

LYSTEDA- tranexamic acid tablet

Amring Pharmaceuticals Inc.

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, for oral use
Initial U.S. Approval: 1986

INDICATIONS AND USAGE

LYSTEDA is an antifibrinolytic indicated for the treatment of cyclic heavy menstrual bleeding in females of reproductive potential. (1)

DOSAGE AND ADMINISTRATION

- 1,300 mg three times a day (3,900 mg/day) for a maximum of 5 days during monthly menstruation (2.1)
- Renal impairment: Lower dosage is needed (for a maximum of 5 days during menstruation) 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 times a day (2,600 mg/day)
 - Cr above 2.8 mg/dL and ≤ 5.7 mg/dL: 1,300 mg once a day (1,300 mg/day)
 - Cr above 5.7 mg/dL: 650 mg once a day (650 mg/day)

DOSAGE FORMS AND STRENGTHS

Tablets: 650 mg (3)

CONTRAINDICATIONS

- Concomitant use of combined hormonal contraceptives (4.1)
- 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

- Thromboembolism including retinal occlusion have been reported with LYSTEDA use. Concomitant use of LYSTEDA with combined hormonal contraceptives, 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 reactions 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 patients with subarachnoid hemorrhage. (5.3)
- Ligneous conjunctivitis has been reported in patients taking LYSTEDA . (5.4)

ADVERSE REACTIONS

Most common adverse reactions in clinical trials (≥ 5%, and more frequent in LYSTEDA-treated subjects compared to placebo-treated 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 Amring Pharmaceuticals Inc. at 1-844-Amring1 (1-844-267-4641) or FDA at 1-800-FDA-1088 or 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

- Geriatric use: LYSTEDA is not indicated for use in postmenopausal women (8.5)
- Renal impairment: A lower dosage is needed. (2.2, 8.6)
- Hepatic impairment: No dosage adjustment is needed. (8.7)

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Testing Prior to LYSTEDA Administration
- 2.2 Recommended Dosage
- 2.3 Dosage Recommendations in Patients with Renal Impairment

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

- 4.1 Thromboembolic Risk
- 4.2 Hypersensitivity to Tranexamic Acid

5 WARNINGS AND PRECAUTIONS

- 5.1 Thromboembolic Risk
- 5.2 Severe Allergic Reactions
- 5.3 Subarachnoid Hemorrhage
- 5.4 Ligneous Conjunctivitis

6 ADVERSE REACTIONS

- 6.1 Clinical Trial Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Combined Hormonal Contraceptives
- 7.2 Tissue Plasminogen Activators
- 7.3 Factor IX Complex Concentrates or Anti-Inhibitor Coagulant Concentrates
- 7.4 All-Trans Retinoic Acid (Oral Tretinoin)

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 Overview of the Clinical Studies
- 14.2 Heavy Menstrual Bleeding in the Three-Cycle Treatment Study
- 14.3 Heavy Menstrual Bleeding in the Six-Cycle Treatment Study

14.4 Heavy Menstrual Bleeding Results over Time

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LYSTEDA[®] is indicated for the treatment of cyclic heavy menstrual bleeding in females of reproductive potential [see *Clinical Studies (14)*].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Testing Prior to LYSTEDA Administration

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

2.2 Recommended Dosage

The recommended dosage of LYSTEDA for patients with normal renal function is 1300 mg orally three times daily (3900 mg/day) for a maximum of 5 days during monthly menstruation. LYSTEDA may be administered with or without food. Swallow tablets whole; do not chew or break apart.

2.3 Dosage Recommendations in Patients with Renal Impairment

The recommended dosage (for a maximum of 5 days during monthly menstruation) in patients with renal impairment with serum creatinine concentration higher than 1.4 mg/dL is described in Table 1.

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

Serum Creatinine (mg/dL)	Recommended Dosage (maximum of 5 days during menstruation)	Total Daily Dose
Above 1.4 and ≤ 2.8	1300 mg two times a day	2600 mg
Above 2.8 and ≤ 5.7	1300 mg once a day	1300 mg
Above 5.7	650 mg once a day	650 mg

3 DOSAGE FORMS AND STRENGTHS

Tablets: 650 mg white oval-shaped debossed with the marking “FP650”

4 CONTRAINDICATIONS

4.1 Thromboembolic Risk

LYSTEDA is contraindicated in females of reproductive potential who are [see *Warnings and Precautions* (5.1)]:

- Using combined hormonal contraception
- Known to have any of the following conditions:
 - Active thromboembolic disease (e.g., deep vein thrombosis, pulmonary embolism, or cerebral thrombosis)
 - A history of thrombosis or thromboembolism, including retinal vein or artery occlusion
 - An intrinsic risk of thrombosis or thromboembolism (e.g., thrombogenic valvular disease, thrombogenic cardiac rhythm disease, or hypercoagulopathy)

4.2 Hypersensitivity to Tranexamic Acid

LYSTEDA is contraindicated in females with reproductive potential with known hypersensitivity to tranexamic acid [see *Warnings and Precautions* (5.2) and *Adverse Reactions* (6.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Risk

Venous and arterial thrombosis or thromboembolism, as well as cases of retinal artery and retinal vein occlusions, have been reported with LYSTEDA.

