

## OFFICE OF CLINICAL PHARMACOLOGY REVIEW

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NDA: 022430	Submission Date: 6/6/2013 (SDN 142)
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 Bone, Reproductive and Urologic Products
Sponsor	Ferring Pharmaceuticals, Inc.
Relevant IND	IND 068096
Submission Type	Labeling
Formulation; Strength(s)	Tablet; tranexamic acid 650 mg
Indication	Treatment of cyclic heavy menstrual bleeding

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On November 13, 2009, a tablet formulation (650 mg) of tranexamic acid for the treatment of heavy menstrual bleeding (HMB) was approved by the FDA as a 505(b)(2) product. The approved dosing regimen in adults is two 650 mg tablets administered 3 times daily, a total of 3,900 mg daily, during menstruation up to five days.

As a post-marketing requirement (PMR), a pediatric study was required under section 2 of the Pediatric Research Equity Act (PREA). Therefore, the sponsor conducted a pharmacokinetics (PK) study in healthy female subjects of 12-17 years of age, with heavy menstrual bleeding. The current submission contains the labeling revision based on the PMR PK study results (review in DARRTS, 3/29/2013). 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 022430 (SDN 142) acceptable from a Clinical Pharmacology perspective.

### **1.2 Phase IV Commitments**

None

### **1.3 Clinical Pharmacology Related Sections of the Final Agreed Label**

The final agreed label is attached.

#### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LYSTEDA safely and effectively. See full prescribing information for LYSTEDA.

LYSTEDA® (tranexamic acid) Tablets  
Initial U.S. Approval: 1986

#### RECENT MAJOR CHANGES

Warnings and Precautions (5.1) 4/2011

#### INDICATIONS AND USAGE

LYSTEDA (tranexamic acid) Tablets is an antifibrinolytic indicated for the treatment of cyclic heavy menstrual bleeding. (1)

#### DOSAGE AND ADMINISTRATION

- 1,300 mg (two 650 mg tablets) three times a day (3,900 mg/day) for a maximum of 5 days during monthly menstruation (2.1)
- Renal impairment: Dosage adjustment is needed if serum creatinine concentration (Cr) is higher than 1.4 mg/dL (2.2)
  - Cr above 1.4 mg/dL and ≤ 2.8 mg/dL: 1,300 mg (two 650 mg tablets) two times a day (2,600 mg/day) for a maximum of 5 days during menstruation
  - Cr above 2.8 mg/dL and ≤ 5.7 mg/dL: 1,300 mg (two 650 mg tablets) once a day (1,300 mg/day) for a maximum of 5 days during menstruation
  - Cr above 5.7 mg/dL: 650 mg (one 650 mg tablet) once a day (650 mg/day) for a maximum of 5 days during menstruation

#### DOSAGE FORMS AND STRENGTHS

Tablets: 650 mg (3)

#### CONTRAINDICATIONS

- Women with active thromboembolic disease or a history or intrinsic risk of thrombosis or thromboembolism, including retinal vein or artery occlusion (4.1)
- Hypersensitivity to tranexamic acid (4.2)

#### WARNINGS AND PRECAUTIONS

- The risk of thrombotic and thromboembolic events may increase further when hormonal contraceptives are administered with LYSTEDA.

especially in women who are obese or smoke cigarettes. 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. Do not use LYSTEDA in women who are taking more than the approved dose of a hormonal contraceptive. (5.1)

- Concomitant use of LYSTEDA with Factor IX complex concentrates, anti-inhibitor coagulant concentrates or all-trans retinoic acid (oral tretinoin) may increase the risk of thrombosis. (5.1)
- Visual or ocular adverse effects may occur with LYSTEDA. Immediately discontinue use if visual or ocular symptoms occur. (5.1)
- In case of severe allergic reaction, discontinue LYSTEDA and seek immediate medical attention. (5.2)
- Cerebral edema and cerebral infarction may be caused by use of LYSTEDA in women with subarachnoid hemorrhage. (5.3)
- Ligneous conjunctivitis has been reported in patients taking tranexamic acid. (5.4)

#### ADVERSE REACTIONS

Most common adverse reactions in clinical trials (≥ 5%, and more frequent in LYSTEDA subjects compared to placebo subjects) are headache, sinus and nasal symptoms, back pain, abdominal pain, musculoskeletal pain, joint pain, muscle cramps, migraine, anemia and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Ferring Pharmaceuticals Inc. at 1-888-FERRING (1-888-337-7464) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

Concomitant therapy with tissue plasminogen activators may decrease the efficacy of both LYSTEDA and tissue plasminogen activators. (7.2)

#### USE IN SPECIFIC POPULATIONS

- Renal impairment: Dosage adjustment is needed. (2.2, 8.6)
- Hepatic impairment: No dosage adjustment is needed. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: XX/20XX

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

LYSTEDA® (tranexamic acid) Tablets is indicated for the treatment of cyclic heavy menstrual bleeding [see *Clinical Studies (14)*].

