CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 78193

Name: Raloxifene Hydrochloride Tablets USP, 60 mg

Sponsor: Teva Pharmaceuticals, USA

Approval Date: March 4, 2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78193

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78193

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 078193

Teva Pharmaceuticals USA
Attention: Scott D. Tomsky
Vice President, N.A. Generics Regulatory Affairs
425 Privet Road
Horsham, PA 19044

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated March 2, 2006, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Raloxifene Hydrochloride Tablets USP, 60 mg.

Reference is also made to the tentative approval and complete response letters issued by this office on April 16, 2008 and May 15, 2013, respectively, and to your amendments dated August 6, November 8, and December 27, 2013; and January 27, 2014.

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 Raloxifene Hydrochloride Tablets USP, 60 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Evista Tablets, 60 mg, of Eli Lilly and Company (Lilly). 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, Lilly's Evista Tablets, 60 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

6,458,811 (the '811 patent)	March 10, 2017
6,797,719 (the '719 patent)	March 10, 2017
6,894,064 (the '064 patent)	March 10, 2017
8,030,330 (the '330 patent)	March 10, 2017

Your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each of these patents is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Raloxifene Hydrochloride Tablets USP, 60 mg, under this ANDA. You have notified the agency that Teva Pharmaceuticals USA (Teva) complied with the requirements of section 505(j)(2)(B) of the Act, and that no action for infringement of any of these patents was brought against Teva within the statutory 45-day period.

With respect to 180-day generic drug exclusivity, Teva and another applicant were the first ANDA applicants to submit a substantially complete ANDA with a paragraph IV certification to the '330 patent.[1] The other applicant was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification to the '811, '719 and '064 patents. The other applicant has relinquished its entitlement to exclusivity with respect to these three patents. Therefore, with this approval Teva is eligible for 180 days of generic drug exclusivity for Raloxifene Hydrochloride Tablets, 60 mg. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, will begin to run from the earlier of the commercial marketing or court decision dates 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.

[1] Because the ANDA of the other applicant was filed before the date of enactment of the Medicare Prescription Drug, Improvement and Modernization Act (MMA) (Public Law 108-173) on December 8, 2003, references to the 180-day exclusivity provision are to the section of the Act as in effect prior to December 8, 2003. See MMA § 1102(b)(1).

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

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

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

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

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

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR

314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

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

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

/s/

ROBERT L WEST

03/04/2014

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78193

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-193

TEVA Pharmaceuticals USA
Attention: Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated March 2, 2006, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Raloxifene Hydrochloride Tablets, 60 mg.

Reference is made to your amendments dated August 4, 2006; January 29, February 22, and September 6, 2007; and January 25, February 14, and March 31, 2008.

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 patent 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.

Please note that there is a USP-PF under development for this drug product. We recommend that Teva Pharmaceuticals USA, communicate with USP to incorporate the ANDA dissolution method and criterion in the monograph.

The reference listed drug (RLD) upon which you have based your ANDA, Evista Tablets, 60 mg, of Eli Lilly and Company, is subject to periods of patent protection. The following patents and 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
5,393,763 (the '763 patent)	July 28, 2012
5,457,117 (the '117 patent)	July 28, 2012
5,478,847 (the '847 patent)	March 2, 2014
5,811,120 (the '120 patent)	March 2, 2014
5,972,383 (the '383 patent)	March 2, 2014
6,458,811 (the '811 patent)	March 10, 2017
6,797,719 (the '719 patent)	March 10, 2017
6,894,064 (the '064 patent)	March 10, 2017
6,906,086 (the '086 patent)	July 28, 2012
RE38,968 (the '968 patent)	July 28, 2012
RE39,049 (the '049 patent)	July 28, 2012
RE39,050 (the '050 patent)	March 2, 2014

Your ANDA contains paragraph IV certifications to each of these patents 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 Raloxifene Hydrochloride Tablets, 60 mg, under this ANDA. Section 505(j)(5)(B)(iii) of the act provides that approval of an ANDA shall be made effective immediately, unless an action was brought against TEVA Pharmaceuticals USA (TEVA) for infringement of one or more of these patents that were the subject of the paragraph IV certifications. This action must have been brought against TEVA prior to the expiration of 45 days from the date the notice you provided under section 505(j)(2)(B)(i) was received by the NDA/patent holder(s). You notified the agency that TEVA complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation for infringement of the '086, '968, '049, and '050 patents was brought against TEVA in the United States District Court for the Southern District of Indianapolis [Eli Lilly and Company v. TEVA Pharmaceuticals USA, Inc., Civil Action No. 1:06-cv-1017-SEB-VSS].

Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii),

b. the date the court decides[1] that the '086, '968, '049, and '050 patents are invalid or not infringed (see sections 505(j)(5)(B)(iii)(I), (II), and (III) of the Act) or,

c. the '086, '968, '049, and '050 patents have expired, and

2. The agency is assured there is no new information that would affect whether final approval should be granted.

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' compliance with current good manufacturing practices (cGMPs) are subject to agency review before final approval of the application 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

[1] This decision may be either a decision of the district court or the court of appeals, whichever court is the first to decide that the patent is invalid or not infringed.

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 application, or prior to submitting additional amendments, please contact Benjamin Danso, Pharm.D., Project Manager, at (240) 276-8527.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
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
4/16/2008 03:13:56 PM
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78193

LABELING

NDC 0093-7290-56

RALOXIFENE HYDROCHLORIDE Tablets USP

60 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

℞ only

30 TABLETS

TEVA

Each film-coated tablet contains 60 mg raloxifene hydrochloride, USP.
Usual Dosage: See package insert for full prescribing information.
Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.
Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Rev. B 6/2012

N 3 0093-7290-56 8

Reference ID: 3447508

NDC 0093-7290-01

RALOXIFENE HYDROCHLORIDE Tablets USP

60 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

℞ only

100 TABLETS

TEVA

Each film-coated tablet contains 60 mg raloxifene hydrochloride, USP.

Usual Dosage: See package insert for full prescribing information.

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

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Rev. B 6/2012

N 3 0093-7290-01 8

Reference ID: 3447508

NDC 0093-7290-10

RALOXIFENE HYDROCHLORIDE Tablets USP

60 mg

PHARMACIST: Dispensе the accompanying Medication Guide to each patient.

℞ only

1000 TABLETS

TEVA

Each film-coated tablet contains 60 mg raloxifene hydrochloride, USP.

Usual Dosage: See package insert for full prescribing information.

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

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Rev. B 6/2012

N 3 0093-7290-10 0

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

RALOXIFENE hydrochloride tablets USP for oral use

Initial U.S. Approval: 1997

WARNING: INCREASED RISK OF VENOUS THROMBOEMBOLISM AND DEATH FROM STROKE

See full prescribing information for complete boxed warning.