Retinal venous and arterial occlusion have been reported in patients using LYSTEDA. 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 retinal venous or arterial occlusion.

Concomitant Use of Hormonal Contraceptives

Combined hormonal contraceptives are known to increase the risk of venous thromboembolism, as well as arterial thromboses such as stroke and myocardial infarction. Because LYSTEDA is antifibrinolytic, the risk of venous thromboembolism, as well as arterial thromboses such as stroke, may increase further when combined hormonal contraceptives are administered with LYSTEDA. This is of particular concern in women who are obese or smoke cigarettes, especially smokers over 35 years of age.

Women using combined 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 combined hormonal contraceptives. However, there have been US postmarketing reports of venous and arterial thrombotic events in women who have used LYSTEDA concomitantly

with combined hormonal contraceptives. For this reason, concomitant use of LYSTEDA with combined hormonal contraceptives is contraindicated [see *Contraindications (4.1) and Drug Interactions (7.1)*].

Concomitant Use with 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 *Drug Interactions (7.3) and Clinical Pharmacology (12.3)*].

Patients with Acute Promyelocytic Leukemia Taking Concomitant All-Trans Retinoic Acid (Oral Tretinoin)

LYSTEDA is not recommended in patients with acute promyelocytic leukemia taking all-trans retinoic acid for remission induction because of possible exacerbation of the procoagulant effect of all-trans retinoic acid [see *Drug Interactions (7.4) and Clinical Pharmacology (12.3)*].

5.2 Severe Allergic Reactions

A case of severe allergic reaction to LYSTEDA was reported in the clinical trials, involving a subject who experienced dyspnea, tightening of her throat, and facial flushing that required emergency medical treatment. A case of anaphylactic shock has also been reported in the literature, involving a patient who received an intravenous bolus of tranexamic acid. LYSTEDA is contraindicated in females of reproductive potential with known hypersensitivity to tranexamic acid.

5.3 Subarachnoid Hemorrhage

Cerebral edema and cerebral infarction may be caused by use of LYSTEDA in patients with subarachnoid hemorrhage.

5.4 Ligneous Conjunctivitis

Ligneous conjunctivitis has been reported in patients taking LYSTEDA. The conjunctivitis resolved following cessation of LYSTEDA.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse Reactions in Short-term Studies

The safety of LYSTEDA in the treatment of heavy menstrual bleeding in females of reproductive potential was studied in two randomized, double-blind, placebo-controlled studies [see *Clinical Studies (14)*].

- Study 1 compared the effects of two doses of LYSTEDA (1950 mg and 3900 mg per day for up to 5 days during each menstrual period) versus placebo over a 3-cycle

treatment duration. A total of 304 women were randomized to this study, with 115 receiving at least one dose of 3900 mg/day of LYSTEDA.

- Study 2 compared the effects of LYSTEDA (3900 mg/day) versus placebo over a 6-cycle treatment duration. A total of 196 women were randomized to this study, with 117 receiving at least one dose of LYSTEDA.

Across the studies, the combined exposure to 3900 mg/day LYSTEDA was 947 cycles and the average duration of use was 3.4 days per cycle. In both studies, subjects were generally healthy women who had menstrual blood loss of ≥ 80 mL. In these studies, 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 body mass index (BMI) of approximately 32 kg/m². On average, subjects had a history of heavy menstrual bleeding for approximately 10 years and 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. Seven percent (7%) of all subjects were of Hispanic origin. Women using hormonal contraception were excluded from the trials.

A list of adverse reactions occurring in $\geq 5\%$ of subjects and more frequently in LYSTEDA-treated subjects receiving 3900 mg/day compared to placebo-treated subjects is provided in Table 2.

Table 2. Adverse Reactions* Reported in Women with Heavy Menstrual Bleeding (Studies 1 and 2)

	LYSTEDA 3900 mg/day n (%) (N=232)	Placebo n (%) (N=139)
Number of Subjects with at Least One Adverse Reaction	208 (89.7%)	122 (87.8%)
Headache ^a	117 (50.4%)	65 (46.8%)
Nasal & 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%)

* Adverse reactions that were reported by $\geq 5\%$ of LYSTEDA-treated subjects and more frequently in LYSTEDA-treated subjects compared to placebo-treated subjects

^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

Adverse Reactions in Long-term Studies

Long-term safety of LYSTEDA was studied in two open-label studies. In one study, subjects with physician-diagnosed heavy menstrual bleeding (not using the alkaline hematin methodology) were treated with 3900 mg/day for up to 5 days during each menstrual period for up to 27 menstrual cycles. A total of 781 subjects were enrolled and 239 completed the study through 27 menstrual cycles. A total of 12.4% of the subjects withdrew due to adverse reactions. Women using hormonal contraception were excluded from the study. The total exposure in this study to 3900 mg/day LYSTEDA was 10,213 cycles. The average duration of LYSTEDA use was 2.9 days per cycle.

