CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

22-430/s002

Trade Name: LYSTEDA tablets.

Generic Name: tranexamic acid

Sponsor: Ferring Pharmaceuticals

Approval Date: August 6, 2004

Indication: Treatment of cyclic heavy menstrual bleeding.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-430/s022

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-430/s022

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022430/S-002

SUPPLEMENT APPROVAL

Ferring Pharmaceuticals Inc.
Attention: John B. Berryman, M.S.
Senior Director Regulatory Affairs
4 Gatehall Drive, 3rd floor
Parsippany, NJ 07054

Dear Mr. Berryman:

Please refer to your Supplemental New Drug Application (sNDA) dated December 2, 2010, and received December 3, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for LYSTEDA (tranexamic acid) tablets 650 mg.

We acknowledge receipt of your amendments dated December 15, 2010, and March 29, 2011.

This supplemental new drug application proposes changes to the WARNING AND PRECAUTIONS section of Physician Labeling and to Patient Labeling. These changes are related to the risk of thromboembolic events, particularly the risk in women who are obese or smoke cigarettes and are using both LYSTEDA and a hormonal contraceptive. New language also states that LYSTEDA should not be used in women taking more than the approved dose of a hormonal contraceptive.

Other changes include:

- Addition of "ligneous conjunctivitis" to Highlights (WARNING AND PRECAUTIONS)
- Rearranging and formatting changes to the WARNING AND PRECAUTIONS section of Physician Labeling to include several topics under the general header of 5.1 Thromboembolic Risk
- Placing "ligneous conjunctivitis" in a separate section in the WARNING AND PRECAUTIONS section of Physician Labeling
- Other formatting and editorial changes

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text with the minor editorial revisions listed below:

- Changed "RECENT CHANGES" to "RECENT MAJOR CHANGES" in HIGHLIGHTS section.
- Revision date changed to April 2011.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling text for the package insert with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Karl Stiller, Regulatory Project Manager, at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

SCOTT E MONROE
04/06/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-430/s022

LABELING

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.*

----------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: 4/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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 ≤ 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 ≤ 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

4 CONTRAINDICATIONS

4.1 Thromboembolic Risk

Do not prescribe LYSTEDA to women who are known to have 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)

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

4.2 Hypersensitivity to Tranexamic Acid

Do not prescribe LYSTEDA to women 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

Concomitant Use of Hormonal Contraceptives

Combination 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 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 [see *Contraindications (4.1)* and *Drug Interactions (7.1)*].

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. There have been US postmarketing reports of venous and arterial thrombotic events in women who have used LYSTEDA concomitantly with combined hormonal contraceptives. Women using hormonal contraception, especially those who are obese or smoke, 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.

Factor IX Complex Concentrates or Anti-Inhibitor Coagulant Concentrates

LYSTEDA is not recommended for women 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)*].

All-Trans Retinoic Acid (Oral Tretinoin)

Exercise caution when prescribing LYSTEDA to women 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)*].

Ocular Effects

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 retinal venous or arterial occlusion.

5.2 Severe Allergic Reaction

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.

5.3 Subarachnoid Hemorrhage

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

5.4 Ligneous Conjunctivitis

Ligneous conjunctivitis has been reported in patients taking tranexamic acid. The conjunctivitis resolved following cessation of the drug.

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.

Short-term Studies

The safety of LYSTEDA in the treatment of heavy menstrual bleeding (HMB) was studied in two randomized, double-blind, placebo-controlled studies [see *Clinical Studies (14)*]. One study compared the effects of two doses of LYSTEDA (1950 mg and 3900 mg given daily 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. A second study 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. In both studies, subjects were generally healthy women who had menstrual blood loss of $\geq$ 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 BMI of approximately 32 kg/m^2. On average, subjects had a history of HMB 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.

The rates of discontinuation due to adverse events during the two clinical trials were comparable between LYSTEDA and placebo. In the 3-cycle study, the rate in the 3900 mg LYSTEDA dose group was 0.8% as compared to 1.4% in the placebo group. In the 6-cycle study, the rate in the LYSTEDA group was 2.4% as compared to 4.1% in the placebo group. 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.

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

Table 2. Adverse Events Reported by ≥ 5% of Subjects Treated with LYSTEDA and More Frequently in LYSTEDA-treated Subjects

	LYSTEDA 3900 mg/day n (%) (N=232)	Placebo n (%) (N=139)
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 & 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

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 events. 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 events. 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 events 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 tranexamic acid. 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.

Based on US and worldwide postmarketing reports, the following have been reported in patients receiving tranexamic acid for various indications:

- Nausea, vomiting, and diarrhea
- Allergic skin reactions
- Anaphylactic shock and anaphylactoid reactions
- Thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, cerebral thrombosis, acute renal cortical necrosis, and central retinal artery and vein obstruction)
- Impaired color vision and other visual disturbances
- Dizziness

7 DRUG INTERACTIONS

No drug-drug interaction studies were conducted with LYSTEDA.

7.1 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 *Clinical Pharmacology (12.3)*].

7.2 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 woman taking LYSTEDA therapy requires tissue plasminogen activators.

7.3 Factor IX Complex Concentrates or Anti-Inhibitor Coagulant Concentrates

LYSTEDA is not recommended for women 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 *Clinical Pharmacology (12.3)*].

7.4 All-Trans Retinoic Acid (Oral Tretinoin)

Exercise caution when prescribing LYSTEDA to women 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)* and *Clinical Pharmacology (12.3)*].

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^2 (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. LYSTEDA has not been studied in adolescents under age 18 with heavy menstrual bleeding.

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

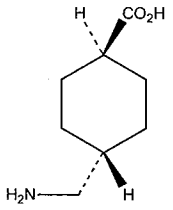
The effect of hepatic impairment on the pharmacokinetics of LYSTEDA has not been studied. Because only a small fraction of the drug is metabolized, dosage adjustment in patients with hepatic impairment is not needed [see *Clinical Pharmacology (12.3)*].

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. 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 $C_8H_{15}N0_2$ and the molecular weight is 157.2.

