CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-430

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	November 13, 2009
From	Scott Monroe, MD Division of Reproductive and Urologic Products
Subject	Division Director Summary Review
NDA	NDA 22-430
Applicant Name	Xanodyne Pharmaceutical, Inc.
Date of Submission	January 30, 2009
PDUFA Goal Date	October 30, 2009 (Priority review + 3 month extension)
Proprietary Name / Established (USAN) Name	Lysteda Tranexamic acid
Dosage Forms/Strength	Oral tablet containing 650 mg tranexamic acid
Proposed Indication	Treatment of heavy menstrual bleeding and amelioration of associated symptoms
Action	***Approve (see Section 13.1)***

Material Reviewed/Consulted OND Action Package, including	**Names of Reviewers**
Medical Officer Review	Daniel Davis, MD
Statistical Review - Efficacy	Xin Fang, PhD/Mahboob Sobhan, PhD
Pharmacology/Toxicology Review	Kimberly Hatfield, PhD/Lynnda Reid, PhD
CMC Review/ONDQA	Gene Holbert, PhD/Moo Jhong Rhee, PhD
Microbiology Review	Not required
Clinical Pharmacology Review	Hyunjin Kim, PharmD, MS /Myong-Jin Kim, PharmD
Statistical Review - Safety	Olivia Lau, PhD/Paul Schuette, PhD
DDMAC	Janice Maniwang, PharmD, MBA
DSI	Roy Blay, PhD/Tejashri Purohit-Sheth, MD
CDTL Review	Lisa Soule, MD (also Clinical Team Leader)
OSE/DMEPA	Anne Crandall, PharmD, Melina Griffis, RPh
OSE/DRISK	Robin Duer, RN, MBA/Jodi Duckhorn, MA

OND	Office of New Drugs
DDMAC	Division of Drug Marketing, Advertising, and Communication
DSI	Division of Scientific Investigations
CDTL	Cross Discipline Team Leader
OSE	Office of Surveillance and Epidemiology
DMEPA	Division of Medication Errors Prevention and Analysis
DRISK	Division of Risk Management

1. INTRODUCTION

The purpose of NDA 22-430 is to obtain marketing approval for tranexamic acid tablets (to be marketed under the proprietary name of Lysteda) for the indication of "treatment of cyclic heavy menstrual bleeding." Tranexamic acid is a synthetic lysine derivative that has anti-fibrinolytic activity. Currently approved treatments in the US for heavy menstrual bleeding (HMB) include interventional surgical procedures (e.g., endometrial ablation) and progestin-based drug therapies. Two currently marketed oral progestin therapies (norethindrone acetate and medroxyprogesterone acetate) are approved "to treat...abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer." On October, 1, 2009, Mirena (a levonorgestrel-releasing intrauterine device) was approved for a secondary indication to treat HMB in women who choose to use intrauterine contraception. Oral contraceptives have also been used off-label in extended/continuous regimens to control HMB.

In support of the safety and efficacy of tranexamic acid tablets (3.9 g/day for a maximum of 5 days during monthly menstruation) for the proposed indication, the Applicant conducted four Phase 3 clinical trials. Two of these trials were randomized, double-blind, placebo-controlled studies for efficacy and safety. The other 2 trials were open-label, non-comparative safety studies.

In this 505(b)(2) application, the Applicant has depended, in part, on nonclinical safety data from NDA 19-281 for Cyklokapron (an intravenous formulation of tranexamic acid approved to reduce or prevent hemorrhage in patients with hemophilia during and following tooth extraction).

There are no outstanding clinical pharmacology, nonclinical toxicology, or chemistry, manufacturing and control (CMC) issues for tranexamic acid tablets. Both Phase 3 clinical trials for tranexamic acid tablets achieved their protocol-defined primary efficacy objectives. The major efficacy issue addressed during the review cycle was the acceptability of a patient-reported outcome (PRO) instrument developed by the Applicant to support inclusion of key secondary efficacy findings in labeling. Safety issues that were carefully assessed during the review cycle related to potential thrombogenic, ophthalmologic, and allergic risks that might be associated with the use of tranexamic acid tablets. Both the primary Clinical Reviewer and the Cross Discipline Team Leader (CDTL, who also was the Clinical Team Leader) have recommended approval of this Application; I concur with their recommendations.

2. BACKGROUND

2.1 Description of Product

Tranexamic acid is a synthetic lysine derivative with anti-fibrinolytic activity that acts by forming a reversible complex with plasminogen. The plasmin/tranexamic acid complex prevents the binding of plasmin to the surface of fibrin and thereby inhibits fibrinolysis.

The Applicant's proposed oral formulation of tranexamic acid tablets (hereafter referred to as tranexamic acid or Lysteda) is not currently marketed anywhere in the world. According to the primary Clinical Reviewer, other oral formulations of tranexamic acid have been marketed for many years outside of the US for the treatment of heavy menstrual bleeding. Countries in which oral tranexamic acid tablets are approved for marketing for the indication of heavy menstrual bleeding include Sweden, the United Kingdom, Japan, Canada, and Australia.

2.2 Regulatory History

During the clinical development of tranexamic acid, there were several meetings between the Applicant and the Division of Reproductive and Urologic Products (DRUP). The design and conduct of the two pivotal Phase 3 trials conducted by the Applicant, as well as the scope of the safety database, are consistent with the recommendations provided by DRUP.

The Applicant requested and was granted priority review status for this Application on the basis of having received Fast Track designation earlier in the development program. Fast Track status was granted based on the potential for tranexamic acid to fill an unmet medical need (i.e., a nonhormonal treatment for heavy menstrual bleeding). Details of the regulatory interactions between the Applicant and DRUP are provided in Section 2.5 of the primary Clinical Review.

2.3 Primary Clinical Reviewer's and Cross Discipline Team Leader's Recommendations regarding Approvability

In the primary Clinical Review for this Application (signed November 6, 2009), Dr. Daniel Davis made the following recommendation and overall assessments:

> *I recommend the approval of tranexamic acid 650 mg administered as two tablets three times a day (3.9 grams/day) for up to five days during monthly menstruation for the following indication: for the treatment of cyclic heavy menstrual bleeding.*
>
> *The overall risk benefit assessment shows that the safety profile of tranexamic acid at the recommended dose is acceptable. The common but non-serious side effects and the rare serious adverse events are discussed in the final label.*
>
> *I do not recommend a Postmarketing Risk Evaluation and Mitigation Strategy (REMS) for this product. Tranexamic acid is approved at the same or higher doses and has been used for the treatment of HMB [heavy menstrual bleeding] in several countries since at least 1986. The overall postmarketing safety experience with tranexamic acid globally is acceptable and does not suggest the need for a REMS.*

In her Cross Discipline Team Leader Review for this Application (signed November 6, 2009), Dr. Soule made the following recommendation and overall assessments:

> *I recommend that Lysteda be approved for the indication "treatment of cyclic heavy menstrual bleeding."*
>
> *The Applicant has demonstrated efficacy for the 3.9 g/day dose of Lysteda, according to the criteria agreed-upon with the Division, in both of the phase 3 safety and efficacy studies... The Applicant further demonstrated efficacy on two of its three pre-specified secondary endpoints, limitations in social and leisure activities and in physical activity.*
>
> *The safety profile of Lysteda is generally reassuring, and risks that have been identified (in part, through the extensive postmarketing experience with tranexamic acid), such as VTEs [venous thromboembolic events], ophthalmologic adverse events and serious allergic reactions, can be adequately addressed in labeling.*

Division Director's Comment

- *I concur with both the recommendations and overall assessments of Drs. Davis and Soule.*

3. CMC

The primary Chemistry Reviewer, Gene Holbert, PhD, made the following recommendation in his review signed on September 24, 2009:

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. All facilities involved are in compliance with cGMP, and labels have adequate information as required. Therefore, from a CMC perspective, this NDA is recommended for "Approval."

