CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 202286

Name: Tranexamic Acid Tablets, 650 mg

Sponsor: Apotex Inc.

Approval Date: January 27, 2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202286

CONTENTS

Reviews / Information Included in this Review	
Approval Letter	**X**
Tentative Approval Letter	**X**
Labeling	**X**
Labeling Review(s)	**X**
Medical Review(s)	
Chemistry Review(s)	**X**
Bioequivalence Review(s)	**X**
Statistical Review(s)	
Microbiology Review(s)	
Other Review(s)	
Administrative & Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202286

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 202286

Apotex Corp.
U.S. Agent for Apotex Inc.
Attention: Kiran Krishnan
Vice President, U.S. Regulatory Affairs
2400 North Commerce Parkway, Suite 400
Weston, FL 33326

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated August 31, 2010, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Tranexamic Acid Tablets, 650 mg.

Reference is also made to the Tentative Approval and Complete Response letters issued by this office on August 10, 2012, and March 1, 2013, respectively. We acknowledge receipt of your amendments dated September 13, September 16, September 17, and October 21, 2013.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Tranexamic Acid Tablets, 650 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Lysteda Tablets, 650 mg, of Ferring Pharmaceuticals AS (Ferring). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA.

The RLD upon which you have based your ANDA, Ferring's Lysteda Tablets, is subject to periods of patent protection. The following patents and their expiration dates are currently listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") for this drug product:

U.S. Patent Number	Expiration Date
7,947,739 (the '739 patent)	March 4, 2025
8,022,106 (the '106 patent)	March 4, 2025
8,273,795 (the '795 patent)	March 4, 2025
8,487,005 (the '005 patent)	March 4, 2025

Your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each of these patents is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Tranexamic Acid Tablets, 650 mg, under this ANDA. You have notified the agency that Apotex Inc. complied with the requirements of section 505(j)(2)(B)of the Act. The agency notes that these patents were submitted to the agency after submission of your ANDA and therefore litigation, if any, with respect to any of these patents creates no statutory stay of approval.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

The Generic Drug User Fee Amendments of 2012 (GDUFA)(Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). 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 via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

ROBERT L WEST

01/27/2014

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202286

TENTATIVE APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 202286

Apotex Corp.
U.S. Agent for: Apotex, Inc.
Attention: Kiran Krishnan
Director, North American Regulatory Affairs
2400 North Commerce Parkway, Suite 400
Weston, Florida 33326

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated August 31, 2010, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Tranexamic Acid Tablets, 650 mg.

Reference is made to your amendments dated November 3, 2010; April 14, September 9, September 16, and October 13, 2011; and March 2, March 6, and June 13, 2012. We also acknowledge receipt of your correspondences dated May 23, May 24, May 25, May 26, May 27, October 14, October 17, and November 1, 2011; and February 13, 2012, addressing patent issues associated with this ANDA.

We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your ANDA at this time because of the exclusivity issue noted below. Therefore, the ANDA is **tentatively approved**. This determination is based upon information available to the agency at this time (i.e., information in your ANDA and the status of current good manufacturing practice (cGMP) at the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention. This letter does not address issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The reference listed drug (RLD) upon which you have based your ANDA, Lysteda Tablets, 650 mg, of Ferring Pharmaceuticals, Inc., is subject to a period of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent Nos. 7,947,739 (the '739 patent) and 8,022,106 (the '106 patent) are both scheduled to expire on March 4, 2025. Your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each of these patents is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Tranexamic Acid Tablets, 650 mg, under this ANDA. You have notified the agency that Apotex, Inc. (Apotex) complied with the requirements of section 505(j)(2)(B) of the Act. The '739 and '106 patents were not listed when you submitted your ANDA; litigation with respect to either of these patents will not give rise to a stay of approval under the Act.

However, we are unable to fully approve your ANDA at this time because of the RLD's unexpired exclusivity (new dosage form). This exclusivity expires on November 13, 2012.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

To reactivate your ANDA prior to final approval, please submit a "MINOR AMENDMENT – FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your ANDA will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, or a settlement or licensing agreement, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a MINOR AMENDMENT – FINAL APPROVAL REQUESTED.

In addition to the amendment requested above, the agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval

status of your ANDA, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' cGMP are subject to agency review before final approval of the ANDA will be made. Such changes should be categorized as representing either “major” or “minor” changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the Act. Also, until the agency issues the final approval letter, this drug product will not be deemed to be approved for marketing under section 505 of the Act, and will not be listed in the “Orange Book.”

For further information on the status of this ANDA, or prior to submitting additional amendments, please contact Linda Park, Project Manager, at (240) 276-8536.

Sincerely yours,

{See appended electronic signature page}

Gregory P. Geba, M.D., M.P.H.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

ROBERT L WEST

08/10/2012

Deputy Director, Office of Generic Drugs
for Gregory P. Geba, M.D., M.P.H.

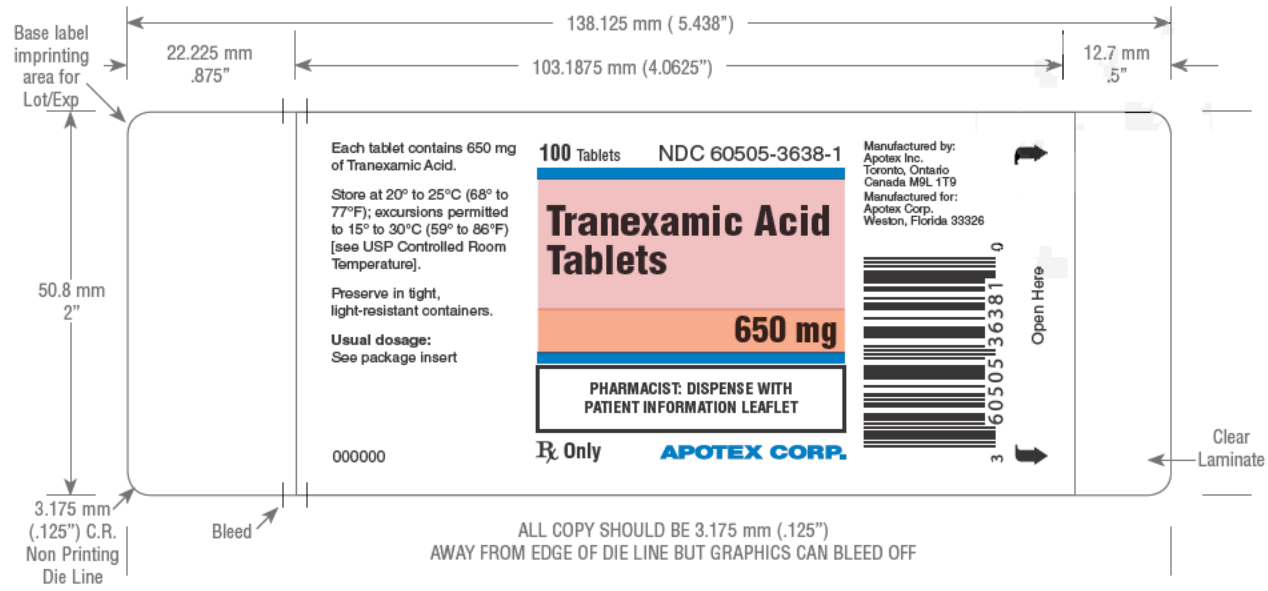
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

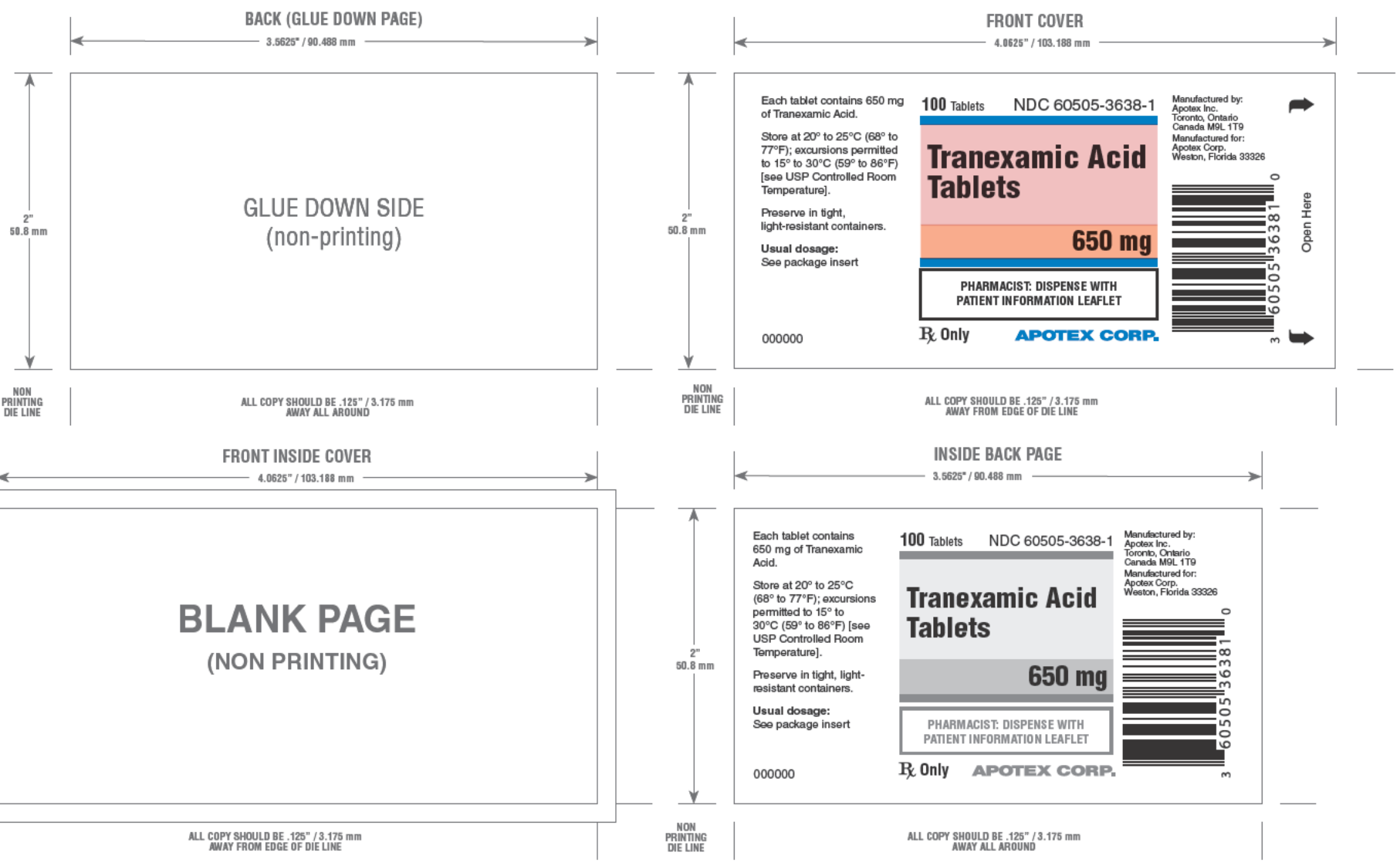
ANDA 202286

LABELING

COMPOSITE



COVER



Reference ID: 3396592

INSIDE SINGLE PAGES

INSIDE PAGES
3.5625" / 90.488 mm

2"
50.8 mm

NON PRINTING DIE LINE

ALL COPY SHOULD BE .125" / 3.175 mm AWAY FROM EDGE OF DIE LINE

ALL COPY SHOULD BE .1562" / 3.967 mm AWAY FROM TOP AND BOTTOM EDGE OF DIE LINE

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

TRANEXAMIC ACID tablets, for oral use
Initial U.S. Approval: 1986

RECENT MAJOR CHANGES

Contraindications (4.1) 10/2013
Warnings and Precautions (5.1) 10/2013

INDICATIONS AND USAGE

Tranexamic acid tablets are 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)

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 who are using combination hormonal contraception (4.1)

2

- 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

- Concomitant use of tranexamic acid 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 tranexamic acid. Immediately discontinue use if visual or ocular symptoms occur. (5.1)
- In case of severe allergic reaction, discontinue tranexamic acid and seek immediate medical attention. (5.2)
- Cerebral edema and cerebral infarction may be caused by use of tranexamic acid in women with subarachnoid hemorrhage. (5.3)
- Ligneous conjunctivitis has been reported in patients taking tranexamic acid. (5.4)

3

ADVERSE REACTIONS

Most common adverse reactions in clinical trials (≥ 5%, and more frequent in tranexamic acid 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 Apotex Corp. at 1-800-706-5575 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 tranexamic acid and tissue plasminogen activators. (7.2)

USE IN SPECIFIC POPULATIONS

- Geriatric Use: Tranexamic acid is not indicated for use in postmenopausal women (8.5)
- Renal impairment: Dosage adjustment is needed. (2.2, 8.6)
- Hepatic impairment: No dosage adjustment is needed. (8.7)

4

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

Revised: 10/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
2.2 Renal Impairment
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
4.1 Thromboembolic Risk
4.2 Hypersensitivity to Tranexamic Acid
5 WARNINGS AND PRECAUTIONS
5.1 Thromboembolic Risk
5.2 Severe Allergic Reaction

5

5.3 Subarachnoid Hemorrhage
5.4 Ligneous Conjunctivitis
6 ADVERSE REACTIONS
6.1 Clinical Trial Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Hormonal Contraceptives
7.2 Tissue Plasminogen Activators
7.3 Factor IX Complex Concentrates or Anti-Inhibitor Coagulant Concentrates
7.4 All-Trans Retinoic Acid (Oral Tretinoin)
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment

6

8.7 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Three-Cycle Treatment Study
14.2 Six-Cycle Treatment Study
14.3 MBL Results over Time
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

7

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
Tranexamic acid tablets are indicated for the treatment of cyclic heavy menstrual bleeding [see *Clinical Studies (14)*].

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

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
The recommended dose of tranexamic acid 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. Tranexamic acid tablets may be administered without regard to meals. Tablets should be swallowed whole and not chewed or broken apart.

8

INSIDE SINGLE PAGES

INSIDE PAGES
3.5625" / 90.488 mm

2"
50.8 mm

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 Tranexamic acid in Patients with Renal Impairment

	Tranexamic acid	
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

9

ALL COPY SHOULD BE .1562" / 3.967 mm AWAY FROM TOP AND BOTTOM EDGE OF DIE LINE

NON PRINTING DIE LINE

ALL COPY SHOULD BE .125" / 3.175 mm AWAY FROM EDGE OF DIE LINE

INSIDE PAGES
3.5625" / 90.488 mm

3 DOSAGE FORMS AND STRENGTHS
650 mg tablets

4 CONTRAINDICATIONS
4.1 Thromboembolic Risk
Do not prescribe tranexamic acid tablets to women who are
- using combination hormonal contraception
- known to have any of the following conditions:
  - Active thromboembolic disease (e.g., deep vein thrombosis, pulmonary embolism, or cerebral thrombosis)
  - A history of thrombosis or thromboembolism, including retinal vein or artery occlusion
  - An intrinsic risk of thrombosis or thromboembolism (e.g., thrombogenic valvular disease, thrombogenic cardiac rhythm disease, or hypercoagulopathy)

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

10

4 2 Hypersensitivity to Tranexamic Acid
Do not prescribe tranexamic acid tablets 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 tranexamic acid is antifibrinolytic, the risk of venous thromboembolism, as well as arterial thromboses such as stroke, may increase further when hormonal contraceptives are administered with tranexamic acid. This is of particular concern in women who are obese or smoke cigarettes, especially smokers over 35 years of age.

Women using hormonal contraception were excluded from the clinical trials supporting the safety and efficacy of tranexamic acid, and there are no clinical trial data on the risk of thrombotic events with the concomitant use of tranexamic acid with hormonal contraceptives. However, there have been US postmarketing reports of venous and arterial thrombotic events in women who have

11

used tranexamic acid concomitantly with combination hormonal contraceptives. For this reason, concomitant use of tranexamic acid with combination hormonal contraceptives is contraindicated. [see *Contraindications (4.1) and Drug Interactions (7.1)*].

Factor IX Complex Concentrates or Anti-Inhibitor Coagulant Concentrates
Tranexamic acid 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 tranexamic acid 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 tranexamic acid immediately and should be referred to an ophthalmologist for a complete ophthalmic evaluation, including dilated retinal examination,

12

to exclude the possibility of retinal venous or arterial occlusion.

5 2 Severe Allergic Reaction
A case of severe allergic reaction to tranexamic acid 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 tranexamic acid 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

13

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 tranexamic acid 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 tranexamic acid (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 tranexamic acid. A second study compared the effects of tranexamic acid (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 tranexamic acid. In both studies, subjects were generally healthy women who had menstrual blood loss of ≥ 80 mL.

In these studies, subjects were 18 to 49 years of age with a mean age of approximately 40 years, had cyclic menses every 21 to 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

14

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 tranexamic acid and placebo. In the 3-cycle study, the rate in the 3900 mg tranexamic acid dose group was 0.8% as compared to 1.4% in the placebo group. In the 6-cycle study, the rate in the tranexamic acid group was 2.4% as compared to 4.1% in the placebo group. Across the studies, the combined exposure to 3900 mg/day tranexamic acid was 947 cycles and the average duration of use was 3.4 days per cycle.

A list of adverse events occurring in ≥ 5% of subjects and more frequently in tranexamic acid treated subjects receiving 3900 mg/day compared to placebo is provided in Table 2.

15

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

	Tranexamic acid 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%)

16

INSIDE SINGLE PAGES

INSIDE PAGES
3.5625" / 90.488 mm

2"
50.8 mm

	Tranexamic acid 3900 mg/day n (%) (N=232)	Placebo n (%) (N=139)
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

17

ALL COPY SHOULD BE .1562" / 3.967 mm AWAY FROM TOP AND BOTTOM EDGE OF DIE LINE

Long-term Studies
Long-term safety of tranexamic acid 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 tranexamic acid was 10,213 cycles. The average duration of tranexamic acid 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 tranexamic acid in this study was 1,956 cycles. The average duration of tranexamic acid 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

18

NON PRINTING DIE LINE

ALL COPY SHOULD BE .125" / 3.175 mm AWAY FROM EDGE OF DIE LINE

reporting them was greater in the 27-month study, most likely because of the longer study duration.

A case of severe allergic reaction to tranexamic acid 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

19

obstruction); cases have been associated with concomitant use of combination hormonal contraceptives
- Impaired color vision and other visual disturbances
- Dizziness

7 DRUG INTERACTIONS
No drug-drug interaction studies were conducted with tranexamic acid.

7.1 Hormonal Contraceptives
Because tranexamic acid is antifibrinolytic, concomitant use of hormonal contraception and tranexamic acid may further exacerbate the increased thrombotic risk associated with combination hormonal contraceptives. For this reason, concomitant use of tranexamic acid with combination hormonal contraceptives is contraindicated [see *Contraindications (4) and Warnings and Precautions (5.1)*].

7.2 Tissue Plasminogen Activators
Concomitant therapy with tissue plasminogen activators may decrease the efficacy of both tranexamic acid and tissue plasminogen activators. Therefore, exercise caution if a woman taking

20

tranexamic acid therapy requires tissue plasminogen activators.

7.3 Factor IX Complex Concentrates or Anti-Inhibitor Coagulant Concentrates
Tranexamic acid 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 tranexamic acid 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)
Tranexamic acid 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

21

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. Tranexamic acid should be used during lactation only if clearly needed.

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

22

8 5 Geriatric Use
Tranexamic acid 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 tranexamic acid 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 tranexamic acid 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 tranexamic acid and no subjects in the clinical program took more than 2 times the prescribed amount of tranexamic acid in a 24-hour period

23

(>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 tranexamic acid. 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.

24

3 of 7 pgs

INSIDE SINGLE PAGES

INSIDE PAGES
3.5625" / 90.488 mm

2"
50.8 mm

11 DESCRIPTION

Tranexamic acid 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 $C_8H_{15}NO_2$ and the molecular weight is 157.2.

Tranexamic acid tablets are provided as white to off-white, oval, biconvex tablets. Engraved "APO" on one side, "TRA 650" on the other side. The active ingredient in each tablet is 650 mg tranexamic

25

ALL COPY SHOULD BE .1562" / 3.967 mm AWAY FROM TOP AND BOTTOM EDGE OF DIE LINE

NON PRINTING DIE LINE

ALL COPY SHOULD BE .125" / 3.175 mm AWAY FROM EDGE OF DIE LINE

INSIDE PAGES
3.5625" / 90.488 mm

acid. The inactive ingredients contained in each tablet are: ethylcellulose 7FP, colloidal silicon dioxide, croscarmellose sodium, 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.

26

12 2 Pharmacodynamics

Tranexamic acid, at *in vitro* concentrations of 25 to 100 M, reduces by 20 to 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 to 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 tranexamic acid 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) tranexamic acid 1300 mg (two 650 mg tablets), (2) tranexamic acid 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

27

dose of tranexamic acid. 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 tranexamic acid, the peak plasma concentration (C_{max}) occurred at approximately 3 hours (T_{max}). The absolute bioavailability of tranexamic acid in women aged 18 to 49 is approximately 45%. Following multiple oral doses (two 650 mg tablets three times daily) administration of tranexamic acid 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 tranexamic acid 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 tranexamic acid are shown in Table 3.

28

Table 3. Mean (CV%) Pharmacokinetic Parameters Following a Single (two 650 mg tablets) and Multiple Oral Dose (two 650 mg tablets three times daily for 5 days) Administration of Tranexamic Acid Tablets 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

29

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: Tranexamic acid may be administered without regard to meals. A single dose administration (two 650 mg tablets) of tranexamic acid 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.

30

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

Specific Populations

Pregnancy (Category B)

Tranexamic acid is not indicated for use in pregnant women. Tranexamic acid is known to

31

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. Tranexamic acid should be used during lactation only if clearly needed [see *Use in Specific Populations (8.3)*].

Pediatric Use

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

32

INSIDE SINGLE PAGES

INSIDE PAGES
3.5625" / 90.488 mm

2"
50.8 mm

Geriatric Use
Tranexamic acid 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 tranexamic acid 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 to 2.8, 2.8 to 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 tranexamic acid 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

NON PRINTING DIE LINE

ALL COPY SHOULD BE .125" / 3.175 mm AWAY FROM EDGE OF DIE LINE

INSIDE PAGES
3.5625" / 90.488 mm

ALL COPY SHOULD BE .1562" / 3.967 mm AWAY FROM TOP AND BOTTOM EDGE OF DIE LINE

2"
50.8 mm

needed in patients with hepatic impairment.

Drug Interactions

No drug-drug interaction studies were conducted with tranexamic acid.

Hormonal Contraceptives
Because tranexamic acid is antifibrinolytic, concomitant use of hormonal contraception and tranexamic acid may further exacerbate the increased thrombotic risk associated with combination hormonal contraceptives. For this reason, concomitant use of tranexamic acid with combination hormonal contraceptives is contraindicated [see *Contraindications (4), Warnings and Precautions (5.1) and Drug Interactions (7.1)*].

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

Tissue Plasminogen Activators
Concomitant therapy with tissue plasminogen activators may decrease the efficacy of both

NON PRINTING DIE LINE

ALL COPY SHOULD BE .125" / 3.175 mm AWAY FROM EDGE OF DIE LINE

INSIDE PAGES
3.5625" / 90.488 mm

2"
50.8 mm

tranexamic acid and tissue plasminogen activators. Therefore, exercise caution if a patient taking tranexamic acid 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 tranexamic acid to patients with acute promyelocytic leukemia taking all-trans retinoic acid [see *Warnings and Precautions (5.1)* and *Drug Interactions (7.4)*].

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
Carcinogenicity studies with tranexamic acid in male mice at doses as high as 6 times the recommended human dose of 3900 mg/day showed an increased incidence of leukemia which

NON PRINTING DIE LINE

ALL COPY SHOULD BE .125" / 3.175 mm AWAY FROM EDGE OF DIE LINE

INSIDE PAGES
3.5625" / 90.488 mm

ALL COPY SHOULD BE .1562" / 3.967 mm AWAY FROM TOP AND BOTTOM EDGE OF DIE LINE

2"
50.8 mm

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

NON PRINTING DIE LINE

ALL COPY SHOULD BE .125" / 3.175 mm AWAY FROM EDGE OF DIE LINE

INSIDE PAGES
3.5625" / 90.488 mm

2"
50.8 mm

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

NON PRINTING DIE LINE

ALL COPY SHOULD BE .125" / 3.175 mm AWAY FROM EDGE OF DIE LINE

INSIDE PAGES
3.5625" / 90.488 mm

ALL COPY SHOULD BE .1562" / 3.967 mm AWAY FROM TOP AND BOTTOM EDGE OF DIE LINE

2"
50.8 mm

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 to 40 times the recommended usual human dose based on mg/m^2 (actual animal doses between 250 to 1600 mg/kg/day).

14 CLINICAL STUDIES
The efficacy and safety of tranexamic acid 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 (6.1)*]. In these studies, HMB was defined as an average menstrual blood loss of ≥ 80 mL as assessed by alkaline hematin analysis of collected sanitary products over two baseline menstrual cycles. Subjects were 18 to 49 years of age with a mean age of approximately 40 years, had cyclic menses every 21 to35 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

NON PRINTING DIE LINE

ALL COPY SHOULD BE .125" / 3.175 mm AWAY FROM EDGE OF DIE LINE

INSIDE PAGES
3.5625" / 90.488 mm

2"
50.8 mm

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 tranexamic acid (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 tranexamic acid 1950 mg/day subjects, 112 tranexamic acid 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 tranexamic acid compared to placebo. Study success also required achieving

NON PRINTING DIE LINE

ALL COPY SHOULD BE .125" / 3.175 mm AWAY FROM EDGE OF DIE LINE

ALL COPY SHOULD BE .1562" / 3.967 mm AWAY FROM TOP AND BOTTOM EDGE OF DIE LINE

2"
50.8 mm

a reduction in MBL that was determined to be clinically meaningful to the subjects. The 1950 mg/day tranexamic acid 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
Tranexamic acid 3900 mg/day	112	169	65*	39%
Tranexamic acid 1950 mg/day	115	178	44	25%
Placebo	67	154	7	5%

* p<0.001 versus placebo

Tranexamic acid 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.

NON PRINTING DIE LINE

ALL COPY SHOULD BE .125" / 3.175 mm AWAY FROM EDGE OF DIE LINE

Reference ID: 3396592

INSIDE SINGLE PAGES

INSIDE PAGES
3.5625" / 90.488 mm

2"
50.8 mm

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 Tranexamic acid	112	3.00	0.98[c]
Placebo	66	2.85	0.39
Physical Activities			
3900 mg/day Tranexamic acid	112	3.07	0.94[c]
Placebo	66	2.96	0.34
	N		**Responders[d]**
Reduction in Large Stains			
3900 mg/day Tranexamic acid	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

ALL COPY SHOULD BE .1562" / 3.967 mm AWAY FROM TOP AND BOTTOM EDGE OF DIE LINE

NON PRINTING DIE LINE

ALL COPY SHOULD BE .125" / 3.175 mm AWAY FROM EDGE OF DIE LINE

INSIDE PAGES
3.5625" / 90.488 mm

[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 tranexamic acid 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 tranexamic acid 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 tranexamic acid 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
Tranexamic acid 3900 mg/day	115	172	66*	38%

2"
50.8 mm

ALL COPY SHOULD BE .1562" / 3.967 mm AWAY FROM TOP AND BOTTOM EDGE OF DIE LINE

NON PRINTING DIE LINE

ALL COPY SHOULD BE .125" / 3.175 mm AWAY FROM EDGE OF DIE LINE

INSIDE PAGES
3.5625" / 90.488 mm

Treatment Arm	N	Baseline Mean MBL (mL)	Least Squares Mean Reduction in MBL (mL)	Percent Reduction in MBL
Placebo	72	153	18	12%

* p<0.001 versus placebo

Limitations on social, leisure, and physical activities were also statistically significantly reduced in the tranexamic acid 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 Tranexamic acid	115	2.92	0.85[c]
Placebo	72	2.74	0.44
Physical Activities			
3900 mg/day Tranexamic acid	115	3.05	0.87[c]

2"
50.8 mm

ALL COPY SHOULD BE .1562" / 3.967 mm AWAY FROM TOP AND BOTTOM EDGE OF DIE LINE

NON PRINTING DIE LINE

ALL COPY SHOULD BE .125" / 3.175 mm AWAY FROM EDGE OF DIE LINE

INSIDE PAGES
3.5625" / 90.488 mm

Outcome Measure	N	Baseline Mean[a]	Least Squares Mean Reduction[b]
Placebo	72	2.90	0.40
	N		**Responders[d]**
Reduction in Large Stains			
3900 mg/day Tranexamic acid	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 tranexamic acid 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).

2"
50.8 mm

ALL COPY SHOULD BE .1562" / 3.967 mm AWAY FROM TOP AND BOTTOM EDGE OF DIE LINE

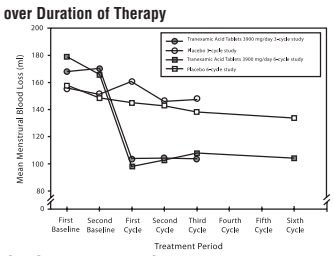
NON PRINTING DIE LINE

ALL COPY SHOULD BE .125" / 3.175 mm AWAY FROM EDGE OF DIE LINE

INSIDE PAGES
3.5625" / 90.488 mm

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

Tranexamic acid tablets are provided as white to off-white, oval, biconvex tablets. Engraved

2"
50.8 mm

ALL COPY SHOULD BE .1562" / 3.967 mm AWAY FROM TOP AND BOTTOM EDGE OF DIE LINE

NON PRINTING DIE LINE

ALL COPY SHOULD BE .125" / 3.175 mm AWAY FROM EDGE OF DIE LINE

INSIDE PAGES
3.5625" / 90.488 mm

"APO" on one side, "TRA 650" on the other side. They are supplied as:

- Bottles of 100s NDC 60505-3638-1

Storage

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Preserve in tight, light-resistant containers.

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 tranexamic acid 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.

2"
50.8 mm

ALL COPY SHOULD BE .1562" / 3.967 mm AWAY FROM TOP AND BOTTOM EDGE OF DIE LINE

NON PRINTING DIE LINE

ALL COPY SHOULD BE .125" / 3.175 mm AWAY FROM EDGE OF DIE LINE

INSIDE PAGES
3.5625" / 90.488 mm

Inform patients that they should stop tranexamic acid 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 tranexamic acid 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.