Tranexamic acid tablets are provided as white oval-shaped tablets and are not scored. Each tablet is debossed with the marking "XP650." 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 μmol/L) and 1 with high affinity (K_d = 1.1 μmol/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 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_{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 (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 5th 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_{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
[a] $AUC_{0\text{-}tau}$ (mcg·h/mL) = area under the drug concentration curve from time 0 to 8 hours
[b] 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. LYSTEDA has not been studied in adolescents under age 18 with heavy menstrual bleeding.

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 (5.4)* 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 (5.5)* 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.

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 doses 1, 2 and 4 times the recommended human oral dose of 3900 mg/day. In a perinatal-postnatal study in rats, tranexamic acid had no adverse effects on pup viability, growth or development when

administered from gestation day 6 through postnatal day 20 at doses 1, 2 and 4 times the recommended human oral dose of 3900 mg/day.

The dose multiples referenced above are based on body surface area (mg/m^2). Actual daily doses in rats were 300, 750 or 1500 mg/kg/day.

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

The efficacy and safety of LYSTEDA in the treatment of heavy menstrual bleeding (HMB) was demonstrated in one 3-cycle treatment and one 6-cycle treatment, randomized, double-blind, placebo-controlled study [see *Adverse Reactions (6)*]. 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 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/m^2. 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.

14.1 Three-Cycle Treatment Study

This study compared the effects of two doses of LYSTEDA (1950 mg and 3900 mg given daily 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 LYSTEDA 1950 mg/day subjects, 112 LYSTEDA 3900 mg/day subjects and 67 placebo subjects took at least one dose of study drug and had post-treatment data available.

Results are shown in Table 4. 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 MBL

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 placebo (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

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

14.2 Six-Cycle Treatment Study

This study compared the effects of LYSTEDA 3900 mg/day given daily for up to 5 days during each menstrual period versus placebo on MBL over a 6-cycle treatment duration. Of the 187 evaluable subjects, 115 LYSTEDA subjects and 72 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 MBL

Treatment Arm	N	Baseline Mean MBL (mL)	Least Squares 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

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

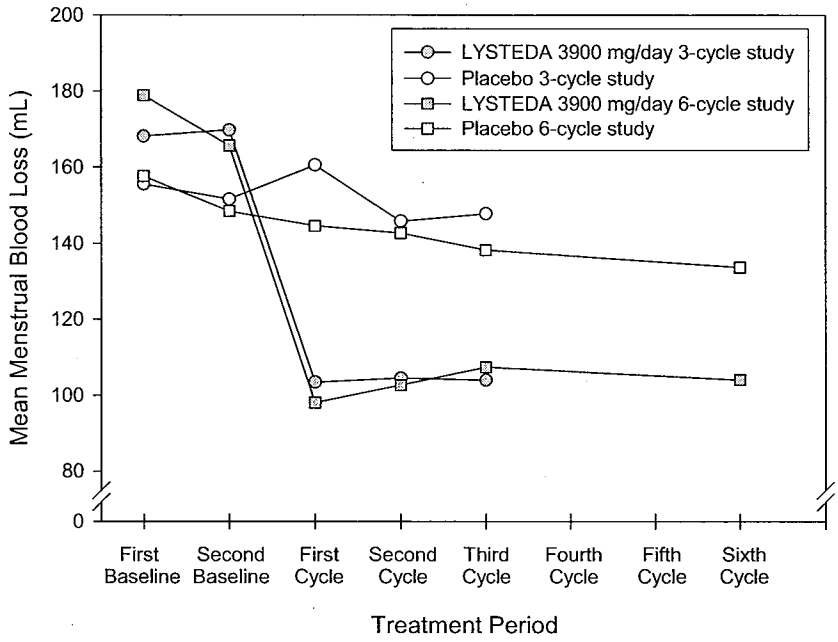
[d] Responders are defined as subjects who experienced a reduction from baseline in frequency of large stains

[e] Non-significant difference versus placebo

14.3 MBL Results over Time

The efficacy of LYSTEDA 3900 mg/day over 3 menstrual cycles and over 6 menstrual cycles was demonstrated versus placebo in the double-blind, placebo-controlled efficacy studies (see Figure 1). The change in MBL from baseline was similar across all post-baseline treatment cycles.

Figure 1: MBL Levels over Duration of Therapy



16 HOW SUPPLIED/STORAGE AND HANDLING

LYSTEDA (tranexamic acid) tablets are provided as white oval-shaped tablets. Each tablet is debossed with the marking "XP650"and are supplied as:

Quantity	Package Type	NDC Number
30 tablets	HDPE bottle	55566-2100-2
30 tablets	Carton containing 5 blister cards with 6 tablets per card	55566-2100-6
100 tablets	HDPE bottle	55566-2100-1
500 tablets	HDPE bottle	55566-2100-5

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

See FDA-approved patient labeling (Patient Information)

Instruct patients that the usual schedule is to take two tablets with liquids, three times a day during menstruation. Patients should be instructed not to exceed 3 doses (6 tablets) in a 24-hour period or to take for more than 5 days in any menstrual cycle.

Inform patients that they should immediately stop LYSTEDA if they notice any eye symptoms or change in their vision. Instruct them to report any such problems promptly to their physician and to follow-up with an ophthalmologist for a complete ophthalmic evaluation, including dilated retinal examination of the retina.

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).

Instruct patients that common side effects of LYSTEDA include headache, sinus and nasal symptoms, back pain, abdominal pain, musculoskeletal pain, joint pain, muscle cramps, migraine, anemia and fatigue.

Advise patients to contact their healthcare provider if their heavy menstrual bleeding symptoms persist or worsen.

Remind patients to read the Patient Labeling carefully.

PATIENT INFORMATION
LYSTEDA (pronounced *lye-sted-a*) tranexamic acid tablets

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.

Who should not take LYSTEDA?