- **Increased risk of deep vein thrombosis and pulmonary embolism have been reported with raloxifene hydrochloride (5.1). Women with active or past history of venous thromboembolism should not take raloxifene hydrochloride (4.1).**
- **Increased risk of death due to stroke occurred in a trial in postmenopausal women with documented coronary heart disease or at increased risk for major coronary events. Consider risk-benefit balance in women at risk for stroke (5.2, 14.5).**

----RECENT MAJOR CHANGES----

Boxed Warning	9/2007
Warnings and Precautions, Death Due to Stroke (5.2)	7/2007
Warnings and Precautions, Cardiovascular Disease (5.3)	7/2007
Warnings and Precautions, Renal Impairment (5.8)	7/2007

----INDICATIONS AND USAGE----

Raloxifene hydrochloride tablets USP are an estrogen agonist/antagonist indicated for:

- Treatment and prevention of osteoporosis in postmenopausal women. (1.1)

--DOSAGE AND ADMINISTRATION--

60 mg tablet orally once daily. (2.1)

-DOSAGE FORMS AND STRENGTHS-

Tablets (not scored): 60 mg (3)

-----CONTRAINDICATIONS-----

- Active or past history of venous thromboembolism, including deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis. (4.1)
- Pregnancy, women who may become pregnant, and nursing mothers. (4.2, 8.1, 8.3)

--WARNINGS AND PRECAUTIONS--

- *Venous Thromboembolism:* Increased risk of deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis. Discontinue use 72 hours prior to and during prolonged immobilization. (5.1, 6.1)
- *Death Due to Stroke:* Increased risk of death due to stroke occurred in a trial in postmenopausal women with documented coronary heart disease or at increased risk for major coronary events. No increased risk of stroke was seen in this trial. Consider risk-benefit balance in women at risk for stroke. (5.2, 14.5)
- *Cardiovascular Disease:* Raloxifene hydrochloride should not be used for the primary or secondary prevention of cardiovascular disease. (5.3, 14.5)
- *Premenopausal Women:* Use is not recommended. (5.4)
- *Hepatic Impairment:* Use with caution. (5.5)
- *Concomitant Use with Systemic Estrogens:* Not recommended. (5.6)
- *Hypertriglyceridemia:* If previous treatment with estrogen resulted in hypertriglyceridemia, monitor serum triglycerides. (5.7)

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

Adverse reactions (> 2% and more common than with placebo) include: hot flashes, leg cramps, peripheral edema, flu syndrome, arthralgia, sweating. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact TEVA USA, PHARMACOVIGILANCE at 1-866-832-8537, or drug.safety@tevapharm.com; or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

- *Cholestyramine:* Use with raloxifene hydrochloride is not recommended. Reduces the absorption and enterohepatic cycling of raloxifene. (7.1, 12.3)
- *Warfarin:* Monitor prothrombin time when starting or stopping raloxifene hydrochloride. (7.2, 12.3)
- *Highly Protein-Bound Drugs:* Use with raloxifene hydrochloride with caution. Highly protein-bound drugs include diazepam, diazoxide, and lidocaine. Raloxifene hydrochloride is more than 95% bound to plasma proteins. (7.3, 12.3)

--USE IN SPECIFIC POPULATIONS--

- *Pediatric Use:* Safety and effectiveness not established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide

Revised: 06/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: INCREASED RISK OF VENOUS THROMBOEMBOLISM AND DEATH FROM STROKE

- Increased risk of deep vein thrombosis and pulmonary embolism have been reported with raloxifene hydrochloride (5.1). Women with active or past history of venous thromboembolism should not take raloxifene hydrochloride (4.1).
- Increased risk of death due to stroke occurred in a trial in postmenopausal women with documented coronary heart disease or at increased risk for major coronary events. Consider risk-benefit balance in women at risk for stroke (5.2, 14.5).

1 INDICATIONS AND USAGE

1.1 Treatment and Prevention of Osteoporosis in Postmenopausal Women

Raloxifene hydrochloride tablets USP are indicated for the treatment and prevention of osteoporosis in postmenopausal women [*see Clinical Studies (14.1, 14.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dosage is one 60 mg raloxifene hydrochloride tablet USP daily, which may be administered any time of day without regard to meals [*see Clinical Pharmacology (12.3)*].

2.2 Recommendations for Calcium and Vitamin D Supplementation

For either osteoporosis treatment or prevention, supplemental calcium and/or vitamin D should be added to the diet if daily intake is inadequate. Postmenopausal women require an average of 1500 mg/day of elemental calcium. Total daily intake of calcium above 1500 mg has not demonstrated additional bone benefits while daily intake above 2000 mg has been associated with increased risk of adverse effects, including hypercalcemia and kidney stones. The recommended intake of vitamin D is 400 to 800 IU daily. Patients at increased risk for vitamin D insufficiency (e.g., over the age of 70 years, nursing home bound, or chronically ill) may need additional vitamin D supplements. Patients with gastrointestinal malabsorption syndromes may require higher doses of vitamin D supplementation and measurement of 25-hydroxyvitamin D should be considered.

3 DOSAGE FORMS AND STRENGTHS

60 mg, white to off-white, capsule-shaped, film-coated tablets, debossed with "7290" on one side of the tablet, and "93" on the other.

4 CONTRAINDICATIONS

4.1 Venous Thromboembolism

Raloxifene hydrochloride tablets are contraindicated in women with active or past history of venous thromboembolism (VTE), including deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis [*see Wa nings and Precautions (5.1)*].

4.2 Pregnancy, Women Who May Become Pregnant, and Nursing Mothers

Raloxifene hydrochloride tablets are contraindicated in pregnancy, in women who may become pregnant, and in nursing mothers [*see Use in Specific Populations (8.1, 8.3)*]. Raloxifene hydrochloride tablets may cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

In rabbit studies, abortion and a low rate of fetal heart anomalies (ventricular septal defects) occurred in rabbits at doses ≥ 0.1 mg/kg (≥ 0.04 times the human dose based on surface area, mg/m^2), and hydrocephaly was observed in fetuses at doses ≥ 10 mg/kg (≥ 4 times the human dose based on surface area, mg/m^2). In rat studies, retardation of fetal development and developmental abnormalities (wavy ribs, kidney cavitation) occurred at doses ≥ 1 mg/kg (≥ 0.2 times the human dose based on surface area, mg/m^2). Treatment of rats at doses of 0.1 to 10 mg/kg (0.02 to 1.6 times the human dose based on surface area, mg/m^2) during gestation and lactation produced effects that included delayed and disrupted parturition; decreased neonatal survival and altered physical development; sex- and age-specific reductions in growth and changes in pituitary hormone content; and decreased lymphoid compartment size in offspring. At 10 mg/kg, raloxifene disrupted parturition, which resulted in maternal and progeny death and morbidity. Effects in adult offspring (4 months of age) included uterine hypoplasia and reduced fertility; however, no ovarian or vaginal pathology was observed.

5 WARNINGS AND PRECAUTIONS

5.1 Venous Thromboembolism

In clinical trials, raloxifene hydrochloride-treated women had an increased risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism). Other venous thromboembolic events also could occur. A less serious event, superficial thrombophlebitis, also has been reported more frequently with raloxifene hydrochloride than with placebo. The greatest risk for deep vein thrombosis and pulmonary embolism occurs during the first 4 months of treatment, and the magnitude of risk appears to be similar to the reported risk associated with use of hormone therapy. Because immobilization increases the risk for venous thromboembolic events independent of therapy, raloxifene hydrochloride should be discontinued at least 72 hours prior to and during prolonged immobilization (e.g., post-surgical recovery, prolonged bed rest), and raloxifene hydrochloride therapy should be resumed only after the patient is fully ambulatory. In addition, women taking raloxifene hydrochloride should be advised to move about periodically during prolonged travel. The risk-benefit balance should be considered in women at risk of thromboembolic disease for other reasons, such as congestive heart failure, superficial thrombophlebitis, and active malignancy [*see Contraindications (4.1) and Adverse Reactions (6.1)*].

5.2 Death Due to Stroke

In a clinical trial of postmenopausal women with documented coronary heart disease or at increased risk for coronary events, an increased risk of death due to stroke was observed after treatment with raloxifene hydrochloride. During an average follow-up of 5.6 years, 59 (1.2%) raloxifene hydrochloride-treated women died due to a stroke compared to 39 (0.8%) placebo-treated women (22 versus 15 per 10,000 women-years; hazard ratio 1.49; 95% confidence interval, 1.00 to 2.24; p = 0.0499). There was no statistically significant difference between treatment groups in the incidence of stroke (249 in raloxifene hydrochloride [4.9%] versus 224 placebo [4.4%]). Raloxifene hydrochloride had no significant effect on all-cause mortality. The risk-benefit balance should be considered in women at risk for stroke, such as prior stroke or transient ischemic attack (TIA), atrial fibrillation, hypertension, or cigarette smoking [*see Clinical Studies (14.5)*].

