CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 202093

Name: Tranexamic Acid Tablets, 650 mg

Sponsor: Watson Laboratories, Inc.

Approval Date: December 27, 2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202093

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202093

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 202093

Watson Laboratories, Inc. - Florida
Attention: Janet Vaughn
Director, Regulatory Affairs
4955 Orange Drive
Fort Lauderdale, FL 33314

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated July 23, 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 February 16, 2012, and to your amendments dated August 29, October 10, November 5, and November 26, 2012.

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, 650 mg, 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

With respect to each of these patents, your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each patent 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 Watson Laboratories, Inc. - Florida (Watson) complied with the requirements of section 505(j)(2)(B) of the Act. The agency notes that the ‘739, ‘106, and ‘795 patents were submitted to the agency after submission of your ANDA and therefore litigation, if any, with respect to it creates no statutory stay of approval.

With respect to 180-day generic drug exclusivity, we note that Watson was one of the first ANDA applicants to submit a substantially complete ANDA with a paragraph IV certification to the '739 patent. Therefore, with this approval, Watson is eligible for 180 days of generic drug exclusivity for Tranexamic Acid Tablets, 650 mg. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, will begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). Please submit correspondence to this ANDA informing the agency of the date the exclusivity begins to run.

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.

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}

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

12/27/2012

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202093

TENTATIVE APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 202093

Watson Laboratories, Inc.-Florida
Attention: Radha Goolabsingh
Manager, Regulatory Affairs
4955 Orange Drive
Fort Lauderdale, FL 33314

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated July 23, 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 February 18, April 26, July 22, August 3, October 6, October 21, and November 29, 2011; and February 6, 2012. We also acknowledge receipt of your correspondences dated May 24, July 11, October 12, and November 30, 2011, addressing the patent and exclusivity 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 practices (cGMPs) of 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 AS, is subject to periods 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 to each of these patents under section 505(j)(2)(A)(vii)(IV) of the Act stating that these patents are 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 Watson Laboratories, Inc.-Florida (Watson) 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 exclusivity (new dosage form) that has not yet expired. 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' cGMPs 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 Frank J. Nice, Project Manager, at (240) 276-8555.

Sincerely yours,

{See appended electronic signature page}

Keith Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
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

02/16/2012

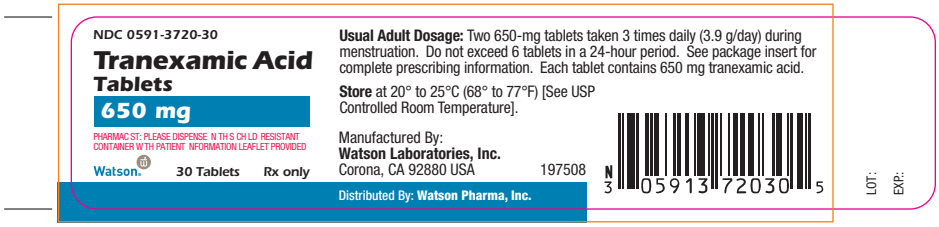
Deputy Director, Office of Generic Drugs
for Keith Webber, Ph.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202093

LABELING



Product Name: Tranexamic Acid - 650 mg - 30 Tablets FL

Designed by: (b) (6) Date: 02/15/2011

Proof by:

Proof by:

Color Chart: (b) (4)

CMYK

Size: 4.5" x 1"

NDC 0591-3720-10

Tranexamic Acid
Tablets

650 mg

PHARMACIST: PLEASE DISPENSE WITH PATIENT INFORMATION LEAFLET PROVIDED SEPARATELY.

Watson®

1000 Tablets Rx only

Usual Adult Dosage: Two 650-mg tablets taken 3 times daily (3.9 g/day) during menstruation. Do not exceed 6 tablets in a 24-hour period. See package insert for complete prescribing information. Each tablet contains 650 mg tranexamic acid.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Manufactured By:
Watson Laboratories, Inc.
Corona, CA 92880 USA 197509

Distributed By: **Watson Pharma, Inc.**

N 05913 72010 7

LOT: EXP:

Product Name: Tranexamic Acid - 650 mg - 1000 Tablets FL

Designed by: (b) (6) Date: 02/15/2011

Proof by:

Proof by:

Color Chart: (b) (4)

CMYK

Size: 8" x 3.4375"

Tranexamic Acid Tablets

Rx Only

Revised: November 2011

197511

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

Initial U.S. Approval: 1986

----------RECENT MAJOR CHANGES----------

WARNINGS AND PRECAUTIONS (5.1) 4/2011

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

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 650 mg (3)

----------CONTRAINDICATIONS----------

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

----------WARNINGS AND PRECAUTIONS----------

- The risk of thrombotic and thromboembolic events may increase further when hormonal contraceptives are administered with Tranexamic acid tablets, especially in women who are obese or smoke cigarettes. Women using hormonal contraception should use Tranexamic acid tablets 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 Tranexamic acid tablets in women who are taking more than the approved dose of a hormonal contraceptive. (5.1)
- Concomitant use of Tranexamic acid tablets 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 tablets. Immediately discontinue use if visual or ocular symptoms occur. (5.1)
- In case of severe allergic reaction, discontinue Tranexamic acid tablets and seek immediate medical attention. (5.2)
- Cerebral edema and cerebral infarction may be caused by use of Tranexamic acid tablets in women with subarachnoid hemorrhage. (5.3)
- Ligneous conjunctivitis has been reported in patients taking tranexamic acid. (5.4)

----------ADVERSE REACTIONS----------

Most common adverse reactions in clinical trials (≥ 5%, and more frequent in Tranexamic acid tablets 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 Watson Laboratories, Inc. at 1-800-272-5525 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 tablets and tissue plasminogen activators. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

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

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

Revised: 11/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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 tablets 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.

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 Tablets in Patients with Renal Impairment

	Tranexamic Acid Tablets	
Serum Creatinine (mg/dL)	**Adjusted Dose**	**Total Daily Dose**
Cr above 1.4 and ≤ 2.8	1300 mg (two 650 mg tablets) two times a day for a maximum of 5 days during menstruation	2600 mg
Cr above 2.8 and ≤ 5.7	1300 mg (two 650 mg tablets) once a day for a maximum of 5 days during menstruation	1300 mg
Cr above 5.7	650 mg (one 650 mg tablet) once a day for a maximum of 5 days during menstruation	650 mg

3 DOSAGE FORMS AND STRENGTHS

650 mg tablets

4 CONTRAINDICATIONS

4.1 Thromboembolic Risk

Do not prescribe Tranexamic acid tablets to women who are known to have the following conditions:

- Active thromboembolic disease (e.g., deep vein thrombosis, pulmonary embolism, or cerebral thrombosis)
- A history of thrombosis or thromboembolism, including retinal vein or artery occlusion
- An intrinsic risk of thrombosis or thromboembolism (e.g., thrombogenic valvular disease, thrombogenic cardiac rhythm disease, or hypercoagulopathy)

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

4.2 Hypersensitivity to Tranexamic Acid

Do not prescribe 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 tablets are 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 tablets. This is of particular concern in women who are obese or smoke cigarettes, especially smokers over 35 years of age [see Contraindications (4.1) and Drug Interactions (7.1)].

Women using hormonal contraception were excluded from the clinical trials supporting the safety and efficacy of Tranexamic acid tablets, and there are no clinical trial data on the risk of thrombotic events with the concomitant use of Tranexamic acid tablets with hormonal contraceptives. There have been US postmarketing reports of venous and arterial thrombotic events in women who have used Tranexamic acid tablets concomitantly with combined hormonal contraceptives. Women using hormonal contraception, especially those who are obese or smoke, should use Tranexamic acid tablets 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 Tranexamic acid tablets in women who are taking more than the approved dose of a hormonal contraceptive.

Factor IX Complex Concentrates or Anti-Inhibitor Coagulant Concentrates

Tranexamic acid tablets 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 tablets 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 tablets immediately and should be referred to an ophthalmologist for a complete ophthalmic evaluation, including dilated retinal examination, to exclude the possibility of retinal venous or arterial occlusion.

5.2 Severe Allergic Reaction

A case of severe allergic reaction to Tranexamic acid tablets 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 tablets in women with subarachnoid hemorrhage.

5.4 Ligneous Conjunctivitis

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

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

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

Short-term Studies

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

In these studies, subjects were 18 to 49 years of age with a mean age of approximately 40 years, had cyclic menses every 21-35 days, and a BMI of approximately 32 kg/m². On average, subjects had a history of HMB for approximately 10 years and 40% had fibroids as determined by transvaginal ultrasound. Approximately 70% were Caucasian, 25% were Black, and 5% were Asian, Native American, Pacific Islander, or Other. Seven percent (7%) of all subjects were of Hispanic origin. Women using hormonal contraception were excluded from the trials.

The rates of discontinuation due to adverse events during the two clinical trials were comparable between Tranexamic acid tablets and placebo. In the 3-cycle study, the rate in the 3900 mg Tranexamic Acid tablets 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 tablets 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 tablets 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 tablets treated subjects receiving 3900 mg/day compared to placebo is provided in **Table 2.**

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

	Tranexamic Acid Tablets 3900 mg/day n (%) (N=232)	Placebo n (%) (N=139)
Total Number of Adverse Events	1500	923
Number of Subjects with at Least One Adverse Event	208 (89.7%)	122 (87.8%)
HEADACHE [a]	117 (50.4%)	65 (46.8%)
NASAL & SINUS SYMPTOMS [b]	59 (25.4%)	24 (17.3%)
BACK PAIN	48 (20.7%)	21 (15.1%)
ABDOMINAL PAIN [c]	46 (19.8%)	25 (18.0%)
MUSCULOSKELETAL PAIN [d]	26 (11.2%)	4 (2.9%)
ARTHRALGIA [e]	16 (6.9%)	7 (5.0%)
MUSCLE CRAMPS & SPASMS	15 (6.5%)	8 (5.8%)
MIGRAINE	14 (6.0%)	8 (5.8%)
ANEMIA	13 (5.6%)	5 (3.6%)
FATIGUE	12 (5.2%)	6 (4.3%)

[a] Includes headache and tension headache

[b] Nasal and sinus symptoms include nasal, respiratory tract and sinus congestion, sinusitis, acute sinusitis, sinus headache, allergic sinusitis and sinus pain, and multiple allergies and seasonal allergies

[c] Abdominal pain includes abdominal tenderness and discomfort

[d] Musculoskeletal pain includes musculoskeletal discomfort and myalgia

[e] Arthralgia includes joint stiffness and swelling

Long-term Studies

Long-term safety of Tranexamic acid tablets 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 tablets was 10,213 cycles. The average duration of Tranexamic acid tablets 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 tablets in this study was 1,956 cycles. The average duration of Tranexamic acid tablets use was 3.5 days per cycle.

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

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

6.2 Postmarketing Experience

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

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

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

7 DRUG INTERACTIONS

No drug-drug interaction studies were conducted with Tranexamic acid tablets.

7.1 Hormonal Contraceptives

Because Tranexamic acid tablets are antifibrinolytic, concomitant use of hormonal contraception and Tranexamic acid tablets may further exacerbate the increased thrombotic risk associated with combination hormonal contraceptives. Women using hormonal contraception should use Tranexamic acid tablets only if there is a strong medical need and the benefit of treatment will outweigh the potential increased risk of a thrombotic event [see *Warnings and Precautions (5.1)* and *Clinical Pharmacology (12.3)*].

7.2 Tissue Plasminogen Activators

Concomitant therapy with tissue plasminogen activators may decrease the efficacy of both Tranexamic acid tablets and tissue plasminogen activators. Therefore, exercise caution if a woman taking Tranexamic acid tablets therapy requires tissue plasminogen activators.

7.3 Factor IX Complex Concentrates or Anti-Inhibitor Coagulant Concentrates

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

An embryo-fetal developmental toxicity study in rats and a perinatal developmental toxicity study in rats were conducted using tranexamic acid. No adverse effects were observed in either study at doses up to 4 times the recommended human oral dose of 3900 mg/day based on mg/m² (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 tablets should be used during lactation only if clearly needed.

8.4 Pediatric Use

Tranexamic acid tablets are indicated for women of reproductive age and are not intended for use in premenarcheal girls. Tranexamic acid tablets have not been studied in adolescents under age 18 with heavy menstrual bleeding.

8.5 Geriatric Use

Tranexamic acid tablets are indicated for women of reproductive age and are not intended for use by postmenopausal women.

8.6 Renal Impairment

The effect of renal impairment on the pharmacokinetics of Tranexamic acid tablets 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

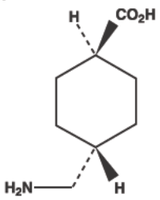
The effect of hepatic impairment on the pharmacokinetics of Tranexamic acid tablets has not been studied. Because only a small fraction of the drug is metabolized, dosage adjustment in patients with hepatic impairment is not needed [see *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

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

11 DESCRIPTION

Tranexamic acid tablets are 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-shaped, film coated tablets, debossed with "WPI 3720" on one side of the tablet. The active ingredient in each tablet is 650 mg tranexamic acid. The inactive ingredients contained in each tablet are: colloidal silicon dioxide, copovidone, crospovidone, eudragit, glyceryl behenate, lactose monohydrate, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, talc, and triethyl citrate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tranexamic acid is a synthetic lysine amino acid derivative, which diminishes the dissolution of hemostatic fibrin by plasmin. In the presence of tranexamic acid, the lysine receptor binding sites of plasmin for fibrin are occupied, preventing binding to fibrin monomers, thus preserving and stabilizing fibrin's matrix structure.

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

12.2 Pharmacodynamics

Tranexamic acid, at *in vitro* concentrations of 25 - 100 µM, reduces by 20 - 60% the maximal rate of plasmin lysis of fibrin catalyzed by tissue plasminogen activator (tPA).

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

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

Cardiac Electrophysiology

The effect of Tranexamic acid tablets 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 tablets 1300 mg (two 650 mg tablets), (2) Tranexamic acid tablets 3900 mg (six 650 mg tablets; three times the recommended single dose), (3) moxifloxacin 400 mg, and (4) placebo. There was no significant increase in the corrected QT interval at any time up to 24 hours after the administration of either dose of Tranexamic acid tablets. 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 tablets, the peak plasma concentration (C_{max}) occurred at approximately 3 hours (T_{max}). The absolute bioavailability of Tranexamic acid tablets in women aged 18-49 is approximately 45%. Following multiple oral doses (two 650 mg tablets three times daily) administration of Tranexamic acid tablets 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 tablets 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 tablets are shown in **Table 3.**

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

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

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

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

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

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

Metabolism
A small fraction of the tranexamic acid is metabolized.

Excretion
Tranexamic acid is eliminated by urinary excretion primarily via glomerular filtration with more than 95% of the dose excreted unchanged. Excretion of tranexamic acid is about 90% at 24 hours after intravenous administration of 10 mg/kg. Most elimination post intravenous administration occurred during the first 10 hours, giving an apparent elimination half-life of approximately 2 hours. The mean terminal half-life of Tranexamic acid tablets is approximately 11 hours. Plasma clearance of tranexamic acid is 110-116 mL/min.

Specific Populations

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

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

Pediatric Use
Tranexamic acid tablets are indicated for women of reproductive age and are not intended for use in premenarcheal girls. Tranexamic acid tablets have not been studied in adolescents under age 18 with heavy menstrual bleeding.

Geriatric Use
Tranexamic acid tablets are indicated for women of reproductive age and are not intended for use by postmenopausal women.

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

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

Drug Interactions
No drug-drug interaction studies were conducted with Tranexamic acid tablets.

Hormonal Contraceptives
Because Tranexamic acid tablets are antifibrinolytic, concomitant use of hormonal contraception and Tranexamic acid tablets may further exacerbate the increased thrombotic risk associated with combination hormonal contraceptives. Women using hormonal contraception should use Tranexamic acid tablets only if there is a strong medical need and the benefit of treatment will outweigh the potential increased risk of a thrombotic event [see *Warnings and Precautions (5.1)* and *Drug Interactions (7.1)*].

Factor IX Complex Concentrates or Anti-inhibitor Coagulant Concentrates
Tranexamic acid tablets are not recommended in patients taking either Factor IX complex concentrates or anti-inhibitor coagulant concentrates because the risk of thrombosis may be increased [see *Warnings and Precautions (5.4) and Drug Interactions (7.3)*].

Tissue Plasminogen Activators
Concomitant therapy with tissue plasminogen activators may decrease the efficacy of both Tranexamic acid tablets and tissue plasminogen activators. Therefore, exercise caution if a patient taking Tranexamic acid tablets 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 tablets to patients with acute promyelocytic leukemia taking all-trans retinoic acid [see *Warnings and Precautions (5.5)* and *Drug Interactions (7.4)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Carcinogenicity studies with tranexamic acid in male mice at doses as high as 6 times the recommended human dose of 3900 mg/day showed an increased incidence of leukemia which may have been related to treatment. Female mice were not included in this experiment. The dose multiple referenced above is based on body surface area (mg/m^2). Actual daily dose in mice was up to 5000 mg/kg/day in food.

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

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

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

In a rat embryo-fetal developmental toxicity study, tranexamic acid had no adverse effects on embryo-fetal development when administered during the period of organogenesis (from gestation days 6 through 17) at doses 1, 2 and 4 times the recommended human oral dose of 3900 mg/day. In a perinatal-postnatal study in rats, tranexamic acid had no adverse effects on pup viability, growth or development when administered from gestation day 6 through postnatal day 20 at doses 1, 2 and 4 times the recommended human oral dose of 3900 mg/day.

The dose multiples referenced above are based on body surface area (mg/m2). Actual daily doses in rats were 300, 750 or 1500 mg/kg/day.

13.2 Animal Toxicology and/or Pharmacology

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

In other studies, focal areas of retinal degeneration were observed in cats, dogs and rats following oral or intravenous tranexamic acid doses at 6-40 times the recommended usual human dose based on mg/m2 (actual animal doses between 250-1600 mg/kg/day).

14 CLINICAL STUDIES
The efficacy and safety of Tranexamic acid tablets in the treatment of heavy menstrual bleeding (HMB) was demonstrated in one 3-cycle treatment and one 6-cycle treatment, randomized, double-blind, placebo-controlled study [see *Adverse Reactions (6)*]. In these studies, HMB was defined as an average menstrual blood loss of ≥ 80 mL as assessed by alkaline hematin analysis of collected sanitary products over two baseline menstrual cycles. Subjects were 18 to 49 years of age with a mean age of approximately 40 years, had cyclic menses every 21-35 days, and a BMI of approximately 32 kg/m2. On average, subjects had an HMB history of approximately 10 years and 40% had fibroids as determined by transvaginal ultrasound. Approximately 70% were Caucasian, 25% were Black, and 5% were Asian, Native American, Pacific Islander, or Other. Seven percent (7%) of all subjects were of Hispanic origin.

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

The key secondary outcome measures were based on specific questions concerning limitations in social or leisure activities (LSLA) and limitations in physical activities (LPA). Large stains (soiling beyond the undergarment) were also included as a key secondary outcome measure.

14.1 Three-Cycle Treatment Study
This study compared the effects of two doses of Tranexamic acid tablets (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 tablets 1950 mg/day subjects, 112 Tranexamic acid tablets 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 tablets compared to placebo. Study success also required achieving a reduction in MBL that was determined to be clinically meaningful to the subjects. The 1950 mg/day Tranexamic acid tablets 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 tablets 3900 mg/day	112	169	65*	39%
Tranexamic acid tablets 1950 mg/day	115	178	44	25%
Placebo	67	154	7	5%

* p<0.001 versus placebo

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

Table 5: Secondary Outcomes in 3-Cycle Study

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

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

[b] Positive means reflect an improvement from baseline.

[c] p-value <0.05 versus placebo

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

[e] Non-significant difference versus placebo

14.2 Six-Cycle Treatment Study
This study compared the effects of Tranexamic acid tablets 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 tablets 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 tablets 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 tablets 3900 mg/day	115	172	66*	38%
Placebo	72	153	18	12%

* p<0.001 versus placebo

Limitations on social, leisure, and physical activities were also statistically significantly reduced in the Tranexamic acid tablets 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 tablets	115	2.92	0.85[c]
Placebo	72	2.74	0.44
Physical Activities			
3900 mg/day			
Tranexamic acid tablets	115	3.05	0.87[c]
Placebo	72	2.90	0.40
	N		**Responders [d]**
Reduction in Large Stains			
3900 mg/day			
Tranexamic acid tablets	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

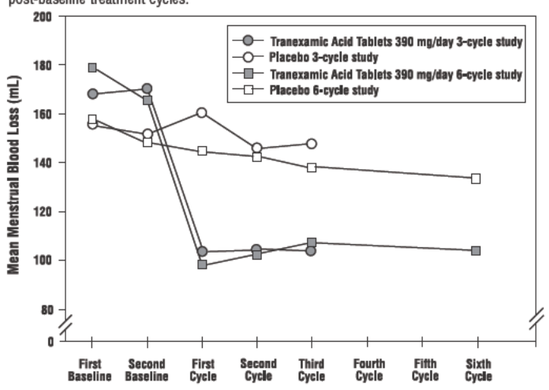
[b] Positive means reflect an improvement from baseline

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



16 HOW SUPPLIED/STORAGE AND HANDLING
Tranexamic acid tablets are provided as white to off-white, oval-shaped, film coated tablets. Each tablet is debossed with "WPI 3720" on one side of the tablet and are supplied as:

Quantity	NDC Number
30 tablets	0591-3720-30
1000 tablets	0591-3720-10

Storage
Store at 20°-25° C (68°-77° F). [See USP Controlled Room Temperature].

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

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

Inform patients that they should stop Tranexamic acid tablets 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 tablets include headache, sinus and nasal symptoms, back pain, abdominal pain, musculoskeletal pain, joint pain, muscle cramps, migraine, anemia and fatigue.

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

Remind patients to read the Patient Labeling carefully.

PATIENT INFORMATION

Tranexamic acid tablets

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

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

Who should not take Tranexamic acid tablets?

Do not take Tranexamic acid tablets if you:
- Currently have a blood clot
- Have ever had a blood clot
- Have been told that you are at risk of having a blood clot
- Are allergic to Tranexamic acid tablets or 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 hormones** (like a birth control pill, patch, vaginal ring or intrauterine device). Also tell your healthcare provider if you are taking higher than your normally-prescribed dose of birth control. Using hormonal products along with Tranexamic acid tablets, especially if you are overweight or smoke, may increase your chance of having a serious blood clot, stroke, or heart attack.
- You are pregnant or think you may be pregnant
- You are breastfeeding or plan to breast-feed. Tranexamic acid tablets 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 clot
- Medicines used to break up blood clots
- Any medicines to treat leukemia

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

How should I take 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 tablets 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 tablets 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. This risk of serious blood clots may be increased when Tranexamic acid tablets are taken with:
  - hormonal contraceptives, especially if you are taking higher than your normal dose of birth control, are overweight, or if you smoke cigarettes
  - medicines used to help your blood clot
  - some medicines used to treat leukemia
- Eye changes. Stop taking 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 Watson Laboratories, Inc. at 1-800-272-5525.

How should I store Tranexamic acid tablets?
Store Tranexamic acid tablets at room temperature between 20°-25° C (68°-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.watson.com or call 1-800-272-5525.

What are the ingredients of Tranexamic acid tablets?

Active ingredient: tranexamic acid

Inactive ingredients: colloidal silicon dioxide, copovidone, crospovidone, eudragit, glyceryl behenate, lactose monohydrate, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, talc, and triethyl citrate.

Manufactured by:
Watson Laboratories, Inc.
Corona, CA 92880 USA

Distributed by:
Watson Pharma, Inc.
Parsippany, NJ 07054 USA

Rev. date: 11/2011

197511

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

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

Who should not take Tranexamic acid tablets?

Do not take Tranexamic acid tablets if you:

- Currently have a blood clot
- Have ever had a blood clot
- Have been told that you are at risk of having a blood clot
- Are allergic to Tranexamic acid tablets or 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 hormones** (like a birth control pill, patch, vaginal ring or intrauterine device). Also tell your healthcare provider if you are taking higher than your normally-prescribed dose of birth control. Using hormonal products along with Tranexamic acid tablets, especially if you are overweight or smoke, may increase your chance of having a serious blood clot, stroke, or heart attack.
- You are pregnant or think you may be pregnant
- You are breastfeeding or plan to breast-feed. Tranexamic acid tablets 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 clot
- Medicines used to break up blood clots
- Any medicines to treat leukemia

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

How should I take 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 tablets 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 tablets 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. This risk of serious blood clots may be increased when Tranexamic acid tablets are taken with:
  - hormonal contraceptives, especially if you are taking higher than your normal dose of birth control, are overweight, or if you smoke cigarettes
  - medicines used to help your blood clot
  - some medicines used to treat leukemia
- Eye changes. Stop taking 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 Watson Laboratories, Inc. at 1-800-272-5525.

How should I store Tranexamic acid tablets?

Store Tranexamic acid tablets at room temperature between 20º-25º C (68º-77º 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.watson.com or call 1-800-272-5525.

What are the ingredients of Tranexamic acid tablets?

Active ingredient: tranexamic acid

Inactive ingredients: colloidal silicon dioxide, copovidone, crospovidone, eudragit, glyceryl behenate, lactose monohydrate, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, talc, and triethyl citrate.

Manufactured by:
Watson Laboratories, Inc.
Corona, CA 92880 USA

Distributed by:
Watson Pharma, Inc.
Parsippany, NJ 07054 USA

Revised: November 2011

197510

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202093

LABELING REVIEWS

This Approval Summary supersedes the AP Summary dated February 28, 2011

APPROVAL SUMMARY#2
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 202093

Date of Submission: November 29, 2011 (Amendment)

Applicant's Name: Watson Laboratories, Inc. - Florida

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 Final Printed Labels and Labeling? E-submission

	Date Submitted	Recommendation
CONTAINER (Bottles of 30 and 1000)	February 18, 2011	Acceptable for Approval
INSERT and PATIENT INFORMATION	November 29, 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/S-002, approved April 6, 2011

2. USP MONOGRAPH – None
   PF – None

3. PATENTS AND EXCLUSIVITIES

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Certification	Labeling Impact	Use Code
N022430	001	7947739	Mar 4, 2025	PIV*	None	
N022430	001	8022106	Mar 4, 2025	PIV**	None	U - 1182

* May 24, 2011 Patent Amendment
** October 12, 2011 Patent Amendment

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration	Labeling Impact
N022430	001	NDF	Nov 13, 2012	Firm will not market prior to expiration.

Code	Definition
U - 1182	TREATMENT OF CYCLIC HEAVY MENSTRUAL BLEEDING
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.

Composition of Tranexamic Acid Extended-release Tablets, 650 mg

Ingredients/Grade	Function	mg/tab	% w/w (per tablet)	IID Max Level for Orally Administered Drug Products
				(b) (4)

Composition of Tranexamic Acid Extended-release Tablets, 650 mg

Ingredients/Grade	Function	mg/tab	% w/w (per tablet)	IID Max Level for Orally Administered Drug Products
[redacted]				(b) (4)

5. MANUFACTURING FACILITY
   Manufactured by:
   Watson Laboratories, Inc. – Florida
   4955 Orange Drive
   Ft. Lauderdale, FL 33314

6. PRODUCT DESCRIPTION
   RLD "…white oval-shaped tablets. Each tablet is debossed with the marking "XP650"…"
   ANDA "…white to off-white, oval-shaped, film coated tablets. Each tablet is debossed with "WPI 3720" on one side of the tablet…"
   Drug Product Specifications: "White to off-white, oval shape tablets debossed with "WPI 3720" on one side of the tablet and film coated"

7. CONTAINER/CLOSURE SYSTEM
   Container: HDPE
   Closure: CRC for bottles of 30, non-CRC for bottles of 1000

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 30 and 1000

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). [See USP Controlled Room Temperature].
Stability: Accelerated 40°C/75% RH; Long term 25°C/60% RH

10. DISPENSING RECOMMENDATIONS
RLD: None
ANDA: PHARMACIST: PLEASE DISPENSE WITH PATIENT INFORMATION LEAFLET PROVIDED SEPARATELY.

11. SPL DATA ELEMENTS
No SPL submission

12. MEDWATCH (checked 12/29/2011)
The information on MedWatch dated January 2011 for the ***injection*** formulation has not been approved for the tablet formulation.

Cyklokapron (tranexamic acid) Injection

Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER) – January 2011

Summary View

WARNINGS

- Convulsions have been reported in association with tranexamic acid treatment

13. REMS (checked 12/29/2011)
No approved REMS

Date of Review: December 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
12/30/2011

KOUNG U LEE
12/31/2011
For Wm. Peter Rickman

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

ANDA Number: 202093

Date of Submission: February 18, 2011 (Amendment)

Applicant's Name: Watson Laboratories, Inc. - Florida

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 Final Printed Labels and Labeling? E-submission

	Date Submitted	Recommendation
CONTAINER (Bottles of 30 and 1000)	February 18, 2011	Acceptable for Approval
INSERT and PATIENT INFORMATION	February 18, 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, approved November 13, 2009

2. USP MONOGRAPH – None
   PF – None

3. PATENTS AND EXCLUSIVITIES
Patents: None

Exclusivity:

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration	Labeling Impact
N022430	001	NDF	Nov 13, 2012	Firm will not market prior to expiration.
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.