Do not take LYSTEDA if you:

- 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 hormones** (like a birth control pill, patch, vaginal ring or intrauterine device). Also tell your healthcare provider if you are taking higher than your normally-prescribed dose of birth control. Using hormonal products along with LYSTEDA, especially if you are overweight or smoke, may increase your chance of having a serious blood clot, stroke, or heart attack.
- 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 clot
- 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. The risk of serious blood clots may be increased when LYSTEDA is taken with:
    - hormonal contraceptives, especially if you are taking higher than your normal dose of birth control, are overweight, or if you smoke cigarettes
    - medicines used to help your blood clot
    - 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 Ferring Pharmaceuticals Inc. at 1-888-FERRING (1-888-337-7464).

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. For more information, go to www.lysteda.com or call 1-888-FERRING (1-888-337-7464).

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.

RX only

Manufactured for:
Ferring Pharmaceuticals Inc.
Parsippany, NJ 07054

By: Mikart, Inc.
Atlanta, GA 30318

Rev. 4/2011

FERRING
PHARMACEUTICALS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-430/s002

MEDICAL REVIEW(S)

Clinical Review Memo: Labeling Supplement

NDA Number:	022430/Labeling Supplement - Changes Being Effected (CBE)
Name of Drug:	LYSTEDA (tranexamic acid) Tablets
Applicant:	Ferring Pharmaceuticals Inc.
Submit Dates:	12-01 (SD #040) and 12-21-2010; SD #045 on 12-28-10
Reviewer:	Daniel Davis, MD
Review Date:	March 4, 2011

Background:
The original labeling for Lysteda was approved on November 13, 2009.

In the 12-01-10 submission, the Sponsor stated the following:
"Proposed changes to the WARNINGS AND PRECAUTIONS section of the PI, and related Highlights and Patient Information sections, are being made in response to post-marketing adverse event reports involving suspected thromboembolic events in patients prescribed LYSTEDA (previously filed as expedited reports to NDA 22-430). In addition, the rearrangement of other warnings from section 5 are proposed (wording unchanged) that groups these under the heading Thromboembolic Risk, since these all relate to this mechanism. The unrelated ocular warning about Ligneous Conjunctivitis is consequently separated out as a stand-alone risk unrelated to the thrombotic mechanism.

(b) (4)

(b) (4) rather than only the term "cyclic heavy menstrual bleeding" (often used in more recent publications). We have received several hundred requests for information about our product from healthcare practitioners by our medical information group, (b) (4) We believe that its inclusion will help reduce confusion and improve understanding.

Also, we have found that, in disagreement with the recommendations on avoiding redundancy from the draft FDA Guidance for Industry: Labeling for Human Prescription Drug and Biological Products — Implementing the New Content and Format Requirements, the content of sections 7 and 8 on DRUG INTERACTIONS and USE IN SPECIFIC POPULATIONS is repeated verbatim in the section on CLINICAL PHARMACOLOGY: Pharmacokinetics. Because of this we have removed these redundant sections."

The Division and reviewers from the Office of Clinical Pharmacology and the Division of Pharmacovigilance 2 held a **teleconference with the Sponsor on 12-14-10** to discuss the following topics:

- Status of the labeling supplement as a Prior Approval (PA) supplement and not a CBE because the Sponsor has requested a change in the (b) (4) (b) (4)
- Proposed label changes; due to the Division's concern about promptly revising the Warnings labeling to reflect postmarketing safety reports, the Sponsor was asked to defer all other revisions to a future supplement
- The possibility of adding new contraindications and/or a Boxed Warning
- Rearranging some subsections of the label, especially in Warnings and Precautions, Drug Interactions, and Pharmacokinetics
- Adding the pharmacologic class of "antifibrinolytic" to the Indications and Usage statement in Highlights
- Need for a Dear Healthcare Provider letter

On 12-16-10, SD #044, the Sponsor submitted all copies of the MedWatch reports and a summary table for the recent postmarketing thromboembolic serious adverse events (SAEs). On 12-21-10, the Division sent a revised label to the Sponsor showing all the changes recommended in the label. The most recent label submitted by the Sponsor is found in the FDA electronic document room (EDR) as SD #045, stamp date 12-28-10. It appears that the Sponsor agrees with the proposed changes made by the Division on 12-21-10.

The following documents are included in the recent submissions:

- Marked up and clean versions of the United States Package Insert and Detailed Patient Labeling incorporating all of the revisions
- Support Document (SD) #044 with the recent MedWatch reports for postmarketing thromboembolic SAEs.
- PADER, SD #041, covering AEs from 8/14/10 to 11/13/10

Clinical Review:

All the above documents were reviewed. Combining data from AERS, the PADER, and SD #044 there were 8 postmarketing thromboembolic SAEs in the US, which included the following:

- 2 strokes: 38 year old (yo) obese woman on Loestrin and a 44 yo woman not on OCs
- 1 intrajugular clot: 31 yo obese non-smoker taking "double dose" of OCs
- 3 DVTs: 69 yo, a 57 yo obese woman not on concomitant medication, and an unknown age woman on hormonal birth control
- 1 bilateral pulmonary embolism (PE) with lower extremity DVT: 44 yo obese woman on Loestrin and IV estrogen
- 1 death (probable PE): 37 yo obese woman on OCs

Although not all cases are associated with OCs, the majority are associated with either obesity or while on OCs, so the Division believes that the label should reflect this postmarketing data. Changes were made in the 5.1 Thromboembolic Risk section under WARNINGS AND PRECAUTIONS. The first subsection in 5.1 now reads as follows:

Concomitant Use of Hormonal Contraceptives
Combination 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 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 [see Contraindications (4.1) and Drug Interactions (7.1)].

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. There have been US postmarketing reports of venous and arterial thrombotic events in women who have used LYSTEDA concomitantly with combined hormonal contraceptives. Women using hormonal contraception, especially those who are obese or smoke, 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.

In addition, the rearrangement of three other warnings from section 5 are added (wording unchanged) under the heading 5.1 Thromboembolic Risk, since these all relate to this mechanism. The unrelated ocular warning about Ligneous Conjunctivitis (now changed to 5.4) is consequently separated out as a stand-alone risk unrelated to the thrombotic mechanism.