A long-term open-label extension study of subjects from the two short-term efficacy studies was also conducted in which subjects were treated with 3900 mg/day for up to 5 days during each menstrual period for up to 9 menstrual cycles. A total of 288 subjects were enrolled and 196 subjects completed the study through 9 menstrual cycles. A total of 2.1% of the subjects withdrew due to adverse reactions. The total exposure to 3900 mg/day LYSTEDA in this study was 1,956 cycles. The average duration of LYSTEDA use was 3.5 days per cycle.

The types and severity of adverse reactions in these two long-term open-label trials were similar to those observed in the double-blind, placebo-controlled studies although the percentage of subjects reporting them was greater in the 27-month study, most likely because of the longer study duration.

A case of severe allergic reaction to LYSTEDA was reported in the extension trial, involving a subject on her fourth cycle of treatment, who experienced dyspnea, tightening of her throat, and facial flushing that required emergency medical treatment.

6.2 Postmarketing Experience

The following adverse reactions have been identified from postmarketing experience with LYSTEDA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Eye disorders:* Impaired color vision and other visual disturbances
- *Gastrointestinal disorders:* Nausea, vomiting, and diarrhea
- *Immune system disorders:* Anaphylactic shock and anaphylactoid reactions
- *Nervous system disorders:* Dizziness
- *Skin and subcutaneous tissue disorders:* Allergic skin reactions
- *Vascular disorders:* Thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, cerebral thrombosis, acute renal cortical necrosis, and central retinal artery and vein obstruction); cases have been associated with concomitant use of combined hormonal contraceptives

7 DRUG INTERACTIONS

No drug-drug interaction studies were conducted with LYSTEDA.

7.1 Combined Hormonal Contraceptives

Because LYSTEDA is antifibrinolytic, concomitant use of combined hormonal contraception and LYSTEDA may increase the thrombotic risk associated with combined hormonal contraceptives. For this reason, concomitant use of LYSTEDA with combined hormonal contraceptives is contraindicated [see *Contraindications (4)* and *Warnings and Precautions (5.1)*].

7.2 Tissue Plasminogen Activators

Concomitant therapy with tissue plasminogen activators may decrease the efficacy of both LYSTEDA and tissue plasminogen activators. Discontinue LYSTEDA if a patient requires tissue plasminogen activators.

7.3 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)*].

7.4 All-Trans Retinoic Acid (Oral Tretinoin)

LYSTEDA is not recommended in patients with acute promyelocytic leukemia taking all-trans retinoic acid for remission induction because of possible exacerbation of the procoagulant effect of all-trans retinoic acid [see *Warnings and Precautions (5.1)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

LYSTEDA is not indicated for use in pregnant women. There are no available data on LYSTEDA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Tranexamic acid crosses the placenta. Animal reproduction studies have not identified adverse developmental outcomes with oral administration of tranexamic acid to pregnant rats at doses up to 4 times the recommended human dose (see *Data*).

In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In a rat embryo-fetal developmental toxicity study, tranexamic acid had no adverse effects on embryo-fetal development when administered during the period of organogenesis (from gestation days 6 through 17) at twice daily doses of 0, 150, 375, and 750 mg/kg (1, 2 and 4 times the recommended human oral dosage of 3900 mg/day based on body surface area (mg/m²)).

In a perinatal-postnatal developmental toxicity study in rats administered tranexamic acid from gestation day 6 through postnatal day 20 at twice daily doses of 0, 150, 375,

and 750 mg/kg, no significant adverse effects on maternal behavior or body weight were observed, and no significant effects on pup viability, body weight, developmental milestones or adult fertility were observed. It was concluded that the no-observed-effect-level (NOEL) for this study was 1500 mg/kg/day in both F₀ and F₁ generations, which is equivalent to 4 times the recommended human oral dose of 3900 mg/day based on body surface area (mg/m²).

8.2 Lactation

Risk Summary

Tranexamic acid is present in the mother's milk at a concentration of about one hundredth of the corresponding serum concentration (see Data). The amount of tranexamic acid a nursing infant would absorb is unknown. There are no adequate data on the effects of tranexamic acid on the breastfed infant or the effects of tranexamic acid on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LYSTEDA and any potential adverse effects on the breast-fed child from LYSTEDA or from the underlying maternal condition.

Data

Human Data

One hour after the last dose following a 2-day treatment course in lactating women, the milk concentration of the tranexamic acid was 1% of the peak serum concentration.

8.4 Pediatric Use

The safety and effectiveness of LYSTEDA have been established in females of reproductive potential. Efficacy is expected to be the same for post-menarchal females under the age of 17 as for those 17 years and older. LYSTEDA is not indicated before menarche.