No postmarketing commitments or risk management steps were recommended.

Environmental Assessment. According to the primary CMC Review, an Environmental Assessment was consulted to Raanan A. Bloom, PhD, Senior Environmental Officer, Office of Pharmaceutical Science. **A Finding of "No Significant Impact (FONSI) was issued 27-MAR-2009."**

Division Director's Comment

- *I concur with the recommendation of Dr. Holbert. There are no outstanding CMC issues.*

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

In addition to relying, in part, on the nonclinical findings of safety for Cyklokapron, as reflected in the approved labeling for the intravenous product (NDA 19-281), the Applicant conducted and submitted 3 nonclinical studies:

- A 39-week repeat dose toxicity study in dogs
- An embryo-fetal-developmental toxicity study in rats
- A perinatal developmental toxicity study in rats

The primary Toxicology Reviewer, Kimberly Hatfield, PhD, made the following recommendations in her review signed on June 22, 2009:

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

***Recommendations for nonclinical studies**: No additional nonclinical studies are required.*

***Recommendations on labeling**: The Sponsor's submitted labeling for Sections 8.1, 8.3, 13.1 and 13.2 are acceptable with minor changes.*

In a memorandum signed on October 27, 2009, Dr. Hatfield noted that: *"Nonclinical recommendations for labeling were made for NDA 22-430 in my review submitted to the NDA and signed on 6-22-09. Subsequent changes that were made during label negotiation to Sections 8.1, 8.2, 8.3, 13.1 and 13.2 are all appropriate, and I concur with the final label submitted to the Sponsor on 10-26-2009."*

Division Director's Comment

- *The labeling recommendations of Dr. Hatfield were incorporated by the Applicant. There are no outstanding nonclinical pharmacology/toxicology issues.*

5. CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS

In support of this NDA, the Applicant submitted the results of 3 pharmacokinetic (PK) studies. These studies were intended to characterize the single and multi-dose (steady state) pharmacokinetics and absolute bioavailability of tranexamic acid. One of the studies assessed the effect of food on the bioavailability of tranexamic acid.

Findings from these studies with oral tranexamic acid included a tmax of 3 hours, with a half-life of 11 hours. Steady state was reached within 32 hours after the first dose. Absolute bioavailability was approximately 44%.

Elimination of tranexamic acid is predominantly via urinary excretion through glomerular filtration. Although the Applicant did not evaluate the PK of orally administered tranexamic acid in renally impaired subjects, the primary Clinical Pharmacology Reviewer, Hyunjin Kim, PharmD, recommended that the oral dose of tranexamic acid be adjusted in accordance with the labeling for Cyklokapron (the approved intravenous formulation of tranexamic acid). The recommended dose adjustment, based on the patient's **serum creatinine concentration, is** included in the to-be-approved labeling.

Dr. Kim, stated the following in his primary Clinical Pharmacology Review, signed on October 16, 2009:

> *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.*

Dr. Kim stated in a subsequent Memorandum, dated October 27, 2009:

> *The agreement on language in the package insert was reached on 10/27/09.*

Dr. Kim did not request any Phase 4 commitments, although he noted that a pediatric study is required under PREA (see Section 10 of this Memorandum).

Division Director's Comment

- *There are no outstanding clinical pharmacology issues.*

6. CLINICAL MICROBIOLOGY

Because the product is an oral tablet, no formal clinical microbiology review was warranted. Dr. Holbert made the following statement in his primary CMC Review:

> *Four of the excipients require microbial testing ... These items are periodically tested upon receipt in order to qualify the vendor and the data are part of the vendor qualification process. Microbial testing is not performed on the final product since the starting materials undergo microbial controls.*

7. CLINICAL/STATISTICAL-EFFICACY

7.1 Overview of Clinical Program

The Applicant conducted 2 placebo-controlled Phase 3 clinical trials (Study XP12B-MR-301 [hereafter referred to as Study 301] and Study XP12B-MR-303 [hereafter referred to as Study 303]) to assess the efficacy and safety of tranexamic acid. The Applicant also conducted

2 additional uncontrolled Phase 3 studies (Studies 302 and 304) and a thorough QT study (XP12B-104) to provide additional safety data. All studies were conducted in the US.

7.2 Pivotal Efficacy Studies 301 and 303

7.2.1 Overview of Study Design

Study 301 and Study 303 were both randomized, double-blind, placebo-controlled, multi-center, parallel-group clinical trials. The primary objective of the studies was to determine the efficacy of tranexamic acid, taken for up to 5 days during menstruation, to reduce menstrual blood loss (MBL) compared with placebo in women with documented heavy menstrual bleeding (HMB). In these studies, HMB was defined as an average menstrual blood loss of $\geq$ 80 mL as assessed by alkaline hematin analysis of collected sanitary products over 2 baseline menstrual cycles. Both studies were similar in terms of overall design, enrollment criteria, and efficacy and safety assessments. The studies differed, however, in terms of treatment groups and duration of treatment. Study 301 consisted of 3 treatment groups: (1) 1.95 g tranexamic acid /day, (2) 3.9 g tranexamic acid/day, and (3) placebo. Subjects were treated for up to 3 menstrual cycles. Study 303 consisted of 2 treatment groups: 3.9 g tranexamic acid/day or placebo. Subjects were treated for up to 6 menstrual cycles. In both studies, study drugs were taken 3 times/day (e.g., 0.65 g administered as 2 tablets 3 times a day for a total of 3.9 g/day).

Division Director's Comments

- *One of the objectives of Study 301 was to determine the lowest effective dose of tranexamic acid to investigate further in confirmatory Study 303. Because treatment with 1.95 g tranexamic acid/day did not meet all of the Applicant's criteria for efficacy (i.e., the mean reduction in MBL from baseline did not attain 50 mL), only the daily 3.9 g tranexamic acid dose was investigated in Study 303.*
- *Although subjects could take study drug 3 times/day (TID) for up to 5 days during menses during each menstrual cycle, subjects were not required to take study drug for 5 days. The decision to take less than 5 days of study drug was to be based on the subject's perception that her menstrual blood loss was not sufficiently heavy or disruptive for her daily activities to warrant continued medical therapy.*

7.2.2 Primary Efficacy Endpoint

In these studies, the primary outcome measure was menstrual blood loss (MBL), measured using the alkaline hematin method. The primary efficacy variable was change from baseline in MBL, calculated by subtracting the mean MBL during treatment from the mean pretreatment MBL.

In order for the Applicant to claim efficacy, the primary efficacy variable had to satisfy the following 3 conditions:

- The comparison between change from baseline in MBL between tranexamic acid and placebo would be statistically significant.
- The point estimate for the reduction from baseline in MBL in the tranexamic acid group would be at least 50 mL.
- The point estimate for the reduction from baseline in MBL in the tranexamic acid group would be greater than or equal to a clinically meaningful reduction, as determined by a Receiver Operator Characteristic (ROC) analysis of efficacy data in Study 301.