Composition of Tranexamic Acid Extended-release Tablets, 650 mg

Ingredients/Grade	Function	mg/tab	% w/w (per tablet)	IID Max Level for Orally Administered Drug Products
[redacted]				(b) (4)

5. MANUFACTURING FACILITY
   Manufactured by:
   Watson Laboratories, Inc. – Florida
   4955 Orange Drive
   Ft. Lauderdale, FL 33314

6. PRODUCT DESCRIPTION
   RLD "…white oval-shaped tablets. Each tablet is debossed with the marking "XP650"…"
   ANDA "…white to off-white, oval-shaped, film coated tablets. Each tablet is debossed with "WPI 3720" on one side of the tablet…"
   Drug Product Specifications: "White to off-white, oval shape tablets debossed with "WPI 3720" on one side of the tablet and film coated"

7. CONTAINER/CLOSURE SYSTEM
   Container: HDPE
   Closure: CRC for bottles of 30, non-CRC for bottles of 1000

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 30 and 1000

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). [See USP Controlled Room Temperature].
   Stability: Accelerated 40°C/75% RH; Long term 25°C/60% RH

10. DISPENSING RECOMMENDATIONS
    RLD: None
    ANDA: PHARMACIST: PLEASE DISPENSE WITH PATIENT INFORMATION LEAFLET PROVIDED SEPARATELY.

11. SPL DATA ELEMENTS
    No SPL submission

12. MEDWATCH (checked 2/28/2011)
    The information on MedWatch dated January 2011 for the ***injection*** formulation has not been approved for the tablet formulation.

Cyklokapron (tranexamic acid) Injection

Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER) – January 2011

Summary View

WARNINGS

- Convulsions have been reported in association with tranexamic acid treatment

13. REMS (checked 2/28/2011)
No approved REMS

Date of Review: February 28, 2011

Primary Reviewer: Sarah Park

Team Leader: Koung Lee

AP Summary

APPEARS THIS WAY ON ORIGINAL

Following this page, 6 Pages of Draft Labeling have been Withheld in Full as (b)(4)

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/s/

SOOJUNG S PARK
02/28/2011

KOUNG U LEE
02/28/2011
For Wm. Peter Rickman

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

ANDA Number:	202093
Date of Submission:	July 23, 2010 (Original)
Applicant's Name:	Watson Laboratories, Inc. - Florida
Established Name:	Tranexamic Acid Tablets, 650 mg

Please 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
N022430	001	NDF	Nov 13, 2012

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.

Composition of Tranexamic Acid Extended-release Tablets, 650 mg

Ingredients/Grade	Function	mg/tab	% w/w (per tablet)	IID Max Level for Orally Administered Drug Products
				(b) (4)

Composition of Tranexamic Acid Extended-release Tablets, 650 mg

Ingredients/Grade	Function	mg/tab	% w/w (per tablet)	IID Max Level for Orally Administered Drug Products
[redacted]				(b) (4)

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   Manufactured by:
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   Container: HDPE
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   ANDA: Bottles of 30 and 1000

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). [See USP Controlled Room Temperature].
   Stability: Accelerated 40°C/75% RH; Long term 25°C/60% RH

10. DISPENSING RECOMMENDATIONS
    RLD: None
    ANDA: PHARMACIST: PLEASE DISPENSE WITH PATIENT INFORMATION LEAFLET PROVIDED SEPARATELY.

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

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/s/

SOOJUNG S PARK
01/31/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202093

CHEMISTRY REVIEWS

ANDA 202093

Tranexamic Acid Tablets, 650 mg

Watson Laboratories, Inc.-Florida (WLF)

Xiaobin Zhao, Ph.D.

Chemistry Division II

Team 21

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. ANDA #: 202093

2. REVIEW #: 3

3. REVIEW DATE: September 17, 2012

4. REVIEWER: Xiaobin Zhao, Ph. D.

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
Original -1	July 26, 2010
Quality/response to information request	November 9, 2010
Chemistry Review 1	May 3, 2011
T-Con record	September 22, 2011
T-Con record	October 5, 2011
Quality/response to information request	July 25, 2011
Quality/response to information request	October 7, 2011
Quality/response to information request	October 7, 2011
Quality/response to information request	October 21, 2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission	August 30, 2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Watson Laboratories, Inc.-Florida (WLF)
Address:	Watson Laboratories, Inc.-Florida 4955 Orange Drive, Ft. Lauderdale, Florida 33314
Representative:	Radha Goolabsingh, Manager
Telephone:	954-358-6149
Fax:	954-358-6350
Email:	radha.goolabsingh@watson.com

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 III

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, held by Xanodyne Pharmaceuticals, Inc. The firm has certified that there are no patents listed and the NDF exclusivity for the RLD will expire on 11/13/2012.

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

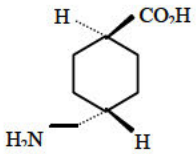
__X__Not a SPOTS product

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

Chemical Name(s): *trans*-4-(Aminomethyl)cyclohexanecarboxylic acid

Chemistry Review Data Sheet

Molecular Formula: $C_8H_{15}N0_2$
Molecular Weight: 157.2
Chemical Structure:



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	9/20/2011	by X. Zhao
	III			4	NA		
	IV			4	NA		
	IV			4	NA		
	IV			4	NA		
	IV			4	NA		
	IV			4	NA		
	IV			4	NA		
	IV			4	NA		
	III			4	NA		
	III			4	NA		
	IV			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 Xanodyne Pharmaceuticals, Inc.

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	2/15/2012; Reevaluation Date: 1/14/13	
Methods Validation	NA		
Labeling	Approval	2/28/2011	PARK, SOOJUNG S
Bioequivalence	Acceptable	8/3/2011	Cui, MingLei
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 202093

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is now recommended for full approval from a Tentative approval status.

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 shape tablets debossed with "WPI 3720" on one side of the tablet and film coated. The product is manufactured, packaged, labeled, warehoused, and tested in Watson Laboratories Inc.-Florida sites. The manufacturing process (b) (4) (b) (4). The drug product specification includes description, assay, identification, content uniformity, dissolution, (b) (4) The ANDA product differs from the RLD in the formulation design. (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) the holder of DMF (b) (4). The DMF is adequate. Tranexamic Acid is white crystalline powder, odorless and with bitter taste. It is freely soluble in water and glacial acetic acid, very slightly soluble in methanol, practically insoluble in alcohol, acetone or ether. The specification includes solubility, identification by IR, pH, LOD, (b) (4) heavy metals, (b) (4) (b) (4) assay, (b) (4)

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 prescription, 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 (3,900 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 approvable from the CMC perspective.

The previously submitted batch records have been updated based on information obtained (b) (4)

The batch record was reviewed and found adequate.

The following changes have been made:

(b) (4)

--ACCEPTABLE

Endorsements:

HFD-640 /X.Zhao/ 9/17/2012

HFD-640 /R.Rajagopalan 9/19/2012

HFD-617/Frank Nice/9/19/12

TYPE OF LETTER: APPROVABLE

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/s/

XIAOBIN ZHAO
09/19/2012

RADHIKA RAJAGOPALAN
09/19/2012

FRANK J NICE
09/19/2012

ANDA 202093

Tranexamic Acid Tablets, 650 mg

Watson Laboratories, Inc.-Florida (WLF)

Xiaobin Zhao, Ph.D.

Chemistry Division II

Team 21

Table of Contents

Chemistry Review Data Sheet

1. ANDA #: 202093

2. REVIEW #: 2

3. REVIEW DATE: October 24, 2011

4. REVIEWER: Xiaobin Zhao, Ph D

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
Original -1	July 26, 2010
Quality/response to information request	November 9, 2010
Chemistry Review 1	May 3, 2011
T-Con record	September 22, 2011
T-Con record	October 5, 2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Quality/response to information request	July 25, 2011
Quality/response to information request	October 7, 2011
Quality/response to information request	October 7, 2011
Quality/response to information request	October 21, 2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Watson Laboratories, Inc.-Florida (WLF)
Address:	Watson Laboratories, Inc.-Florida 4955 Orange Drive, Ft. Lauderdale, Florida 33314
Representative:	Radha Goolabsingh, Manager
Telephone:	954-358-6149
Fax:	954-358-6350
Email:	radha.goolabsingh@watson.com

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 III

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, held by Xanodyne Pharmaceuticals, Inc. The firm has certified that there are no patents listed and the NDF exclusivity for the RLD will expire on 11/13/2012.

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

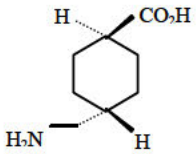
__X__Not a SPOTS product

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

Chemical Name(s): *trans*-4-(Aminomethyl)cyclohexanecarboxylic acid

Chemistry Review Data Sheet

Molecular Formula: $C_8H_{15}N0_2$
Molecular Weight: 157.2
Chemical Structure:



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	9/5/2011	by X. Zhao
	III			4	NA		
	IV			4	NA		
	IV			4	NA		
	IV			4	NA		
	IV			4	NA		
	IV			4	NA		
	IV			4	NA		
	IV			4	NA		
	III			4	NA		
	III			4	NA		
	IV			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 Xanodyne Pharmaceuticals, Inc.

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Pending Foreign Inspection	10/302010	
Methods Validation	NA		
Labeling	Approval	2/28/2011	PARK, SOOJUNG S
Bioequivalence	Acceptable	8/3/2011	Cui, MingLei
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 202093

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is now recommended for approval from chemistry perspective.

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 shape tablets debossed with "WPI 3720" on one side of the tablet and film coated. The product is manufactured, packaged, labeled, warehoused, and tested in Watson Laboratories Inc.-Florida sites. The manufacturing process (b) (4) (b) (4) The drug product specification includes description, assay, identification, content uniformity, dissolution, (b) (4). The ANDA product differs from the RLD in the formulation design, (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) the holder of DMF (b) (4). The DMF is adequate. Tranexamic Acid is white crystalline powder, odorless and with bitter taste. It is freely soluble in water and glacial acetic acid, very slightly soluble in methanol, practically insoluble in alcohol, acetone or ether. The specification includes solubility, identification by IR, pH, LOD, (b) (4) heavy metals, (b) (4) (b) (4) assay, (b) (4)

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 prescription, 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 (3,900 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 approvable from the CMC perspective. The firm has addressed all the questions through the amendments.

Following this page, 92 Pages Withheld in Full as (b)(4)

III. List Of Deficiencies To Be Communicated

Chemistry Comments to be Provided to the Applicant

ANDA: 202093

APPLICANT: Watson Laboratories, Inc.-Florida (WLF)

DRUG PRODUCT: Tranexamic Acid Tablets, 650 mg

No further comments. ANDA forwarded for approval.

Endorsements:

HFD-640 /Xiaobin Zhao/ 9/12/2011, 10/19/2011, 10/24/2011

HFD-640 /Radhika Rajagopalan/9/20/2011 (T-con recommended); 10/24/2011

HFD-617/Frank Nice/10/25/11

TYPE OF LETTER: APPROVABLE

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/s/

XIAOBIN ZHAO
10/25/2011

RADHIKA RAJAGOPALAN
10/25/2011

FRANK J NICE
10/25/2011

ANDA 202093

Tranexamic Acid Tablets, 650 mg

Watson Laboratories, Inc.-Florida (WLF)

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

Table of Contents

Chemistry Review Data Sheet

1. ANDA #: 202093

2. REVIEW #: 1

3. REVIEW DATE: March 1, 2011 – March 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	July 26, 2010
Quality/response to information request	November 9, 2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Watson Laboratories, Inc.-Florida (WLF)
Address:	Watson Laboratories, Inc.-Florida 4955 Orange Drive, Ft. Lauderdale, Florida 33314
Representative:	Radha Goolabsingh, Manager
Telephone:	954-358-6149
Fax:	954-358-6350
Email:	radha.goolabsingh@watson.com

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 III

9. LEGAL BASIS FOR SUBMISSION:

Chemistry Review Data Sheet

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, held by Xanodyne Pharmaceuticals, Inc. The firm has certified that there are no patents listed and the NDF exclusivity for the RLD will expire on 11/13/2012.

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**

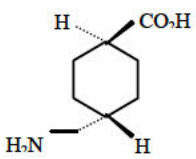
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____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: $C_8H_{15}NO_2$
Molecular Weight: 157.2
Chemical Structure:



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	Inadequate	4/28/11	by X. Zhao
	III			4	NA		
	IV			4	NA		
	IV			4	NA		
	IV			4	NA		
	IV			4	NA		
	IV			4	NA		
	IV			4	NA		
	III			4	NA		
	III			4	NA		
	IV			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 Xanodyne Pharmaceuticals, Inc.

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Pending	10/28/2010	
Methods Validation	NA		
Labeling	Deficiencies	2/10/2011	PARK, SOOJUNG S
Bioequivalence	Incomplete deficiencies – dissolution Pending-BE studies	2/28/2011	ZHANG, HONGLING
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 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 shape tablets debossed with "WPI 3720" on one side of the tablet and film coated. The product is manufactured, packaged, labeled, warehoused, and tested in Watson Laboratories Inc.-Florida sites. The manufacturing process (b) (4) (b) (4). The drug product specification includes description, assay, identification, content uniformity, dissolution, (b) (4) The ANDA product differs from NDA in the formulation design. (b) (4) We recommend that the firm conduct additional in-process controls for critical manufacturing steps, the analytical methods be further improved for (b) (4) (b) (4) 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) the holder of DMF (b) (4). The DMF is inadequate upon review. Tranexamic Acid is white crystalline powder, odorless and with bitter taste. It is freely soluble in water and glacial acetic acid, very slightly soluble in methanol, practically insoluble in alcohol, acetone or ether. The specification includes solubility, identification by IR, pH, LOD, (b) (4) heavy metals, (b) (4) assay, (b) (4) (b) (4). Upon evaluation, we suggest that the firm should improve the analytical methods for impurities.

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

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

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: 202093

APPLICANT: Watson Laboratories, Inc.-Florida (WLF)

DRUG PRODUCT: Tranexamic Acid Tablets, 650 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

(b) (4)

1.

2.

3.

4.

5.

6.

7.

Following this page, 2 Pages Withheld in Full as (b)(4)

28. (b) (4)

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

1. In the QbR-QOS, you have referenced the RLD as a modified release dosage form. The RLD is not labeled as such. In addition, Tranexamic acid tablets are referred to as (b) (4) in multiple sessions of your submission. Please comment.

2. Please provide dissolution data per DBE deficiency letter request faxed to you on 2/25/2011. Two-tiered dissolution test with more than one time point for quality control may be applied to accurately reflect the physiological condition.

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

4. 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
Acting Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Endorsements:

HFD-640 /Xiaobin Zhao/ 3/18/2011, 4/26/2011

HFD-640 /Radhika Rajagopalan/ 3/24/2011;4/29/11 (After UV's concurrence)

HFD-617/Frank Nice/5/3/11

F/T by

TYPE OF LETTER: NOT APPROVABLE - MINOR

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/s/

XIAOBIN ZHAO
05/03/2011

FRANK J NICE
05/03/2011

RADHIKA RAJAGOPALAN
05/03/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202093

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE DISSOLUTION ACKNOWLEDGEMENT REVIEW

ANDA No.	202093
Drug Product Name	Tranexamic Acid Tablets
Strength	650 mg
Applicant Name	Watson Laboratories, Inc. - Florida
Submission Date	August 3, 2011
Reviewer	Chitra Mahadevan , Pharm.D.
Outcome	Adequate

EXECUTIVE SUMMARY

This is a review of the dissolution specification acknowledgement from the firm, dated August 3, 2011.

The firm has accepted the FDA-recommended dissolution method and specification.

The bioequivalence section of the application is complete.

COMMENTS:

Watson Laboratories, Inc. – Florida acknowledges the FDA-recommended dissolution method at the S1 level listed below:

Apparatus:	USP Apparatus II (paddle)
Speed:	50 rpm
Medium:	pH 1.2 SGF
Volume:	900 ml
Temperature:	37°C ± 0.5°C
Specification:	NLT (b)(4)% (Q) in 90 minutes

DEFICIENCY COMMENTS:

None

RECOMMENDATIONS:

From a bioequivalence point of view, the firm has met the requirements for in-vivo bioequivalence and in-vitro dissolution testing. The bioequivalence section of the application is **ADEQUATE.**

I. Completed Assignment for 202093 ID: 14709

Reviewer: Mahadevan, Chitra **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Dissolution Acknowledgement for Tranexamic Acid

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
14709	8/3/2011	Dissolution Data	Dissolution Acknowledgement	1	0
				Bean Total:	0

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/s/

CHITRA MAHADEVAN
08/19/2011

AARON W SIGLER
08/29/2011

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	202093		
Drug Product Name	Tranexamic Acid Tablets		
Strength(s)	650 mg		
Applicant Name	Watson Laboratories, Inc.-Florida		
Address	4955 Orange Drive Ft. Lauderdale, FL 33314		
Applicant's Point of Contact	Radha Goolabsingh, Manager Regulatory Affairs		
Contact's Telephone Number	(954) 358-6147		
Contact's Fax Number	(954) 358-6350		
Original Submission Date(s)	July 23, 2010		
Submission Date(s) of Amendment(s) Under Review	April 26, 2011		
Reviewer	Minglei Cui, Ph.D.		
Study Number (s)	02361VH	02364VF	
Study Type (s)	Fasting	Fed	
Strength (s)	1 x 650 mg	1 x 650 mg	
Clinical Site	**Cedra Clinical Research, LLC**		
Clinical Site Address	2455 N.E. Loop 410, Suite 150 San Antonio, Texas 78217		
Analytical Site	(b) (4)		
Analytical Site Address			
Overall Review Result	**Inadequate (pending the firm's acknowledgement on the FDA-recommended dissolution specification)**		
Waiver Request Result	**N/A**		
DSI Report Result	**Adequate**		
Bioequivalence Study	**Study/Test Type**	**Bioequivalence Study**	**Review Result**
1	**Dissolution**	**650 mg**	**Inadequate**
1	**Fasting Study**	**650 mg**	**Adequate**
1	**Fed Study**	**650 mg**	**Adequate**

1 EXECUTIVE SUMMARY

This is a review of a study amendment.

In the original application (07/23/2010) [DARRTS: REV-BIOEQ-01(General Review), ANDA 202093, 04/07/2011], the firm submitted fasting and fed bioequivalence (BE) studies comparing a test product, Watson Laboratories, Inc.-Florida's Tranexamic Acid Tablets, 650 mg to the corresponding reference product, Ferring Pharms AS' Lysteda® (tranexamic acid) tablets, 650 mg. The firm's fasting and fed BE studies were incomplete due to deficiencies on long-term stability data and dissolution.

The deficiency letters were sent to the firm on 2/28/2011 ("dissolution only review") and 04/07/2011. In response to deficiencies, the firm submitted the current amendment (04/26/2011) to the DBE. In the amendment, the firm confirmed that plasma samples were stored at -70°C not -20°C at the clinical center, Worldwide Clinical Trials Drug Development Solutions (WCTDDS). Thus, the firm does not need to provide long-term stability data for -20°C. The long-term storage stability data, 44 days at -70°C, (the firm previously submitted) is sufficient to cover the maximum storage period of the study samples, 34 days. The firm's response is adequate.

There is no USP method for this product, but there is an FDA-recommended method (900 ml of **Water** @ 37.0 ± 0.5°C, USP apparatus II at 50 rpm). In the original application, the firm conducted dissolution testing using its own method (900 ml of **pH 1.2SGF** @ 37.0 ± 0.5◦C, USP apparatus II at 50 rpm). Upon the FDA's request, the firm conducted the dissolution testing using the FDA-recommended method and the firm's new dissolution data showed incomplete drug release (39%) at 120 min for the test product but not for the reference product. On the other hand, using the firm's own method, both the test and reference product showed a completed drug release. The firm, thus, proposes to use its own method as the QC dissolution method for the test product. The DBE accepts the firm's dissolution method but not specification (see Dissolution consult in attachment 1). Based on the firm's data, the FDA recommends the following data-driven specification for which the firm's data meet at S1 level:

USP Apparatus:	II (Paddle)
Speed (rpm):	50 rpm
Medium:	pH 1.2 SGF
Volume (mL):	900mL
Temperature:	37°C ±0.5°C

Specification: NLT (b)(4)% (Q) in 90 min.

The application is incomplete pending the firm's acknowledgement on the FDA-recommended dissolution specification.

2 TABLE OF CONTENTS

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 are indicated for the treatment of cyclic heavy menstrual bleeding.

3.2 PK/PD Information

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
Metabolism	A small fraction of the tranexamic acid is metabolized
Excretion	Tranexamic acid is eliminated by urinary excretion primarily via glomerular filtration with more than 95% of the dose excreted unchanged. Excretion of tranexamic acid is about 90% at 24 hours after intravenous administration of 10 mg/kg. Most elimination post intravenous administration occurred during the first 10 hours, giving an apparent elimination half-life of approximately 2 hours. The mean terminal half-life of LYSTEDA is approximately 11 hours. Plasma clearance of tranexamic acid is 110-116 mL/min.
Half-life	11 hours
Drug Specific Issues (if any)	None

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:	Normal healthy males and 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:	Normal healthy males and 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:	Draft Guidance on Tranexamic Acid at http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM238065.pdf
Summary of OGD or DBE History (for details, see Appendix Error! Reference source not found.**):**	The DBE has received the following ANDAs for this drug product: ANDA 202093 (WATSON LABORATORIES INC FLORIDA, the first generic) ANDA 202286 (APOTEX INC) For similar product TRANEXAMIC ACID, Injection ANDA 201580 (CUSTOPHARM INC) ANDA 091657 (BIONICHE PHARMA USA LLC) ANDA202755 (INVIGA PHARMACEUTICALS) ANDA 202373 (VERSAPHARM INC) ANDA 202436 (ACIC FINE CHEMICALS INC) ANDA 201885 (PHARMAFORCE INC)

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

Current Amendment under review	Yes	Apr. 26, 2011 (Long-term stability and dissolution data)

3.5 In Vitro Dissolution

Location of DBE Dissolution Review	DARRTS: REV-BIOEQ-02(Dissolution Review), 2/25/2011
Source of Method (USP, FDA or Firm)	Firm's own method
Medium	pH 1.2 SGF
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm
DBE-recommended specifications	NLT (b) (4)% (Q) in 90 minutes
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	Yes
If no, reason why F2 not calculated	N?A
Is method acceptable?	**METHOD INCOMPLETE (pending firm's acknowledgement on FDA-recommended dissolution specification)**
If not then why?	

F2 metric, Test vs. Reference in pH 1.2 SGF		
Test	**Reference**	**F2 metric**
650 mg	650 mg	34.07

3.6 Waiver Request(s)

Strengths for which waivers are requested	None (only one dose)
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	No
Waivers granted?	**N/A**
If not then why?	

3.7 Deficiency Comments

1. The DBE accepts the firm's dissolution method but not specification. The firm should acknowledge the FDA-recommended dissolution specification.

3.8 Recommendations

1. The Division of Bioequivalence accepts the fasting BE study (02361VH) conducted by the Watson Laboratories, Inc.-Florida on its Tranexamic Acid Tablets, 650 mg, lot# 3720R0012A comparing it to Ferring Pharms AS' Lysteda® (tranexamic acid) tablets, 650 mg, lot# A100018A.

2. The Division of Bioequivalence accepts the fed BE study (02364VF) conducted by the Watson Laboratories, Inc.-Florida on its Tranexamic Acid Tablets, 650 mg, lot# 3720R0012A comparing it to Ferring Pharms AS' Lysteda® (tranexamic acid) tablets, 650 mg, lot# A100018A.

3. The dissolution testing is incomplete pending the acknowledgement of the firm on FDA-recommended dissolution specification. The firm should conduct dissolution testing using the following FDA-recommended dissolution method and specification:

USP Apparatus:	II (Paddle)
Speed (rpm):	50 rpm
Medium:	pH 1.2 SGF
Volume (mL):	900mL
Temperature:	37°C ±0.5°C

Specification: NLT (b)(4)% (Q) in 90 min.

3.9 Comments for Other OGD Disciplines

Discipline	Comment
	None

4 REVIEW OF AN AMENDMENT

4.1 Long-Term Stability Data

Deficiencies:

1. We acknowledge that you have submitted the long-term storage stability data, i.e. 44 days at -70°C. However, according to your study report, samples were stored at -20°C at the clinical center before they were shipped to the analytical center. Please provide long term stability data at -20°C that is sufficient to cover the time period when samples were stored at the clinical center at -20°C, i.e. at least 18 days (from June 4 to June 22, 2010).

Firm's Response

The clinical center, Worldwide Clinical Trials Drug Development Solutions (WCTDDS), confirmed that plasma samples collected for the Tranexamic Acid fasting (02361VH) and fed (02364VF) studies were stored at -70°C from the time of processing until the dates of shipment to the bioanalytical facility. As indicated in Section 5.6 of the fasting and fed study protocols (Section 5.3.1.2; Appendix 16.1.1), PK samples were to be stored at -20°C or lower, within 60 minutes of blood draw. As described in the memo from WCTDDS (Attachment 1 of this Cover Letter), the standard procedure at WCTDDS is to store the samples at -70°C when protocols indicate to store the samples at "-20°C or lower." Therefore, the previously submitted long-term storage stability data (i.e., 44 days at -70°C) is sufficient to cover the maximum 18-day time period (from June 4 to June 22, 2010) when samples were stored at -70°C at the clinical center.

Reviewer's comments:

In the original submission (fasting study report (02361vh--comp-ba-be-stdy-rprt.pdf, page 32)), the firm stated that within 60 minutes of collection, samples were frozen at approximately **-20 °C or lower** pending shipment to (b) (4) for analysis.
In the current amendment, firm indicated that it has confirmed with the clinical center, Worldwide Clinical Trials Drug Development Solutions (WCTDDS), that plasma samples were stored at -70°C not -20°C. Thus, the firm does not need to provide long stability data for -20°C. The long-term storage stability, 44 days at -70°C (the firm previously submitted) is sufficient to cover the maximum storage period of the study samples, 34 days. The firm's response is accepted.

4.2 New Dissolution Testing Data

Deficiency:

2. As indicated in the DBE deficiency letter (2/28/2011), your dissolution testing is incomplete. Please conduct and submit dissolution testing on twelve (12) dosage units of the test and reference product using the following FDA-recommended dissolution method:

USP Apparatus:	II (Paddle)
Speed (rpm):	50 rpm
Medium:	Water
Volume (mL):	900mL
Temperature:	37°C ±0.5°C
Sampling Times:	15,30,45,60,90, 120 minutes, and/or until 80% of the labeled amount of drug is dissolved.

Please submit the comparative dissolution results which should include the individual tablet data as well as the mean, range, % coefficient of variation (CV) at each time point for the 12 tablets tested, and dates of dissolution testing for each drug product. Also, please resubmit the dissolution testing data summary table with the above data.

Firm's Response:

WLF have conducted dissolution testing on the test and reference products using the FDA-recommended method. Please refer to Section 2.7.1.2, for dissolution results, which includes the individual tablet data as well as the mean, range (minimum and maximum values), the percentage of coefficient of variation (%CV) at each time point for the 12 tablets tested, and the dates of dissolution testing. The dissolution testing data summary table which was previously provided in the original submission in Sequence 0000 has been revised to include the dissolution testing on the test and reference products using the FDA-recommended method.

The graph below provides a comparison of the dissolution data conducted using the FDA's method (900 ml of Water, USP Apparatus II, 50 rpm at 37°C ± 0.5°C*)* and Watson's proposed method (900 ml of pH 1.2 SGF, USP Apparatus II, 50 rpm at 37°C ± 0.5°C*).* As can be observed from the graph, the extent of drug release of the test product at the last time point (T=120 minutes) is much higher using Watson's proposed method (900 ml of pH 1.2 SGF, USP Apparatus II, 50 rpm at 37°C ± 0.5°C*)* as compared to FDA's recommended method (900 ml of Water, USP Apparatus II, 50 rpm at 37°C ± 0.5 ^{o}C*).* In the FDA's recommended method, the mean percentage of drug released after 120 minutes was 39% (n=12 units), whereas, in Watson's method, the mean percentage of drug released was much higher at 100% (n=12 units). This reflects an incomplete drug release at the last sampling time point using the FDA's recommended method and accordingly this method may not be a suitable quality control tool.

We therefore request that the agency accept our proposed method with the previously proposed acceptance criteria (see below), as it appears to be more appropriate for our drug product.