8.5 Geriatric Use

LYSTEDA is indicated for females of reproductive potential 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, the recommended dosage in patient with renal impairment is lower than the recommended dosage in patients with normal renal function [see *Dosage and Administration* (2.2) and *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

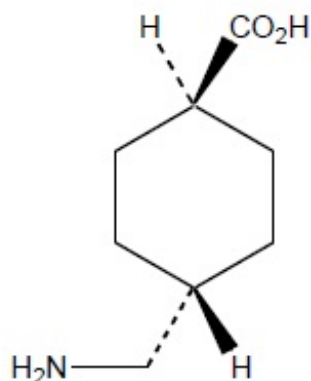
The effect of hepatic impairment on the pharmacokinetics of LYSTEDA has not been studied. Because only a small fraction of the drug is metabolized, the recommended dosage in patients with hepatic impairment is the same as in patients with normal hepatic function [see *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

There are no known cases of intentional overdose with LYSTEDA and no subjects in the clinical program took more than 2 times the prescribed amount of LYSTEDA in a 24-hour period (>7800 mg/day). However, cases of overdose of tranexamic acid have been reported. Based on these reports, symptoms of overdose may include gastrointestinal (nausea, vomiting, diarrhea); hypotensive (e.g., orthostatic symptoms); thromboembolic (arterial, venous, embolic); visual impairment; mental status changes; myoclonus; or rash. No specific information is available on the treatment of overdose with LYSTEDA. In the event of overdose, employ the usual supportive measures (e.g., clinical monitoring and supportive therapy) as dictated by the patient's clinical status.

11 DESCRIPTION

LYSTEDA is an antifibrinolytic drug administered orally. The chemical name is trans-4-aminomethyl-cyclohexanecarboxylic acid. The structural formula is:



Tranexamic acid is a white crystalline powder. It is freely soluble in water and in glacial acetic acid and is very slightly soluble in ethanol and practically insoluble in ether. The molecular formula is $C_8H_{15}NO_2$ and the molecular weight is 157.2.

LYSTEDA is provided as white oval-shaped tablets and are not scored. Each tablet is debossed with the marking "FP650." The active ingredient in each tablet is 650 mg tranexamic acid. The inactive ingredients contained in each tablet are: microcrystalline cellulose, colloidal silicon dioxide, pregelatinized corn starch, povidone, hypromellose, stearic acid, and magnesium stearate.

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 μM , 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 LYSTEDA 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 (2) LYSTEDA 3900 mg (three times the maximum 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 14.1 msec mean increase in corrected QT interval (moxifloxacin - placebo) at 3 hours after administration.

12.3 Pharmacokinetics

Absorption

After a single oral administration of 1300 mg of LYSTEDA, the peak plasma concentration (C_{max}) occurred at approximately 3 hours (T_{max}). The absolute bioavailability of LYSTEDA in women aged 18-49 is approximately 45%. Following multiple oral doses (1300 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 (1300 mg). Plasma concentrations reached steady state at the 5th dose of LYSTEDA on Day 2.

The mean plasma pharmacokinetic parameters of tranexamic acid determined in 19 healthy women following a single (1300 mg) and multiple (1300 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 (1300 mg) and Multiple Dose (1300 mg three times daily for 5 days) Oral 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 _{tldc} (mcg•h/mL)	77.96 (31.14)	77.67 ^a (29.39)
AUC _{inf} (mcg•h/mL)	80.19 (30.43)	-
T _{max} (h) ^b	2.5 (1 - 5)	2.5 (2 - 3.5)
t _{1/2} (h)	11.08 (16.94)	-

C_{max} = maximum concentration

AUC_{tldc} = 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

^aAUC_{0-tau} (mcg•h/mL) = area under the drug concentration curve from time 0 to 8 hours

^bData presented as median (range)

Effect of food: LYSTEDA may be administered with or without food. A single dose administration (1300 mg) 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.

Elimination

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

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.

Specific Populations

Pediatric Patients

LYSTEDA is indicated for females of reproductive age (not approved for use in premenarcheal girls).

In a randomized, single dose, two-way crossover study of two dose levels (650 mg and 1,300 mg), 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)]

Patients with 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, a lower dosage is needed in patients with renal impairment [see *Dosage and Administration* (2.2)].

Patients with 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, the recommended dosage in patients with hepatic impairment is the same as in patients with normal hepatic impairment.

Drug Interactions Studies

No drug-drug interaction studies were conducted with LYSTEDA.

All-Trans Retinoic Acid (Oral Tretinoin)

In a study involving 28 patients with acute promyelocytic leukemia who were given either orally administered (1) all-trans retinoic acid plus intravenously administered tranexamic acid, (2) all-trans retinoic acid plus chemotherapy, or (3) 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. The procoagulant effect of all-trans retinoic acid may have been exacerbated by concomitant use of tranexamic acid. Therefore, LYSTEDA is not recommended in patients with acute promyelocytic leukemia taking all-trans retinoic acid [see *Warnings and Precautions* (5.1)]

and Drug Interactions (7.4)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies with tranexamic acid in male mice at doses as high as 6 times the recommended human dose of 3900 mg/day showed an increased incidence of leukemia which may have been related to treatment. Female mice were not included in this experiment.

The dose multiple referenced above is based on body surface area (mg/m^2). Actual daily dose in mice was up to 5000 mg/kg/day in food.