7.2.3 Key Secondary Endpoints

As discussed with DRUP during various meetings regarding the clinical development program, the Applicant (1) sought to evaluate several key secondary endpoints based upon a Patient-Reported Outcome (PRO) instrument (the Menorrhagia Impact Questionnaire [MIQ]) and (2) proposed to use the same instrument to help determine the magnitude of a reduction in MBL that was clinically meaningful to women with HMB, through an anchoring technique. Based on an agreement with DRUP, the Applicant identified 3 pre-specified key secondary endpoints that would be assessed in Studies 301 and 303. Two of these endpoints were based on subject responses to specific questions in the MIQ. These key endpoints were:

- The Limitation of Social and Leisure Activities (LSLA) score (based on MIQ Question 4)
- The Limitation of Physical Activities (LPA) score (based on MIQ Question 3)
- Total number of large stains reported during a subject's menstrual period based on information recorded in her daily diary

Division Director's Comment

- *Dr. Soule carefully reviewed the processes that the Applicant followed in developing and assessing the validity of the MIQ PRO Instrument (see Section 7.4.1.2 of her CDTL Review for details). She concluded that the MIQ "is an acceptable instrument for use in measuring the key secondary endpoints of limitation in physical activity (LPA, MIQ Question 3), and limitation in social and leisure activity (LSLA, MIQ Question 4). The bleeding diary appears appropriate for assessment of large stains." I concur with Dr. Soule's assessment and conclusion.*

7.2.4 Demographics and Disposition of Subjects

Subjects were 18 to 49 years of age with a mean age of approximately 40 years, had cyclic menses every 21-35 days, and a BMI of approximately 32 kg/m^2. On average, subjects had a history of heavy menstrual bleeding for approximately 10 years and approximately 40% had fibroids as determined by transvaginal ultrasound. Approximately 70% were Caucasian, 25% were Black, and 5% were Asian, Native American, Pacific Islander, or Other.

The dispositions of subjects in Study 301 and Study 303 are shown in Table 1. In Study 301, the percentages of subjects who withdrew prematurely in the tranexamic acid groups were numerically greater than in the placebo group. In contrast, in Study 303 the percentage of subjects who withdrew prematurely in the tranexamic acid group was numerically slightly lower than in the placebo group. The percentage of subjects who withdrew primarily because of an adverse in the tranexamic acid 3.9 g/day groups was comparable (Study 301) or slightly lower (Study 303) than in the respective placebo group.

Table 1 Subject Disposition in Studies 301 and 303

	Study 301			Study 303	
	Tranexamic Acid 3.9 g/day N (%)	Tranexamic Acid 1.95 g/day N (%)	Placebo N (%)	Tranexamic Acid 3.9 g/day N (%)	Placebo N (%)
Randomized	118	117	69	123	73
Completed	103 (87.3)	106 (90.6)	63 (91.3)	94 (76.4)	54 (74.0)
Withdrew	15 (12.7)	11 (9.4)	6 (8.7)	29 (23.6)	19 (26.0)
Withdrawal Reason					
Failed to return	6 (5.1)	5 (4.3)	1 (1.4)	10 (8.1)	6 (8.2)
Other	3 (2.5)	2 (1.7)	2 (2.9)	8 (6.5)	1 (1.4)
Protocol violation	3 (2.5)	1 (0.9)	1 (1.4)	2 (1.6)	5 (6.8)
Subject request	2 (1.7)	0	1 (1.4)	6 (4.9)	2 (2.7)
Adverse Event	1 (0.8)	3 (2.6)	1 (1.4)	3 (2.4)	3 (4.1)

Source: Modified from Tables 4 and 5 of the CDTL Review, signed November 6, 2009.

7.2.5 Primary Efficacy Findings

Study 301. The mean reduction from baseline in MBL in Study 301 was 65.3 mL in the 3.9 g/day tranexamic acid group, 44.1 mL in the 1.95 g/day tranexamic acid group, and 7.1 mL in the placebo group (see Table 2). Both tranexamic acid doses were statistically significantly better than placebo in reducing MBL.

Division Director's Comment

- *Only the reduction in the 3.9 g/day treatment group met the criterion of a change of at least 50 mL from baseline. Therefore, the 3.9 g/day dose of tranexamic acid was considered the lowest effective dose by the Applicant and was the dose that was investigated further in Studies 302, 303, and 304.*
- *The dose of 3.9 g tranexamic acid/day is the only dose for which the Applicant seeks marketing approval.*

Table 2 Mean Reduction from Baseline in Menstrual Blood Loss (mL) (Study 301 - LOCF Analysis [A])

Treatment	N	Baseline Mean (SD) MBL (mL)[B]	Least Squares Mean Reduction in MBL (mL)	P-value
Tranexamic Acid (3.9 g/day)	112	168.99 (82.992)	65.32	<0.0001
Tranexamic Acid (1.95 g/day)	115	178.03 (112.159)	44.07	<0.0001
Placebo	67	153.58 (67.881)	7.06	

A: LOCF = last observation carried forward.
B: MBL = menstrual blood loss.
Source: Table 3.2.3 of the primary Statistical Review, signed June 15, 2009.

Study 303. The mean reduction from baseline in MBL in Study 303 was 66.3 mL in the 3.9 g/day tranexamic acid group and 17.8 mL in the placebo group (See Table 3). The difference between tranexamic acid and placebo was statistically significant. Again, the reduction from baseline in MBL met the criterion of a change of at least 50 mL.

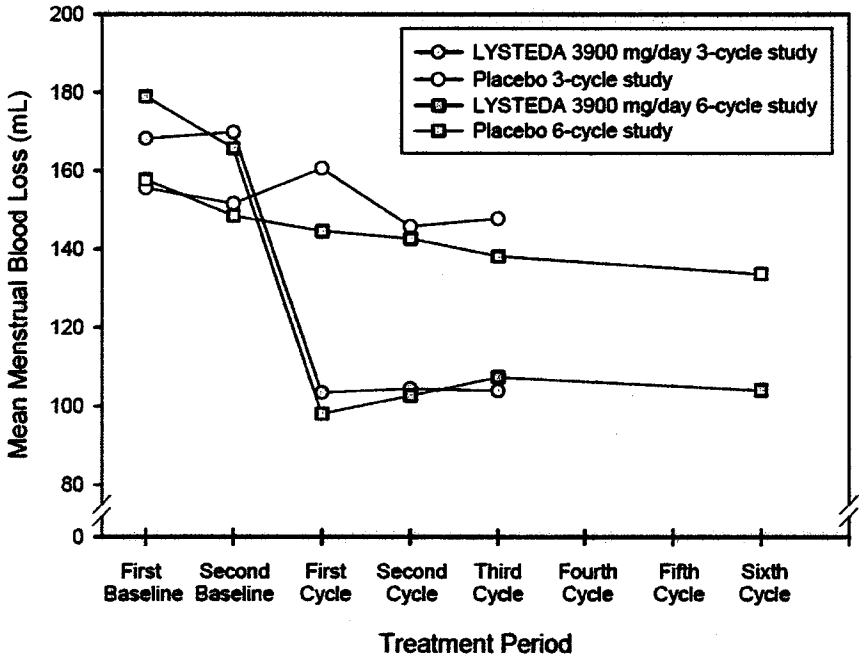
Table 3 Mean Reduction from Baseline in Menstrual Blood Loss (mL) (Study 303 - LOCF Analysis [A])

Treatment	N	Baseline Mean (SD) MBL (mL)[B]	Least Squares Mean Reduction in MBL (mL)	P-value
Tranexamic Acid (3.9 g/day)	115	172.29 (95.552)	66.30	<0.0001
Placebo	72	152.98 (66.583)	17.82	

A: LOCF = last observation carried forward.
B: MBL = menstrual blood loss.
Source: Table 3.3.3 of the primary Statistical Review, signed June 15, 2009.