2"
50.8 mm

ALL COPY SHOULD BE .1562" / 3.967 mm AWAY FROM TOP AND BOTTOM EDGE OF DIE LINE

NON PRINTING DIE LINE

ALL COPY SHOULD BE .125" / 3.175 mm AWAY FROM EDGE OF DIE LINE

APOTEX INC.

Tranexamic Acid Tablets

650 mg

RX Only

Manufactured by:	Manufactured for:
Apotex Inc.	Apotex Corp.
Toronto, Ontario	Weston, Florida
Canada M9L 1T9	33326, USA

Revision 3
October 2013

6 of 7 pgs

ALL COPY BE 0.15625" (3.96875mm) AWAY FROM EDGE OF DIELINE ON THE TOP & BOTTOM SIDES

1st START OF COPY FLOW

FRONT PANEL 1

0.25" (6.35mm) STITCH GUTTER & FOLD

PATIENT INFORMATION
Tranexamic Acid Tablets
(pronounced *tran-ex-am-ik as-id*)

Read the Patient Information that comes with tranexamic acid tablets 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 are Tranexamic Acid Tablets?

Tranexamic acid tablets are a prescription medicine used to treat your heavy monthly period (menstruation) when your bleeding gets in the way of social, leisure and physical activities. Tranexamic acid tablets do not contain any hormones. On average, tranexamic acid tablets have 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.

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

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

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

Who should not take Tranexamic Acid Tablets?

Do not take tranexamic acid tablets if you:

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

What should I tell my healthcare provider before taking Tranexamic Acid Tablets?

Before taking tranexamic acid tablets, tell your healthcare provider about all of your medical conditions, including whether:

- **You have ever had a blood clot or been told that you are at risk of having a blood clot**
- **You are using a form of birth control that contains** estrogen and a progestin (like a birth control pill, patch, or vaginal ring). Using hormonal birth control along with tranexamic acid may increase your chance of having a serious blood clot, stroke, or heart attack. For this reason, do not use tranexamic acid if you use a form of birth control that contains estrogen and a progestin.
- You are pregnant or think you may be pregnant
- You are breastfeeding or plan to breast-feed. Tranexamic acid can pass into your milk. Talk to your healthcare provider about the best way to feed your baby if you take tranexamic acid tablets.
- 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. Tranexamic acid tablets and other medicines can affect each other, causing side effects. Tranexamic acid tablets can affect the way other medicines work and other medicines can affect how tranexamic acid tablets work.

Especially tell your healthcare provider if you take:

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

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

How should I take Tranexamic Acid Tablets?

- Take tranexamic acid tablets exactly as your healthcare provider tells you.
- Do not take tranexamic acid tablets until your period has started.
- Do not take tranexamic acid tablets for more than 5 days in a row.
- Do not take tranexamic acid tablets when you do not have your period.
- Once your period has started, take 2 tablets of tranexamic acid three times per day (e.g., in the morning, afternoon, and evening).
- Tranexamic acid tablets should be swallowed whole and not chewed or broken apart.
- Tranexamic acid tablets may be taken with or without food.
- Do not take more than 6 tablets of tranexamic acid 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 tranexamic acid tablets do 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 Tranexamic Acid Tablets?

Tranexamic acid tablets can cause serious side effects, including:

- Blood clots. You may have a higher risk of having serious blood clots if you take tranexamic acid tablets with:
  - medicines used to help your blood form clots
  - some medicines used to treat leukemia
- Eye changes. Stop taking tranexamic acid tablets and promptly report any eye problems you have while taking tranexamic acid tablets. 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 tranexamic acid tablets and get medical care right away.

The most common side effects of tranexamic acid tablets 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 tranexamic acid tablets. 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 Apotex Corp at 1-800-706-5575.

How should I store Tranexamic Acid Tablets?

Store tranexamic acid tablets at 20° to 25°C (68° to 77°F).

Keep tranexamic acid tablets and all medicines out of the reach of children.

General information about

Tranexamic Acid Tablets

Medicines are sometimes prescribed for conditions that are not mentioned in Patient Information Leaflets. Do not use tranexamic acid tablets for a condition for which it was not prescribed. Do not give tranexamic acid tablets 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 tranexamic acid tablets. If you would like more information about tranexamic acid tablets, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about tranexamic acid tablets that is written for healthcare professionals. For more information, go to www.apotex.com or call Apotex Drug Information Service at 1-800-706-5575.

What are the ingredients of Tranexamic Acid Tablets?

Active ingredient: tranexamic acid

Inactive ingredients: ethylcellulose 7FP, colloidal silicon dioxide, croscarmellose sodium, and magnesium stearate.

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

APOTEX INC.
Tranexamic Acid Tablets
650 mg

RX only

Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, Florida
33326, USA

Revision 3
October 2013

2nd START OF COPY FLOW

INSIDE PANEL 1

FRONT INSERT

INSIDE INSERT

3.5" 88.9mm

3.375" 85.725mm

27.5" 698.5mm

ALL COPY BE 0.125" (3.175mm) AWAY FROM EDGE OF DIELINE ON THE LEFT & RIGHT SIDES

2" 50.8mm

16 PAGE INSERT

7 of 7 pgs

Reference ID: 3396592

FRONT PPI PAD

FRONT PANEL #1

PATIENT INFORMATION
Tranexamic Acid Tablets
(pronounced tran-ex-am-ik as-id)

Read the Patient Information that comes with tranexamic acid tablets 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 are Tranexamic Acid Tablets?

Tranexamic acid tablets are a prescription medicine used to treat your heavy monthly period (menstruation) when your bleeding gets in the way of social, leisure and physical activities. Tranexamic acid tablets do not contain any hormones. On average, tranexamic acid tablets have 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.

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

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

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

Who should not take Tranexamic Acid Tablets?

Do not take tranexamic acid tablets if you:

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

What should I tell my healthcare provider before taking Tranexamic Acid Tablets?

Before taking tranexamic acid tablets, tell your healthcare provider about all of your medical conditions, including whether:

- **You have ever had a blood clot or been told that you are at risk of having a blood clot**
- **You are using a form of birth control that contains** estrogen and a progestin (like a birth control pill, patch, or vaginal ring). Using hormonal birth control along with tranexamic acid may increase your chance of having a serious blood clot, stroke, or heart attack. For this reason, do not use tranexamic acid if you use a form of birth control that contains estrogen and a progestin.
- You are pregnant or think you may be pregnant
- You are breastfeeding or plan to breast-feed. Tranexamic acid can pass into your milk. Talk to your healthcare provider about the best way to feed your baby if you take tranexamic acid tablets.
- 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. Tranexamic acid tablets and other medicines can affect each other, causing side effects. Tranexamic acid tablets can affect the way other medicines work and other medicines can affect how tranexamic acid tablets work.

Especially tell your healthcare provider if you take:

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

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

How should I take Tranexamic Acid Tablets?

- Take tranexamic acid tablets exactly as your healthcare provider tells you.
- Do not take tranexamic acid tablets until your period has started.
- Do not take tranexamic acid tablets for more than 5 days in a row.
- Do not take tranexamic acid tablets when you do not have your period.
- Once your period has started, take 2 tablets of tranexamic acid three times per day (e.g., in the morning, afternoon, and evening).
- Tranexamic acid tablets should be swallowed whole and not chewed or broken apart.
- Tranexamic acid tablets may be taken with or without food.
- Do not take more than 6 tablets of tranexamic acid in a day. If you take more than 6 tablets, call your healthcare provider.

000000

INSIDE PPI PAD

INSIDE PANEL #1

- 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 tranexamic acid tablets do 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 Tranexamic Acid Tablets?

Tranexamic acid tablets can cause serious side effects, including:

- Blood clots. You may have a higher risk of having serious blood clots if you take tranexamic acid tablets with:
  - medicines used to help your blood form clots
  - some medicines used to treat leukemia
- Eye changes. Stop taking tranexamic acid tablets and promptly report any eye problems you have while taking tranexamic acid tablets. 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 tranexamic acid tablets and get medical care right away.

The most common side effects of tranexamic acid tablets 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 tranexamic acid tablets. 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 Apotex Corp at 1-800-706-5575.

How should I store Tranexamic Acid Tablets?

Store tranexamic acid tablets at 20° to 25°C (68° to 77°F).

Keep tranexamic acid tablets and all medicines out of the reach of children.

General information about Tranexamic Acid Tablets

Medicines are sometimes prescribed for conditions that are not mentioned in Patient Information Leaflets. Do not use tranexamic acid tablets for a condition for which it was not prescribed. Do not give tranexamic acid tablets 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 tranexamic acid tablets. If you would like more information about tranexamic acid tablets, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about tranexamic acid tablets that is written for healthcare professionals. For more information, go to www.apotex.com or call Apotex Drug Information Service at 1-800-706-5575.

What are the ingredients of Tranexamic Acid Tablets?

Active ingredient: tranexamic acid

Inactive ingredients: ethylcellulose 7FP, colloidal silicon dioxide, croscarmellose sodium, and magnesium stearate.

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

APOTEX INC.
Tranexamic Acid Tablets
650 mg

RX only

Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, Florida
33326, USA

Revision 3
October 2013

INSIDE PANEL #2

FRONT PANEL #2

FRONT PANEL #1

STD PPI PAD
04/25/09

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202286

LABELING REVIEWS

(This APS #4 supersedes the APS #3 based on the submission of 9/13/2013.)

(APPROVAL SUMMARY #4)

Office of Generic Drugs

REVIEW OF PROFESSIONAL LABELING (4th Cycle)

ANDA Number:	202286
Date of Submission:	October 21, 2013
Applicant:	Apotex Inc.
Established Name and Strength:	Tranexamic Acid Tablets, 650 mg
Proposed Proprietary Name:	None

Labeling Comments below are considered:

☐ Minor Deficiency *

* Please note that the RPM may change the status from Minor Deficiency to Easily Correctable Deficiency if other disciplines are acceptable.

☒ No Comments **(**Labeling Approval Summary or Tentative Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated October 21, 2013.

Please continue to monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book and the NF-USP online for recent updates, and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

Note RPM - Labeling comments end here

REMS required? No

MedGuides and/or PPIs (505-1(e)) ☐ Yes ☒ No

Revised October 2013

Communication plan (505-1(e)) ☐ Yes ☒ No

Elements to assure safe use (ETASU) (505-1(f)(3)) ☐ Yes ☒ No

Implementation system if certain ETASU (505-1(f)(4)) ☐ Yes ☒ No

Timetable for assessment (505-1(d)) ☐ Yes ☒ No

ANDA REMS acceptable? ☐ Yes ☐ No ☒ N/A

	Date submitted	Final or Draft	Recommendation
CONTAINER – 100s	**September 9, 2011**	Final	AP for AC
INSERT	October 21, 2013	Final (6 pts)	AP for AC
PATIENT INFORMATION	October 21, 2013	Final (10 pts)	AP for AC
REMS PLAN	N/A	N/A	N/A
SPL - DLDE	October 21, 2013	N/A	AP for AC

REVISIONS NEEDED POST APPROVAL? No

NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER: None

---

FOR THE RECORD: Part of the information is from the review done by Sarah Park.

1. MODEL LABELING - Lysteda® Tablets (NDA 022430/004), approved October 3, 2013..

   MedWatch – MEDWATCH (checked 10/24/2013)
   No new alerts or labeling changes.

2. USP & PF – No (10/24/2013)
   The active ingredient is subject of the USP.

3. PATENT AND EXCLUSIVITY

	Patent No.	Expiry date	Patent Use Code	Code Definition	Patent Certification
	7947739	March 4, 2025			IV
	8022106	March 4, 2025	U-1182	Treatment of cyclic heavy menstrual bleeding	IV
	8273795	March 4, 2025	U-1182		IV
	8487005	March 4, 2025	U-1182		IV

The sponsor amended the patent certification as above on 9/16/2013.
Revised October 2013

No pending exclusivity.

4. INACTIVE INGREDIENTS - Consistent

	Lysteda® (marketed by Xanodyne Pharmaceuticals Inc., applicant is Ferring Pharms AS)	Tranexamic Acid Tablets (Apotex Inc.)
Active Ingredient(s)	Tranexamic acid	Tranexamic acid
Inactive Ingredients	Microcrystalline cellulose Colloidal silicon dioxide Pregelatinized corn starch Povidone Hypromellose Stearic acid Magnesium stearate	Ethylcellulose Croscarmellose sodium Magnesium stearate Colloidal silicon dioxide

The active ingredient in each tablet is 650 mg tranexamic acid. The inactive ingredients contained in each tablet are: ethylcellulose 7FP, colloidal silicon dioxide, croscarmellose sodium, and magnesium stearate.

5. MANUFACTURING FACILITY
   Apotex Inc.
   150 Signet Drive Toronto, Ontario Canada M9L 1T9

6. FINISHED PRODUCT DESCRIPTION – Accurate description in the insert:

   RLD: "…white oval-shaped tablets. Each tablet is debossed with the marking "XP650"…"

   ANDA: Tranexamic acid tablets are provided as white to off-white, oval, biconvex tablets. Engraved "APO" on one side, "TRA 650" on the other side.

7. STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS

   RLD: Store at 25° C (77° F); excursions permitted to 15° - 30° C (59° - 86° F). [see USP Controlled Room Temperature].
   ANDA: Store at 20°- 25° C (68°-77° F); excursions permitted to 15° - 30° C (59° - 86° F) [See USP Controlled Room Temperature].

   Stability: Accelerated 40°C/75% RH; Long term 25°C/60% RHP

   Dispensing Recommendations:
   RLD: None
   ANDA: Preserve in tight, light-resistant containers.
   PHARMACIST: DISPENSE WITH PATIENT INFORMATION LEAFLET

8. RODUCT LINE

   RLD:30s, 100s, and 500s

Revised October 2013

ANDA: 100s

9. CONTAINER/CLOSURE SYSTEM
Container: HDPE
Closure: non-CRC

10. REMS (checked 10/24/2013)
No approved

Date of Review: 10/24/20313

Primary Reviewer: ChanPark

Team Leader: Loung Lee

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

/s/

CHAN H PARK
10/25/2013

KOUNG U LEE
10/31/2013

(This APS supersedes the APS based on the 9/9/2011 submission0
(APROVAL SUMMARY)
REVIEW OF PROFESSIONAL LABELING #3
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 202286

Date of Submission: September 13, 2013

Applicant's Name: Apotex, Inc.

Established Name and Strength: Tranexamic Acid Tablets,

Proposed Proprietary Name: None

Labeling Comments below are considered:

☐ NOT easily correctable (applicant cannot respond within 10 business days)

☐ Easily correctable (respond within 10 business days)

☒ No Comments **(**Labeling Approval Summary or Tentative Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated September 13, 2013.

Please continue to monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book and the NF-USP online for recent updates, and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

Note RPM - Labeling comments end here

REMS required? No

MedGuides and/or PPIs (505-1(e)) ☐ Yes ☒ No

Communication plan (505-1(e)) ☐ Yes ☒ No

Elements to assure safe use (ETASU) (505-1(f)(3)) ☐ Yes ☒ No

Implementation system if certain ETASU (505-1(f)(4)) ☐ Yes ☒ No

Timetable for assessment (505-1(d)) ☐ Yes ☒ No

ANDA REMS acceptable? ☐ Yes ☐ No ☒ N/A

	Date submitted	Final or Draft	Recommendation
CONTAINER – 100s	**September 9, 2011**	Final	AP for AC
INSERT	September 13, 2013	Final (6 pts)	AP for AC
PATIENT INFORMATION	September 13, 2013	Final (10 pts)	AP for AC
REMS PLAN	N/A	N/A	N/A
SPL - DLDE	September 13, 2013	N/A	AP for AC

REVISIONS NEEDED POST APPROVAL? Yes

a. Add the route of administration in association with the drug product name in the HIGHLIGHTS section and revise to read "TRANEXAMIC ACID tablets for oral use".
b. Delete the phrase "Rx only" from the H.S. section**.**

NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER: None

---

FOR THE RECORD: Part of the information is from the review done by Sarah Park.

1. MODEL LABELING - Lysteda® Tablets (NDA 022430), approved August 21, 2013.

MedWatch – MEDWATCH (checked 9/24/2013)
No new alerts or labeling changes.

2. USP & PF – No (9/24/2013)
   The active ingredient is subject of the USP.

3. PATENT AND EXCLUSIVITY

	Patent No.	Expiry date	Patent Use Code	Code Definition	Patent Certification
	7947739	March 4, 2025			IV
	8022106	March 4, 2025	U-1182	Treatment of cyclic heavy menstrual bleeding	IV
	8273795	March 4, 2025	U-1182		IV
	8487005	March 4, 2025	U-1182		IV

The sponsor amended the patent certification as above on 9/16/2013.

No pending exclusivity.

4. INACTIVE INGREDIENTS - Consistent

	Lysteda® (marketed by Xanodyne Pharmaceuticals Inc., applicant is Ferring Pharms AS)	Tranexamic Acid Tablets (Apotex Inc.)
Active Ingredient(s)	Tranexamic acid	Tranexamic acid
Inactive Ingredients	Microcrystalline cellulose Colloidal silicon dioxide Pregelatinized corn starch Povidone Hypromellose Stearic acid Magnesium stearate	Ethylcellulose Croscarmellose sodium Magnesium stearate Colloidal silicon dioxide

The active ingredient in each tablet is 650 mg tranexamic acid. The inactive ingredients contained in each tablet are: ethylcellulose 7FP, colloidal silicon dioxide, croscarmellose sodium, and magnesium stearate.

5. MANUFACTURING FACILITY
   Apotex Inc.
   150 Signet Drive Toronto, Ontario Canada M9L 1T9

6. FINISHED PRODUCT DESCRIPTION – Accurate description in the insert:

   RLD: "…white oval-shaped tablets. Each tablet is debossed with the marking "XP650"…"

   ANDA: Tranexamic acid tablets are provided as white to off-white, oval, biconvex tablets. Engraved "APO" on one side, "TRA 650" on the other side.

7. STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS

   RLD: Store at 25° C (77° F); excursions permitted to 15° - 30° C (59° - 86° F). [see USP Controlled Room Temperature].
   ANDA: Store at 20°- 25° C (68°-77° F); excursions permitted to 15° - 30° C (59° - 86° F) [See USP Controlled Room Temperature].

   Stability: Accelerated 40°C/75% RH; Long term 25°C/60% RHP
   RLD: None
   ANDA: Preserve in tight, light-resistant containers.
   PHARMACIST: DISPENSE WITH PATIENT INFORMATION LEAFLET

8. RODUCT LINE

   RLD:30s, 100s, and 500s
   ANDA: 100s

9. CONTAINER/CLOSURE SYSTEM
Container: HDPE
Closure: non-CRC

10. REMS (checked 9/24/2013)
No approved

Date of Review: 9/24/20313

Primary Reviewer: ChanPark

Team Leader: Loung Lee

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

/s/

CHAN H PARK
09/24/2013

KOUNG U LEE
09/25/2013

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 202286

Date of Submission: September 9, 2011 (Amendment)

Applicant's Name: Apotex, Inc.

Established Name: Tranexamic Acid Tablets, 650 mg

REMS required?

MedGuides and/or PPIs (505-1(e))	☐ Yes ☒ No
Communication plan (505-1(e))	☐ Yes ☒ No
Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes ☒ No
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes ☒ No
Timetable for assessment (505-1(d))	☐ Yes ☒ No

ANDA REMS acceptable?
☐ Yes ☐ No ☒ n/a

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? E-submission

	Date Submitted	Recommendation
CONTAINER (bottles of 100)	September 9, 2011	Acceptable for Approval
INSERT	September 9, 2011	Acceptable for Approval
PATIENT INFORMATION	September 9, 2011	Acceptable for Approval

Revisions needed post-approval: No

NOTES/QUESTIONS TO THE CHEMIST: None

FOR THE RECORD:

1. MODEL LABELING
   Lysteda Tablets, NDA 022430/002, approved April 6, 2011

2. USP MONOGRAPH – None

3. PATENTS AND EXCLUSIVITIES

Patent:

Appl No	Prod No	Patent No	Patent Expiration	Certification	Labeling Impact	Use Code
N022430	001	7947739	Mar 4, 2025	PIV	None	

Exclusivity:

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration	Labeling Impact
N022430	001	NDF	Mar 4, 2025	**will not market until after expiry**

Code	**Definition**
NDF	NEW DOSAGE FORM (treatment of cyclic heavy menstrual bleeding)

4. INACTIVE INGREDIENTS
   The listing of inactive ingredients in the DESCRIPTION section of the insert is consistent with the application.

	Lysteda® (marketed by Xanodyne Pharmaceuticals Inc., applicant is Ferring Pharms AS)	**Tranexamic Acid Tablets (Apotex Inc.)**
Active Ingredient(s)	Tranexamic acid	Tranexamic acid
Inactive Ingredients	Microcrystalline cellulose Colloidal silicon dioxide Pregelatinized corn starch Povidone Hypromellose Stearic acid Magnesium stearate	Ethylcellulose Croscarmellose sodium Magnesium stearate Colloidal silicon dioxide

5. MANUFACTURING FACILITY
   Apotex Inc.
   150 Signet Drive
   Toronto, Ontario
   Canada M9L 1T9

6. PRODUCT DESCRIPTION
   RLD: "…white oval-shaped tablets. Each tablet is debossed with the marking "XP650"…"
   ANDA: "…white to off-white, oval, biconvex tablets. Engraved "APO" on one side, "TRA 650" on the other side…"
   Drug Product Specifications: White to off-white, oval, biconvex tablets. Engraved "APO" on one side, "TRA 650" on the other side."

7. CONTAINER/CLOSURE SYSTEM
   Container: HDPE
   Closure: non-CRC

8. PRODUCT LINE
   RLD:

Quantity	Package Type	NDC Number
30 tablets	HDPE bottle	66479-650-30
30 tablets	Carton containing 5 blister cards with 6 tablets per card	66479-650-31
100 tablets	HDPE bottle	66479-650-01
500 tablets	HDPE bottle	66479-650-50

   ANDA: Bottles of 100

9. STORAGE CONDITIONS
   RLD: Store at 25° C (77° F); excursions permitted to 15° - 30° C (59° - 86° F). [see USP Controlled Room Temperature].
   ANDA: Store at 20°- 25° C (68°-77° F); excursions permitted to 15° - 30° C (59° - 86° F) [See USP Controlled Room Temperature].
   Stability: Accelerated 40°C/75% RH; Long term 25°C/60% RH

10. DISPENSING RECOMMENDATIONS
    RLD: None
    ANDA: Preserve in tight, light-resistant containers.
    PHARMACIST: DISPENSE WITH PATIENT INFORMATION LEAFLET

11. SPL DATA ELEMENTS
    No SPL submission

12. MEDWATCH (checked 9/29/2011)
    No new alerts or labeling changes.

13. REMS (checked 9/29/2011)
    No approved REMS

Date of Review: September 29, 2011

Primary Reviewer: Sarah Park

Team Leader: Koung Lee

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

/s/

SOOJUNG S PARK
09/29/2011

KOUNG U LEE
09/30/2011
For Wm. Peter Rickman - Exclusivity expires 11/13/12

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 202286

Date of Submission: August 31, 2010 (Original)

Applicant's Name: Apotex, Inc.

Established Name: Tranexamic Acid Tablets, 650 mg

Labeling Deficiencies:

1. CONTAINER

   We recommend addition of a statement to dispense with a Patient Information Leaflet.

2. INSERT

   a. The three major sections, HIGHLIGHTS OF PRESCRIBING INFORMATION, FULL PRESCRIBING INFORMATION: CONTENTS, and FULL PRESCRIBING INFORMATION, should be separated by a solid horizontal line.

   b. HIGHLIGHTS OF PRESCRIBING INFORMATION

      i. Please replace "Tranexamic acid (b) (4) tablet for oral use" with "Tranexamic acid tablets"

      ii. The headings should appear in the center of a horizontal line, for example:

      ----------**INDICATIONS AND USAGE**----------

   c. PATIENT INFORMATION, How should I store Tranexamic acid? – Replace "(b) (4) in tight, light-resistant containers [see USP]" with "Preserved in tight, light-resistant containers."

Please revise your labels and labeling, as instructed above, and submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

{See appended electronic signature page}

_____
Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

NOTES/QUESTIONS TO THE CHEMIST: None

FOR THE RECORD:

1. MODEL LABELING
   Lysteda Tablets, NDA 022430, approved November 13, 2009

2. USP MONOGRAPH – None

3. PATENTS AND EXCLUSIVITIES

   Patents: None

   Exclusivity:

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration	Labeling Impact
N022430	001	NDF	Nov 13, 2012	will not market until after expiry

Code	Definition
NDF	NEW DOSAGE FORM

treatment of cyclic heavy menstrual bleeding.

4. INACTIVE INGREDIENTS
   The listing of inactive ingredients in the DESCRIPTION section of the insert is consistent with the application.

	Lysteda® (marketed by Xanodyne Pharmaceuticals Inc., applicant is Ferring Pharms AS)	Tranexamic Acid Tablets (Apotex Inc.)
Active Ingredient(s)	Tranexamic acid	Tranexamic acid
Inactive Ingredients	Microcrystalline cellulose Colloidal silicon dioxide Pregelatinized corn starch Povidone Hypromellose Stearic acid Magnesium stearate	Ethylcellulose Croscarmellose sodium Magnesium stearate Colloidal silicon dioxide

5. MANUFACTURING FACILITY
   Apotex Inc.
   150 Signet Drive
   Toronto, Ontario
   Canada M9L 1T9

6. PRODUCT DESCRIPTION
   RLD "…white oval-shaped tablets. Each tablet is debossed with the marking "XP650"…"
   ANDA "…white to off-white, oval, biconvex tablets. Engraved "APO" on one side, "TRA 650" on the other side…"
   Drug Product Specifications: White to off-white, oval, biconvex tablets. Engraved "APO" on one side, "TRA 650" on the other side."

7. CONTAINER/CLOSURE SYSTEM
   Container: HDPE
   Closure: non-CRC

8. PRODUCT LINE
   RLD:

Quantity	Package Type	NDC Number
30 tablets	HDPE bottle	66479-650-30
30 tablets	Carton containing 5 blister cards with 6 tablets per card	66479-650-31
100 tablets	HDPE bottle	66479-650-01
500 tablets	HDPE bottle	66479-650-50

   ANDA: Bottles of 100

9. STORAGE CONDITIONS
   RLD: Store at 25° C (77° F); excursions permitted to 15° - 30° C (59° - 86° F). [see USP Controlled Room Temperature].
   ANDA: Store at 20°- 25° C (68°-77° F); excursions permitted to 15° - 30° C (59° - 86° F) [See USP Controlled Room Temperature].
   Stability: Accelerated 40°C/75% RH; Long term 25°C/60% RH

10. DISPENSING RECOMMENDATIONS
    RLD: None
    ANDA: (b) (4) in tight, light-resistant containers [see USP].

11. SPL DATA ELEMENTS
    No SPL submission

12. MEDWATCH (checked 1/31/2011)
    No new alerts or labeling changes.

13. REMS (checked 1/31/2011)
    No approved REMS

Date of Review: January 31, 2011

Primary Reviewer: Sarah Park

Team Leader: Koung Lee

Review – NA1

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

/s/

SOOJUNG S PARK
01/31/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202286

CHEMISTRY REVIEWS

ANDA 202286

Tranexamic Acid Tablets, 650 mg

Apotex Inc.

Xiaobin Zhao, Ph.D.
Chemistry Division II
Team 21

Table of Contents

Table of Contents ii

Chemistry Review Data Sheet 4

Executive Summary 10

I. Recommendations 10

A. Recommendation and Conclusion on Approvability 10

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 10

II. Summary of Chemistry Assessments 10

A. Description of the Drug Product(s) and Drug Substance(s) 10

B. Description of How the Drug Product is Intended to be Used 11

Basis for Approvability or Not-Approval Recommendation 11

Chemistry Assessment 12

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data based on QbR-QOS 12

2.3 Introduction to the Quality Overall Summary 12

2.3.S DRUG SUBSTANCE 12
- 2.3.S.1 General Information 12
- 2.3.S.2 Manufacture 16
- 2.3.S.3 Characterization 18
- 2.3.S.4 Control of Drug Substance 19
- 2.3.S.5 Reference Standards or Materials 28
- 2.3.S.6 Container Closure System 31
- 2.3.S.7 Stability 31

2.3.P DRUG PRODUCT 32
- 2.3.P.1 Description and Composition of the Drug Product 32
- 2.3.P.2 Pharmaceutical Development 36
- 2.3.P.3 Manufacture 49
- 2.3.P.4 Control of Excipients 63
- 2.3.P.5 Control of Drug Product 64
- 2.3.P.6 Reference Standards or Materials 77
- 2.3.P.7 Container Closure System 77
- 2.3.P.8 Stability 80

A APPENDICES 86
- A.1 Facilities and Equipment (biotech only) 86
- A.2 Adventitious Agents Safety Evaluation 86
- A.3 Novel Excipients 86

R REGIONAL INFORMATION 86
R.1 Executed Batch Records 86
R.2 Comparability Protocols 86
R.3 Methods Validation Package 86
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 88
A. Labeling & Package Insert 88
B. Environmental Assessment Or Claim Of Categorical Exclusion 88
III. List Of Deficiencies To Be Communicated 88

Chemistry Review Data Sheet

1. ANDA #: 202286

2. REVIEW #: 3

3. REVIEW DATE: June 25, 2012

4. REVIEWER: Xiaobin Zhao, Ph D

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
Original -1	August 31, 2010
Amendment	March 6, 2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	June 13, 2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex Inc.
Address:	150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Representative:	Bernice Tao
Telephone:	416-749-9300
Fax:	416-401-3849
US Agent:	Kiran Krishnan
Telephone:	954-384-3986
Fax:	954-349-4233
Address:	Apotex Corp, 2400 N. Commerce Parkway Suite 400, Weston, Florida, 33326

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: Lysteda™
Non-Proprietary Name (USAN): Tranexamic Acid Tablets, 650 mg

- Chem. Type: Small molecule
- Submission Priority: Paragraph IV

9. LEGAL BASIS FOR SUBMISSION:

The basis for the ANDA application for Tranexamic Acid Tablets, 650 mg, is the approved reference listed drug, Lysteda™ (Tranexamic Acid) Tablets, listed in the Electronic Orange Book. Lysteda™ is the subject of New Drug Application 22430, and is the subject of NDA # N022430 held by Ferring Pharms AS. On 5/27/2011, the firm filed a patent amendment to file a Paragraph IV Certification for US Patent No. 7,947,739.