Hyperplasia of the biliary tract and cholangioma and adenocarcinoma of the intrahepatic biliary system have been reported in one strain of rats after dietary administration of doses exceeding the maximum tolerated dose for 22 months. Hyperplastic, but not neoplastic, lesions were reported at lower doses. Subsequent long-term dietary administration studies in a different strain of rat, each with an exposure level equal to the maximum level employed in the earlier experiment, have failed to show such hyperplastic/neoplastic changes in the liver.

Mutagenesis

Tranexamic acid was neither mutagenic nor clastogenic in the *in vitro* Bacterial Reverse Mutation Assay (Ames test), *in vitro* chromosome aberration test in Chinese hamster cells, and in *in vivo* chromosome aberration tests in mice and rats.

Impairment of Fertility

Reproductive studies performed in mice, rats and rabbits have not revealed any evidence of impaired fertility or adverse effects on the fetus due to tranexamic acid.

13.2 Animal Toxicology and/or Pharmacology

Ocular Effects

In a 9-month toxicology study, dogs were administered tranexamic acid in food at doses of 0, 200, 600, or 1200 mg/kg/day. These doses are approximately 2, 5, and 6 times, respectively, the recommended human oral dose of 3900 mg/day based on AUC. At 6 times the human dose, some dogs developed reversible reddening and gelatinous discharge from the eyes. Ophthalmologic examination revealed reversible changes in the nictitating membrane/conjunctiva. In some female dogs, the presence of inflammatory exudate over the bulbar conjunctival mucosa was observed. Histopathological examinations did not reveal any retinal alteration. No adverse effects were observed at 5 times the human dose.

In other studies, focal areas of retinal degeneration were observed in cats, dogs and rats following oral or intravenous tranexamic acid doses at 6-40 times the recommended usual human dose based on mg/m^2 (actual animal doses between 250-1600 mg/kg/day).

14 CLINICAL STUDIES

14.1 Overview of the Clinical Studies

The efficacy of LYSTEDA in the treatment of heavy menstrual bleeding (HMB) in women of reproductive potential was demonstrated in two randomized, double-blind, placebo-controlled studies: one 3-cycle treatment study (Study 1) and one 6-cycle treatment study (Study 2) [see *Adverse Reactions* (6.1)]. In these studies, HMB was defined as an average menstrual blood loss of ≥ 80 mL as assessed by alkaline hematin analysis of collected sanitary products over two baseline menstrual cycles. 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/m². On average, subjects had an HMB history of approximately 10 years and 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. Seven percent (7%) of all subjects were of Hispanic origin.

In these studies, the primary outcome measure was menstrual blood loss (MBL), measured using the alkaline hematin method. The endpoint was change from baseline in MBL, calculated by subtracting the mean MBL during treatment from the mean pretreatment MBL. The key secondary outcome measures were based on specific questions concerning limitations in social or leisure activities (LSLA) and limitations in physical activities (LPA). Large stains (soiling beyond the undergarment) were also included as a key secondary outcome measure.

14.2 Heavy Menstrual Bleeding in the Three-Cycle Treatment Study

Study 1 compared the effects of two doses of LYSTEDA (1950 mg and 3900 mg per day for up to 5 days during each menstrual period) versus placebo on MBL over a 3-cycle treatment duration. Of the 294 evaluable subjects, 115 subjects received LYSTEDA 1950 mg/day, 112 subjects received LYSTEDA 3900 mg/day and 67 subjects received placebo (subjects took at least one dose of study drug and had post-treatment data available).

Results are shown in Table 4. Menstrual blood loss (MBL) was statistically significantly reduced in patients treated with 3900 mg/day LYSTEDA compared to placebo. Study success also required achieving a reduction in MBL that was determined to be clinically meaningful to the subjects. The 1950 mg/day LYSTEDA dose did not meet the criteria for success.

Table 4. Mean Reduction from Baseline in Menstrual Blood Loss in Women with Heavy Menstrual Bleeding (Study 1)

Treatment Arm	N	Baseline Mean MBL (mL)	Least Squares Mean Reduction in MBL (mL)	Percent Reduction in MBL
LYSTEDA 3900 mg/day	112	169	65*	39%
LYSTEDA 1950 mg/day	115	178	44	25%
Placebo	67	154	7	5%

* p<0.001 versus placebo

LYSTEDA also statistically significantly reduced limitations on social, leisure, and physical activities in the 3900 mg/day dose group compared to the placebo group (see Table 5). No statistically significant treatment difference was observed in response rates on the number of large stains.

Table 5: Secondary Outcomes in 3-Cycle Study in Women with Heavy Menstrual Bleeding (Study 1)

Outcome Measure	N	Baseline Mean ^a	Least Squares Mean Reduction ^b
Social and Leisure Activities			
3900 mg/day LYSTEDA	112	3.00	0.98 ^c
Placebo	66	2.85	0.39
Physical Activities			
3900 mg/day LYSTEDA	112	3.07	0.94 ^c
Placebo	66	2.96	0.34
	N		Responders ^d
Reduction in Large Stains			
3900 mg/day LYSTEDA	111		64% ^e
Placebo	67		52%

^a Response categories: 1=not at all limited; 2=slightly limited; 3=moderately limited; 4=quite a bit limited; 5=extremely limited

^b Positive means reflect an improvement from baseline.

