fed states, the 90% CI did not fall within 80-125% (Table 6). Figure 2 shows the concentration time profiles following single administration of tranexamic acid TBM and DR under fasting vs. fed states.

Table 5. Tranexamic acid PK Values and relative bioavailability following single administration of tranexamic acid TBM 1,300 mg (2 x 650 mg) under fed vs. fasting state (n=26); Trial XP12B-102

Parameter	Arithmetic Mean [CV]		Least Square Mean Ratio (Test : Ref)	90% Confidence Interval
	Tranexamic acid TBM - fed (Test)	Tranexamic acid TBM – fasting (Reference)		
C _{max} (mcg/mL)	13.47 [25.2 %]	12.80 [30.3 %]	106.8 %	97.2 – 117.3
AUC _{0-t_ldc} (mcg·h/mL)	83.44 [23.1 %]	72.08 [24.8 %]	116.5 %	107.8 – 126.0
AUC _{inf} (mcg·h/mL)	85.53 [23.0 %]	75.11 [23.4 %]	115.4 %	106.5 – 124.9
t _{max} (h) ^a	3.5 [2.5 - 5]	3 [2 - 4]	-	-
t _{1/2} (h)	10.62 [27.5 %]	13.07 [38.2 %]	-	-

^aData presented as median [range]

Table 6. Tranexamic acid PK Values and relative bioavailability following single administration of tranexamic acid DR 1,300 mg (2 x 650 mg) under fed vs. fasting state (n=28); Trial XP12B-102

Parameter	Arithmetic Mean [CV]		Least Square Mean Ratio (Test : Ref)	90% Confidence Interval
	Tranexamic acid DR - fed (Test)	Tranexamic acid DR – fasting (Reference)		
C _{max} (mcg/mL)	8.63 [57.4 %]	9.98 [31.4 %]	75.9 %	60.7 – 95.0
AUC _{0-t_ldc} (mcg·h/mL)	66.53 [42.1 %]	58.10 [30.5 %]	107.4 %	90.7 – 127.3
AUC _{inf} (mcg·h/mL)	71.00 [38.4 %]	61.65 [28.7 %]	110.6 %	94.7 – 129.2
t _{max} (h) ^a	5 [3.5 -28]	3.5 [2.5 - 5]	-	-
t _{1/2} (h)	10.34 [50.8 %]	12.07 [25.5 %]	-	-

^aData presented as median [range]

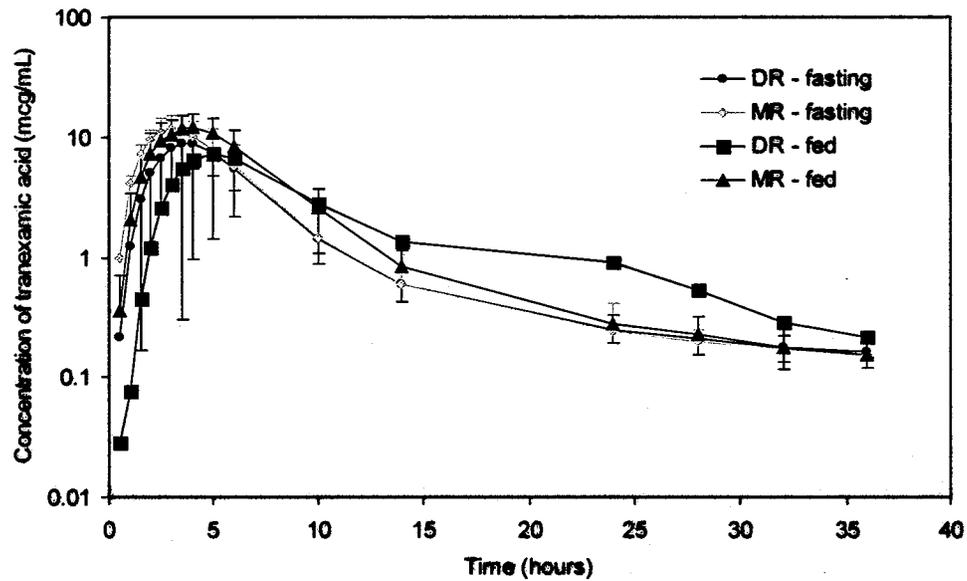
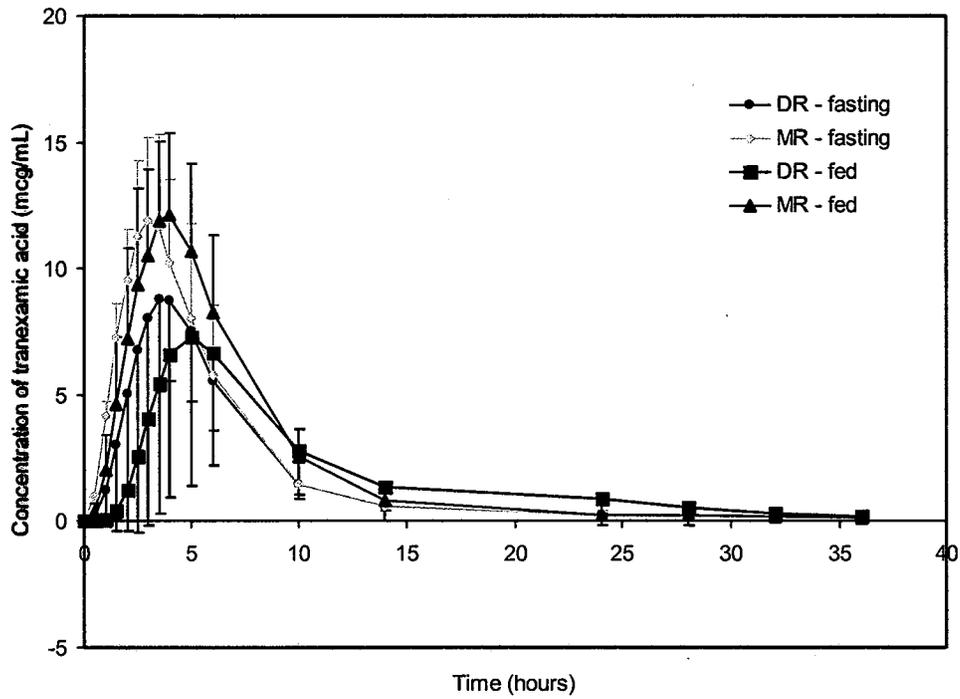


Figure 2. Mean (\pm SD) tranexamic acid concentration-time profiles following single administration of tranexamic acid DR and TBM 1,300 mg (2 x 650 mg) under fasting vs. fed states (n=28 (DR) and 26 (TBM)) in linear and semi-logarithmic scales; Trial XP12B-102

4.1.3 Trial XP12B-103: A randomized single dose and multiple dose PK assessment in healthy nonsmoking adult female volunteers under fasting state