5.3 Cardiovascular Disease

Raloxifene hydrochloride should not be used for the primary or secondary prevention of cardiovascular disease. In a clinical trial of postmenopausal women with documented coronary heart disease or at increased risk for coronary events, no cardiovascular benefit was demonstrated after treatment with raloxifene for 5 years [*see Clinical Studies (14.5)*].

5.4 Premenopausal Use

There is no indication for premenopausal use of raloxifene hydrochloride. Safety of raloxifene hydrochloride in premenopausal women has not been established and its use is not recommended.

5.5 Hepatic Impairment

Raloxifene hydrochloride should be used with caution in patients with hepatic impairment. Safety and efficacy have not been established in patients with hepatic impairment [*see Clinical Pharmacology (12.3)*].

5.6 Concomitant Estrogen Therapy

The safety of concomitant use of raloxifene hydrochloride with systemic estrogens has not been established and its use is not recommended.

5.7 History of Hypertriglyceridemia When Treated With Estrogens

Limited clinical data suggest that some women with a history of marked hypertriglyceridemia (> 5.6 mmol/L or > 500 mg/dL) in response to treatment with oral estrogen or estrogen plus progestin may develop increased levels of triglycerides when treated with raloxifene hydrochloride. Women with this medical history should have serum triglycerides monitored when taking raloxifene hydrochloride.

5.8 Renal Impairment

Raloxifene hydrochloride should be used with caution in patients with moderate or severe renal impairment. Safety and efficacy have not been established in patients with moderate or severe renal impairment [*see Clinical Pharmacology (12.3)*].

5.9 History of Breast Cancer

Raloxifene hydrochloride has not been adequately studied in women with a prior history of breast cancer.

5.10 Use in Men

There is no indication for the use of raloxifene hydrochloride in men. Raloxifene hydrochloride has not been adequately studied in men and its use is not recommended.

5.11 Unexplained Uterine Bleeding

Any unexplained uterine bleeding should be investigated as clinically indicated. Raloxifene hydrochloride-treated and placebo-treated groups had similar incidences of endometrial proliferation [*see Clinical Studies (14.1, 14.2)*].

5.12 Breast Abnormalities

Any unexplained breast abnormality occurring during raloxifene hydrochloride therapy should be investigated. Raloxifene hydrochloride does not eliminate the risk of breast cancer.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

The data described below reflect exposure to raloxifene hydrochloride in 8429 patients who were enrolled in placebo-controlled trials, including 6666 exposed for 1 year and 5685 for at least 3 years.

Osteoporosis Treatment Clinical Trial (MORE) — The safety of raloxifene in the treatment of osteoporosis was assessed in a large (7705 patients) multinational, placebo-controlled trial. Duration of treatment was 36 months, and 5129 postmenopausal women were exposed to raloxifene (2557 received 60 mg/day, and 2572 received 120 mg/day). The incidence of all-cause mortality was similar among groups: 23 (0.9%) placebo, 13 (0.5%) raloxifene hydrochloride-treated (raloxifene 60 mg), and 28 (1.1%) raloxifene 120 mg women died. Therapy was discontinued due to an adverse reaction in 10.9% of raloxifene hydrochloride-treated women and 8.8% of placebo-treated women.

Venous Thromboembolism: The most serious adverse reaction related to raloxifene hydrochloride was VTE (deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis). During an average of study-drug exposure of 2.6 years, VTE occurred in about 1 out of 100 patients treated with raloxifene hydrochloride. Twenty-six raloxifene hydrochloride-treated women had a VTE compared to 11 placebo-treated women, the hazard ratio was 2.4 (95% confidence interval, 1.2, 4.5), and the highest VTE risk was during the initial months of treatment.

Common adverse reactions considered to be related to raloxifene hydrochloride therapy were hot flashes and leg cramps. Hot flashes occurred in about one in 10 patients on raloxifene hydrochloride and were most commonly reported during the first 6 months of treatment and were not different from placebo thereafter. Leg cramps occurred in about one in 14 patients on raloxifene hydrochloride.

Placebo-Controlled Osteoporosis Prevention Clinical Trials — The safety of raloxifene has been assessed primarily in 12 Phase 2 and Phase 3 studies with placebo, estrogen, and estrogen-progestin therapy control groups. The duration of treatment ranged from 2 to 30 months, and 2036 women were exposed to raloxifene (371 patients received 10 to 50 mg/day, 828 received 60 mg/day, and 837 received from 120 to 600 mg/day).

Therapy was discontinued due to an adverse reaction in 11.4% of 581 raloxifene hydrochloride-treated women and 12.2% of 584 placebo-treated women. Discontinuation rates due to hot flashes did not differ significantly between raloxifene hydrochloride and placebo groups (1.7% and 2.2%, respectively).

Common adverse reactions considered to be drug-related were hot flashes and leg cramps. Hot flashes occurred in about one in four patients on raloxifene hydrochloride versus about one in six on placebo. The first occurrence of hot flashes was most commonly reported during the first 6 months of treatment.

Table 1 lists adverse reactions occurring in either the osteoporosis treatment or in five prevention placebo-controlled clinical trials at a frequency ≥ 2.0% in either group and in more raloxifene hydrochloride-treated women than in placebo-treated women. Adverse reactions are shown without attribution of causality. The majority of adverse reactions occurring during the studies were mild and generally did not require discontinuation of therapy.

Table 1: Adverse Reactions Occurring in Placebo-Controlled Osteoporosis Clinical Trials at a Frequency ≥ 2.0% and in More Raloxifene Hydrochloride-Treated (60 mg Once Daily) Women Than Placebo-Treated Women[a]

	Treatment		Prevention	
	Raloxifene Hydrochloride N = 2557 %	Placebo N = 2576 %	Raloxifene Hydrochloride N = 581 %	Placebo N = 584 %
Body as a Whole				
Infection	A	A	15.1	14.6
Flu Syndrome	13.5	11.4	14.6	13.5
Headache	9.2	8.5	A	A
Leg Cramps	7.0	3.7	5.9	1.9
Chest Pain	A	A	4.0	3.6
Fever	3.9	3.8	3.1	2.6
Cardiovascular System				
Hot Flashes	9.7	6.4	24.6	18.3
Migraine	A	A	2.4	2.1
Syncope	2.3	2.1	B	B
Varicose Vein	2.2	1.5	A	A
Digestive System				
Nausea	8.3	7.8	8.8	8.6
Diarrhea	7.2	6.9	A	A
Dyspepsia	A	A	5.9	5.8
Vomiting	4.8	4.3	3.4	3.3
Flatulence	A	A	3.1	2.4
Gastrointestinal Disorder	A	A	3.3	2.1
Gastroenteritis	B	B	2.6	2.1
Metabolic and Nutritional				
Weight Gain	A	A	8.8	6.8
Peripheral Edema	5.2	4.4	3.3	1.9
Musculoskeletal System				
Arthralgia	15.5	14.0	10.7	10.1
Myalgia	A	A	7.7	6.2
Arthritis	A	A	4.0	3.6
Tendon Disorder	3.6	3.1	A	A
Nervous System				
Depression	A	A	6.4	6.0
Insomnia	A	A	5.5	4.3
Vertigo	4.1	3.7	A	A
Neuralgia	2.4	1.9	B	B
Hypesthesia	2.1	2.0	B	B
(continued)				
Respiratory System				
Sinusitis	7.9	7.5	10.3	6.5
Rhinitis	10.2	10.1	A	A
Bronchitis	9.5	8.6	A	A
Pharyngitis	5.3	5.1	7.6	7.2
Cough Increased	9.3	9.2	6.0	5.7
Pneumonia	A	A	2.6	1.5
Laryngitis	B	B	2.2	1.4
Skin and Appendages				
Rash	A	A	5.5	3.8
Sweating	2.5	2.0	3.1	1.7
Special Senses				
Conjunctivitis	2.2	1.7	A	A
Urogenital System				
Vaginitis	A	A	4.3	3.6
Urinary Tract Infection	A	A	4.0	3.9
Cystitis	4.6	4.5	3.3	3.1
Leukorrhea	A	A	3.3	1.7
Uterine Disorder[b,c]	3.3	2.3	A	A
Endometrial Disorder[b]	B	B	3.1	1.9
Vaginal Hemorrhage	2.5	2.4	A	A
Urinary Tract Disorder	2.5	2.1	A	A

[a] A: Placebo incidence greater than or equal to raloxifene hydrochloride incidence; B: Less than 2% incidence and more frequent with raloxifene hydrochloride.