10. PHARMACOL. CATEGORY:

Treatment of cyclic heavy menstrual bleeding

11. DOSAGE FORM:

Tablets

12. STRENGTH/POTENCY:

650 mg

13. ROUTE OF ADMINISTRATION:

Oral

14. Rx/OTC DISPENSED:

X Rx __OTC

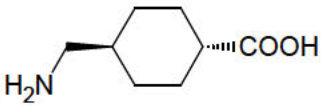
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): *trans*-4-(Aminomethyl)cyclohexanecarboxylic acid
Molecular Formula: $C_8H_{15}N0_2$
Molecular Weight: 157.2

Chemical Structure: 

CAS #: 1197-18-8

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	8/9/11	by X. Zhao
	III			4	NA		
	IV			4	NA		
	III			4	NA		
	III			4	NA		
	III			4	NA		
	III			4	NA		
	III			4	NA		
	III			4	NA		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	22430	Lysteda™, held by Ferring Pharms AS

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Pending	6/28/12	
Methods Validation	NA		
Labeling	Acceptable	9/30/11	PARK, SOOJUNG S
Bioequivalence	Adequate	3/29/2012	XIA, LI
EA	Categorical Exclusion		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _X_ Yes ____ No If no, explain reason(s) below:

Chemistry Review for ANDA 202286

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

a) Drug product:

Tranexamic Acid Tablets, 650 mg, are White to off-white, oval, biconvex tablets. Engraved "APO" on one side, (b) (4) on the other side. This will change to (b) (4) during commercial distribution (post-approval). The product is manufactured at the Apotex Signet site. The manufacturing process is (b) (4) (b) (4) (b) (4) (b) (4) The drug product specification includes (b) (4) The ANDA product differs from the RLD in the formulation design, since the ANDA product (b) (4) (b) (4). At present there is a BP monograph for this drug product.

b) Drug substance:

Tranexamic acid is a compendial item covered by the USP and EP. It is manufactured by (b) (4) and the DMF holder is (b) (4) (b) (4) The DMF is adequate upon review. Tranexamic Acid is white to off-white powder. It is freely soluble in water and glacial acetic acid, practically insoluble in alcohol, or ether. The specification includes (b) (4) (b) (4). The impurities include the USP Impurities A, B, C and D, with an unidentified impurity level at NMT (b) (4)% and total impurity at NMT 0.2%. The proposed re-test period is (b) (4) months.

B. Description of How the Drug Product is Intended to be Used

Tranexamic acid tablets are indicated for the treatment of cyclic heavy menstrual bleeding. Prior to prescribing, exclude endometrial pathology that can be associated with heavy menstrual bleeding.

The recommended dose 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. It may be administered without regard to meals. Tablets should be swallowed whole and not chewed or broken apart.

Therefore, the **MDD is 3,900 mg.**
Based on the MDD, the IT for drug product is 0.10% and QT is 0.15% per ICHQ3B.

C. Basis for Approvability or Not-Approval Recommendation

This application is ***approvable***.

Following this page, 77 Pages Withheld in Full as (b)(4)

III. List Of Deficiencies To Be Communicated

Chemistry Comments to be Provided to the Applicant

ANDA: 202286

APPLICANT: Apotex, Inc.

DRUG PRODUCT: Tranexamic Acid Tablets, 650 mg

The application is approvable from chemistry perspective.

Endorsements:

HFD-640 /Xiaobin Zhao/ 6/25/2012
HFD-640 /Radhika Rajagopalan/ 6/28/12
HFD-617/Frank Nice/6/28/12

TYPE OF LETTER: APPROVABLE

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

/s/

FRANK J NICE on behalf of XIAOBIN ZHAO
06/28/2012

RADHIKA RAJAGOPALAN
06/28/2012

FRANK J NICE
06/28/2012

ANDA 202286

Tranexamic Acid Tablets, 650 mg

Apotex Inc.

Xiaobin Zhao, Ph.D.
Chemistry Division II
Team 21

Table of Contents

Table of Contents ii

Chemistry Review Data Sheet 4

Executive Summary 10

I. Recommendations 10

A. Recommendation and Conclusion on Approvability 10

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 10

II. Summary of Chemistry Assessments 10

A. Description of the Drug Product(s) and Drug Substance(s) 10

B. Description of How the Drug Product is Intended to be Used 11

Basis for Approvability or Not-Approval Recommendation 11

Chemistry Assessment 12

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data based on QbR-QOS 12

2.3 Introduction to the Quality Overall Summary 12

2.3.S DRUG SUBSTANCE 12
- 2.3.S.1 General Information 12
- 2.3.S.2 Manufacture 15
- 2.3.S.3 Characterization 17
- 2.3.S.4 Control of Drug Substance 19
- 2.3.S.5 Reference Standards or Materials 28
- 2.3.S.6 Container Closure System 31
- 2.3.S.7 Stability 31

2.3.P DRUG PRODUCT 32
- 2.3.P.1 Description and Composition of the Drug Product 32
- 2.3.P.2 Pharmaceutical Development 36
- 2.3.P.3 Manufacture 50
- 2.3.P.4 Control of Excipients 66
- 2.3.P.5 Control of Drug Product 66
- 2.3.P.6 Reference Standards or Materials 79
- 2.3.P.7 Container Closure System 79
- 2.3.P.8 Stability 82

A APPENDICES 88
- A.1 Facilities and Equipment (biotech only) 88
- A.2 Adventitious Agents Safety Evaluation 88
- A.3 Novel Excipients 88

R REGIONAL INFORMATION 88
R.1 Executed Batch Records 88
R.2 Comparability Protocols 88
R.3 Methods Validation Package 88
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 90
A. Labeling & Package Insert 90
B. Environmental Assessment Or Claim Of Categorical Exclusion 90
III. List Of Deficiencies To Be Communicated 90

Chemistry Review Data Sheet

1. ANDA #: 202286

2. REVIEW #: 2

3. REVIEW DATE: May 7, 2012

4. REVIEWER: Xiaobin Zhao, Ph D

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
Original -1	August 31, 2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	March 6, 2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex Inc.
Address:	150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Representative:	Bernice Tao
Telephone:	416-749-9300
Fax:	416-401-3849
US Agent:	Kiran Krishnan
Telephone:	954-384-3986
Fax:	954-349-4233
Address:	Apotex Corp, 2400 N. Commerce Parkway Suite 400, Weston, Florida, 33326

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: Lysteda™
Non-Proprietary Name (USAN): Tranexamic Acid Tablets, 650 mg

- Chem. Type: Small molecule
- Submission Priority: Paragraph IV

9. LEGAL BASIS FOR SUBMISSION:

The basis for the ANDA application for Tranexamic Acid Tablets, 650 mg, is the approved reference listed drug, Lysteda™ (Tranexamic Acid) Tablets, listed in the Electronic Orange Book. Lysteda™ is the subject of New Drug Application 22430, and is the subject of NDA # N022430 held by Ferring Pharms AS. On 5/27/2011, the firm filed a patent amendment to file a Paragraph IV Certification for US Patent No. 7,947,739.

10. PHARMACOL. CATEGORY:

Treatment of cyclic heavy menstrual bleeding

11. DOSAGE FORM:

Tablets

12. STRENGTH/POTENCY:

650 mg

13. ROUTE OF ADMINISTRATION:

Oral

14. Rx/OTC DISPENSED:

X Rx __OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

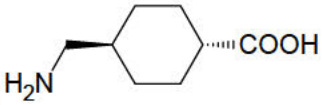
_____SPOTS product – Form Completed

__X__Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): *trans*-4-(Aminomethyl)cyclohexanecarboxylic acid
Molecular Formula: $C_8H_{15}N0_2$
Molecular Weight: 157.2

Chemical Structure: 

CAS #: 1197-18-8

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	8/9/11	by X. Zhao
	III			4	NA		
	IV			4	NA		
	III			4	NA		
	III			4	NA		
	III			4	NA		
	III			4	NA		
	III			4	NA		
	III			4	NA		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	22430	Lysteda™, held by Ferring Pharms AS

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	EES Pending OAI	2/11/11	
Methods Validation	NA		
Labeling	Acceptable	9/30/11	PARK, SOOJUNG S
Bioequivalence	Adequate	3/29/2012	XIA, LI
EA	Categorical Exclusion		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _X_ Yes ____ No If no, explain reason(s) below:

Chemistry Review for ANDA 202286

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is still not approvable based on the CMC status. It is recommended that a ***Not Approvable***, ***Minor deficiencies***, letter be sent to the applicant.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

a) Drug product:

Tranexamic Acid Tablets, 650 mg, are White to off-white, oval, biconvex tablets. Engraved "APO" on one side, (b) (4) on the other side. This will change to (b) (4) during commercial distribution (post-approval). The product is manufactured at the Apotex Signet site. The manufacturing process is (b) (4) The drug product specification includes (b) (4) (b) (4) (b) (4). The ANDA product differs from the RLD in the formulation design, since the ANDA product (b) (4) (b) (4)

b) Drug substance:

Tranexamic acid is a compendial item covered by the USP and EP. It is manufactured by (b) (4) and the DMF holder is (b) (4) (b) (4) The DMF is adequate upon review. Tranexamic Acid is white to off-white powder. It is freely soluble in water and glacial acetic acid, practically insoluble in alcohol, or ether. The specification includes (b) (4)

(b) (4). The impurities include the USP Impurities A, B, C and D, with an unidentified impurity level at NMT (b) (4)% and total impurity at NMT 0.2%. The proposed re-test period is (b) (4) months.

B. Description of How the Drug Product is Intended to be Used

Tranexamic acid tablets are indicated for the treatment of cyclic heavy menstrual bleeding. Prior to prescribing, exclude endometrial pathology that can be associated with heavy menstrual bleeding.

The recommended dose 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. It may be administered without regard to meals. Tablets should be swallowed whole and not chewed or broken apart.

Therefore, the **MDD is 3,900 mg.**
Based on the MDD, the IT for drug product is 0.10% and QT is 0.15% per ICHQ3B.

C. Basis for Approvability or Not-Approval Recommendation

This application is ***not approvable*** based on the ***minor CMC deficiencies***. Outstanding issues are listed in the deficiency letter.

Following this page, 79 Pages Withheld in Full as (b)(4)

III. List Of Deficiencies To Be Communicated

Chemistry Comments to be Provided to the Applicant

ANDA: 202286

APPLICANT: Apotex, Inc.

DRUG PRODUCT: Tranexamic Acid Tablets, 650 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)

2.

3.

4. Please update ambient stability data for the drug product (all configurations).

Sincerely yours,

{See appended electronic signature page}

Glen J. Smith
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Endorsements:

HFD-640 /Xiaobin Zhao/ 5/11/2011, 5/14/2012
HFD-640 /Radhika Rajagopalan/ 5/14/12; 5/15/12
HFD-617/Frank Nice/5/15/12

TYPE OF LETTER: NOT APPROVABLE - MINOR

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

/s/

XIAOBIN ZHAO
05/15/2012

FRANK J NICE
05/15/2012

RADHIKA RAJAGOPALAN
05/15/2012

ANDA 202286

Tranexamic Acid Tablets, 650 mg

Apotex Inc.

Xiaobin Zhao, Ph.D.
Chemistry Division II
Team 21

Table of Contents

Table of Contents ii

Chemistry Review Data Sheet 4

Executive Summary 10

I. Recommendations 10

A. Recommendation and Conclusion on Approvability 10

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 10

II. Summary of Chemistry Assessments 10

A. Description of the Drug Product(s) and Drug Substance(s) 10

B. Description of How the Drug Product is Intended to be Used 11

Basis for Approvability or Not-Approval Recommendation 11

Chemistry Assessment 12

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data based on QbR-QOS 12

2.3 Introduction to the Quality Overall Summary 12

2.3.S DRUG SUBSTANCE 12
- 2.3.S.1 General Information 12
- 2.3.S.2 Manufacture 14
- 2.3.S.3 Characterization 16
- 2.3.S.4 Control of Drug Substance 17
- 2.3.S.5 Reference Standards or Materials 25
- 2.3.S.6 Container Closure System 27
- 2.3.S.7 Stability 27

2.3.P DRUG PRODUCT 28
- 2.3.P.1 Description and Composition of the Drug Product 28
- 2.3.P.2 Pharmaceutical Development 30
- 2.3.P.3 Manufacture 42
- 2.3.P.4 Control of Excipients 55
- 2.3.P.5 Control of Drug Product 55
- 2.3.P.6 Reference Standards or Materials 65
- 2.3.P.7 Container Closure System 65
- 2.3.P.8 Stability 67

A APPENDICES 73
- A.1 Facilities and Equipment (biotech only) 73
- A.2 Adventitious Agents Safety Evaluation 73
- A.3 Novel Excipients 73

R REGIONAL INFORMATION 73
R.1 Executed Batch Records 73
R.2 Comparability Protocols 73
R.3 Methods Validation Package 73
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 75
A. Labeling & Package Insert 75
B. Environmental Assessment Or Claim Of Categorical Exclusion 75
III. List Of Deficiencies To Be Communicated 75

Chemistry Review Data Sheet

1. ANDA #: 202286

2. REVIEW #: 1

3. REVIEW DATE: August 10, 2011 – August 25, 2011

4. REVIEWER: Xiaobin Zhao, Ph D

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
NA	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original -1	August 31, 2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex Inc.
Address:	150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Representative:	Bernice Tao
Telephone:	416-749-9300
Fax:	416-401-3849
US Agent:	Kiran Krishnan
Telephone:	954-384-3986
Fax:	954-349-4233
Address:	Apotex Corp, 2400 N. Commerce Parkway Suite 400, Weston, Florida, 33326

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: Lysteda™
Non-Proprietary Name (USAN): Tranexamic Acid Tablets, 650 mg

- Chem. Type: Small molecule
- Submission Priority: Paragraph IV

9. LEGAL BASIS FOR SUBMISSION:

The basis for the ANDA application for Tranexamic Acid Tablets, 650 mg, is the approved reference listed drug, Lysteda™ (Tranexamic Acid) Tablets, listed in the Electronic Orange Book. Lysteda™ is the subject of New Drug Application 22430, and is the subject of NDA # N022430 held by Ferring Pharms AS. On 5/27/2011, the firm filed a patent amendment to file a Paragraph IV Certification for US Patent No. 7,947,739.

10. PHARMACOL. CATEGORY:

Treatment of cyclic heavy menstrual bleeding

11. DOSAGE FORM:

Tablets

12. STRENGTH/POTENCY:

650 mg

13. ROUTE OF ADMINISTRATION:

Oral

14. Rx/OTC DISPENSED:

X Rx __OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

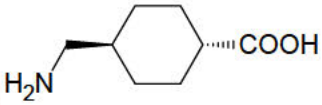
_____SPOTS product – Form Completed

__X__Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): *trans*-4-(Aminomethyl)cyclohexanecarboxylic acid
Molecular Formula: $C_8H_{15}N0_2$
Molecular Weight: 157.2

Chemical Structure: 

CAS #: 1197-18-8

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	8/9/11	by X. Zhao
	III			4	NA		
	IV			4	NA		
	III			4	NA		
	III			4	NA		
	III			4	NA		
	III			4	NA		
	III			4	NA		
	III			4	NA		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	22430	Lysteda™, held by Ferring Pharms AS

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES*	EES Pending OAI	2/11/11	
Methods Validation	NA		
Labeling	Deficiencies	2/10/2011	PARK, SOOJUNG S
Bioequivalence	Incomplete deficiencies – dissolution Pending-BE studies	8/14/2011	JOHNSON, GLENDOLYNN S
EA	Categorical Exclusion		
Radiopharmaceutical	NA		

* TL has a copy of draft ees.

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _X_ Yes ____ No If no, explain reason(s) below:

Chemistry Review for ANDA 202093

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is not approvable based on the CMC status. It is recommended that a ***Not Approvable***, ***Minor deficiencies***, letter be sent to the applicant.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

a) Drug product:

Tranexamic Acid Tablets, 650 mg, are White to off-white, oval, biconvex tablets. Engraved "APO" on one side, (b) (4)" on the other side. The product is manufactured at the Apotex Signet site, but the firm proposed (b) (4) (b) (4) (b) (4) We will request them to (b) (4) The manufacturing process is (b) (4) (b) (4) (b) (4). The drug product specification includes (b) (4) (b) (4). The ANDA product differs from the RLD in the formulation design, since the ANDA product (b) (4) (b) (4). We recommend that the firm conduct additional in-process controls for critical manufacturing steps, and additional tests be conducted for product release and stability studies.

b) Drug substance:

Tranexamic acid is a compendial item covered by the USP and EP. It is manufactured by (b) (4). and the DMF holder is (b) (4) (b) (4) The DMF is adequate upon review. Tranexamic Acid is white to off-white powder. It is freely soluble in water and glacial acetic acid, practically insoluble in alcohol, or ether. The specification includes (b) (4)

(b) (4). The impurities include the USP Impurities A, B, C and D, with an unidentified impurity level at NMT (b) (4)% and total impurity at NMT 0.2%. The proposed re-test period is (b) (4) months.

B. Description of How the Drug Product is Intended to be Used

Tranexamic acid tablets are indicated for the treatment of cyclic heavy menstrual bleeding. Prior to prescribing, exclude endometrial pathology that can be associated with heavy menstrual bleeding.

The recommended dose 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. It may be administered without regard to meals. Tablets should be swallowed whole and not chewed or broken apart.

Therefore, the **MDD is 3,900 mg.**
Based on MDD, the IT for drug product is 0.10% and QT is 0.15% per ICHQ3B.

C. Basis for Approvability or Not-Approval Recommendation

This application is ***not approvable*** based on the ***minor CMC deficiencies***. Outstanding issues are listed in the deficiency letter.

III. List Of Deficiencies To Be Communicated

Chemistry Comments to be Provided to the Applicant

ANDA: 202286

APPLICANT: Apotex, Inc.

DRUG PRODUCT: Tranexamic Acid Tablets, 650 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)
2.
3.
4.
5.
6.

(b) (4)

7.

8.

9.

10.

11.

12.

13.

14.

15.

16.

17.

18.

19. (b) (4)

20.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please update ambient stability data for the drug product (all configurations).

2. Please provide your product and RLD samples (2 package units each) for evaluation. Samples can be sent to the attention of:
   Frank J. Nice, RPh, DPA, CPHP
   Project Manager
   Office of Generic Drugs
   Food and Drug Administration
   HFD-617, Rm E254, MPN 2
   240-276-8555

Sincerely yours,

{See appended electronic signature page}

Glen J. Smith
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Endorsements:

HFD-640 /Xiaobin Zhao/ 8/25/2011, 10/21/2011
HFD-640 /Radhika Rajagopalan/ 8/31/2011; 9/6/2011; 10/21/2011
HFD-617/Frank Nice/10/25/11

TYPE OF LETTER: NOT APPROVABLE - MINOR

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

/s/

XIAOBIN ZHAO
10/25/2011

FRANK J NICE
10/25/2011

RADHIKA RAJAGOPALAN
10/25/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202286

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	202286		
Drug Product Name	Tranexamic Acid Tablets		
Strength(s)	650 mg		
Applicant Name	Apotex Inc.		
Address	150 Signet Drive, Toronto, Ontario, Canada, M9L 1T9		
Applicant's Point of Contact	Bernice Tao 150 Signet Drive, Toronto, Ontario, Canada, M9L 1T9		
Contact's Telephone Number	1- 416- 401-7889		
Contact's Fax Number	1- 416- 401-3817		
Original Submission Date(s)	August 31, 2010		
Submission Date(s) of Amendment(s) Under Review	4/14/2011 (dissolution data) September 16, 2011 (SD-10, Dissolution Acknowledgement)		
Reviewer	Li Xia, Ph.D.		
Study Number (s)	TRAC-IMTB-05SB01-2FA (XC6312)	TRAC-IMTB-05SB02-2FE (XC6313)	
Study Type (s)	Fasting	Fed	
Strength (s)	1 x 650 mg	1 x 650 mg	
Clinical Site	Apotex Inc.,		
Clinical Site Address	BioClinical Development Clinical Operations Department 465 Garyray Drive Toronto, Ontario		
Analytical Site	Apotex Inc.		
Analytical Site Address	BioClinical Development Bioanalytical Laboratory 440 Garyray Drive Toronto, Ontario		
Overall Review Result	**ADEQUATE**		
Waiver Request Result	**N/A**		
DSI Report Result	**ADEQUATE**		
Bioequivalence Study	**Study/Test Type**	**Bioequivalence Study**	**Review Result**
1	**Dissolution**	**650 mg**	**ADEQUATE**
1	**Fasting Study**	**650 mg**	**ADEQUATE**
1	**Fed Study**	**650 mg**	**ADEQUATE**

1 EXECUTIVE SUMMARY

This application contains the results of fasting and fed bioequivalence (BE) studies comparing a test product, Apotex Inc.'s Tranexamic Acid Tablets, 650 mg to the corresponding reference product, Ferring Pharms As' LYSTEDA™ (tranexamic acid) Tablets, 650 mg. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy female subjects. The firm's fasting and fed BE studies are acceptable. The results are summarized in the tables below.

Tranexamic Acid Tablets, 1 x 650 mg
Fasting Bioequivalence Study [No. TRAC-IMTB-05SB01-2FA (XC6312)], N=28 (female)
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (ng·hr/mL)	61243.58	61510.48	1.00	92.99	106.61
AUC∞ (ng·hr/mL)*	63690.36	63748.33	1.00	93.06	107.26
Cmax (ng/mL)	9559.16	9642.23	0.99	92.43	106.33

* Computation of AUC∞ is based on 28 subjects for the test product, and 27 subjects for the reference listed drug (excluding subject #2 whose kel can not be reliably determined).

Tranexamic Acid Tablets, 1 x 650 mg
Fed Bioequivalence Study [No. TRAC-IMTB-05SB02-2FE (XC6313)], N=28 (female)
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (ng·hr/mL)	54455.99	54449.30	1.00	96.81	103.32
AUC∞ (ng·hr/mL)*	56354.89	56473.68	1.00	96.75	102.93
Cmax (ng/mL)	8664.45	8199.74	1.06	101.31	110.21

* Computation of AUC∞ is based on 27 subjects for the test product (excluding subject #68 whose kel can not be reliably determined), and 28 subjects for the reference listed drug.

There is no USP method but there is a FDA-recommended method for this product (900 mL of water using apparatus II at 50 rpm). In its original submission, the firm's dissolution method (900 mL of (b) (4) using apparatus II at (b) (4) rpm) was different from the FDA-recommended method. In DB's deficiency letter dated 2/28/2011, the firm was requested to repeat dissolution testing using the FDA - recommended method[1]. In its amendment dated 4/14/2011, the firm had submitted acceptable dissolution testing data using the FDA-recommended method.[2]. In its amendment dated 9/16/2011, Apotex acknowledged the acceptance of the FDA-recommended dissolution method and specification.

[1] DARRTS: REV-BIOEQ-02(Dissolution Review) for ANDA 202286, final date 2/25/2011.

[2] DARRTS: REV-BIOEQ-02(Dissolution Review) for ANDA 202286, final date 8/4/2011.

A "For Cause" of Office of Scientific Investigation's (OSI) inspection for the clinical site was requested for ANDA 090960 on 10/27/10 and was completed on 11/21/10 with an outcome of VAI. The DB reviewed the inspection report and concurred with the OSI's recommendations, the clinical data are acceptable for ANDA 090960[3]. In current reviewer's opinion, the reasons of "For Cause" inspection" for parent ANDA 090960 are not relevant to this application. Therefore, the OSI inspection for the clinical site is acceptable. A "For Cause" inspection for the analytical site for ANDA 090960 was requested on 10/27/10 and completed on 11/21/10 with an outcome of NAI. Therefore, no OSI inspection is pending or necessary for the clinical site and analytical site.

The application is adequate.

2 TABLE OF CONTENTS

1 Executive Summary 2
2 Table of Contents 3
3 Submission Summary 4
3.1 Drug Product Information 4
3.2 PK/PD Information 4
3.3 OGD Recommendations for Drug Product 5
3.4 Contents of Submission 6
3.5 Pre-Study Bioanalytical Method Validation 6
3.6 In Vivo Studies 8
3.7 Formulation 12
3.8 In Vitro Dissolution 12
3.9 Waiver Request(s) 13
3.10 Deficiency Comments 13
3.11 Recommendations 13
3.12 Comments for Other OGD Disciplines 14
4 Appendix 15
4.1 Individual Study Reviews 15
4.1.1 Single-dose Fasting Bioequivalence Study 15
4.1.1.1 Study Design 15
4.1.1.2 Clinical Results 17
4.1.1.3 Bioanalytical Results 20
4.1.1.4 Pharmacokinetic Results 21
4.1.2 Single-dose Fed Bioequivalence Study 25
4.1.2.1 Study Design 25
4.1.2.2 Clinical Results 27
4.1.2.3 Bioanalytical Results 29
4.1.2.4 Pharmacokinetic Results 30
4.2 Formulation Data 35
4.3 Dissolution Data 37
4.4 SAS Output 39
4.4.1 Fasting Study Data 39
4.4.2 Fasting Study Codes 44
4.4.3 Fasting Study Output 71
4.4.4 Fed Study Data 87
4.4.5 Fed Study Codes 93
4.4.6 Fed Study Output 120
4.5 Outcome Page 137

[3] DARRTS: REV-BIOEQ-01(General Review) for ANDA 090960, final date 3/8/2012.

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Tranexamic Acid Tablets, 650 mg
Reference Product	LYSTEDA ™ (tranexamic acid) Tablets, 650 mg
RLD Manufacturer	FERRING PHARMS AS
NDA No.	N022430
RLD Approval Date	Nov 13, 2009
Indication	LYSTEDA™ (tranexamic acid) Tablets is an antifibrinolytic indicated for the treatment of cyclic heavy menstrual bleeding.

3.2 PK/PD Information[4]

Bioavailability	After a single oral administration of two 650 mg tablets of LYSTEDA, the peak plasma concentration (Cmax) occurred at approximately 3 hours (Tmax). 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 Cmax 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.
Food Effect	LYSTEDA may be administered without regard to meals. A single dose administration (two 650 mg tablets) of LYSTEDA with food increased both Cmax and AUC by 7% and 16%, respectively.
Tmax	3 hours
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

[4] Labeling Repository of LYSTEDA™ (tranexamic acid) Tablets.

	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.
Half-life	11 hours
Drug Specific Issues (if any)	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. • 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. • Visual or ocular adverse effects may occur with LYSTEDA. Immediately discontinue use if visual or ocular symptoms occur. • In case of severe allergic reaction, discontinue LYSTEDA and seek immediate medical attention. • Cerebral edema and cerebral infarction may be caused by use of LYSTEDA in women with subarachnoid hemorrhage. • Ligneous conjunctivitis has been reported in patients taking tranexamic acid.

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2, fasting and fed

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	650 mg
	Subjects:	Healthy males and nonpregnant females, general population
	Additional Comments:	None

2.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	650 mg
	Subjects:	Healthy males and nonpregnant females, general population
	Additional Comments:	Please refer to the Amantadine Hydrochloride Tablet Draft Guidance for additional information regarding fed studies.

Analytes to measure (in plasma/serum/blood):	Tranexamic acid in plasma
Bioequivalence based on:	90% CI of Tranexamic acid
Waiver request of in-vivo testing:	N/A
Source of most recent recommendations:	CDER Draft Guidance on Individual Product Bioequivalence Recommendations for Tranexamic Acid at http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM238065.pdf
Summary of OGD or DBE History	The DBE has received the following ANDAs for this drug product: ANDA 202093 (Watson, the first generic) – tentative approval ANDA 202286 (Apotex) – pending ANDA (b) (4)

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	0
In vitro dissolution	Yes	1
Waiver requests	No	0
BCS Waivers	No	0
Clinical Endpoints	No	0
Failed Studies	No	0
Amendments	Yes	September 16, 2011 (SD-10, Dissolution Acknowledgement)

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	Section 16.6.4
Analyte	Tranexamic Acid (XC)
Internal standard (IS)	(b) (4)
Method description	Solid phase extraction with mass spectrometry detection
Limit of quantitation	20.0 ng/mL
Average recovery of drug (%)	QC A: 59.57 QC B: 63.53 QC C: 62.50 Average: 61.87 %
Average recovery of IS (%)	74.66 %
Standard curve concentrations (units/mL)	20.0, 40.0, 80.0, 200.0, 500.0, 2000.0, 4000.0, 6000.0,

	8000.0 and 10000.0 ng/mL
QC concentrations (units/mL)	QC A: 60.0 ng/mL QC B: 3000.0 ng/mL QC C: 7500.0 ng/mL
QC Intraday precision range (%)	QC A: 1.8 to 5.1 % QC B: 1.5 to 6.8 % QC C: 1.7 to 4.4 %
QC Intraday accuracy range (%)	QC A: -3.0 to 2.0 % QC B: 3.2 to 9.5 % QC C: -0.4 to 6.3 %
QC Interday precision range (%)	3.1 to 3.7 %
QC Interday accuracy range (%)	-0.5 to 5.8 %
Bench-top stability (hrs)	19.5 hours @ room temperature
Stock stability (days)	112 days @ refrigerated for XCMS and 35 days @ refrigerated for (b) (4)-MS
Processed stability (hrs)	74 hours @ refrigerated 21 hours @ room temperature
Freeze-thaw stability (cycles)	5 cycles
Long-term storage stability (days)	86 days @ -30°C set point freezer
Dilution integrity	Diluted 2 fold and 4 fold
Selectivity	No known metabolites, endogenous plasma components, common drug or their metabolites or commonly used female contraceptives interfere with the analytical assay

SOPs submitted	ABM-BL-0153 Analytical Method Validation	ABM-BL-0154 Routine Batch Sample Analysis
	ABM-BL-0156 Chromatography Acceptance	ABM-BL-0155 Assay Failure Investigation
	ABM-BL-0158 Analytical Run Analysis and Documentation Procedures	ABM-BL-0160 Event Resolution
	ABM-BL-0163 Incurred Sample Repeat Analysis	
Bioanalytical method is acceptable	No, see comments below	

Comments on the Pre-Study Method Validation:

The long-term storage stability duration of 86 days at -30°C exceeds the storage period of the study samples for both the fasted (25 days) and fed (29 days) studies.

Method validation is acceptable.