Method: 900 m1 of pH 1.2 SGF, USP Apparatus II (Paddle), 50 rpm at 37 ± 0.5 °C

Specifications: NLT (b) (4)% (Q) in (b) (4) minutes

Reviewer's Response:

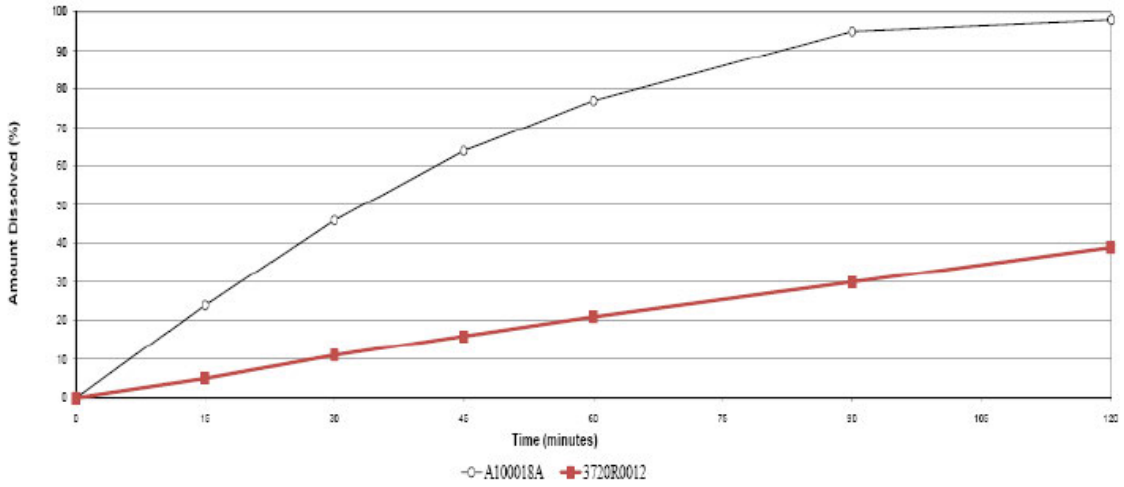
There is no USP method for this product, but there is an FDA-recommended method. The firm conducted dissolution testing using its own proposed method (900 ml of **pH 1.2SGF** @ 37.0 ± 0.5°C, USP apparatus II at 50 rpm). In the deficiency letter dated 4/7/2011, the DBE requested the firm to conduct and submit dissolution testing on twelve (12) dosage units of the test and reference product using the FDA-recommended method (900 ml of **Water** @ 37.0 ± 0.5°C, USP apparatus II at 50 rpm).

In the current amendment (4/26/2011), the firm submitted new dissolution data with FDA-recommended method. The firm's new data (FDA method) showed incomplete drug release (39%) at 120 min for the test product but not for the reference product. Such a difference in dissolution may be due to the difference in formulation for the test and reference products. As indicated in the CMC review, the test product used a (b) (4) (b) (4) (b) (4). On the other hand, using the firm's proposed method (900 mL of pH 1.2 SGF, USP Apparatus II, 50 rpm at 37 ± 0.5 °C), both the test and reference product showed a completed drug release (see two graphs below). Thus, the reviewer agrees with the firm that the FDA-recommended method is not suitable as a quality control method. Instead, the firm's method is more appropriate to be the QC dissolution method for the test product. However, the DBE disagrees with the firm's proposed specification. Based on the firm's data, the DBE recommends the following data-driven specification (see attachment 1, consult from dissolution Focal Point) for which the firm's data meet at S1 level:

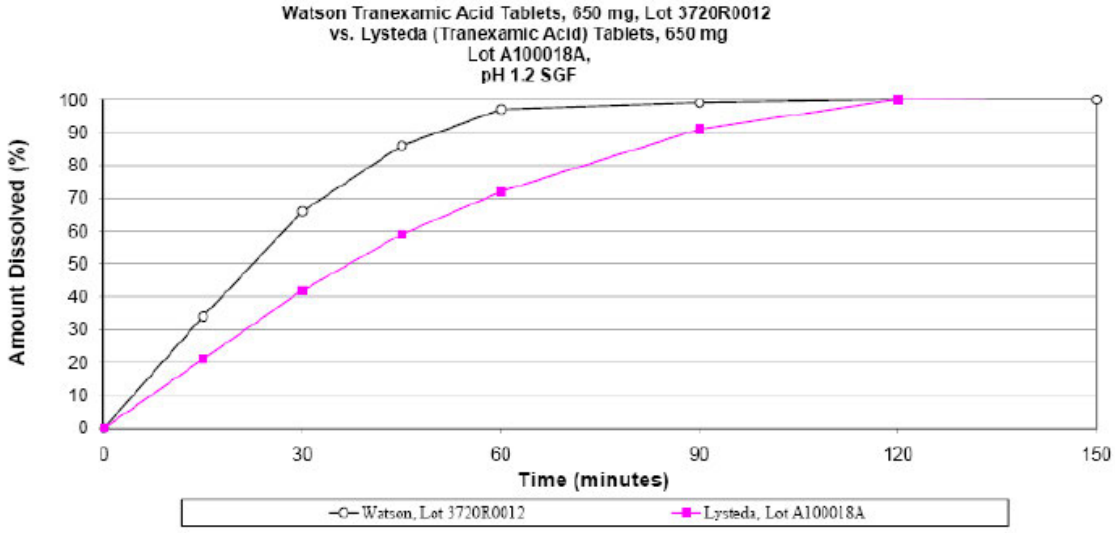
USP Apparatus:	II (Paddle)
Speed (rpm):	50 rpm
Medium:	pH 1.2 SGF
Volume (mL):	900mL
Temperature:	37°C ±0.5°C

Specification: NLT (b) (4)% (Q) in 90 min.

Tranexamic Acid Tablets, 650 mg in Medium of Water- FDA's Recommended Method [Watson's Tranexamic Acid Tablets, 650 mg, Lot 3720R0012 vs Lysteda (Tranexamic Acid) Tablets. Lot A100018A in Water]



Tranexamic Acid Tablets, 650 mg in Medium of SGF- WLF's Proposed Method



4.3 Dissolution Data

Dissolution Review Path	DARRTS: REV-BIOEQ-02(Dissolution Review), 2/25/2011

Table 1. Dissolution Data

Table 5.1 Summary of In Vitro Dissolution Studies – medium of SGF –WLF's Proposed Method

Dissolution Conditions	**Apparatus:**	II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	pH 1.2 SFG
	Volume:	900 mL
	Temperature:	37 ± 0.5 °C
Dissolution Testing Site (Name, Address)	Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston Fl, 33331	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (min) 15	30	45	60	90	120	150	Study Report Location
WSR1749, pg 3	12/08/09	Test Product Tranexamic Acid Tablets Lot # 3720R0012 (Mfg. 11/18/09)	650 mg	12	Mean	34	66	86	97	99	100	100	See pages 3 and 4
					Range	(b) (4)							
					%RSD	13.4	11.6	9.3	5.3	0.9	1.0	0.9	
WSR1749, pg 28	05/25/10	Reference Product Lysteda™ Lot # A100081A (Exp. 12/2011)	650 mg	12	Mean	21	42	59	72	91	100	101	
					Range	(b) (4)							
					%RSD	7.0	6.9	6.6	4.8	2.7	1.8	1.2	

Table 5.2 Summary of In Vitro Dissolution Studies – FDA's Recommended Method

Dissolution Conditions	**Apparatus:**	II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	Water
	Volume:	900 mL
	Temperature:	37 ± 0.5 °C
Dissolution Testing Site (Name, Address)	Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston Fl, 33331	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (min) 15	30	45	60	90	120	Study Report Location
WSR1749, pg 74	03/16/11	Test Product Tranexamic Acid Tablets Lot # 3720R0012 (Mfg. 11/18/09)	650 mg	12	Mean	5	11	16	21	30	39	See pages 6 and 7
					Range	(b) (4)						
					%RSD	7.5	5.3	4.2	4.4	4.6	10.9	
WSR1749, pg 74	03/15/11	Reference Product Lysteda™ Lot # A100018A (Exp. 12/2011)	650 mg	12	Mean	24	46	64	77	95	98	
					Range	(b) (4)						
					%RSD	9.4	10.2	8.4	6.3	3.4	3.7	

4.4 Additional Attachments

Attachment 1:

From: Anand, Om*
Sent: Monday, June 20, 2011 4:51 PM
To: Cui, Minglei
Cc: Anand, Om*; Jiang, Xiaojian
Subject: RE: Dissolution consult on ANDA 202093
Hi Minglei,

It is my opinion that we can accept the firm's method. The differences in the release may be due to the formulation differences.

In my opinion the firm should follow the following method and specification which the data meets at S1 level:

Method: 900 ml of pH 1.2 SGF @ 37.0 ± 0.5ºC, USP apparatus II at 50 rpm.

Specification: NLT (b) (4) (Q) % in 90 minutes.

Please note that this is just my opinion and consult your TL for the final decision.

Thanks

Om

From: Cui, Minglei
Sent: Wednesday, June 08, 2011 2:49 PM
To: Anand, Om*
Cc: Jiang, Xiaojian; Cui, Minglei
Subject: Dissolution consult on ANDA 202093

Dear Om,

I would like to request a dissolution consult for ANDA 202093. This drug is first generic product.

The firm conducted dissolution testing using its own proposed method (900 ml of pH 1.2 SGF @ 37.0 ± 0.5ºC, USP apparatus II at 50 rpm) which is not acceptable. The firm is then recommended to use the FDA-recommended method (900 ml of Water @ 37.0 ± 0.5ºC, USP apparatus II at 50 rpm) in both dissolution review and BE review.

The firm then submitted the dissolution data (4/26/2011) with FDA method. However, with the FDA recommended medium (water), the test product shows incomplete release whereas the reference product shows complete drug release. Contrast with this, in the firm proposed medium, pH 1.2 SGF, both the test and reference drug products show complete drug release. This dissolution difference between the test and reference products is not reflected in *in vivo* Tmax. Due to the incomplete release of the test product in FDA-recommended medium, the firm proposes to use its own method as QC dissolution method (i.e. pH 1.2 SGF as the medium).

Please advise us the following:

1. Whether it is OK to accept the firm's method as QC dissolution method despite the dissolution difference using FDA-recommended method and the status of the first generic?
2. Is this difference caused by formulation? Do we need to request firm to explain first and then accept the method?

I attached the BE review and the new dissolution data here for your convenience.

Thank you very much,

Minglei

<< File: 202093N0710_final.doc >> << File: 2-7-1-2-sum-rslts-ind-stdy.pdf >>

BIOEQUIVALENCE DEFICIENCY:

ANDA: 202093

APPLICANT: Watson Laboratories, Inc.-Florida

DRUG PRODUCT: Tranexamic Acid Tablets, 650 mg

The Division of Bioequivalence (DBE) has completed its review of your submission acknowledge on the cover sheet. The following deficiency has been identified:

You have conducted the dissolution testing using the FDA-recommended dissolution method. However, with this method, your test product showed incomplete drug release at 120 min. Thus, the DBE agrees with the use of your proposed method as a quality control dissolution method but with a tightened specification. Please acknowledge the following FDA-recommended data-driven specification for which your test product meets at the S1 level:

USP Apparatus:	II (Paddle)
Speed (rpm):	50 rpm
Medium:	pH 1.2 SGF
Volume (mL):	900mL
Temperature:	37°C ±0.5°C

Specification: NLT (b) (4)% (Q) in 90 min.

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

4.5 Outcome Page

ANDA: 202093

Enter Review Productivity and Generate Report

Reviewer: Cui, Minglei **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Tranexamic Acid Tablets, 650 mg

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
14517	4/26/2011	Other	Study Amendment	1	1
				Bean Total:	1

Typical BE Study Applications

Study amendment	1

Grand 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/

MINGLEI CUI
07/24/2011

XIAOJIAN JIANG
07/25/2011

BARBARA M DAVIT
07/29/2011

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	202093		
Drug Product Name	Tranexamic Acid Tablets		
Strength(s)	650 mg		
Applicant Name	Watson Laboratories, Inc.-Florida		
Address	4955 Orange Drive Ft. Lauderdale, FL 33314		
Applicant's Point of Contact	Radha Goolabsingh, Manager Regulatory Affairs		
Contact's Telephone Number	(954) 358-6147		
Contact's Fax Number	(954) 358-6350		
Original Submission Date(s)	July 23, 2010		
Submission Date(s) of Amendment(s) Under Review	November 9, 2010 (bio-analytical validation report, pharmacy records and clinical summary report)		
Reviewer	Minglei Cui, Ph.D.		
Study Number (s)	02361VH	02364VF	
Study Type (s)	Fasting	Fed	
Strength (s)	1 x 650 mg	1 x 650 mg	
Clinical Site	**Cedra Clinical Research, LLC**		
Clinical Site Address	2455 N.E. Loop 410, Suite 150 San Antonio, Texas 78217		
Analytical Site	(b) (4)		
Analytical Site Address			
Overall Review Result	**Inadequate**		
Waiver Request Result	**N/A**		
DSI Report Result	**Adequate**		

Bioequivalence Study	**Study/Test Type**	**Bioequivalence Study**	**Review Result**
1	**Dissolution**	**650 mg**	**Inadequate**
1	**Fasting Study**	**650 mg**	**Inadequate (pending long-term stability data)**
1	**Fed Study**	**650 mg**	**Inadequate (pending long-term stability data)**

1 EXECUTIVE SUMMARY

This application contains the results of fasting and fed bioequivalence (BE) studies comparing a test product, Watson Laboratories, Inc.-Florida'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 subjects. The firm's fasting and fed BE studies are incomplete due to deficiencies on long-term stability data and dissolution. The results are summarized in the tables below.

Tranexamic Acid Tablets, 1 x 650 mg
Fasting Bioequivalence Study No. 02361VH, N=28[1]
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (ng·hr/mL)	44718.67	45616.35	0.98	91.31	105.25
AUC∞ (ng·hr/mL)	46536.91	47638.49	0.98	91.30	104.53
Cmax (ng/mL)	8421.30	8425.95	1.00	91.81	108.80

Tranexamic Acid Tablets, 1 x 650 mg
Fed Bioequivalence Study No. 02364VF, N=32
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (ng·hr/mL)	47863.59	48844.79	0.98	94.26	101.87
AUC∞ (ng·hr/mL)	49723.11	50553.67	0.98	94.60	102.26
Cmax (ng/mL)	8019.65	8123.63	0.99	94.23	103.43

There is no USP method for this product, but there is an FDA-recommended method. The firm conducted dissolution testing using its own proposed method (900 ml of **pH 1.2 SGF** @ 37.0 ± 0.5°C, USP apparatus II at 50 rpm) which is not acceptable. The firm should conduct and submit dissolution testing on twelve (12) dosage units of the test and reference product using the FDA-recommended method (900 ml of **Water** @ 37.0 ± 0.5°C, USP apparatus II at 50 rpm).

A routine DSI inspection was conducted for clinical site on 7/8/09 for NDA 022456 with an outcome of NAI. Thus, the clinical site is acceptable. For analytical site, a "For Cause Inspection" was completed for ANDA 090747 on (b) (4) with an outcome of (b) (4) The DBE reviewers have reviewed DSI report documents[2, 3] for ANDA 090747 (found adequate). In this reviewer's opinion, the reasons of "For Cause" inspection" are

[1] The pre-dose concentration for Subject 726 during Period 1 (Treatment B) was greater than 5% of the respective Cmax and Subject 726 was excluded from the pharmacokinetic and statistical analyses.
[2] ANDA 090747, DARRTS: CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review, 6/17/ 2009 and 6/19/2009
[3] ANDA 090747, DARRTS: REV-BIOEQ-01(General Review), 7/13/2009

not relevant to this application. Therefore, the DSI inspection for analytical site is acceptable.

The application is incomplete due to the deficiencies.

2 TABLE OF CONTENTS

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 are 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
Metabolism	A small fraction of the tranexamic acid is metabolized
Excretion	Tranexamic acid is eliminated by urinary excretion primarily via glomerular filtration with more than 95% of the dose excreted unchanged. Excretion of tranexamic acid is about 90% at 24 hours after intravenous administration of 10 mg/kg. Most elimination post intravenous administration occurred during the first 10 hours, giving an apparent elimination half-life of approximately 2 hours. The mean terminal half-life of LYSTEDA is approximately 11 hours. Plasma clearance of tranexamic acid is 110-116 mL/min.
Half-life	11 hours
Drug Specific Issues (if any)	None

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

[4] Labeling Repository: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=32330#nlm34068-7

	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:	Draft Guidance on 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 LABORATORIES INC FLORIDA, the first generic) ANDA 202286 (APOTEX INC) For similar product TRANEXAMIC ACID, Injection ANDA 201580 (CUSTOPHARM INC) ANDA 091657 (BIONICHE PHARMA USA LLC) ANDA202755 (INVIGA PHARMACEUTICALS) ANDA 202373 (VERSAPHARM INC) ANDA 202436 (ACIC FINE CHEMICALS INC) ANDA 201885 (PHARMAFORCE INC)

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	1, November 9, 2010 (bio-

		analytical validation report, pharmacy records and clinical summary report)

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	Refer to Module 5.3.1.4
Analyte	Tranexamic Acid
Internal standard (IS)	(b) (4)
Method description	Protein Precipitation
Limit of quantitation	50.0 ng/mL
Average recovery of drug (%)	94.9%
Average recovery of IS (%)	89.0%
Standard curve concentrations (ng/mL)	50.0 to 12,000
QC concentrations (ng/mL)	150, 750, 4500, and 11,000
QC Intraday precision range (%)	0.72 to 7.5
QC Intraday accuracy range (%)	101 to 109
QC Interday precision range (%)	2.3 to 5.0
QC Interday accuracy range (%)	102 to 106
Short-Term Stock Solution Stability	24 hours at ambient temperature
Short-Term Working Solution Stability	24 hours at ambient temperature
Long-Term Stock Solution Stability	57 days at 2-8°C
Long-Term Working Solution Stability	57 days at 2-8°C
Short-Term (Bench-Top) Matrix Stability	19 hours at ambient temperature
Long-Term Matrix Storage Stability	8 days at -20°C or -70°C 44 days at -70°C
Freeze/Thaw Stability	4 cycles
Autosampler Stability	15.5 hours at 2-8°C
Processed Extract Stability	866 hours at 2-8°C
Selectivity	No interfering peaks noted in blank plasma samples

Note:
1. In the validation report, the dilution integrity study shows 106% accuracy and 3.9% CV for diluting 20,000 ng/mL for ten-fold.

2. The firm submitted an amendment (11/9/2010) in response to deficiencies listed in the First Generic Checklist Review[5]. In the amendment, the firm included a validation report, pharmacy records, and the updated Pre-Study Bioanalytical Method Validation table. The updated table (above) indicates that the long-term storage stability is 44 days at -70°C[6], which does cover the maximum storage period of the study samples, 34 days.

[5] ANDA 202093, DARRTS: REV-BIOEQ-07(Filing Review), 10/18/2010.
[6] In the document, 5-3-1-4-02361vh-fasting-study.pdf (page 13) from firm's amendment (11/9/2010), it stated that samples were stored frozen at approximately -70 °C at analytical center.

However, according to the firm's study report, the samples were stored at -20°C[7] at the clinical center before they were shipped to analytical center (stored at -70°C at analytical center). Thus, the firm needs to provide long term stability data at -20 °C that is sufficient to cover the time period when samples were stored at clinical center, i.e. at least 18 days (from June 4 to June 22, 2010[8, 9]).

SOPs submitted	Yes
Bioanalytical method is acceptable	No, see comments below

Comments on the Pre-Study Method Validation:

Method validation is incomplete due to the deficiency above.

[7] In the fasting study report (02361vh--comp-ba-be-stdy-rprt.pdf, page 32), it stated that within 60 minutes of collection, samples were frozen at approximately -20 °C or lower pending shipment to (b) (4) for analysis.

[8] In the anaytical report for fasting BE study, 5-3-1-4-02361vh-fasting-study.pdf (page 13), samples were shipped on June 14, 2010 on dry ice and received on June 15, 2010. Samples were then store at -70 °C for analysis. The fasting study started on June 4, 2010.

[9] The firm's study report for fed study (02364vf--comp-ba-be-stdy-rprt.pdf, page 32) indicated that "within 60 minutes of collection, samples were frozen at approximately -20 °C or lower pending shipment to (b) (4) for analysis." In addition, in the analytical report (5-3-1-4-02364vf-fed-study.pdf, page 13), it indicated that samples were shipped on June 21 and received on June 22. Furthermore, the fed study started on June 4, 2010. Thus samples may have been stored at -20°C for 18 days.

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 (units/mL)	Tmax (hr)	AUC0-t (units)	AUC∞ (units)	T½ (hr)	Kel (hr-1)	
02361VH	A Single-Dose, 2-Period, 2-Treatment, 2-Way Crossover Bioequivalence Study of Tranexamic Acid 650 mg Tablets under Fasting Conditions	Single-dose, open-label, randomized, 2-period, 2-treatment crossover study	Test formulation Tranexamic Acid Dose = 1 x 650 mg tablet p.o. [3720R0012A] Ref. product LYSTEDA™ Dose = 1 x 650 mg tablet p.o. [A100018A]	29 (19/10) Healthy subjects 35 (19-55)	8630 ± 2070 (23.98%) 8850 ± 2870 (32.42%)	3.00 (2.00-4.00) 2.50 (1.50-4.00)	46190 ± 11890 (25.75%) 47440 ± 13270 (27.98%)	47870 ± 11880 (24.82%) 49820 ± 13200 (26.49%)	8.61 ± 2.92 (33.93%) 9.60 ± 4.46 (46.50%)	0.0882 ± 0.0257 (29.07%) 0.0824 ± 0.0246 (29.88%)	5.3.1.2
02364VF	A Single-Dose, 2-Period, 2-Treatment, 2-Way Crossover Bioequivalence Study of Tranexamic Acid 650 mg Tablets under Fed Conditions	Single-dose, open-label, randomized, 2-period, 2-treatment crossover study	Test formulation Tranexamic Acid Dose = 1 x 650 mg tablet p.o. [3720R0012A] Ref. product LYSTEDA™ Dose = 1 x 650 mg tablet p.o. [A100018A]	32 (14/18) Healthy subjects 33 (20-54)	8190 ± 1720 (21.00%) 8300 ± 1730 (20.85%)	3.00 (1.50-6.00) 3.25 (2.00-7.00)	48970 ± 10650 (21.75%) 49660 ± 9003 (18.13%)	51450 ± 11040 (21.45%) 51820 ± 9506 (18.34%)	7.32 ± 1.63 (22.20%) 7.24 ± 1.69 (23.31%)	0.0994 ± 0.0232 (23.34%) 0.1008 ± 0.0242 (24.00%)	5.3.1.2

Note: In above table, the Cmax values for test product in the fasting and fed studies are slightly off. The correct values for Cmax under fasting and fed conditions should be 8633.929 ng/mL and 8191.875 ng/mL, respectively[10]. Also, the subject number in analysis for the fasting study should be 28[11] not 29.

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

Tranexamic Acid Tablets, 1 x 650 mg Fasting Bioequivalence Study No. 02361VH, N=28[1] Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	44718.67	45616.35	0.98	91.31	105.25
AUC∞ (ng·hr/mL)	46536.91	47638.49	0.98	91.30	104.53
Cmax (ng/mL)	8421.30	8425.95	1.00	91.81	108.80

Tranexamic Acid Tablets, 1 x 650 mg Fed Bioequivalence Study No. 02364VF, N=32 Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	47863.59	48844.79	0.98	94.26	101.87
AUC∞ (ng·hr/mL)	49723.11	50553.67	0.98	94.60	102.26
Cmax (ng/mL)	8019.65	8123.63	0.99	94.23	103.43

[10] In *in vivo* table, the firm's Arithmetic Mean values for Cmax of the test product in both fasting and fed studies are slightly different from those of reviewer. Using firm submitted PK data, the reviewer has confirmed that the values in *in vivo* table (the firm provided) are incorrect. Furthermore, the geometric means obtained from reviewers' analysis are same as those of firm.

[11] In the study report (02361vh--comp-ba-be-stdy-rprt.pdf, page 41), the firm stated that "Although 32 subjects were planned per protocol, 29 subjects completed the study. Data from 28 subjects were included in the pharmacokinetic and statistical analyses." Subject 726 was excluded from the analysis because the pre-dose concentration (Period 1, Treatment B) was greater than 5% of the respective Cmax.

Table 3. Reanalysis of Study Samples

Study No. 02361VH Additional information in Study 2180, pages 19-24								
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[1]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Analytical repeat								
Failure to meet acceptance criteria	154	159	27.0	27.0	0.0	0.0	0.0	0.0
Sample concentration above the upper limit of quantification	0.0	6	0.0	1.02	0.0	0.0	0.0	0.0
Sample preparation error	1	0.0	0.175	0.0	0.0	0.0	0.0	0.0
Total	155	165	27.2	28.0	0.0	0.0	0.0	0.0

1 - If no repeats were performed for pharmacokinetic reasons, insert "0.0."

Comments:

1. Although 27.6% samples[12] (or 30% runs[13]) were re-assayed, the majority repeats were from rejected runs. Among 320 repeated samples, 7 samples are individual repeated samples, the rest of 309 samples are repeated due to "the rejected runs" listed as the follows:

Batch 5 (Batch failure due to analyte in blanks), Batch 14 (Batch failure due to standard accuracy[14]), Batch 15 (Batch failure due to standard accuracy), Batch 16 (Batch failure due to standard accuracy), batch 20 (Batch failure due to analyte in blanks), Batch 26 (Batch failure due to QC accuracy[15]), Batch 29 (Batch failure due to analyte in blanks), Batch 30 (Batch failure due to analyte in blanks).

[12] 320 samples out of 1159 sample were re-assayed.
[13] Out of 46 batches analyzed, 32 were accepted. In addition to 8 rejected batches listed in the text, batches 32, 41 are reanalysis batches which are then rejected. Batched 6, 7, 8, 9 were not analyzed due to preparation error.
[14] Analytical batch failure because the calibration curve did not meet acceptance criteria, i.e. "standards accuracy".
[15] Analytical batch failure because the quality control samples did not meet acceptance criteria, i.e. "quality control accuracy".

2. The reviewer checked the analytical report (02361vh--rpt-bio-analyt-stdy.pdf Page 24-33). All repeats are due to the following reasons which are defined as analytical reasons in the repeat analysis SOP. Since the firm followed its SOP for rejecting the analytical batch and individual subject repeats, therefore, the repeat analyses are acceptable.

Reasons for repeated analysis:
BF-AB = Batch failure due to analyte in blanks
BF-PQ = Batch failure due to poor chromatography
BF-SA = Batch failure due to standard accuracy
SP = Sample preparation error
BF-QCA = Batch failure due to QC accuracy
ALOQ = Above upper limit of quantitation

Study No. 02364VF Additional information in Study 2181, pages 19-24								
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[1]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Analytical repeat								
Failure to meet acceptance criteria	156	155	25.7	25.5	0.0	0.0	0.0	0.0
Sample concentration above the upper limit of quantification	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Sample preparation error	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total	156	155	25.7	25.5	0.0	0.0	0.0	0.0

Comments:

1. Although 26.2% samples[16] (or 20% runs[17]) were re-assayed, the majority repeats were from rejected runs. Among 318 repeated samples, 7[18] samples are individual repeated samples, the rest of 304 samples are repeated due to "the rejected runs" listed as the follows:

Batch 6 (Batch failure due to QC accuracy), Batch 7 (Batch failure due to QC accuracy), Batch 8 (Batch failure due to QC accuracy), Batch 9 (Batch failure due to QC accuracy), batch 10 (Batch failure due to QC accuracy), Batch 11 (Batch failure due to QC accuracy), Batch 13 (Batch failure due to QC accuracy), Batch 15 (Batch failure due to standard accuracy).

2. The reviewer checked the analytical report (02364vf--rpt-bio-analyt-stdy.pdf, Page 22-30). All repeats are due to the following reasons which are defined as analytical reasons in the repeat analysis SOP. Therefore, the repeat analyses are acceptable.

Reasons for repeated analysis:
BLOQ = Below lower limit of quantitation
BF-QCA = Batch failure due to QC accuracy
BF-SA = Batch failure due to standard accuracy

Did use of recalculated plasma concentration data change study outcome?

NA

Comments from the Reviewer:

Acceptable

[16] 318 out of 1216 samples were re-assayed
[17] Out of 40 batches analyzed, 32 were accepted.
[18] Seven samples were repeated because the concentration is below lower limit of quantization, i.e. "BLOQ". The firm did not list these 7 samples as individual repeats in the above re-assay table.

3.7 Formulation

Location in appendix	Section 4.2, Page 8
If a tablet, is the RLD scored?	Not scored
If a tablet, is the test product biobatch scored	Not scored
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	N/A

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DARRTS: REV-BIOEQ-02(Dissolution Review), 2/25/2011
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 90 minutes
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No*
If no, reason why F2 not calculated	See below
Is method acceptable?	**METHOD INCOMPLETE**
If not then why?	

* The current dissolution data is generated using the firm's own method. The firm should submit new dissolution data as requested in the dissolution deficiency letter dated on 2/28/2011. F2 calculation will be performed on the new dissolution data.