This was a parallel trial of single and multiple doses performed on two groups of 20 healthy non-smoking adult females with age between 18 to 45. Half the subjects in each group received the DR formulation and the other half received the TBM formulation. A total of 39 subjects completed the clinical phase of the trial. After an overnight fast, subjects received a single oral dose of tranexamic acid (1,300 mg (2 x 650 mg)) on day 1. Blood samples were taken before dosing and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 14, 24, 28, 32 and 36 hours post dose. Subjects received another single oral dose (1,300 mg (2 x 650 mg)) on the evening of day 2, and 3 times a day (every 8 hours) starting the morning of day 3 until last single dose in the morning of day 7. Blood samples were taken before the 6th, 9th, 12th, and 15th dose for determination of C_{min} , and up to 8 hours (0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8) after the last dose, for determination of drug concentration at steady-state. Subjects were housed from at least 10 hours before the 1st dose on day 1 until after 8-hour blood draw following the 15th dose (day 7). The objective of this trial was to assess the PK linearity of two formulations of tranexamic acid (DR and TBM), after a single oral dose (Day 1) compared to a daily (1,300 mg (2 x 650 mg) every 8 hours) dosage regimen (Days 2 to 7), under fasting state. 39 out of 40 subjects completed the trial. Subject 32 did not want to continue the study for personal reason.

The results are provided in Tables 7 to 9. The results revealed that both TBM and DR formulations exhibited linear PK following repeated administration (5 days) of a 1,300 mg (2 x 650 mg) dose under fasting states since the AUC_{τ}/AUC_{inf} ratio was close to 100%.

Table 7. PK linearity; XP12B-103

Formulation	Ratio AUC_{τ} / AUC_{inf}	90% Confidence Interval	
		Lower Limit	Upper Limit
Combined (A and B)	102.5	91.9	114.3
DR (A)	107.7	89.2	130.1
MR (B)	97.3	86.5	109.5

Table 8. Steady State Analysis; XP12B-103

Formulation	Day	Time (hour)	LSM Derived From the ANOVA
Combined (A and B)	4	-72	5.48506
	5	-48	4.80606
	6	-24	5.57891
	7	0	5.66691
DR (A)	4	-72	6.11142
	5	-48	4.84722
	6	-24	5.93658
	7	0	6.21402
MR (B)	4	-72	4.90536
	5	-48	4.77323
	6	-24	5.23678
	7	0	5.15389

Abbreviations: ANOVA=analysis of variance; DR=Delayed Release; LSM=least squares mean; MR=Modified Release

Table 9. Tranexamic acid PK values following single and multiple dose administration (Day 7) of tranexamic acid DR and TBM under fasting state (n=19 (TBM), n=20 (DR)); Trial XP12B-103

Parameter	Single dose - Arithmetic Mean [CV]	
	DR	TBM
C_{max} (mcg/mL)	8.86 [52.69 %]	13.83 [32.14 %]
$AUC_{0-t_{1dc}}$ (mcg·h/mL)	47.76 [47.90 %]	77.96 [31.14 %]
AUC_{inf} (mcg·h/mL)	50.49 [44.53 %]	80.19 [30.43 %]
t_{max} (h) ^a	3.5 [2 - 6]	2.5 [1 - 5]
$t_{1/2}$ (h)	13.17 [35.04 %]	11.08 [16.94 %]
Parameter	Multiple dose - Arithmetic Mean [CV]	
	DR	TBM
C_{max} (mcg/mL)	10.48 [36.74 %]	16.41 [26.19 %]
$AUC_{0-\tau}$ (mcg·h/mL)	52.64 [37.39 %]	77.67 [29.39 %]
t_{max} (h) ^a	2.5 [0 - 5]	2.5 [2 - 3.5]

^a Data presented as median [range]

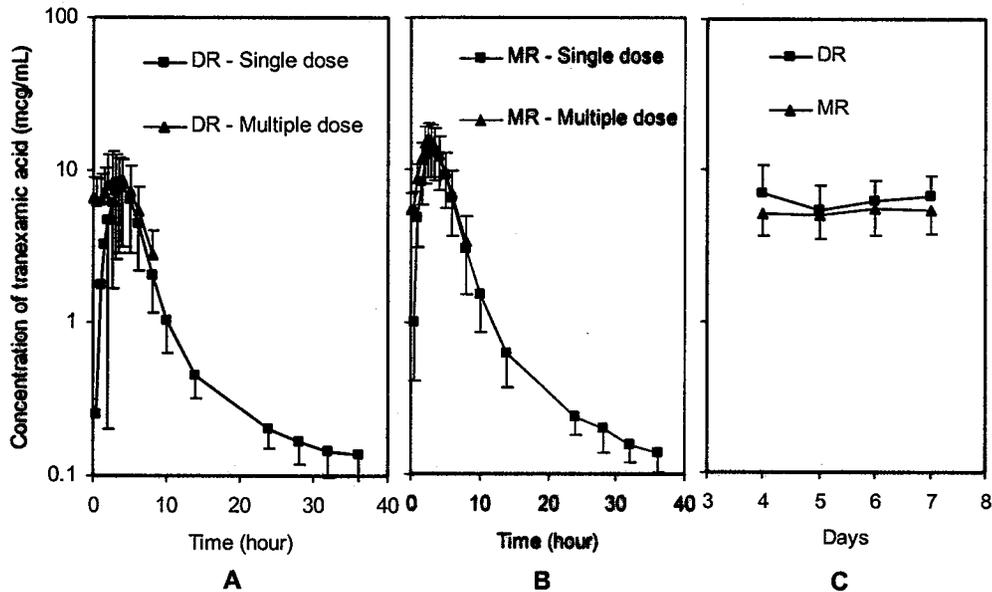


Figure 3. A (tranexamic acid DR) & B (tranexamic acid MR): Mean (\pm SD) tranexamic acid concentration-time profiles following single (Day 1) and multiple dose (Day 7) administration of Lysteda 1,300 mg (2 x 650 mg) under fasting state (n=19) in a linear scale; C: Mean (\pm SD) tranexamic acid trough concentrations on Day 4 to 7 following multiple dose (Day 2 to 7) administration of tranexamic acid DR and MR 1,300 mg (2 x 650 mg) under fasting state (n=19) in a linear scale; Trial XP12B-103

4.2 Cover Sheet and OCP Filing

Office of Clinical Pharmacology <i>New Drug Application Filing and Review Form</i>				
General Information About the Submission				
	Information		Information	
NDA Number	22-430	Brand Name	Lysteda	
OCP Division	DCP3	Generic Name	Tranexamic acid 650 mg modified release (MR)	
Medical Division	DRUP	Drug Class	Antifibrinolytic	
OCP Reviewer	Hyunjin Kim, Pharm.D., M.S.	Indication(s)	Treatment of heavy menstrual bleeding (menorrhagia) and the amelioration of symptoms associated with heavy menstrual bleeding, including limitations on social, leisure, and physical activities	
OCP Team Leader	Myong-Jin Kim, Pharm.D.	Dosage Form	Tablets	
		Dosing Regimen	Two 650 mg tablets taken 3 times daily (3.9 g/day) during menstruation	
Date of Submission	January 30, 2009	Route of Administration	Oral	
Estimated Due Date of OCP Review	May 30, 2009	Sponsor	Xanodyne Pharmaceuticals, Inc.	
PDUFA Due Date	July 30, 2009	Priority Classification	Priority	
Division Due Date	May 30, 2009			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			Labeling in Physician Labeling Rule (PLR) format
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		XP12B-103
multiple dose:	X	1		XP12B-103
Patients-				
single dose:				

multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	X	1		XP12B-101
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		XP12B-101
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		XP12B-102
Dissolution:				
(IVVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan	X	1		A request of deferral of the pediatric study until the product is approved