The Division rejected the request to (b) (4) for the treatment of cyclic heavy menstrual bleeding." This is primarily based on the fact that two other products approved for heavy menstrual bleeding do not use (b) (4) (b) (4) their approved indications. In addition, the focus of this labeling supplement was on communicating new safety information, not on revising the indication.

Reviewer's comments:

The proposed changes to the Lysteda label are supported by the sponsor's submitted rationale and documents. Agreement was reached between the Division and the Sponsor on the label changes. Re-ordering of subsection within a major heading simply improves the readability of the label while not changing the substance. The major and most important change is in the Subsection 5.1 Thromboembolic Risk, which now reflects the safety concern for women on Lysteda who are also using hormonal contraceptives, especially those who are obese or smoke.

If further SAEs are reported that raise the level of safety concern, especially for thromboembolic events, then future changes to the label may be warranted. The need for a Dear Healthcare Provider has been discussed with the Sponsor and the general agreement is that this will be issued soon after the label changes are finalized.

Final Clinical Recommendation:

The labeling supplement (SD-040), originally received (stamp date) by the Division on 12-03-10, has been reviewed and final changes agreed to. I do not recommend any further changes. The label submitted by the Sponsor dated January 14, 2011, is acceptable as a revision of the original approved label dated November 13, 2009.

Daniel Davis, MD
3-04-11

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

/s/

DANIEL DAVIS
03/04/2011
Clinical labeling review

LISA M SOULE
03/04/2011
I concur with Dr. Davis' conclusions and recommendations.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-430/s002

CHEMISTRY REVIEW(S)

Chemistry Review: 1	Division: HFD-580	NDA Number: 22-430

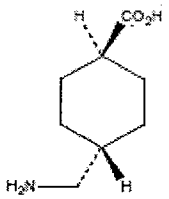
Name and Address of Applicant:	4. Supplement(s):
Ferring Pharmaceutical, Inc 4 Gatehall Drive Parsippany, NJ 07054	**Number:** 002 (SDN 40) **Date(s): 03-Dec-2010**
5. Name of Drug: Lysteda	**6. Nonproprietary name:** Tranexamic acid

7.Supplement Provides for	8. Amendment(s):
Change to the WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS, USE IN SPECIFIC POPULATIONS, and CLINICAL PHARMACOLOGY sections of the Physician's Insert (PI).	NA

9. Pharmacological Category:	10. How Dispensed:	11. Related Documents:
Antifibrinolytic	R_x	N/A

12. Dosage Form:	13. Potency:
Tablet	650 mg

14. Chemical Name and Structure:



trans-4-Aminomethyl-cyclohexanecarboxylic acid

15. Comments

This labeling supplement seeks approval to change the WARNINGS AND PRECAUTIONS section of the PI in response to post-marketing adverse event reports involving suspected thromboembolic events. In addition, other warnings are rearranged without a change in wording. Sponsor also seeks to (b) (4) (b) (4) "cyclic heavy menstrual bleeding" (b) (4) indication statement. Sponsor also seeks to delete redundant wording in the DRUG INTERACTIONS, USE IN SPECIFIC POPULATIONS, and CLINICAL PHARMACOLOGY sections. There are no changes to the CMC-related sections of the label.

16. Conclusion:

This Supplement is recommended for approval from CMC perspective. Because this is an OND-managed supplement, any correspondence with the sponsor will be made by the OND PM.

17. Name:	Signature:	Date:
Donna F. Christner, Ph.D.		**22-Dec-2010**
18. Concurrence:	**Signature:**	**Date:**
Thomas Oliver, Ph.D.		

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/s/

DONNA F CHRISTNER
12/27/2010

THOMAS F OLIVER
01/03/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-430/s002

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY REVIEW

Date: January 20, 2011
NDA #/SS#/date: NDA 022430, Supplement 2, eCTD #0037, SD#40, 12/03/2010
Reviewer: Kimberly Hatfield, PhD
Secondary/Expert Reviewer: Alexander Jordan, PhD

Sponsor: Ferring Pharmaceuticals, Inc.
Drug: Lysteda (tranexamic acid)
Indication: Treatment of cyclic heavy menstrual bleeding

RE: Labeling supplement to make changes in response to post-marketing adverse event reports

Background:
Lysteda was approved in November 2009 for the treatment of cyclic heavy menstrual bleeding. The current supplement seeks approval to 1) make changes to the WARNINGS AND PRECAUTIONS section of the PI, and related Highlights and Patient Information sections in response to post-marketing adverse event reports involving suspected thromboembolic events in patients prescribed Lysteda; 2) rearrange other warnings without a change in wording; 3) (b) (4) the indication statement; and 4) delete redundant wording in the DRUG INTERACTIONS, USE IN SPECIFIC POPULATIONS, and CLINICAL PHARMACOLOGY sections.

Nonclinical Review of Labeling Supplement:
There are no changes proposed for Section 8 USE IN SPECIFIC POPULATIONS (8.1 Pregnancy and 8.3 Nursing Mothers) or Section 13 NONCLINICAL TOXICOLOGY, which primarily contain nonclinical information. The deletion of redundant wording that is proposed occurs in Section 12.3 (SPECIFIC POPULATIONS), where the same information from Sections 8.1-8.4 is repeated.

It was noted that the original approval labeling did not list a pharmacologic class for Lysteda in the Indications and Usage section of Highlights, though it was listed in Section 11 DESCRIPTION. The Sponsor proposed the following change (*italics*) to Highlights:

Original statement: LYSTEDA (tranexamic acid) Tablets is indicated for the treatment of cyclic heavy menstrual bleeding. (1)

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

'Antifibrinolytic' is an approved pharmacological class. We concur with this change.

Conclusions:
This supplement is recommended for approval from a nonclinical perspective, pending the addition of pharmacologic class to the Highlights portion of the label.

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/s/

KIMBERLY P HATFIELD
02/11/2011

ALEXANDER W JORDAN
02/11/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-430/s002

OTHER REVIEW(S)

Division of Reproductive and Urologic Products

REGULATORY PROJECT MANAGER LABELING REVIEW ADDENDUM

Application: NDA 022430/S-002 Labeling Supplement

Name of Drug: Lysteda (tranexamic acid) Tablets

Applicant: Ferring Pharmaceuticals Inc.