Mean values for MBL during the baseline period and during each treatment cycle are shown in Figure 1. There was no evidence of a decrease in efficacy over the 3-cycle (Study 301) and 6-cycle (Study 303) treatment periods.

Figure 1 Mean Values for Menstrual Blood Loss during the Baseline and Treatment Periods for Study 301 (3-Cycle Study) and Study 303 (6-Cycle Study)



Source: Figure 1 from to-be-approved labeling for Lysteda, November 2009.

7.2.6 Principal Secondary Efficacy Findings

The pre-specified secondary endpoints of Limitation of Social and Leisure Activities (LSLA), Limitation of Physical Activities (LPA), and large stains were analyzed in both Studies 301 and 303 for the 3.9 g/day tranexamic acid and placebo treatment groups.

Response options for LSLA (MIQ Question 4: **"During your most recent menstrual period, how** much did your bleeding limit your social and leisure **activities?") and LPA (MIQ Question 3: "During your most recent menstrual period, how** much did your bleeding limit your physical **activities?") were:**

1. Not at all
2. Slightly
3. Moderately
4. Quite a bit
5. Extremely

For large stains, a responder analysis was performed, with a responder defined as a subject with a decrease in the number of large stains reported in her daily diary.

Results of the analyses for these key secondary endpoints are listed in Table 4 for Study 301 and Table 5 for Study 303. The endpoints of LSLA and LPA were each statistically significantly improved in the 3.9 g/day tranexamic acid treatment groups compared to the respective placebo treatment group in both clinical trials. No statistically significant treatment difference was observed in response rates for a reduction in the frequency of large stains in either clinical trial.

Table 4 Key Secondary Endpoints (Study 301)

Treatment Arm	N	Baseline Mean (SD)	Least Squares Mean Change [A]	p-value
LSLA (MIQ Question 4)[B]				
3.9 g/day tranexamic acid	112	3.0 (1.08)	0.98	< 0.0001
Placebo	66	2.9 (0.97)	0.39	
LPA (MIQ Question 3)[C]				
3.9 g/day tranexamic acid	112	3.1 (1.04)	0.94	< 0.0001
Placebo	66	3.0 (0.87)	0.34	
Large Stains				
		% Responders [D]		
3.9 g/day tranexamic acid	111	64%		0.16
Placebo	67	52%		

A: Positive means reflect an improvement from baseline.
B: LSLA = Limitation of Social and Leisure Activities.
C: LPA = Limitation of Physical Activities.
D: Responders are defined as subjects who experienced a reduction from baseline in frequency of large stains.
Source: Table 11 of the CDTL Review, signed November 6, 2009.

Table 5 Key Secondary Endpoints (Study 303)

Treatment Arm	N	Baseline Mean (SD)	Least Squares Mean Change [A]	p-value
		LSLA (MIQ Question 4)[B]		
3.9 g/day tranexamic acid	115	2.9 (1.02)	0.85	< 0.0001
Placebo	72	2.7 (0.98)	0.44	
		LPA (MIQ Question 3)[C]		
3.9 g/day tranexamic acid	115	3.1 (0.95)	0.87	< 0.0001
Placebo	72	2.9 (0.95)	0.40	
		Large Stains		
		% Responders [D]		
3.9 g/day tranexamic acid	115	57%		0.45
Placebo	72	51%		

A: Positive means reflect an improvement from baseline.
B: LSLA = Limitation of Social and Leisure Activities.
C: LPA = Limitation of Physical Activities.
D: Responders are defined as subjects who experienced a reduction from baseline in frequency of large stains.
Source: Table 12 of the CDTL Review, signed November 6, 2009.

Division Director's Comment

- *In his statistical review, Dr. Fang (the FDA Statistical Reviewer) raised a concern about validity and reliability of the MIQ. Dr. Fang, however, was not asked to review the validation substudy for the MIQ in Study 302, and it is likely that he was not aware of the process and methodology employed by the Applicant to develop and validate the instrument. His recommendation was that "inclusion of such secondary endpoints in the label should be exercised with caution." The Applicant proposed* [redacted] *in* [redacted] *but this was denied. The outcomes for these key secondary endpoints, however, will be included in the Clinical Studies section of product labeling. Both the primary Medical Reviewer and the Clinical Team Leader recommended inclusion of these secondary endpoint outcomes in labeling, and I support this recommendation.* b(4)

7.3 FDA Statistical Assessment of Efficacy Finding from Studies 301 and 303

The primary Statistical Reviewer, Xin Fang, PhD, **confirmed the Applicant's primary and key** secondary efficacy analyses. Dr. Fang made the following statements in his statistical review (signed on June 15, 2009):

> *We have reviewed the two Phase 3 clinical studies in supporting tranexamic acid for the treatment of HMB. There were no statistical issues with regards to the method of analysis.*
>
> *The results support the efficacy of 3.9 g/day tranexamic acid in reducing the MBL. The 3.9 g/day dose was considered both clinically and statistically effective. The improvements in two secondary endpoints, namely, LSLA and LPA were also statistically significantly superior to placebo.*
>
> *From a statistical perspective, the efficacy data provided in this application do support the efficacy of 3.9 g/day tranexamic acid in the treatment of HMB and associated LSLA and LPA.*

7.4 Overall Assessment of Efficacy

The efficacy of tranexamic acid tablets (3.9 g/day for a maximum of 5 consecutive days) in the treatment of cyclic heavy menstrual bleeding was demonstrated in 2 randomized, double-blind, placebo-controlled studies. In both studies, treatment with tranexamic acid, compared to placebo, resulted in a statistically significantly greater reduction in mean menstrual blood loss (MBL). In Study 301, the least square mean decreases from baseline in MBL were 65.3 mL and 7.1 mL in the tranexamic acid and placebo groups, respectively ($p < 0.0001$). In Study 303, the least square mean decreases from baseline in MBL were 66.3 mL and 17.8 mL in the tranexamic acid and placebo groups, respectively ($p < 0.0001$).

In both Phase 3 studies, treatment with 3.9 g/day tranexamic acid, compared to placebo, also statistically significantly reduced mean scores for limitations on social and leisure activities (LSLA) and limitations on physical activities (LPA) as assessed by the Menorrhagia Impact Questionnaire. No statistically significant treatment difference was observed in response rates for the number of large stains in the tranexamic acid treatment groups compared to the respective placebo treatment groups.