^c p-value <0.05 versus placebo

^d Responders are defined as subjects who experienced a reduction from baseline in frequency of large stains.

^e Non-significant difference versus placebo

14.3 Heavy Menstrual Bleeding in the Six-Cycle Treatment Study

Study 2 compared the effects of LYSTEDA 3900 mg/day given daily for up to 5 days during each menstrual period versus placebo on menstrual blood loss (MBL) over a 6-cycle treatment duration. Of the 187 evaluable subjects, 115 subjects received LYSTEDA and 72 subjects received placebo (subjects took at least one dose of study drug and had post-treatment data available).

Results are shown in Table 6. MBL was statistically significantly reduced in patients treated with 3900 mg/day LYSTEDA compared to placebo. Study success also required achieving a reduction in MBL that was determined to be clinically meaningful to the subjects.

Table 6. Mean Reduction from Baseline in Menstrual Blood Loss in Women with Heavy Menstrual Bleeding (Study 2)

	Baseline	Least Squares	Percent
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Treatment Arm	N	Baseline Mean MBL (mL)	Mean Reduction in MBL (mL)	Percent Reduction in MBL
LYSTEDA 3900 mg/day	115	172	66*	38%
Placebo	72	153	18	12%

* p<0.001 versus placebo

Limitations on social, leisure, and physical activities were also statistically significantly reduced in the LYSTEDA group compared to placebo (see Table 7). No statistically significant treatment difference was observed in response rates on the number of large stains.

Table 7. Secondary Outcomes in 6-Cycle Study in Women with Heavy Menstrual Bleeding (Study 2)

Outcome Measure	N	Baseline Mean ^a	Least Squares Mean Reduction ^b
Social and Leisure Activities			
3900 mg/day LYSTEDA	115	2.92	0.85 ^c
Placebo	72	2.74	0.44
Physical Activities			
3900 mg/day LYSTEDA	115	3.05	0.87 ^c
Placebo	72	2.90	0.40
	N		Responders ^d
Reduction in Large Stains			
3900 mg/day LYSTEDA	115		57% ^e
Placebo	72		51%

^a Response categories: 1=not at all limited; 2=slightly limited; 3=moderately limited; 4=quite a bit limited; 5=extremely limited

^b Positive means reflect an improvement from baseline

^c p-value <0.05 versus placebo

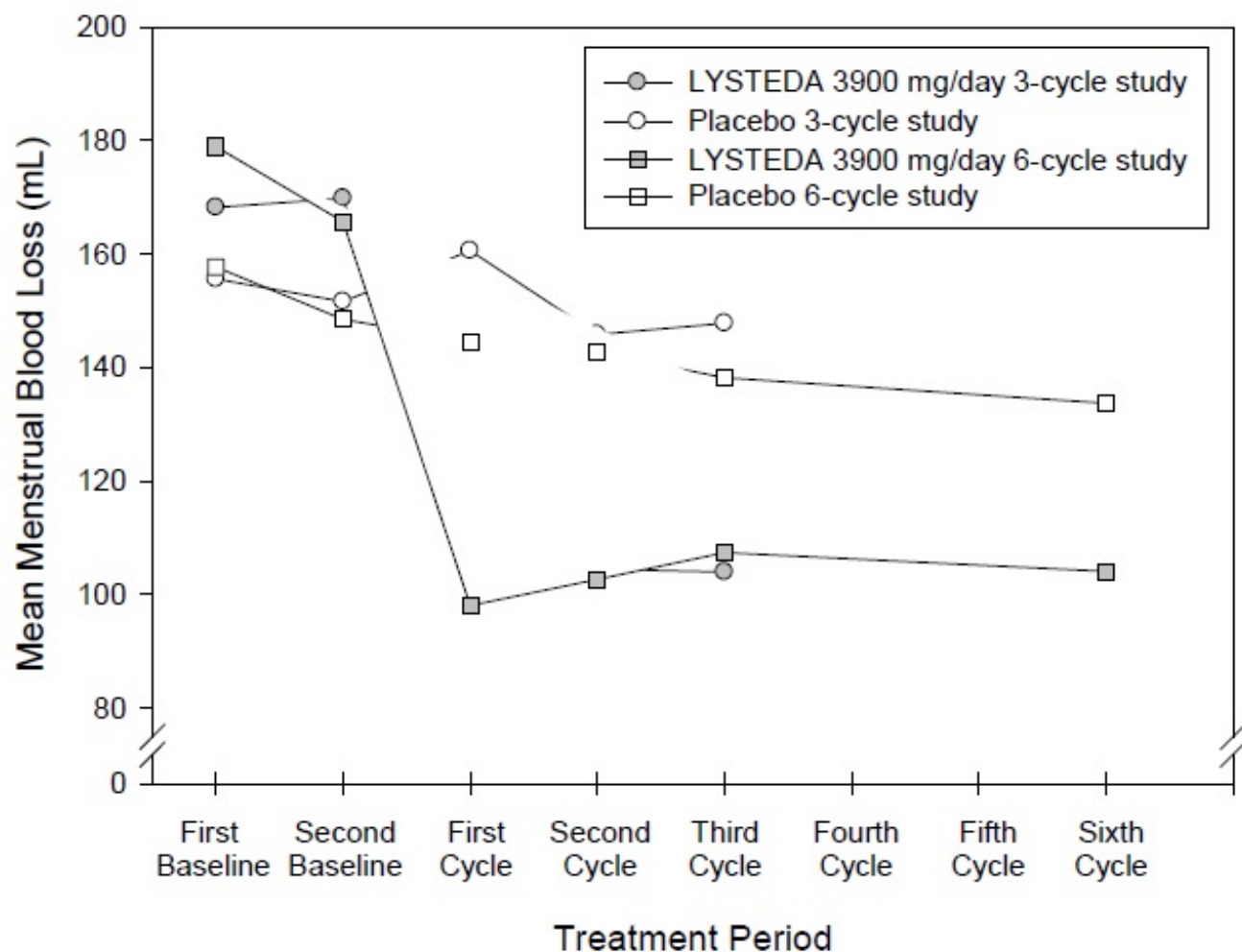
^d Responders are defined as subjects who experienced a reduction from baseline in frequency of large stains