Labeling Reviewed

Description	Submission Date	Received Date
Draft Labeling	December 21, 2010	January 13, 2011
Draft Labeling	March 29, 2011	March 29, 2011

Background and Summary Description: On December 3, 2010, Ferring Pharmaceuticals Inc. submitted a new supplement proposing changes to the WARNINGS AND PRECAUTIONS section of the package insert (PI), (b) (4) to the indication statement, and removal of redundant labeling sections. Following labeling negotiations, the Applicant submitted draft labeling incorporating agreed-upon labeling changes on January 13, 2011.

On March 23, 2011, the Division sent additional proposed labeling changes to Ferring to update the HIGHLIGHTS Section to reflect labeling changes accepted on January 13, 2011, remove 17.1 and 17.2 from FULL PRESCRIBING INFORMATION: CONTENTS and FULL PRESCRIBING INFORMATION, add left margin vertical markers next to section 5.1, and update revision dates to the current month/year (March 2011).

Ferring accepted the Division's proposed changes by email on March 29, 2011.

The Division contacted Ferring (John Berryman, Senior Director Regulatory Affairs) on April 5, 2011, and received concurrence on the additional two minor labeling changes that will be included in the labeling attached to the action letter. The changes are 1) correcting "RECENT CHANGES" in the HIGHLIGHTS section to "RECENT MAJOR CHANGES," and 2) changing the revision dates to the current month/year (April 2011).

Recommendations

The proposed labeling with minor editorial changes listed above provides for changes to the Package Insert for NDA 022430/S-002 that are consistent with labeling changes negotiated with FDA. An approval letter is recommended.

Karl Stiller, R.Ph.

Regulatory Project Manager — Date

Margaret Kober, R.Ph., M.P.A.

Chief, Project Management Staff — Date

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/s/

KARL J STILLER
04/05/2011

MARGARET M KOBER
04/05/2011

Division of Reproductive and Urologic Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 022430/S-002 Labeling Supplement

Name of Drug: Lysteda (tranexamic acid) Tablets

Applicant: Ferring Pharmaceuticals Inc.

Labeling Reviewed

Description	Submission Date	Received Date
Last Approved Labeling (approved November 13, 2009.)	November 24, 2009	November 24, 2009
New Supplement	December 3, 2010	December 3, 2010
Draft Labeling	December 21, 2010	January 13, 2011

Background and Summary Description: On December 3, 2010, Ferring Pharmaceuticals Inc. submitted a new supplement proposing changes to the WARNINGS AND PRECAUTIONS section of the package insert (PI), (b) (4) indication statement, and removal of redundant labeling sections. Following labeling negotiations, the Applicant submitted draft labeling incorporating agreed-upon labeling changes on January 13, 2011.

On March 15, 2011, minor Division-proposed edits to the HIGHLIGHTS, Table of Contents, and PATIENT COUNSELING INFORMATION sections (Table 2) were sent to the Applicant. Ferring accepted the proposed changes on March 15, 2011.

Review

Additions to current labeling are shown by **bold underlined** text and deletions are shown by ~~strike-through~~ text

Table 1

Current Approved Language	Language Proposed by Applicant
INDICATIONS AND USAGE LYSTEDA (tranexamic acid) tablets is indicated for the treatment of cyclic heavy menstrual bleeding. (1)	**INDICATIONS AND USAGE** LYSTEDA (tranexamic acid) ~~t~~Tablets is **an antifibrinolytic** indicated for the treatment of cyclic heavy menstrual bleeding. (1)
	ACCEPTABLE per the Medical Officer's Review
WARNINGS AND PRECAUTIONS • Concomitant therapy with hormonal contraceptives may further increase the risk of blood clots, stroke, or myocardial infarction. 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. (5.1) • In case of severe allergic reaction, discontinue LYSTEDA and seek immediate medical attention. (5.2) • Visual or ocular adverse effects may occur with LYSTEDA. Immediately discontinue use if visual or ocular symptoms occur. (5.3) • 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. (5.4, 5.5) • Cerebral edema and cerebral infarction may be caused by use of LYSTEDA in women with subarachnoid hemorrhage. (5.6)	**WARNINGS AND PRECAUTIONS** • (b) (4) **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. (b) (4)**5.1**) • Visual or ocular adverse effects may occur with LYSTEDA. Immediately discontinue use if visual or ocular symptoms occur. (~~5.3~~ **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. (b)**5.3**) (4) • **Ligneous conjunctivitis has been reported in patients taking tranexamic acid. (5.4)**
	ACCEPTABLE per the Medical Officer's Review

DRUG INTERACTIONS Concomitant therapy with tissue plasminogen activators may decrease the efficacy of both LYSTEDA and tissue plasminogen activators. (7.3)	**DRUG INTERACTIONS** Concomitant therapy with tissue plasminogen activators may decrease the efficacy of both LYSTEDA and tissue plasminogen activators (b) (4) **7.2**)
	ACCEPTABLE per the Medical Officer's Review
5 WARNINGS AND PRECAUTIONS 5.1 Hormonal Contraceptives 5.2 Severe Allergic Reaction 5.3 Ocular Effects 5.4 Factor IX Complex Concentrates or Anti-Inhibitor Coagulant Concentrates 5.5 All-Trans Retinoic Acid (Oral Tretinoin) 5.6 Subarachnoid Hemorrhage	**5 WARNINGS AND PRECAUTIONS** (b) (4) **5.1 Thromboembolic Risk** 5.2 Severe Allergic Reaction (b) (4) **5.3 Subarachnoid Hemorrhage** (b) (4) **5.4 Ligneous Conjunctivitis** (b) (4)
	ACCEPTABLE per the Medical Officer's Review
7 DRUG INTERACTIONS 7.1 Hormonal Contraceptives 7.2 Factor IX Complex Concentrates or Anti-Inhibitor Coagulant Concentrates 7.3 Tissue Plasminogen Activators 7.4 All-Trans Retinoic Acid (Oral Tretinoin)	**7 DRUG INTERACTIONS** 7.1 Hormonal Contraceptives (b) **7.2** Tissue Plasminogen Activators (b) **7.3** Factor IX Complex Concentrates or Anti-Inhibitor Coagulant Concentrates 7.4 All-Trans Retinoic Acid (Oral Tretinoin)
	ACCEPTABLE per the Medical Officer's Review
5 WARNINGS AND PRECAUTIONS **5.1 Hormonal Contraceptives** Combination 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, concomitant use of hormonal contraception and LYSTEDA may further	**5 WARNINGS AND PRECAUTIONS** (b) (4) **5.1 Thromboembolic Risk** **Concomitant Use of Hormonal Contraceptives** Combination hormonal contraceptives are known to increase the risk of