[b] Includes only patients with an intact uterus: Prevention Trials: Raloxifene hydrochloride, n = 354, Placebo, n = 364; Treatment Trial: Raloxifene hydrochloride, n = 1948, Placebo, n = 1999.

[c] Actual terms most frequently referred to endometrial fluid.

Comparison of Raloxifene Hydrochloride and Hormone Therapy — Raloxifene hydrochloride was compared with estrogen-progestin therapy in three clinical trials for prevention of osteoporosis. **Table 2** shows adverse reactions occurring more frequently in one treatment group and at an incidence ≥ 2.0% in any group. Adverse reactions are shown without attribution of causality.

Table 2: Adverse Reactions Reported in the Clinical Trials for Osteoporosis Prevention With Raloxifene Hydrochloride (60 mg Once Daily) and Continuous Combined or Cyclic Estrogen Plus Progestin (Hormone Therapy) at an Incidence ≥ 2.0% in any Treatment Group[a]

	Raloxifene Hydrochloride (N = 317) %	Hormone Therapy-Continuous Combined[b] (N = 96) %	Hormone Therapy-Cyclic[c] (N = 219) %
Urogenital			
Breast Pain	4.4	37.5	29.7
Vaginal Bleeding[d]	6.2	64.2	88.5
Digestive			
Flatulence	1.6	12.5	6.4
Cardiovascular			
Hot Flashes	28.7	3.1	5.9
Body as a Whole			
Infection	11.0	0	6.8
Abdominal Pain	6.6	10.4	18.7
Chest Pain	2.8	0	0.5

[a] These data are from both blinded and open-label studies.

[b] Continuous Combined Hormone Therapy = 0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate.

[c] Cyclic Hormone Therapy = 0.625 mg conjugated estrogens for 28 days with concomitant 5 mg medroxyprogesterone acetate or 0.15 mg norgestrel on Days 1 through 14 or 17 through 28.

[d] Includes only patients with an intact uterus: Raloxifene hydrochloride, n = 290; Hormone Therapy-Continuous Combined, n = 67; Hormone Therapy-Cyclic, n = 217.

Breast Pain — Across all placebo-controlled trials, raloxifene hydrochloride was indistinguishable from placebo with regard to frequency and severity of breast pain and tenderness. Raloxifene hydrochloride was associated with less breast pain and tenderness than reported by women receiving estrogens with or without added progestin.

Gynecologic Cancers — Raloxifene hydrochloride-treated and placebo-treated groups had similar incidences of endometrial cancer and ovarian cancer.

Placebo-Controlled Trial of Postmenopausal Women at Increased Risk for Major Coronary Events (RUTH) — The safety of raloxifene hydrochloride (60 mg once daily) was assessed in a placebo-controlled multinational trial of 10,101 postmenopausal women (age range 55 to 92) with documented coronary heart disease (CHD) or multiple CHD risk factors. Median study drug exposure was 5.1 years for both treatment groups [*see Clinical Studies (14.5)*]. Therapy was discontinued due to an adverse reaction in 25% of 5044 raloxifene hydrochloride-treated women and 24% of 5057 placebo-treated women. The incidence per year of all-cause mortality was similar between the raloxifene (2.07%) and placebo (2.25%) groups.

Adverse reactions reported more frequently in raloxifene hydrochloride-treated women than in placebo-treated women included peripheral edema (14.1% raloxifene versus 11.7% placebo), muscle spasms/leg cramps (12.1% raloxifene versus 8.3% placebo), hot flashes (7.8% raloxifene versus 4.7% placebo), venous thromboembolic events (2.0% raloxifene versus 1.4% placebo), and cholelithiasis (3.3% raloxifene versus 2.6% placebo) [*see Clinical Studies (14.5)*].

6.2 Postmarketing Experience

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.

Adverse reactions reported very rarely since market introduction include retinal vein occlusion, stroke, and death associated with venous thromboembolism (VTE).

7 DRUG INTERACTIONS

7.1 Cholestyramine

Concomitant administration of cholestyramine with raloxifene hydrochloride is not recommended. Although not specifically studied, it is anticipated that other anion exchange resins would have a similar effect. Raloxifene hydrochloride should not be coadministered with other anion exchange resins [*see Clinical Pharmacology (12.3)*].

7.2 Warfarin

If raloxifene hydrochloride is given concomitantly with warfarin or other warfarin derivatives, prothrombin time should be monitored more closely when starting or stopping therapy with raloxifene hydrochloride [*see Clinical Pharmacology (12.3)*].

7.3 Other Highly Protein-Bound Drugs

Raloxifene hydrochloride should be used with caution with certain other highly protein-bound drugs such as diazepam, diazoxide, and lidocaine. Although not examined, raloxifene hydrochloride might affect the protein binding of other drugs. Raloxifene is more than 95% bound to plasma proteins [*see Clinical Pharmacology (12.3)*].

7.4 Systemic Estrogens

The safety of concomitant use of raloxifene hydrochloride with systemic estrogens has not been established and its use is not recommended.

7.5 Other Concomitant Medications

Raloxifene hydrochloride can be concomitantly administered with ampicillin, amoxicillin, antacids, corticosteroids, and digoxin [*see Clinical Pharmacology (12.3)*].

The concomitant use of raloxifene hydrochloride and lipid-lowering agents has not been studied.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy category X

Raloxifene hydrochloride should not be used in women who are or may become pregnant [*see Contraindications (4.2)*].

8.3 Nursing Mothers

Raloxifene hydrochloride should not be used by lactating women [*see Contraindications (4.2)*]. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when raloxifene is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients in placebo-controlled clinical studies of raloxifene hydrochloride, 61% were 65 and over, while 15.5% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Based on clinical trials, there is no need for dose adjustment for geriatric patients [*see Clinical Pharmacology (12.3)*].

8.6 Renal Impairment

Raloxifene hydrochloride should be used with caution in patients with moderate or severe renal impairment [*see Warnings and Precautions (5.8) and Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

Raloxifene hydrochloride should be used with caution in patients with hepatic impairment [*see Warnings and Precautions (5.5) and Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

In an 8 week study of 63 postmenopausal women, a dose of raloxifene HCl 600 mg/day was safely tolerated. In clinical trials, no raloxifene overdose has been reported.

In postmarketing spontaneous reports, raloxifene overdose has been reported very rarely (less than 1 out of 10,000 [< 0.01%] patients treated). The highest overdose has been approximately 1.5 grams. No fatalities associated with raloxifene overdose have been reported. Adverse reactions were reported in approximately half of the adults who took ≥ 180 mg raloxifene and included leg cramps and dizziness.