^e Non-significant difference versus placebo

14.4 Heavy Menstrual Bleeding Results over Time

The efficacy of LYSTEDA 3900 mg/day over 3 menstrual cycles and over 6 menstrual cycles was demonstrated versus placebo in Studies 1 and 2 (see Figure 1). The change in menstrual bleeding loss from baseline was similar across all post-baseline treatment cycles.

Figure 1: Menstrual Bleeding Loss Levels over Duration of Therapy in Women with Heavy Menstrual Bleeding (Studies 1 and 2)



16 HOW SUPPLIED/STORAGE AND HANDLING

LYSTEDA (tranexamic acid) tablets, USP are provided as white oval-shaped 650 mg tablets. Each tablet is debossed with the marking “FP650” and are supplied as:

Quantity	Package Type	NDC Number
30 tablets	HDPE bottle	69918-300-30

Storage

Store at room temperature 25° C (77° F); excursions permitted to 15-30° C (59-86° F). [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Thromboembolic Risk

Inform patients that LYSTEDA may increase the risk of venous and arterial thrombosis or thromboembolism and to contact their healthcare provider for any signs or symptoms suggestive of thromboembolism [see *Warnings and Precautions* (5.1)].

Advise patients to discontinue use of LYSTEDA and promptly report visual and ocular symptoms to their health care provider as retinal venous and arterial occlusion have been reported in patients using LYSTEDA [see *Warnings and Precautions* (5.1)].

Severe Allergic Reactions

Inform patients that they should stop LYSTEDA and seek immediate medical attention if they notice symptoms of a severe allergic reaction (e.g., shortness of breath or throat tightening) [see *Warnings and Precautions* (5.2)].

Administration Instructions

Instruct patients to take LYSTEDA only during menstruation and for a maximum of 5 days each month [see *Recommended Dosage* (2.1)].

Manufactured for:

Amring Pharmaceuticals Inc.

Berwyn, PA 19312

www.amringusa.com



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Manufactured by:

Mikart, LLC

Atlanta, GA 30318

PATIENT INFORMATION

LYSTEDA (*lye-sted-a*)

tranexamic acid, tablets, for oral use

Read the Patient Information that comes with LYSTEDA before you start using the drug and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is LYSTEDA?

LYSTEDA is a prescription medicine used to treat your heavy monthly period (menstruation) when your bleeding gets in the way of social, leisure and physical activities. LYSTEDA does not contain any hormones. On average, LYSTEDA has been shown to lower the amount of blood lost during your monthly period by about one-third, but it is not meant to stop your period.

LYSTEDA is taken only during your period and is not meant to treat pre-menstrual symptoms (symptoms that occur before your bleeding starts). LYSTEDA does not affect your fertility and cannot be used as birth control. LYSTEDA does not protect you against diseases that you may get if you have unprotected sex.

LYSTEDA has not been studied in adolescents younger than 18 years of age.

LYSTEDA is not for women who have already gone through menopause (post-menopausal).

Who should not take LYSTEDA?

Do not take LYSTEDA if you:

- Are using a form of birth control that contains estrogen and a progestin (like a birth control pill, patch, or vaginal ring). Ask your healthcare provider before taking LYSTEDA if you are not sure if your birth control method contains estrogen and a progestin.
- Currently have a blood clot
- Have ever had a blood clot
- Have been told that you are at risk of having a blood clot
- Are allergic to LYSTEDA or tranexamic acid

What should I tell my healthcare provider before taking LYSTEDA?