exacerbate this increased thrombotic risk. 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.	venous thromboembolism, as well as arterial thromboses such as stroke and myocardial infarction. Because LYSTEDA is antifibrinolytic, (b) (4) (b) (4) **the risk of venous thromboembolism, as well as arterial thromboses such as stroke, may increase further when 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 [see *Contraindications (4.1) and Drug Interactions (7.1)*]**. 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. **There have been US postmarketing reports of venous and arterial thrombotic events in women who have used LYSTEDA concomitantly with combined hormonal contraceptives.** (b) (4) **N**omen using hormonal contraception**, especially those who are obese or smoke,** 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.**
	ACCEPTABLE per the Medical Officer's Review
	Factor IX Complex Concentrates or Anti-Inhibitor Coagulant Concentrates **LYSTEDA is not recommended for women 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)*].**
	ACCEPTABLE per the Medical Officer's Review
	All-Trans Retinoic Acid (Oral Tretinoin)

	Exercise caution when prescribing LYSTEDA to women 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)*].
	ACCEPTABLE per the Medical Officer's Review
	Ocular Effects 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 retinal venous or arterial occlusion.
	ACCEPTABLE per the Medical Officer's Review
5.3 Ocular Effects 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 retinal venous or arterial occlusion. Ligneous conjunctivitis also has been reported in patients taking tranexamic acid. The conjunctivitis resolved following cessation of the drug.	(b) (4) 5.3 Subarachnoid Hemorrhage (b) (4) Cerebral edema and cerebral infarction may be caused by use of LYSTEDA in women with subarachnoid hemorrhage.
	ACCEPTABLE per the Medical Officer's Review

5.4 Factor IX Complex Concentrates or Anti-Inhibitor Coagulant Concentrates LYSTEDA is not recommended for women taking either Factor IX complex concentrates or anti-inhibitor coagulant concentrates because the risk of thrombosis may be increased [see *Drug Interactions (7.2)* and *Clinical Pharmacology (12.3)*].	(b) (4) **5.4 Ligneous Conjunctivitis** (b) (4) **Ligneous conjunctivitis has been reported in patients taking tranexamic acid. The conjunctivitis resolved following cessation of the drug.**
	ACCEPTABLE per the Medical Officer's Review
5.5 All-Trans Retinoic Acid (Oral Tretinoin) Exercise caution when prescribing LYSTEDA to women with acute promyelocytic leukemia taking alltrans 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)*].	(b) (4)
	ACCEPTABLE per the Medical Officer's Review
5.6 Subarachnoid Hemorrhage Cerebral edema and cerebral infarction may be caused by use of LYSTEDA in women with subarachnoid hemorrhage.	(b) (4)
	ACCEPTABLE per the Medical Officer's Review
6.2 Postmarketing Experience The following adverse reactions have been identified from postmarketing experience with tranexamic acid. 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. Based on worldwide postmarketing reports, the following have been reported in patients receiving tranexamic acid for various indications:	**6.2 Postmarketing Experience** The following adverse reactions have been identified from postmarketing experience with tranexamic acid. 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. Based on **US and** worldwide postmarketing reports, the following have been reported in patients receiving tranexamic acid for various

• Nausea, vomiting, and diarrhea • Allergic skin reactions • Anaphylactic shock and anaphylactoid reactions • Thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, cerebral thrombosis, acute renal cortical necrosis, and central retinal artery and vein obstruction) • Impaired color vision and other visual disturbances • Dizziness	indications: • Nausea, vomiting, and diarrhea • Allergic skin reactions • Anaphylactic shock and anaphylactoid reactions • Thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, cerebral thrombosis, acute renal cortical necrosis, and central retinal artery and vein obstruction) • Impaired color vision and other visual disturbances • Dizziness
	ACCEPTABLE per the Medical Officer's Review
7.2 Factor IX Complex Concentrates or Anti-Inhibitor Coagulant Concentrates LYSTEDA is not recommended for women taking either Factor IX complex concentrates or anti-inhibitor coagulant concentrates because the risk of thrombosis may be increased [see *Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)*].	(b) (4) **7.2 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 woman taking LYSTEDA therapy requires tissue plasminogen activators (b) (4) (b) (4)
	ACCEPTABLE per the Medical Officer's Review
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 woman taking LYSTEDA therapy requires tissue plasminogen activators [see *Clinical Pharmacology (12.3)*].	(b) (4) **7.3 Factor IX Complex Concentrates or Anti-Inhibitor Coagulant Concentrates** LYSTEDA is not recommended for women taking either Factor IX complex concentrates or anti-inhibitor coagulant concentrates because the risk of thrombosis may be increased [see *Warnings and Precautions* (b) (4) *and Clinical Pharmacology (12.3)*].
	ACCEPTABLE per the Medical Officer's Review
7.4 All-Trans Retinoic Acid (Oral Tretinoin) Exercise caution when prescribing LYSTEDA to women 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 (5.5)* and *Clinical Pharmacology (12.3)*].	**7.4 All-Trans Retinoic Acid (Oral Tretinoin)** Exercise caution when prescribing LYSTEDA to women 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* (b) (4) ***5.1***) and *Clinical Pharmacology (12.3)*].