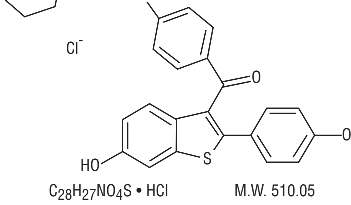
Two 18-month-old children each ingested raloxifene 180 mg. In these two children, symptoms reported included ataxia, dizziness, vomiting, rash, diarrhea, tremor, and flushing, as well as elevation in alkaline phosphatase.

There is no specific antidote for raloxifene.

No mortality was seen after a single oral dose in rats or mice at 5000 mg/kg (810 times the human dose for rats and 405 times the human dose for mice based on surface area, mg/m^2) or in monkeys at 1000 mg/kg (80 times the AUC in humans).

11 DESCRIPTION

Raloxifene hydrochloride is an estrogen agonist/antagonist, commonly referred to as a selective estrogen receptor modulator (SERM) that belongs to the benzothiophene class of compounds. The chemical structure is:



$C_{28}H_{27}NO_4S \cdot HCl$ M.W. 510.05

The chemical designation is methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]-, hydrochloride. Raloxifene HCl is an off-white to pale-yellow solid that is very slightly soluble in water.

Raloxifene hydrochloride is supplied in a tablet dosage form for oral administration. Each raloxifene hydrochloride tablet USP contains 60 mg of raloxifene HCl, which is the molar equivalent of 55.71 mg of free base. Inactive ingredients include colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, povidone, pregelatinized starch, and titanium dioxide.

USP Dissolution Test Pending

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Raloxifene is an estrogen agonist/antagonist, commonly referred to as a selective estrogen receptor modulator (SERM). The biological actions of raloxifene are largely mediated through binding to estrogen receptors. This binding results in activation of estrogenic pathways in some tissues (agonism) and blockade of estrogenic pathways in others (antagonism). The agonistic or antagonistic action of raloxifene depends on the extent of recruitment of coactivators and corepressors to estrogen receptor (ER) target gene promotors.

Raloxifene appears to act as an estrogen agonist in bone. It decreases bone resorption and bone turnover, increases bone mineral density (BMD) and decreases fracture incidence. Preclinical data demonstrate that raloxifene is an estrogen antagonist in uterine and breast tissues. These results are consistent with findings in clinical trials, which suggest that raloxifene hydrochloride lacks estrogen-like effects on the uterus and breast tissue.

12.2 Pharmacodynamics

Decreases in estrogen levels after oophorectomy or menopause lead to increases in bone resorption and accelerated bone loss. Bone is initially lost rapidly because the compensatory increase in bone formation is inadequate to offset resorptive losses. In addition to loss of estrogen, this imbalance between resorption and formation may be due to age-related impairment of osteoblasts or their precursors. In some women, these changes will eventually lead to decreased bone mass, osteoporosis, and increased risk for fractures, particularly of the spine, hip, and wrist. Vertebral fractures are the most common type of osteoporotic fracture in postmenopausal women.

In both the osteoporosis treatment and prevention trials, raloxifene hydrochloride therapy resulted in consistent, statistically significant suppression of bone resorption and bone formation, as reflected by changes in serum and urine markers of bone turnover (e.g., bone-specific alkaline phosphatase, osteocalcin, and collagen breakdown products). The suppression of bone turnover markers was evident by 3 months and persisted throughout the 36 month and 24 month observation periods.

In a 31 week, open-label, radiocalcium kinetics study, 33 early postmenopausal women were randomized to treatment with once-daily raloxifene hydrochloride 60 mg, cyclic estrogen/progestin (0.625 mg conjugated estrogens daily with 5 mg medroxyprogesterone acetate daily for the first 2 weeks of each month [hormone therapy]), or no treatment. Treatment with either raloxifene hydrochloride or hormone therapy was associated with reduced bone resorption and a positive shift in calcium balance (-82 mg Ca/day and +60 mg Ca/day, respectively, for raloxifene hydrochloride and -162 mg Ca/day and +91 mg Ca/day, respectively, for hormone therapy).

There were small decreases in serum total calcium, inorganic phosphate, total protein, and albumin, which were generally of lesser magnitude than decreases observed during estrogen or hormone therapy. Platelet count was also decreased slightly and was not different from estrogen therapy.

12.3 Pharmacokinetics

The disposition of raloxifene has been evaluated in more than 3000 postmenopausal women in selected raloxifene osteoporosis treatment and prevention clinical trials, using a population approach. Pharmacokinetic data also were obtained in conventional pharmacology studies in 292 postmenopausal women. Raloxifene exhibits high within-subject variability (approximately 30% coefficient of variation) of most pharmacokinetic parameters. **Table 3** summarizes the pharmacokinetic parameters of raloxifene.

Absorption — Raloxifene is absorbed rapidly after oral administration. Approximately 60% of an oral dose is absorbed, but presystemic glucuronide conjugation is extensive. Absolute bioavailability of raloxifene is 2%. The time to reach average maximum plasma concentration and bioavailability are functions of systemic interconversion and enterohepatic cycling of raloxifene and its glucuronide metabolites.

Administration of raloxifene HCl with a standardized, high-fat meal increases the absorption of raloxifene (C_{max} 28% and AUC 16%), but does not lead to clinically meaningful changes in systemic exposure. Raloxifene hydrochloride can be administered without regard to meals.

Distribution — Following oral administration of single doses ranging from 30 to 150 mg of raloxifene HCl, the apparent volume of distribution is 2348 L/kg and is not dose dependent.

Raloxifene and the monoglucuronide conjugates are highly (95%) bound to plasma proteins. Raloxifene binds to both albumin and α1-acid glycoprotein, but not to sex-steroid binding globulin.

Metabolism — Biotransformation and disposition of raloxifene in humans have been determined following oral administration of ^{14}C-labeled raloxifene. Raloxifene undergoes extensive first-pass metabolism to the glucuronide conjugates: raloxifene-4´-glucuronide, raloxifene-6-glucuronide, and raloxifene-6, 4´-diglucuronide. No other metabolites have been detected, providing strong evidence that raloxifene is not metabolized by cytochrome P450 pathways. Unconjugated raloxifene comprises less than 1% of the total radiolabeled material in plasma. The terminal log-linear portions of the plasma concentration curves for raloxifene and the glucuronides are generally parallel. This is consistent with interconversion of raloxifene and the glucuronide metabolites.

Following intravenous administration, raloxifene is cleared at a rate approximating hepatic blood flow. Apparent oral clearance is 44.1 L/kg•hr. Raloxifene and its glucuronide conjugates are interconverted by reversible systemic metabolism and enterohepatic cycling, thereby prolonging its plasma elimination half-life to 27.7 hours after oral dosing.

Results from single oral doses of raloxifene predict multiple-dose pharmacokinetics. Following chronic dosing, clearance ranges from 40 to 60 L/kg•hr. Increasing doses of raloxifene HCl (ranging from 30 to 150 mg) result in slightly less than a proportional increase in the area under the plasma time concentration curve (AUC).

Excretion — Raloxifene is primarily excreted in feces, and less than 0.2% is excreted unchanged in urine. Less than 6% of the raloxifene dose is eliminated in urine as glucuronide conjugates.

Table 3: Summary of Raloxifene Pharmacokinetic Parameters in the Healthy Postmenopausal Woman

	C_{max}[a,b] (ng/mL)/ (mg/kg)	$t_{1/2}$ (hr)[a]	$AUC_{0-\infty}$[a,b] (ng•hr/mL)/ (mg/kg)	CL/F[a] (L/kg•hr)	V/F[a] (L/kg)
Single Dose					
Mean	0.50	27.7	27.2	44.1	2348
CV[a] (%)	52	10.7 to 273[c]	44	46	52
Multiple Dose					
Mean	1.36	32.5	24.2	47.4	2853
CV[a] (%)	37	15.8 to 86.6[c]	36	41	56

[a] Abbreviations: C_{max} = maximum plasma concentration, $t_{1/2}$ = half-life, AUC = area under the curve, CL = clearance, V = volume of distribution, F = bioavailability, CV = coefficient of variation.