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age†: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					Cmax (ng/ml)	Tmax‡ (h)	AUCt (ng*h/ml)	AUCinf (ng*h/ml)	Thalf (h)	Kel (1/h)	
TRAC-IMTB-05SB01-2FA (XC6312)	Comparative, randomized, 2-way crossover bioavailability study of Tranexamic Acid Tablets (Apotex Inc.) and Lysteda™ Tablets (Xanodyne® Pharmaceuticals, Inc.), (USA) under fasting conditions	Randomized single-dose 2-way crossover	Tranexamic Acid Tablets, (1 x 650 mg Oral Dose) [Lot # FD149-13]	28 (0/28) completing Healthy subjects 40.7 (19 - 55)	9971.9 ±2862.6	3.18 (1.50 – 4.00)	62603.3 ±13163.0	64965.3 ±13215.2	18.82 ±6.53	0.04035 ±0.01135	5.3.1.2
			Lysteda™ Tablets, (1 x 650 mg Oral Dose) [Lot# A100018A]		9857.9 ±2148.5	3.19 (2.00 – 4.52)	62989.0 ±13960.8	65070.6 ±14090.6	17.91 ±5.91	0.04187 ±0.01082	
TRAC-IMTB-05SB02-2FE (XC6313)	Comparative, randomized, 2-way crossover bioavailability study of Tranexamic Acid Tablets (Apotex Inc.) and Lysteda™ Tablets (Xanodyne® Pharmaceuticals, Inc.), (USA) under fed conditions	Randomized single-dose 2-way crossover	Tranexamic Acid Tablets, (1 x 650 mg Oral Dose) [Lot # FD149-13]	28 (28/0) completing Healthy subjects 39.5 (23 - 55)	8905.0 ±1978.5	3.17 (2.00 – 5.00)	55938.0 ±12142.7	58101.8 ±12617.9	17.66 ±8.48	0.04457 ±0.01350	5.3.1.2
			Lysteda™ Tablets, (1 x 650 mg Oral Dose) [Lot# A100018A]		8392.5 ±1698.9	4.25 (2.67 – 7.00)	56162.0 ±12935.8	59001.6 ±12148.5	17.00 ±5.84	0.04462 ±0.01265	

† Based on number of subjects dosed in period 1
‡ Tmax is presented as median (range)

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Tranexamic Acid Tablets, 1 x 650 mg Fasting Bioequivalence Study [No. TRAC-IMTB-05SB01-2FA (XC6312)], N=28 (female) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	61243.58	61510.48	1.00	92.99	106.61
AUC∞ (ng·hr/mL)*	63690.36	63748.33	1.00	93.06	107.26
Cmax (ng/mL)	9559.16	9642.23	0.99	92.43	106.33

* Computation of AUC∞ is based on 28 subjects for the test product, and 27 subjects for the reference listed drug (excluding subject #2 whose kel can not be reliably determined).

Tranexamic Acid Tablets, 1 x 650 mg Fed Bioequivalence Study No. TRAC-IMTB-05SB02-2FE (XC6313), N=28 (female) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	54455.99	54449.30	1.00	96.81	103.32
AUC∞ (ng·hr/mL)*	56354.89	56473.68	1.00	96.75	102.93
Cmax (ng/mL)	8664.45	8199.74	1.06	101.31	110.21

* Computation of AUC∞ is based on 27 subjects for the test product (excluding subject #68 whose kel can not be reliably determined), and 28 subjects for the reference listed drug.

Table 3. Reanalysis of Study Samples

Study No. TRAC-IMTB-05SB01-2FA Additional information in Section 16.5.1.6.3								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.0	0.0	0	0	0.0	0.0
B: Analysis Incomplete – extraction Error	0	1	0.0	0.1	0	1	0.0	0.1
C: Poor Chromatography	0	1	0.0	0.1	0	1	0.0	0.1
F: Outside Range	72	64	6.1	5.4	72	64	6.1	5.4
G: Highest and/or Lowest Std Missing	2	2	0.2	0.2	2	2	0.2	0.2
Total	74	68	6.0	5.5	74	68	6.0	5.5

Study No. TRAC-IMTB-05SB02-2FE Additional information in Section 16.5.1.6.3								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.0	0.0	0	0	0.0	0.0
B: Analysis Incomplete – extraction Error	1	0	0.1	0.0	1	0	0.1	0.0
B: Analysis Incomplete – lost, solvent blank injected	0	1	0.0	0.1	0	1	0.0	0.1
F: Outside Range	26	19	2.1	1.5	26	19	2.1	1.5
H: Anomalous IS Response	0	1	0.0	0.1	0	1	0.0	0.1
Total	27	21	2.2	1.7	27	21	2.2	1.7

Did use of recalculated plasma concentration data change study outcome?

N/A.

Reviewer's Comments:

In the fasting study, 136 plasma samples (72 for test and 64 samples for the RLD) were repeated due to the values exceed the ULOQ of the run (10000 ng/mL), 4 samples were repeated due to missing highest/lowest standard, 2 samples were repeated due to poor chromatography or extraction error.

In the fed study, 45 samples (26 for test and 19 for the RLD) were repeated due to the values exceed the ULOQ of the run(10000 ng/mL), 2 samples were repeated due to analysis incomplete, and 1 sample was repeated due to anomalous IS response.

Since the firm followed its SOP "Routine Batch Sample Analysis (ABM-BL-0154)" for all the repeats, therefore, the repeat analyses are acceptable.

3.7 Formulation

Location in appendix	Section 4.2, Page 34
If a tablet, is the RLD scored?	Not scored
If a tablet, is the test product biobatch scored	Not scored
Is the formulation acceptable?	**ACCEPTABLE**
If not acceptable, why?	N/A

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DARRTS: REV-BIOEQ-02(Dissolution Review) for ANDA 202286, final date 2/25/2011 DARRTS: REV-BIOEQ-02(Dissolution Review) for ANDA 202286, final date 8/4/2011
Source of Method (USP, FDA or Firm)	FDA
Medium	Water
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm
DBE-recommended specifications	NLT (b) (4)% (Q) in 60 minutes for current ANDA[5]
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	quickly dissolving
Is method acceptable?	**Yes**
If not then why?	

Reviewer's Comments:

1. There is no USP method for this product but there is a FDA-recommended method (900 mL of water using apparatus II at 50 rpm). Originally, firm conducted dissolution testing using its own method (900 mL of (b) (4) (b) (4) using apparatus II at (b) (4) rpm), which was different from the FDA recommended method. In DB's deficiency letter dated 2/28/2011, the firm was requested to repeat dissolution testing using the FDA -recommended method[1].

[5] The FDA-recommended method is the same dissolution method as the RLD LYSTEDA™ (tranexamic acid) Tablets, 650 mg (NDA 022430). However, the specification recommended for the test product (NLT (b) (4)% (Q) in 60 minutes) is different from the specification for the RLD product (NLT (b) (4)% (Q) in 90 minutes).

2. In its amendment dated 4/14/2011, the firm had submitted acceptable dissolution testing data using the FDA recommended method. Per dissolution review[2], the data using the firm's method were not very different from the data using the FDA-recommended method after comparing the dissolution results. Thus the firm was requested to acknowledge the FDA-recommended dissolution method and a specification of NLT (b)(4)% (Q) in 60 minutes. In its amendment dated 9/16/2011, Apotex acknowledged the acceptance of the FDA-recommended dissolution method and specification.

3.9 Waiver Request(s)

Strengths for which waivers are requested	N/A
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	Yes
Waivers granted?	N/A
If not then why?	N/A

3.10 Deficiency Comments

N/A

3.11 Recommendations

1. The Division of Bioequivalence **accepts** the fasting BE study (No. TRAC-IMTB-05SB01-2FA (XC6312). Apotex Inc. conducted the fasting BE study on its Tranexamic Acid Tablets, 650 mg, lot# FD149-13, comparing it to Ferring Pharms As' LYSTEDA™ (tranexamic acid) Tablets, 650 mg, lot# A100018A.

2. The Division of Bioequivalence **accepts** the fed BE study (No. TRAC-IMTB-05SB02-2FE (XC6313)]. Apotex Inc. conducted the fed BE study on its Tranexamic Acid Tablets, 650 mg, lot# FD149-13, comparing it to Ferring Pharms As' LYSTEDA™ (tranexamic acid) Tablets, 650 mg, lot# A100018A.

3. The firm's in vitro dissolution testing is **acceptable**. The firm should conduct the following FDA-recommended dissolution method and specification:

   Medium: Water
   Volume: 900 mL
   Apparatus: USP Apparatus II (paddles)
   Speed: 50 rpm
   Temperature: 37°C ± 0.5°C
   Specification: Not less than (b)(4)% (Q) in 60 minutes

4. The Division of Bioequivalence deems the test product Tranexamic Acid Tablets , manufactured by Apotex Inc., to be bioequivalent to the reference product, LYSTEDA™ (tranexamic acid) Tablets, manufactured by Ferring Pharms As.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
	None

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	TRAC-IMTB-05SB01-2FA (XC6312)
Study Title	Comparative, Randomized, 2-way Crossover Bioavailability Study of Tranexamic Acid Tablets (Apotex) and Lysteda Tablets (Xanodyne Pharm) (USA) Under Fasting Conditions
Clinical Site (Name, Address, Phone #)	Apotex Inc., BioClinical Development Clinical Operations Department 465 Garyray Drive Toronto, Ontario Tel#: (416) 741-4256
Principal Investigator	G. Rai, M.D.
Dosing Dates	1st dosing date (Period 1: 06/14/10) and 2nd dosing date for (Period 2: 06/21/10)
Analytical Site (Name, Address, Phone #)	Apotex Inc. BioClinical Development Bioanalytical Laboratory 440 Garyray Drive Toronto, Ontario 416-749-9300
Analysis Dates	June 29, 2010 to July 9, 2010
Analytical Director	(b) (6) B.Sc.
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	25 days

Table 5. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Tranexamic Acid Tablets	Lysteda® Tablets
Manufacturer	Apotex Inc.	Xanodyne Pharmaceuticals Inc.
Batch/Lot No.	FD149-13	A100018A
Manufacture Date	April 2010	NA
Expiration Date	April 2012	Dec 2011
Strength	650 mg	650 mg
Dosage Form	Tablets	Tablets

Bio-batch Size	(b) (4)	NA
Production Batch Size		NA
Potency	101.4%	100.7%
Content Uniformity (mean, %CV)	101.4% (%CV 0.6)	NA
Dose Administered	1 x 650 mg	1 x 650 mg
Route of Administration	Oral	Oral

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	30 subjects were dosed, 28 subjects* completed and were included in analysis
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	TR: XC01, XC04, XC05, XC08, XC11, XC12, XC13, XC15, XC17, XC19, XC22, XC23, XC25, XC27, XC30 RT: XC02, XC03, XC06, XC07, XC09, XC10, XC14, XC16, XC18, XC20, XC21, XC24, XC26, XC28, XC29
Blood Sampling Times	0.00 (x1) (5-45 minutes prior to dosing) followed by 0.5, 1, 1.5, 2, 2.3333, 2.6667, 3, 3.3333, 3.6667, 4, 4.5, 5, 6, 7, 9, 12, 16, 24, 36 and 48 hours post-dosing.
Blood Volume Collected/Sample	Blood samples were collected using 6 mL lavender cap vacuum tubes containing K2EDTA at the above sampling time-points.
Blood Sample Processing/Storage	Blood samples were centrifuged and the plasma was transferred into labeled polypropylene storage tubes and stored in a -30°Cset point freezer pending assay.
IRB Approval	January 29, 2010
Informed Consent	January 29, 2010
Length of Fasting	Overnight fast of at least 10 hours,
Length of Confinement	Subjects reported for check-in and confinement at the clinic site on the morning prior to each study period in order to comply with the requisite pre-dose fasting period.
Safety Monitoring	Vital signs (blood pressure, pulse & temperature) at check-in and check-out of each period • Adverse event monitoring • Diagnostic testing at 48 hours post dose for CBC using a 4 mL lavender cap vacuum tube containing EDTA

*Subject #8 withdrew from the study due to adverse events. Subject #18 voluntarily withdrew from the study.

Comments on Study Design:

The study design is acceptable.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. TRAC-IMTB-05SB01-2FA Internal Code: XC6312			
		Treatment Groups	
		Test Product Tranexamic Acid Tablets N = 28	Reference Product Lysteda Tablets N = 28
Age (years)	Mean ± SD	41.0 ± 10.1	41.0 ± 10.1
	Range	19 - 55	19 - 55
Age Groups	< 18	0.0(%)	0.0(%)
	18 – 39	11.0(39.29%)	11.0(39.29%)
	40 – 64	17.0(60.71%)	17.0(60.71%)
	65 – 75	0.0(%)	0.0(%)
	> 75	0.0(%)	0.0(%)
Sex	Male	0.0 (%)	0.0(%)
	Female	28.0(100.0%)	28.0(100.0%)
Race	Asian	4.0(14.29%)	4.0(14.29%)
	Black	4.0(14.29%)	4.0(14.29%)
	Caucasian	14.0(50.0%)	14.0(50.0%)
	Hispanic or Latino	5.0(17.85%)	5.0(17.85%)
	Multi-racial	1.0(3.57%)	1.0(3.57%)
	Native Hawaiian	0.0(%)	0.0(%)
	Aboriginal	0.0(%)	0.0(%)
BMI	Mean ± SD	24.7 ± 2.7	24.7 ± 2.7
	Range	19.9 – 29.2	19.9 – 29.2

Table 8. Dropout Information, Fasting Bioequivalence Study

Protocol No. TRAC-IMTB-05SB01-2FA-(1) Study Code No. XC6312				
Subject No	**Reason for dropout/replacement***	**Period**	**Replaced?**	**Replaced with**
XC08	Withdrawn due to adverse event (allergic reaction) on 06/15/10 at 08:57 possibly due to the test product.	Post period 1 dosing	No	NAP
XC18	Voluntary withdrawal on 06/13/10 at 19:50, not related to the reference product.	Period 2 check in night	No	NAP

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study Protocol No. TRAC-IMTB-05SB01-2FA-(1) Study Code No. XC6312	
	Test	Reference
Skin and subcutaneous tissue disorders		
Rash	NAP	1 (3.44%)
Reproductive system and breast disorders		
Dysmenorrhoea	NAP	1 (3.44%)
Nervous system disorders		
Dizziness	1 (3.44%)	1 (3.44%)
Headache	1 (3.44%)	1 (3.44%)
Paraesthesia	NAP	1 (3.44%)
Somnolence	1 (3.44%)	NAP
Burning sensation	NAP	1 (3.44%)
Immune system disorders		
Hypersensititvity	1 (3.44%)	NAP
General disorders administration site conditions		
Catheter site haematoma	1 (3.44%)	NAP
Fatigue	1 (3.44%)	NAP
Vessel puncture site haematoma	1 (3.44%)	1 (3.44%)
Vessel puncture site pain	1 (3.44%)	2 (6.89%)
Gastrointestinal disorders		
Abdominal pain	NAP	1 (3.44%)
Constipation	1 (3.44%)	NAP
Cardiac disorders		
Sinus bradycardia	NAP	1 (3.44%)
Total	4 (13.79 %)	7 (24.13 %)
Number of subject dosed	29	29

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Protocol No. TRAC-IMTB-05SB01-2FA-(1) Study Code No. XC6312		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
NAP	NAP	NAP

Comments on Dropouts/Adverse Events/Protocol Deviations:

Dropouts

Subject XC08 was withdrawn due to adverse event (allergic reaction) post period 1 dosing possibly produced by the test drug. Subject XC18 voluntarily withdrew (subject did not show up period 2 check-in night). Their samples were not included in PK and statistical analysis.

Adverse Events

Total of nine (9) mild adverse events (AEs), occurred in four (4) subjects after they received the test preparation. A total of one (1) moderate AE, occurred in one (1) subject after she received the test preparation. A total of twelve (12) mild AEs, occurred in seven (7) subjects after they received the reference preparation.

There were no serious or unexpected AEs reported during the study.

Protocol Deviations

There were 91 blood sampling time deviations during the entire study, the majority variations are less than 5 minutes, the time deviations were considered unlikely to affect the PK analysis or overall PK conclusions. The firm used the actual time and the reviewer used the scheduled time points for PK and statistical analysis.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Bioequivalence Study No. TRAC-IMTB-05SB01-2FA Tranexamic Acid										
Parameter	**Standard Curve Samples**									
Concentration (ng./mL)	20.0	40.0	80.0	200.0	500.0	2000.0	4000.0	6000.0	8000.0	10000.0
Inter day Precision (%CV)	3.9	5.5	3.5	3.2	2.3	3.1	4.1	2.7	2.9	2.0
Inter day Accuracy (%Dev)	3.0	0.5	-4.6	-1.6	1.3	3.1	2.4	0.0	0.5	-3.5
Linearity	0.9990 – 0.9999									
Linearity Range (ng/mL)	20.0 – 10000.0									
Sensitivity/LOQ (ng/mL)	20.0									

Bioequivalence Study No. TRAC-IMTB-05SB01-2FA Tranexamic Acid			
Parameter	**Quality Control Samples**		
Concentration (ng/mL)	60.0	3000.0	7500.0
Inter day Precision (%CV)	8.9	4.8	4.8
Inter day Accuracy (%Dev)	2.5	7.9	2.0

Comments on Study Assay Validation:

Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes (Subjects XC01, XC02, XC03, XC04, XC05, XC06)
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

Acceptable.

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
ABM-BL-0154	October 22, 2009	Routine Batch Sample Analysis

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	N/A
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays:

Acceptable.

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 18 and Figure 1

Fasting Bioequivalence Study, Study No. TRAC-IMTB-05SB01-2FA (XC6312)									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	62589.79	21.02	37243.22	92617.03	62965.17	22.17	37420.65	101608.8	0.99
AUC∞ (hr *ng/ml)	64996.08	20.32	41153.69	95115.63	65094.82	21.64	39541.39	103184.1	1.00
Cmax (ng/ml)	9971.896	28.71	5410.20	15643.90	9857.886	21.80	6240.40	14402.90	1.01
Tmax* (hr)	3.167	.	1.50	4.00	3.167	.	2.00	4.50	1.00
Kel (hr^{-1})	0.039	26.71	0.02	0.06	0.041	25.37	0.02	0.06	0.96
T1/2 (hr)	19.211	33.15	11.37	36.90	18.338	31.42	10.76	39.16	1.05

* Tmax values are presented as median, range

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated

TRANEXAMIC ACID TABLETS Dose (1 x 650 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study [Study No. TRAC-IMTB-05SB01-2FA (XC6312)]				
Parameter	Test	Reference	Ratio	90% C.I.
AUCt (ng*h/ml)	61254.8	61533.7	99.5	93.0 – 106.6
AUCinf (ng*h/ml)	63657.6	63729.5	99.9	93.2 – 107.1
Cmax (ng/ml)	9559.2	9642.2	99.1	92.4 – 106.3

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Tranexamic Acid Tablets, 1 x 650 mg Fasting Bioequivalence Study [No. TRAC-IMTB-05SB01-2FA (XC6312)], N=28 (female) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (ng·hr/mL)	61243.58	61510.48	1.00	92.99	106.61
AUC∞ (ng·hr/mL)	63690.36	63748.33	1.00	93.06	107.26
Cmax (ng/mL)	9559.16	9642.23	0.99	92.43	106.33

Please note: the firm used the actual time and the reviewer used the scheduled time points for PK and statistical analysis.

Table 17. Additional Study Information, Fasting Study No. TRAC-IMTB-05SB01-2FA (XC6312)

Root mean square error, AUC0-t	0.1499	
Root mean square error, AUC∞	0.1498	
Root mean square error, Cmax	0.1536	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	28	27
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	28	0.96	0.89	0.99
Reference	27	0.97	0.90	0.99

Comments on Pharmacokinetic and Statistical Analysis:

Computation of AUC∞ is based on 28 subjects for test product, and 27 subjects for the reference listed drug (excluding subject #2 whose kel can not be reliably determined). The reviewer agrees with firm's decision.

In summary, the 90% confidence intervals for lnAUC0-t, lnAUC∞ and lnCmax are within the acceptable limits of 80-125%.

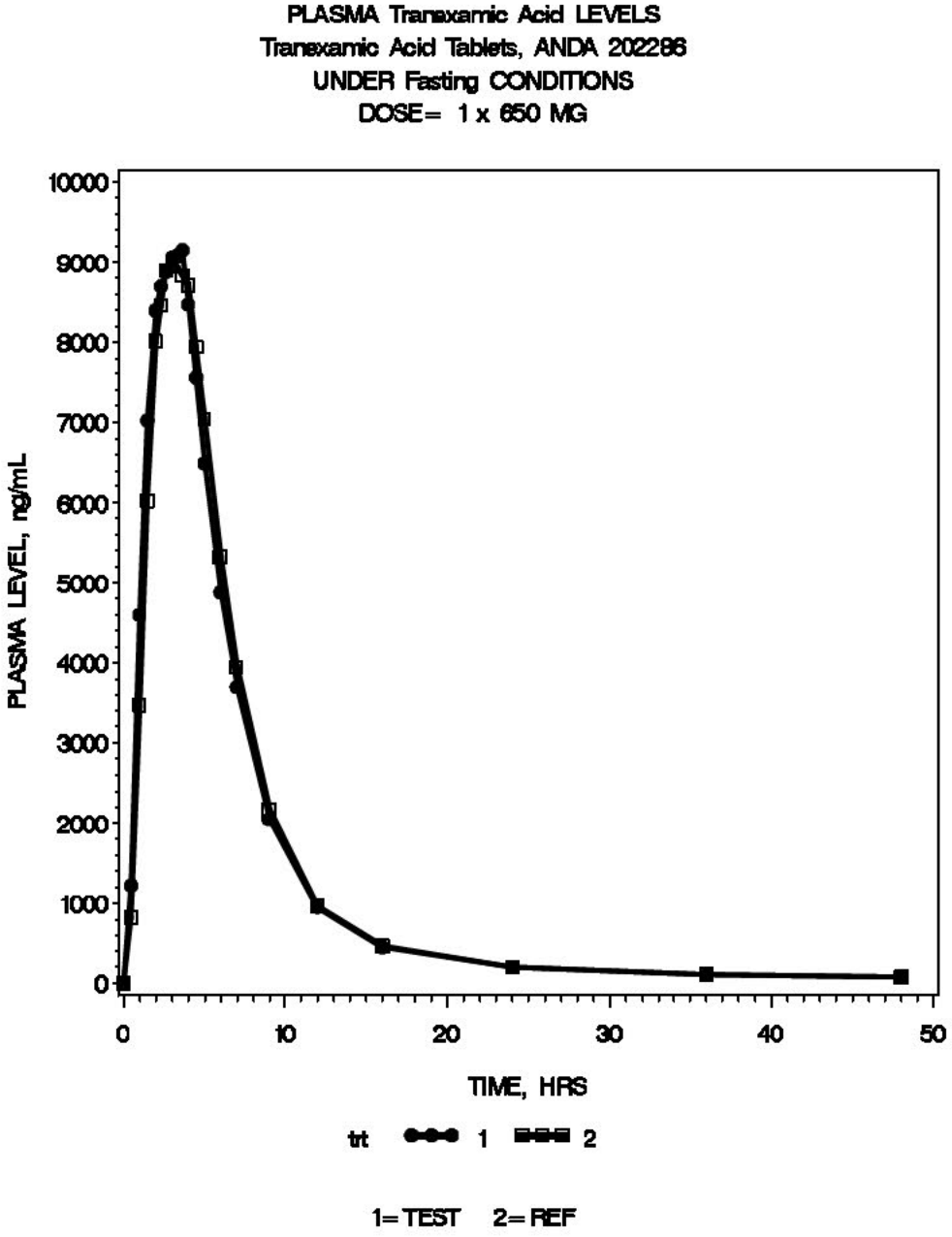
Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

Acceptable.

Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

	Test (n=28)		Reference (n=28)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.50	1222.68	80.66	829.94	48.52	1.47
1.00	4598.97	38.32	3477.30	36.51	1.32
1.50	7027.35	31.40	6028.94	35.63	1.17
2.00	8400.73	33.01	8016.49	28.31	1.05
2.33	8702.40	32.72	8470.23	25.78	1.03
2.67	8883.49	29.67	8908.24	22.41	1.00
3.00	9053.70	28.68	8975.01	25.34	1.01
3.33	9086.98	26.28	8940.22	24.50	1.02
3.67	9151.22	27.05	8833.07	25.17	1.04
4.00	8475.45	25.20	8721.42	26.73	0.97
4.50	7566.25	25.09	7946.73	26.51	0.95
5.00	6491.28	25.68	7042.83	26.47	0.92
6.00	4884.85	27.37	5328.20	26.98	0.92
7.00	3698.87	32.38	3949.41	32.81	0.94
9.00	2051.23	38.06	2169.24	42.07	0.95
12.00	957.03	35.90	972.95	46.56	0.98
16.00	456.63	30.85	465.71	37.85	0.98
24.00	206.92	23.93	210.91	28.06	0.98
36.00	108.92	24.70	115.55	42.38	0.94
48.00	82.64	29.52	81.29	28.29	1.02

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 19. Study Information

Study Number	TRAC-IMTB-05SB02-2FE (XC6313)
Study Title	Comparative, Randomized, 2-way Crossover Bioavailability Study of Tranexamic Acid Tablets (Apotex) and Lysteda Tablets (Xanodyne Pharm) (USA) Under Fed Conditions
Clinical Site (Name, Address, Phone #)	Apotex Inc., BioClinical Development Clinical Operations Department 465 Garyray Drive Toronto, Ontario Tel#: (416) 741-4256
Principal Investigator	G. Rai, M.D.
Dosing Dates	1st dosing date (Period 1: 06/21/10) and 2nd dosing date for (Period 2: 06/28/10)
Analytical Site (Name, Address, Phone #)	Apotex Inc. BioClinical Development Bioanalytical Laboratory 440 Garyray Drive Toronto, Ontario 416-749-9300
Analysis Dates	July 12, 2010 to July 20, 2010
Analytical Director	(b) (6), B.Sc.
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	29 days

Table 20. Product Information

Product	**Test**	**Reference**
Treatment ID	A	B
Product Name	Tranexamic Acid Tablets	Lysteda® Tablets
Manufacturer	Apotex Inc.	Xanodyne Pharmaceuticals Inc.
Batch/Lot No.	FD149-13	A100018A
Manufacture Date	April 2010	NA
Expiration Date	April 2012	Dec 2011
Strength	650 mg	650 mg
Dosage Form	Tablets	Tablets
Bio-batch Size	(b) (4)	NA
Production Batch Size		NA
Potency	101.4%	100.7%
Content Uniformity (mean, %CV)	101.4% (%CV 0.6)	NA

Dose Administered	1 x 650 mg	1 x 650 mg
Route of Administration	Oral	Oral

Table 21. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	30 subjects were dosed, 28 subjects* completed and were included in analysis
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	TR: XC42, XC44, XC46, XC48, XC49, XC52, XC53, XC55, XC57, XC58, XC62, XC63, XC66, XC68, XC69 RT: XC41, XC43, XC45, XC47, XC50, XC51, XC54, XC56, XC59, XC60, XC61, XC64, XC65, XC67, XC70
Blood Sampling Times	0.00 (x1) (5-45 minutes prior to dosing) followed by 1, 1.5, 2, 2.3333, 2.6667, 3, 3.3333, 3.6667, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 24, 36 and 48 hours post-dosing
Blood Volume Collected/Sample	Blood samples were collected using 6 mL lavender cap vacuum tubes containing K2EDTA at the above sampling time-points.
Blood Sample Processing/Storage	Blood samples were centrifuged and the plasma was transferred into labeled polypropylene storage tubes and stored in a -30°Cset point freezer pending assay.
IRB Approval	January 29, 2010
Informed Consent	January 29, 2010
Length of Fasting Before Meal	Following an overnight fast of at least 10 hours, subjects consumed a standard high-calorie, high-fat breakfast meal that began 30 minutes prior to each dose.
Length of Confinement	For each period, subjects were confined from at least 11 hours before the dosing until after the 24.0 hour post-dose blood draw
Safety Monitoring	Vital signs (blood pressure, pulse & temperature) at check-in and check-out of each period • Adverse event monitoring • Diagnostic testing at 48 hours post dose for CBC using a 4 mL lavender cap vacuum tube containing EDTA

*subjects #56 and 60 did not complete the study.

Standard FDA Meal Used?	Yes

Comments on Study Design:

The study design is acceptable.

4.1.2.2 Clinical Results

Table 22. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. TRAC-IMTB-05SB02-2FE-(1) Internal Code: XC6313			
		Treatment Groups	
		Test Product Tranexamic Acid Tablets N = 28	Reference Product Lysteda Tablets N = 28
Age (years)	Mean ± SD	38.7 ± 10.12	38.7 ± 10.12
	Range	23 - 55	23 - 55
Age Groups	< 18	0(0.0%)	0(0.0%)
	18 – 39	13(46.4%)	13(46.4%)
	40 – 64	15(53.6%)	15(53.6%)
	65 – 75	0(0.0%)	0(0.0%)
	> 75	0(0.0%)	0(0.0%)
Sex	Male	0(0.0%)	0(0.0%)
	Female	28(100.0%)	28(100.0%)
Race	Asian	4(14.3%)	4(14.3%)
	Black	3(10.7%)	3(10.7%)
	Caucasian	12(42.9%)	12(42.9%)
	Hispanic or Latino	7(25.0%)	7(25.0%)
	Multi-racial	2(7.1%)	2(7.1%)
	Native Hawaiian	0(0.0%)	0(0.0%)
	Aboriginal	0(0.0%)	0(0.0%)
BMI	Mean ± SD	24.7 ± 2.7	24.7 ± 2.7
	Range	20.1-28.8	20.1-28.8

Table 23. Dropout Information, Fed Bioequivalence Study

Protocol No. TRAC-IMTB-05SB02-2FE-(1) Study Code No. XC6313				
Subject No	**Reason for dropout/replacement***	**Period**	**Replaced?**	**Replaced with**
XC56	Reference/ Withdrawn due to poor veins on 06/23/10 at 13:44	Post period 1 dosing	No	NAP
XC60	Reference/ Voluntary withdrawal on 06/27/10 at 19:30	Period 2 check in night	No	NAP

Table 24. Study Adverse Events, Fed Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fed Bioequivalence Study: Protocol No. TRAC-IMTB-05SB02-2FE-(1) Study Code No. XC6313	
	Test	Reference
Investigations		
White blood cell count decreased	1 (3.6%)	1 (3.1%)
Neutrophil count decreased	1 (3.6%)	1 (3.1%)
Blood pressure increased	0 (0.0%)	3 (10.0%)
Heart rate increased	0 (0.0%)	1 (3.1%)
General Disorders and Administration Site Conditions		
Vessel puncture site haematoma	1 (3.6%)	1 (3.1%)
Vessel puncture site pain	1 (3.6%)	0 (0.0%)
Vessel puncture site swelling	0 (0.0%)	1 (3.1%)
Catheter site pain	2 (7.1%)	1 (3.1%)
Catheter site haematoma	0 (0.0%)	1 (3.1%)
Fatigue	1 (3.6%)	0 (0.0%)
Gastrointestinal Disorders		
Stomach discomfort	0 (0.0%)	1 (3.1%)
Diarrhoea	0 (0.0%)	1 (3.1%)
Total	5 (17.9%)	7 (23.3%)
Number of subject dosed	28	30

Table 25. Protocol Deviations, Fed Bioequivalence Study

Protocol No. TRAC-IMTB-05SB02-2FE-(1) Study Code No. XC6313		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Technical	XC44	NAP

Comments on Dropouts/Adverse Events/Protocol Deviations:

Dropouts

Subject XC56 was withdrawn due to poor vein and subject XC 60 was voluntarily withdrawn. Their samples were not included in PK and statistical analysis.