8. SAFETY FINDINGS

8.1 Overview of Safety Studies and Safety Data

Data to support the safety of tranexamic acid was provided primarily from the Applicant's four Phase 3 clinical trials and a thorough QT study (XP12B-104). The design of Studies 301 and 303 (also the source of data supporting the effectiveness of tranexamic acid) was provided previously in Section 7.1. In Study 301, the safety population consisted of 115 subjects in each of the 1.95 g/day and 3.9 g/day tranexamic acid groups and 67 subjects in the placebo group. In Study 303, the safety population consisted of 117 and 72 subjects in the 3.9 g/day tranexamic acid and placebo treatment groups, respectively. Over both placebo-controlled studies, a total of 232 subjects were exposed to 3.9 g tranexamic acid/day and used tranexamic acid for an average of 3.4 days per menstrual cycle.

Study 302 was an open-label, single-arm clinical trial in which subjects with heavy menstrual bleeding were treated with cyclic tranexamic acid (3.9 g/day for a maximum of 5 days during menses) for up to 27 menstrual cycles. In this study, a total of 723 subjects took at least one dose of tranexamic acid. Study 304 was an open-label, single-arm roll-over clinical trial in which subjects who had completed their participation in Studies 301 or 303 (regardless of prior treatment assignment) were treated with cyclic tranexamic acid (3.9 g/day) for up to 9 additional menstrual cycles. In Study 304, 260 subjects took at least one dose of tranexamic acid. Although the two long-term safety studies (Studies 302 and 304) were ongoing at the time of the NDA submission, the Applicant provided two safety updates, in April and September 2009, which provided safety data through completion of these latter 2 studies.

According to the CDTL review, Studies 302 and 304 combined provided safety data from 12,169 treatment cycles (10,213 in Study 302 and 1,956 in Study 304) with 3.9 g tranexamic acid/day. This is equivalent to approximately 936 women-years of exposure. Across all 4 studies, which included over 1,200 subjects exposed to the 3.9 g/day dose, over 1,000 subjects had at least 3 cycles of exposure, over 800 subjects had at least 6 cycles of exposure,

387 subjects had at least 12 cycles of exposure, and 227 subjects had at least 24 cycles of exposure.

Division Director's Comments

- *The subject exposure data provided by the Applicant exceeded that which was requested by DRUP (i.e., 10,000 treatment cycles and at least 200 women completing one year of treatment).*
- *Based on the lack of concerning safety findings in this Application, the exposure data are adequate to support approval of tranexamic acid for the proposed indication.*
- *Both the primary Clinical Reviewer and the CDTL have provided in their respective reviews very thorough and detailed assessments of the safety data provided in this Application. Because I concur with their respective assessments and conclusions, this Memorandum focuses primarily on those areas and issues that are of particular importance to the overall safety assessment of tranexamic acid for the proposed indication of treatment of cyclic heavy menstrual bleeding.*

8.2 Deaths and Other Serious Adverse Events

8.2.1 Deaths

The Applicant reported a total of 3 deaths in the tranexamic acid development program. Two deaths occurred during the screening period (one each in Studies 301 and 302) prior to the women receiving study medication. The single on-treatment death was that of Subject 525-2005 in Study 302. This subject was a 34-year old woman who completed 3 cycles of treatment with 3.9 g/day tranexamic acid. Approximately 6 weeks following her last dose she was admitted to a hospital in respiratory distress and diagnosed with bilateral pneumonia (community acquired) and sepsis. During her hospital course, she experienced a cardiac arrest followed by multisystem organ failure and death approximately 6 weeks after admission. Neither the primary Clinical Reviewer nor the Clinical Team Leader thought that her death was related to treatment with tranexamic acid; I concur with their assessment.

8.2.2 Other Serious Adverse Events

Placebo-Controlled Studies. Subjects experiencing one or more serious adverse events (SAEs) in Studies 301 and 303 are listed in Table 6. In Study 301, one subject (0.9% of subjects) on 3.9 g/day tranexamic acid experienced 3 SAEs, and one subject (0.9% of subjects) on 1.95 g/day tranexamic acid experienced a single SAE. No placebo subjects experienced an SAE. In Study 303, 3 subjects (2.6% of subjects) on 3.9 g/day tranexamic acid experienced a SAE, and 3 subjects (4.2% of subjects) on placebo experienced 4 SAEs.

Table 6 Serious Adverse Events in Placebo-Controlled Studies (Studies 301 and 303)

Subject #	Serious Adverse Event	Study Drug	Severity	Reviewer Assessment of Association [A]
		Study 301		
752-1002	Dyspepsia	3.9 g/day	Hospitalization	Unlikely
	Gastritis	3.9 g/day	Hospitalization	Unlikely
	Chest pain	3.9 g/day	Severe	Unlikely
721-1008	Ovarian torsion	1.95 g/day	Hospitalization	Unlikely
		Study 303		
619-3002	Tachycardia (SVT)	3.9 g/day	Hospitalization	Unlikely
633-3003	Blood sugar decreased	3.9 g/day	Life-threatening	Unlikely
653-3010	Menorrhagia	3.9 g/day	Hospitalization	Probable – lack of efficacy
616-3009	Acute bronchitis	Placebo	Hospitalization	Unlikely
	Post Traumatic Stress Disorder	Placebo	Hospitalization	Unlikely
626-3010	Deep Venous Thrombosis	Placebo	Moderate	Unlikely
654-3003	Urticaria	Placebo	(omitted)	Unlikely

A: Assessment represents that of both the primary Clinical Reviewer and the Clinical Team Leader.

Open-Label Studies. There were 46 SAEs in 32 subjects (4.4% of subjects) in Study 302, and 7 SAEs in 5 subjects (1.9% of subjects) in Study 304. Assessment of the likely association or lack of association between each reported SAE and treatment with tranexamic acid was made by both the primary Clinical Reviewer and the Clinical Team Leader. There was complete agreement between both reviewers on assessments of SAEs. Based on their joint assessments, a total of 6 of the SAEs (involving 5 subjects) across Studies 302 and 304 were considered as possibly related to treatment and one SAE (a case of menorrhagia) was considered as probably related to treatment. The SAEs assessed as possibly related to treatment and the number of reports for each was: menorrhagia (n = 4), anemia (n = 1, in a woman with menorrhagia), and seizure (n = 1).

Division Director's Comments

- *Across the four Phase 3 studies, the most commonly reported SAEs included menorrhagia (7), migraine (4), and enlarging fibroids (3). Menorrhagia and fibroids would be expected in a population with heavy menstrual bleeding, particularly where fibroids were not an exclusion criterion. Migraine is relatively common in the population of reproductive-aged women, and is included in labeling, as it was also a common AE noted slightly more often in tranexamic acid treated women than in placebo-treated subjects (see Section 8.4).*
- *The overall number of SAEs and the nature of the SAEs do not raise any significant safety concerns.*

8.3 Discontinuations Due to Adverse Events

Placebo-Controlled Studies. The rates of discontinuation due to adverse events during the 2 clinical trials were comparable between the tranexamic acid and placebo groups. In Study 301 (3-cycle study), the rate of discontinuation in the 3.9 g/day tranexamic acid group was 0.8% as compared to 1.4% in the placebo group. In Study 303 (6-cycle study), the rate of discontinuation in the tranexamic acid group was 2.4% as compared to 4.1% in the placebo group.

Open-Label Studies. In Study 302 (subjects treated for up to 27 cycles), 97 of 781 randomized subjects (12.4%) withdrew primarily because of an adverse event. In Study 304 (subjects treated for up to 9 cycles), 6 of 288 randomized subjects (2.1%) withdrew primarily because of an adverse event.