Comments:

There is no USP method for this product, but there is an FDA-recommended method. The firm conducted dissolution testing using its own proposed method (900 ml of **pH 1.2 SGF** @ 37.0 ± 0.5◦C, USP apparatus II at 50 rpm) which is not acceptable. The firm should conduct and submit dissolution testing on twelve (12) dosage units of the test and reference product using the FDA-recommended method (900 ml of **Water** @ 37.0 ± 0.5◦C, USP apparatus II at 50 rpm).

3.9 Waiver Request(s)

Strengths for which waivers are requested	None (only one dose)
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	No
Waivers granted?	**N/A**

If not then why?	N/A

3.10 Deficiency Comments

1. The firm provided the long-term storage stability data, i.e. 44 days at -70°C in the amendment dated 11/9/2010. However, according to the firm's study report, the samples were stored at -20°C at the clinical center before they were shipped to analytical center. Thus, the firm needs to provide long term stability data at -20 °C that is sufficient to cover the time period when samples were stored at clinical center at -20 °C, i.e. at least 18 days (from June 4 to June 22, 2010)

2. There is no USP method for this product, but there is an FDA-recommended method. The firm conducted dissolution testing using its own proposed method (900 ml of pH 1.2 SGF @ 37.0 ± 0.5 °C, USP apparatus II at 50 rpm) which is not acceptable. The firm should conduct and submit dissolution testing on twelve (12) dosage units of the test and reference product using the FDA-recommended method (900 ml of Water @ 37.0 ± 0.5 °C, USP apparatus II at 50 rpm).

3.11 Recommendations

1. The Division of Bioequivalence finds the fasting BE study (02361VH) incomplete due to the deficiency mentioned above. Watson Laboratories, Inc.-Florida conducted the fasting BE study on its Tranexamic Acid Tablets, 650 mg, lot# 3720R0012A comparing it to Ferring Pharms AS' Lysteda® (tranexamic acid) tablets, 650 mg, lot# A100018A.

2. The Division of Bioequivalence finds the fed BE study (02364VF) incomplete due to the deficiency mentioned above. Watson Laboratories, Inc.-Florida conducted the fed BE study on its Tranexamic Acid Tablets, 650 mg, lot# 3720R0012A comparing it to Ferring Pharms AS' Lysteda® (tranexamic acid) tablets, 650 mg, lot# A100018A.

3. The dissolution testing conducted is incomplete. The firm should conduct dissolution testing using the following FDA-recommended dissolution method in 900 mL of water at 37°C ±0.5°C using USP apparatus II at 50 rpm. The sampling times are 15, 30, 45, 60, 90 and 120 minutes or until at least 80% of the drug is dissolved.

4. The Division of Bioequivalence can not deem the test product Tranexamic Acid Tablets , manufactured by Watson Laboratories, Inc.-Florida, to be bioequivalent to the reference product, Lysteda® (tranexamic acid) tablets, manufactured by Ferring Pharms AS due to the above deficiencies.

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	02361VH
Study Title	A Single-Dose, 2 Period, 2 Treatment, 2-Way Crossover Bioequivalence Study of Tranexamic Acid 650 mg Tablets under Fasting Conditions
Clinical Site (Name, Address, Phone #)	Cedra Clinical Research, LLC 2455 N.E. Loop 410, Suite 150 San Antonio, Texas 78217 Phone: (210) 635-1500
Principal Investigator	Cynthia A. Zamora, M.D.
Dosing Dates	Period 1: 4 June, 2010 Period 2: 9, June 2010
Analytical Site (Name, Address, Phone #)	(b) (4)
Analysis Dates	June 16, 2010 to July 8, 2010
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	34 Days; June 4, 2010 to July 8, 2010

Table 5. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Tranexamic Acid Extended Release	Lysteda™ (Tranexamic Acid)
Manufacturer	Watson Laboratories-Florida	Xanodyne Pharmaceuticals, Inc.
Batch/Lot No.	3720R0012A	A100018A
Manufacture Date	11/18/09	N/A
Expiration Date	N/A	12/2011
Strength	650mg	650mg
Dosage Form	Tablets	Tablets
Bio-batch Size	(b) (4) tablets	N/A
Production Batch Size	tablets	N/A
Potency	99.2%	100.5%
Content Uniformity (mean, %CV)	99.4%LC	100.5%LC
Dose Administered	650mg	650mg

Route of Administration	Tablets	Tablets

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

Number of Subjects	32 **enrolled,** 29 subjects completed, 28 were included in analysis[1]
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	5 days
Randomization Scheme	AB: 702, 703, 705, 708, 711, 712, 713, 715, 717, 718, 719, 722, 729, 730, 731, 732. BA: 701, 704, 706, 707, 709, 710, 714, 716, 720, 721, 723, 724, 725, 726, 727, 728.
Blood Sampling Times	Blood samples were drawn within 60 minutes prior to dose administration and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 20, and 24 hours after dose administration.
Blood Volume Collected/Sample	6 ml/sample
Blood Sample Processing/Storage	Samples were collected in appropriately labeled, 6 mL Vacutainer tubes containing K_2-EDTA. Blood samples were centrifuged at approximately 3000 rpm for 10 minutes at approximately 4 °C and the resulting plasma was transferred into duplicate appropriately-labeled polypropylene screw-cap tubes. Within 60 minutes of collection, samples were frozen at approximately -20 °C or lower pending shipment to (b) (4) for analysis.
IRB Approval	5/21/2010
Informed Consent	5/21/2010
Length of Fasting	10 hours
Length of Confinement	34 hours
Safety Monitoring	Vital signs (blood pressure, pulse rate, respiration rate, and temperature) were evaluated at screening, prior to each dose administration, and at end-of-study visit. Blood pressure and pulse rate were evaluated at approximately 2, 4, and 24 hours after each dose of study drug.

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

Fasting Study No. 02361VH			
Category		**Treatment Groups**	
		Test Product A N =29	**Reference Product B N =29**
Age (years)	Mean ± SD	35 ± 10	35 ± 10
	Range	19 - 55	19 - 55
Age Groups	< 18	0 (0.00%)	0 (0.00%)
	18 – 40	19 (65.52%)	19 (65.52%)
	41 – 64	10 (34.48%)	10 (34.48%)
	65 – 75	0 (0.00%)	0 (0.00%)
	> 75	0 (0.00%)	0 (0.00%)
Sex	Male	10 (34.48%)	10 (34.48%)
	Female	19 (65.52%)	19 (65.52%)
Race	Asian	1 (3.45%)	1 (3.45%)
	Black	6 (20.69%)	6 (20.69%)
	Caucasian	20 (68.97%)	20 (68.97%)
	Hispanic	0 (0.00%)	0 (0.00%)
	Other	2 (6.90%)	2 (6.90%)
BMI	Mean ± SD	24.2 ± 3.3	24.2 ± 3.3
	Range	18.1 - 29.8	18.1 - 29.8
Height (cm)	Mean ± SD	173.1 ± 12.3	173.1 ± 12.3
	Range	151.5 - 201.5	151.5 - 201.5
Weight (kg)	Mean ± SD	72.6 ± 13.0	72.6 ± 13.0
	Range	51.4 - 103.6	51.4 - 103.6

Table 8. Dropout Information, Fasting Bioequivalence Study

Study No. 02361VH				
Subject No	**Reason for dropout/replacement**	**Period**	**Replaced**	**Replaced with**
709	Subject was withdrawn for protocol non-compliance: positive urine drug screen at period 2 check in.	2,Test formulation	No	NA
724	Subject withdrawn due to adverse events prior to period 2 check in.	1, Reference product	No	NA
729	Subject withdrawn due to lost to follow-up.	2, Reference product	No	NA

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study Study No. 02361VH	
	Test	Reference
Abdominal pain	0 (0%)	1 (3%)
Headache	2 (7%)	1 (3%)
Muscle cramps	1 (3%)	0 (0%)
Nausea	1 (3%)	2 (6%)
Near syncope	0 (0%)	2 (6%)
Vomiting	0 (0%)	1 (3%)
Total*	3 (10%)	5 (16%)

* Number of subjects reporting at least one adverse event

724	1	B	Subject was withdrawn after 24 hour timepoint due to adverse event of vomiting 16 hours post dose. End of study procedures were performed on 06/08/10.

Comment:

Although subject 724 vomited at 16 hours post dose which is outside 2 times median of Tmax (i.e. the vomiting event should not affect PK), the subject is not included in analysis because the subject withdrew from the study prior period 2 due to the adverse effect.

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Study No. 02361VH		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Period 1: Subject did not complete the study.		724
Period 1 Meal Consumption: Subject did not consume entire meal on Day 1.	730	704, 707, 725, 728
Period 1 Sample Collection: Samples not collected at the protocol specified timepoints. Samples collected 1 to 6 minutes late.	702, 705, 712, 730, 731	707, 716, 721, 725, 727
Period 2: Subject did not complete the study.	709	729
Period 2 Meal Consumption: Subject did not consume entire meal on Day 1.	704, 707, 725, 728	713
Period 2 Water Consumption: Protocol requirements for water consumption not met.	701	
Period 2 Sample Collection: Samples not collected at the protocol specified timepoints. Samples collected 1 to 31 minutes late.	701, 707, 714, 720, 725, 727	703, 711, 718, 722, 731

Comments on Dropouts/Adverse Events/Protocol Deviations:

There are 35 blood sampling time deviations during the entire study. For 34 sampling deviations, the difference of each individual blood sampling time from the scheduled time is less than 5%, which is not considered to be significant. For 1 blood sampling deviation, the difference of each individual blood sampling time from the scheduled time is larger than 5% (significant). However, since this deviation occurred at the earlier sampling time (at 30 min) and is away from Cmax, thus, the reviewer used the scheduled sampling time for SAS analysis.

Subject	Initials	Timepoint	Early (-)/Late (+)	Reason
702	(b) (6)	3 hour	+1 minute	Restick
705		20 hour	+2 minutes	Reason unknown
707		2.5 hour	+1 minute	Restick
707		3 hour	+1 minute	Restick
712		7 hour	+1 minute	Subject late
712		24 hour	+1 minute	Subject late
716		6 hour	+2 minutes	Subject late
721		20 hour	+1 minute	Subject late
725		2.5 hour	+2 minutes	Restick
725		5 hour	+2 minutes	Restick
725		6 hour	+1 minute	Subject late
725		10 hour	+4 minutes	Restick
725		16 hour	+6 minutes	Restick
727		20 hour	+2 minutes	Subject late
730		2.5 hour	+2 minutes	Restick
730		20 hour	+2 minutes	Restick
731		2 hour	+2 minutes	Restick
731		3 hour	+4 minutes	Restick

Subject	Initials	Timepoint	Early (-)/Late (+)	Reason
701	(b) (6)	2.5 hour	+2 minutes	Resticks
701		4 hour	+2 minutes	Restick
701		10 hour	+1 minute	Restick
701		16 hour	+1 minute	Restick
701		24 hour	+31 minutes	Resticks
703		7 hour	+6 minutes	Subject late
707		8 hour	+1 minute	Subject late
711		7 hour	+1 minute	Subject late
714		7 hour	+1 minute	Subject late
718		5 hour	+1 minute	Restick
720		8 hour	+1 minute	Subject late
720		16 hour	+1 minute	Subject late
720		20 hour	+1 minute	Subject late
722		10 hour	+1 minute	Subject late
725		2.5 hour	+2 minutes	Restick
727		2.5 hour	+2 minutes	Reason unknown
731		0.5 hour	+8 minutes	Restick

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

	Study No. 02361VH Tranexamic Acid							
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	50.0	100	250	1000	2500	5000	8000	12000
Inter day Precision (%CV)	13	19	7.1	5.4	3.6	4.0	3.3	3.1
Inter day Accuracy (%Actual)	107	104	97.2	97.6	99.4	101	100	99.8
Linearity	0.9946 to 0.9998							
Linearity Range (ng/mL)	50.0 to 12000							
Sensitivity/LOQ (ng/mL)	50.0							

	Study No. 02361VH Tranexamic Acid				
Parameter	**Quality Control Samples**				
Concentration (ng/mL)	150	750	4500	11000	20000
Inter day Precision (%CV)	10	7.2	5.3	5.9	3.4
Inter day Accuracy (%Actual)	99.0	97.2	98.0	97.9	106

Comments on Study Assay Validation:

Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes (Subjects 711-716)
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
(b) (4)	(b) (4)	Bioanalytical Sample Reanalysis

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. 02361VH									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	46185.53	25.73	22422.50	73356.00	47443.72	27.99	18000.00	72137.50	0.97
AUC∞ (hr *ng/ml)	47974.31	25.15	23939.47	75206.66	49441.32	27.73	19707.70	74364.49	0.97
Cmax (ng/ml)	8633.929	23.98	5180.00	13900.00	8850.357	32.42	3770.00	15000.00	0.98
Tmax* (hr)	3.000	.	2.00	4.00	2.750	.	1.50	4.00	1.09
Kel (hr^{-1})	0.105	18.98	0.06	0.14	0.100	20.08	0.06	0.15	1.06
T1/2 (hr)	6.852	22.37	4.91	11.65	7.255	22.21	4.63	11.17	0.94

* Tmax values are presented as median, range

Note: Since this drug product is the first generic product, no other ANDAs' PK values can be used as references. In NDA 22430 ClinPharm Review[19], the arithmetic Means of Cmax, AUCt and AUCi for Lysteda under fasting condition are 11.70 mg/mL, 68.97 mg·h/mL and 71.3 mg·h/mL, respectively (2 x 650 mg dose). The firm did not conduct PK study for 1X650 mg dose. However, the firm did conduct a PK study for a dose of 1.3 g (2 x650 mg) and 3.9 g (6x450 mg, see table below). The Cmax and AUCinf following therapeutic dose (3.9 g) in the study were 1.8 and 1.9 fold[20], respectively when compared to the therapeutic dose (1.3 g). The increase in 3-fold dose produced approximately 2-fold increase in exposures indicating less than dose proportional PK of tranexamic acid at the studied doses. Therefore, comparing to PK values produced by 2x 650 mg tranexamic acid in NDA 022430, more than 1/2 –fold Cmax, AUCt and AUCi produced by only half dose (650 mg) in this ANDA are considered in comparable range.

Table 4: Pharmacokinetic parameters (Arithmetic mean ± SD) following 1.3 and 3.9g of Tranexamic acid[20] -----Information only

[19] NDA 22430 DARRTS: REV-CLINPHARM-01(General Review), 10/16/2009.
[20] NDA 22430 DARRTS: REV-CLINPHARM-01(General Review), 5/18/2009.

Table 4: Pharmacokinetic parameters (Arithmetic mean ± SD) following 1.3 and 3.9g of Tranexamic acid

PK parameters	Treatment A (1300 mg)	Treatment B (3900 mg)
AUC 0-t (mcg·h/mL)	67.7 ± 19.5	123 ± 37.0
AUCinf (mcg·h/mL)	69.4 ± 19.6	127 ± 37.2
AUC 0-t/AUCinf (%)	97.3 ± 1.20	96.8 ± 1.15
Cmax (mcg/mL)	11.6 ± 3.50	21.5 ± 5.63
tmax (h)	3.60 ± 0.835	3.20 ± 0.788
Half-life (h)	5.52 ± 1.21	6.21 ± 1.12
kel (1/h)	0.135 ± 0.0545	0.115 ± 0.0206

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

Tranexamic Acid: Dose (1 x 650 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (02361VH)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC_{0-t}	44720.9229	45618.9562	98.03	91.32	105.24
AUC_{∞}	46966.0311	47991.8592	97.86	90.70	105.59
C_{max}	8421.2982	8425.9513	99.94	91.81	108.80

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

Tranexamic Acid Tablets, 1 x 650 mg Fasting Bioequivalence Study No. 02361VH, N=28[21] Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	44718.67	45616.35	0.98	91.31	105.25
AUC∞ (ng·hr/mL)	46536.91	47638.49	0.98	91.30	104.53
Cmax (ng/mL)	8421.30	8425.95	1.00	91.81	108.80

Note: The pre-dose value for subject 726 is 5.25% of Cmax which is at boarder line for excluding the subject from analysis according to Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations [22]. Thus, the reviewer also performed SAS analysis with subject 726 included. The result of the study remains same (see the table below).

Tranexamic Acid Tablets, 1 x 650 mg Fasting Bioequivalence Study No. 02361VH, N=29[23]

[21] The pre-dose concentration for Subject 726 during Period 1 (Treatment B) was greater than 5% of the respective Cmax and Subject 726 was excluded from the pharmacokinetic and statistical analyses.
[22] Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations: "If the predose concentration is ≤ 5 percent of Cmax value in that subject, the subject's data without any adjustments can be included in all pharmacokinetic measurements and calculations. We recommend that if the predose value is > than 5 percent of Cmax, the subject be dropped from all BE study evaluations".
[23] The reviewer includes subject 726 for analysis.

Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	44495.84	45822.37	0.97	90.54	104.15
AUC∞ (ng·hr/mL)	46312.09	47845.06	0.97	90.55	103.48
Cmax (ng/mL)	8320.69	8399.23	0.99	91.19	107.63

Table 17. Additional Study Information, Fasting Study No. 02361VH

Root mean square error, AUC0-t	0.1555	
Root mean square error, AUC∞	0.1481	
Root mean square error, Cmax	0.1858	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	28	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	28	0.96	0.90	0.98
Reference	28	0.96	0.90	0.98

Comments on Pharmacokinetic and Statistical Analysis:

Acceptable.

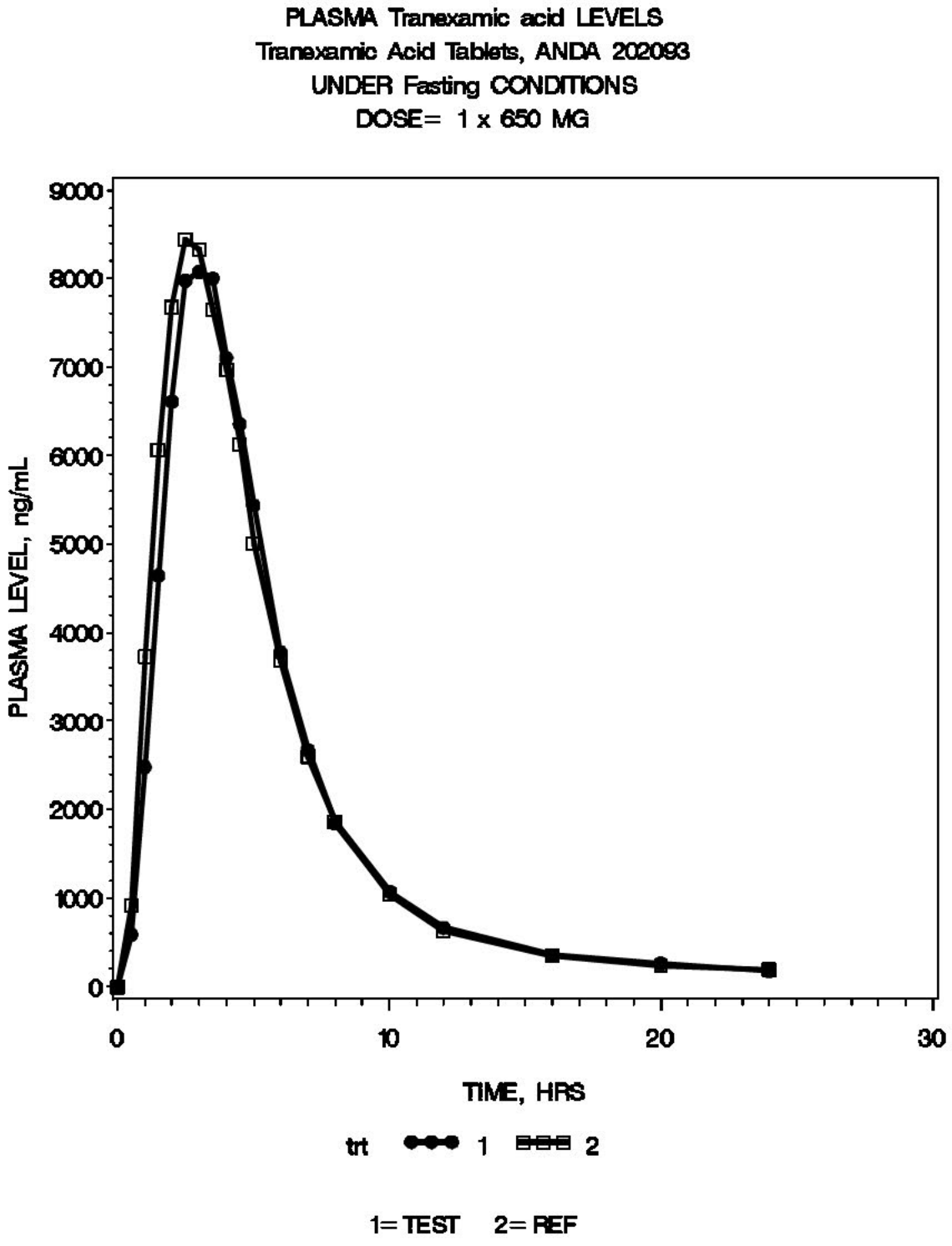
Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The fasting study met the confidence interval acceptance criteria for log-transformed AUC0-t, AUC∞ and Cmax of Tranexamic Acid Tablets. However, the fasting study is incomplete pending the long-term stability data.

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	589.18	71.19	919.05	52.06	0.64
1.00	2483.11	50.86	3725.36	41.09	0.67
1.50	4645.71	37.78	6061.43	36.03	0.77
2.00	6611.79	31.69	7676.79	35.52	0.86
2.50	7976.79	30.62	8445.00	33.13	0.94
3.00	8075.00	26.50	8330.36	34.94	0.97
3.50	8002.86	24.64	7652.86	31.44	1.05
4.00	7107.86	28.40	6966.43	30.52	1.02
4.50	6355.36	28.72	6118.57	32.24	1.04
5.00	5439.64	28.51	5002.14	31.16	1.09
6.00	3776.43	33.22	3687.86	31.74	1.02
7.00	2674.64	35.24	2599.64	31.73	1.03
8.00	1850.43	39.80	1855.96	32.01	1.00
10.00	1073.21	35.22	1037.93	32.66	1.03
12.00	665.75	35.40	627.75	31.04	1.06
16.00	354.86	30.43	346.96	32.00	1.02
20.00	258.54	43.52	237.39	28.89	1.09
24.00	179.01	26.18	188.11	35.60	0.95

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	02364VF
Study Title	A Single-Dose, 2 Period, 2 Treatment, 2-Way Crossover Bioequivalence Study of Tranexamic Acid 650 mg Tablets under Fed Conditions
Clinical Site (Name, Address, Phone #)	Cedra Clinical Research, LLC 2455 N.E. Loop 410, Suite 150 San Antonio, Texas 78217 Phone: (210) 635-1500
Principal Investigator	Cynthia A. Zamora, M.D.
Dosing Dates	Period 1: 4 June, 2010 Period 2: 9, June 2010
Analytical Site (Name, Address, Phone #)	(b) (4)
Analysis Dates	June 16, 2010 to June 29, 2010
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	25 Days; June 4, 2010 to June 29, 2010

Note: The firm's study report (02364vf--comp-ba-be-stdy-rprt.pdf, page 32) indicated that "within 60 minutes of collection, samples were frozen at approximately -20 °C or lower pending shipment to (b) (4) for analysis." In the analytical report, it indicated that samples were shipped on June 21 and received on June 22 (the last shipment). Thus samples may have been stored at clinical center at -20°C[24] for 18 days. The current long-term storage stability data is 44 days at -70°C and 8 days at -20°C. The firm needs to provide long-term stability data which is sufficient to cover the period that samples were stored at clinical center at -20° C, i.e. at least 18 days.

Table 20. Product Information

Product	Test	Reference
Treatment ID	A	B
Product Name	Tranexamic Acid Extended Release	Lysteda™ (Tranexamic Acid)
Manufacturer	Watson Laboratories-Florida	Xanodyne Pharmaceuticals, Inc.
Batch/Lot No.	3720R0012A	A100018A
Manufacture Date	11/18/09	N/A
Expiration Date	N/A	12/2011
Strength	650mg	650mg
Dosage Form	Tablets	Tablets

[24] The Samples were stored at -70 °C at analytical center.

Bio-batch Size	(b) (4) tablets	N/A
Production Batch Size	tablets	N/A
Potency	99.2%	100.5%
Content Uniformity (mean, %CV)	99.4%LC	100.5%LC
Dose Administered	650mg	650mg
Route of Administration	Tablets	Tablets

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

No. of Subjects	32 subject enrolled, 32 subjected completed study, 32 subjects were involved in statistical analysis.
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	5 days
Randomization Scheme	AB: 601,603, 604, 605, 611, 612, 613, 614, 618, 619, 623, 624, 625, 628, 631, 632. BA: 602, 606, 607, 608, 609, 610, 615, 616, 617, 620, 621, 622, 626, 627, 629, 630.
Blood Sampling Times	Blood samples were drawn within 60 minutes prior to dose administration and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 20, and 24 hours after dose administration.
Blood Volume Collected/Sample	6 ml/sample
Blood Sample Processing/Storage	Samples were collected in appropriately labeled, 6 mL Vacutainer tubes containing K_2-EDTA. Blood samples were centrifuged at approximately 3000 rpm for 10 minutes at approximately 4 °C and the resulting plasma was transferred into duplicate appropriately-labeled polypropylene screw-cap tubes. Within 60 minutes of collection, samples were frozen at approximately -20 °C or lower pending shipment to (b) (4) for analysis.
IRB Approval	5/21/2010
Informed Consent	5/1/2010
Length of Fasting Before Meal	10 hours
Length of Confinement	34 hours
Safety Monitoring	Vital signs (blood pressure, pulse rate, respiration rate, and temperature) were evaluated at screening, prior to each dose administration, and at end-of-study visit. Blood pressure and pulse rate were evaluated at approximately 2, 4, and 24 hours after each dose of study drug.

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

Fasting Study No. 02364VF			
Category		Treatment Groups	
		Test Product A N =32	Reference Product B N =32
Age (years)	Mean ± SD	33 ± 11	33 ± 11
	Range	20 - 54	20 - 54
Age Groups	< 18	0 (0.00%)	0 (0.00%)
	18 – 40	23 (71.88%)	23 (71.88%)
	41 – 64	9 (28.13%)	9 (28.13%)
	65 – 75	0 (0.00%)	0 (0.00%)
	> 75	0 (0.00%)	0 (0.00%)
Sex	Male	18 (56.25%)	18 (56.25%)
	Female	14 (43.75%)	14 (43.75%)
Race	Asian	0 (0.00%)	0 (0.00%)
	Black	6 (18.75%)	6 (18.75%)
	Caucasian	25 (78.13%)	25 (78.13%)
	Hispanic	0 (0.00%)	0 (0.00%)
	Other	1 (3.13%)	1 (3.13%)
BMI	Mean ± SD	24.5 ± 2.9	24.5 ± 2.9
	Range	18.9 - 29.9	18.9 - 29.9
Height (cm)	Mean ± SD	170.5 ± 10.0	170.5 ± 10.0
	Range	153.0 - 190.5	153.0 - 190.5
Weight (kg)	Mean ± SD	71.4 ± 10.8	71.4 ± 10.8
	Range	51.4 - 90.8	51.4 - 90.8

Table 23. Dropout Information, Fed Bioequivalence Study

Study No. 02364VF				
Subject No	Reason for dropout/replacement	Period	Replaced	Replaced with
	No dropouts or replacements			

Table 24. Study Adverse Events, Fed Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fed Bioequivalence Study Study No. 02364VF	
	Test	Reference
Abdominal cramps	2 (6%)	0 (0%)
Abdominal pain	1 (3%)	0 (0%)
Back pain	1 (3%)	0 (0%)
Contact dermatitis	1 (3%)	0 (0%)
Dizziness	0 (0%)	1 (3%)
Headache	1 (3%)	2 (6%)
Intermittent headache	0 (0%)	1 (3%)
Irregular menses	0 (0%)	1 (3%)
Nausea	3 (9%)	1 (3%)
Swollen left finger	1 (3%)	0 (0%)
Total*	5 (16%)	5 (16%)

Table 25. Protocol Deviations, Fed Bioequivalence Study

Study No. 02364VF		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Period 1 Meal Consumption: Subject did not consume entire meal on Day 1.	614, 618, 625	609
Period 1 Water Consumption: Protocol requirements for water consumption not met.	619	620
Period 1 Sample Collection: Samples not collected at the protocol specified timepoints. Samples collected 1 to 9 minutes late.	601, 605, 613, 623, 632	602, 610, 617, 626
Period 1 Vital Signs: Vital signs not performed per protocol requirements.		608
Period 2 Meal Consumption: Subject did not consume entire meal on Day 1.	606, 609	603, 604, 605, 618, 623, 628, 631
Period 2 Water Consumption: Protocol requirements for water consumption not met.		604
Period 2 Sample Collection: Samples not collected at the protocol specified timepoints. Samples collected 1 to 7 minutes late.	602, 609, 610, 616	601, 604, 612, 613, 623, 624, 625, 628, 631, 632
Period 2 Vital Signs: Vital signs not performed per protocol requirements.		624
End of Study Lab Work: Hematology not performed due to sample clotting.		623

Comments on Adverse Events/Protocol Deviations:

There are 33 blood sampling time deviations during the entire study. The difference of each individual blood sampling time from the scheduled time for 32sampling deviations

is less than 5%, which is not considered to be significant. For 2 blood sampling deviations, the difference of each individual blood sampling time from the scheduled time is larger than 5% (significant). However, since these deviations occurred at the earlier sampling time (at 30 min) and are away from Cmax, thus, the reviewer used the scheduled sampling time for SAS analysis.