Adverse Events

A total of seven (7) mild adverse events (AEs) occurred in five (5) subjects after they received the test preparation. A total of thirteen (13) mild AEs occurred in seven (7) subjects after they received the reference preparation.

There were no serious or unexpected AEs reported during the study.

Protocol Deviations

During sample transfer, it was noticed that the polypropylene tube at the period 1, 24 hr time point for sample XC44 was an empty tube. However, the data in Initiator indicates that the sample was collected and processed. It was found out that the blood tube was inadvertently discarded without physically aliquotting the plasma. This occurrence was an isolated event and impacted no other samples. Since all other samples were obtained from subject XC44, period 1, except for the 24 hr sample, which can be reliably interpolated from the 16 hr and 36 hr samples, the absence of the 24 hr sample should not significantly affect the pharmacokinetic assessment. Therefore, it was recommended to consider 24 hr sample as missing sample and all other samples for this subject to be analyzed.

There are 150 blood sample time deviations during the entire study. The majority variations are less than 5 minutes, the time variations were considered unlikely to affect the PK analysis or overall PK conclusions. The firm used the actual time and the reviewer used the scheduled time points for PK and statistical analysis.

4.1.2.3 Bioanalytical Results

Table 26. Assay Validation – Within the Fed Bioequivalence Study

Bioequivalence Study No. TRAC-IMTB-05SB02-2FE Tranexamic Acid										
Parameter	**Standard Curve Samples**									
Concentration (ng./mL)	20.0	40.0	80.0	200.0	500.0	2000.0	4000.0	6000.0	8000.0	10000.0
Inter day Precision (%CV)	2.4	3.3	2.7	2.5	3.0	2.3	3.0	2.3	2.7	2.2
Inter day Accuracy (%Dev)	3.5	-2.0	-2.3	-2.4	0.9	3.7	2.2	-0.1	0.3	-3.4
Linearity	0.9995 – 0.9999									
Linearity Range (ng/mL)	20.0 – 10000.0									
Sensitivity/LOQ (ng/mL)	20.0									

Bioequivalence Study No. TRAC-IMTB-05SB02-2FE Tranexamic Acid			
Parameter	**Quality Control Samples**		
Concentration (ng/mL)	60.0	3000.0	7500.0
Inter day Precision (%CV)	6.7	4.7	3.5
Inter day Accuracy (%Dev)	-3.3	5.5	0.7

Comments on Study Assay Validation:

Acceptable.

Any interfering peaks in chromatograms?	No

Were 20% of chromatograms included?	Yes (Subject XC41, XC42, XC43, XC44, XC45, XC46)
Were chromatograms serially or randomly selected?	Serial

Comments on Chromatograms:

Acceptable.

Table 27. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
ABM-BL-0154	October 22, 2009	Routine Batch Sample Analysis

Table 28. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	N/A
Does the reviewer agree with the outcome of the repeat assays?	N/A
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays:

Acceptable.

4.1.2.4 Pharmacokinetic Results

Table 29. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 33 and Figure 2

Fed Bioequivalence Study, Study No. TRAC-IMTB-05SB02-2FE (XC6313)									
Parameter (units)	**Test**				**Reference**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC0-t (hr *ng/ml)	55918.10	21.71	32046.00	85350.22	56142.25	23.05	30487.44	80668.13	1.00
AUC∞ (hr *ng/ml)	58098.40	21.71	36488.68	88050.89	58085.13	22.14	33441.20	82748.74	1.00
Cmax (ng/ml)	8904.964	22.22	4414.00	12446.50	8392.536	20.24	4325.40	11276.40	1.06
Tmax* (hr)	3.167	.	2.00	5.00	4.250	.	2.67	7.00	0.75
Kel (hr^{-1})	0.043	28.29	0.01	0.07	0.043	26.16	0.02	0.06	1.02

T1/2 (hr)	17.907	46.65	10.66	52.28	17.627	33.13	11.06	35.80	1.02

* Tmax values are presented as median, range

Table 30. Geometric Means and 90% Confidence Intervals - Firm Calculated

Fed Bioequivalence Study [Study No. TRAC-IMTB-05SB02-2FE (XC6313)]				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUCt (ng*h/ml)	54476.0	54472.4	100.0	96.8 – 103.3
AUCinf (ng*h/ml)	56358.4	56665.5	99.5	96.3 – 102.7
Cmax (ng/ml)	8664.5	8199.7	105.7	101.3 – 110.2

Table 31. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Tranexamic Acid Tablets, 1 x 650 mg Fed Bioequivalence Study No. TRAC-IMTB-05SB02-2FE (XC6313), N=28 (female) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	54455.99	54449.30	1.00	96.81	103.32
AUC∞ (ng·hr/mL)	56354.89	56473.68	1.00	96.75	102.93
Cmax (ng/mL)	8664.45	8199.74	1.06	101.31	110.21

Please note: the firm used the actual time and the reviewer used the scheduled time points for PK and statistical analysis.

Table 32. Additional Study Information

Root mean square error, AUC0-t	0.0713	
Root mean square error, AUC∞	0.0676	
Root mean square error, Cmax	0.0921	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	27	28
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**

Test	27	0.97	0.87	0.99
Reference	28	0.96	0.88	0.99

Comments on Pharmacokinetic and Statistical Analysis:

Computation of AUC∞ is based on 27 subjects for test product (excluding subject #68 whose kel can not be reliably determined), and 28 subjects for reference listed drug. The reviewer agrees with firm's decision.

In summary, the 90% confidence intervals for lnAUC0-t, lnAUC∞ and lnCmax are within the acceptable limits of 80-125% in fed study.

Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

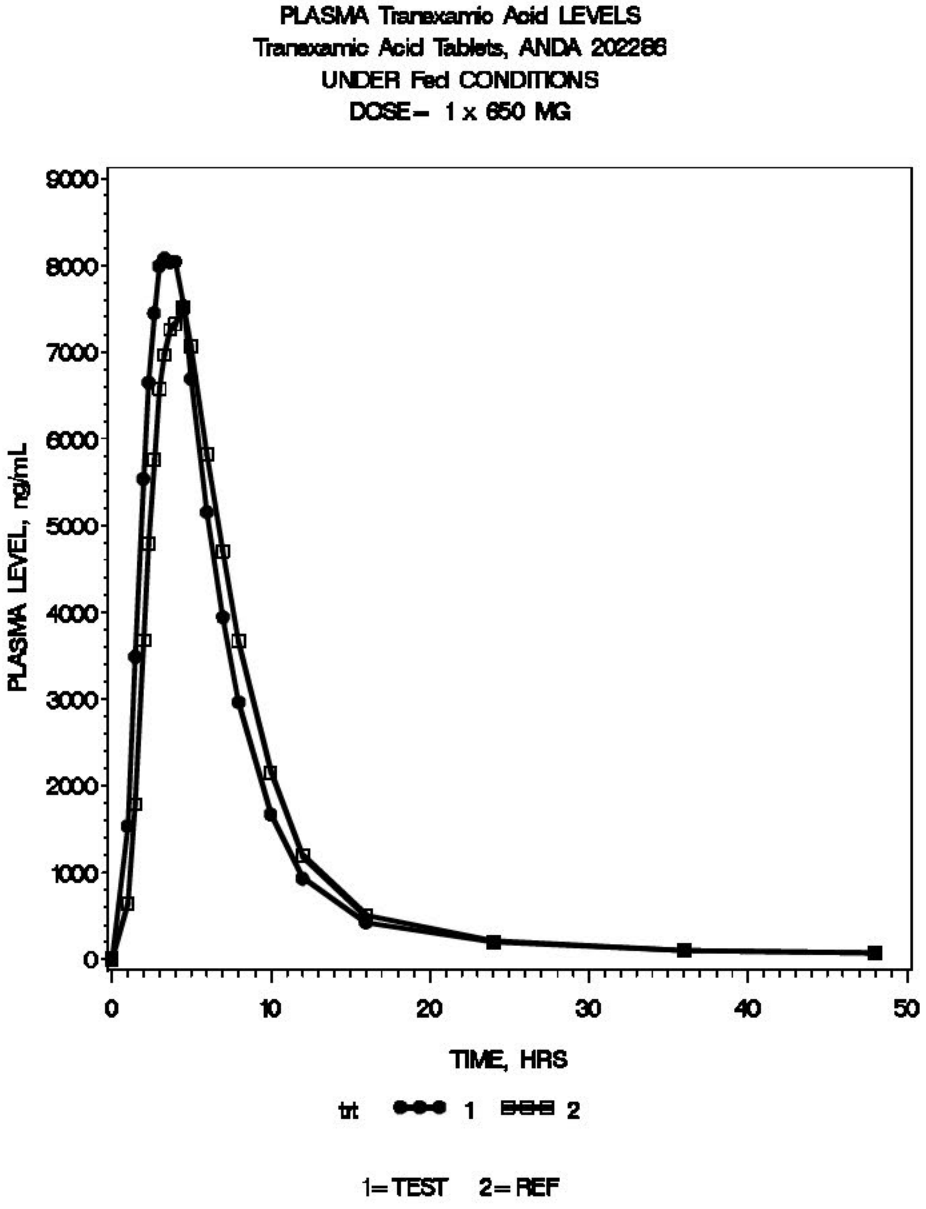
Acceptable.

Table 33. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

	Test (n=28)		Reference (n=28)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
1.00	1536.27	103.06	643.23	90.91	2.39
1.50	3489.87	68.63	1790.56	67.03	1.95
2.00	5541.41	47.36	3679.16	52.09	1.51
2.33	6652.03	38.07	4793.35	48.80	1.39
2.67	7451.32	30.43	5754.86	40.91	1.29
3.00	7997.58	26.51	6586.74	35.52	1.21
3.33	8081.64	23.91	6969.16	31.22	1.16
3.67	8042.55	21.48	7264.44	28.88	1.11
4.00	8047.60	24.08	7326.31	25.31	1.10
4.50	7535.13	26.41	7526.65	22.68	1.00
5.00	6696.12	24.34	7074.90	23.93	0.95
6.00	5159.08	29.73	5826.84	28.25	0.89
7.00	3947.92	30.98	4712.54	34.30	0.84
8.00	2965.04	34.20	3672.90	40.22	0.81
10.00	1673.53	37.71	2150.80	49.75	0.78
12.00	933.07	36.84	1196.33	51.21	0.78

	Test (n=28)		Reference (n=28)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
16.00	427.26	34.91	503.85	51.12	0.85
24.00	192.54	31.32	205.57	35.26	0.94
36.00	98.56	27.29	99.52	29.59	0.99
48.00	73.73	44.16	73.48	31.25	1.00

Figure 2. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



4.2 Formulation Data

Tranexamic Acid Tablets 650 mg

Ingredient	Quality standard	Function	%w/w	(mg/tablet)
Tranexamic Acid	NA	Active	75.58	650
Ethylcellulose 7FP	NF/EP	(b) (4)		
Croscarmellose Sodium	NF			
Magnesium Stearate	NF			
Colloidal Silicon Dioxide	NF			
		TOTAL	**100**	**860**

The amounts of individual excipients used in the formulation are within the IIG limits and acceptable.

Component	mg per tablet	Maximum amount/day based on MDD of Tranexamic Tablets 3900 mg	Maximum Potency (mg) listed in IIG / Route of Administration
Ethylcellulose 7FP	(b) (4)		1545 mg[6] Oral ;Tablet, Sustained Action
Croscarmellose Sodium			180 mg Oral ;Tablet
Magnesium Stearate, NF			400.748 Oral ;Tablet
Colloidal Silicon Dioxide			100 mg Oral;Granule

Is there an overage of the active pharmaceutical ingredient (API)?	NO
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will	N/A

(b) (4)

bioequivalence be impacted?	
Comments on the drug product formulation:	Comments see below.

Reviewer's Comments:

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. Therefore with Maximal daily dose, 3900 mg/day, all the inactive ingredients are below the levels published in the IIG data base.

The formulation of the test product is **acceptable**.

4.3 Dissolution Data

Dissolution Review Path	DARRTS: REV-BIOEQ-02(Dissolution Review) for ANDA 202286, final date 2/25/2011 DARRTS: REV-BIOEQ-02(Dissolution Review) for ANDA 202286, final date 8/4/2011

Table 34. Dissolution Data

A. Dissolution data submitted in original application (firm's own method)

Dissolution Conditions	**Apparatus:**	USP#2
	Speed of Rotation:	(b) (4) rpm
	Medium:	(b) (4)
	Volume:	900 mL
	Temperature:	37°C ±5
Firm's Proposed Specifications	Q= (b) (4)% in 60 minutes	
Dissolution Testing Site (Name, Address)	Apotex Inc 150 Signet Drive Toronto, ON M9L 1T9 Canada	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours) Tranexamic Acid**								**Study Report Location**
						5 min	**10 min**	**15 min**	**20 min**	**30 min**	**45 min**	**60 min**	**90 min**	
Comparative Dissolution Report trac_imtb_02_u_cdr_01	May 2010	Tranexamic Acid Tablets (FD149-13) April 2010	650 mg Tablets	12	Mean Range %RSD	(b) (4)								5.3.1.2

		Lysteda® Tablets (A100018A) Exp: 12/2011	650 mg Tablets	12	Mean Range %RSD	(b) (4)

B. Dissolution data submitted in its amendment dated 4/12/2011 (FDA-recommended method)

FDA-Recommended Dissolution Method

Method:

Method No.: TRAC-IMTB-41-SG (as per OGD)

Medium: USP Purified Water, 900ml

Apparatus: USP apparatus 2, 50 rpm

Quantitation: Measured by HPLC, UV-Vis Detector at 210nm

Individual Sample Dissolution Data:

Refer to Table 1 and Table 2.

Table 1: Tranexamic Acid Tablets 650 mg Lot FD149-13, Apotex Inc.

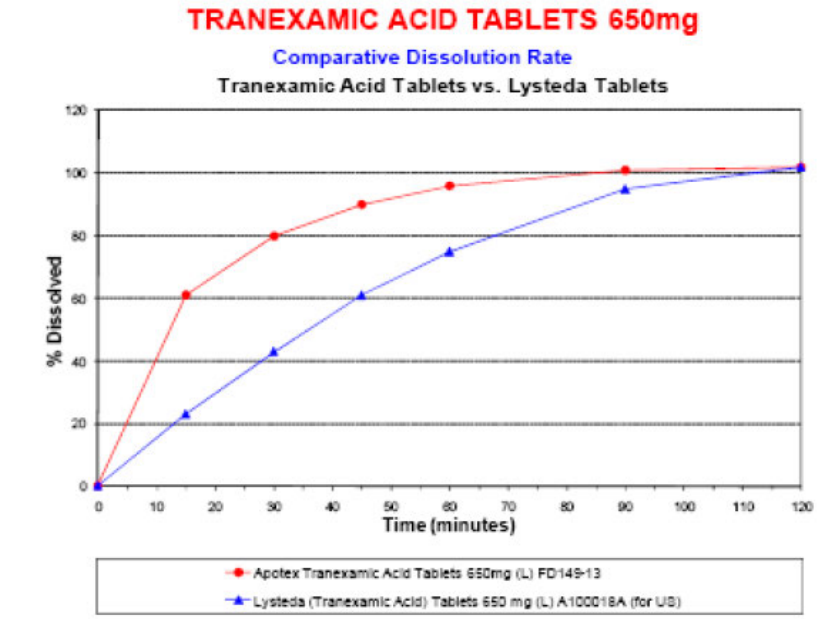
Time (minutes)	% Dissolved														
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Mean	%RSD
15													(b) (4)	61	8
30														80	4
45														90	3
60														96	3
90														101	1
120														102	1

Table 2: Lysteda (Tranexamic Acid) Tablets 650mg Lot A100018A, Xanodyne Pharmaceuticals Inc. for US, Expiry Date: 12/2011.

Time (minutes)	% Dissolved														
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Mean	%RSD
15													(b) (4)	23	5
30														43	5
45														61	5
60														75	4
90														95	3
120														102	1

References: 029976, 029977.

Date Tested: 03/28/11.



Method: USP apparatus#2, 50 rpm
Medium: USP Purified Water, 900ml

4.4 SAS Output

4.4.1 Fasting Study Data

Fasting CONCENTRATION DATASET

(b) (4)

Following this page, 96 Pages Withheld in Full as (b)(4)

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 202286

APPLICANT: Apotex Inc.

DRUG PRODUCT: Tranexamic Acid Tablets, 650 mg

The Division of Bioequivalence II (DBII) has completed its review and has no further questions at this time.

We acknowledge that you have accepted the following FDA-recommended dissolution method and specification for your Tranexamic Acid Tablets, 650 mg:

Medium:	Water
Volume:	900 mL
Apparatus:	USP Apparatus II (paddles)
Speed:	50 rpm
Temperature:	37°C ± 0.5°C
Specification:	Not less than (b) (4) % (Q) in 60 minutes

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

4.5 Outcome Page

ANDA: 202286

Enter Review Productivity and Generate Report

Completed Assignment for 202286 ID: 16414

Reviewer: Xia, Li **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description: Tranexamic Acid Tablets, 650 mg

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
16414	8/31/2010	Bioequivalence Study	Fasting Study	1	1
16414	8/31/2010	Bioequivalence Study	Fed Study	1	1
				Bean Total:	2

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Typical BE Study Applications

BE Study Fasting	
Clinical (Common to all APIs)	1
Bioanalytical (API 1)	1
Statistical Analysis (API 1)	1
Fasting Study Total	*3*
BE Study Fed	
Clinical (Common to all APIs)	1
Bioanalytical (API 1)	1
Statistical Analysis (API 1)	1
Fed Study Total	*3*
Grand Total	**6**

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

/s/

LI XIA
03/28/2012

XIAOJIAN JIANG
03/28/2012

BARBARA M DAVIT
03/29/2012

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	202286	
Drug Product Name	Tranexamic Acid Tablets	
Strength (s)	650 mg	
Applicant Name	Apotex Inc.	
Address	150 Signet Drive, Toronto, Ontario, Canada, M9L 1T9	
Applicant's Point of Contact	Kiran Krishnan, Director Regulatory Affairs 2400 North Commerce Parkway, Suite 400 Weston, Florida 33326	
Contact's Phone Number	(954) 384-3986	
Contact's Fax Number	(866) 392-1774	
Submission Date(s)	August 31, 2010	
Submission Date(s) of Amendment(s) Under Review	April 14, 2011	
First Generic	No	
Reviewer	Glendolynn S. Johnson, Pharm.D.	
Study Number (s)	TRAC-IMTB-05SB01-2FA (XC6312)	TRAC-IMTB-05SB02-2FE (XC6313)
Study Type (s)	Fasting	Fed
Strength(s)	650 mg	650 mg
Clinical Site	Apotex Inc., BioClinical Development Clinical Operations Department	
Clinical Site Address	465 Garyray Drive Toronto, Ontario	
Analytical Site	Apotex Inc. BioClinical Development Bioanalytical Laboratory	
Analytical Address	440 Garyray Drive Toronto, Ontario	
OVERALL REVIEW	**INADEQUATE**	
WAIVER REQUEST	**N/A**	

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
3	**DISSOLUTION**	**650 MG**	**INADEQUATE**

Review of a Dissolution Amendment

I. EXECUTIVE SUMMARY

In this dissolution amendment, the firm, Apotex Inc., submitted its response to the deficiency letter dated February 28, 2011, from the Division of Bioequivalence (DBE) for its proposed drug product, Tranexamic Acid Tablets, 650 mg. The firm has submitted additional dissolution testing data using the FDA recommended method. The firm's responses to the deficiency comments are acceptable. However, the dissolution testing is still incomplete until the firm acknowledges the FDA recommended dissolution method and specification.

The DBE will review the fasted and fed BE studies at a later date.

II. Background

The DBE previously reviewed[1] the firm's *in vitro* dissolution testing data submitted on August 31, 2010, comparing the test product, Tranexamic Acid Tablets, 650 mg, to the reference listed drug (RLD) product, Lysteda™ (Tranexamic Acid) Tablets, 650 mg. The *in vitro* dissolution testing was incomplete as the firm did not submit dissolution data using the FDA recommended method. The firm was asked to conduct dissolution testing using the following FDA recommended method:

USP Apparatus type:	Apparatus II (paddles)
Rotation:	50 rpm
Medium:	Water
Volume:	900 mL
Temperature:	37ºC ± 0.5ºC
Sampling Times:	15, 30, 45, 60, 90 and 120 minutes

III. Review of the Submission

DBE Comment No. 01
Please conduct and submit dissolution testing on the test and reference products (12 units each) using the FDA-recommended method (listed above).

Firm's Response:
As requested, comparative dissolution testing on the test and reference product was performed on 12 units each using the above FDA-recommended method.

[1] DARRTS: ANDA 202286, REV-BIOEQ-02(Dissolution Review), 2/25/2011

FDA-Recommended Dissolution Method

Method:

Method No.: TRAC-IMTB-41-SG (as per OGD)

Medium: USP Purified Water, 900ml

Apparatus: USP apparatus 2, 50 rpm

Quantitation: Measured by HPLC, UV-Vis Detector at 210nm

Individual Sample Dissolution Data:

Refer to Table 1 and Table 2.

Table 1: Tranexamic Acid Tablets 650 mg Lot FD149-13, Apotex Inc.

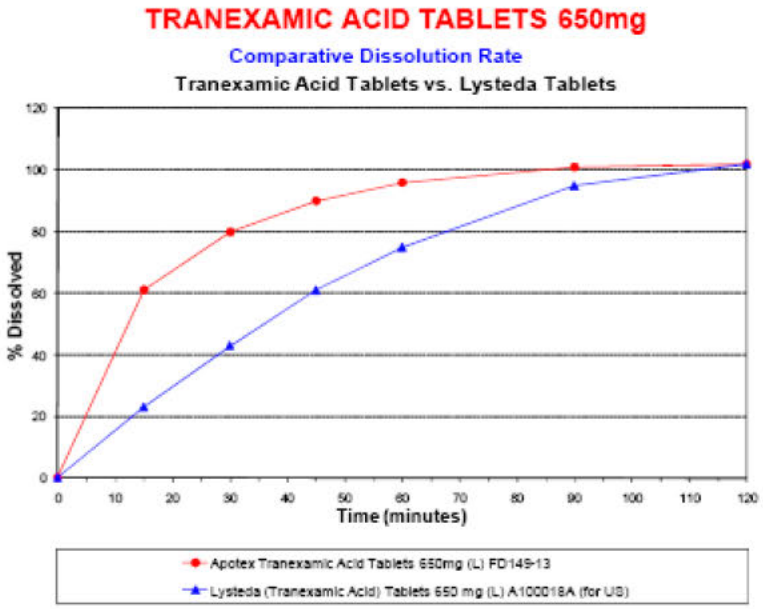
Time (minutes)	% Dissolved														
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Mean	%RSD
15													(b) (4)	61	8
30														80	4
45														90	3
60														96	3
90														101	1
120														102	1

Table 2: Lysteda (Tranexamic Acid) Tablets 650mg Lot A100018A, Xanodyne Pharmaceuticals Inc. for US, Expiry Date: 12/2011.

Time (minutes)	% Dissolved														
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Mean	%RSD
15													(b) (4)	23	5
30														43	5
45														61	5
60														75	4
90														95	3
120														102	1

References: 029976, 029977.

Date Tested: 03/28/11.



Method: USP apparatus#2, 50 rpm
Medium: USP Purified Water, 900ml

Firm's Dissolution Method (previously submitted)

Dissolution Conditions	**Apparatus:**	USP#2
	Speed of Rotation:	(b) (4) rpm
	Medium:	(b) (4)
	Volume:	900 mL
	Temperature:	37°C ±5
Firm's Proposed Specifications	Q (b) (4) % in 60 minutes	
Dissolution Testing Site (Name, Address)	Apotex Inc 150 Signet Drive Toronto, ON M9L 1T9 Canada	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours) Tranexamic Acid								Study Report Location
						5 min	10 min	15 min	20 min	30 min	45 min	60 min	90 min	
Comparative Dissolution Report trac_imtb_02_u_cdr_01	May 2010	Tranexamic Acid Tablets (FD149-13) April 2010	650 mg Tablets	12	Mean Range %RSD	(b) (4)								5.3.1.2
		Lysteda® Tablets (A100018A) Exp: 12/2011	650 mg Tablets	12	Mean Range %RSD									

Reviewer's Comment:

The firm has conducted dissolution testing using the FDA-recommended method (900 mL of water using apparatus II at 50 rpm). Previously, the firm conducted dissolution testing using its dissolution method (900 mL of (b) (4) using apparatus II at (b) (4) rpm). After comparing the dissolution results, it is deemed that the data using the firm's method are not very different from the data using the FDA-recommended method. Thus the firm will be requested to acknowledge the FDA recommended dissolution method and a specification of NLT (b) (4)% (Q) in 60 minutes. The FDA recommended method is the same dissolution method as the RLD Lysteda™ (tranexamic acid) Tablets, 650 mg (NDA 022430), however, the specification recommended for the firm's test product is different from the specification for the RLD product (NLT (b) (4)% (Q) in 90 minutes).

(b) (4)

Since the drug product does not behave as MR product, the DBE will not ask for dissolution testing in multiple pH media or for testing for dose dumping in alcohol for the test product.

II. DEFICIENCY COMMENTS:

None

III. RECOMMENDATION:

The in vitro dissolution testing conducted by Apotex Inc., on its Tranexamic Acid Tablets, 650 mg (lot # FD149-13), comparing it to Ferring Pharms' Lysteda™ Tablets, 650 mg (Lot # A100018A) is **incomplete** pending the firm's acknowledgment of its acceptance of the FDA recommended dissolution method and specification.

The firm should be informed of the above recommendation.

---

[2] (b) (4)

[3] DARRTS: NDA 022430, REV-QUALITY-03(General Review), 9/24/2009

BIOEQUIVALENCE DEFICIENCY COMMENT TO BE PROVIDED TO THE APPLICANT

ANDA: 202286

APPLICANT: Apotex Inc.

DRUG PRODUCT: Tranexamic Acid Tablets, 650 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the fasted and fed bioequivalence studies will be conducted later. The following deficiency has been identified:

Your dissolution testing for the test product using the following FDA recommended dissolution method is acceptable

USP Apparatus type:	Apparatus II (paddles)
Rotation:	50 rpm
Medium:	Water
Volume:	900 mL
Temperature:	37°C ± 0.5°C
Sampling Times:	15, 30, 45, 60, 90 and 120 minutes

Based on the data submitted, the DBE recommends the following specification: Not less than (b) (4)% (Q) in 60 minutes.

Please acknowledge your acceptance of the FDA-recommended dissolution method and specification.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

IV. OUTCOME

ANDA: 202286

Enter Review Productivity and Generate Report

http://cdsogd1/bioprod

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
14550	4/14/2011	Other	Dissolution Amendment	1	1
				Bean Total:	1

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

/s/

GLENDOLYNN S JOHNSON
08/02/2011

NILUFER M TAMPAL
08/02/2011

ETHAN M STIER on behalf of BARBARA M DAVIT
08/04/2011

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	202286		
Drug Product Name	Tranexamic Acid Tablets		
Strength (s)	650 mg		
Applicant Name	Apotex Inc.		
Address	150 Signet Drive, Toronto, Ontario, Canada, M9L 1T9		
Applicant's Point of Contact	Bernice Tao 2400 North Commerce Parkway, Suite 400 Weston, Florida 33326		
Contact's Phone Number	(416) 401-7889		
Contact's Fax Number	(416) 401-3817		
Submission Date(s)	August 31, 2010		
First Generic	No		
Reviewer	Glendolynn S. Johnson, Pharm.D.		
Study Number (s)	TRAC-IMTB-05SB01-2FA (XC6312)	TRAC-IMTB-05SB02-2FE (XC6313)	
Study Type (s)	Fasting	Fed	
Strength(s)	650 mg	650 mg	
Clinical Site	Apotex Inc., BioClinical Development Clinical Operations Department		
Clinical Site Address	465 Garyray Drive Toronto, Ontario		
Analytical Site	Apotex Inc. BioClinical Development Bioanalytical Laboratory		
Analytical Address	440 Garyray Drive Toronto, Ontario		
OVERALL REVIEW	**INADEQUATE**		
WAIVER REQUEST	**N/A**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1	**DISSOLUTION**	**650 MG**	**INADEQUATE**

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP method for this product but there is a FDA-recommended method (900 mL of water using apparatus II at 50 rpm). The firm's dissolution method (900 mL of (b) (4) using apparatus II at (b) (4) rpm) is different from the FDA-recommended method. The firm is requested to repeat dissolution testing using the FDA-recommended method.

The long-term storage stability duration of 86 days at -30°C exceeds the storage period of the study samples for both the fasted (25 days) and fed (29 days) studies.

The DBE will review the fasted and fed BE studies and waiver requests at a later date.