Before taking LYSTEDA, tell your healthcare provider about all of your medical conditions, including whether:

- **You have ever had a blood clot or been told that you are at risk of having a blood clot**
- **You are using a form of birth control that contains** estrogen and a progestin (like a birth control pill, patch, or vaginal ring). Using hormonal birth control along with LYSTEDA may increase your chance of having a serious blood clot, stroke, or heart attack. For this reason, do not use LYSTEDA if you use a form of birth control that contains estrogen and a progestin.
- You are pregnant or think you may be pregnant
- You are breastfeeding or plan to breast-feed. LYSTEDA can pass into your milk. Talk to your healthcare provider about the best way to feed your baby if you take LYSTEDA.
- The time between the start of your periods is less than 21 days or more than 35 days
- You have any other medical conditions

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. LYSTEDA and other medicines can affect each other, causing side effects. LYSTEDA can affect the way other medicines work and other medicines can affect how LYSTEDA works.

Especially tell your healthcare provider if you take:

- Birth control pills or other hormonal birth control
- Medicines used to help your blood form clots
- Medicines used to break up blood clots
- Any medicines to treat leukemia

Ask your healthcare provider if you are not sure if your medicine is one that is described above.

How should I take LYSTEDA?

- Take LYSTEDA exactly as your healthcare provider tells you.
- Do not take LYSTEDA until your period has started.
- Do not take LYSTEDA for more than 5 days in a row.
- Do not take LYSTEDA when you do not have your period.
- Once your period has started, take 2 tablets of LYSTEDA three times per day (e.g., in the morning, afternoon, and evening).
- LYSTEDA tablets should be swallowed whole and not chewed or broken apart.
- LYSTEDA may be taken with or without food.
- Do not take more than 6 tablets of LYSTEDA in a day. If you take more than 6 tablets, call your healthcare provider.
- If you miss a dose, take it when you remember, and then take your next dose at least six hours later. Do not take more than two tablets at a time to make up for missed doses.
- If LYSTEDA does not help to lessen bleeding with your periods after 2 cycles or seems to stop working, talk to your healthcare provider.

What are the possible side effects of LYSTEDA?

LYSTEDA can cause serious side effects, including:

- Blood clots. You may have a higher risk of having serious blood clots if you take LYSTEDA with:
 - medicines used to help your blood form clots
 - some medicines used to treat leukemia
- Eye changes. Stop taking LYSTEDA and promptly report any eye problems you have while taking LYSTEDA. Your doctor will refer you to an eye doctor who will examine your eyes.
- Allergic reaction. If you have severe shortness of breath and your throat feels tight, stop taking LYSTEDA and get medical care right away.

The most common side effects of LYSTEDA include:

- Headaches
- Sinus and nasal problems
- Back pain
- Pain in your abdomen
- Pain in your muscles or joints
- Anemia
- Fatigue

Tell your healthcare provider if you have any side effect that bothers you or does not go away.

These are not all of the possible side effects of LYSTEDA. For more information, ask your healthcare provider or pharmacist.

If you notice a change in your usual bleeding pattern that worries you, or your heavy bleeding continues, contact your healthcare provider right away. This may be a sign of a more serious condition.

Call your healthcare provider for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088. You may also report side effects to Amring Pharmaceuticals Inc. at 1-844-Amring1 (1-844-267-4641).

How should I store LYSTEDA?

Store LYSTEDA at room temperature between 59°F to 86°F (15°C to 30°C).

Keep LYSTEDA and all medicines out of the reach of children.

General information about LYSTEDA

Medicines are sometimes prescribed for conditions that are not mentioned in Patient Information Leaflets. Do not use LYSTEDA for a condition for which it was not prescribed. Do not give LYSTEDA to other people, even if they have the same symptoms that you have. It may harm them.

This patient information leaflet summarizes the most important information about LYSTEDA. If you would like more information about LYSTEDA, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about LYSTEDA that is written for healthcare professionals.

What are the ingredients of LYSTEDA?

Active ingredient: tranexamic acid

Inactive ingredients: microcrystalline cellulose, colloidal silicon dioxide, pregelatinized corn starch, povidone, hypromellose, stearic acid, and magnesium stearate.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured for:

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Berwyn, PA 19312

www.amringusa.com



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Manufactured by:

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Atlanta, GA 30318

Rev. 12/2020

PRINCIPAL DISPLAY PANEL - 650 mg Tablet Bottle Label

Rx only

NDC 69918-300-30

Lysteda®

(tranexamic acid, USP) tablets

650 mg
30 tablets



LYSTEDA

tranexamic acid tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:69918-300
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
TRANEXAMIC ACID (UNII: 6T84R30KC1) (TRANEXAMIC ACID - UNII: 6T84R30KC1)	TRANEXAMIC ACID	650 mg

Inactive Ingredients

Ingredient Name	Strength
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
STARCH, CORN (UNII: O8232NY3SJ)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
STEARIC ACID (UNII: 4ELV7Z65AP)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

Product Characteristics

Color	white	Score	score with uneven pieces
Shape	OVAL	Size	17mm
Flavor		Imprint Code	FP650
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:69918-300-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	05/17/2010	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA022430	05/17/2010	

Labeler - Amring Pharmaceuticals Inc. (079843051)**Establishment**

Name	Address	ID/FEI	Business Operations
Mikart, LLC		013322387	manufacture(69918-300)

Establishment

Name	Address	ID/FEI	Business Operations
Mikart, LLC		030034847	pack(69918-300)

Revised: 12/2021

Amring Pharmaceuticals Inc.