[b] Data normalized for dose in mg and body weight in kg.

[c] Range of observed half-life.

Special Populations

Pediatric — The pharmacokinetics of raloxifene has not been evaluated in a pediatric population [*see Use in Specific Populations (8.4)*].

Geriatric — No differences in raloxifene pharmacokinetics were detected with regard to age (range 42 to 84 years) [*see Use in Specific Populations (8.5)*].

Gender — Total extent of exposure and oral clearance, normalized for lean body weight, are not significantly different between age-matched female and male volunteers.

Race — Pharmacokinetic differences due to race have been studied in 1712 women, including 97.5% White, 1.0% Asian, 0.7% Hispanic, and 0.5% Black in the osteoporosis treatment trial and in 1053 women, including 93.5% White, 4.3% Hispanic, 1.2% Asian, and 0.5% Black in the osteoporosis prevention trials.

MEDICATION GUIDE

Raloxifene Hydrochloride Tablets USP for Oral Use

Read the Medication Guide that comes with raloxifene hydrochloride tablets before you start taking them and each time you refill your prescription. The information may have changed. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment. Talk with your doctor about raloxifene hydrochloride tablets when you start taking them and at regular checkups.

What is the most important information I should know about raloxifene hydrochloride tablets?

Serious and life-threatening side effects can occur while taking raloxifene hydrochloride tablets. These include blood clots and dying from stroke:

- Increased risk of blood clots in the legs (deep vein thrombosis) and lungs (pulmonary embolism) have been reported with raloxifene hydrochloride tablets. Women who have or have had blood clots in the legs, lungs, or eyes should not take raloxifene hydrochloride tablets.
- Women who have had a heart attack or are at risk for a heart attack may have an increased risk of dying from stroke when taking raloxifene hydrochloride tablets.

1. Before starting raloxifene hydrochloride tablets, tell your doctor if you have had blood clots in your legs, lungs, or eyes, a stroke, mini-stroke (transient ischemic attack), or have an irregular heartbeat.
2. Stop taking raloxifene hydrochloride tablets and call your doctor if you have:
   - leg pain or a feeling of warmth in the lower leg (calf).
   - swelling of the legs, hands, or feet.
   - sudden chest pain, shortness of breath, or coughing up blood.
   - sudden change in your vision, such as loss of vision or blurred vision.
3. Being still for a long time (such as sitting still during a long car or airplane trip or being in bed after surgery) can increase your risk of blood clots (see "**What should I avoid if I am taking raloxifene hydrochloride tablets?**").

What are raloxifene hydrochloride tablets?

Raloxifene hydrochloride tablets are a type of prescription medicine called a Selective Estrogen Receptor Modulator (SERM). Raloxifene hydrochloride tablets are for women after menopause.

Osteoporosis: Raloxifene hydrochloride tablets treat and prevent osteoporosis by helping make your bones stronger and less likely to break.

Raloxifene hydrochloride tablets are not for use in premenopausal women (women who have not passed menopause).

Who should not take raloxifene hydrochloride tablets?

Do not take raloxifene hydrochloride tablets if you:

- have or have had blood clots in your legs, lungs, or eyes. Taking raloxifene hydrochloride tablets may increase the risk of getting blood clots.
- are pregnant or could become pregnant. Raloxifene hydrochloride tablets could harm your unborn child.
- are nursing a baby. It is not known if raloxifene hydrochloride passes into breast milk or what effect it might have on the baby.

What should I tell my doctor before taking raloxifene hydrochloride tablets?

Raloxifene hydrochloride tablets may not be right for you. Before taking raloxifene hydrochloride tablets, tell your doctor about all your medical conditions, including if you:

- have had blood clots in your legs, lungs, or eyes, a stroke, mini-stroke (TIA/transient ischemic attack), or a type of irregular heartbeat (atrial fibrillation).
- have had breast cancer. Raloxifene hydrochloride tablets have not been fully studied in women who have a history of breast cancer.
- have liver or kidney problems.
- have taken estrogen in the past and had a high increase of triglycerides (a kind of fat in the blood).
- are pregnant, planning to become pregnant, or breast-feeding (see "**Who should not take raloxifene hydrochloride tablets?**").

Tell your doctor about all medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine. Especially tell your doctor if you take:

- warfarin (Coumadin®, Jantoven®)

If you are taking warfarin or other coumarin blood thinners, your doctor may need to do a blood test when you first start or if you need to stop taking raloxifene hydrochloride tablets. Names for this test include "prothrombin time," "pro-time," or "INR." Your doctor may need to adjust the dose of your warfarin or other coumarin blood thinner.

- cholestyramine
- estrogens

Raloxifene hydrochloride tablets should not be taken with cholestyramine or estrogens.

How should I take raloxifene hydrochloride tablets?

- Take raloxifene hydrochloride tablets exactly how your doctor tells you to.
- Keep taking raloxifene hydrochloride tablets for as long as your doctor prescribes them for you.
- It is important to get your refills on time so you do not run out of the medicine.
- Take one raloxifene hydrochloride tablet each day.
- Take raloxifene hydrochloride tablets at any time of the day, with or without food.
- To help you remember to take raloxifene hydrochloride tablets, it may be best to take them at about the same time each day.
- Calcium and vitamin D may be taken at the same time as raloxifene hydrochloride tablets. It is important to take calcium and vitamin D, as directed by your physician, to prevent or treat osteoporosis.
- If you miss a dose, take it as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and take only your next regularly scheduled dose. Do not take two doses at the same time.

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RALOXIFENE HYDROCHLORIDE TABLETS USP 7290

What should I avoid while taking raloxifene hydrochloride tablets?

- Being still for a long time (such as during long trips or being in bed after surgery) can increase the risk of blood clots. Raloxifene hydrochloride tablets may add to this risk. If you will need to be still for a long time, talk with your doctor about ways to reduce the risk of blood clots. On long trips, move around periodically. Stop taking raloxifene hydrochloride tablets at least 3 days before a planned surgery or before you plan on being still for a long time. You should start taking raloxifene hydrochloride tablets again when you return to your normal activities.
- Some medicines should not be taken with raloxifene hydrochloride tablets (see **"What should I tell my doctor before taking raloxifene hydrochloride tablets?"**).

What are the possible side effects of raloxifene hydrochloride tablets?

Serious and life-threatening side effects can occur while taking raloxifene hydrochloride tablets. These include blood clots and dying from stroke:

- Increased risk of blood clots in the legs (deep vein thrombosis) and lungs (pulmonary embolism) have been reported with raloxifene hydrochloride tablets. Women who have or have had blood clots in the legs, lungs, or eyes should not take raloxifene hydrochloride tablets.
- Women who have had a heart attack or are at risk for a heart attack may have an increased risk of dying from stroke when taking raloxifene hydrochloride tablets.

See **"What is the most important information I should know about raloxifene hydrochloride tablets?"**

The most common side effects of raloxifene hydrochloride tablets are hot flashes, leg cramps, swelling of the feet, ankles, and legs, flu syndrome, joint pain, and sweating. Hot flashes are more common during the first 6 months after starting treatment.

These are not all the side effects of raloxifene hydrochloride tablets. Tell your doctor about any side effect that bothers you or that does not go away. If you have any problems or questions that concern you while taking raloxifene hydrochloride tablets, ask your doctor or pharmacist for more information.

What else should I know about raloxifene hydrochloride tablets?