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☐	☒	☐
Did the firm use the USP dissolution method			☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing			☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)			☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method			☒	☐	☐
Is FDA method in the public dissolution database (on the web)			☒	☐	☐
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are the DBE Summary Tables present an in either PDF and/or MS Word Format?			☒	☐	☐
If any of the tables are missing or incomplete please indicate that in the comments and request the firm to provide the complete DBE Summary Tables 1-16.					
Is the Long Term Storage Stability (LTSS) sufficient to cover the maximum storage time of the study samples?			☒	☐	☐
If the LTSS is NOT sufficient please request the firm to provide the necessary data.					

Method Listed in the External OGD Database

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Tranexamic Acid	Tablet	II (Paddle	50	Water	900	15, 30, 45, 60, 90 and 120	12/23/2010

There is no dissolution reference for Tranexamic Acid Tablets from Internal Dissolution Database. The following dissolution method and specification are from the RLD Lysteda™ (tranexamic acid) tablets, 650 mg, NDA 022430.

Lysteda™ Tablets NDA Method[1],[2]

Medium	Water
Volume (mL)	900 mL
Temperature	37.0 ± 0.5°C
USP Apparatus type	Paddles
Rotation (rpm)	50 rpm
Pull Volume	About 10 mL
Filter	0.45 µm (b) (4) syringe filter
DBE-recommended specifications	NLT (b) (4)% (Q) at 90 minutes
If a modified-release tablet, testing to be done on ½ tablets?	N/A

[1] DARRTS: REV-QUALITY-03(General Review) for NDA 022430 dated 9/24/2009
[2] DARRTS: REV-BIOEQ-07 (Filing Review) for ANDA 202093. Note this review also contained the control correspondence for tranexamic acid

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Dissolution Conditions	**Apparatus:**	USP#2
	Speed of Rotation:	(b) (4) rpm
	Medium:	(b) (4)
	Volume:	900 mL
	Temperature:	37°C ±5
Firm's Proposed Specifications	Q (b) (4) % in 60 minutes	
Dissolution Testing Site (Name, Address)	Apotex Inc 150 Signet Drive Toronto, ON M9L 1T9 Canada	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours) Tranexamic Acid**								**Study Report Location**
						5 min	**10 min**	**15 min**	**20 min**	**30 min**	**45 min**	**60 min**	**90 min**	
Comparative Dissolution Report trac_imtb_02_u_cdr_01	May 2010	Tranexamic Acid Tablets (FD149-13) April 2010	650 mg Tablets	12	Mean Range %RSD	(b) (4)								5.3.1.2
		Lysteda® Tablets (A100018A) Exp: 12/2011	650 mg Tablets	12	Mean Range %RSD									

II. COMMENTS:

1. The current FDA-recommended dissolution method for Tranexamic Acid is:

USP Apparatus type:	Apparatus II (paddles)
Rotation:	50 rpm
Medium:	Water
Volume:	900 mL
Temperature:	37ºC ± 0.5ºC
Sampling Times:	15, 30, 45, 60, 90 and 120 minutes
Specifications:	NLT (b)(4)% (Q) at 90 minutes

2. The firm did not use the FDA-recommended dissolution method; therefore, the dissolution testing conducted is incomplete. The firm should conduct dissolution testing using the FDA-recommended dissolution method listed in comment #1 above.

III. DEFICIENCY COMMENT:

1. The firm did not use the FDA-recommended dissolution method. The firm should conduct additional dissolution testing using the FDA-recommended dissolution method below:

USP Apparatus type:	Apparatus II (paddles)
Rotation:	50 rpm
Medium:	Water
Volume:	900 mL
Temperature:	37ºC ± 0.5ºC
Sampling Times:	15, 30, 45, 60, 90 and 120 minutes

IV. RECOMMENDATIONS:

The in vitro dissolution testing conducted by Apotex Inc., on its Tranexamic Acid Tablets, 650 mg (lot # FD149-13), comparing it to Ferring Pharms' Lysteda™ Tablets, 650 mg (Lot # A100018A) is **incomplete.**

BIOEQUIVALENCE DEFICIENCY COMMENT TO BE PROVIDED TO THE APPLICANT

ANDA: 202286

APPLICANT: Apotex Inc.

DRUG PRODUCT: Tranexamic Acid Tablets, 650 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the fasted and fed bioequivalence studies will be conducted later. The following deficiency has been identified:

Please conduct and submit dissolution testing on the test and reference product (12 units each) using the following FDA-recommended recommended method:

USP Apparatus type:	Apparatus II (paddles)
Rotation:	50 rpm
Medium:	Water
Volume:	900 mL
Temperature:	37°C ± 0.5°C
Sampling Times:	15, 30, 45, 60, 90 and 120 minutes

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

V. OUTCOME

ANDA: 202286

Enter Review Productivity and Generate Report

http://cdsogd1/bioprod

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
13189	8/31/2010	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

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

/s/

GLENDOLYNN S JOHNSON
02/24/2011

QING LIU on behalf of NILUFER M TAMPAL
02/24/2011

ETHAN M STIER on behalf of BARBARA M DAVIT
02/25/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202286

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ROUTING SHEET

☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ CGMP

Division: II	Team: 21	PM: Erin Lee

Electronic ANDA: Yes ☒ No ☐

ANDA #:202286
Firm Name:Apotex Inc.
ANDA Name:Tranexamic Acid Tablets, 650 mg
RLD Name:Lysteda Tablets, 650 mg

Electronic AP Routing Summary Located:
V:\Chemistry Division II\Team 21\Electronic AP-TA-NAcGMPSummaries

AP/TA Letter Located:
V:\Chemistry Division II\Team 21\AP TA_NAcGMP CR WD Letters

Project Manager Evaluation: **Date: 1/8/14 Initials:** EL

☒ Previously reviewed and tentatively approved --- Date 8/10/12
☒ Previously reviewed and CGMP Complete Response issued -- Date 3/1/13

Original Rec'd date 8/31/10	Date of Application 8/31/10	Date Acceptable for Filing 11/24/10
Patent Certification (type) P II & PIV	Date Patent/Excl. expires 3/4/25	Citizens' Petition/Legal Case? Yes☐ No ☐ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☐ **DMF#:** (b) (4) (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☐ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☐ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

GDUFA User Fee Obligation Status: ☐ Met ☐ Unmet**:** ☐ Facility Fee not paid, ☐ Backlog fee not paid
EER Status: ☐ Pending ☐☐ ☒ Acceptable ☐ OAI *EES Date Acceptable: 1/8/14* ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☒ Comment:
Date of Acceptable Quality (Chemistry) 6/28/12 Addendum Needed: Yes ☐ No ☐ Comment:
Date of Acceptable Bio 3/29/12 Bio reviews in DARRTS: Yes ☐ No ☐ (Volume location:)
Date of Acceptable Labeling 10/31/13 Attached labeling to Letter: Yes ☐ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) _____

Methods Val. Samples Pending: Yes ☐ No ☐**;** Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☐ No ☐ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☐ No ☐ (If yes, enter dissolution information in Letter)

Routing:

☒ Labeling Endorsement, Date emailed: 1/9/14 REMS Required: Yes ☐ No ☐ REMS Acceptable: Yes ☐ No ☐

☒ Regulatory Support

☒ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: 1/14/14

☒ Division

☒ Bob West / Peter Rickman

☐ Kathleen Uhl

☐Filed AP Routing Summary in DARRTs	☐Notified Firm and Faxed Copy of Approval Letter	☐ Sent Email to "CDER-OGDAPPROVALS" distribution list

OGD APPROVAL ROUTING SUMMARY

1. ***Regulatory Support Branch Evaluation***

Martin Shimer **Date: 1/14/2014**

Chief, Reg. Support Branch **Initials:** MHS

Contains GDEA certification: Yes ☒ No ☐	Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD = Lysteda NDA# 22-430 Date Checked 1/25/14 Nothing Submitted ☒ Written request issued ☐ Study Submitted ☐
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☒ No ☐ Was applicant sued w/in 45 days:Yes ☐ No ☐ Has case been settled: Yes ☐ No ☐ Date settled: Is applicant eligible for 180 day NO Is a forfeiture memo needed: Yes ☐ No ☒ If yes, has it been completed	
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒	
Date of latest Labeling Review/Approval Summary _____	
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒☐	

Type of Letter:
☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐CGMP ☐ OTHER:

Comments:ANDA previously TA'd on 8/10/2012. At the time the TA was issued the reason cited for TA was unexpired NDF exclusivity which expired on 11/13/2012.
Second TA routing summary completed in anticipation of Apotex's ANDA being granted Full Approval. However, cGMP letter issued to the sponsor on 3/1/2013 instead. The RS that accompanied the cGMP letter in DARRTs indicates that Apotex was originally determined to have the sole exclusivity seat for this product. This exclusivity seat was solely associated with the '739 patent which was listed in NDA 22430 on 5/24/2011 and was also the same date that Apotex provided a PIV cert to this patent. Ultimately Apotex provided PIV certifications to the '739, '106 and '795 patents with separate CAs filed in the D of NV for infringement of the '739(11 CV 0485), '106(CA # not indicated on CA). There are no 30 month stays of approval associated with either of these CAs since neither patent was listed in the OB at the time this ANDA was submitted.
Apotex also provided a PIV to the later-listed '795 patent in a patent amendment rec'd on 11/6/2012. Notice corresponding to this PIV was sent via (b) (4) to Ferring in Saint-Prex Switzerland with notice delivered on 11/8/2012, notice sent via (b) (4) to Ferring B.V. in Hoofddorp Netherlands with notice delivered on 11/8/2012, notice sent via (b) (4) to Xanodyne in Newport Kentucky with notice delivered on 11/7/2012, notice sent via (b) (4) to Ferring Pharmaceuticals in Parsippany NJ with notice rec'd on 11/8/2012. Again, since the '795 patent was not present in the OB at the time this ANDA was submitted there can be no 30 month stay associated with any CA so the Agency is only concerned that notice was provided.
Patent Amendment rec'd on 9/13/2013-PIV to '005.
Request for final approval rec'd on 9/16/2013.
Patent Amendment rec'd on 9/17/2013-documentation of notice for the '005 patent: notice sent via (b) (4) to Xanodyne in Newport KY with notice delivered on 9/16/2013, notice sent to Ferring in Parsippany NJ with notice delivered on 9/16/2013, notice sent to Ferring B.V. in Hoofddorp Netherlands with notice delivered on 9/16/2013, notice sent via (b) (4) (b) (4) to Ferring Pharmaceuticals in Saint-Prex Switzerland with notice delivered on 9/17/2013.
Second request for Final Approval rec'd on 10/21/2013.
The original 180 day exclusivity analysis concluded that Apotex was the sole first applicant for purposes of 180 day exclusivity. Watson challenged this finding based on the Agency's original determination that their PIV certification was submitted one day after Apotex's PIV certification due to the Office of Business Informatic's 4:30 deadline for receiving electronic submissions on the same business day. See memo in DARRTs with subject line 'Receipt Date of Watson's Paragraph IV Certification to the '739 Patent' dated 12/21/2012. With this find, both Watson and Apotex became co-first applicants for this drug product. Watson's ANDA was approved on 12/27/2012 and they triggered 180 day a couple of weeks later. The shared 180 day exclusivity period for this drug product expired on July 2, 2013.

This ANDA is eligible for Full Approval but is NO LONGER eligible for 180 day exclusivity as this period was triggered by Watson and has expired. Apotex provided PIV certifications to all four later-listed patents and has provided documentation that notice was sent and rec'd by all parties. Since none of these four patents was present in the OB at the time the ANDA was submitted there can be no 30 month stay of approval associated with any of these patents and the

Agency is not concerned with the outcome of litigation.

2. ***Labeling Endorsement***

Reviewer, : Labeling Team Leader, rlw/for:
Date_____ Date 1/25/14

REMS required? REMS acceptable?
☐Yes ☒No ☐Yes ☐No ☐n/a

Comments:
From: Lee, Koung U
Sent: Friday, January 10, 2014 11:23 AM
To: Park, Chan H; Lee, Erin
Subject: RE: ANDA 202286/Tranexamic Acid tabs/Apotex

I concur. Thanks.

Koung

From: Park, Chan H
Sent: Thursday, January 09, 2014 1:04 PM
To: Lee, Erin
Cc: Lee, Koung U
Subject: FW: ANDA 202286/Tranexamic Acid tabs/Apotex

Dear Erin,

Please endorse the ARS for me.
Thanks,

Chan

3. ***Paragraph IV Evaluation*** **PIV's Only**
David Read **Date 22Jan2014**
OGD Regulatory Counsel **InitialsDTR**
Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:Minor changes to AP letter saved to V drive.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 1/9/2014**
Chemistry Div. **II (Smith)** **InitialsGJS**
Comments:CMC Acceptable.

OGD Office Management Evaluation

5. Peter Rickman **Date 1/25/14**
Director, DLPS **Initials rlw/for**
Para.IV Patent Cert: Yes☐ ☐ ☐ No☐
Pending Legal Action: Yes☐ ☐ No☐
Petition: Yes☐ No☐
Entered to APTrack database ☐
GDUFA User Fee Obligation Status Met☐ Unmet☐
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: This ANDA was granted tentative approval on August 10, 2012. Aptoex requested final approval, but final approval was withheld via N/A cGMP letter on March 1, 2013 due to cGMP issues associated with Apotex's Signet

finished dosage form manufacturing site. At this time, Apotex has successfully resolved its cGMP issues and CDER's Office of Compliance has provided an acceptable overall recommendation for this ANDA. Refer to the administrative summaries prepared at the time of the tentative approval and issuance of the cGMP letter for historical context. With the successful resolution of the cGMP issues associated with the Signet manufacturing site, this ANDA is once again eligible for final approval.

Final-printed labeling (FPL) found acceptable for approval 10/31/13, as endorsed 1/10/14. No REMS is required.

CMC remains acceptable for approval (11/5/13 NAI notation in DARRTS) as endorsed 1/9/14 (above).

OR

6. Robert L. West **Date 1/25/14**
Deputy Director, OGD **Initials RLWest**

Para.IV Patent Cert: Yes☒ No☐
Pending Legal Action: Yes☐ No☒
Petition: Yes☐ No☒
Entered to APTrack database ☒
GDUFA User Fee Obligation Status Met☒ Unmet☐
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: Acceptable EES dated 1/8/14 (Verified 1/25/14) No "OAI" Alerts noted.

Apotex provided paragrtaph IV certifications to the '739, '106, '795 and '005 patents. Notification of each of these patents was received by the agency after Apotex's ANDA was received. Therefore, each patent is regarded as "late listed" with respect to this ANDA. Any litigation resulting between the parties as a result of the paragraph IV certifications is not a barrier to the agency's approval of this ANDA. There are no additional patents or exclusivity currently listed in the "Orange Book" for this drug product.

There are no 180-day generic drug exclusivity issues with regard to this drug product. Previously granted exclusivity has expired.

This ANDA is recommended for final approval.

7. ***OGD Director Evaluation***
Kathleen Uhl

Comments: RLWest for Kathleen Uhl, M.D., Acting Director, Office of Generic Drugs 1/25/14.
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg. Issue ☐
Press Release Acceptable ☐

Comments:

8. Project Manager **Date** _____
Initials _____

Comments:

Check Communication and Routing Summary into DARRTS

EES DATA:


Establishment Evaluation System
File Edit Search Navigate Options Help Window
ORACLE
Application
Establishments
Status
Milestones
Comments
Contacts
Product
Application: A 202286/000
Subtype: N/A
Sponsor: APOTEX
Drug Name: TRANEXAMIC ACID
FEI / CFN
Establishment Name
Profile Code
Last Milestone Name
Last Compliance Date
Status
Date
OAI Alert
EER Re-eval Date
3002906944 APOTEX TCM OC RECOMMENDATION 08-JAN-2014 AC 08-JAN-2014 20-AUG-2015
(b) (4)
3002808376 APOTEX, INC. CTL OC RECOMMENDATION 07-NOV-2012 AC 07-NOV-2012 28-SEP-2014
Current Overall OC Recmnd:
Date: 08-JAN-2014
Recommendation: ACCEPTABLE
Overall Re-eval Date: 28-SEP-2014
Overall OC Recommendation History:
Date
Recommendation
Overall Re-eval Date
09-DEC-2013 PENDING
09-DEC-2013 PENDING
OAI Alert Comments
10:21 AM
1/25/2014

Orange Book Report:

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Patent and Exclusivity Search Results from query on Appl No 022430 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N022430	001	7947739	Mar 4, 2025		Y		
N022430	001	8022106	Mar 4, 2025			U - 1182	
N022430	001	8273795	Mar 4, 2025			U - 1182	
N022430	001	8487005	Mar 4, 2025		Y	U - 1182	

Revised, Jun 2013

Reference ID: 3442275

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N022430	001	NDF	Nov 13, 2012

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

/s/

ERIN M LEE
01/27/2014

ROUTING SHEET

☐ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☒ CGMP

Division: II	Team: 21	PM: Linda Park

Electronic ANDA: Yes ☒ No ☐

ANDA #:202286
Firm Name:Apotex, Inc.
ANDA Name:Tranexamic Acid Tablets, 650 mg
RLD Name:Lysteda Tablets, 650 mg, of Ferring Pharmaceuticals, Inc.

CGMP

Electronic AP Routing Summary Located:
V:\Chemistry Division II\Team 21\Electronic AP-TA-NAcGMPSummaries

AP/TA Letter Located:
V:\Chemistry Division II\Team 21\AP TA NAcGMP CR WD Letters

Date: 11-7-12 , 2-4-13

Project Manager Evaluation:
Initials: LP
☒ Previously reviewed and tentatively approved --- Date 8-10-12
☐ Previously reviewed and CGMP Complete Response issued -- Date _____

Original Rec'd date 8-31-10	Date of Application 8-31-10	Date Acceptable for Filing 11-24-10
Patent Certification (type) PIV	Date Patent/Excl. expires	Citizens' Petition/Legal Case? Yes☐ No ☐ (If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐ **DMF#:** _____ (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☒ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☐ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

EER Status: ☐ Pending ☐☐ ☐ Acceptable ☒ OAI *EES Date Acceptable:*_____ ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☒ Comment:
Date of Acceptable Quality (Chemistry) 6-28-12 Addendum Needed: Yes ☐ No ☒ Comment:
Date of Acceptable Bio 3-29-12 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location:)
Date of Acceptable Labeling 9-30-11 Attached labeling to Letter: Yes ☐ No ☒ Comment:
Date of Acceptable Sterility Assurance (Micro) na

Methods Val. Samples Pending: Yes ☐ No ☒; Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☐ No ☒ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☐ No ☒ (If yes, enter dissolution information in Letter)

Routing:
☐ Office of Management, Fee Verification, Date emailed: _____; Date Response in DARRTS: _____

☒ Labeling Endorsement, Date emailed: _____ REMS Required: Yes ☐ No ☐ REMS Acceptable: Yes ☐ No ☐

☒ Regulatory Support

☒ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: _____

☒ Division 2/15/13

☐ 1st Generic Review

☐ Bob West / Peter Rickman
☐ Gregory Geba
2/26/13

☐ Filed AP Routing Summary in DARRTs	☐ Notified Firm and Faxed Copy of Approval Letter	☐ Sent Email to "CDER-OGDAPPROVALS" distribution list

Reference ID: 3273403

OGD APPROVAL ROUTING SUMMARY

1. ***Office of Management***
CDER-OM-COLLECTIONS (cder-om-collections@fda.hhs.gov)

Date Emailed:
Date Verification response received from OM:

Fee Verification (check all that apply):

☐ Backlog Fee
☐ ANDA New Application Fee
☐ API Manufacturer Fee
☐ FDF Manufacturer Fee
☐ DMF Fee

☐ Misbranding statement required in letter for no Facility Fee payment
☐ Misbranding statement required in letter for Failure to Self-ID

☐ Backlog ANDA TA/AP'd prior to being able to collect fees statement (Limbo TA/AP)

Comments:

2. ***Regulatory Support Branch Evaluation***
Martin Shimer **Date:**
Chief, Reg. Support Branch **Initials:**

Contains GDEA certification: Yes ☐ No ☐	Determ. of Involvement? Yes ☐ No ☐
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD =_____ NDA#_____ Date Checked _____ Nothing Submitted ☐ Written request issued ☐ Study Submitted ☐
Patent/Exclusivity Certification: Yes ☐ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☐ No ☐ Was applicant sued w/in 45 days:Yes ☐ No ☐ Has case been settled: Yes ☐ No ☐ Date settled: Is applicant eligible for 180 day	
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐	
Date of latest Labeling Review/Approval Summary _____	
Any filing status changes requiring addition Labeling Review Yes ☐ No ☐☐	
Type of Letter: ☐ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐CGMP ☐ OTHER:	
Comments:ANDA submitted on 8/31/2010, BOS=Lysteda NDA 22430, no relevant patent statement provided, NDF exp. 11/13/2012. ANDA ack for filing on 8/31/2010(LO dated 11/24/2010). Patent Amendment rec'd on 5/23/2011-PIV to '739 patent, again 5/24, 5/25, 5/26, 5/27. Patent Amendment rec'd on 10/24/2011-CA 11 CV 0485 filed on 7/8/2011 in the D of Nevada for infringement of the '739 patent, Ferring admits to receipt of notice on 5/26/2011(notice dated 5/23/2011), since this patent was not listed in the OB at the time Apotex's ANDA was submitted there can be no 30 month stay of approval associated with this CA. Since there can be no 30 month stay and because a CA was filed there is no need for Apotex to submit proof of notice from the NDA holder as the RR's are used only to ensure that notice was provided-we know this to be true since a CA was filed-and to calculate the stay of approval-there can be no stay in this case. Patent Amendment rec'd on 10/17/2011-PIV to the '106, Apotex also provided a copy of the factual and legal basis of noninfringement for this patent. Patent Amendment rec'd on 11/1/2011-notice sent via (b) (4) to Ferring Pharmaceuticals in Parsippany NJ with notice delivered on 10/20/2011, notice sent via (b) (4) to Xanodyne Pharmaceuticals in Newport KY with notice delivered on 10/20/2011, notice sent via (b) (4) to Ferring B.V. in Hoofddorp Netherlands with notice delivered on 10/21/2011, notice sent via (b) (4) to Ferring Pharmaceuticals S.A. in Saint-Prex Switzerland with notice delivered on 10/21/2011. Patent Amendment rec'd on 2/13/2012-suit brought in the D of Nevada on 11/25/2011 for infringement of the '106 patent.	

Again, like the CA for the '739 patent, there can be no 30 month stay of approval associated with this CA since the '106 patent was not listed in the OB at the time Apotex's ANDA was submitted.
ANDA TA'd on 8/10/2012-reason cited for TA was the unexpired NDF exclusivity which will expire on 11/13/2012.
Patent Amendmnet rec'd on 11/6/2012-PIV to the '795 patent.
The patent listing dates under NDA 22430 for the '739, '106 and '795 are the following:
'739-FDA form 3542 rec'd on 5/24/2011-this is the listing date for this patent.
'106-FDA form 3542 rec'd on 9/20/2011-this is the listing date for this patent.
'795-FDA form 3542 rec'd on 9/25/2012-this is the listing date for this patent. Firm submitted a revised 3542 on 10/23/2012 to correct the expiration date of the '795 patent.
180 day exclusivity for this product hinges solely upon the '739 patent. Apotex submitted a PIV cert for the '739 patent on 5/24/2011-the same date the patent was listed.
OGD currently has (b) (4) ANDAs pending for Tranexamic Acid Tablets, 650 mg: Watson's ANDA 202093, Apotex's ANDA 202286 (b) (4). Watson's first PIV certification to the '739 patent was rec'd on 5/25/2011 (b) (4) (b) (4) Therefore, Apotex will be the sole applicant that is eligible for 180 day exclusivity for this product.
ANDA is eligible for Full Approval with an award of 180 day exclusivity once the NDF exclusivity expires on 11/13/2012.
Patent Amendment rec'd on 11/8/2012-notice for the '795 patent on 11/6/2012 via (b) (4) and delivered to Ferring Pharmaceuticals in Saint-Prex, Switzerland on 11/8/2012, also sent via (b) (4) to Ferring B.V. in Hoofddorp Netherlands with notice delivered on 11/8/2012, also sent via (b) (4) to Xanodyne Pharmaceuticals in Newport KY with notice delivered on 11/7/2012, also sent via (b) (4) to Ferring Pharmaceuticals in Parsippany NJ with notice delivered on 11/7/2012. Since this patent was not present in the OB at the time this ANDA was rec'd there can be no 30 month stay of approval in the event that the NDA holder chooses to sue Apotex.

3. ***Labeling Endorsement***

Reviewer, :
Date_____
Initials_____

Labeling Team Leader, :
Date_____
Initials_____

REMS required?
☐Yes ☐No

REMS acceptable?
☐Yes ☐No ☐n/a

Comments:

From: Lee, Koung U
Sent: Wednesday, November 07, 2012 4:04 PM
To: Park, Sarah Soojung; Park, Linda; Park, Chan H
Subject: RE: ANDA 202286/Apotex/Tranexamic Acid Tablets

I concur.

Koung

From: Park, Sarah Soojung
Sent: Wednesday, November 07, 2012 3:07 PM
To: Park, Linda; Lee, Koung U; Park, Chan H
Subject: FW: ANDA 202286/Apotex/Tranexamic Acid Tablets

Hi Linda,

The Labeling AP Summary signed by Koung Lee on 9/30/2011 is still acceptable.

Thanks,
Sarah

4. ***Paragraph IV Evaluation*** **PIV's Only**

David Read **Date _____**
OGD Regulatory Counsel **Initials_____**
Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:

5. ***Quality Division Director /Deputy Director Evaluation*** **Date 2/5/2013**
Chemistry Div. **II (Smith)** **InitialsGJS**
Comments:CMC Acceptable - cGMP letter

6. ***First Generic Evaluation*** **First Generics Only**
Frank Holcombe **Date_____**
Assoc. Dir. For Chemistry **Initials_____**
Comments: (First generic drug review)

OGD Office Management Evaluation

7. Peter Rickman **Date_____**
Director, DLPS **Initials_____**
Para.IV Patent Cert: Yes☐☐No☐
Pending Legal Action: Yes ☐☐No ☐
Petition: Yes☐ No☐
Comments:

AND/OR

8. Robert L. West **Date 2/28/13**
Deputy Director, OGD **Initials TWAmes for RLWest**
Para.IV Patent Cert: Yes☒ No☐
Pending Legal Action: Yes☒ No☐
Petition: Yes☐ No☐
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: ANDA is now eligible for full approval, but cGMP issues remain and Overall Compliance Recommendation remains WITHHOLD. Complete Response cGMP letter to issue./twa

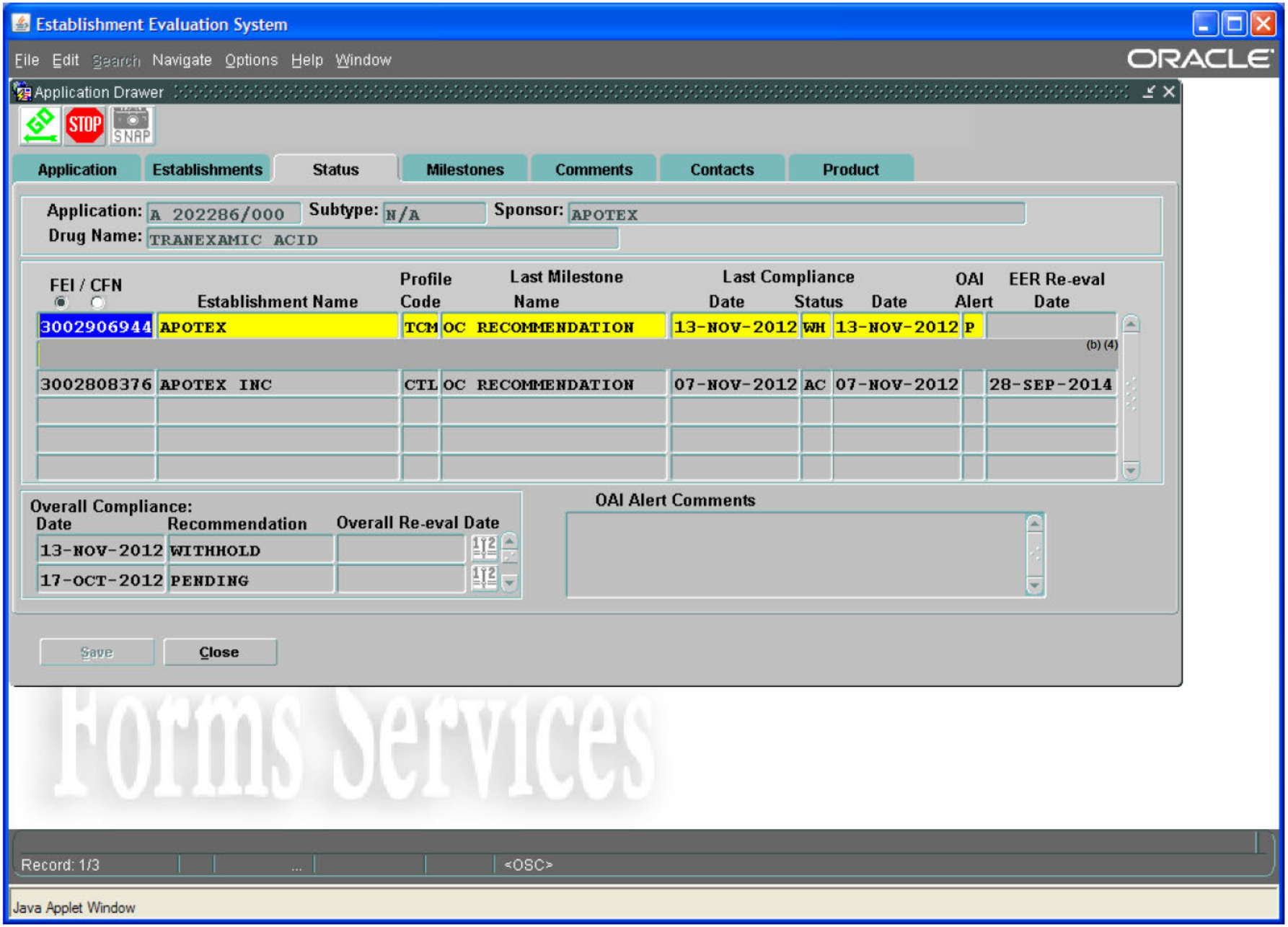
9. ***OGD Director Evaluation***
Gregory Geba
Deputy Director, OPS
Comments:
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

Comments:

10. Project Manager
Date _____
Initials _____

Check Communication and Routing Summary into DARRTS

EER DATA:



Reference ID: 3273403

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

/s/

LINDA M PARK
03/08/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 202286

Apotex Corp.
U.S. Agent for: Apotex Inc.
Attention: Kiran Krishnan
Vice President, US Regulatory Affairs
2400 North Commerce Parkway, Suite 400
Weston, Florida 33326

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated August 31, 2010, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Tranexamic Acid Tablets, 650 mg.