Literature References		2		
Total Number of Studies		8		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X			
Comments sent to firm ?				
QBR questions (key issues to be considered)	Is the clinical trial formulation same as the to be marketed formulation? What is the absolute bioavailability of tranexamic acid MR tablet compared to parenteral reference drug? What is the effect of food on the exposure of tranexamic acid MR tablet? What are the pharmacokinetic (PK) characteristics of single and multiple dose of tranexamic acid MR tablet?			
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

Filing Memo

Clinical Pharmacology Review

NDA: 22-430
Compound: Lysteda (Tranexamic acid 650 mg modified release [MR] tablet)
Sponsor: Xanodyne Pharmaceuticals, Inc.
Date: February 25, 2009
Reviewer: Hyunjin Kim, Pharm.D., M.S.

Background

Xanodyne Pharmaceuticals, Inc. is developing tranexamic acid as a modified-release (MR) oral dose formulation (650 mg) for the treatment of menorrhagia. The objective of developing tranexamic acid MR oral formulation is to develop a stable, orally administered tablet with minimal gastrointestinal irritation. Per sponsor, gastrointestinal complaints (nausea, dyspepsia, vomiting, and diarrhea) are the most commonly observed adverse effects associated with oral tranexamic acid marketed outside of the U.S.

The proposed indication is the treatment of heavy menstrual bleeding (menorrhagia; in excess of 80 mL of blood loss per menstrual cycle) and the amelioration of symptoms associated with heavy menstrual bleeding, including limitations of social, leisure, and physical activities. The proposed dosage regimen is two 650 mg tablets administered 3 times daily, a total of 3.9 g daily, during menstruation. Tranexamic acid is an antifibrinolytic agent, currently approved in U.S. for the short term (10 mg/kg, 3-4 times daily for 2-8 days) treatment in hemophilic patients to reduce or prevent hemorrhagia following tooth extraction procedures. Only the intravenous (IV) formulation is currently available in U.S (Cyklokapron, NDA 19-281 approved on December 30, 1986). Per current sponsor, the tablet formulation (Cyklokapron 500 mg, NDA 19-280 approved on December 30, 1985) has never been marketed in U.S., although it was approved with IV formulation. The current submission is being filed as a 505(b)(2) application referencing the Cyklokapron IV, NDA 19-281.

In support of NDA 22-430, the sponsor submitted four phase 1 studies and four phase 3 studies including two pivotal phase 3 safety and efficacy studies.

Contents of submission

- Three phase 1 biopharmaceutics studies (XP12B-101, XP12B-102, and XP12B-103)
 - XP12B-101: Randomized single dose absolute bioavailability (immediate release-IR, modified release-MR, delayed release-DR) and bioequivalence crossover study in healthy non-smoking young female volunteers
 - XP12B-102: Randomized single dose comparative bioavailability 4-way crossover study with healthy nonsmoking adult female volunteers under fed to fasting conditions (MR and DR formulations)
 - XP12B-103: Randomized single dose and multiple dose pharmacokinetic assessment in healthy nonsmoking adult female volunteers under fasting

conditions (MR and DR formulations)

- Three study specific bioanalytical study reports for three phase 1 biopharmaceutics studies with one method validation study report
- SAS transport files for three phase 1 biopharmaceutics studies
- Label of tranexamic acid MR in accordance with the Physician Labeling Rule (PLR)
- A request for deferral of pediatric studies with clinical development plan for pharmacokinetic study demonstrating acceptable dosing in the adolescent population.
- One phase 1 thorough QT study (XP12B-MR-104)
- Two pivotal phase 3 efficacy and safety studies (XP12B-MR-301 and XP12B-MR-303)
The active treatment arms in all phase 3 studies were given tranexamic acid MR formulation.
- Two ongoing phase 3 safety studies (XP12B-MR-302 and XP12B-MR-304)
The active treatment arms in all phase 3 studies were given tranexamic acid MR formulations.
- Literature search for clinical scientific literature on tranexamic acid from 2002 through 2008

Previous Clinical Pharmacology comments and agreements

1. Pre-NDA meeting on October 31, 2008

- Dosing requirements for the proposed tranexamic acid MR formulation in presence of renal impairment should be adequately addressed. Ideally, a PK study of the proposed formulation in subjects with various degrees of renal impairment should be conducted in order to optimize dosing regimens in such patients. If such a study has not been conducted and the sponsor believes that adequate data are available in this regard, provide this information to the Division along with adequate justification that addresses how this information would be applicable to the proposed modified release oral formulation. This will be a review issue.
There is no PK study conducted in patients with renal impairment. The section 8.6 renal impairment of the sponsor's proposed label has dosage adjustment for renal impairment based on two literature data.
- Address the robustness of the proposed MR formulation in presence of alcohol. An in vitro release comparison of the proposed MR formulation in presence of various alcohol concentrations (0, 5, 10, 20 and 40%) should be conducted using 0.1 N HCl and the optimal dissolution medium for the formulation as the release media. Alternatively, the study can be conducted in media with three different pH levels (1.2, 4.5 and 6.8).
The sponsor submitted in vitro dissolution profiles of tranexamic acid MR in different concentrations (5, 10, 20, and 40%) of alcohol as well as in different pH (1.2, 4.5, and 6.8).
- The Division will review the request for a pediatric deferral when submitted. To obtain a deferral, the Sponsor should submit certification of the reason for deferring pediatric assessments, a description of the planned or ongoing studies, and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time. In other words, propose a "comprehensive pediatric study in adolescents" as part of the request for deferral.

ADDITIONAL DISCUSSION AT THE MEETING: The Sponsor agreed to send a proposal for a pediatric study with the deferral request in the NDA submission. The Sponsor is considering a pediatric PK study. A PK study might be acceptable; the Division will seek the opinion of internal pediatric consultants during the review cycle.

The sponsor submitted a request for deferral of pediatric studies with clinical development plan for PK study demonstrating acceptable dosing in the adolescent population.

2. Pre-NDA meeting on February 26, 2008

- _____ facility _____, was employed for the three phase 1 trials. During the pre-NDA meeting, the sponsor confirmed that _____ did not conduct the bioanalysis or validation. Therefore, it was agreed that no follow-up in this regard was needed.

b(4)

3. Guidance meeting on September 20, 2004

- Sparse sampling was recommended in phase 3 clinical trials to characterize PK following three times daily dosing regimen.

Referring to the Clinical Pharmacology review prepared by Dr. Sandhya Apparaju (DARRTS November 05, 2008), the sponsor stated that the information to justify that sparse sampling is not warranted was provide with a previous SPA submission dated May 11, 2005. However, it is not clear whether the Clinical Pharmacology reviewer concurred with this during the SPA review because Clinical Pharmacology review of the SPA submission is not available in DARRTS.