	ACCEPTABLE per the Medical Officer's Review
14.1 Three-Cycle Treatment Study This study compared the effects of two doses of LYSTEDA (1950 mg and 3900 mg given daily for up to 5 days during each menstrual period) versus placebo on MBL over a 3-cycle treatment duration. Of the 294 evaluable subjects, 112 LYSTEDA 1950 mg/day subjects, 115 LYSTEDA 3900 mg/day subjects and 67 placebo subjects took at least one dose of study drug and had post-treatment data available.	**14.1 Three-Cycle Treatment Study** This study compared the effects of two doses of LYSTEDA (1950 mg and 3900 mg given daily for up to 5 days during each menstrual period) versus placebo on MBL over a 3-cycle treatment duration. Of the 294 evaluable subjects (b)**115** LYSTEDA 1950 mg/day subjects, (b)**115** LYSTEDA 3900 mg/day subjects and 67 placebo subjects took at least one dose of study drug and had post-treatment data available.
	ACCEPTABLE per the Medical Officer's Review
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 hormones** (like a birth control pill, patch, vaginal ring or intrauterine device). Using hormonal products along with LYSTEDA may increase your chance of having a blood clot, stroke, or heart attack. • 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	**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 hormones** (like a birth control pill, patch, vaginal ring or intrauterine device). **Also tell your healthcare provider if you are taking higher than your normally-prescribed dose of birth control.** Using hormonal products along with LYSTEDA**, especially if you are overweight or smoke,** may increase your chance of having a serious blood clot, stroke, or heart attack. • 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
	ACCEPTABLE per the Medical Officer's Review
What are the possible side effects of LYSTEDA? **LYSTEDA can cause serious side effects, including:** Blood clots. This risk may be increased when LYSTEDA is taken	**What are the possible side effects of LYSTEDA?** **LYSTEDA can cause serious side effects, including:** Blood clots. The risk **of serious blood clots** may be increased

with: • hormonal contraceptives • medicines used to help your blood clot • some medicines used to treat leukemia	when LYSTEDA is taken with: • hormonal contraceptives**, especially if you are taking higher than your normal dose of birth control, are overweight, or if you smoke cigarettes** • medicines used to help your blood clot • some medicines used to treat leukemia
	ACCEPTABLE per the Medical Officer's Review
	Capitalization, updated section references, updated NDC numbers, Applicant name and contact information
	Acceptable minor edits

Table 2

Current Approved Language	Language Proposed by Applicant	Proposed Edits by Division
HIGHLIGHTS OF PRESCRIBING INFORMATION ... **Revised: 11/2009**	**HIGHLIGHTS OF PRESCRIBING INFORMATION** ... **Revised: ~~11/2009~~** (b) (4)	**HIGHLIGHTS OF PRESCRIBING INFORMATION** ... **Revised:** (b) (4) **3/2011**
		CDTL approved/Applicant accepted 3-15-2011
(Table of Contents) **FULL PRESCRIBING INFORMATION: CONTENTS*** **17 PATIENT COUNSELING INFORMATION** 17.1 Information for Patients 17.2 FDA Approved Patient Labeling	(Table of Contents) **FULL PRESCRIBING INFORMATION: CONTENTS*** **17 PATIENT COUNSELING INFORMATION** (b) (4)	(Table of Contents) **FULL PRESCRIBING INFORMATION: CONTENTS*** **17 PATIENT COUNSELING INFORMATION** (b) (4)
		CDTL approved/Applicant accepted 3-15-2011
FULL PRESCRIBING INFORMATION	**FULL PRESCRIBING INFORMATION**	**FULL PRESCRIBING INFORMATION**

17 PATIENT COUNSELING INFORMATION **17.1 Information for Patients** ... **17.2 FDA Approved Patient Labeling** ... **Rev. 12/2010**	**17 PATIENT COUNSELING INFORMATION** (b) (4) ... (b) (4) ... **Rev. ~~11/2009~~** (b) (4)	**17 PATIENT COUNSELING INFORMATION** (b) (4) ... (b) (4) (b) (4)**<u>3/2011</u>**
		CDTL approved/Applicant accepted 3-15-2011

No other substantive changes were noted in the proposed labeling.

Recommendations

The proposed labeling provides for changes to the Package Insert for NDA 022430/S-002 that are consistent with labeling changes negotiated with FDA. An approval letter is recommended.

Karl Stiller, R.Ph.

Regulatory Project Manager — Date

Margaret Kober, R.Ph., M.P.A.

Chief, Project Management Staff — Date

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/s/

KARL J STILLER
03/15/2011

MARGARET M KOBER
03/29/2011

Reference ID: 2918419

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

PRE-DECISIONAL AGENCY MEMO

Date: January 14, 2011

To: Lisa Soule, M.D.
Clinical Team Leader
Division of Reproductive and Urologic Products (DRUP)

Karl Stiller, R.Ph.
Regulatory Project Manager
DRUP

From: Janice Maniwang, Pharm.D., M.B.A., Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Re: **NDA 022430**
DDMAC comments for LYSTEDA (tranexamic acid) tablets DHCP letter

Background

This consult is in response to DRUP's January 13, 2011 request for DDMAC's review on a draft Dear Healthcare Provider letter (DHCP letter) for LYSTEDA (tranexamic acid) tablets (Lysteda). Please note that our comments are based on the draft PI found at EDR Location: \\CDSESUB1\EVSPROD\NDA022430\022430.enx

DDMAC has reviewed the draft DHCP letter and offer the following comments:

1. Please remind the sponsor to refer to 21 CFR §200.5 (Mailing of important information about drugs) regarding the format for recommended mailing of important information regarding drug warnings. We recommend that the distinctive box appear in the letter as well as on the envelope.

2. The draft DHCP letter primarily focuses on the recent changes, specifically the thromboembolic risk, in the product labeling. However, there are several other important risks presented in the PI that should also be conveyed in the DHCP letter. We recommend including a statement in the draft DHCP letter such as, "Please note that this presentation of the risk profile for LYSTEDA is not comprehensive. Please

see the accompanying prescribing information for a complete discussion of the risks associated with LYSTEDA."