Division Director's Comment

- *The low percentage of subjects who withdrew primarily because of adverse events in Study 302 may reflect an underreporting of the true number of withdrawals. For Study 302, "failed to return" was listed as the primary reason for withdrawal for 20% of subjects. It is possible that some of these subjects may have actually withdrawn because of an unreported adverse event.*

8.4 Most Common Adverse Events

A list of adverse events occurring in ≥ 5% of subjects and more frequently in tranexamic acid treated subjects receiving 3.9 g/day compared to placebo is provided in Table 7.

Table 7 Adverse Events Reported by ≥ 5% of Subjects Treated with Tranexamic Acid and More Frequently in Tranexamic Acid Treated Subjects (Studies 301 and 303)

	Tranexamic Acid 3.9 g/day (N=232) n (%)	Placebo (N=139) n (%)
Total Number of Adverse Events	1500	923
Number of Subjects with at Least One Adverse Event	208 (89.7%)	122 (87.8%)
Headache[a]	117 (50.4%)	65 (46.8%)
Nasal and Sinus Symptoms[b]	59 (25.4%)	24 (17.3%)
Back Pain	48 (20.7%)	21 (15.1%)
Abdominal Pain[c]	46 (19.8%)	25 (18.0%)
Musculoskeletal Pain[d]	26 (11.2%)	4 (2.9%)
Arthralgia[e]	16 (6.9%)	7 (5.0%)
Muscle Cramps & Spasms	15 (6.5%)	8 (5.8%)
Migraine	14 (6.0%)	8 (5.8%)
Anemia	13 (5.6%)	5 (3.6%)
Fatigue	12 (5.2%)	6 (4.3%)

[a] Includes headache and tension headache
[b] Nasal and sinus symptoms include nasal, respiratory tract and sinus congestion, sinusitis, acute sinusitis, sinus headache, allergic sinusitis and sinus pain, and multiple allergies and seasonal allergies
[c] Abdominal pain includes abdominal tenderness and discomfort
[d] Musculoskeletal pain includes musculoskeletal discomfort and myalgia
[e] Arthralgia includes joint stiffness and swelling
Source: Table 2 from to-be-approved labeling for Lysteda, November 2009,

Division Director's Comments

- *The largest absolute differences in the incidence of specific adverse events between the 2 treatment groups were for the adverse events of nasal and sinus symptoms, back pain, and musculoskeletal pain.*
- *The types of adverse events that were more common in the tranexamic acid treatment group and their frequency do not raise any significant safety concerns.*

8.5 Adverse events of Special Interest

8.5.1 Thromboembolic Events and Thromboembolic Risk

No pulmonary emboli or deep vein thromboses (DVTs) were reported for any subject in Studies 301, 302, or 304. One subject treated with placebo in Study 303 experienced a DVT. Subject 774-1004 (in rollover Study 304) was evaluated for a possible cerebrovascular accident after having taken at least 6 cycles of 3.9 g/day tranexamic acid in Study 304. She presented 6 days after her last dose of tranexamic acid with left-sided weakness, numbness, and tingling, and was found on a cerebral angiogram to have a fusiform basilar artery aneurysm with 3 daughter aneurysms. She also was diagnosed as having a right pontine infarct secondary to the fusiform aneurysm. A transcranial Doppler study showed no emboli in the right posterior circulation.

Division Director's Comment

- *According to the CDTL review "hemodynamic factors related to lumenal geometry, as well as factors related to hypercoagulability, may affect the risk of spontaneous thrombosis in a fusiform basilar aneurysm, in particular, where the hemodynamics and geometry of the aneurysm result in relatively stagnant flow and/or low shear in one or more areas of the aneurysm. Therefore, I believe that there are features of this case that make it questionable whether treatment with Lysteda had any relationship to the event." I agree with this assessment by Dr. Soule.*

The Division of Pharmacovigilance II (DPV II) was asked to review **the FDA's AERS database** with respect to VTE reports in association with the use of tranexamic acid (e.g., Cyklokapron). According to the CDTL review, DPV II found 40 cases of possible VTEs associated with tranexamic acid formulations reported over the interval from 1993 to 1998 in the AERS database. Of these, 60% were associated with the oral formulation, and none was a US report. One case involved a fatal pulmonary embolism associated with use of oral tranexamic acid for menorrhagia, and 18 cases involved hospitalizations. Three cases of retinal venous or arterial thrombosis were reported.

Division Director's Comment

- *In to-be-approved labeling, tranexamic acid (Lysteda) is contraindicated in women with active thromboembolic disease, a history of thrombosis or thromboembolism, or an intrinsic risk of thrombosis or thromboembolism. The Warnings and Precautions section discusses potential increased risk of VTEs if Lysteda is used concomitantly with combined hormonal contraceptives, which have a known association with VTE (see discussion below). Retinal vascular thrombosis is also addressed in the Warnings and Precautions sections.*

Combination hormonal contraceptives are known to increase the risk of venous thromboembolism, as well as arterial thromboses such as stroke and myocardial infarction. Because tranexamic acid is antifibrinolytic, concomitant use of hormonal contraception and tranexamic acid may further exacerbate this increased thrombotic risk. Women using hormonal contraception were excluded from the clinical trials supporting the safety and efficacy of tranexamic acid.

Division Director's Comment

- *The clinical reviewers discussed whether the use of hormonal contraception should be a contraindication for women who would use tranexamic acid for heavy menstrual bleeding or if the concomitant use of tranexamic acid and hormonal contraceptives could be addressed in a strong statement in the Warnings and Precautions section of labeling. It was decided that this issue would be addressed in a strong labeling statement, which includes the following:*

  "...Women using hormonal contraception were excluded from the clinical trials supporting the safety and efficacy of LYSTEDA, and there are no clinical trial data on the risk of thrombotic events with the concomitant use of LYSTEDA with hormonal contraceptives. Therefore, women using hormonal contraception should use LYSTEDA only if there is a strong medical need and the benefit of treatment will outweigh the potential increased risk of a thrombotic event."

- *While combined oral contraceptives tend to decrease heavy menstrual bleeding, there may be a subset of women who use hormonal contraception but still have bleeding that is bothersome enough that they desire an additional treatment modality, such as tranexamic acid. To obtain information on the extent to which hormonal contraceptives and tranexamic acid will be used concomitantly, the Applicant was asked to conduct a postmarketing study to address this question. The study to be conducted will be a pharmacoepidemiologic study that will be based on drug use information (e.g., available in a claims database). The primary objective will be to assess the patterns of concomitant use of Lysteda and hormonal contraception, including assessment of the ages of women using both products as compared to women using Lysteda alone. Information obtained from this study (which is to be conducted in accordance with a postmarketing commitment), will provide information as to whether the population of women using both products concomitantly is large enough to study, if further study is warranted.*

8.5.2 Ocular Events

Because of potential signals of ocular toxicity in nonclinical studies, additional testing to assess ocular safety was performed in the clinical development program. The Applicant conducted ophthalmologic examinations as recommended by **DRUP's ophthalmology** consultant, Dr. Wiley Chambers, Director (acting) of the Division of Anti-infective and Ophthalmologic Products. The findings from the ophthalmologic examinations, as well as the reports of ocular adverse events, were reviewed by Dr. Chambers as well as by the primary Clinical Reviewer and the Clinical Team Leader (Dr. Soule) in DRUP.