- No drug-drug interaction studies, including those with drugs that are predominantly renally eliminated are needed.

There is no drug interaction study submitted.

4. Guidance meeting on August 25, 2004

- The Division recommended that the sponsor consider conducting a Phase 2 dose ranging trial to determine the Lowest Effective Dose (LED). The sponsor proposed including a lower dose treatment arm in their phase 3 clinical trials to confirm that 3.9 gm per day of tranexamic acid is the LED. This approach would be acceptable to the Division. However, if both the 3.9 gm dose and the lower dose (1.95 g/day) are equally effective, this will not identify the LED. Ideally, the Division would like the sponsor to identify a dose that fails to meet the prespecified efficacy endpoints in order to identify the LED. *Per sponsor's conclusion of study XP12B-MR-301, the result of the study demonstrated the safety and efficacy of tranexamic acid MR 3.9 g/day, whereas it failed to demonstrate the safety and efficacy of tranexamic acid MR 1.95 g/day.*

Three phase 1 biopharmaceutics studies

1. XP12B-101: Randomized single dose absolute bioavailability and bioequivalence crossover study with healthy non-smoking young female volunteers

This was a randomized, single dose, 4-way crossover absolute bioavailability and bioequivalence study performed on 28 healthy non-smoking female volunteers under fasting condition. There are four treatment groups; tranexamic acid delayed release (DR), modified release (MR), immediate release (IR), and tranexamic acid injection. A total of 26 subjects completed the study. In each period, subjects were housed from at least 10 hours before dosing until after 36-hour post dose events. The tranexamic acid dose administration (1.3 g for oral formulations and 1 g for intravenous formulation) were separated by a washout period of 7 days. The objective of this study was to assess bioequivalence of 2 test tablet formulations of tranexamic acid (DR [A] and MR [B]) compared to the reference tablet formulation of tranexamic acid (IR [C]), and to determine the absolute bioavailability of the tablet formulations (A, B, C) to the Canadian approved IV formulation [D]. Sponsor's results are provided in the tables 1 and 2. Sponsor

concluded that tranexamic acid MR 650 mg tablet formulation and immediate release formulation are bioequivalent under fasting conditions.

Although tranexamic acid MR and IR were found to be bioequivalent, the MR formulation had a slower dissolution profile than IR formulation.

Table 1. Ratios of Least Squares Means for All Formulations (90% CI)

Parameter	Delayed-Release Tablet (A) vs. Immediate-Release Tablet (C)	Modified-Release Tablet (B) vs. Immediate-Release Tablet (C)
AUC _{0-t}	64.8% (59.5 – 70.5%)	95.6% (87.8 – 104.0%)
AUC _{inf}	67.8% (62.2 – 73.9%)	95.1% (87.4 – 103.5%)
C _{max}	66.4% (60.4 – 73.0%)	92.4% (84.0 – 101.6%)

Table 2. Absolute Bioavailability of the Tablet Formulations

Formulations	F (%)
Delayed-Release Tablet (A)	32.4
Modified-Release Tablet (B)	44.9
Immediate-Release Tablet (C)	46.0

XP12B-102: Randomized single dose comparative bioavailability 4-way crossover study with healthy nonsmoking adult female volunteers under fed to fasting conditions

This was a randomized, single dose, 4-way crossover comparative bioavailability study, under fasting and fed conditions, performed on 28 healthy non-smoking adult female volunteers and 4 alternates. A total of 26 subjects completed the clinical phase of the study. In each period, subjects were housed from at least 10 hours before dosing until after 36-hour post dose events. The tranexamic acid dose administrations were separated by a washout period of 7 days. The objective of this study was to assess the single dose relative bioavailability of two test tablet formulations of 650 mg tranexamic acid (MR and DR) tablets, following a 1.3 g dose, under fasting and fed conditions. Sponsor's results are provided in tables 3 and 4. The sponsor concluded that the results revealed that the 90% CIs for the MR formulation fell within the BE acceptance range of 80%-125% for AUC_{inf} and C_{max} indicating that the extent of absorption was clinically equivalent between the fasted and the fed state.

Table 3. Ratios of Least Squares Means of MR Tablets Under Fed and Fasting Conditions (90% CI)

Parameter	MR tablet fed (D) vs. fasting (B)
AUC _{0-t} (mcg/mL·hr)	116.5 % (107.8 – 126.0)
AUC _{inf} (mcg/mL·hr)	115.4 % (106.5 – 124.9)
C _{max} (mcg/mL)	106.8 % (97.2 – 117.3)

Table 4. Ratios of Least Squares Means of DR Tablets Under Fed and Fasting Conditions (90% CI)

Parameter	DR tablet fed (C) vs. fasting (A)
AUC _{0-t} (mcg/mL·hr)	107.4 % (90.7 – 127.3)
AUC _{inf} (mcg/mL·hr)	110.6 % (94.7 – 129.2)
C _{max} (mcg/mL)	75.9 % (60.7 – 95.0)

XP12B-103: Randomized single dose and multiple dose pharmacokinetic assessment in healthy nonsmoking adult female volunteers under fasting conditions

This was a parallel study of single and multiple doses performed on 2 groups of 20 healthy non-smoking adult female volunteers. Half the subjects in each group received the DR formulation and the other half received the MR formulation. A total of 39 subjects completed the clinical phase of the study. After an overnight fast, subjects received a single oral dose of tranexamic acid (1.3 g) on day 1. Blood samples were taken before dosing and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 14, 24, 28, 32 and 36 hours postdose. Subjects received another single oral dose (1.3 g) on the evening of day 2, and 3 times a day (every 8 hours) starting the morning of day 3 until last single dose in the morning of day 7. Blood samples were taken before the 6th, 9th, 12th, and 15th dose for determination of C_{min}, and up to 8 hours (0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8) after the last dose, for determination of drug concentration at steady-state. Subjects were housed from at least 10 hours before the 1st dose on day 1 until after 8-hour blood draw following the 15th dose (day 7). The objective of this study was to assess the PK linearity of two test tablets of the formulations of tranexamic acid (DR and MR), after a single oral dose (day1) compared to a daily (1.3 g every 8 hours) dosage regimen (days 2 to 7), under fasting conditions. Sponsor's results are provided in tables 5 and 6. The sponsor concluded that the results revealed that the MR formulation exhibited linear pharmacokinetics following repeated administration (5 days) of a 1.3 g dose under fasting conditions, whereas DR formulation seemed to exhibit linear pharmacokinetics after multiple dose administrations (5 days) since the AUC_t/AUC_{inf} ratio was close to 100%.