Reference is also made to the tentative approval letter issued by this Office on August 10, 2012 and to your amendments dated August 17, November 6 and November 8, 2012.

We have completed the review of this ANDA and have determined that we cannot approve this ANDA in its present form because the Center for Drug Evaluation and Research (CDER) is unable to find that the methods used in, and the facilities and controls used for, the manufacture, processing, packaging, or holding of Tranexamic Acid Tablets, 650 mg by Apotex Inc., located at 150 Signet Drive, Toronto, Canada, comply with current good manufacturing practice (cGMP) regulations.

Our conclusion is based upon the findings revealed during an inspection of Apotex Inc., located at 150 Signet Drive, Toronto, Canada, conducted during the period of August 13, 2012 to August 24, 2012, by representatives of the United States Food and Drug Administration and the cGMP Warning Letter issued on February 21, 2013.

Upon review of this report and the inspectional observations noted during this inspection, we have received a recommendation from our Office of Manufacturing and Product Quality (OMPQ), Office of Compliance, to withhold approval of your ANDA.

Until such time that you can demonstrate to the Agency that the problems have been corrected and the Agency's concerns are otherwise satisfied, your ANDA cannot be approved.

You should amend this ANDA when the cGMP-related issues have been satisfactorily resolved. Your amendment to the ANDA submitted in response to this Complete Response Not Approvable cGMP letter will be considered a "COMPLETE RESPONSE - MINOR AMENDMENT" provided that the amendment contains no significant additional information necessary to remedy the cGMP problems, and includes a statement from a responsible corporate official certifying that your facilities have been found to be in compliance with cGMPs and have been cleared for approval of the drug product by representatives of the local FDA District Office. If, as a result of follow-up inspections related to the ongoing evaluation of this or other applications, it is necessary for you to significantly revise your procedures, controls or practices to correct the deficiencies, then the amendment will be considered to represent a "COMPLETE RESPONSE - MAJOR AMENDMENT". Your amendment should be plainly marked as such in your cover letter.

The file on this ANDA is now closed. You are required to take an action described under 21 CFR 314.110(4)(b)(1) which will either amend or withdraw this ANDA. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

{See appended electronic signature page}

Gregory P. Geba, M.D., M.P.H.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

ROBERT L WEST

03/01/2013

Deputy Director, Office of Generic Drugs, for
Gregory P. Geba, M.D., M.P.H.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 202286

Stephen R. Auten, Esq.
Cozen O'Connor
333 W. Wacker Drive, Suite 1900
Chicago, IL 60606-1293

Dr. Mr. Auten:

This letter is in response to your e-mail of December 28, 2012, sent on behalf of Apotex, Inc. (Apotex), in which you challenge the eligibility of Watson Laboratories, Inc. (Watson) for "first applicant" status for its abbreviated new drug application (ANDA) 202093, which FDA approved on December 27, 2012. Dave Read and Kim Dettelbach referred your e-mail to me for response.

I. BACKGROUND

The Drug Price Competition and Patent Term Restoration Act of 1984 (known as the "Hatch-Waxman Amendments") permits the submission of ANDAs for approval of generic versions of approved drug products.[1] ANDA applicants need not submit clinical data to demonstrate the safety and efficacy of their product, as in an NDA. Rather, an ANDA relies on FDA's previous findings that the product approved under the NDA is safe and effective. Among other things, an ANDA must contain one of four specified certifications for each patent that "claims the listed drug" or "a use for such listed drug for which the applicant is seeking approval."[2] This certification must state one of the following:

(I) that the required patent information relating to such patent has not been filed;
(II) that such patent has expired;
(III) that such patent will expire on a particular date; or
(IV) that such patent is invalid or will not be infringed by the drug for which approval is being sought.[3]

If an applicant wishes to challenge the validity of a patent, or to claim that the patent would not be infringed by the product proposed in the ANDA, the applicant must submit a "paragraph IV certification" pursuant to section 505(j)(2)(A)(vii)(IV) of the FD&C Act. The applicant must provide notice of its paragraph IV certification to the NDA holder and the patent owner explaining the factual and legal basis for the applicant's opinion that the patent is invalid or not infringed.[4]

[1] Section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).
[2] Section 505(j)(2)(A)(vii) of the FD&C Act.
[3] Id.
[4] Section 505(j)(2)(B) of the FD&C Act.

The statute provides an incentive and reward to certain generic drug manufacturers that expose themselves to the risk of patent litigation. It does so by granting a manufacturer who is a "first applicant" to file and maintain an ANDA containing a paragraph IV certification a 180-day exclusivity period vis-à-vis other ANDA applicants that filed a paragraph IV certification, so long as certain forfeiture provisions do not apply.[5] The 180-day exclusivity period begins on the date any first applicant commences commercial marketing of its drug product.[6]

The date on which FDA "receives" an amendment to an ANDA that contains a paragraph IV certification thus is significant. To be a "first applicant" and therefore eligible for 180-day exclusivity, the ANDA must be "substantially complete," and the relevant paragraph IV certification must be submitted "on the first day on which a substantially complete application that contains and lawfully maintains" a paragraph IV certification is submitted for the drug.[7] Where the first paragraph IV certification for a drug is submitted in an amendment, and not in an original application as was the case here, FDA uses the date the amendment containing the paragraph IV certification is "received" as the date on which first applicant status is determined.[8] In considering circumstances in which multiple ANDAs are submitted on the same day, the agency has rejected a minute-by-minute, "first in time" determination of first applicant status. Instead, FDA employs a "multiple-first-applicant" approach such that applicants that submit on the same day can share "first applicant" status.[9] Thus, if multiple ANDAs are submitted on the same day on the first day on which a substantially complete application is submitted, FDA treats "all ANDAs containing a paragraph IV certification to a listed patent that are submitted on the same day as being submitted at the same time for purposes of 180-day exclusivity when no ANDA for the same drug product containing a paragraph IV certification to the same patent has been submitted on a previous day."[10]

II. DISCUSSION

In your e-mail, you request the factual and legal bases for FDA's determination that Watson is a first applicant for Tranexamic Acid Tablets, 650 mg.

The reference listed drug (RLD) for Watson's ANDA 202093 and Apotex's ANDA 202286 is Lysteda, the new drug application (NDA) for which is held by Ferring, B.V. (Ferring). At the time of the original submission of the Watson and Apotex ANDAs in 2010, no patents were listed for Lysteda. On May 24, 2011, the U.S. Patent and Trademark Office issued U.S. Patent No. 7,947,739 (the '739 patent). On the same day, FDA received the '739 patent from Ferring for listing in FDA's Orange Book under the NDA for Lysteda. Later that day, Apotex and Watson both transmitted via FDA's electronic submissions gateway (ESG), an amendment containing a paragraph IV certification to the '739 patent. Both applicants sent timely notifications to the NDA/patent holder(s). Upon review of the relevant record, FDA determined that Watson is a first applicant for purposes of 180-day exclusivity, because FDA "received" the

[5] Section 505(j)(5)(B)(iv) of the FD&C Act.
[6] Section 505(j)(5)(B)(iv)(I) of the FD&C Act.
[7] Section 505(j)(5)(B)(iv)(II)(bb) of the FD&C Act.
[8] Guidance for Industry on *180-Day Exclusivity When Multiple ANDAs Are Submitted on the Same Day*, at 4 (July 2003.
[9] Id., at 5.
[10] Id.

company's substantially complete ANDA on May 24, 2011, and Watson has lawfully maintained its paragraph IV certification to the '739 patent.[11]

You also assert in your email that on November 19, 2012, an FDA employee advised Apotex that the company was the sole first applicant for the purposes of 180-day exclusivity. At this juncture, FDA has not been able to confirm such communication. Even if such communication took place, however, FDA notes that statements of individual employees do not constitute official agency action.[12] Therefore, your assertion that FDA has "revers[ed] its November 2012 determination that Apotex was sole first applicant" is inaccurate. Apotex's reliance on such a statement is further undermined by FDA's well-documented practice of not making 180-day eligibility determinations until an applicant that is affected by the exclusivity determination is eligible for tentative or final approval.[13] In this instance, consistent with this long-standing agency practice, FDA made the determination with regard to first-applicant status only when an application (here, Watson's ANDA) was eligible for approval, on or about December 27, 2012.

We apologize for any confusion that may have been caused.

Sincerely,

{See appended electronic signature page}

Gregory P. Geba, M.D., M.P.H.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

[11] Letter to J. Vaughn, Watson Labs., Inc.-FL fr. G. Geba, FDA Office of Generic Drugs, at 2 (Dec. 27, 2011) (approving Watson's ANDA 202093 for Tranexamic Acid Tablets, 650 mg).

[12] 21 CFR 10.85(k) ("A statement or advice given by an FDA employee orally, or given in writing but not under this section [pertaining to advisory opinions] or 10.90, is an informal communication that represents the best judgment of that employee at that time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed").

[13] See, e.g., Letter to W. Rakoczy fr. G. Buehler, OGD, at 1, note 1 (May 7, 2008) (Acarbose Letter) (addressing 180-day exclusivity for acarbose tablets). As described in the Acarbose Letter, "[t]his approach is necessary because of the many factors that may influence eligibility for exclusivity up to the time an application is ready for approval (e.g., patent expiration, patent delisting, failure to obtain a tentative approval within 30 months, withdrawal of ANDA) and could thus render a premature eligibility determination incorrect." Id.

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

/s/

GREGORY P GEBA

01/03/2013

Please note typo ref 11. Date should be Dec. 27, 2012.

ROUTING SHEET

☐ **APPROVAL** ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **CGMP**

Division: II	**Team: 21**	**PM: Linda Park**

Electronic ANDA: Yes ☒ No ☐

ANDA #:202286
Firm Name:Apotex, Inc.
ANDA Name:Tranexamic Acid Tablets, 650 mg
RLD Name:LYSTEDA (tranexamic acid) Tablets, 650 mg

Electronic AP Routing Summary Located:
V:\Chemistry Division II\Team 21\Electronic AP-TA-NAcGMPSummaries

AP/TA Letter Located:
V:\Chemistry Division II\Team 21\Final Version For DARRTS\AP TA_NAcGMP CR WD Letters

Project Manager Evaluation: **Date: 7-5-12 Initials:** LP

☐ Previously reviewed and tentatively approved --- Date _____
☐ Previously reviewed and CGMP Complete Response issued -- Date _____

Original Rec′d date 8-31-10	Date of Application 8-31-10	Date Acceptable for Filing 11-24-10
Patent Certification (type) _____	Date Patent/Excl. expires	Citizens' Petition/Legal Case? Yes☐ No ☐ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☐ **DMF#:** _____ (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☐ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☐ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

EER Status: ☐ Pending ☒ Acceptable ☐ OAI *EES Date Acceptable: 7-3-12* ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☒ Comment:
Date of Acceptable Quality (Chemistry) 6-28-12 Addendum Needed: Yes ☐ No ☒ Comment:
Date of Acceptable Bio 3-29-12 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location:)
Date of Acceptable Labeling 9-30-11 Attached labeling to Letter: Yes ☐ No ☒ Comment:
Date of Acceptable Sterility Assurance (Micro) na

Methods Val. Samples Pending: Yes ☐ No ☒**;** Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☐ No ☒ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☐ No ☒ (If yes, enter dissolution information in Letter)

Routing:
☒ Labeling Endorsement, Date emailed: 7/5/12 REMS Required: Yes ☐ No **x** REMS Acceptable: Yes ☐ No ☐

☒ Regulatory Support

☒ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: 7/26/12

☒ Division

☐ 1st Generic Review

☒ Bob West / Peter Rickman
☐ Keith Webber

X Filed AP Routing Summary in DARRTs	X Notified Firm and Faxed Copy of Approval Letter	X Sent Email to "CDER-OGDAPPROVALS″ distribution list

OGD APPROVAL ROUTING SUMMARY

1. ***Regulatory Support Branch Evaluation***

Martin Shimer **Date: 7/9/2012**
Chief, Reg. Support Branch **Initials:** MHS

Contains GDEA certification: Yes ☒ No ☐	Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD = Lysteda NDA# 22-430 Date Checked 8/10/12 Nothing Submitted ☒ Written request issued ☐ Study Submitted ☐
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☒ No ☐ Was applicant sued w/in 45 days:Yes ☐ No ☐ Has case been settled: Yes ☐ No ☐ Date settled: Is applicant eligible for 180 day	
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐	
Date of latest Labeling Review/Approval Summary _____	
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒	
Type of Letter: ☐ APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ CGMP ☐ OTHER:	
Comments:ANDA submitted on 8/31/2010, BOS=Lysteda NDA 22-430, no relevant patent statement provided, NDF expires on 11/13/2012. ANDA accepted for filing on 8/31/2010 (LO dated 11/24/2010). Patent Amendment rec'd on 5/23/2011-PIV to '739. Patent Amendment rec'd on 5/24/2011-PIV to '739. Patent Amendment rec'd on 5/25/2011-PIV to '739. Patent Amendment rec'd on 5/26/2011-PIV to '739. Patent Amendment rec'd on 5/27/2011-PIV to '739. Patent Amendment rec'd on 10/14/2011-CA 11 CV 0485 filed in the D of NV on 7/8/2011 for infringement of the '739 patent-since this patent was not listed at the time this ANDA was submitted there can be no 30 month stay associated with this CA. Patent Amendment rec'd on 11/1/2011-PIV to '106. Patent Amendment rec'd on 2/13/2012-CA brought in the D of NV on 11/25/2011 for infringement of the '106, no CA number on the complaint-since this patent was not listed at the time this ANDA was submitted there can be no 30 month stay associated with this CA. ANDA is eligible for TA only due to unexpired NDF exclusivity. Furthermore, even though there are no 30 month stays associated with either of the CAs brought against Apotex on the '739 or '106 patents, Apotex may be subject to another applicants eligibility for 180 day exclusivity with respect to the '739 patent. Since Apotex submitted serial certifications to this patent it would appear that Apotex has secured a FTF seat for this product. This will be verified once this ANDA nears Full Approval eligibility once the NDF expires. ANDA is eligible for TA only.	

2. ***Labeling Endorsement***

Reviewer, :
Date_____
Initials_____

Labeling Team Leader, :
Date 8/10/12
Initials rlw/for

REMS required?
☐Yes ☒No

REMS acceptable?
☐Yes ☐No ☐n/a

Comments:

From: Lee, Koung U
Sent: Thursday, July 05, 2012 3:47 PM
To: Park, Linda; Park, Sarah Soojung
Subject: RE: ANDA 202286/Tranexamic Acid Tablet/Apotex Inc. - TA ready

Hi Linda,

I concur and concur on Sarah's behalf. Thanks.

Koung

From: Park, Linda
Sent: Thursday, July 05, 2012 3:18 PM
To: Park, Sarah Soojung
Cc: Lee, Koung U
Subject: ANDA 202286/Tranexamic Acid Tablet/Apotex Inc. - TA ready

Hello Sarah and Koung,

Please endorse the ARS for ANDA 202286.

<< File: 202286_TA_LETTER.doc >>
<< File: 202286_AP_Labeling.pdf >>

Thanks,

Linda

3. ***Paragraph IV Evaluation*** **PIV's Only**
David Read **Date 31Jul2012**
OGD Regulatory Counsel **InitialsDTR**
Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:Changes to TA letter saved to V drive.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 7/20/2012**
Chemistry Div. **II (Smith)** **InitialsGJS**
Comments:CMC Acceptable.

5. ***First Generic Evaluation*** **First Generics Only**
Frank Holcombe **Date 8/10/12**
Assoc. Dir. For Chemistry **Initials rlw/for**
Comments: (First generic drug review)
N/A. Watson's ANDA 202093 for this drug product was granted tentative approval on 2/16/12.

OGD Office Management Evaluation

6. Peter Rickman **Date8/10/12**
Director, DLPS **Initials rlw/for**
Para.IV Patent Cert: Yes☐ No☐
Pending Legal Action: Yes ☐ No ☐
Petition: Yes☐ No☐
Comments: Bioequivalence studies (fasting and non-fasting) found acceptable. In-vitro dissolution testing also found acceptable. Bio study sites have acceptable OSI inspection hisgtories. Office-level bio endorsed 3/29/12.

Labeling found acceptable 9/30/11, as endorsed 7/5/12. No REMS is required.

CMC found acceptable for approval (Chemistry Review #3) 6/28/12.

7. Robert L. West **Date 8/10/12**
Deputy Director, OGD **Initials RLWest**
Para.IV Patent Cert: Yes☒ No☐
Pending Legal Action: Yes☒ No☐
Petition: Yes☐ No☒
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: Acceptable EES dated 7/3/12 (Verified 8/10/12). No "OAI" Alerts noted.

Apotex provided paragraph IV certifications to the '739 and '106 patents and was sued on each patent within the 45-day period. However, neither of these patents were listed in the "Orange Book" at the time this ANDa was received. As a result, there is no 30-month stay associated with the ongoing patent litigation. Final approval is blocked at this time by Ferring's NDF (new dosage form) exclusivity due to expire on November 13, 2012 and by potential first-to-file issues regarding eligibility for 180-day generic drug exclusivity. The exclusivity issues will be decided at a later date. There are no additional patents or exclusivity currently listed in the "Orange Book" for this drug product.

This ANDA is recommended for tentative approval.

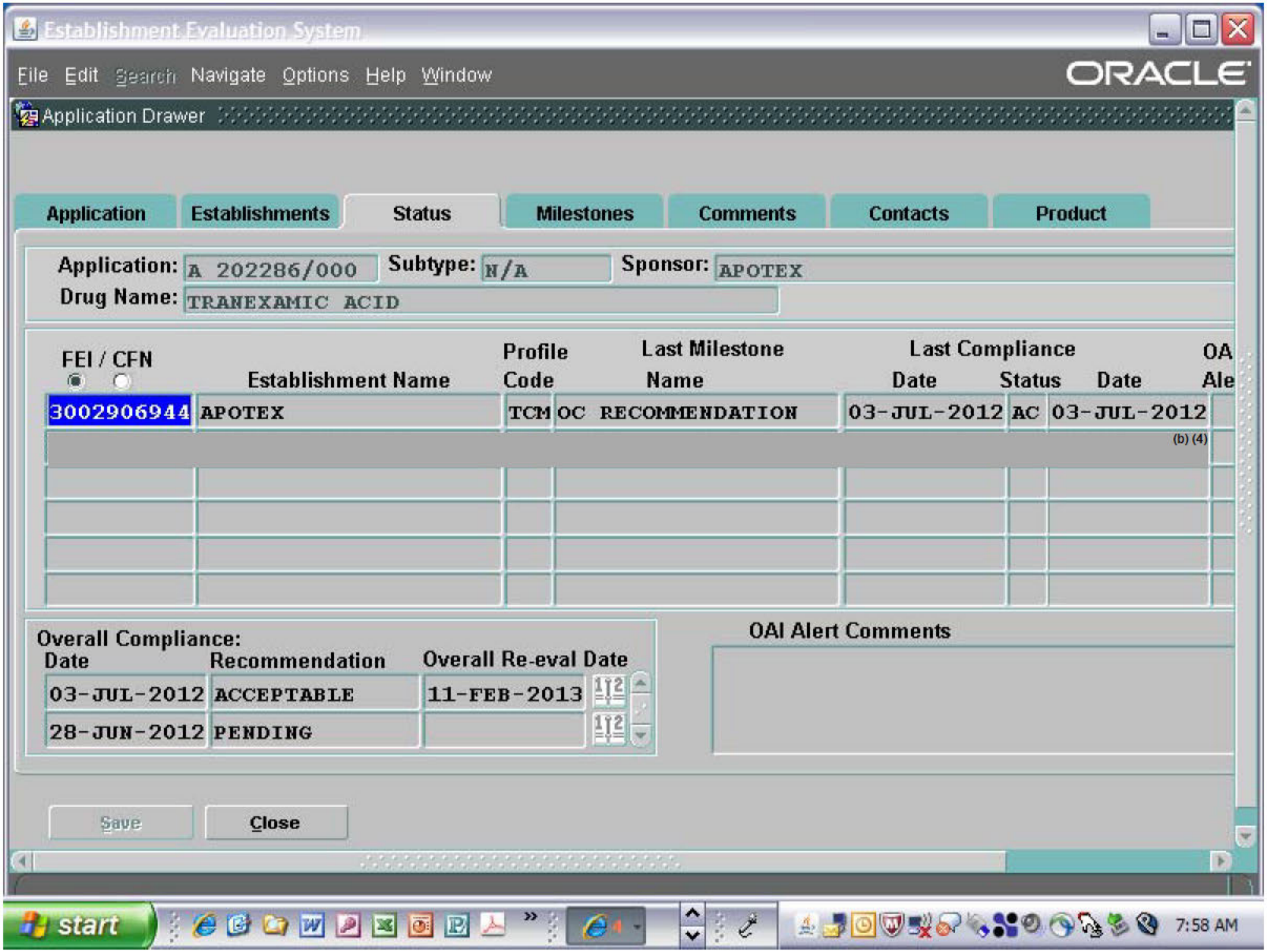
8. ***OGD Director Evaluation***
Keith Webber
Deputy Director, OPS
Comments: RLWest for Gregory P. Geba, M.D., M.P.H. 8/10/12.
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

Comments:

9. Project Manager
Date 8/10/12
Initials fjn

Check Communication and Routing Summary into DARRTS

EER DATA:



Reference ID: 3172708

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

- 
-  [1]
-  [2]

- FDA Home[3]
- Drug Databases[4]
- Orange Book[5]

-

Patent and Exclusivity Search Results from query on Appl No 022430 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N022430	001	7947739	Mar 4, 2025		Y		
N022430	001	8022106	Mar 4, 2025			U - 1182	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N022430	001	NDF	Nov 13, 2012

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

/s/

FRANK J NICE
08/10/2012

QUALITY DEFICIENCY - MINOR

ANDA 202286

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

TO: Apotex Inc.

TEL: (954) 384-3986

ATTN: Kiran Krishnan

FAX: (954) 349-4233

FROM: Frank J. Nice

FDA CONTACT PHONE: (240) 276-8555

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated August 31, 2010, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Tranexamic Acid Tablets, 650 mg.

Reference is also made to your amendment dated March 6, 2012.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

ANDA: 202286

APPLICANT: Apotex, Inc.

DRUG PRODUCT: Tranexamic Acid Tablets, 650 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)

2.

3.

4. Please update ambient stability data for the drug product (all configurations).

Sincerely yours,

{See appended electronic signature page}

Glen J. Smith
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

RADHIKA RAJAGOPALAN
05/15/2012
For Glen Smith,

QUALITY DEFICIENCY - MINOR

ANDA 202286

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Apotex Inc. TEL: (954) 384-3986

ATTN: Kiran Krishnan FAX: (954) 349-4233

FROM: Frank J. Nice FDA CONTACT PHONE: (240) 276-8555

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated August 31, 2010, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Tranexamic Acid Tablets, 650 mg.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

ANDA: 202286

APPLICANT: Apotex, Inc.

DRUG PRODUCT: Tranexamic Acid Tablets, 650 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)
2.
3.
4.
5.
6.
7.

8. (b) (4)

9.

10.

11.

12.

13.

14.

15.

16.

17.

18.

19.

20.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please update ambient stability data for the drug product (all configurations).

2. Please provide your product and RLD samples (2 package units each) for evaluation. Samples can be sent to the attention of:
   Frank J. Nice, RPh, DPA, CPHP
   Project Manager
   Office of Generic Drugs
   Food and Drug Administration
   HFD-617, Rm E254, MPN 2
   240-276-8555

Sincerely yours,

{See appended electronic signature page}

Glen J. Smith
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

RADHIKA RAJAGOPALAN
10/25/2011
For Glen Smith,

BIOEQUIVALENCE AMENDMENT

ANDA 202286

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Apotex, Inc. TEL: (954) 384-3986

ATTN: Kiran Krishnan FAX: (866) 392-1774

FROM: Chitra Mahadevan FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on August 31, 2010, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Tranexamic Acid Tablets, 650 mg.

Reference is also made to your amendment dated April 14, 2011.

The Division of Bioequivalence II has completed its review of the submissions referenced above and has identified deficiencies which are presented on the attached **2** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Dissolution Acknowledgement

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20857

*After the effective date, **01-Aug-2010**, ANDAs will only be accepted at the new mailing address listed above. **DO NOT submit your ANDA Regulatory documents to this address prior to 01-Aug-2010.** For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/*

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCY

ANDA: 202286

APPLICANT: Apotex Inc.

DRUG PRODUCT: Tranexamic Acid Tablets, 650 mg

The Division of Bioequivalence II (DB2) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the fasted and fed bioequivalence studies will be conducted later. The following deficiency has been identified:

Your dissolution testing for the test product using the following FDA-recommended dissolution method is acceptable.

USP Apparatus type:	Apparatus II (paddles)
Rotation:	50 rpm
Medium:	Water
Volume:	900 mL
Temperature:	37°C ± 0.5°C
Sampling Times:	15, 30, 45, 60, 90 and 120 minutes

Based on the data submitted, the DB2 recommends the following specification: Not less than (b) (4) % (Q) in 60 minutes.

Please acknowledge your acceptance of the FDA-recommended dissolution method and specification.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

BARBARA M DAVIT
08/15/2011

BIOEQUIVALENCE AMENDMENT

ANDA 202286

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Apotex, Inc. TEL: (416) 401-7889

ATTN: Bernice Tao FAX: (416) 401-3817

FROM: Chitra Mahadevan FDA CONTACT PHONE: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalence data submitted on August 31, 2010, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Tranexamic Acid Tablets, 650 mg.

The Division of Bioequivalence has completed its review of the submission referenced above and has identified deficiencies which are presented on the attached **2** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:*

Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCY

ANDA: 202286

APPLICANT: Apotex, Inc.

DRUG PRODUCT: Tranexamic Acid Tablets, 650 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the fasted and fed bioequivalence studies will be conducted later. The following deficiency has been identified:

Please conduct and submit dissolution testing on the test and reference product (12 units each) using the following FDA-recommended method:

USP Apparatus type:	Apparatus II (paddles)
Rotation:	50 rpm
Medium:	Water
Volume:	900 mL
Temperature:	37°C ± 0.5°C
Sampling Times:	15, 30, 45, 60, 90 and 120 minutes

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

BARBARA M DAVIT
02/28/2011

Labeling Comments

ANDA 202286

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2773
240-276-8995

TO: Apotex Inc.

TEL: (954) 384-3986

ATTN: Kiran Krishnan

FAX: (866) 392-1774

FROM: Sarah Park

Dear Sir or Madam:

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Tranexamic Acid Tablets, 650 mg.

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

1. Labeling comments are attached.

2. Please note the following:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents has become:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 202286

Date of Submission: August 31, 2010 (Original)

Applicant's Name: Apotex, Inc.

Established Name: Tranexamic Acid Tablets, 650 mg

Labeling Deficiencies:

1. CONTAINER

   We recommend addition of a statement to dispense with a Patient Information Leaflet.

2. INSERT

   a. The three major sections, HIGHLIGHTS OF PRESCRIBING INFORMATION, FULL PRESCRIBING INFORMATION: CONTENTS, and FULL PRESCRIBING INFORMATION, should be separated by a solid horizontal line.

   b. HIGHLIGHTS OF PRESCRIBING INFORMATION

      i. Please replace "Tranexamic acid (b) (4) tablet for oral use" with "Tranexamic acid tablets"

      ii. The headings should appear in the center of a horizontal line, for example:

      ----------**INDICATIONS AND USAGE**----------

   c. PATIENT INFORMATION, How should I store Tranexamic acid? – Replace "(b) (4) in tight, light-resistant containers [see USP]" with "Preserve in tight, light-resistant containers."

Please revise your labels and labeling, as instructed above, and submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

{See appended electronic signature page}

_____
Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

SOOJUNG S PARK
02/10/2011
For Wm Peter Rickman

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
*** **A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ ***

ANDA #: 202286 **FIRM NAME**: APOTEX, INC.