DDMAC appreciates the opportunity to provide comments on these materials. If you have any questions, please contact:

- Janice Maniwang (Professional directed materials)
  (301) 796-3821, or janice.maniwang@fda.hhs.gov

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/s/

JANICE L MANIWANG
01/14/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-430/s002

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

For Internal Use Only

Labeling PMR/PMC Discussion**

(Use when sending labeling and/or PMR/PMC comments in writing)

INSTRUCTIONS: Upload email or fax containing language communicating labeling and/or PMR/PMC comments sent to the sponsor/applicant into DARRTS, in place of this form. For language to be used in the email, please reference one of the following templates, as appropriate: Labeling PMR-PMC Discussion Comments (COR-NDAIR-23) or Labeling PMR-PMC Discussion Comments (COR-SNDAIR-08)

From: John.Berryman@ferring.com [mailto:John.Berryman@ferring.com]
Sent: Tuesday, March 15, 2011 10:03 AM
To: Stiller, Karl
Subject: RE: NDA 022430/S-002 Division-Proposed Labeling Edits

Thank you Karl!
The changes as shown in the table you provided, relating to the Patient Counseling Information, are acceptable.
Kindly yours,
John

John B. Berryman
Senior Director, Regulatory Affairs
Ferring Pharmaceuticals, Inc.
Tel. 973-796-1746
Fax 973-796-1694
Cell 973-610-6626
Email john.berryman@ferring.com

From: Stiller, Karl [mailto:Karl.Stiller@fda.hhs.gov]
Sent: Tuesday, March 15, 2011 8:52 AM
To: Berryman, John
Subject: NDA 022430/S-002 Division-Proposed Labeling Edits

Mr. Berryman,

Per my voicemail from this morning, the table below illustrates the changes proposed by the Division for the Lysteda labeling. Please reply to this email and indicate whether the proposed changes are acceptable. Changes to approved and proposed labeling are shown by underlined text and deletions are shown by ~~strike-through~~ text.

Current Approved Language	Language Proposed by Applicant	Proposed Edits by Division
HIGHLIGHTS OF PRESCRIBING INFORMATION ... **Revised: 11/2009**	**HIGHLIGHTS OF PRESCRIBING INFORMATION** ... **Revised: ~~11/2009~~** (b) (4)	**HIGHLIGHTS OF PRESCRIBING INFORMATION** ... **Revised:** (b) (4) **3/2011**
(Table of Contents) **FULL PRESCRIBING INFORMATION: CONTENTS*** **17 PATIENT COUNSELING INFORMATION** 17.1 Information for Patients 17.2 FDA Approved Patient Labeling	(Table of Contents) **FULL PRESCRIBING INFORMATION: CONTENTS*** **17 PATIENT COUNSELING INFORMATION** (b) (4)	(Table of Contents) **FULL PRESCRIBING INFORMATION: CONTENTS*** **17 PATIENT COUNSELING INFORMATION** (b) (4)
FULL PRESCRIBING INFORMATION **17 PATIENT COUNSELING INFORMATION** **17.1 Information for Patients** ... **17.2 FDA Approved Patient Labeling** ... **Rev. 12/2010**	**FULL PRESCRIBING INFORMATION** **17 PATIENT COUNSELING INFORMATION** (b) (4) **~~Rev. 11/2009~~**	**FULL PRESCRIBING INFORMATION** **17 PATIENT COUNSELING INFORMATION** (b) (4) **Rev.** (b) (4) **3/2011**

LCDR Karl Stiller, R.Ph.
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
301-796-1993

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/s/

KARL J STILLER
03/15/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DDMAC-RPM	Division of Reproductive and Urologic Products Karl Stiller, Project Manager 301-796-1993

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
January 13, 2011		022430	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Lysteda (tranexamic acid)	Standard	Antifibrinolytic drug	(Generally 1 week before the wrap-up meeting) ASAP

NAME OF FIRM:	
Ferring Pharmaceuticals Inc.	PDUFA Date: None

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☐ PACKAGE INSERT (PI)
☐ PATIENT PACKAGE INSERT (PPI)
☐ CARTON/CONTAINER LABELING
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☐ IND
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☐ LABELING REVISION

XX DHCP Letter Review

EDR link to submission:

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

Ferring Pharmaceuticals Inc. provided a Dear Healthcare Provider letter for review and comment from DRUP. Edits from DRUP are included in the attached letter. DRUP is now requesting input from DDMAC on the proposed letter. A copy of the letter with tracked changes from DRUP was sent separately via email to DDMAC.

SIGNATURE OF REQUESTER Karl Stiller 301-796-1993

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) XX eMAIL ☐ HAND

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/s/

KARL J STILLER
01/13/2011

Reference ID: 2891552

MEMORANDUM

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

DATE: December 14, 2010

TO: Ferring Pharmaceuticals Inc.

THROUGH : John Berryman, M.S., Senior Director Regulatory Affairs

FROM: FDA/CDER/DRUP

SUBJECT: MedWatch data information request

APPLICATION/DRUG: NDA 022430/S-002 Lysteda (tranexamic acid) tablets, 650 mg

The following request for additional information was sent to Ferring regarding adverse events included in their December 3, 2010, supplement.

From: Stiller, Karl
Sent: Tuesday, December 14, 2010 2:44 PM
To: 'John.Berryman@ferring.com'
Subject: NDA 022430/s-002 Information Request

Mr. Berryman:

We request that you provide additional information regarding MedWatch reports.

1) Search for all post-marketing reports for Lysteda using the following Standardized MedDRA Queries (SMQs):

- Embolic and thrombotic events, arterial
- Embolic and thrombotic events, venous
- Embolic and thrombotic events, vessel type unspecified.

2) Search for all post-marketing reports for Lysteda with a fatal outcome

We don't have a preference for the format for the search results (MedWatch vs. line listing in Excel), whatever is quickest. Please submit the search results to the Application by December 17, 2010.

LCDR Karl Stiller, R.Ph.
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
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KARL J STILLER
12/14/2010

The review division has determined that NDA 022430/S-002 is a Prior Approval Supplement.

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/s/

KARL J STILLER
12/13/2010