Table 5. Time-Dependent Pharmacokinetic Linearity

Formulation	Ratio AUC _t / AUC _{inf}	90% Confidence Interval	
		Lower Limit	Upper Limit
Combined (A and B)	102.5	91.9	114.3
DR (A)	107.7	89.2	130.1
MR (B)	97.3	86.5	109.5

Table 6. Steady State Analysis

Formulation	Day	Time (hour)	LSM Derived From the ANOVA
Combined (A and B)	4	-72	5.48506
	5	-48	4.80606
	6	-24	5.57891
	7	0	5.66691
DR (A)	4	-72	6.11142
	5	-48	4.84722
	6	-24	5.93658
	7	0	6.21402
MR (B)	4	-72	4.90536
	5	-48	4.77323
	6	-24	5.23678
	7	0	5.15389

Abbreviations: ANOVA=analysis of variance; DR=Delayed Release; LSM=least squares mean; MR=Modified Release

Formulation

- Tranexamic acid MR formulation used in the three phase 1 PK studies (lot A040045) was film coated. However, all subsequent clinical studies in the phase 3 were conducted using tranexamic acid MR formulation without coating. The sponsor submitted in vitro dissolution profile of coated vs. non-coated tranexamic acid MR.
- The sponsor stated in the pharmaceutical development section (3.2.P.2) of the submission that there were no changes to the formulation, method of manufacture or equipment class of clinical supply products and the to-be-marketed products.

Information Request from Office of Clinical Pharmacology:

- Provide the demographic information including sex, age, and weight of the patients enrolled in the study (Anderson L. et al., Urological Research 6, 83-88, 1978) to calculate those patients' creatinine clearance.
- Provide the information of equation used to estimate Glomerular Filtration Rate (GFR) from serum creatinine in 8.6 Renal Impairment section of your proposed label.

The above Information Request was sent out to the sponsor on March 12, 2009. The sponsor submitted the response letter to the above Information Request on March 13, 2009.

Clinical Pharmacology comments to be included in the 74-day letter

- Your proposed dosage adjustment in patients with renal impairment is based on serum creatinine concentration and estimated Glomerular Filtration Rate (GFR). This will be a review issue.
- The robustness of the tranexamic acid modified release formulation in presence of various alcohol concentrations (0, 5, 10, 20 and 40%) as well as in different pH will be reviewed.

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 22-430 is fileable.

Hyunjin Kim, Pharm.D., M.S.

Date

Myong-Jin Kim, Pharm.D., Team Leader

Date

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22430

ORIG-1

XANODYNE
PHARMACEUTICS
INC

Lysteda

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/s/

HYUNJIN KIM

10/15/2009

MYONG JIN KIM

10/16/2009

EDWARD D BASHAW

10/16/2009

Concur with PREA required study

BIOPHARMACEUTICS REVIEW

NDA#	22430
Drug	Tranexamic acid
Formulation	Modified release 650 mg tablets
Type	Original NDA
Sponsor	Xanodyne Pharmaceuticals Inc
Letter Date	January 30 2009
Reviewer/Team Leader	Patrick Marroum, Ph.D.

Background:

Xanodyne Pharmaceuticals is submitting this application to seek approval of a new formulation of tranexamic acid 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. It is to be noted that another Immediate Release formulation of tranexamic acid (Cyklokapron) was approved in 1986 but was never marketed in the US. This review addresses whether the new formulation is a modified release formulation or a different IR formulation.

Results:

Study XP12B-101 a single dose 4 way crossover absolute bioavailability and bioequivalence study of Xanodyne Tranexamic acid tablet formulations in healthy adult women volunteers under fasting conditions showed that practically there was no difference in the plasma concentrations time profiles between the IR formulation of tranexamic acid and this new modified release formulation as can be seen in Figure 1. Table 1 shows that the PK parameters expressed as CMAX, TMAX and AUC were very similar between the 2 formulations. Table 2 gives the 90 % confidence intervals for the ratios of the CMAX and AUC of the MR formulations compared to the IR formulation and shows that these 2 formulations are bioequivalent to each other. Table 3 gives the comparative compositional formula for the three formulations used in the single dose bioavailability/bioequivalence study. Figure 2 shows the comparative dissolution profiles for the 3 formulations used in the study

Comments:

- 1- The results of the study conducted by the sponsor show that the IR formulation is bioequivalent to the MR formulations and the profiles are almost superimposable.

2-The comparative dissolution profiles show that the dissolution of the MR formulation is relatively slower than the dissolution of the IR formulation. However, complete dissolution is occurring within 90 minutes, a time frame clearly shorter than what is usually seen for a modified release formulation.

3-The IR and MR formulations have very a similar composition formula except for _____ by the sponsor.

b(4)

Mean Plasma Tranexamic Acid Concentration (mcg/mL) versus Time (Semi-Log Scale)

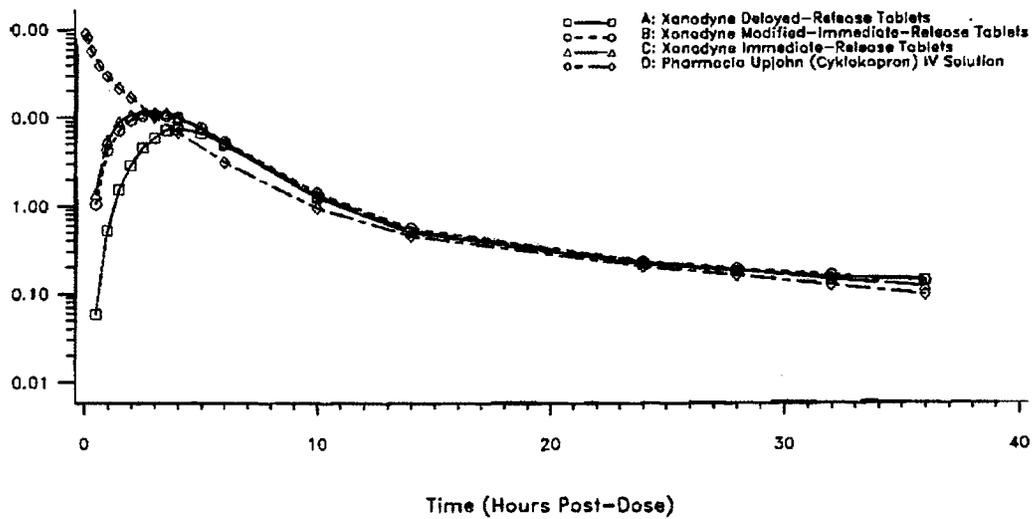


Table 1
Project No: AA06722
Summary of Results - Tenoxicam Acid in Plasma
Pharmacokinetic Parameters
(N = 26)