4.1.2.3 Bioanalytical Results

Table 26. Assay Validation – Within the Fed Bioequivalence Study

	Study No. 02364VF Tranexamic Acid							
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	50.0	100	250	1000	2500	5000	8000	12000
Inter day Precision (%CV)	13	16	4.9	3.9	5.6	4.0	3.7	4.5
Inter day Accuracy (%Actual)	93.5	100	99.9	102	103	102	99.6	98.2
Linearity	0.9930 to 0.9998							
Linearity Range (ng/mL)	50.0 to 12000							
Sensitivity/LOQ (ng/mL)	50.0							

	Study No. 02364VF Tranexamic Acid			
Parameter	**Quality Control Samples**			
Concentration (ng/mL)	150	750	4500	11000
Inter day Precision (%CV)	4.4	3.7	4.2	3.8
Inter day Accuracy (%Actual)	94.6	95.4	96.2	94.0

Comments on Study Assay Validation:

Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes (Subject 624 to 630)
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
(b) (4)	(b) (4)	Bioanalytical Sample Reanalysis

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. 02364VF									
Parameter (units)	**Test**				**Reference**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC0-t (hr *ng/ml)	48965.69	21.74	32424.00	65757.00	49650.25	18.12	31501.00	67382.50	0.99
AUC∞ (hr *ng/ml)	50810.24	21.17	33346.58	67907.25	51390.17	18.19	32994.03	69851.24	0.99
Cmax (ng/ml)	8191.875	21.00	5640.00	11600.00	8300.313	20.85	5760.00	11500.00	0.99
Tmax* (hr)	3.250	.	1.50	6.00	3.250	.	2.00	7.00	1.00
Kel (hr^{-1})	0.118	19.62	0.05	0.17	0.122	17.08	0.09	0.18	0.97
T1/2 (hr)	6.173	26.76	4.13	13.57	5.845	15.48	3.80	7.94	1.06

* Tmax values are presented as median, range

In NDA 22430 ClinPharm Review[25], the arithmetic Means of Cmax, AUCt and AUCi for Lysteda under fed condition are 13.47 mg/mL, 83.44 mg·h/mL and 85.53 mg·h/mL, respectively (2 x 650 mg dose). The PK values produced by dose of 1 x 650 mg Tranexamic Acid in this ANDA are considered comparable.[26]

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

Tranexamic Acid: Dose (1 x 650 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals
Fed Bioequivalence Study (02364VF)

[25] NDA 22430 DARRTS: REV-CLINPHARM-01(General Review), 10/16/2009.
[26] NDA 22430 DARRTS: REV-CLINPHARM-01(General Review), 5/18/2009. The increase in 3-fold dose produced approximately 2-fold increase in exposures indicating less than dose proportional PK of tranexamic acid at the studied doses.

Parameter	Test	Reference	Ratio	90% C.I.	
AUC_{0-t}	47871.1704	48855.3375	97.99	94.26	101.86
AUC_{∞}	50258.8813	51483.8918	97.62	93.87	101.52
C_{max}	8019.6530	8123.6343	98.72	94.23	103.43

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

Tranexamic Acid Tablets, 1 x 650 mg Fed Bioequivalence Study No. 02364VF, N=32 Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	47863.59	48844.79	0.98	94.26	101.87
AUC∞ (ng·hr/mL)	49723.11	50553.67	0.98	94.60	102.26
Cmax (ng/mL)	8019.65	8123.63	0.99	94.23	103.43

Table 32. Additional Study Information

Root mean square error, AUC0-t	0.0914	
Root mean square error, AUC∞	0.0918	
Root mean square error, Cmax	0.1097	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	32	32
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	1*
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

* Subject 623 (period 2, reference) has a positive pre-dose. Since the pre-dose value is 0.8% of Cmax (<5% Cmax), the subject is included in the statistical analysis.

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	32	0.96	0.88	0.98
Reference	32	0.97	0.95	0.98

Comments on Pharmacokinetic and Statistical Analysis:

Acceptable.

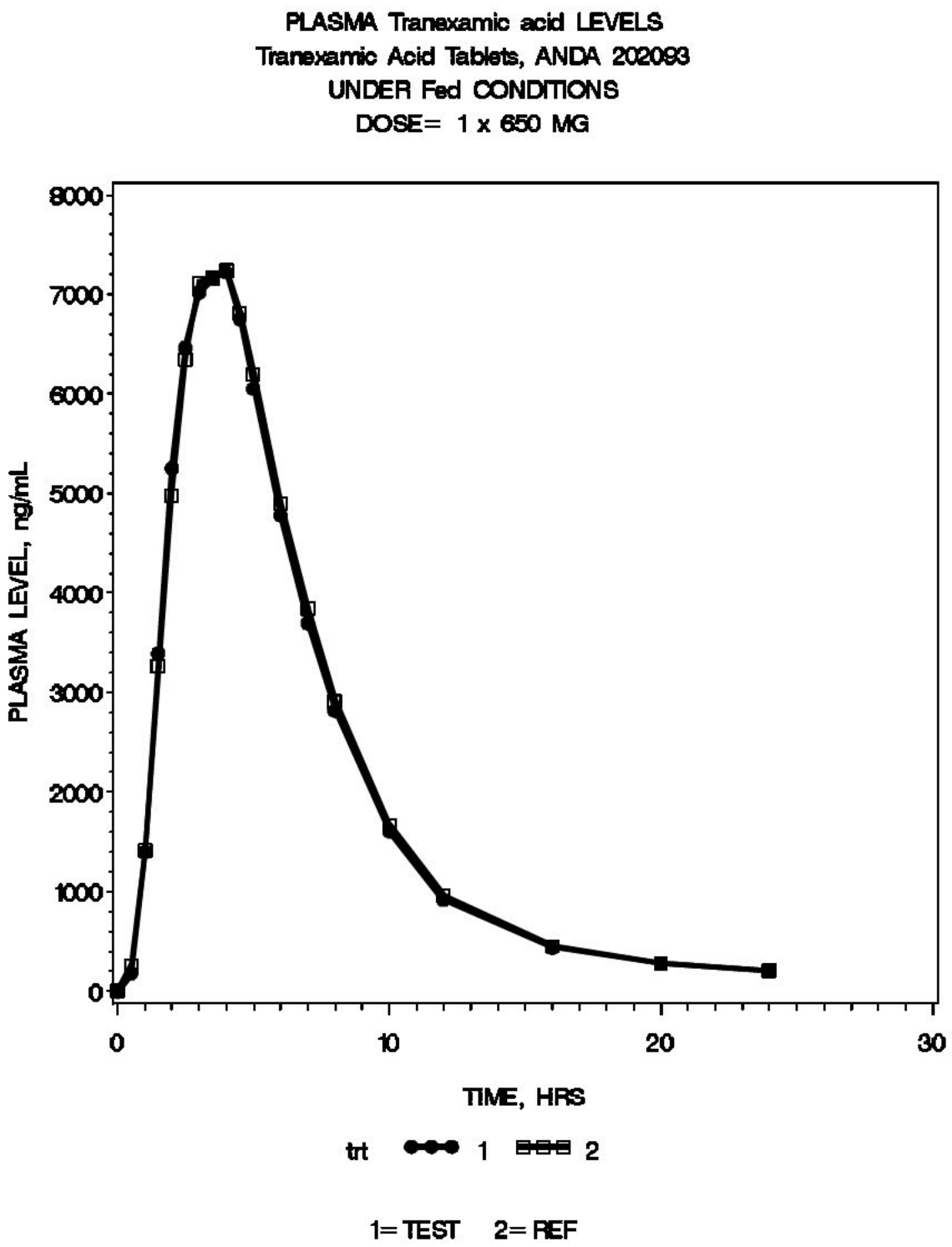
Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

The fed study met the confidence interval acceptance criteria for log-transformed AUC0-t, AUC∞ and Cmax of Tranexamic Acid Tablets. However, the fed study is incomplete pending the long-term stability data.

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

	Test (n=32)		Reference (n=32)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	1.73	565.69	0.00
0.50	182.43	174.94	262.46	107.17	0.70
1.00	1401.58	97.94	1412.29	76.40	0.99
1.50	3395.41	69.14	3269.19	64.47	1.04
2.00	5253.84	51.67	4976.56	52.21	1.06
2.50	6466.25	41.35	6348.44	42.52	1.02
3.00	7020.00	33.41	7121.25	34.80	0.99
3.50	7165.00	28.66	7160.63	29.15	1.00
4.00	7224.69	27.53	7236.25	25.77	1.00
4.50	6753.44	27.25	6809.06	24.71	0.99
5.00	6053.13	28.09	6196.25	23.09	0.98
6.00	4781.56	32.26	4906.56	27.18	0.97
7.00	3697.81	38.77	3844.06	31.20	0.96
8.00	2818.75	44.44	2910.31	36.89	0.97
10.00	1610.38	46.95	1667.66	46.58	0.97
12.00	919.84	43.62	961.66	47.13	0.96
16.00	439.88	38.99	454.22	37.14	0.97
20.00	282.97	29.78	283.34	28.11	1.00
24.00	207.69	23.93	208.97	26.10	0.99

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



4.2 Formulation Data

Composition of Tranexamic Acid Tablets, 650 mg

Ingredients/Grade	mg/tab	% w/w (per tablet)
(b) (4)		

Composition of Tranexamic Acid Tablets, 650 mg

Ingredients/Grade	Function	mg/tab	% w/w (per tablet)	IID Max Level for Orally Administered Drug Products
[redacted]				(b) (4)

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

Comments:

4.3 Dissolution Data

Dissolution Review Path	DARRTS: REV-BIOEQ-02(Dissolution Review), 2/25/2011

Table 34. Dissolution Data

Dissolution Conditions	**Apparatus:**	II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	pH 1.2 SFG
	Volume:	900 mL
	Temperature:	37 ± 0.5 °C
Dissolution Testing Site (Name, Address)	Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston Fl, 33331	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (min) 15	30	45	60	90	120	150	Study Report Location
WSR1749, pg 3	12/08/09	Test Product Tranexamic Acid Tablets Lot # 3720R0012 (Mfg. 11/18/09)	650 mg	12	Mean	34	66	86	97	99	100	100	See pages 9 and 10
					Range	(b) (4)							
					%RSD	13.4	11.6	9.3	5.3	0.9	1.0	0.9	
WSR1749, pg 28	05/25/10	Reference Product Lysteda™ Lot # A100081A (Exp. 12/2011)	650 mg	12	Mean	21	42	59	72	91	100	101	
					Range	(b) (4)							
					%RSD	7.0	6.9	6.6	4.8	2.7	1.8	1.2	

4.4 SAS Output

4.4.1 Fasting Study Data

Fasting CONCENTRATION DATASET

Following this page, 83 Pages Withheld in Full as (b)(4)

BIOEQUIVALENCE DEFICIENCIES:

ANDA: 202093

APPLICANT: Watson Laboratories, Inc.-Florida

DRUG PRODUCT: Tranexamic Acid Tablets, 650 mg

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. We acknowledge that you have submitted the long-term storage stability data, i.e. 44 days at -70°C. However, according to your study report, samples were stored at -20°C at the clinical center before they were shipped to the analytical center. Please provide long term stability data at -20°C that is sufficient to cover the time period when samples were stored at the clinical center at -20°C, i.e. at least 18 days (from June 4 to June 22, 2010).

2. As indicated in the DBE deficiency letter (2/28/2011), your dissolution testing is incomplete. Please conduct and submit dissolution testing on twelve (12) dosage units of the test and reference product using the following FDA-recommended dissolution method:

USP Apparatus :	II (Paddle)
Speed (rpm) :	50
Medium :	Water
Volume (mL) :	900 mL
Temperature :	37°C ± 0.5°C
Sampling Times :	15, 30, 45, 60, 90, 120 minutes, and/or until 80% of the labeled amount of drug is dissolved

Please submit the comparative dissolution results which should include the individual tablet data as well as the mean, range, % coefficient of variation (CV) at each time point for the 12 tablets tested and dates of dissolution testing for each drug product. Also, please resubmit the dissolution testing data summary table with the above data.

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

4.5 Outcome Page

ANDA: 202093

Enter Review Productivity and Generate Report

Reviewer: Cui, Minglei **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Tranexamic Acid Tablets, 650 mg

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
13529	7/23/2010	Bioequivalence Study	Fasting Study	1	1
13529	7/23/2010	Bioequivalence Study	Fed Study	1	1
13529	11/9/2010	Other	Study Amendment	1	1
				Bean Total:	3

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*
Study Amendment	1

Grand Total	**7**

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/s/

MINGLEI CUI
04/07/2011

XIAOJIAN JIANG
04/07/2011

BARBARA M DAVIT
04/07/2011

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	202093	
Drug Product Name	Tranexamic Acid Tablets	
Strength (s)	650 mg	
Applicant Name	Watson Laboratories, Inc.-Florida	
Address	4955 Orange Drive Ft. Lauderdale, FL 33314	
Applicant's Point of Contact	Radha Goolabsingh, Manager Regulatory Affairs	
Contact's Phone Number	(954) 358-6147	
Contact's Fax Number	(954) 358-6350	
Submission Date(s)	7/23/2010	
First Generic	Yes	
Reviewer	Hongling Zhang, Ph.D.	
Study Number (s)	02361VH	02364VF
Study Type (s)	Fasting	Fed
Strength(s)	1 x 650 mg	1 x 650 mg
Clinical Site	**Cedra Clinical Research, LLC**	
Clinical Site Address	2455 N.E. Loop 410, Suite 150 San Antonio, Texas 78217	
Analytical Site	(b) (4)	
Analytical Address		

OUTCOME DECISION	**INADEQUATE**		
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 an FDA-recommended method. The firm conducted dissolution testing using its own proposed method (900 ml of **pH 1.2 SGF** @ 37.0 ± 0.5°C, USP apparatus II at 50 rpm). Therefore, the firm should conduct and submit dissolution testing on twelve (12) dosage units of the test and reference product using the FDA-recommended method (900 ml of **Water** @ 37.0 ± 0.5°C, USP apparatus II at 50 rpm).

NON DISSOLUTION TESTING ITEMS:

The long-term storage stability data that the firm provided, which is 8 days at -70°C or -20°C, does not cover the maximum storage period of the study samples for the submitted bioequivalence studies, which is 34 days.

The firm provided the SAS files in the electronic format for fast and fed BE studies.

The DBE will review the fast and fed BE study at a later date.

The in vitro dissolution testing is **inadequate**.

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.					

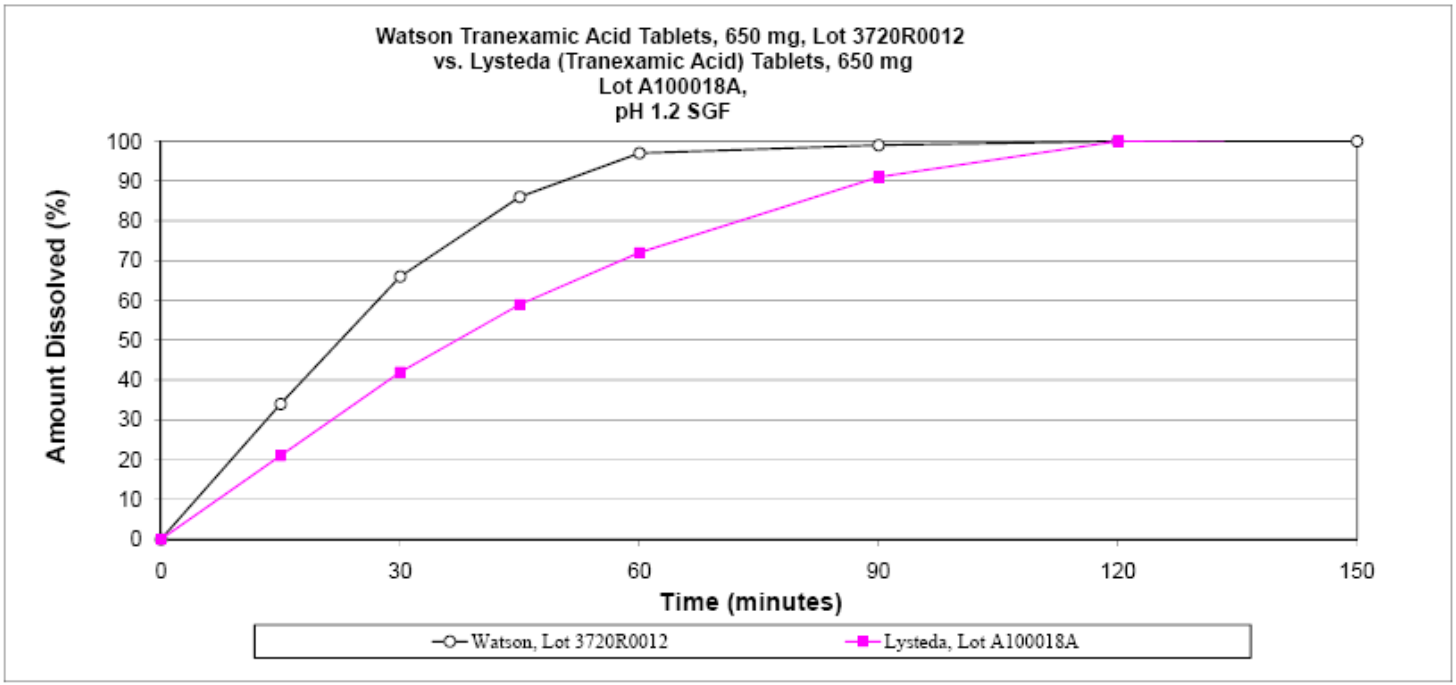
*The long-term storage stability data that the firm provided, which is 8 days at -70°C or -20°C, does not cover the maximum storage period of the study samples for the submitted bioequivalence studies, which is 34 days.

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Dissolution Conditions	**Apparatus:**	II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	pH 1.2 SFG
	Volume:	900 mL
	Temperature:	37 ± 0.5 °C
Dissolution Testing Site (Name, Address)	Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston Fl, 33331	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (min) 15	30	45	60	90	120	150	Study Report Location
WSR1749, pg 3	12/08/09	Test Product Tranexamic Acid Tablets Lot # 3720R0012 (Mfg. 11/18/09)	650 mg	12	Mean	34	66	86	97	99	100	100	See pages 9 and 10
					Range	(b) (4)							
					%RSD	13.4	11.6	9.3	5.3	0.9	1.0	0.9	
WSR1749, pg 28	05/25/10	Reference Product Lysteda™ Lot # A100081A (Exp. 12/2011)	650 mg	12	Mean	21	42	59	72	91	100	101	
					Range	(b) (4)							
					%RSD	7.0	6.9	6.6	4.8	2.7	1.8	1.2	

Dissolution Profile:



II. COMMENT:

- There is no USP-method for Tranexamic Acid Tablets, but there is an FDA-recommended dissolution method which is available in the public dissolution database on the Office of Generic Drugs (OGD) website[1], http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm. The current FDA-recommended dissolution method for Tranexamine Acid Tablets is as follows:

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

- The FDA-recommended dissolution method is the same as the RLD product (NDA 022430). The dissolution specification for the RLD product is "NLT (b)(4)% (Q) in 90 minutes" (NOT TO BE RELEASED UNDER FOI)[2].

- The firm conducted the dissolution test using the following method:

USP Apparatus :	II (Paddle)
Speed (rpm) :	50
Medium :	**pH 1.2 SGF**
Volume (mL) :	900 mL
Temperature :	37°C ± 0.5°C

The specification that the firm proposed is "NLT (b)(4)% (Q) in (b)(4) minutes".

- The firm will be asked to conduct the dissolution method using FDA-recommended method.

III. DEFICIENCY COMMENT:

- The firm did not conduct dissolution testing using the FDA-recommended dissolution method. Therefore, the firm should conduct and submit dissolution testing on both test and reference product using the FDA-recommended dissolution method.

- The long-term storage stability data that the firm provided, which is 8 days at -70°C or -20°C, does not cover the maximum storage period of the study samples for the submitted bioequivalence studies, which is 34 days.

---

[1] The FDA-recommended dissolution method was updated on 12/23/2010 and the firm submitted the application on 7/23/2010.

[2] DARRTS, NDA 022430, REV-QUALITY-03 (General Review), dated 9/24/2009 (Reference the Checklist Review of Current ANDA, dated 10/18/2010)

IV. RECOMMENDATION:

The *in vitro* dissolution testing conducted by Watson Laboratories Inc.-Florida, on its Tranexamic Acid Tablets, 650 mg (lot #3720R0012), along with the reference product, Lysteda® (tranexamic acid) Tablets, 650 mg (lot #A100018A) by Ferring Pharms. is incomplete for the reason provided in the deficiency comment.

The firm should conduct and submit dissolution testing on twelve (12) dosage units of the test and reference product using the following FDA-recommended dissolution method:

USP Apparatus :	II (Paddle)
Speed (rpm) :	50
Medium :	Water
Volume (mL) :	900 mL
Temperature :	37°C ± 0.5°C
Sampling Times :	15, 30, 45, 60, 90, 120 minutes, and/or until 80% of the labeled amount of drug is dissolved

The firm should be informed of the above deficiency comments and recommendations.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 202093

APPLICANT: Watson Laboratories, Inc.-Florida.

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 bioequivalence studies will be done at a later date. The following deficiencies have been identified:

1. Your dissolution testing is incomplete. Please conduct and submit dissolution testing on twelve (12) dosage units of the test and reference product using the following FDA-recommended dissolution method:

USP Apparatus :	II (Paddle)
Speed (rpm) :	50
Medium :	Water
Volume (mL) :	900 mL
Temperature :	37°C ± 0.5°C
Sampling Times :	15, 30, 45, 60, 90, 120 minutes, and/or until 80% of the labeled amount of drug is dissolved

Please submit the comparative dissolution results which should include the individual tablet data as well as the mean, range, % coefficient of variation (CV) at each time point for the 12 tablets tested and dates of dissolution testing for each drug component. Also, please resubmit the dissolution testing data summary table with the above data.

The dissolution method is available in the public dissolution database on the Office of Generic Drugs (OGD) website, http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm

2. The long-term storage stability data that you provided, which is 8 days at -70°C or -20°C, does not cover the maximum storage period of the study samples for the submitted bioequivalence studies, which is 34 days.

Please provide long term storage stability data of tranexamic acid in frozen plasma for at least 34 days.

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: 202093

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
13199	7/23/2010	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/

HONGLING ZHANG
02/23/2011

BING V LI
02/25/2011

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202093

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ROUTING SHEET

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

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

Electronic ANDA: Yes ☒ No ☐

ANDA #:202093
Firm Name:Watson Laboratories, Inc - Florida
ANDA Name:Tranexamic Acid Tablets, 650 mg
RLD Name:Lysteda Tablets, 650 mg, of Ferring Pharmaceuticals, Inc.

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: 11-7-12 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 _____
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 8-29-11 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location:)
Date of Acceptable Labeling 12-31-11 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

☐ 1st Generic Review

☒ Bob West / Peter Rickman
☐ Gregory Geba

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

Date Emailed: 11-28-12
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: 11/9/2012**
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 12/27/12 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 previously TA'd on 2/16/2012-at the time the TA was issued the reason cited for TA was unexpired NDF exclusivity which protected the RLD. At the time of TA, Watson had PIV certs to the '739 and '106 patents. Patent Amendment rec'd on 11/5/2012-PIV to the '795 patent.	

The patent listing dates 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. According to DARRTs- Watson's PIV cert to the '739 patent was not received until the next day 5/25/2011. It has been confirmed that Watson's amendment which contained the PIV certification to the '739 patent was not received via the EDR until 18:17:41. This is both after the 4:30 cutoff time for submissions that is the policy of the ESG and after the 6:00 pm closing time of the OGD Document Room which has been used on a few ocassions for adjustment of the receipt date. Since Watson's submission time is clearly after each of these cutoffs their submission date for the PIV cert to the '739 patent will remain 5/25/2011 making them a subsequent applicant.
OGD currently has 3 ANDAs pending for Tranexamic Acid Tablets, 650 mg: Watson's ANDA 202093, Apotex's ANDA 202286 and Amerigen's ANDA 203256. Watson's first PIV certification to the '739 patent was rec'd on 5/25/2011 and Amerigen's original ANDA wasn't submitted until 10/24/2011. Therefore, Apotex will be the sole applicant that is eligible for 180 day exclusivity for this product.
ANDA is eligible for second TA only due to their PIV certification being rec'd one day after Watson.

UPDATE - 11/28/2012- The Office of Generic Drugs has decided to Fully Approve Watson's ANDA. This will be done by considering Watson's patent amendment to the '739 patent as being received on 5/24/2011. In doing so, Watson will no longer be blocked from Full Approval by Apotex's 180 day exclusivity.

ANDA is eligible for Full Approval with an award of 180 day exclusivity.

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 3:59 PM
To: Park, Sarah Soojung; Park, Linda; Park, Chan H
Subject: RE: ANDA 202093/Watson/Tranexamic Tab

I concur.

Koung

From: Park, Sarah Soojung
Sent: Wednesday, November 07, 2012 3:04 PM
To: Park, Linda; Lee, Koung U; Park, Chan H
Subject: FW: ANDA 202093/Watson/Tranexamic Tab

HI Linda,

The Labeling AP Summary signed by Koung Lee on 12/31/2011 is still acceptable.

Thanks,
Sarah

4. ***Paragraph IV Evaluation*** **PIV's Only**
David Read **Date 12/26/12**
OGD Regulatory Counsel **Initials SL**
Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:Changes saved to the v drive.

5. ***Quality Division Director /Deputy Director Evaluation*** **Date 11/8/2012**
Chemistry Div. **II (Smith)** **Initials GJS**
Comments:CMC Acceptable.

6. ***First Generic Evaluation*** **First Generics Only**
Frank Holcombe **Date 12/27/12**
Assoc. Dir. For Chemistry **Initials rlw/for**
Comments: (First generic drug review)
This ANDA was granted tentative approval on February 16, 2012.

OGD Office Management Evaluation

7. Peter Rickman **Date 12/27/12**
Director, DLPS **Initials rlw/for**
Para.IV Patent Cert: Yes☐☐No☐
Pending Legal Action: Yes ☐☐No ☐

Petition: Yes☐ No☐
Comments: This ANDA was granted tentative approval on February 16, 2012. Final approval at that time was blocked by the RLD holder's new dosage form (NDF) exclusivity that would expire on November 13, 2012. Refer to the administrative summary prepared at the time of the tentative approval. As the NDF exclusivity has now expired, Watson's ANDA is eligible for final approval.

Final-printed labeling (FPL) found acceptable for approval 11/7/12. No REMS is required.

CMC found acceptable for approval (Chemistry Review #3) 9/19/12.

AND/OR

8. Robert L. West
Deputy Director, OGD

Date 12/27/12
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 10/17/12 (Verified 12/27/12). No "OAI" Alerts noted.

Watson provided paragraph IV certifications to the '739, '106 and '795 patents. The agency has concluded that each of these patents were submitted by the NDA holder after Watson submitted its ANDA and therefore litigation, if any, with respect to these patents creates no statutory stay of approval. There are no additional patents or exclusivity currently listed in the "Orange Book" for this drug product.