Dr. Soule's review of the ocular findings was extremely thorough, and she made the following concluding statement in her CDTL review:

Overall, I do not find a signal for adverse impact of Lysteda on vision or ocular safety based on the results of the ophthalmologic testing. While the number of subjects tested at the end of each study was significantly less than the number initially enrolled, there is no indication that subjects were discontinuing on the basis of ophthalmologic AEs, which would introduce a serious bias.

Division Director's Comments

- *The clinical reviewers from DRUP, Dr. Chambers, and DPV II staff met to discuss the Applicant's submission of September 11, 2009. Following review, Dr. Chambers agreed with the Applicant that the ocular AEs of greatest concern would not be detected with baseline and interval visual examinations, and therefore no longer recommended baseline or routine on-treatment examinations. He also concurred with the modification of the Contraindication Section, and with the Applicant's proposed Warnings and Precautions language with slight modifications. This warning now reads:*

  "Retinal venous and arterial occlusion has been reported in patients using tranexamic acid. Patients should be instructed to report visual and ocular symptoms promptly. In the event of such symptoms, patients should be instructed to discontinue LYSTEDA immediately and should be referred to an ophthalmologist for a complete ophthalmic evaluation, including dilated retinal examination, to exclude the possibility of venous or arterial retinal occlusion. Ligneous conjunctivitis also has been reported in patients taking tranexamic acid. The conjunctivitis resolved following cessation of the drug."

- *I agree that the ocular safety findings in this Application do not raise any concerns that would impact on the approvability of tranexamic acid. To-be-approved labeling adequately addresses the risks associated with the use of tranexamic acid and provides appropriate guidance to both healthcare providers and patients should adverse ocular signs or symptoms occur during treatment.*

8.5.3 Serious Allergic Reactions

Late in the review of this Application, a single case of what appeared to be a potentially serious systemic allergic reaction, possibly anaphylaxis, was identified in a tranexamic acid treated subject. Information provided in the application stated that a subject in Study 304 had experienced dyspnea, throat tightening, and facial flushing on a day that she was taking tranexamic acid. The subject was seen in the emergency room where she was treated with intravenous diphenhydramine and methylprednisolone. The subject discontinued treatment with tranexamic acid and was terminated from the clinical trial.

Division Director's Comment

- *The Applicant was able to obtain additional information regarding this subject, including emergency room records. Based on review of these records, it is unclear if this case truly represented an anaphylactic or serious allergic reaction to tranexamic acid..*

The Applicant also was asked to search the entire clinical trial databases for any other possible cases of anaphylaxis or severe allergic reactions. Based on the Clinical Team Leader's review of additional information supplied by the Applicant, including data from the WHO safety database, Dr. Soule stated the following in her review:

Overall, I consider that the database includes three likely cases of allergic reactions ... and two possible cases ... I concur with the Applicant that there were no cases of anaphylaxis.

Although the number of events in the WHO database is extremely small, it is notable that almost 10% relate to allergic reactions. Based on this, and the signal in the clinical trials, I believe that discussion of allergy and hypersensitivity should be included in labeling,

including Contraindications, Warnings, Adverse Reactions (Clinical Trials and Postmarketing subsections) and Patient Labeling.

Division Director's Comment

- *I believe that the labeling changes recommended by Dr. Soule (which are included in the to-be-approved labeling) are appropriate and adequate (based on currently available information) to manage the risk of a potential severe allergic reaction.*

8.6 Thorough QT Study

The effect of tranexamic acid on the QT interval was evaluated in a randomized, single-dose, 4-way crossover study in 48 healthy females aged 18 to 49 years (Study XP12B-104). There was no significant increase in the corrected QT interval at any time up to 24 hours after the administration of tranexamic acid.

8.7 Overall Assessment of Safety

Safety data for tranexamic acid tablets (3.9 g/day) were obtained from four Phase 3 clinical trials. These trials provided safety data from over 12,000 treatment cycles, including safety data from more than 200 women who used the drug for at least 2 years. The exposure data were consistent with that requested by DRUP. Based on the lack of concerning safety findings in this Application, the exposure data are adequate to support approval of tranexamic acid for the proposed indication.

There was one on-treatment death in the clinical development program. Based on review of the information provided about this subject's hospital course and diagnostic work-up, neither Dr. Davis nor Dr. Soule believed that this death was related to treatment with tranexamic acid. I concur with their assessment.

No pulmonary emboli or deep venous thromboses were reported for any subject treated with tranexamic acid. One subject, however, with a basilar artery aneurysm experienced a pontine infarct. No signals for an adverse effect of tranexamic acid on vision or ocular safety were identified based on review of reported adverse event data and ophthalmologic testing results. While the number of subjects undergoing ocular testing at the end of each of the Phase 3 studies was significantly less than the number tested at enrollment, there was no indication that subjects were discontinuing because of ophthalmologic adverse events, which would have introduced bias in assessing ocular safety. A single case of a potentially severe systemic allergic reaction, involving dyspnea, throat tightening, and facial flushing was reported in the clinical trials. Two additional cases of allergic reaction, involving primarily rash and/or hives were reported. Product labeling adequately addresses the potential for thrombotic, ocular, and allergic risks that may be associated with the use of tranexamic acid and provides appropriate guidance to both healthcare providers and patients.

Common adverse events were reviewed based on both the placebo-controlled and open-label studies. The placebo-controlled data helped with the interpretation of whether the events were likely related to treatment with tranexamic acid, per se, while the open-label studies provided information on extended exposure to tranexamic acid. Adverse events occurring in > 5% of subjects treated with tranexamic acid in the controlled trials and more frequently than in placebo subjects involved headaches, including migraines; sinus/nasal/allergic conditions; abdominal pain; muscle and joint complaints; anemia; and fatigue.

An appropriately conducted thorough QT study was submitted and reviewed. There was no signal of QT prolongation with tranexamic acid treatment at therapeutic and supra-therapeutic doses.

In summary, the overall safety profile for tranexamic acid tablets, based on the data in the Application, was reassuring and acceptable for the proposed indication. Postmarketing non-US safety data for tranexamic acid tablets used for the treatment of heavy menstrual bleeding are also supportive.

9. ADVISORY COMMITTEE MEETING

An Advisory Committee meeting was not held for this Application because (1) tranexamic acid is not a new molecular entity and (2) no safety or efficacy issues were identified that warranted Advisory Committee discussion or guidance.

10. PEDIATRICS

The Applicant requested a partial waiver (for premenarcheal girls) and a deferral (for postmenarcheal girls) of pediatric studies. DRUP recommended a partial waiver from age 0-12 years on the grounds that necessary studies would be impossible or highly impractical because (1) the condition does not exist in premenarcheal girls and (2) too few postmenarcheal girls under the age of 12 with heavy menstrual bleeding exist to allow for a study in this subpopulation. DRUP also recommended that the pediatric studies be conducted postapproval, once this product had been determined to be safe and effective for women 18 years and older for the proposed indication.