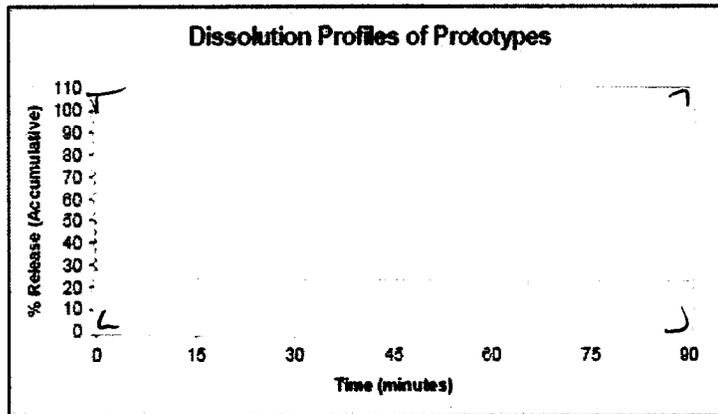
	ln AUC 0-t* (mcg·h/mL)	ln AUCinf* (mcg·h/mL)	ln Cmax* (mcg/mL)	tmax (h)	Half-life (h)	kel (1/h)	F (%)
Xenodyne DR (A)							
Mean	45.385	49.913	8.126326	4.000	12.470	0.05955	32.37
CV	36.1	35.3	35.2	23.2	26.1	27.5	30.4
n	26	23	26	26	24	24	23
Xenodyne MR (B)							
Mean	66.703	69.442	11.291088	2.942	11.370	0.04300	44.93
CV	26.8	27.2	29.1	22.7	17.6	19.4	25.3
n	26	24	26	26	26	26	24
Xenodyne IR (C)							
Mean	70.157	72.656	12.260414	2.803	11.013	0.04439	46.04
CV	16.2	16.4	23.0	20.8	15.5	15.3	16.1
n	26	24	26	26	24	24	24
Least-Squares Means							
Xenodyne DR (A)	45.365	49.095	8.139082				
Xenodyne MR (B)	66.835	68.891	11.321313				
Xenodyne IR (C)	70.051	72.411	12.258222				
Ratio of Least-Squares Means							
(B/C) %	64.6	67.8	66.4				
(B/C) %	95.6	95.1	92.4				

* For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.
AUCinf, half-life, kel and F could not be estimated for some subjects.

Ratios of LSM (90% Confidence Intervals)

Parameter	Delayed-Release Tablet (A) vs. Immediate-Release Tablet (C)	Modified-Immediate-Release Tablet (B) vs. Immediate-Release Tablet (C)
AUC 0-t	64.8% (59.5 – 70.5%)	95.6% (87.8 – 104.0%)
AUCinf	67.8% (62.2 – 73.9%)	95.1% (87.4 – 103.5%)
Cmax	66.4% (60.4 – 73.0%)	92.4% (84.0 – 101.6%)

Figure 2: Dissolution Profiles of the Prototype Formulations



b(4)

Table 5: Prototype Formulations

Raw material name	Immediate Release	Delayed Release	Modified-Immediate Release
Tranexamic Acid	650.00 mg	650.00 mg	650.00 mg
Microcrystalline Cellulose NF			
Colloidal Silicon Dioxide NF			
Pregelatinized Corn Starch NF			
Povidone USP			
Hypromellose USP			
Microcrystalline Cellulose NF			
Stearic Acid NF			

b(4)

b(4)

b(4)

RECOMMENDATION

In the opinion of the Office of New Drug Quality Assessment, Lysteda is not a modified release formulation because it has a pharmacokinetic plasma concentration profile that is very similar to the already approved Cyklokapron IR formulation. The results of the study conducted by the sponsor show that Lysteda and Cyklokapron are bioequivalent to each other. In summary Lysteda does not exhibit release characteristics that are typical of a modified release formulation.

 Patrick Marroum, Ph. D.
 Office of New Drug Quality Assessment

Date _____

cc: Heiman, claffey, Henry

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

/s/

Patrick Marroum
5/14/2009 04:46:41 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission				
	Information		Information	
NDA Number	22-430	Brand Name	Lysteda	
OCP Division	DCP3	Generic Name	Tranexamic acid 650 mg modified release (MR)	
Medical Division	DRUP	Drug Class	Antifibrinolytic	
OCP Reviewer	Hyunjin Kim, Pharm.D., M.S.	Indication(s)	Treatment of heavy menstrual bleeding (menorrhagia) and the amelioration of symptoms associated with heavy menstrual bleeding, including limitations on social, leisure, and physical activities	
OCP Team Leader	Myong-Jin Kim, Pharm.D.	Dosage Form	Tablets	
		Dosing Regimen	Two 650 mg tablets taken 3 times daily (3.9 g/day) during menstruation	
Date of Submission	January 30, 2009	Route of Administration	Oral	
Estimated Due Date of OCP Review	May 30, 2009	Sponsor	Xanodyne Pharmaceuticals, Inc.	
PDUFA Due Date	July 30, 2009	Priority Classification	Priority	
Division Due Date	May 30, 2009			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			Labeling in Physician Labeling Rule (PLR) format
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		XP12B-103
multiple dose:	X	1		XP12B-103
Patients-				
single dose:				

multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	X	1		XP12B-101
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		XP12B-101
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		XP12B-102
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan	X	1		A request of deferral of the pediatric study until the product is approved

Literature References		2		
Total Number of Studies		8		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X			
Comments sent to firm ?				
QBR questions (key issues to be considered)	<p>Is the clinical trial formulation same as the to be marketed formulation? What is the absolute bioavailability of tranexamic acid MR tablet compared to parenteral reference drug? What is the effect of food on the exposure of tranexamic acid MR tablet? What are the pharmacokinetic (PK) characteristics of single and multiple dose of tranexamic acid MR tablet?</p>			
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

Filing Memo

Clinical Pharmacology Review

NDA: 22-430
Compound: Lysteda (Tranexamic acid 650 mg modified release [MR] tablet)
Sponsor: Xanodyne Pharmaceuticals, Inc.
Date: February 25, 2009
Reviewer: Hyunjin Kim, Pharm.D., M.S.

Background

Xanodyne Pharmaceuticals, Inc. is developing tranexamic acid as a modified-release (MR) oral dose formulation (650 mg) for the treatment of menorrhagia. The objective of developing tranexamic acid MR oral formulation is to develop a stable, orally administered tablet with minimal gastrointestinal irritation. Per sponsor, gastrointestinal complaints (nausea, dyspepsia, vomiting, and diarrhea) are the most commonly observed adverse effects associated with oral tranexamic acid marketed outside of the U.S.

The proposed indication is the treatment of heavy menstrual bleeding (menorrhagia; in excess of 80 mL of blood loss per menstrual cycle) and the amelioration of symptoms associated with heavy menstrual bleeding, including limitations of social, leisure, and physical activities. The proposed dosage regimen is two 650 mg tablets administered 3 times daily, a total of 3.9 g daily, during menstruation. Tranexamic acid is an antifibrinolytic agent, currently approved in U.S. for the short term (10 mg/kg, 3-4 times daily for 2-8 days) treatment in hemophilic patients to reduce or prevent hemorrhagia following tooth extraction procedures. Only the intravenous (IV) formulation is currently available in U.S (Cyklokapron, NDA 19-281 approved on December 30, 1986). Per current sponsor, the tablet formulation (Cyklokapron 500 mg, NDA 19-280 approved on December 30, 1985) has never been marketed in U.S., although it was approved with IV formulation. The current submission is being filed as a 505(b)(2) application referencing the Cyklokapron IV, NDA 19-281.

In support of NDA 22-430, the sponsor submitted four phase 1 studies and four phase 3 studies including two pivotal phase 3 safety and efficacy studies.