PIV: NO **Electronic or Paper Submission:** ELECTRONIC (GATEWAY)

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: TRANEXAMIC ACID
DOSAGE FORM: TABLETS, 650 MG

Review Team: (Bolded/Italicized & Checked indicate Assignment or DARRTS designation)

Quality Team: DC2 Team 7 ☒***Activity***	***Bio Team 7: Jiang Xiaojian*** ☒***Activity***
ANDA/Quality RPM: Frank Nice ☒ ***FYI***	Bio PM: Chitra Mahadevan ☐ ***FYI***
Quality Team Leader: Rajagopalan, Radhika No assignment needed in DARRTS	***Clinical Endpoint Team Assignment: (No)*** ☐***Activity***
Labeling Reviewer: Sarah Park ☒***Activity***	***Micro Review (No)*** ☐***Activity***

*****Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s). *****

Letter Date: AUGUST 31, 2010 **Received Date**: AUGUST 31, 2010

Comments: EC - 1 YES **On Cards:** YES
Therapeutic Code: 8052009 FIBRINOLYTICS/ANTIFIBRINOLYTICS

Archival copy: ELECTRONIC (GATEWAY) **Sections** I
Review copy: NA E-Media Disposition: NA
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Tim Jetton **Date**	**Recommendation:** ☐ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: ____	**Date:** ____

1. Edit Application Property Type in DARRTS where applicable for
   a. First Generic Received
      ☐ Yes ☒ No
   b. Market Availability
      ☒ Rx ☐ OTC
   c. Pepfar
      ☐ Yes ☒ No
   d. Product Type
      ☐ Small Molecule Drug (usually for most ANDAs except protein drug products)
   e. USP Drug Product (at time of filing review)
      ☐ Yes ☒ No
2. Edit Submission Patent Records
   ☒ Yes
3. Edit Contacts Database with Bioequivalence Recordation where applicable
   ☐ Yes
4. Requested EER
   ☐ Yes

ADDITIONAL COMMENTS REGARDING THE ANDA:

1. **Kirian Krishnan 954-384-3986**
2. **Max mark up of commercial batch is 10X – explained see below charts**
3. **Need source of inactive ingredients identified** in sec 3.2.r.1.p.2

Response:

(b) (4)

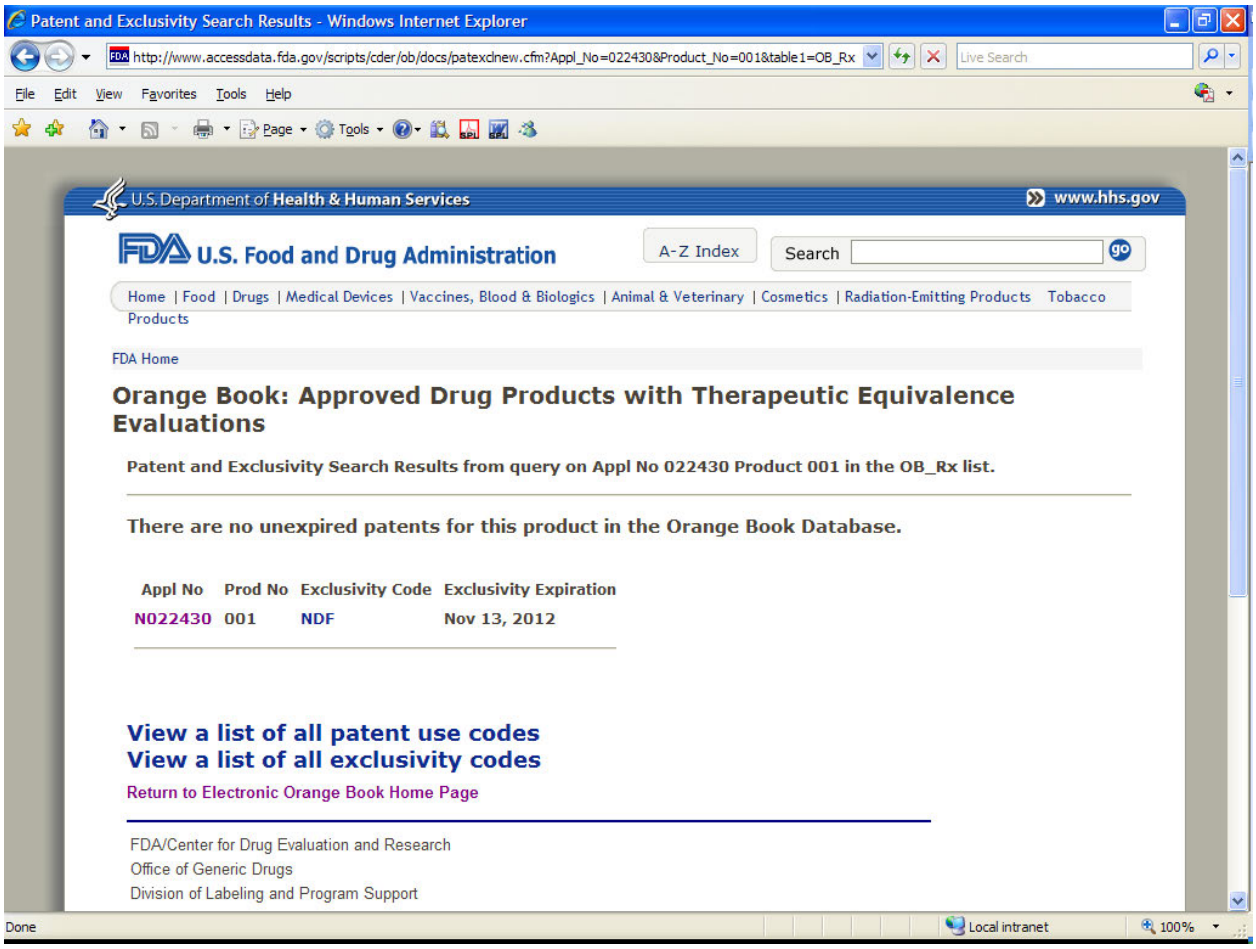
MODULE 1
ADMINISTRATIVE

ACCEPTABLE

1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: AUGUST 31, 2010	☒
1.2.1	**Form FDA 3674 (PDF) YES – box b**	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** NA	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) SAME	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES Disclosure Statement (Form FDA 3455, submit copy to Regulatory Branch Chief) NA	☒
1.3.5	**1.3.5.1 Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 1. Patent number(s) na 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☒ PII ☐ PIII ☐ PIV ☐ (Statement of Notification) ☐ 3. Expiration of Patent(s): NA a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES	☒

Name	Exclusivity Code	Exclusivity Expires
Lysteda Tablets 650 mg	NDF	November 13, 2012

Apotex Inc. certifies that sale of Tranexamic Acid Tablets 650 mg will not begin until after expiry of the above exclusivity.


Patent and Exclusivity Search Results - Windows Internet Explorer
http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=022430&Product_No=001&table1=OB_Rx
File Edit View Favorites Tools Help
U.S. Department of Health & Human Services
www.hhs.gov
U.S. Food and Drug Administration
A-Z Index
Search
Home | Food | Drugs | Medical Devices | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Radiation-Emitting Products | Tobacco Products
FDA Home
Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
Patent and Exclusivity Search Results from query on Appl No 022430 Product 001 in the OB_Rx list.
There are no unexpired patents for this product in the Orange Book Database.
Appl No
Prod No
Exclusivity Code
Exclusivity Expiration
N022430
001
NDF
Nov 13, 2012
View a list of all patent use codes
View a list of all exclusivity codes
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Done
Local intranet
100%

1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient yes Type II DMF No. (b) (4) b. Type III DMF authorization letter(s) for container closure yes 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) yes	☒

(b) (4)

1.12.11	**Basis for Submission** NDA# : 22-430 Ref Listed Drug: LYSTEDA Firm: FERRING PHARMS AS ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use yes 2. Active ingredients yes 3. Inactive ingredients yes 4. Route of administration yes 5. Dosage Form yes 6. Strength yes	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): NA	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) yes **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained yes **1.14.1.3** 1 package insert (content of labeling) submitted electronically yes ***Was a proprietary name request submitted? no (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained yes **1.14.3.3** 1 RLD label and 1 RLD container label yes	☒

MODULE 2
SUMMARIES ACCEPTABLE

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** yes **Word Processed e.g., MS Word** yes A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR)** yes **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** yes **2.3.S.1 General Information** **2.3.S.2 Manufacture** **2.3.S.3 Characterization** **2.3.S.4 Control of Drug Substance** **2.3.S.5 Reference Standards or Materials** **2.3.S.6 Container Closure System** **2.3.S.7 Stability** **2.3.P** **Drug Product** yes **2.3.P.1 Description and Composition of the Drug Product** **2.3.P.2 Pharmaceutical Development** **2.3.P.2.1 Components of the Drug Product** **2.3.P.2.1.1 Drug Substance** **2.3.P.2.1.2 Excipients** **2.3.P.2.2 Drug Product** **2.3.P.2.3 Manufacturing Process Development** **2.3.P.2.4 Container Closure System** **2.3.P.3 Manufacture** **2.3.P.4 Control of Excipients** **2.3.P.5 Control of Drug Product** **2.3.P.6 Reference Standards or Materials** **2.3.P.7 Container Closure System** **2.3.P.8 Stability**	☒
2.7	**Clinical Summary (Bioequivalence)** **Model Bioequivalence Data Summary Tables** **E-Submission: PDF** yes **Word Processed e.g., MS Word** yes **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary yes Table 4. Bioanalytical Method Validation yes Table 6. Formulation Data yes **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution yes **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies yes Table 3. Statistical Summary of the Comparative BA Data yes **2.7.1.4 Appendix** **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study yes **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies yes	☒

MODULE 3

3.2.S DRUG SUBSTANCE ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Name and Full Address(es)of the Facility(ies) yes 2. Function or Responsibility yes 3. Type II DMF number for API yes 4. CFN or FEI numbers	☒
3.2.S.3	**Characterization**	☒
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) yes **3.2.S.4.2 Analytical Procedures** yes **3.2.S.4.3 Validation of Analytical Procedures** 1. Spectra and chromatograms for reference standards and test samples yes 2. Samples-Statement of Availability and Identification of: 3.2.S.4.3 Validation of Analytical Procedures **Sample Availability** Samples will be available upon Agency request for the tranexamic acid (Lots JL0350, JL0351, and JL0352) and applicable reference standards as used in the submission exhibit batches. **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) yes 2. Applicant certificate of analysis yes **3.2.S.4.5 Justification of Specification**	☒
3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems**	☒
3.2.S.7	**Stability**	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1 **Description and Composition of the Drug Product** ☒

1. Unit composition

Strength (Label Claim):		650 mg		
Component	**Quality Standard/ Grade**	**Function**	**Quantity (mg) per Unit Dose**	**%w/w total unit dose weight**
Tranexamic Acid	N/A	Active	650	75.58
Ethylcellulose 7FP	NF/EP	(b) (4)		(b) (4)
Croscarmellose Sodium	NF			
Magnesium Stearate	NF			
Colloidal Silicon Dioxide	NF			
TOTAL:			860	100

2. Inactive ingredients and amounts are appropriate per IIG yes

ETHYLCELLULOSE	ORAL; TABLET, SUSTAINED ACTION	9004573	(b) (4)	600	308.8MG
CROSCARMELLOSE SODIUM	ORAL; TABLET	74811657		600	180MG
MAGNESIUM STEARATE	ORAL; TABLET	557040		600	400.748MG
SILICON DIOXIDE, COLLOIDAL	ORAL; TABLET	7631869		600	99MG

3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report yes	☒
3.2.P.3	**Manufacture** **3.2.P.3.1 Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) yes 2. CGMP Certification: YES 3. Function or Responsibility yes 4. CFN or FEI numbers 3002906944 **3.2.P.3.2 Batch Formula** **3.2.P.3.3 Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified 3. If sterile product: Aseptic fill / Terminal sterilization 4. Reprocessing Statement **Reprocessing Statement** In the event that a reprocessing procedure is required for Tranexamic Acid Tablets 650 mg, Apotex Inc. hereby commits to follow the policy set forth in the FDA Guidance for Industry: "Changes to an Approved NDA or ANDA" (Revision 1), Section VII B.7. Apotex Inc hereby commits to submit an appropriate ANDA supplement for the reprocessing procedure as per FDA's guidance. Furthermore, Apotex Inc. commits to follow written procedures to document the processing of reprocessed batches as regulated by 21 CFR 211.115. Samples of all batches that are manufactured with any reprocessing procedure (excluding re-packaging) will be placed into the on-going stability evaluation program. **3.2.P.3.4 Controls of Critical Steps and Intermediates** **3.2.P.3.5 Process Validation and/or Evaluation** 1. Microbiological sterilization validation 2. Filter validation (if aseptic fill)	☐
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified yes in sec 3.2.r.1.p.2 **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) yes 2. Suppliers' COA (specifications and test results) yes **3.2.P.4.2 Analytical Procedures** **3.2.P.4.3 Validation of Analytical Procedures** **3.2.P.4.4 Justification of Specifications** Applicant COA yes	☒

MODULE 3
3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s)** yes **3.2.P.5.2 Analytical Procedures** yes **3.2.P.5.3 Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: **Sample Availability Statement – Drug Product** Samples of Tranexamic Acid Tablets 650 mg batch FD149-13 and applicable reference standards, with appropriate identification, will be made available upon request. **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form yes **3.2.P.5.5 Characterization of Impurities** **3.2.P.5.6 Justification of Specifications**	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) yes 2. Components Specification and Test Data yes 3. Packaging Configuration and Sizes yes 4. Container/Closure Testing yes 5. Source of supply and suppliers address yes	☒
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted yes 2. Expiration Dating Period **Conclusions** Based upon the stability data available, Apotex proposes a shelf life of 24 months for Tranexamic Acid Tablets 650 mg, when packaged in HDPE bottles. **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments yes **3.2.P.8.3 Stability Data** 1. 3 month accelerated stability data yes 2. Batch numbers on stability records the same as the test batch **yes**	☒

(b) (4)

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available)** **3.2.R.2.S Comparability Protocols** **3.2.R.3.S Methods Validation Package** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

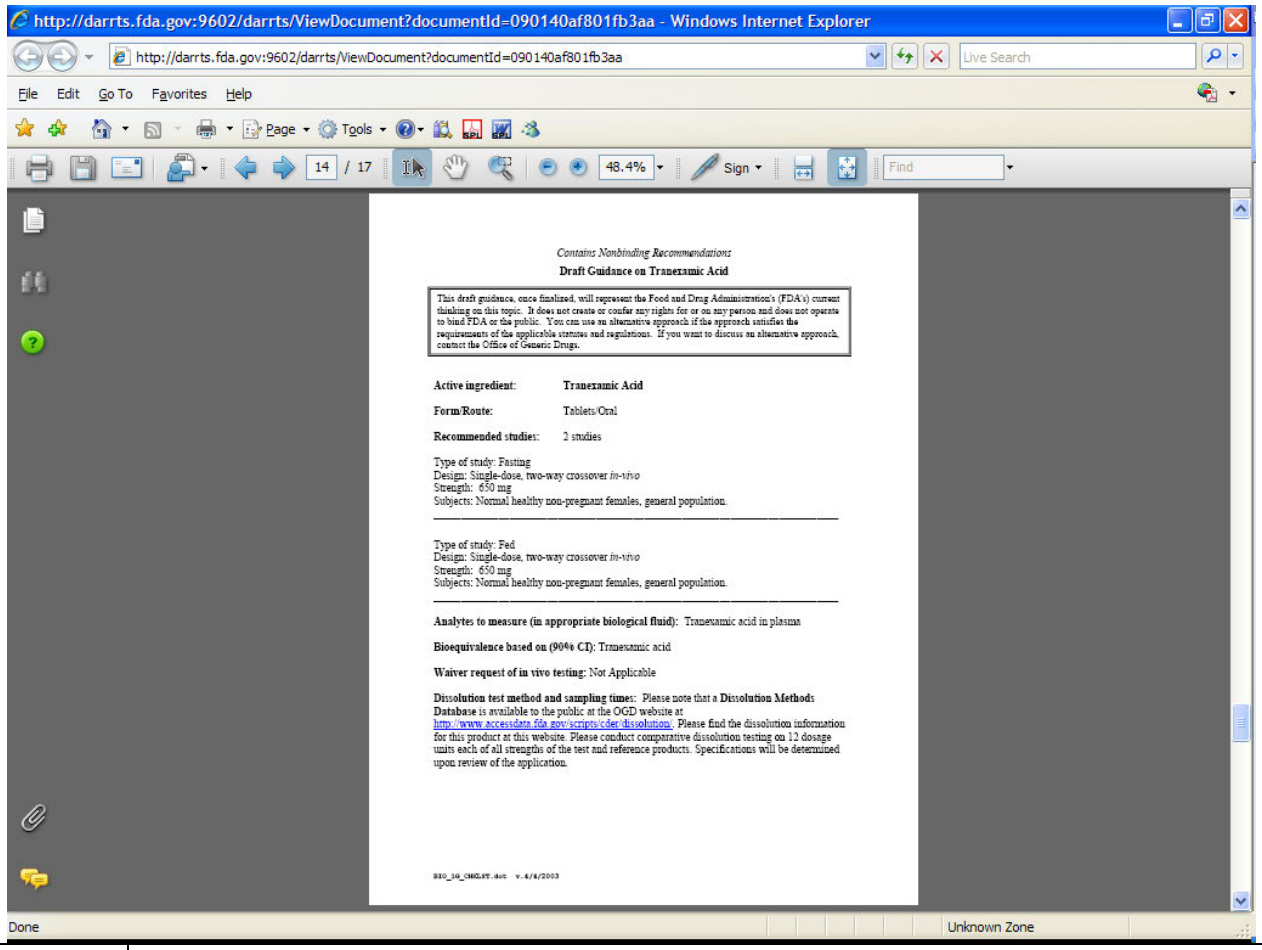
3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation 3.2.R.1.P.1 Executed Production Records (b) (4) [redacted] **3.2.R.1.P.2 Information on Components** yes **3.2.R.2.P Comparability Protocols** yes **3.2.R.3.P Methods Validation Package** yes Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5

CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☐



5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **2. Lot Numbers of Products used in BE Study(ies):** **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☐

5.3.1.2 Comparative BA/BE Study Reports ☐

1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC)

Table 3 Statistical Summary of the Comparative Bioavailability Data

TRANEXAMIC ACID TABLETS Dose (1 x 650 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasted Bioequivalence Study [Study No. TRAC-IMTB-05SB01-2FA (XC6312)]				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUCt (ng*h/ml)	61254.8	61533.7	99.5	93.0 – 106.6
AUCinf (ng*h/ml)	63657.6	63729.5	99.9	93.2 – 107.1
Cmax (ng/ml)	9559.2	9642.2	99.1	92.4 – 106.3
Fed Bioequivalence Study [Study No. TRAC-IMTB-05SB02-2FE (XC6313)]				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUCt (ng*h/ml)	54476.0	54472.4	100.0	96.8 – 103.3
AUCinf (ng*h/ml)	56358.4	56665.5	99.5	96.3 – 102.7
Cmax (ng/ml)	8664.5	8199.7	105.7	101.3 – 110.2

2. Summary Bioequivalence tables:
   - Table 10. Study Information yes
   - Table 12. Dropout Information yes
   - Table 13. Protocol Deviations yes

5.3.1.3
In Vitro-In-Vivo Correlation Study Reports

1. Summary Bioequivalence tables:
   - Table 11. Product Information yes
   - Table 16. Composition of Meal Used in Fed Bioequivalence Study yes

5.3.1.4
Reports of Bioanalytical and Analytical Methods for Human Studies

1. Summary Bioequivalence table:
   - Table 9. Reanalysis of Study Samples yes
   - Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses yes
   - Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples yes

5.3.7
Case Report Forms and Individual Patient Listing

5.4 **Literature References** ☐

Possible Study Types:

Study Type

IN-VIVO BE STUDY(IES) with PK ENDPOINTS (i.e., fasting/fed/sprinkle) FASTING AND FED ON 650 MG ☒

1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC)yes
2. EDR Email: Data Files Submitted: NA
3. In-Vitro Dissolution: YES

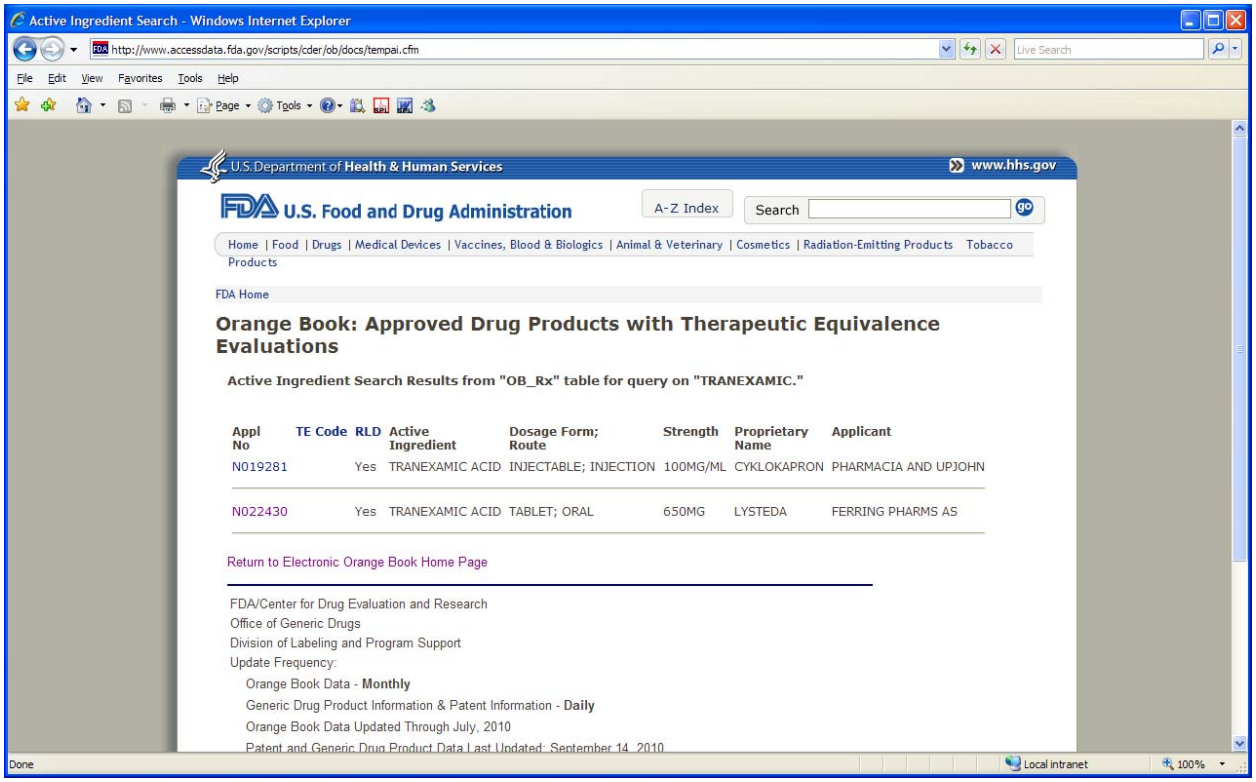
Study Type

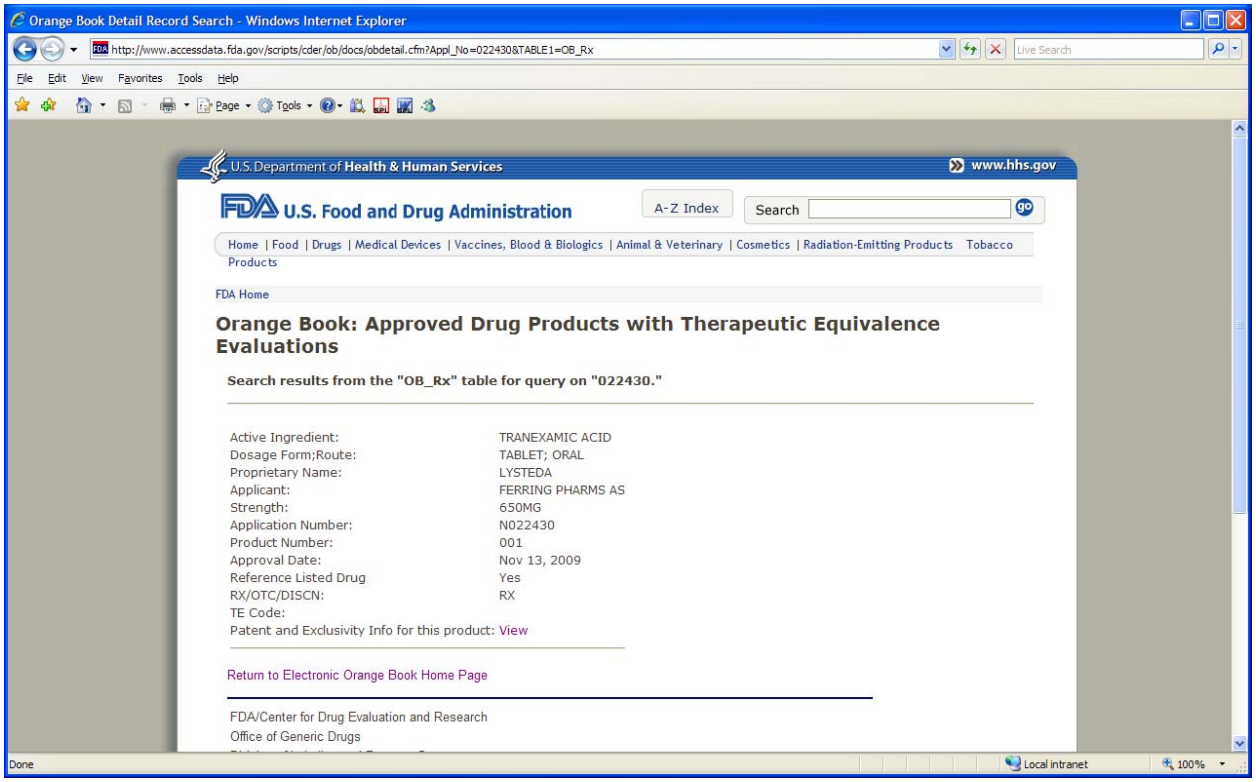
IN-VIVO BE STUDY with CLINICAL ENDPOINTS NO ☐

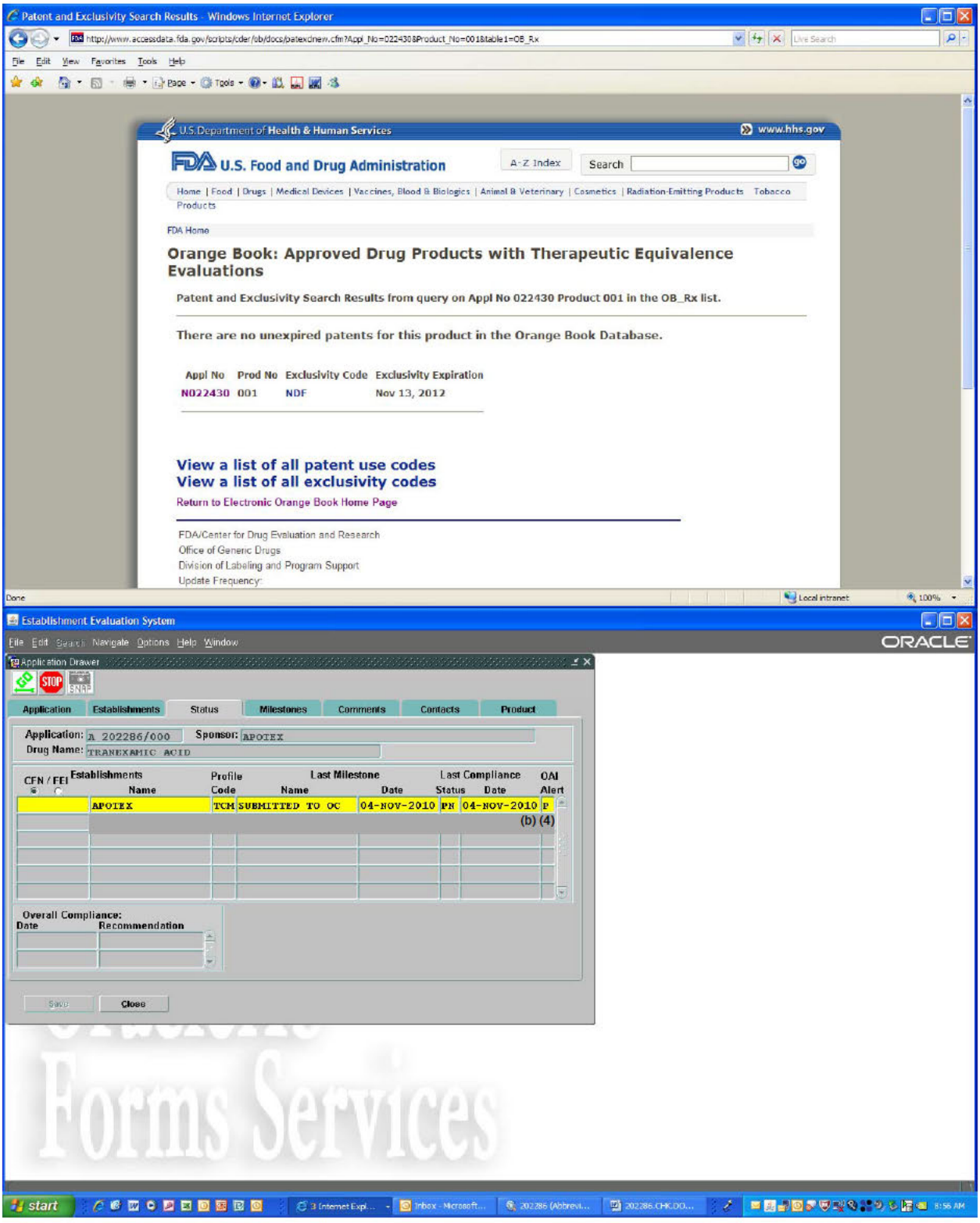
1. Properly defined BE endpoints (eval. by Clinical Team)
2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25).
3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team)
4. EDR Email: Data Files Submitted

Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 10/19/2009


Active Ingredient Search - Windows Internet Explorer
http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm
File Edit View Favorites Tools Help
U.S. Department of Health & Human Services
www.hhs.gov
U.S. Food and Drug Administration
A-Z Index
Search
go
Home | Food | Drugs | Medical Devices | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Radiation-Emitting Products | Tobacco Products
FDA Home
Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
Active Ingredient Search Results from "OB_Rx" table for query on "TRANEXAMIC."
Appl No | TE Code | RLD | Active Ingredient | Dosage Form; Route | Strength | Proprietary Name | Applicant
N019281 | | Yes | TRANEXAMIC ACID | INJECTABLE; INJECTION | 100MG/ML | CYKLOKAPRON | PHARMACIA AND UPJOHN
N022430 | | Yes | TRANEXAMIC ACID | TABLET; ORAL | 650MG | LYSTEDA | FERRING PHARMS AS
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through July, 2010
Patent and Generic Drug Product Data Last Updated: September 14, 2010
Done
Local intranet
100%


Orange Book Detail Record Search - Windows Internet Explorer
http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=022430&TABLE1=OB_Rx
File Edit View Favorites Tools Help
U.S. Department of Health & Human Services
www.hhs.gov
U.S. Food and Drug Administration
A-Z Index
Search
Home | Food | Drugs | Medical Devices | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Radiation-Emitting Products | Tobacco Products
FDA Home
Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
Search results from the "OB_Rx" table for query on "022430."
Active Ingredient: TRANEXAMIC ACID
Dosage Form;Route: TABLET; ORAL
Proprietary Name: LYSTEDA
Applicant: FERRING PHARMS AS
Strength: 650MG
Application Number: N022430
Product Number: 001
Approval Date: Nov 13, 2009
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Done
Local intranet
100%



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

/s/

TIMOTHY G JETTON
11/18/2010

MARTIN H Shimer
11/24/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 202286

Apotex Corp.
U.S. Agent for Apotex Inc.
Attention: Kiran Krishnan
2400 North Commerce Parkway
Suite 400
Weston, FL 33326

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated November 2, 2010 and your correspondence dated November 3, 2010.

NAME OF DRUG: Tranexamic Acid Tablets, 650 mg

DATE OF APPLICATION: August 31, 2010

DATE (RECEIVED) ACCEPTABLE FOR FILING: August 31, 2010

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Frank J. Nice
Project Manager
240-276-8555

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

MARTIN H Shimer
11/24/2010
Signing for Wm Peter Rickman