Prior to prescribing LYSTEDA, exclude endometrial pathology that can be associated with heavy menstrual bleeding.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Recommended Dosage

The recommended dose of LYSTEDA for women with normal renal function is two 650 mg tablets taken three times daily (3900 mg/day) for a maximum of 5 days during monthly menstruation. LYSTEDA may be administered without regard to meals. Tablets should be swallowed whole and not chewed or broken apart.

#### 2.2 Renal Impairment

In patients with renal impairment, the plasma concentration of tranexamic acid increased as serum creatinine concentration increased [see *Clinical Pharmacology (12.3)*]. Dosage adjustment is needed in patients with serum creatinine concentration higher than 1.4 mg/dL (Table 1).

**Table 1. Dosage of LYSTEDA in Patients with Renal Impairment**

LYSTEDA		
Serum Creatinine (mg/dL)	Adjusted Dose	Total Daily Dose
Cr above 1.4 and $\leq$ 2.8	1300 mg (two 650 mg tablets) two times a day for a maximum of 5 days during menstruation	2600 mg
Cr above 2.8 and $\leq$ 5.7	1300 mg (two 650 mg tablets) once a day for a maximum of 5 days during menstruation	1300 mg
Cr above 5.7	650 mg (one 650 mg tablet) once a day for a maximum of 5 days during menstruation	650 mg

### 3 DOSAGE FORMS AND STRENGTHS

650 mg tablets

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy (Category B)

LYSTEDA is not indicated for use in pregnant women. Reproduction studies have been performed in mice, rats and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to tranexamic acid. However, tranexamic acid is known to cross the placenta and appears in cord blood at concentrations approximately equal to the maternal concentration. There are no adequate and well-controlled studies in pregnant women [see *Nonclinical Toxicology (13.1)*].

An embryo-fetal developmental toxicity study in rats and a perinatal developmental toxicity study in rats were conducted using tranexamic acid. No adverse effects were observed in either study at doses up to 4 times the recommended human oral dose of 3900 mg/day based on mg/m<sup>2</sup> (actual animal dose 1500 mg/kg/day).

#### 8.3 Nursing Mothers

Tranexamic acid is present in the mother's milk at a concentration of about one hundredth of the corresponding serum concentration. LYSTEDA should be used during lactation only if clearly needed.

#### 8.4 Pediatric Use

LYSTEDA is indicated for women of reproductive age and is not intended for use in premenarcheal girls. Based on a pharmacokinetic study in 20 adolescent females, 12 to 16 years of age, no dose adjustment is needed in the adolescent population [see *Clinical Pharmacology* (12.3)].

#### 8.5 Geriatric Use

LYSTEDA is indicated for women of reproductive age and is not intended for use by postmenopausal women.

#### 8.6 Renal Impairment

The effect of renal impairment on the pharmacokinetics of LYSTEDA has not been studied. Because tranexamic acid is primarily eliminated via the kidneys by glomerular filtration with more than 95% excreted as unchanged in urine, dosage adjustment in patient with renal impairment is needed [see *Dosage and Administration* (2.2) and *Clinical Pharmacology* (12.3)].

#### 8.7 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of LYSTEDA has not been studied. Because only a small fraction of the drug is metabolized, dosage adjustment in patients with hepatic impairment is not needed [see *Clinical Pharmacology* (12.3)].

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

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 binding to fibrin monomers, thus preserving and stabilizing fibrin's matrix structure.

The antifibrinolytic effects of tranexamic acid are mediated by reversible interactions at multiple binding sites within plasminogen. Native human plasminogen contains 4 to 5 lysine binding sites with low affinity for tranexamic acid ( $K_d = 750 \mu\text{mol/L}$ ) and 1 with high affinity ( $K_d = 1.1 \mu\text{mol/L}$ ). The high affinity lysine site of plasminogen is involved in its binding to fibrin. Saturation of the high affinity binding site with tranexamic acid displaces plasminogen from the surface of fibrin. Although plasmin may be formed by conformational changes in plasminogen, binding to and dissolution of the fibrin matrix is inhibited.