Contents of submission

- Three phase 1 biopharmaceutics studies (XP12B-101, XP12B-102, and XP12B-103)
 - XP12B-101: Randomized single dose absolute bioavailability (immediate release-IR, modified release-MR, delayed release-DR) and bioequivalence crossover study in healthy non-smoking young female volunteers
 - XP12B-102: Randomized single dose comparative bioavailability 4-way crossover study with healthy nonsmoking adult female volunteers under fed to fasting conditions (MR and DR formulations)
 - XP12B-103: Randomized single dose and multiple dose pharmacokinetic

assessment in healthy nonsmoking adult female volunteers under fasting conditions (MR and DR formulations)

- Three study specific bioanalytical study reports for three phase 1 biopharmaceutics studies with one method validation study report
- SAS transport files for three phase 1 biopharmaceutics studies
- Label of tranexamic acid MR in accordance with the Physician Labeling Rule (PLR)
- A request for deferral of pediatric studies with clinical development plan for pharmacokinetic study demonstrating acceptable dosing in the adolescent population.
- One phase 1 thorough QT study (XP12B-MR-104)
- Two pivotal phase 3 efficacy and safety studies (XP12B-MR-301 and XP12B-MR-303)
The active treatment arms in all phase 3 studies were given tranexamic acid MR formulation.
- Two ongoing phase 3 safety studies (XP12B-MR-302 and XP12B-MR-304)
The active treatment arms in all phase 3 studies were given tranexamic acid MR formulations.
- Literature search for clinical scientific literature on tranexamic acid from 2002 through 2008

Previous Clinical Pharmacology comments and agreements

1. Pre-NDA meeting on October 31, 2008

- Dosing requirements for the proposed tranexamic acid MR formulation in presence of renal impairment should be adequately addressed. Ideally, a PK study of the proposed formulation in subjects with various degrees of renal impairment should be conducted in order to optimize dosing regimens in such patients. If such a study has not been conducted and the sponsor believes that adequate data are available in this regard, provide this information to the Division along with adequate justification that addresses how this information would be applicable to the proposed modified release oral formulation. This will be a review issue.
There is no PK study conducted in patients with renal impairment. The section 8.6 renal impairment of the sponsor's proposed label has dosage adjustment for renal impairment based on two literature data.
- Address the robustness of the proposed MR formulation in presence of alcohol. An in vitro release comparison of the proposed MR formulation in presence of various alcohol concentrations (0, 5, 10, 20 and 40%) should be conducted using 0.1 N HCl and the optimal dissolution medium for the formulation as the release media. Alternatively, the study can be conducted in media with three different pH levels (1.2, 4.5 and 6.8).
The sponsor submitted in vitro dissolution profiles of tranexamic acid MR in different concentrations (5, 10, 20, and 40%) of alcohol as well as in different pH (1.2, 4.5, and 6.8).
- The Division will review the request for a pediatric deferral when submitted. To obtain a deferral, the Sponsor should submit certification of the reason for deferring pediatric assessments, a description of the planned or ongoing studies, and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time. **In other words, propose a "comprehensive pediatric study in adolescents"** as part of the request for deferral.

ADDITIONAL DISCUSSION AT THE MEETING: The Sponsor agreed to send a proposal for a pediatric study with the deferral request in the NDA submission. The

Sponsor is considering a pediatric PK study. A PK study might be acceptable; the Division will seek the opinion of internal pediatric consultants during the review cycle. *The sponsor submitted a request for deferral of pediatric studies with clinical development plan for PK study demonstrating acceptable dosing in the adolescent population.*

2. Pre-NDA meeting on February 26, 2008

- _____ facility _____, was employed for the three phase 1 trials. During the pre-NDA meeting, the sponsor confirmed that _____ did not conduct the bioanalysis or validation. Therefore, it was agreed that no follow-up in this regard was needed. b(4)

3. Guidance meeting on September 20, 2004

- Sparse sampling was recommended in phase 3 clinical trials to characterize PK following three times daily dosing regimen. *Referring to the Clinical Pharmacology review prepared by Dr. Sandhya Apparaju (DARRTS November 05, 2008), the sponsor stated that the information to justify that sparse sampling is not warranted was provide with a previous SPA submission dated May 11, 2005. However, it is not clear whether the Clinical Pharmacology reviewer concurred with this during the SPA review because Clinical Pharmacology review of the SPA submission is not available in DARRTS.*
- No drug-drug interaction studies, including those with drugs that are predominantly renally eliminated are needed. *There is no drug interaction study submitted.*

4. Guidance meeting on August 25, 2004

- The Division recommended that the sponsor consider conducting a Phase 2 dose ranging trial to determine the Lowest Effective Dose (LED). The sponsor proposed including a lower dose treatment arm in their phase 3 clinical trials to confirm that 3.9 gm per day of tranexamic acid is the LED. This approach would be acceptable to the Division. However, if both the 3.9 gm dose and the lower dose (1.95 g/day) are equally effective, this will not identify the LED. Ideally, the Division would like the sponsor to identify a dose that fails to meet the prespecified efficacy endpoints in order to identify the LED. *Per sponsor's conclusion of study XP12B-MR-301, the result of the study demonstrated the safety and efficacy of tranexamic acid MR 3.9 g/day, whereas it failed to demonstrate the safety and efficacy of tranexamic acid MR 1.95 g/day.*

Three phase 1 biopharmaceutics studies

1. XP12B-101: Randomized single dose absolute bioavailability and bioequivalence crossover study with healthy non-smoking young female volunteers

This was a randomized, single dose, 4-way crossover absolute bioavailability and bioequivalence study performed on 28 healthy non-smoking female volunteers under fasting condition. There are four treatment groups; tranexamic acid delayed release (DR), modified release (MR), immediate release (IR), and tranexamic acid injection. A total of 26 subjects completed the study. In each period, subjects were housed from at least 10 hours before dosing until after 36-hour post dose events. The tranexamic acid dose administration (1.3 g for oral formulations and 1 g for intravenous formulation) were separated by a washout period of 7 days. The objective of this study was to assess bioequivalence of 2 test tablet formulations of tranexamic acid (DR [A] and

MR [B]) compared to the reference tablet formulation of tranexamic acid (IR [C]), and to determine the absolute bioavailability of the tablet formulations (A, B, C) to the Canadian approved IV formulation [D]. Sponsor's results are provided in the tables 1 and 2. Sponsor concluded that tranexamic acid MR 650 mg tablet formulation and immediate release formulation are bioequivalent under fasting conditions.

Although tranexamic acid MR and IR were found to be bioequivalent, the MR formulation had a slower dissolution profile than IR formulation.