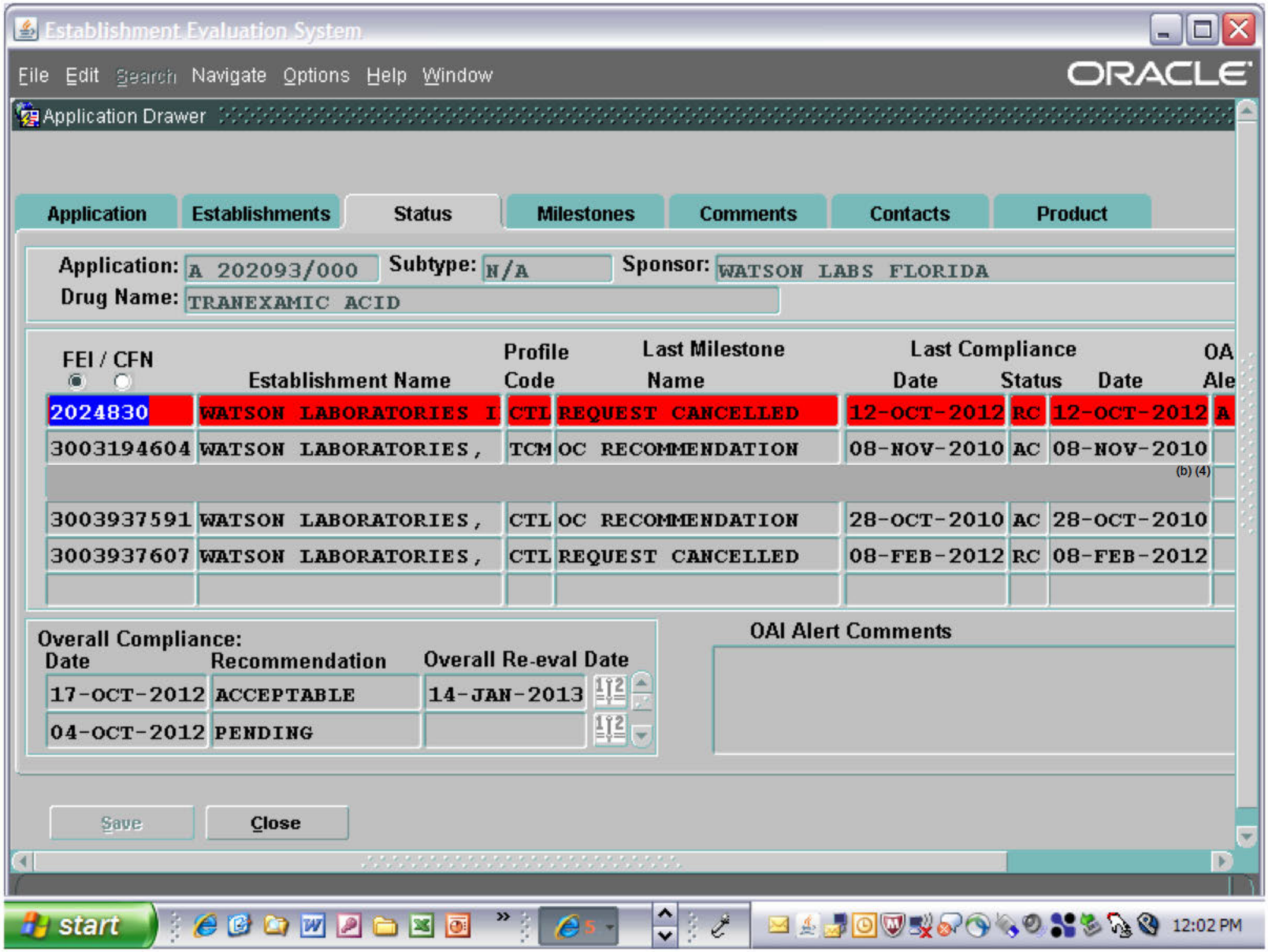
This first-generic ANDA is recommended for approval.

9. ***OGD Director Evaluation***
Gregory Geba
Deputy Director, OPS

Comments: RLWest for Gregory P. Geba, M.D., M.P.H. 12/27/12.
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

Comments:

10. Project Manager



Reference ID: 3236938

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	

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/

LINDA M PARK
12/27/2012

M E M O R A N D U M

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

DATE: December 21, 2012

FROM: Martin Shimer
Branch Chief, Regulatory Support Branch, Office of Generic Drugs (HFD-600)

TO: ANDA 202093 (Tranexamic Acid Tablets, 650 mg)

SUBJECT: Receipt Date of Watson's Paragraph IV Certification to the '739 Patent

Watson Laboratories, Inc.-Florida (Watson) submitted abbreviated new drug application (ANDA) 202093 for Tranexamic Acid Tablets, 650 mg, on Friday, July 23, 2010, to the U.S. Food and Drug Administration (FDA) via FDA's electronic submissions gateway (ESG), and initially was considered received the following Monday, July 26, 2011. Apotex Inc. (Apotex) submitted ANDA 202286 for the same product via FDA's ESG; it was submitted and received on August 31, 2010. The reference listed drug for this ANDA 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, so the date of receipt of the original ANDAs is not significant.

Of significance are the following events, all of which occurred on May 24, 2011. Early that day, the U.S. Patent and Trademark Office issued U.S. Patent No. 7,947,739 (the '739 patent). FDA received the '739 patent from Ferring for listing in FDA's Orange Book under the NDA 22430 for Lysteda at 8:47:52 a.m. At 2:03:57 p.m., Apotex transmitted via ESG an amendment containing a paragraph IV certification to the '739 patent, and it was received at 2:07:37 p.m. At 6:16:38 p.m., Watson transmitted via ESG a similar amendment, and it was received at 6:17:41 p.m. Both applicants sent timely notifications to the NDA/patent holder(s).

The issue presented by these circumstances is whether Watson and Apotex are co-first applicants with paragraph IV certifications to the '739 patent, or whether Apotex alone is the first applicant. This question does not arise because Apotex submitted its amendment about four hours before Watson. The agency has rejected a minute-by-minute, "first in time" determination of first applicant status, and instead employs a "multiple-first-applicant" approach such that applicants that submit on the same day can share "first applicant" status.[1] Rather, the issue here concerns what constitutes the end of the day for the purposes of determining the date of receipt of ANDA submissions. The issue arose because Watson's amendment was successfully submitted to the

[1] See Letter to J. Haggerty, Mylan Pharmaceuticals, Inc. fr. K. Webber, FDA Office of Generic Drugs re ANDA 076594 for Modafinil Tablets (April 4, 2012) (Modafinil Letter); see also Guidance for Industry on *180-Day Exclusivity When Multiple ANDAs Are Submitted on the Same Day*, at 5 (July 2003) (Camping Guidance).

ESG at approximately 6:16 p.m. Under the practice of FDA's Center for Drug Evaluation and Research (CDER) of treating submissions to the ESG that are made after 4:30 p.m. as officially "received" on the next business day, FDA initially regarded this amendment as received on the next business day, May 25, 2011. This approach is consistent with FDA's Electronic Submissions User Guide, which states that "[i]f your submission was received at (Center name or Programmatic entity) after 4:30 PM EST, the official receipt date for the submission is the next government business day."[2]

The official date on which FDA "receives" an amendment to an ANDA that contains a paragraph IV certification 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 (see section 505(j)(5)(B)(iv)(II)(bb) of the Act). Where the first paragraph IV certification for a drug is submitted in an amendment, and not in an original application, FDA uses the date the amendment containing the paragraph IV certification is "received" as the date on which first applicant status is determined.[3] As described by the agency in its decision concerning 180-day exclusivity for acarbose tablets, for paper submissions, this date corresponds to the date it was date stamped by the mailroom, "[w]hen an ANDA containing the paragraph IV certification is determined, upon review, to have been substantially complete as of the day it was submitted to FDA, it will be deemed to have been received as of the date it was submitted (i.e. date-stamped by appropriate FDA mail-room.)"[4]

For electronic submissions, the electronic gateway is open 24 hours a day and, although applicants receive a time stamp that tells FDA and the applicant the exact time the transmission to the ESG began and was concluded, as mentioned above, CDER considers the official receipt date of submissions that are time-stamped after 4:30 PM on a business day to be the next business day. Because Watson would not be eligible as a first applicant for the purposes of 180-day exclusivity for Tranexamic Acid Tablets if the company's amendment was considered "received" on May 25, 2011, but would be eligible for first applicant status if it were considered "received" on May 24, 2011, the date it was submitted to the ESG, FDA offered Watson the opportunity to comment on the question of the ANDA's proper receipt date, which the company did in a letter from its attorney dated November 26, 2012.[5] In this letter, Watson sets forth several bases on which the company believes application of the 4:30 p.m. cut-off time in determining the receipt date for submissions made through the ESG is arbitrary and capricious and procedurally defective in violation of the Administrative Procedure Act.[6]

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[2] *Electronic Submissions User Guide*, at 4.8.2 (Feb. 9, 2010), available at: http://www.accessdata.fda.gov/esg/userguide/webhelp/default.htm.

[3] Mylan Letter, at 5; Camping Guidance, at 4.

[4] See, e.g., Letter to W. Rakoczy fr. G. Buehler, OGD, at 6, n.10 (May 7, 2008) (Acarbose Letter) (addressing 180-day exclusivity for acarbose tablets).

[5] Letter to G. Geba fr. C. Landmon re Watson Laboratories, Inc.-Florida's ANDA No 202093 for Tranexamic Acid Tablets, 650 mg (Nov. 26, 2012).

[6] Id. at 3-11.

The critical question here is what constitutes the end of one "day" and the beginning of the next day for the purposes of determining date of receipt. Upon review of the relevant facts, FDA has determined that the agency has an inconsistent practice with respect to what time a "day" ends. As indicated above, CDER's ESG applies a 4:30 p.m. cut-off time for the close of the day. Notification of this time is available in FDA's *Electronic Submissions User Guide*, on FDA's website page regarding ESG,[7] and is indicated on computer-generated acknowledgements of electronic submissions sent to individual applicants. With respect to non-ESG submissions, however, CDER accepts submissions in its physical document room until 6:00 p.m.[8] In addition, in implementing a GDUFA provision that required an application pending on October 1, 2012, that has not received a tentative approval prior to that date to pay a backlog fee, FDA's Office of Generic Drugs recently considered requests for withdrawals of ANDAs for the purpose of avoiding the payment of the backlog user fee to have been received as of September 28th (the business day previous to October 1) if they were received by 11:59:59 p.m. on September 28, 2012. CDER routinely issues NDA and ANDA approvals after 4:30 PM and after 6:00 p.m. (the time the paper document room closes) and for regulatory purposes considers the action to have been taken on the date that the approval was issued, not the next business day.[9] To note, CDER recently decided to extend the business day for electronic submissions to 11:59:59 p.m. for purposes of determining the official receipt date, although this decision has not been publicly announced.

FDA also notes that it has made several public statements that could be construed to support a 11:59:59 p.m. cut-off for the day. First, in FDA's guidance for industry on *180-Day Exclusivity When Multiple ANDAs Are Submitted on the Same Day*, the agency announced its decision "to treat 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] Second, the agency's statement in the Acarbose Letter referenced above could be construed to mean the date is the critical fact for the purposes of determining receipt for review, and not a particular time of day. Third, FDA, in reiterating in the Modafinil Letter the agency's rejection of the first-in-time minute-by-minute approach for first-applicant determination, stated that:

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[7] *Electronic Submissions Gateway Frequently Asked Questions*, available at http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/ucm114807 htm

[8] *Generic Drugs: Information for Industry*, available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm142112.htm

[9] *The Medicines Co. v. Kappos*, 731 F. Supp. 2d 470, 473 (E.D. Va. 2010) (noting CDER's 4:30 p.m. cut-off with respect to receipt of submissions and 11:59 cut-off for issuance of approvals).

[10] Camping Guidance, at 5. See also draft guidance for industry on *Providing Regulatory Submissions in Electronic Format — Receipt Date*, at 2 (June 2007) ("[f]or a submission entirely in an electronic format, the FDA has determined the official receipt date to be the date the submission arrived at the appropriate, designated document room (e.g., submission on a CD-ROM) or into the electronic submission gateway (ESG)"); compare id., at 3("[i]f a submission passes technical validation, then the receipt date will be the business day on which the submission arrived at the appropriate, designated document room or into the ESG).

> [W]e do not agree … that when multiple substantially complete applications are submitted on the same first day, the precise time of day on which an ANDA is stamped or the lowest ANDA number determines which application is the first-filed application for the purposes of determining entitlement to 180-day generic drug exclusivity under section 505(j)(5)(B)(iv) of the Act. Rather, we employ a "multiple-first-applicant" approach, and have determined that [an applicant that submitted an ANDA later in the day than another] would share "first applicant" status as to the [relevant] patent with any other ANDA applicants who filed [an] ANDAs with paragraph IV certifications to the [relevant]patent the same day that [the first-in-day applicant] filed its ANDA.[11]

Although none of these statements is facially inconsistent with CDER's use of 4:30 p.m. cut-off to the business day, FDA acknowledges that there is a lack of clarity in these statements about what constitutes a "day."

In light of CDER's inconsistent practices and FDA's statements that could be construed to support Watson's position, FDA has determined Watson's amendment containing the PIV certification to the '739 patent to be received as of May 24, 2011. To note, FDA has not identified any other instance in which an ANDA applicant made a submission through the ESG that was received after 4:30 p.m. but before 11:59:59 p.m., and as a result lost its first-applicant status for the purposes of determining eligibility for 180 day exclusivity. Thus, it does not appear that the agency is providing Watson any benefit that it has denied another applicant in similar circumstances. In addition, FDA's anticipated change from 4:30 p.m. to 11:59:59 p.m. for determining official receipt date for electronic submissions will avoid any similar issues in the future.

[11] Modafinil Letter, at 1.

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
12/21/2012

ROUTING SHEET

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

Division: II	Team: 7	PM: Frank Nice

Electronic ANDA: Yes ☒ No ☐

ANDA #:202093
Firm Name:Watson Laboratories, Inc.-Florida (WLF)
ANDA Name:Tranexamic Acid Tablets, 650 mg_
RLD Name:Lysteda

Electronic AP Routing Summary Located:
V:\Chemistry Division II\Team 7\Electronic AP Summaries

AP/TA Letter Located:
V:\Chemistry Division II\Team 7\Final Version For DARRTS\AP TA Letters

Project Manager Evaluation: **Date: 10/26/11 Initials:** fjn

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

Original Rec'd date July 26, 2010	Date of Application July 23, 2010	Date Acceptable for Filing October 18, 2010
Patent Certification (type) PIV	Date Patent/Excl. expires March 4, 2025	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) 10/25/11 Addendum Needed: Yes ☐ No ☒ Comment:
Date of Acceptable Bio 8/29/11 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location:)
Date of Acceptable Labeling 2/28/11 Attached labeling to Letter: Yes ☒ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) n/a

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: 1/3/12 REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☐

x Regulatory Support

x Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: 1/27/12

x Division

☒ 1st Generic Review

X 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: 1/5/2012**

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 2/16/12 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 7/26/2010, BOS=Lysteda NDA 22-430, PI cert, NDF exp. 11/13/12. ANDA ack for filing on 7/26/2010 (LO dated 11/18/2010). Patent Amendment rec'd on 5/25/2011-PIV to the '739. Patent Amendment rec'd on 7/12/2011-notice sent via (b) (4) to Ferring in East Hanover NJ with notice delivered on 5/25/2011, notice sent to Fish and Richardson in New Castle DE with notice delivered on 5/25/2011, notice sent to Ferring NV in Hoofddorp Netherlands with notice delivered on 5/30/2011, CA 11 CV 0481 filed on 7/7/2011 in the D of NV for infringement of the '739 patent. Patent Amendment rec'd on 10/13/2011-PIV to the '106. Patent Amendment rec'd on 11/30/2011-notice sent via (b) (4) to Ferring in Parsippany NJ with notice delivered on 10/13/2011, notice sent via (b) (4) to Ferring BV in Hoofddorp Netherlands with notice delivered on 10/14/2011, notice sent to Fish and Richardson in Wilmington DE with notice delivered on 10/13/2011, CA 11 CV 0853 filed in the D of NV on 11/25/2011 for infringement of the '106. There are no 30 month stays of approval associated with either of the two CAs brought in the D of NV as the patents associated with these CAs were not listed in the OB at the time this ANDA was submitted. Application is eligible for TA only due to the unexpired NDF exclusivity. A 180 day exclusivity analysis has not been completed for this drug product.	

2. ***Labeling Endorsement***

Reviewer, Sarah Park:
Date1/3/12
Initialssp

Labeling Team Leader, Koung Lee:
Date1/3/12
Initialskl

REMS required?
☐Yes ☒No

REMS acceptable?
☐Yes ☐No ☒n/a

Comments:
Hi Frank,

The Labeling AP Summary signed by Koung Lee on 12/31/2011 is still acceptable.

Thanks,

Sarah

Happy New Year!

I concur however, please revise the second paragraph.

Reference is also made to your amendments dated February 18, April 26, July 22, August 3, October 6, October 6, and October 21, and November 29, 2011.

Change to:

Reference is also made to your amendments dated February 18, April 26, July 22, August 3, October 6 and 21, and November 29, 2011.

Koung

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

David Read **Date 27Jan2012**
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 1/25/2012**

Chemistry Div. **II (Fang)** **InitialsGJS**
Comments:CMC Acceptable.

5. ***First Generic Evaluation*** **First Generics Only**

Frank Holcombe **Date 2/1/6/12**
Assoc. Dir. For Chemistry **Initials rlw/for**
Comments: (First generic drug review)
N/A. By endorsing this tentative approval package, the CMC division director has concurred that there are no precident setting issues associated with the CMC review and approval of this ANDA. Thus, no further CMC review is necessary.

OGD Office Management Evaluation

6. Peter Rickman **Date 2/16/12**

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 histories. Office-level bio endorsed 4/7/11, 7/29/11 and 8/29/11.

Labeling found acceptable for tentative approval (Approval Summary #2) 12/31/11, as endorsed 1/3/12.
No REMS is required.

CMC found acceptable for final approval (Chemistry Review #2) 10/25/11, 1/25/12.

7. Robert L. West **Date 2/16/12**
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 2/15/12 (Verified 2/16/12). No "OAI" Alerts noted.

Watson Laboratories - Florida provided paragraph IV certifications to the '739 and '106 patents currently listed in the "Orange Book". Watson was sued within the 45-day periods on each of these patents. There can be no 30-month stay of approval associated with this litigation because neither patent was listed in the"Orange Book" when this ANDA was submitted. There is a new dosage form (NDF) exclusivity listed in the "Orange Book" that is due to expire on November 13, 2012. There are no additional patents or exclusivity listed in the current "Orange Book" for this drug product.

This ANDA is recommended for tentative approval. Final approval is currently blocked by Ferring's NDF exclusivity until November 13, 2012.

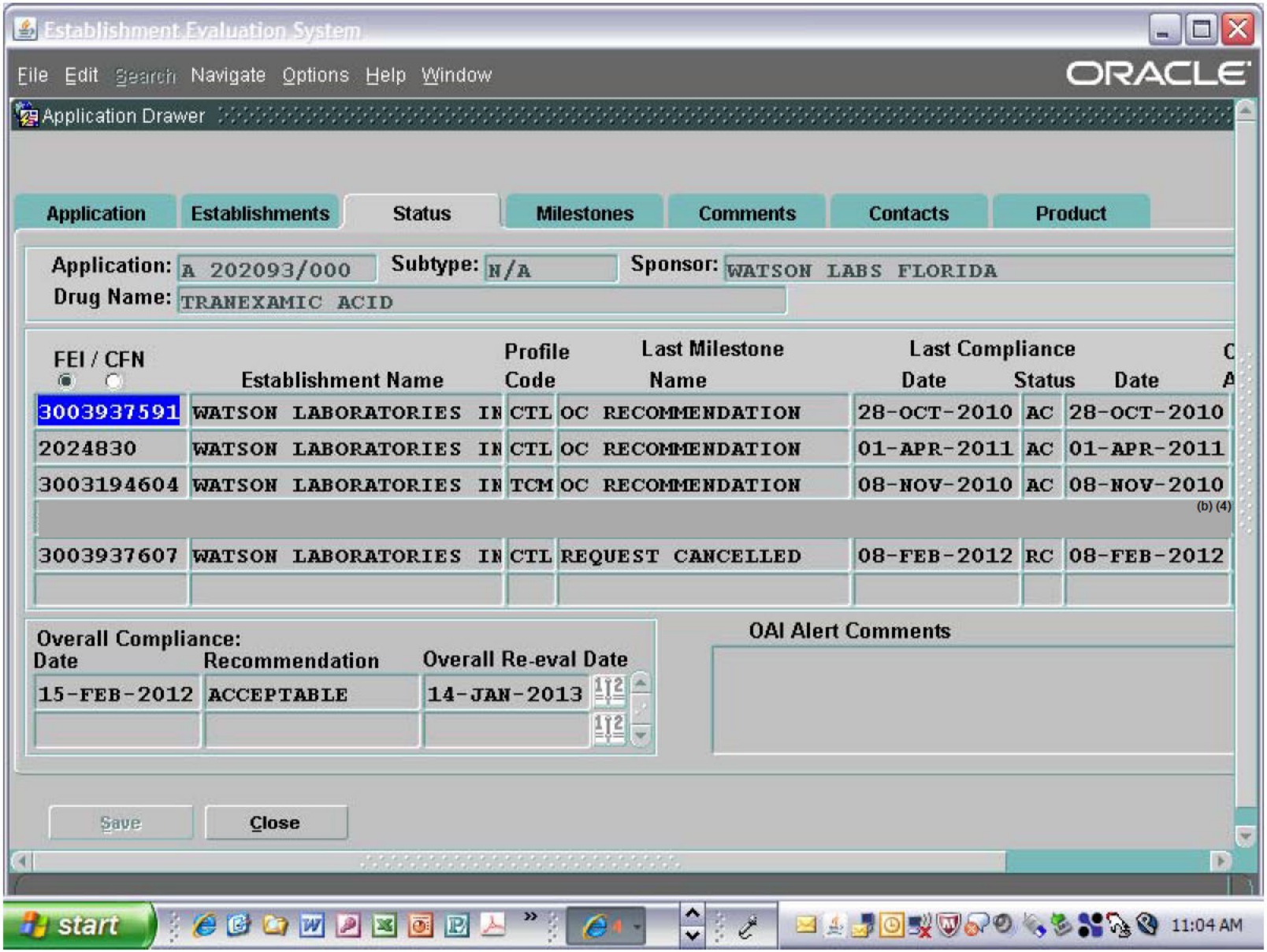
8. ***OGD Director Evaluation***
Keith Webber
Deputy Director, OPS
Comments: RLWest for Keith Webber, Ph.D. 2/16/12.
First Generic Approval ☒
PD or Clinical for BE ☐
Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

Comments: First-generic tentative approval for the tablet dosage form. Multiple ANDAs have been approved for Tranexamic Acid Injection.

9. Project Manager
Date 2/16/12
Initials fjn

Check Communication and Routing Summary into DARRTS

EER DATA:



Reference ID: 3088786

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	

Exclusivity Data

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

Additional information:

Applications referencing NDA 021992 Pristiq (Desvenlafaxine Succinate) and challenging the listed patent may be received by the Agency beginning on Feb 29, 2012, four years from the NDA approval date.

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

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/s/

FRANK J NICE
02/16/2012

Record of Telephone Conversation

On Oct.6, 2011, a teleconference was made with Watson, to communicate the following minor chemistry deficiencies related to ANDA 202093 (Tranexamic acid tablets 650 mg):

1. The product is still labeled as [redacted] (b) (4) tablets, while the ANDA does not state such.

2. The drug product specification describes the product as "Oval shape tablets debossed with "WPI 3720" on one side of the tablet and film coated". However, the samples we received were not debossed.

The firm acknowledged the 2 minor deficiencies and explained briefly that the commercial product will be immediate release tablets and the label will be revised. For the debossing, they will clarify in the amendment that the commercial product will be debossed.

ANDA Number:
202093

Product Name:
Tranexamic acid tablets, 650 mg

Firm Name:
Watson

Firm Representative:
Radha Goolabsingh

Phone Number:
954-358-6149

FDA Representative:
Xiaobin Zhao, Ph.D.

Signatures:

Xiaobin Zhao

CC: ANDA 202093

V:\FIRMSAM\ \TELECONS\ 202093 .doc

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/s/

XIAOBIN ZHAO
10/06/2011

FRANK J NICE
10/06/2011

Record of Telephone Conversation

On Sep 22, 2011, a teleconference was made with Watson to communicate the following minor chemistry deficiencies in the 7/25/2011 Quality Minor Amendment related to ANDA 202093 (Tranexamic acid tablets, 650 mg):

(b) (4)

5. Update dissolution spec in drug product release and stability studies.
-They agree to update spec with the recently accepted NLT (b) (4)% Q in 90 min

6. Availability of 24 month stability data
- Only 18 month data available at this point. The firm will provide updated dissolution result. 24 month data will be available end of year.

The firm committed to submit related information in an amendment in less than 10 days.

ANDA Number:
202093

Product Name:
Tranexamic acid tablets
650 mg

Firm Name:
Watson Laboratories Inc. Florida

Firm Representative:
Janet Vaughn (RA)
(b) (6)
Radha Goolabsingh
Manager, Regulatory Affairs

Phone Number:
(b) (4)

FDA Representative:
Xiaobin Zhao, Ph.D.

Signatures:

Xiaobin Zhao

CC: ANDA 202093

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/s/

XIAOBIN ZHAO
09/22/2011

RADHIKA RAJAGOPALAN
09/22/2011

BIOEQUIVALENCE AMENDMENT

ANDA 202093

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Watson Laboratories,Inc. - Florida

TEL: (954) 358-6147

ATTN: Radha Goolabsingh

FAX: (954) 358-6350

FROM: Chitra Mahadevan

FDA CONTACT PHONE: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalence data submitted on July 23, 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 26, 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 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: 202093

APPLICANT: Watson Laboratories, Inc. - Florida

DRUG PRODUCT: Tranexamic Acid Tablets, 650 mg

The Division of Bioequivalence II (DB2) has completed its review of your submission acknowledge on the cover sheet. The following deficiency has been identified:

You have conducted the dissolution testing using the FDA-recommended dissolution method. However, with this method, your test product showed incomplete drug release at 120 min. Thus, the DBE agrees with the use of your proposed method as a quality control dissolution method but with a tightened specification. Please acknowledge the following FDA-recommended data-driven specification for which your test product meets at the S1 level:

USP Apparatus:	II (Paddle)
Speed (rpm):	50 rpm
Medium:	pH 1.2 SGF
Volume (mL):	900mL
Temperature:	37°C ±0.5°C

Specification: NLT (b) (4) % (Q) in 90 min.

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

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/s/

BARBARA M DAVIT
07/29/2011

QUALITY DEFICIENCY - MINOR

ANDA 202093

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

APPLICANT: Watson Laboratories, Inc.-Florida TEL: (954) 358-6125

ATTN: Janet Vaughn FAX: (954) 358-6350

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

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated July 26, 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 November 9, 2010.

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: 202093

APPLICANT: Watson Laboratories, Inc.-Florida (WLF)

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.
9.

Following this page, 1 Page Withheld in Full as (b)(4)

(b) (4)

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

1. In the QbR-QOS, you have referenced the RLD as a modified release dosage form. The RLD is not labeled as such. In addition, Tranexamic acid tablets are referred to as (b) (4) in multiple sessions of your submission. Please comment.

2. Please provide dissolution data per DBE deficiency letter request faxed to you on 2/25/2011. Two-tiered dissolution test with more than one time point for quality control may be applied to accurately reflect the physiological condition.

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

4. 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
Acting 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
05/03/2011
For Glen Smith,

BIOEQUIVALENCE AMENDMENT

ANDA 202093

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Watson Laboratories, Inc - Florida TEL: (954) 358-6147

ATTN: Radha Goolabsingh FAX: (954) 358-6350

FROM: Chitra Mahadevan FDA CONTACT PHONE: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalence data submitted on July 23, 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 November 9, 2010.

The Division of Bioequivalence has completed its review of the submission referenced above and has identified deficiencies which are presented on the attached **3** 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 **Bioequivalence Long Term Stability**

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.

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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 DEFICIENCIES

ANDA: 202093

APPLICANT: Watson Laboratories, Inc. - Florida

DRUG PRODUCT: Tranexamic Acid Tablets, 650 mg

The Division of Bioequivalence (DBE) has completed its review of your submissions acknowledged on the cover sheet. The following deficiencies have been identified:

1. We acknowledge that you have submitted the long-term storage stability data, i.e. 44 days at -70°C. However, according to your study report, samples were stored at -20°C at the clinical center before they were shipped to the analytical center. Please provide long term stability data at -20°C that is sufficient to cover the time period when samples were stored at the clinical center at -20°C, i.e. at least 18 days (from June 4 to June 22, 2010).

2. As indicated in the DBE deficiency letter (2/28/2011), your dissolution testing is incomplete. Please conduct and submit dissolution testing on twelve (12) dosage units of the test and reference product using the following FDA-recommended dissolution method:

USP Apparatus :	II (Paddle)
Speed (rpm) :	50
Medium :	Water
Volume (mL) :	900 mL
Temperature :	37°C ± 0.5°C
Sampling Times :	15, 30, 45, 60, 90, 120 minutes, and/or until 80% of the labeled amount of drug is dissolved

Please submit the comparative dissolution results which should include the individual tablet data as well as the mean, range, % coefficient of variation (CV) at each time point for the 12 tablets tested, and dates of dissolution testing for each drug product. Also, please resubmit the dissolution testing data summary table with the above data.

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
04/07/2011

BIOEQUIVALENCE AMENDMENT

ANDA 202093

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Watson Laboratories, Inc - Florida TEL: (954) 358-6147

ATTN: Radha Goolabsingh FAX: (954) 358-6350

FROM: Chitra Mahadevan FDA CONTACT PHONE: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalence data submitted on July 23, 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 **3** 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 **Bioequivalence Long Term Stability**

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 DEFICIENCIES

ANDA: 202093

APPLICANT: Watson Laboratories, Inc. - Florida

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 bioequivalence studies will be done at a later date. The following deficiencies have been identified:

1. Your dissolution testing is incomplete. Please conduct and submit dissolution testing on twelve (12) dosage units of the test and reference product using the following FDA-recommended dissolution method:

USP Apparatus :	II (Paddle)
Speed (rpm) :	50
Medium :	Water
Volume (mL) :	900 mL
Temperature :	37°C ± 0.5°C
Sampling Times :	15, 30, 45, 60, 90, 120 minutes, and/or until 80% of the labeled amount of drug is dissolved

Please submit the comparative dissolution results which should include the individual tablet data as well as the mean, range, % coefficient of variation (CV) at each time point for the 12 tablets tested, and the dates of dissolution testing for each drug component. Also, please resubmit the dissolution testing data summary table with the above data.