### 12.2 Pharmacodynamics

Tranexamic acid, at *in vitro* concentrations of 25 - 100  $\mu\text{M}$ , reduces by 20 - 60% the maximal rate of plasmin lysis of fibrin catalyzed by tissue plasminogen activator (tPA).

Elevated concentrations of endometrial, uterine, and menstrual blood tPA are observed in women with heavy menstrual bleeding (HMB) compared to women with normal menstrual blood loss. The effect of tranexamic acid on lowering endometrial tPA activity and menstrual fluid fibrinolysis is observed in women with HMB receiving tranexamic acid total oral doses of 2-3 g/day for 5 days.

In healthy subjects, tranexamic acid at blood concentrations less than 10 mg/mL has no effect on the platelet count, the coagulation time or various coagulation factors in whole blood or citrated blood. Tranexamic acid, however, at blood concentrations of 1 and 10 mg/mL prolongs the thrombin time.

#### *Cardiac Electrophysiology*

The effect of LYSTEDA on QT interval was evaluated in a randomized, single-dose, 4-way crossover study in 48 healthy females aged 18 to 49 years. Subjects received (1) LYSTEDA 1300 mg (two 650 mg tablets), (2) LYSTEDA 3900 mg (six 650 mg tablets; three times the recommended single dose), (3) moxifloxacin 400 mg, and (4) placebo. There was no significant increase in the corrected QT interval at any time up to 24 hours after the administration of either dose of LYSTEDA. Moxifloxacin, the active control, was associated with a maximum 14.11 msec mean increase in corrected QT interval (moxifloxacin – placebo) at 3 hours after administration.

### 12.3 Pharmacokinetics

#### *Absorption*

After a single oral administration of two 650 mg tablets of LYSTEDA, the peak plasma concentration ( $C_{\text{max}}$ ) occurred at approximately 3 hours ( $T_{\text{max}}$ ). The absolute bioavailability of LYSTEDA in women aged 18-49 is approximately 45%. Following multiple oral doses (two 650 mg tablets three times daily)

administration of LYSTEDA for 5 days, the mean  $C_{max}$  increased by approximately 19% and the mean area under the plasma concentration-time curve (AUC) remained unchanged, compared to a single oral dose administration (two 650 mg tablets). Plasma concentrations reached steady state at the 5<sup>th</sup> dose of LYSTEDA on Day 2.

The mean plasma pharmacokinetic parameters of tranexamic acid determined in 19 healthy women following a single (two 650 mg tablets) and multiple (two 650 mg tablets three times daily for 5 days) oral dose of LYSTEDA are shown in Table 3.

**Table 3. Mean (CV%) Pharmacokinetic Parameters Following a Single (two 650 mg tablets) and Multiple Oral Dose (two 650 mg tablets three time daily for 5 days) Administration of LYSTEDA in 19 Healthy Women under Fasting Conditions**

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

$C_{max}$  = maximum concentration

$AUC_{t_{dc}}$  = area under the drug concentration curve from time 0 to time of last determinable concentration

$AUC_{inf}$  = area under the drug concentration curve from time 0 to infinity

$T_{max}$  = time to maximum concentration

$t_{1/2}$  = terminal elimination half-life

<sup>a</sup> $AUC_{0-8h}$  (mcg·h/mL) = area under the drug concentration curve from time 0 to 8 hours

<sup>b</sup>Data presented as median (range)

Effect of food: LYSTEDA may be administered without regard to meals. A single dose administration (two 650 mg tablets) of LYSTEDA with food increased both  $C_{max}$  and AUC by 7% and 16%, respectively.

#### *Distribution*

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

Tranexamic acid crosses the placenta. The concentration in cord blood after an intravenous injection of 10 mg/kg to pregnant women is about 30 mg/L, as high as in the maternal blood.

Tranexamic acid concentration in cerebrospinal fluid is about one tenth of the plasma concentration.

The drug passes into the aqueous humor of the eye achieving a concentration of approximately one tenth of plasma concentrations.

#### *Metabolism*

A small fraction of the tranexamic acid is metabolized.