Table 1. Ratios of Least Squares Means for All Formulations (90% CI)

Parameter	Delayed-Release Tablet (A) vs. Immediate-Release Tablet (C)	Modified-Release Tablet (B) vs. Immediate-Release Tablet (C)
AUC _{0-t}	64.8% (59.5 – 70.5%)	95.6% (87.8 – 104.0%)
AUC _{inf}	67.8% (62.2 – 73.9%)	95.1% (87.4 – 103.5%)
C _{max}	66.4% (60.4 – 73.0%)	92.4% (84.0 – 101.6%)

Table 2. Absolute Bioavailability of the Tablet Formulations

Formulations	F (%)
Delayed-Release Tablet (A)	32.4
Modified-Release Tablet (B)	44.9
Immediate-Release Tablet (C)	46.0

XP12B-102: Randomized single dose comparative bioavailability 4-way crossover study with healthy nonsmoking adult female volunteers under fed to fasting conditions
 This was a randomized, single dose, 4-way crossover comparative bioavailability study, under fasting and fed conditions, performed on 28 healthy non-smoking adult female volunteers and 4 alternates. A total of 26 subjects completed the clinical phase of the study. In each period, subjects were housed from at least 10 hours before dosing until after 36-hour post dose events. The tranexamic acid dose administrations were separated by a washout period of 7 days. The objective of this study was to assess the single dose relative bioavailability of two test tablet formulations of 650 mg tranexamic acid (MR and DR) tablets, following a 1.3 g dose, under **fasting and conditions**. Sponsor's results are provided in tables 3 and 4. The sponsor concluded that the results revealed that the 90% CIs for the MR formulation fell within the BE acceptance range of 80%-125% for AUC_{inf} and C_{max} indicating that the extent of absorption was clinically equivalent between the fasted and the fed state.

Table 3. Ratios of Least Squares Means of MR Tablets Under Fed and Fasting Conditions (90% CI)

Parameter	Modified-Release Tablet Fed (D) vs. Fasting (B)
AUC _{0-t}	116.5% (107.8 – 126.0%)
AUC _{inf}	115.4% (106.5 – 124.9%)
C _{max}	106.8% (97.2 – 117.3%)

Table 4. Ratios of Least Squares Means of MR Tablets Under Fed and Fasting Conditions (90% CI)

Parameter	Modified-Release Tablet Fed (D) vs. Fasting (B)
AUC _{0-t}	116.5% (107.8 – 126.0%)
AUC _{inf}	115.4% (106.5 – 124.9%)
C _{max}	106.8% (97.2 – 117.3%)

XP12B-103: Randomized single dose and multiple dose pharmacokinetic assessment in healthy nonsmoking adult female volunteers under fasting conditions

This was a parallel study of single and multiple doses performed on 2 groups of 20 healthy non-smoking adult female volunteers. Half the subjects in each group received the DR formulation and the other half received the MR formulation. A total of 39 subjects completed the clinical phase of the study. After an overnight fast, subjects received a single oral dose of tranexamic acid (1.3 g) on day 1. Blood samples were taken before dosing and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 14, 24, 28, 32 and 36 hours postdose. Subjects received another single oral dose (1.3 g) on the evening of day 2, and 3 times a day (every 8 hours) starting the morning of day 3 until last single dose in the morning of day 7. Blood samples were taken before the 6th, 9th, 12th, and 15th dose for determination of C_{min}, and up to 8 hours (0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8) after the last dose, for determination of drug concentration at steady-state. Subjects were housed from at least 10 hours before the 1st dose on day 1 until after 8-hour blood draw following the 15th dose (day 7). The objective of this study was to assess the PK linearity of two test tablets of the formulations of tranexamic acid (DR and MR), after a single oral dose (day1) compared to a **daily (1.3 g every 8 hours) dosage regimen (days 2 to 7), under fasting conditions**. Sponsor's results are provided in tables 5 and 6. The sponsor concluded that the results revealed that the MR formulation exhibited linear pharmacokinetics following repeated administration (5 days) of a 1.3 g dose under fasting conditions, whereas DR formulation seemed to exhibit linear pharmacokinetics after multiple dose administrations (5 days) since the AUC_t/AUC_{inf} ratio was close to 100%.

Table 5. Time-Dependent Pharmacokinetic Linearity

Formulation	Ratio AUC_t / AUC_{inf}	90% Confidence Interval	
		Lower Limit	Upper Limit
Combined (A and B)	102.5	91.9	114.3
DR (A)	107.7	89.2	130.1
MR (B)	97.3	86.5	109.5

Table 6. Steady State Analysis

Formulation	Day	Time (hour)	LSM Derived From the ANOVA
Combined (A and B)	4	-72	5.48506
	5	-48	4.80606
	6	-24	5.57891
	7	0	5.66691
DR (A)	4	-72	6.11142
	5	-48	4.84722
	6	-24	5.93658
	7	0	6.21402
MR (B)	4	-72	4.90536
	5	-48	4.77323
	6	-24	5.23678
	7	0	5.15389

Abbreviations: ANOVA=analysis of variance; DR=Delayed Release; LSM=least squares mean; MR=Modified Release

Formulation

- In study XP12B-101, the Canadian approved formulation of Cyklokapron injection owned by Pharmacia Canada Inc. was used as the reference product. Referring to the **meeting minutes dated on November 3, 2003, the Division concurred to the sponsor's proposal to use Canadian approved formulation of Cyklokapron injection for IV administration in study XP12B-101, if information can be submitted to show both Canadian and US approved formulations of Cyklokapron injection are identical.** It is a review issue whether Canadian approved vs. U.S. approved formulation of Cyklokapron injection (NDA 19-281) is identical, because this submission is referencing the nonclinical safety and human safety information of tranexamic acid in the US approved formulation of Cyklokapron injection under 505(b)(2).
- Tranexamic acid MR formulation used in the three phase 1 PK studies (lot A040045) was film coated. However, all subsequent clinical studies in the phase 3 were conducted using tranexamic acid MR formulation without coating. The sponsor submitted in vitro dissolution profile of coated vs. non-coated tranexamic acid MR.
- The sponsor stated in the pharmaceutical development section (3.2.P.2) of the submission that there were no changes to the formulation, method of manufacture or equipment class of clinical supply products and the to-be-marketed products.

Information Request from Office of Clinical Pharmacology:

- Provide the demographic information including sex, age, and weight of the patients enrolled in the study (Anderson L. et al., Urological Research 6, 83-88, 1978) to **calculate those patients' creatinine clearance.**
- Provide the information of equation used to estimate Glomerular Filtration Rate (GFR) from serum creatinine in 8.6 Renal Impairment section of your proposed label.

The above Information Request was sent out to the sponsor on March 12, 2009. The sponsor submitted the response letter to the above Information Request on March 13, 2009.

Clinical Pharmacology comments to be included in the 74-day letter

- Your proposed dosage adjustment in patients with renal impairment is based on serum creatinine concentration and estimated Glomerular Filtration Rate (GFR). This will be a review issue.
- The robustness of the tranexamic acid modified release formulation in presence of various alcohol concentrations (0, 5, 10, 20 and 40%) as well as in different pH will be reviewed.

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 22-430 is fileable.

Hyunjin Kim, Pharm.D., M.S.

Date

Myong-Jin Kim, Pharm.D., Team Leader

Date

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

/s/

Hyunjin Kim
3/24/2009 05:04:59 PM
BIOPHARMACEUTICS

Myong-Jin Kim
3/24/2009 05:05:50 PM
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