- Do not use raloxifene hydrochloride tablets to prevent heart disease, heart attack, or strokes.
- To get the calcium and vitamin D you need, your doctor may advise you to change your diet and/or take supplemental calcium and vitamin D. Your doctor may suggest other ways to help treat or prevent osteoporosis, in addition to taking raloxifene hydrochloride tablets and getting the calcium and vitamin D you need. These may include regular exercise, stopping smoking, and drinking less alcohol.
- Women who have hot flashes can take raloxifene hydrochloride tablets. Raloxifene hydrochloride tablets do not treat hot flashes, and they may cause hot flashes in some women (see **"What are the possible side effects of raloxifene hydrochloride tablets?"**).
- Raloxifene hydrochloride tablets have not been found to cause breast tenderness or enlargement. If you notice any changes in your breasts, call your doctor to find out the cause. Before starting and while taking raloxifene hydrochloride tablets you should have breast exams and mammograms, as directed by your doctor. Because raloxifene hydrochloride tablets do not eliminate the chance of developing breast cancers, you need these examinations to find any breast cancers as early as possible.
- Raloxifene hydrochloride tablets should not cause spotting or menstrual-type bleeding. If you have any vaginal bleeding, call your doctor to find out the cause. Raloxifene hydrochloride tablets have not been found to increase the risk for cancer of the lining of the uterus.
- Women in clinical trials have taken raloxifene hydrochloride for up to eight years.

How should I store raloxifene hydrochloride tablets?

- Store raloxifene hydrochloride tablets at 20° to 25°C (68° to 77°F).
- **Keep raloxifene hydrochloride tablets and all medicines out of the reach of children.**

General Information about the safe and effective use of raloxifene hydrochloride tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use raloxifene hydrochloride tablets for a condition for which they were not prescribed. Do not give your raloxifene hydrochloride tablets to other people, even if they have the same symptoms you have. They may harm them.

This Medication Guide is a summary of the most important information about raloxifene hydrochloride tablets. If you would like more information about raloxifene hydrochloride tablets, talk with your doctor. You can ask your doctor or pharmacist for information about raloxifene hydrochloride tablets that is written for health professionals. For more information, call 1-888-838-2872, MEDICAL AFFAIRS.

What are the ingredients in raloxifene hydrochloride tablets?

Active Ingredient: raloxifene hydrochloride

Inactive Ingredients: colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, povidone, pregelatinized starch, and titanium dioxide.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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There were no discernible differences in raloxifene plasma concentrations among these groups; however, the influence of race cannot be conclusively determined.

Renal Impairment — In the osteoporosis treatment and prevention trials, raloxifene concentrations in women with mild renal impairment are similar to women with normal creatinine clearance. When a single dose of 120 mg raloxifene HCl was administered to 10 renally impaired males [7 moderate impairment (CrCl = 31 to 50 mL/min); 3 severe impairment (CrCl ≤ 30 mL/min)] and to 10 healthy males (CrCl > 80 mL/min), plasma raloxifene concentrations were 122% ($AUC_{0-\infty}$) higher in renally impaired patients than those of healthy volunteers. Raloxifene should be used with caution in patients with moderate or severe renal impairment [*see Warnings and Precautions (5.8) and Use in Specific Populations (8.6)*].

Hepatic Impairment — The disposition of raloxifene was compared in 9 patients with mild (Child-Pugh Class A) hepatic impairment (total bilirubin ranging from 0.6 to 2 mg/dL) to 8 subjects with normal hepatic function following a single dose of 60 mg raloxifene HCl. Apparent clearance of raloxifene was reduced 56% and the half-life of raloxifene was not altered in patients with mild hepatic impairment. Plasma raloxifene concentrations were approximately 150% higher than those in healthy volunteers and correlated with bilirubin concentrations. The pharmacokinetics of raloxifene has not been studied in patients with moderate or severe hepatic impairment. Raloxifene should be used with caution in patients with hepatic impairment [*see Warnings and Precautions (5.5) and Use in Specific Populations (8.6)*].

Drug Interactions

Cholestyramine — Cholestyramine, an anion exchange resin, causes a 60% reduction in the absorption and enterohepatic cycling of raloxifene after a single dose. Although not specifically studied, it is anticipated that other anion exchange resins would have a similar effect [*see Drug Interactions (7.1)*].

Warfarin — In vitro, raloxifene did not interact with the binding of warfarin. The concomitant administration of raloxifene hydrochloride and warfarin, a coumarin derivative, has been assessed in a single-dose study. In this study, raloxifene had no effect on the pharmacokinetics of warfarin. However, a 10% decrease in prothrombin time was observed in the single-dose study. In the osteoporosis treatment trial, there were no clinically relevant effects of warfarin coadministration on plasma concentrations of raloxifene [*see Drug Interactions (7.2)*].

Other Highly Protein-Bound Drugs — In the osteoporosis treatment trial, there were no clinically relevant effects of coadministration of other highly protein-bound drugs (e.g., gemfibrozil) on plasma concentrations of raloxifene. *In vitro*, raloxifene did not interact with the binding of phenytoin, tamoxifen, or warfarin [*see above*] [*see Drug Interactions (7.3)*].

Ampicillin and Amoxicillin — Peak concentrations of raloxifene and the overall extent of absorption are reduced 28% and 14%, respectively, with coadministration of ampicillin. These reductions are consistent with decreased enterohepatic cycling associated with antibiotic reduction of enteric bacteria. However, the systemic exposure and the elimination rate of raloxifene were not affected. In the osteoporosis treatment trial, coadministration of amoxicillin had no discernible differences in plasma raloxifene concentrations [*see Drug Interactions (7.5)*].

Antacids — Concomitant administration of calcium carbonate or aluminum and magnesium hydroxide-containing antacids does not affect the systemic exposure of raloxifene [*see Drug Interactions (7.5)*].

Corticosteroids — The chronic administration of raloxifene in postmenopausal women has no effect on the pharmacokinetics of methylprednisolone given as a single oral dose [*see Drug Interactions (7.5)*].

Digoxin — Raloxifene has no effect on the pharmacokinetics of digoxin [*see Drug Interactions (7.5)*].

Cyclosporine — Concomitant administration of raloxifene hydrochloride with cyclosporine has not been studied.

Lipid-Lowering Agents — Concomitant administration of raloxifene hydrochloride with lipid-lowering agents has not been studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis — In a 21 month carcinogenicity study in mice, there was an increased incidence of ovarian tumors in female animals given 9 to 242 mg/kg, which included benign and malignant tumors of granulosa/theca cell origin and benign tumors of epithelial cell origin. Systemic exposure (AUC) of raloxifene in this group was 0.3 to 34 times that in postmenopausal women administered a 60 mg dose. There was also an increased incidence of testicular interstitial cell tumors and prostatic adenomas and adenocarcinomas in male mice given 41 or 210 mg/kg (4.7 or 24 times the AUC in humans) and prostatic leiomyoblastoma in male mice given 210 mg/kg.

In a 2 year carcinogenicity study in rats, an increased incidence in ovarian tumors of granulosa/theca cell origin was observed in female rats given 279 mg/kg (approximately 400 times the AUC in humans). The female rodents in these studies were treated during their reproductive lives when their ovaries were functional and responsive to hormonal stimulation.

Mutagenesis — Raloxifene HCl was not genotoxic in any of the following test systems: the Ames test for bacterial mutagenesis with and without metabolic activation, the micronucleated DNA synthesis assay in rat hepatocytes, the mouse lymphoma assay for mammalian cell mutation, the chromosomal aberration assay in Chinese hamster ovary cells, the *in vivo* sister chromatid exchange assay in Chinese hamsters, and the *in vivo* micronucleus test in mice.