#### *Excretion*

Tranexamic acid is eliminated by urinary excretion primarily via glomerular filtration 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/kg. Most elimination post intravenous administration occurred during the first 10 hours, giving an apparent elimination half-life of approximately 2 hours. The mean

terminal half-life of LYSTEDA is approximately 11 hours. Plasma clearance of tranexamic acid is 110-116 mL/min.

### ***Specific Populations***

#### *Pregnancy (Category B)*

LYSTEDA is not indicated for use in pregnant women. Tranexamic acid is known to cross the placenta and appears in cord blood at concentrations approximately equal to maternal concentration. There are no adequate and well-controlled studies in pregnant women [see *Use in Specific Populations (8.1)*].

#### *Nursing Mothers*

Tranexamic acid is present in the mother's milk at a concentration of about one hundredth of the corresponding serum concentrations. LYSTEDA should be used during lactation only if clearly needed [see *Use in Specific Populations (8.3)*].

#### *Pediatric Use*

LYSTEDA is indicated for women of reproductive age and is not intended for use in premenarcheal girls. In a randomized, single dose, two-way crossover study of two dose levels (650 mg and 1,300 mg [two 650 mg tablets]), pharmacokinetics of tranexamic acid was evaluated in 20 female adolescents (12 to 16 years of age) with heavy menstrual bleeding. The  $C_{max}$  and AUC values after a single oral dose of 650 mg in the adolescent females were 32 – 36% less than those after a single oral dose of 1,300 mg in the adolescent females. The  $C_{max}$  and AUC values after a single oral dose of 1300 mg in the adolescent females were 20 – 25% less than those in the adult females given the same dose in a separate study. [See *Use in Specific Populations (8.4)*]

#### *Geriatric Use*

LYSTEDA is indicated for women of reproductive age and is not intended for use by postmenopausal women.

#### *Renal Impairment*

The effect of renal impairment on the disposition of LYSTEDA has not been evaluated. Urinary excretion following a single intravenous injection of tranexamic acid declines as renal function decreases. Following a single 10 mg/kg intravenous injection of tranexamic acid in 28 patients, the 24-hour urinary fractions of tranexamic acid with serum creatinine concentrations 1.4 – 2.8, 2.8 – 5.7, and greater than 5.7 mg/dL were 51, 39, and 19%, respectively. The 24-hour tranexamic acid plasma concentrations for these patients demonstrated a direct relationship to the degree of renal impairment. Therefore, dose adjustment is needed in patients with renal impairment [see *Dosage and Administration (2.2)*].

#### *Hepatic Impairment*

The effect of hepatic impairment on the disposition of LYSTEDA has not been evaluated. One percent and 0.5 percent of an oral dose are excreted as a dicarboxylic acid and acetylated metabolite, respectively. Because only a small fraction of the drug is metabolized, no dose adjustment is needed in patients with hepatic impairment.

### ***Drug Interactions***

No drug-drug interaction studies were conducted with LYSTEDA.

#### *Hormonal Contraceptives*

Because LYSTEDA is antifibrinolytic, concomitant use of hormonal contraception and LYSTEDA may further exacerbate the increased thrombotic risk associated with combination hormonal contraceptives.

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 [see *Warnings and Precautions (5.1)* and *Drug Interactions (7.1)*].

*Factor IX Complex Concentrates or Anti-inhibitor Coagulant Concentrates*

LYSTEDA is not recommended in patients taking either Factor IX complex concentrates or anti-inhibitor coagulant concentrates because the risk of thrombosis may be increased [see *Warnings and Precautions (5.1)* and *Drug Interactions (7.3)*].

*Tissue Plasminogen Activators*

Concomitant therapy with tissue plasminogen activators may decrease the efficacy of both LYSTEDA and tissue plasminogen activators. Therefore, exercise caution if a patient taking LYSTEDA therapy requires tissue plasminogen activators [see *Drug Interactions (7.2)*].

*All-Trans Retinoic Acid (Oral Tretinoin)*

In a study involving 28 patients with acute promyelocytic leukemia who were given either orally administered all-trans retinoic acid plus intravenously administered 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. It appears that the procoagulant effect of all-trans retinoic acid may be exacerbated by concomitant use of tranexamic acid. Therefore, exercise caution when prescribing LYSTEDA to patients with acute promyelocytic leukemia taking all-trans retinoic acid [see *Warnings and Precautions (5.1)* and *Drug Interactions (7.4)*].

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/s/  
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06/20/2013

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