The Applicant provided a synopsis for a proposed pediatric PK study to be conducted as a Phase 4 requirement. The single dose PK study would enroll 18 adolescent females, aged 12 to 17 years. Eligibility requirements would include **"evidence of heavy menstrual bleeding." The** Pediatric Review Committee (PeRC) reviewed the request and the synopsis of the proposed pediatric protocol on May 27, 2009. They agreed with the Division and granted a partial waiver and deferral of pediatric studies for this product.

The Applicant provided agreement on September 15, 2009, to conduct the adolescent PK study and agreed to the following milestones:

Protocol Submission Date:	February 2010
Study Start Date:	September 2010
Final Report Submission Date:	March 2012

11. OTHER RELEVANT REGULATORY ISSUES

11.1 Financial Disclosure

According to the primary Clinical Review, only one investigator, [redacted], reported disclosable information ($75,000 in payments from the Applicant for consulting services). [redacted] enrolled [redacted] in Study [redacted] of who continued into Study [redacted] DRUP requested an inspection of [redacted] site by the Division of Scientific Investigation (DSI), along with inspection of 2 other sites (see Section 11.2). b(6) b(6)

Division Director's Comment

- *Based in part on the DSI inspection of her site that raised no concerns, data from this site were included in the primary and secondary efficacy analyses.*

11.2 DSI Audits

Inspections of 3 clinical sites, including that of Dr. Lukes, were conducted by DSI. Inspection of **Dr. Lukes' site revealed no deviations** from regulations, and she received a final classification of no action indicated (NAI). **Inspection of Dr. Baker's** site disclosed some minor irregularities. The DSI summary report for this site, however, **stated that "the deviations noted...would not** appear to have a significant impact on data integrity and the data appear acceptable in support of the respective application." **Inspection of Dr. Mabey's site disclosed that 3 subjects in Study 302** each took 4 doses of tranexamic acid per day on various occasions, a violation of the protocol-specified maximum of 3 doses per day. The DSI report stated that the review division might consider excluding data from these 4 subjects. No other regulatory deviations were noted at this site.

Division Director's Comment

- *Because Study 302 was primarily a safety study (data from Study 302 were not considered in the primary assessment of efficacy for tranexamic acid), it was decided that data from these 4 subjects would not be excluded. Safety data from subjects who take extra doses of study drug are useful, as overdosing may occur in actual post approval use.*

12. LABELING

The Applicant proposed the trade name Lysteda. The Division of Medication Error Prevention and Analysis (DMEPA) found this trade name acceptable in its review dated September 22, 2009.

Carton and container labeling was reviewed and revised by the Applicant in accordance with recommendations made by DMEPA and by the CMC reviewer. The final carton and container labeling submitted by the Applicant on September 15, 2009, was acceptable to DMEPA and CMC reviewers.

Consults on the proposed Package Insert (PI) were obtained from the Division of Risk Management (DRISK) and the Division of Drug Marketing, Advertising and Communication (DDMAC). Their comments were incorporated into the PI as appropriate. Additional revisions to the PI were made based on suggestions from the Division of Pharmacovigilance II and Dr. Wiley Chambers (Division of Anti-infective and Ophthalmologic Products).

The revised labeling adequately addresses the potential safety issues and risks, which both healthcare providers and patients should be aware of, in making an informed decision regarding whether to use the product. Labeling also adequately warns healthcare providers and patients regarding signs and/or symptoms that would warrant discontinuation of therapy with tranexamic acid tablets and the appropriate follow-up actions that should be taken.

Labeling received by DRUP on November 6, 2009 was considered to be acceptable by all disciplines. Minor editorial changes/corrections in the clinical sections of this version were subsequently made on November 10, 2009, and final agreed-upon labeling was submitted by the Applicant on November 13, 2009.

13. DECISION/ACTION/BENEFIT RISK ASSESSMENT

13.1 Regulatory Action

Lysteda (tranexamic acid) tablets will **be approved for the indication of "*treatment of cyclic heavy menstrual bleeding.*" The Applicant has submitted sufficient information to conclude that** Lysteda (tranexamic acid) tablets, when used in accordance with to-be-approved labeling, will be safe and effective for the treatment of cyclic heavy menstrual bleeding. The recommended dosing regimen for Lysteda for women with normal renal function is two 650 mg tablets taken 3 times daily (3.9 g/day) for a maximum of 5 days during monthly menstruation.

13.2 Benefit/Risk Assessment

The efficacy of tranexamic acid tablets (3.9 g/day) for the treatment of cyclic heavy menstrual bleeding was demonstrated in 2 randomized, double-blind, placebo-controlled studies. In both studies, treatment with tranexamic acid, compared to placebo, resulted in a statistically significantly greater reduction in mean menstrual blood loss (MBL). In Study 301, the mean decreases from baseline in MBL were 65.3 mL and 7.1 mL in the tranexamic acid and placebo groups, respectively ($p < 0.0001$). In Study 303, the mean decreases from baseline in MBL were 66.3 mL and 17.8 mL in the tranexamic acid and placebo groups, respectively ($p < 0.0001$). In both Phase 3 studies, treatment with 3.9 g/day tranexamic acid, compared to placebo, also statistically significantly reduced mean scores for limitations on social and leisure activities (LSLA) and limitations on physical activities (LPA) as assessed by the Menorrhagia Impact Questionnaire.

The overall safety profile for tranexamic acid tablets, based on the data in the Application, was reassuring and acceptable. No pulmonary emboli or deep venous thromboses were reported for any subject treated with tranexamic acid. One subject, however, with a basilar artery aneurysm experienced a pontine infarct. No signals for an adverse effect of tranexamic acid on vision or ocular safety were identified based on review of reported adverse event data and ophthalmologic testing results. A single case of a potentially severe systemic allergic reaction was reported in the clinical trials. Product labeling adequately addresses the potential for thrombotic, ocular, and allergic risks that may be associated with the use of tranexamic acid and provides appropriate guidance to both healthcare providers and patients. Postmarketing non-US safety data for tranexamic acid tablets used for the treatment of heavy menstrual bleeding are also supportive.

In summary, the overall benefit/risk profile for tranexamic acid tablets (3.9 g/day for up to 5 days during monthly menses) is favorable for the treatment of cyclic heavy menstrual bleeding. Tranexamic acid tablets will offer women a non-hormonal medical option for reducing heavy menstrual bleeding.

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies (REMS)

The Applicant proposes to conduct routine pharmacovigilance activities and to implement appropriate risk mitigation strategies should they be warranted during the postmarketing period. Based on the safety profile for tranexamic acid in this Application and the postmarketing experience with tranexamic acid outside of the US for treatment of heavy menstrual bleeding, a REMS is not warranted at this time.

13.4 Recommendation for Other Postmarketing Requirements and Commitments

The Applicant will conduct in accordance with the Pediatric Research Equity Act (PREA) a pediatric study for the assessment of the pharmacokinetics of tranexamic acid in healthy pediatric patients, ages 12 to 17 years, with heavy menstrual bleeding (see Section 10).

The Applicant also will conduct, under a postmarketing commitment, a pharmacoepidemiologic study based on drug use information to assess the patterns of concomitant use of tranexamic acid (Lysteda) and hormonal contraception. This study will include assessment of the ages of women using both products as compared to women using Lysteda alone. Information obtained from this study will provide data as to whether the population of women using both products concomitantly is large enough to study, if further study is warranted (see Section 8.5.1).

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

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/s/

SCOTT E MONROE
11/13/2009