The dissolution method is available in the public dissolution database on the Office of Generic Drugs (OGD) website, http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm

2. The long-term storage stability data that you provided, which is 8 days at -70°C or -20°C, does not cover the maximum storage period of the study samples for the submitted bioequivalence studies, which is 34 days. Please provide long term storage stability data of tranexamic acid in frozen plasma for at least 34 days.

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 202093

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2773
240-276-8995

TO: Watson Laboratories, Inc. - Florida

TEL: 954-358-6125

ATTN: Janet Vaughn

FAX: 954-358-6350

FROM: Sarah Park

Dear 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:	202093
Date of Submission:	July 23, 2010 (Original)
Applicant's Name:	Watson Laboratories, Inc. - Florida
Established Name:	Tranexamic Acid Tablets, 650 mg

Please 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 #: 202093 **FIRM NAME**: WATSON LABORATORIES INC. -FLORIDA

PIV: NO **Electronic or Paper Submission:** ELECTRONIC (GATEWAY)

RELATED APPLICATION(S): NA

First Generic Product Received? YES

DRUG NAME: TRANEXAMIC ACID
DOSAGE FORM: TABLETS, 650 MG

Review Team: (Bolded/Italicized & Checked indicate Assignment or DARRTS designation)

Quality Team: DC2 Team 21 ☒***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: JULY 23, 2010 **Received Date**: JULY 26, 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 FELECIA (LISA) TAN **Date 11/9/2010**	**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

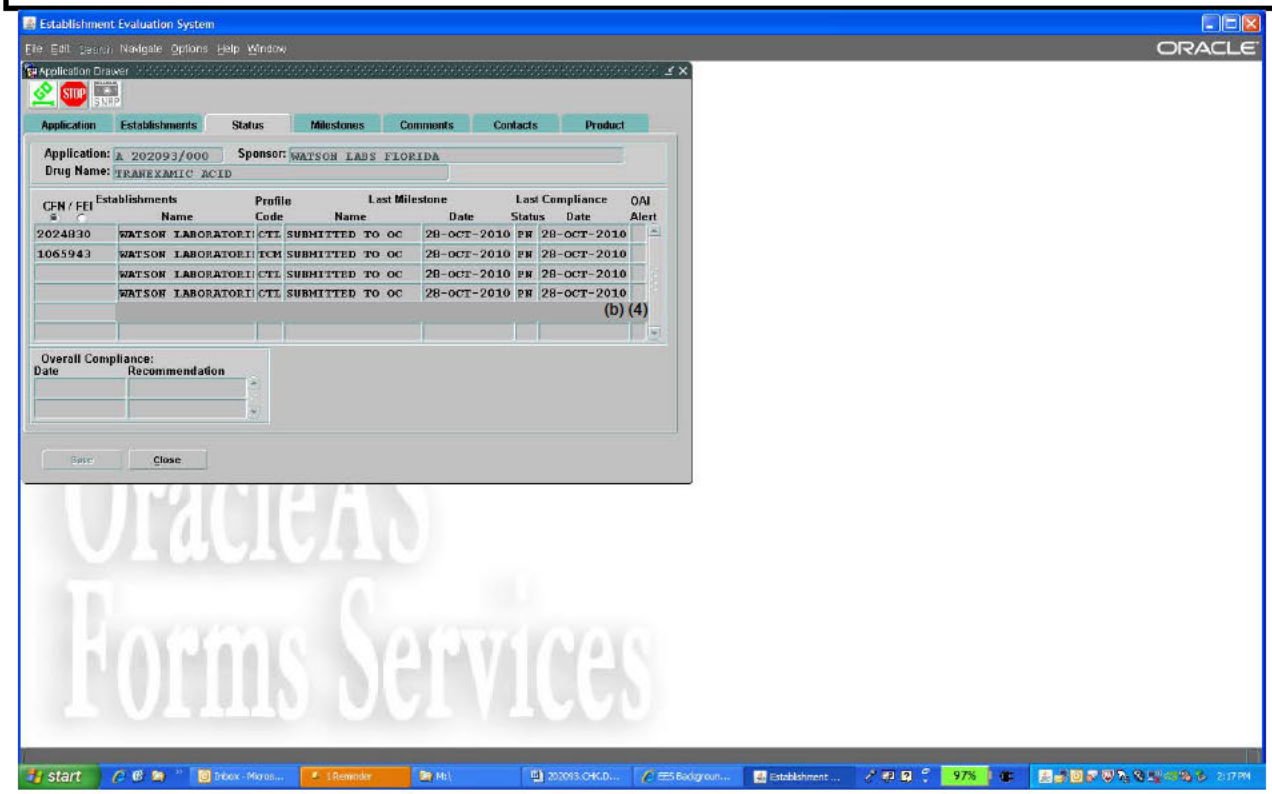
ADDITIONAL COMMENTS REGARDING THE ANDA:

NOTES: THE NEW BIO GUIDANCE FOR INDUSTRY FOR THIS DRUG PRODUCT IS ATTACHED BELOW.
THE 1ST GENERIC BIO REVIEW WAS COMPLETED AND ENTERED INTO DARRTS ON 10/18/2010.

CONTACT INFO: JANET VAUGHN

REQUEST:
1.) PLEASE PROVIDE BIOANALYTICAL VALIDATION REPORT AND PHARMACY RECORDS AND DISPENSING LOGS FOR THE TEST AND REFERENCE PRODUCTS FOR BOTH FAST AND FED STUDIE
2.) SUBMIT CGMP FOR API MANUF.

COMMUNICATION:
10/28/2010: EMAILED FOR ABOVE ITEMS.
11/9/2010: REQUESTED ITEMS RECED.



Reference ID: 2863866

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 202093 **FIRM NAME** Watson Laboratories, Inc.

DRUG NAME Tranexamic acid

DOSAGE FORM Tablets, 650 mg

SUBJ: Request for examination of: if Watson's Tranexamic acid Tablets, 650 mg, satisfies the statutory requirements of "completeness".

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☐	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason: N/A

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

ACCEPTABLE FOR FILLING – ADDITIONAL INFO. REQUESTED:

Contains Nonbinding Recommendations

Draft Guidance on Tranexamic Acid

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: **Tranexamic Acid**

Form/Route: Tablets/Oral

Recommended studies: 2 studies

Type of study: Fasting
Design: Single-dose, two-way crossover *in-vivo*
Strength: 650 mg
Subjects: Normal healthy non-pregnant females, general population.

Type of study: Fed
Design: Single-dose, two-way crossover *in-vivo*
Strength: 650 mg
Subjects: Normal healthy non-pregnant females, general population.

Analytes to measure (in appropriate biological fluid): Tranexamic acid in plasma

Bioequivalence based on (90% CI): Tranexamic acid

Waiver request of in vivo testing: Not Applicable

Dissolution test method and sampling times: Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

Fed Bioequivalence studies:

Co-administration of food with oral drug products can influence BE. Therefore, fed BE studies can determine whether test and RLD products are bioequivalent when co-administered with meals. We usually recommend a single-dose, two-period, two-treatment, two-sequence, crossover study for fed BE studies.

When a fasting in vivo BE study is indicated for an orally administered, immediate release product, we also recommend that applicants conduct a fed study, except as follows:

- When both test product and RLD are rapidly dissolving, have similar dissolution profiles, and contain a drug substance with high solubility and high permeability (BCS Class I)

- When the *dosage and administration* section of the RLD labeling states that the product should be taken only on an empty stomach (e.g., the labeling states that the product should be administered one hour before or two hours after a meal).

For orally administered, immediate release products labeled to be taken only with food, fasting and fed studies are recommended, except when serious adverse events are anticipated with fasting administration. In these cases, we recommend that applicants conduct only a fed study; a fasting study is not recommended.

For all orally administered, modified release drug products, we recommend that applicants conduct a fed BE study in addition to a fasting BE study. These studies are usually conducted on the highest strength of the drug product, unless safety considerations preclude the use of that dose in study subjects.

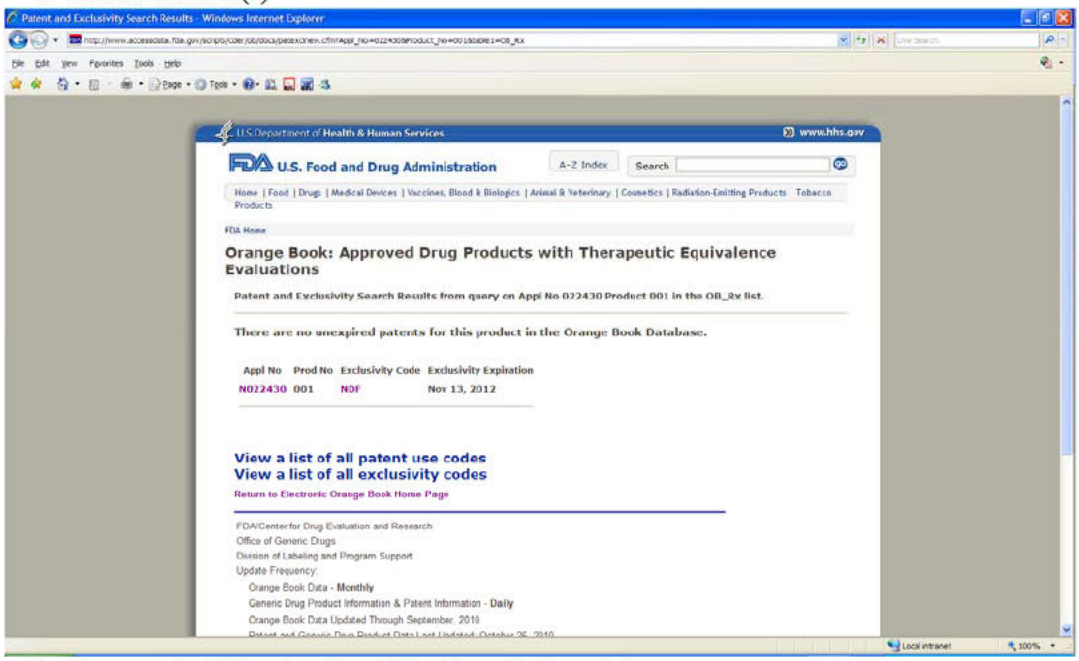
b. Test Meal Composition

We recommend that applicants conduct fed BE studies using meals that provide the greatest effects on GI physiology and systemic drug availability. We recommend a high-fat (approximately 50 percent of total caloric content of the meal), high-calorie (approximately 800 to 1000 calories) test meal for fed BE studies. This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively[1]. The caloric breakdown of the test meal should be provided in the study report.

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: JULY 23, 2010 YES	☒
1.2.1	**Form FDA 3674** **(PDF)** **YES** OPTION B	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** NA **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) YES	☒

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)  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? N/A b. Expiration of Pediatric Exclusivity? N/A 4. Exclusivity Statement: YES NO UNEXPIRED EXCLUSIVITY	☒
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 (b) (4) 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) N/A	☒
1.12.11	**Basis for Submission** NDA# : 22-430 YES Ref Listed Drug: LYSTEDA YES Firm: XANODYNE PHARMACEUTICALS INC. YES 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 SAME 2. Active ingredients SAME 3. Inactive ingredients JUSTIFIED 4. Route of administration SAME 5. Dosage Form SAME 6. Strength SAME	☒
1.12.14	**Environmental Impact Analysis Statement** YES 21CFR25.31	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): NA PLEASE SEE NEW DBE GUIDANCE FOR INDUSTRY FOR THIS DRUG PRODUCT ATTACHED ABOVE.	☒
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.) ++COMMITMENT FOR SPL ON COVER.	☒
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 SUBMITTED** **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) (b) (4) 2. Function or Responsibility YES 3. Type II DMF number for API (b) (4) 4. CFN or FEI numbers NOT PROVIDED	☒
3.2.S.3	**Characterization SUBMITTED**	☒
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: a. Drug Substance YES b. Same lot number(s) 1. **Drug Substance** Tranexamic Acid– (b) (4) WLF's receiving number (b) (4) 2. **Reference Standards** Reference Standard / Manufacturer / Lot Number / Retest/Expiration (b) (4) **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 SUBMTITED**	☒
3.2.S.5	**Reference Standards or Materials SUBMITTED**	☒
3.2.S.6	**Container Closure Systems DMF**	☒
3.2.S.7	**Stability DMF**	☒

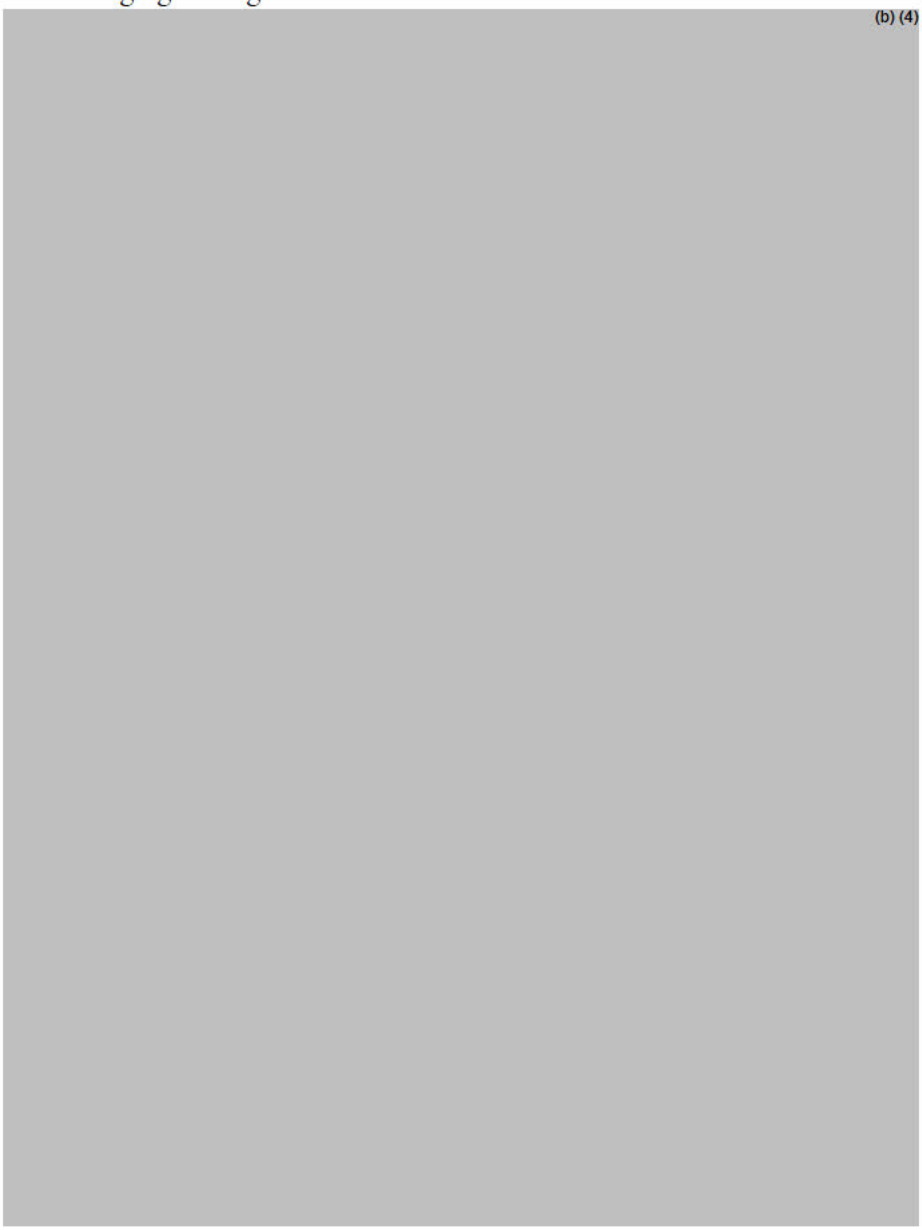
MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1. Unit composition YES 2. Inactive ingredients and amounts are appropriate per IIG JUSTIFIED PER IIG	☒
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 WATSON LAB INC FLORIDA 4. CFN or FEI numbers 3003194604 **3.2.P.3.2 Batch Formula** YES **3.2.P.3.3 Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified (b) (4) 3. If sterile product: Aseptic fill / Terminal sterilization N/A 4. Reprocessing Statement 21CFR211.115 **3.2.P.3.4 Controls of Critical Steps and Intermediates SUBMITTED** **3.2.P.3.5 Process Validation and/or Evaluation N/A** 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 **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 SUBMITTED** **3.2.P.4.3 Validation of Analytical Procedures SUBMITTED** **3.2.P.4.4 Justification of Specifications SUBMITTED** 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: 1. Finished Dosage Form YES 2. Same lot numbers 3720R0012/A100018A **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form YES **3.2.P.5.5 Characterization of Impurities SUBMITTED** **3.2.P.5.6 Justification of Specifications SUBMITTED**	☒
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  (b) (4) 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 (b)(4) MONTH EXP **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:** 3720R0012	☒

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 N/A** **3.2.R.3.S Methods Validation Package YES** 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 YES Theoretical Yield SEE BELOW Actual Yield SEE BELOW Packaged Yield SEE BELOW **3.2.R.1.P.2 Information on Components** N/A **3.2.R.2.P Comparability Protocols** N/A **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 SUBMITTED**	☒
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: Dose (1 x 650 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (02361VH)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC_{0-t}	44720.9229	45618.9562	98.03	91.32	105.24
AUC_{∞}	46966.0311	47991.8592	97.86	90.70	105.59
C_{max}	8421.2982	8425.9513	99.94	91.81	108.80
Fed Bioequivalence Study (02364VF)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC_{0-t}	47871.1704	48855.3375	97.99	94.26	101.86
AUC_{∞}	50258.8813	51483.8918	97.62	93.87	101.52
C_{max}	8019.6530	8123.6343	98.72	94.23	103.43

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 YES

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 650 MG ☐

1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC)
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

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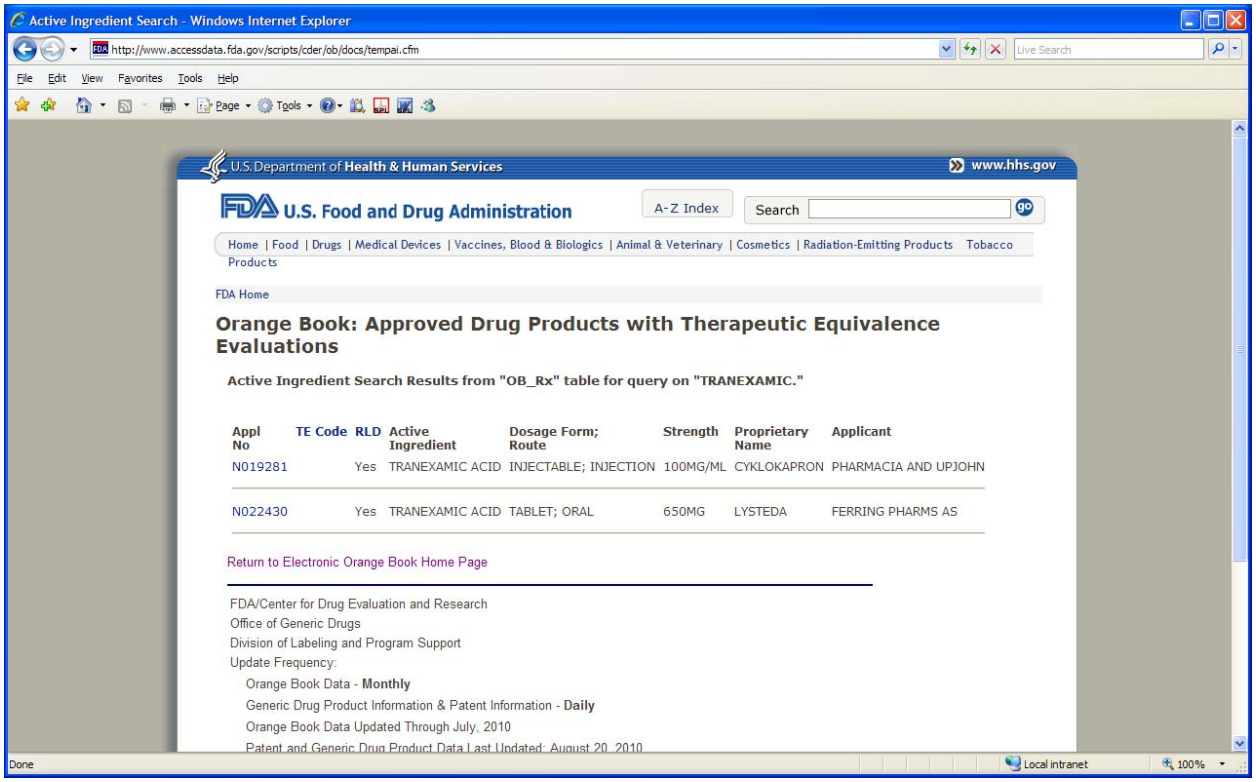
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FDA Home
Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
Active Ingredient Search Results from "OB_Rx" table for query on "TRANEXAMIC."
Appl No | TE Code | RLD | Active Ingredient | Dosage Form; Route | Strength | Proprietary 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: August 20, 2010
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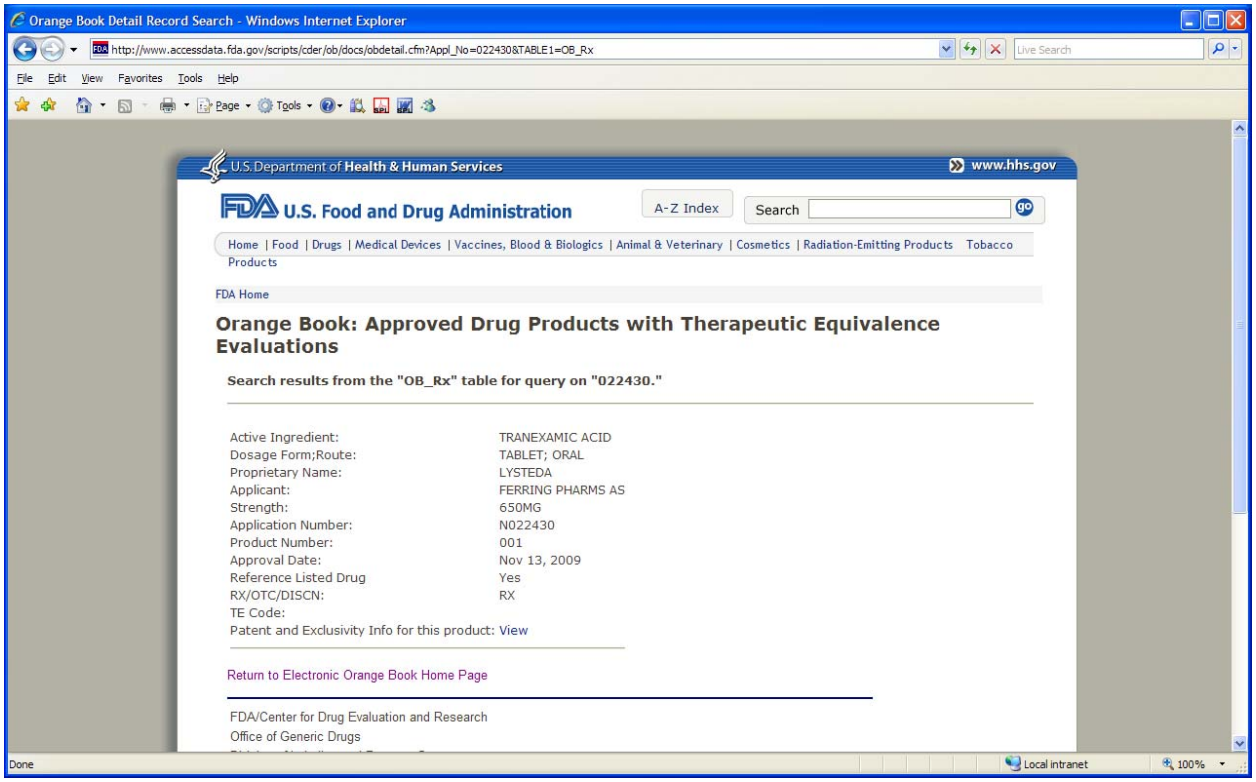
Orange Book Detail Record Search - Windows Internet Explorer
http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=022430&TABLE1=OB_Rx
File Edit View Favorites Tools Help
U.S. Department of Health & Human Services
www.hhs.gov
U.S. Food and Drug Administration
A-Z Index
Search
Home | 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
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FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
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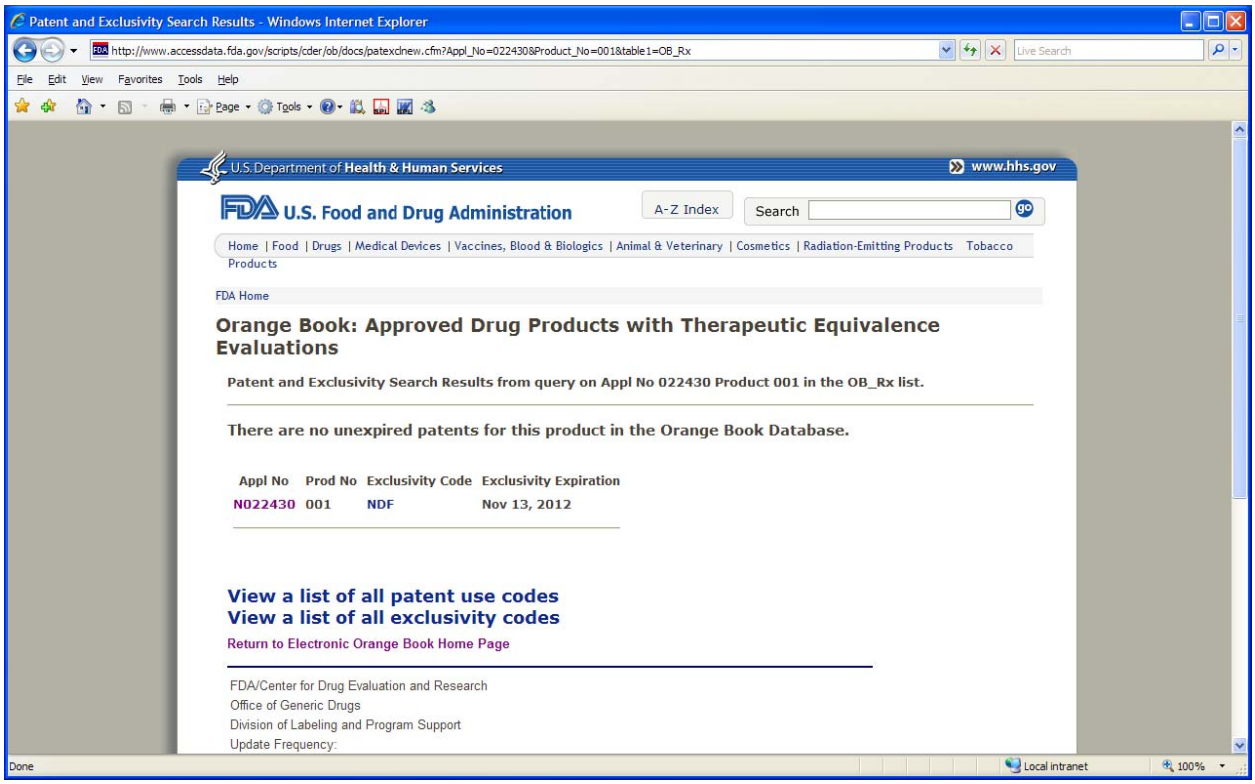
Patent and Exclusivity Search Results - Windows Internet Explorer
http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=022430&Product_No=001&table1=OB_Rx
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FDA Home
Orange Book: Approved Drug Products with Therapeutic Equivalence 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
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/s/

FELECIA TAN
11/16/2010

MARTIN H Shimer
11/18/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 202093

Watson Laboratories Inc.-Florida
Attention: Janet Vaughn
4955 Orange Drive
Fort Lauderdale, FL 33314

Dear Madam:

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 email correspondence dated October 28, 2010 and your correspondence dated November 9, 2010.

NAME OF DRUG: Tranexamic Acid Tablets, 650 mg

DATE OF APPLICATION: July 23, 2010

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 26, 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/

FELECIA TAN
11/15/2010

MARTIN H Shimer
11/18/2010
Signing for Wm Peter Rickman

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 202093 **FIRM NAME** Watson Laboratories, Inc.

DRUG NAME Tranexamic acid

DOSAGE FORM Tablets, 650 mg

SUBJ: Request for examination of: if Watson's Tranexamic acid Tablets, 650 mg, satisfies the statutory requirements of "completeness".

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☐	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason: N/A

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

ACCEPTABLE FOR FILLING – ADDITIONAL INFO. REQUESTED:

The firm is requested to provide bioanalytical method validation report and pharmacy records and dispensing logs for the test and reference products for both fasting and fed studies.

Reviewed by:

_____ Date: 9/27/2010_____
Li Xia
Reviewer

_____Date: 10/6/2010_____
Xiaojian Jiang
Team Leader

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☒	☐			Module 5: 5.3.1.2. 02361vh-Fasting study 5.3.1.2.1. Legacy Study Report Module 5: 5.3.1.2. 02364vh-Fed study 5.3.1.2.1. Legacy Study Report
Assay Methodology	☒	☐			Module 5: 5.3.1.2. 02361vh-Fasting study 5.3.1.2.1. Legacy Study Report Module 5: 5.3.1.2. 02364vh-Fed study 5.3.1.2.1. Legacy Study Report
Procedure SOP	☒	☐			Module 5: 5.3.1.2. 02361vh-Fasting study 5.3.1.2.1. Legacy Study Report Module 5: 5.3.1.2. 02364vh-Fed study 5.3.1.2.1. Legacy Study Report
Methods Validation	☐	☒			The firm did not provide bioanalytical method validation report
Study Results Ln/Lin	☒	☐			Module 5: 5.3.1.2. 02361vh-Fasting study 5.3.1.2.1. Legacy Study Report Module 5: 5.3.1.2. 02364vh-Fed study 5.3.1.2.1. Legacy Study Report
Adverse Events	☒	☐			Module 5: 5.3.1.2. 02361vh-Fasting study 5.3.1.2.1. Legacy Study Report Module 5: 5.3.1.2. 02364vh-Fed study 5.3.1.2.1. Legacy Study Report
IRB Approval	☒	☐			Module 5: 5.3.1.2. 02361vh-Fasting study 5.3.1.2.1. Legacy Study Report

					Module 5: 5.3.1.2. 02364vh-Fed study 5.3.1.2.1. Legacy Study Report
Dissolution Data	☒	☐			Module 2: 2.7. Clinical Summary. (summary table #5, 12 individual data was attached following table #5)
Pre-screening of Patients	☒	☐			Module 5: 5.3.1.2. 02361vh-Fasting study 5.3.1.2.24. Case Report Forms [Site ID] Module 5: 5.3.1.2. 02364vh-Fed study 5.3.1.2.24. Case Report Forms [Site ID]
Chromatograms	☒	☐			Module 5: 5.3.1.2. 02361vh-Fasting study 5.3.1.2.1. Legacy Study Report Module 5: 5.3.1.2. 02364vh-Fed study 5.3.1.2.1. Legacy Study Report
Consent Forms	☒	☐			Module 5: 5.3.1.2. 02361vh-Fasting study 5.3.1.2.1. Legacy Study Report Module 5: 5.3.1.2. 02364vh-Fed study 5.3.1.2.1. Legacy Study Report
Composition	☒	☐			Module 2: 2.3. Quality Overall Summary, 2.3.P Drug Product Module 3: 3.2.P.1. Description and Composition of the Drug Product
Summary of Study	☒	☐			Module 5: 5.3.1.2. 02361vh-Fasting study 5.3.1.2.1. Legacy Study Report Module 5: 5.3.1.2. 02364vh-Fed study 5.3.1.2.1. Legacy Study Report
Individual Data & Graphs, Linear & Ln	☒	☐			Module 5: 5.3.1.2. 02361vh-Fasting study 5.3.1.2.1. Legacy Study Report Module 5: 5.3.1.2. 02364vh-Fed study 5.3.1.2.1. Legacy Study Report

PK/PD Data Disk Submitted)	☒	☐			Module 5: 5.3.1.2. 02361vh-Fasting Study 5.3.1.2.25. Individual Subject Data Listing Module 5: 5.3.1.2. 02364vh-Fed study 5.3.1.2.25. Individual Subject Data Listing
Randomization Schedule	☒	☐			Module 5: 5.3.1.2. 02361vh-Fasting study 5.3.1.2.1. Legacy Study Report Module 5: 5.3.1.2. 02364vh-Fed study 5.3.1.2.1. Legacy Study Report
Protocol Deviations	☒	☐			Module 5: 5.3.1.2. 02361vh-Fasting study 5.3.1.2.1. Legacy Study Report Module 5: 5.3.1.2. 02364vh-Fed study 5.3.1.2.1. Legacy Study Report
Clinical Site	☒	☐			Module 2: 2.7. Clinical Summary. (summary table 10)
Analytical Site	☒	☐			Module 2: 2.7. Clinical Summary. (summary table 10)
Study Investigators	☒	☐			Module 5: 5.3.1.2. 02361vh-Fasting study 5.3.1.2.1. Legacy Study Report Module 5: 5.3.1.2. 02364vh-Fed study 5.3.1.2.1. Legacy Study Report
Medical Records	☒	☐			Module 5: 5.3.1.2. 02361vh-Fasting study 5.3.1.2.24. Case Report Forms [Site ID] Module 5: 5.3.1.2. 02364vh-Fed study 5.3.1.2.24. Case Report Forms [Site ID]
Clinical Raw Data	☒	☐			Module 5: 5.3.1.2. 02361vh-Fasting study 5.3.1.2.24. Case Report Forms [Site ID] Module 5: 5.3.1.2. 02364vh-Fed study 5.3.1.2.24. Case Report Forms [Site ID]
Test Article Inventory	☐	☒			The firm did not provide the pharmacy records and dispensing logs for the test and reference

					products for both fasting and fed studies
BIO Batch Size	☒	☐			Module 2: 2.7. Clinical Summary. (BE summary table #11 Product information)
Assay of Active Content Drug	☒	☐			Module 5: 5.3.1.2. 02361vh-Fasting study 5.3.1.2.1. Legacy Study Report Module 5: 5.3.1.2. 02364vh-Fed study 5.3.1.2.1. Legacy Study Report
Content Uniformity	☒	☐			Module 2: 2.7. Clinical Summary. (BE summary table #11 Product information)
Date of Manufacture	☒	☐			Module 2: 2.7. Clinical Summary. (BE summary table #11 Product information)
Exp. Date of RLD	☒	☐			Module 2: 2.7. Clinical Summary. (BE summary table #11 Product information)
BioStudy Lot Numbers	☒	☐			Module 2: 2.7. Clinical Summary. (BE summary table #11 Product information)
Statistics	☒	☐			Module 5: 5.3.1.2. 02361vh-Fasting study 5.3.1.2.1. Legacy Study Report Module 5: 5.3.1.2. 02364vh-Fed study 5.3.1.2.1. Legacy Study Report
Summary results provided by the firm indicate studies pass BE criteria	☒	☐			Module 5: 5.3.1.2. 02361vh-Fasting study 5.3.1.2.1. Legacy Study Report Module 5: 5.3.1.2. 02364vh-Fed study 5.3.1.2.1. Legacy Study Report Module 2: 2.7. Clinical Summary (BE summary table #3)
Waiver requests for other strengths / supporting data	☐	☐			N/A

Additional Comments regarding the ANDA:

The test drug product is Tranexamic Acid Tablets, 650 mg. The reference listed drug (RLD) is Ferring pharms' Lysteda ™ (tranexamic acid) Tablets, 650 mg (NDA 022430) which was approved on 11/13/2009 for the treatment of cyclic heavy menstrual bleeding. This application contains the results of fasting and fed bioequivalence (BE) studies comparing Watson's test product, Tranexamic Acid Tablets, 650 mg, to the corresponding RLD Ferring pharms' Lysteda ™ (tranexamic acid) Tablets, 650 mg. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male and female subjects.

Currently, there are no individual draft guidance, controlled correspondence, protocols, and ANDAs for Tranexamic Acid Tablets. Based on the OCPB's review of NDA 022430 and in accordance with the current general BA/BE guidance and current DBE practice, the DBE recommended a single-dose fasting and a single-dose fed bioequivalence studies comparing the test product, Tranexamic Acid Tablets, 650 mg, to its RLD, Lysteda ™ (tranexamic acid) Tablets, 650 mg in health non-pregnant women (see details in section 7).

For this application the study population is a mixture of males (fasting: 34%; fed: 56%) and females (fasting: 66%; fed: 44%) and there were no serious adverse events reported. Since the drug is intended for use in women only, the attempt to include males in the study could potentially increase the variability of the study. As a result, the study could likely be more sensitive to detect the formulation difference between test and RLD product. According to firm's analysis, 90% CIs of AUCt, AUCi and Cmax are within the acceptable BE criteria of 80-125%, with the enrollment of males in the study. In other words, males' participation did not affect the results of the BE study. Therefore, this application is accepted for filling. However, the firm is requested to provide bioanalytical method validation report and pharmacy records and dispensing logs for the test and reference products.

Bioequivalence Recommendations for Tranexamic Acid Tablets

1. Drug product Information

Test Product	Tranexamic Acid Tablets
Reference Product	LYSTEDA ™ (tranexamic acid) tablets
RLD Manufacturer	FERRING PHARMS AS
NDA No.	N022430
RLD Approval Date	Nov 13, 2009

Indication and Usage

LYSTEDA™ (tranexamic acid) tablets is indicated for the treatment of cyclic heavy menstrual bleeding.
Prior to prescribing LYSTEDA, exclude endometrial pathology that can be associated with heavy menstrual bleeding.

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 (Kd = 750 umol/L) and 1 with high affinity (Kd = 1.1 umol/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, its binding to and dissolution of the fibrin matrix is inhibited.

2. Safety issues

Black Box Warning	**NO**

[Additional safety concerns/notes here]

Clinical Consult Required?	**NO**

3. Pharmacokinetics [1]

Absorption	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, from RLD Label	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.
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.

1 Labeling repository for RLD LYSTEDA at http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=18193&CFID=200704&CFTOKEN=fd15e7646b2858d8-2CAEC5F9-F14A-89D8-26D7887281A3403F&jsessionid=ca30c9ebd9513b6d7619#nlm34068-7

Metabolism	A small fraction of the tranexamic acid is metabolized.
Excretion	Tranexamic acid is eliminated by urinary excretion primarily via glomerular filtration with more than 95% of the dose excreted unchanged. Excretion of tranexamic acid is about 90% at 24 hours after intravenous administration of 10 mg/kg. Most elimination post intravenous administration occurred during the first 10 hours, giving an apparent elimination half-life of approximately 2 hours. The mean terminal half-life of LYSTEDA is approximately 11 hours. Plasma clearance of tranexamic acid is 110-116 mL/min.
Recommended Dosage/Administration	The recommended dose of LYSTEDA for women with normal renal function is two 650 mg tablets taken three times daily (3900 mg/day) for a maximum of 5 days during monthly menstruation. LYSTEDA may be administered without regard to meals. Tablets should be swallowed whole and not chewed or broken apart.

4. NDA Bioavailability/Bioequivalence Studies [2, 3]

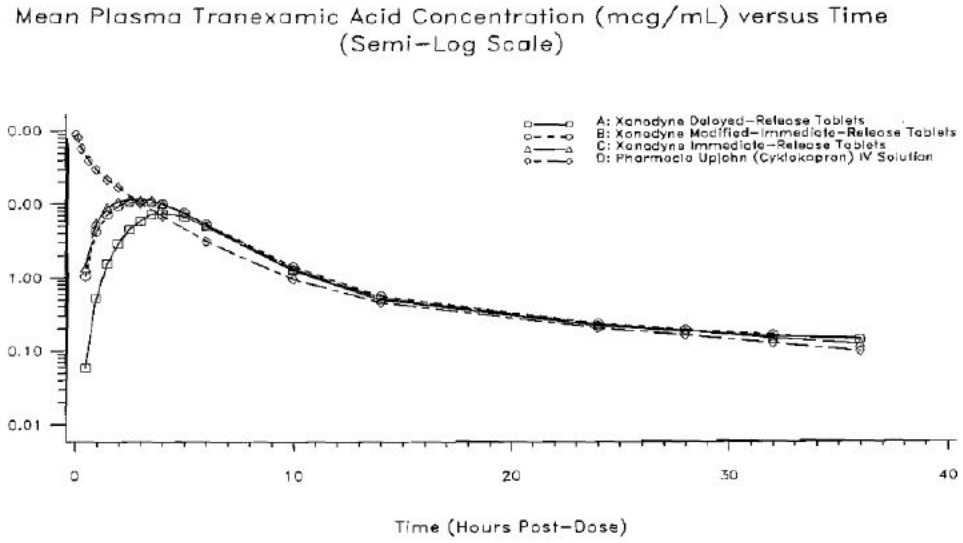
Tranexamic acid is an antifibrinolytic drug which inhibits breakdown of fibrin in clotted blood by blocking the activation of plasminogen. This helps in the slowing or cessation of further bleeding. Tranexamic acid was first approved in the U.S. (as an orphan drug) in 1986, in both tablet and injectable formulations as Cyklokapron® (NDA 19-280 for 500 mg tablet; NDA 19-281 for 100 mg/ml injectable). The approved indication was for treatment of patients with hemophilia for short term use (2-8 days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction. The oral formulation was discontinued and the NDA was withdrawn in 2002 for reasons unrelated to safety. Currently in the US, Cyklokapron® (tranexamic acid) is available only as an IV injection. The approval of Lysteda™ (tranexamic acid) Tablets, 650 mg (NDA 022430, approved on 11/13/2009) was the first time that US marketing approval for tranexamic acid for the treatment of cyclic heavy menstrual bleeding (i.e.,menorrhagia). This Applicant submitted a 505(b)(2) application, which relies in part on the Agency's findings of safety for tranexamic acid with respect to nonclinical data in NDAs 19-280 and 19-281 for Cyklokapron (tranexamic acid).

Formulation Development

In the early stage of the development for the Tranexamic Acid tablets, the sponsor developed immediate-release (IR) tablets, delayed-release (DR) tablets and modified-release (MR) tablets.

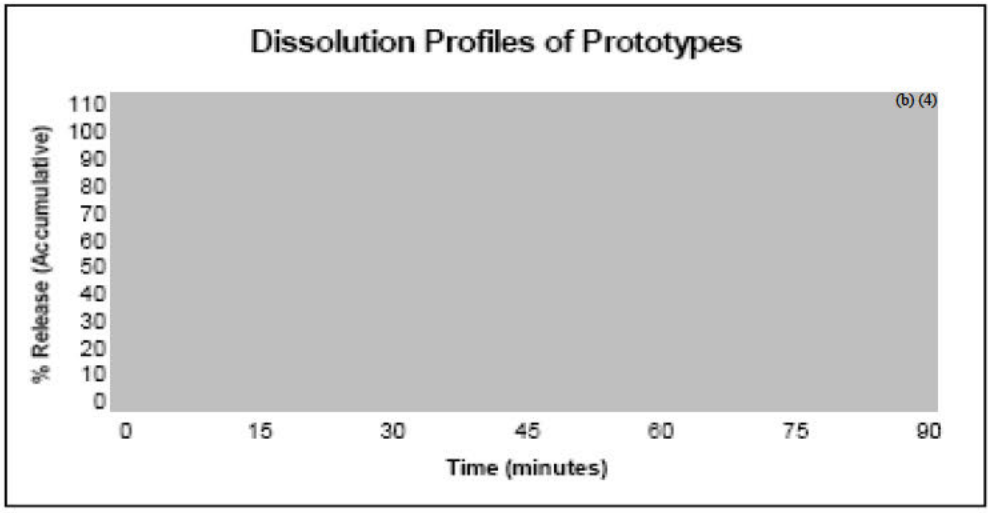
The three prototypes were compared to an approved IV formulation, Cyklokapron IV in clinical study# XP12B-101, a comparative, randomized, single-dose, 4-way crossover absolute bioavailability and bioequivalence study conducted in 28 healthy non-smoking adult women volunteers under fasting conditions. The Sponsor concluded that tranexamic acid MR 650 mg tablet formulation and IR formulation are bioequivalent under fasting conditions and PK profiles are almost superimposable (see figure below). The absolute bioavailability of DR, MR, and IR is 32.4%, 44.9% and 46%, respectively. Based on the results of this trial, the applicant decided to proceed with the development of the product with the modified-release dissolution profile.

2 DARRTS: REV-CLINPHARM-01(General Review) for NDA 022430 dated 3/24/2009.
3 DARRTS: REV-CLINPHARM-01(General Review) for NDA 022430 dated 10/16/2009.



During the NDA review cycle, the proposed MR formulation was found not to exhibit the release characteristics of a typical MR formulation[4]. Although tranexamic acid MR and IR were found to be bioequivalent, the comparative dissolution profiles show that the dissolution of the MR formulation is relatively slower than the dissolution of the IR formulation. However, complete dissolution is occurring within 90 minutes, a time frame clearly shorter than what is usually seen for a modified release formulation (see figure below). The IR and MR formulations have a very similar composition formula except for (b) (4) by the sponsor. Lysteda had a pharmacokinetic plasma concentration profile that is very similar to the already approved Cyklokapron IR formulation. After a thorough FDA review and discussions with the Applicant, it was decided that the to-be-marketed product had the characteristics of an immediate-release product and should not be labeled as modified release. In its amendment dated 6/30/2009 the firm agreed to remove the "modified-release" from LYSTEDA labeling and updated it as "LYSTEDA (tranexamic acid) tablet".

Figure 2: Dissolution Profiles of the Prototype Formulations



4 DARRTS: REV-CLINPHARM-01(General Review) under NDA 022430 dated 5/14/2009

Food Effect Studies
A randomized single dose comparative bioavailability 4-way crossover trial with healthy nonsmoking adult female volunteers was conducted to assess the single dose relative bioavailability of Lysteda following a 1,300 mg (2 x 650 mg) dose, under fasting and fed states (study# XP12B-102). A single dose administration (two 650 mg tablets) of Lysteda ™ MR with food increased both C_{max} and AUC_{inf} by 7% and 16%, respectively. The 90% CI fell within the range of 80-125% for AUC_{inf} and C_{max} indicating that Lysteda is bioequivalent under fasting and fed states for TBM formulation (MR). Therefore, Lysteda may be administered without regard to meals. In the phase 3 clinical trials, patients were instructed to take Lysteda without regards to meals.

Dose Proportionality Stud(ies)
Dose proportionality study was performed in Phase I thorough QT study (XP12B-MR-104)[5]. The C_{max} and AUC_{inf} following supratherapeutic dose (3.9 g) in the thorough QT study were 1.8 and 1.9 fold, respectively when compared to the therapeutic dose (1.3 g). The increase in 3-fold dose produced approximately 2-fold increase in exposures indicating less than dose proportional PK of tranexamic acid at the studied doses.

Analytical Section
Blood samples were collected during each phase I trial period at pre dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 10, 14, 24, 28, 32, and 36 hours post-dose for female subjects who were given Lysteda. Plasma tranexamic acid was separated from heparinized plasma by liquid/liquid
extraction. All tranexamic acid samples were derivatized using Methyliodide. The concentrations of tranexamic acid samples were determined by GC/MS method using Negative Chemical Ionization and Selected Ion Monitoring.

As per labeling 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. In most of the PK studies the female volunteers were dosed by a single oral administration of two 650 mg tablets of Lysteda ™ (2 x 650 mg). In the study of dosage adjustment for renal impairment, 650 mg (1x650 mg) once a day for a maximum of 5 days during menstruation was used, and the plasma concentration of tranexamic was detectable. In addition, in fasting and fed BE studies in ANDA 202093 (1st generic drug), the plasma concentration of tranexamic acid is well above the limit of quantitation (50 ng/mL) with a single oral administration of one 650 mg tablets, therefore, administration of one 650 mg dosage is recommended to establish the bioequivalence to the RLD Lysteda ™.

In vitro alcohol dose dumping
In the original submission, since the To-Be-Marketed formulation was proposed to be the MR formulation by the sponsor, the sponsor was asked to address the robustness of the MR formulation in presence of alcohol [6]. The impact of different ratios of alcohol in the dissolution medium on the drug release from the dosage form was studied. The f_2 comparisons show that the dissolution profiles in 5%, 10%, and 20% alcohol were similar to the dissolution profile in DI water (f2 >50). The dissolution profile in 40% alcohol was, however, dissimilar from the dissolution profile in DI water (f2=26.74). There was also a trend showing a reduction in the dissolution rate as the amount of alcohol in the dissolution

5 DARRTS: REV-CLINPHARM-01(General Review) for NDA 022430 dated 5/18/2009.
6 DARRTS: REV-CLINPHARM-01(General Review) under IND 68096 dated 11/5/2008

medium increases with dissolution in 40% alcohol being the slowest. These results show that that the tablets are not expected to show dose dumping in the presence of alcohol.

As per the current DBE practice, in vitro alcohol dose dumping study is recommended for modified release products only. Since the RLD, Lysteda ™ was not qualified as modified release formulation and is an immediate release formulation, although in vitro alcohol dose dumping was conducted in NDA 022430, in vitro alcohol dose dumping test is not recommended to establish the bioequivalence to the RLD Lysteda ™.

5. Formulation of RLD Lysteda ™ [7]

Exhibit Batch Formulation		
Component	**mg/tablet**	**Batch Quantity**
Tranexamic Acid	650.00	(b) (4)
Microcrystalline Cellulose NF	(b) (4)	
Colloidal Silicon Dioxide NF		
Pregelatinized Corn Starch NF		
Hypromellose USP (b) (4)		
Magnesium Stearate NF		
Stearic Acid NF		
Povidone USP (b) (4)		
Total	950.00	(b) (4)

(b) (4)

Proportionally Formulated?	**N/A**

6. Dissolution[7] (the following dissolution method and specification is from NDA 022430)

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

7 DARRTS: REV-QUALITY-03(General Review) for NDA 022430 dated 9/24/2009

Dissolution Sample Preparation: At pull times, withdraw approximately 10 mL from each dissolution vessel and filter through a (b) (4) 0.45 m Nylon filter, discarding the first 2-3 mL of filtrate.

In the original submission dated 1/30/2009, since the sponsor claimed Lysteda™ as a modified release tablet, the firm proposed the following dissolution specification: (b) (4) (b) (4) After removing the "modified-release" from LYSTEDA labeling and updated it as "LYSTEDA (tranexamic acid) tablet" in its amendment dated 6/30/2009, the firm revised the finished drug product dissolution specification to a single time point of NLT (b) (4)% (Q) at 90 minutes, which was found acceptable.

The firm also conducted dissolution testing in different pH (0.1N HCl, pH 1.2, 4.5 and 6.8). The f_2 comparisons show similar dissolution profiles in all media (f2>60) except pH 6.8 Phosphate buffer (f2=48.01). There was also a trend showing a reduction in the dissolution rate as the pH of the dissolution medium increased with the slowest dissolution occurring at pH 6.8.

7. Summary and Conclusions

The DBE requests the following to demonstrate bioequivalence to Lysteda™ (tranexamic acid) tablets:

Fasting Study[8]: The DBE requests a single-dose, two-way crossover, fasting *in-vivo* bioequivalence study comparing Tranexamic Acid Tablets, 650 mg, to the reference listed drug (RLD), Lysteda™ (tranexamic acid) Tablets, 650 mg.

Fed Study: The DBE requests a single-dose, two-way crossover, fed *in-vivo* bioequivalence study comparing Tranexamic Acid Tablets, 650 mg, to the reference listed drug (RLD), Lysteda™ (tranexamic acid) Tablets, 650 mg.

As per the DBE's current policy, a fed BE study can be exempt under the following situations:

a) The drug product is classified as a BCS Class 1; or
b) When the RLD label clearly indicates that the drug should be taken on an empty stomach; or
c) A study population of cancer patients has difficulty in successfully ingesting a high fat meal; or
d) A fed study would cause safety or efficacy concerns.

The RLD labeling for Lysteda™ stated that "LYSTEDA may be taken with or without food." Therefore, based on the current DBE policy, a fed BE study is requested.

Special Consideration: DBE recommends that in vivo BE studies be conducted in normal healthy non-pregnant females for the following reasons: (1)Tranexamic Acid Tablets, 650 mg is indicated for the treatment of woman cyclic heavy menstrual bleeding and (2) the

8 FDA's Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations (posted March, 2003) states that a BE study under fasting conditions should be conducted for all orally administered immediate-release drug products. Since this is an orally administered immediate-release drug product, the DBE requests a fasting BE study as per the guidance.

NDA used female subjects in all PK studies (e.g., XP12B-101, XP12B-102 and XP12B-103, etc) for this indication.

Measurement of Parent Drug in Plasma: The DBE requests that only the parent drug, tranexamic acid be measured in plasma.

FDA's Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations states that metabolite plasma concentrations should be measured if the metabolite is formed by presystemic metabolism and contributes meaningfully to safety and efficacy.

As per labeling of RLD Lysteda™, only a small fraction of the tranexamic acid is metabolized. Tranexamic acid is eliminated by urinary excretion primarily via glomerular filtration with more than 95% of the dose excreted unchanged. Therefore, only the parent drug, tranexamic should be measured in plasma.

Waiver request of in vivo testing: Not Applicable

Dissolution Method: FDA-recommended method

Apparatus: USP apparatus II (paddles)
Speed: 50 rpm
Medium: water at 37°C
Volume: 900 mL
Sampling Times: 15, 30, 45, 60, 75 and 90 minutes
Specification: NLT (b)(4)% (Q) in 90 minutes

8. Recommendations to the firm

The firm should be recommended the following:

The firm is requested to provide bioanalytical method validation report and pharmacy records and dispensing logs for the test and reference products..

Contains Nonbinding Recommendations

Draft Guidance on Tranexamic Acid

Active ingredient: **Tranexamic Acid**

Form/Route: Tablets/Oral

Recommended studies: 2 studies

Type of study: Fasting
Design: Single-dose, two-way crossover *in-vivo*
Strength: 650 mg
Subjects: Normal healthy non-pregnant females, general population.

Type of study: Fed
Design: Single-dose, two-way crossover *in-vivo*
Strength: 650 mg
Subjects: Normal healthy non-pregnant females, general population.

Analytes to measure (in appropriate biological fluid): Tranexamic acid in plasma

Bioequivalence based on (90% CI): Tranexamic acid

Waiver request of in vivo testing: Not Applicable

Dissolution test method and sampling times: Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

Appendix

Fed Bioequivalence studies:

Co-administration of food with oral drug products can influence BE. Therefore, fed BE studies can determine whether test and RLD products are bioequivalent when co-administered with meals. We usually recommend a single-dose, two-period, two-treatment, two-sequence, crossover study for fed BE studies.

When a fasting in vivo BE study is indicated for an orally administered, immediate release product, we also recommend that applicants conduct a fed study, except as follows:

- When both test product and RLD are rapidly dissolving, have similar dissolution profiles, and contain a drug substance with high solubility and high permeability (BCS Class I)

- When the *dosage and administration* section of the RLD labeling states that the product should be taken only on an empty stomach (e.g., the labeling states that the product should be administered one hour before or two hours after a meal).

For orally administered, immediate release products labeled to be taken only with food, fasting and fed studies are recommended, except when serious adverse events are anticipated with fasting administration. In these cases, we recommend that applicants conduct only a fed study; a fasting study is not recommended.

For all orally administered, modified release drug products, we recommend that applicants conduct a fed BE study in addition to a fasting BE study. These studies are usually conducted on the highest strength of the drug product, unless safety considerations preclude the use of that dose in study subjects.

b. Test Meal Composition

We recommend that applicants conduct fed BE studies using meals that provide the greatest effects on GI physiology and systemic drug availability. We recommend a high-fat (approximately 50 percent of total caloric content of the meal), high-calorie (approximately 800 to 1000 calories) test meal for fed BE studies. This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively[1]. The caloric breakdown of the test meal should be provided in the study report.

[1] An example test meal would be: two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes and eight ounces of whole milk. Substitutions in this test meal (e.g., beef instead of bacon) can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume, density, and viscosity. In general, completely vegetarian meals are not recommended.

9. Enter Review Productivity and Generate Report

ANDA: 202093

Completed Assignment for 202093 ID: 12131

Reviewer: Xia, Li **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description: checklist for Tranexamic acid tablets

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
12131	7/23/2010	Paragraph 4	Paragraph 4 Checklist	1	1
12131	7/23/2010	Controlled Correspondence	Controlled Correspondence	1	1
				Bean Total:	2

DBE2 Productivity points:

Checklist	
First Generic Checklist	1
Control Correspondence	1
Total	*2*

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
10/16/2010

XIAOJIAN JIANG
10/17/2010

ETHAN M STIER on behalf of BARBARA M DAVIT
10/18/2010

M E M O R A N D U M

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

DATE : August 23, 2010

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 202093 for Tranexamic Acid Tablets, 650 mg to determine if the application is substantially complete for filing.

Watson Laboratories Inc. (Florida) has submitted ANDA 202093 for Tranexamic Acid Tablets, 650 mg. It is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Watson Laboratories Inc. (Florida) on July 23, 2010 for its Tranexamic Acid product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-202093	ORIG-1	WATSON LABORATORIES INC FLORIDA	TRANEXAMIC ACID

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

/s/

EDA E HOWARD
08/24/2010