Impairment of Fertility — When male and female rats were given daily doses ≥ 5 mg/kg (≥ 0.8 times the human dose based on surface area, mg/m^2) prior to and during mating, no pregnancies occurred. In male rats, daily doses up to 100 mg/kg (16 times the human dose based on surface area, mg/m^2) for at least 2 weeks did not affect sperm production or quality or reproductive performance. In female rats, at doses of 0.1 to 10 mg/kg/day (0.02 to 1.6 times the human dose based on surface area, mg/m^2), raloxifene disrupted estrous cycles and inhibited ovulation. These effects of raloxifene were reversible. In another study in rats in which raloxifene was given during the preimplantation period at doses ≥ 0.1 mg/kg (≥ 0.02 times the human dose based on surface area, mg/m^2), raloxifene delayed and disrupted embryo implantation, resulting in prolonged gestation and reduced litter size. The reproductive and developmental effects observed in animals are consistent with the estrogen receptor activity of raloxifene.

13.2 Animal Toxicology and/or Pharmacology

The skeletal effects of raloxifene treatment were assessed in ovariectomized rats and monkeys. In rats, raloxifene prevented increased bone resorption and bone loss after ovariectomy. There were positive effects of raloxifene on bone strength, but the effects varied with time. Cynomolgus monkeys were treated with raloxifene or conjugated estrogens for 2 years. In terms of bone cycles, this is equivalent to approximately 6 years in humans. Raloxifene and estrogen suppressed bone turnover and increased BMD in the lumbar spine and in the central cancellous bone of the proximal tibia. In this animal model, there was a positive correlation between vertebral compressive breaking force and BMD of the lumbar spine.

Histologic examination of bone from rats and monkeys treated with raloxifene showed no evidence of woven bone, marrow fibrosis, or mineralization defects.

These results are consistent with data from human studies of radiocalcium kinetics and markers of bone metabolism, and are consistent with the action of raloxifene hydrochloride as a skeletal antiresorptive agent.

14 CLINICAL STUDIES

14.1 Treatment of Postmenopausal Osteoporosis

Effect on Fracture Incidence

The effects of raloxifene hydrochloride on fracture incidence and BMD in postmenopausal women with osteoporosis were examined at 3 years in a large randomized, placebo-controlled, double-blind, multinational osteoporosis treatment trial (MORE). All vertebral fractures were diagnosed radiographically; some of these fractures also were associated with symptoms (i.e., clinical fractures). The study population consisted of 7705 postmenopausal women with osteoporosis as defined by: a) low BMD (vertebral or hip BMD at least 2.5 standard deviations below the mean value for healthy young women) without baseline vertebral fractures or b) one or more baseline vertebral fractures. Women enrolled in this study had a median age of 67 years (range 31 to 80) and a median time since menopause of 19 years.

Effect on Bone Mineral Density

Raloxifene hydrochloride, 60 mg administered once daily, increased spine and hip BMD by 2 to 3%. Raloxifene hydrochloride decreased the incidence of the first vertebral fracture from 4.3% for placebo to 1.9% for raloxifene hydrochloride (relative risk reduction = 55%) and subsequent vertebral fractures from 20.2% for placebo to 14.1% for raloxifene hydrochloride (relative risk reduction = 30%) (see **Table 4**). All women in the study received calcium (500 mg/day) and vitamin D (400 to 600 IU/day). Raloxifene hydrochloride reduced the incidence of vertebral fractures whether or not patients had a vertebral fracture upon study entry. The decrease in incidence of vertebral fracture was greater than could be accounted for by increase in BMD alone.

Table 4: Effect of Raloxifene Hydrochloride on Risk of Vertebral Fractures

	Number of Patients		Absolute Risk Reduction (ARR)	Relative Risk Reduction (95% CI)
	Raloxifene Hydrochloride	Placebo		
Fractures diagnosed radiographically				
Patients with no baseline fracture[a]	n = 1401	n = 1457		
Number (%) of patients with ≥ 1 new vertebral fracture	27 (1.9%)	62 (4.3%)	2.4%	55% (29%, 71%)
Patients with ≥ 1 baseline fracture[a]	n = 858	n = 835		
Number (%) of patients with ≥ 1 new vertebral fracture	121 (14.1%)	169 (20.2%)	6.1%	30% (14%, 44%)
Symptomatic vertebral fractures				
All randomized patients	n = 2557	n = 2576		
Number (%) of patients with ≥ 1 new clinical (painful) vertebral fracture	47 (1.8%)	81 (3.1%)	1.3%	41% (17%, 59%)

[a] Includes all patients with baseline and at least one follow-up radiograph.

The mean percentage change in BMD from baseline for raloxifene hydrochloride was statistically significantly greater than for placebo at each skeletal site (*see* **Table 5**).

Table 5: Raloxifene Hydrochloride- (60 mg Once Daily) Related Increases in BMD[a] for the Osteoporosis Treatment Study Expressed as Mean Percentage Increase vs. Placebo[b,c]

	Time		
	12 Months	24 Months	36 Months
Site	%	%	%
Lumbar Spine	2.0	2.6	2.6
Femoral Neck	1.3	1.9	2.1
Ultradistal Radius	ND[d]	2.2	ND[d]
Distal Radius	ND[d]	0.9	ND[d]
Total Body	ND[d]	1.1	ND[d]

[a] Note: all BMD increases were significant ($p < 0.001$).
[b] Intent-to-treat analysis; last observation carried forward.
[c] All patients received calcium and vitamin D.
[d] ND = not done (total body and radius BMD were measured only at 24 months).

Discontinuation from the study was required when excessive bone loss or multiple incident vertebral fractures occurred. Such discontinuation was statistically significantly more frequent in the placebo group (3.7%) than in the raloxifene hydrochloride group (1.1%).

Bone Histology

Bone biopsies for qualitative and quantitative histomorphometry were obtained at baseline and after 2 years of treatment. There were 56 paired biopsies evaluable for all indices. In raloxifene hydrochloride-treated patients, there were statistically significant decreases in bone formation rate per tissue volume, consistent with a reduction in bone turnover. Normal bone quality was maintained; specifically, there was no evidence of osteomalacia, marrow fibrosis, cellular toxicity, or woven bone after 2 years of treatment.

Effect on Endometrium

Endometrial thickness was evaluated annually in a subset of the study population (1781 patients) for 3 years. Placebo-treated women had a 0.27 mm mean decrease from baseline in endometrial thickness over 3 years, whereas the raloxifene hydrochloride-treated women had a 0.06 mm mean increase. Patients in the osteoporosis treatment study were not screened at baseline or excluded for preexisting endometrial or uterine disease. This study was not specifically designed to detect endometrial polyps. Over the 36 months of the study, clinically or histologically benign endometrial polyps were reported in 17 of 1999 placebo-treated women, 37 of 1948 raloxifene hydrochloride-treated women, and in 31 of 2010 women treated with raloxifene HCl 120 mg/day. There was no difference between raloxifene hydrochloride- and placebo-treated women in the incidences of endometrial carcinoma, vaginal bleeding, or vaginal discharge.

14.2 Prevention of Postmenopausal Osteoporosis

The effects of raloxifene hydrochloride on BMD in postmenopausal women were examined in three randomized, placebo-controlled, double-blind osteoporosis prevention trials: (1) a North American trial enrolled 544 women; (2) a European trial, 601 women; and (3) an international trial, 619 women who had undergone hysterectomy. In these trials, all women received calcium supplementation (400 to 600 mg/day). Women enrolled in these trials had a median age of 54 years and a median time since menopause of 5 years (less than 1 year up to 15 years postmenopause). The majority of the women were White (93.5%). Women were included if they had spine BMD between 2.5 standard deviations below and 2 standard deviations above the mean value for healthy young women. The mean T scores (number of standard deviations above or below the mean in healthy young women) for the three trials ranged from -1.01 to -0.74 for spine BMD and included women both with normal and low BMD. Raloxifene hydrochloride, 60 mg administered once daily, produced increases in bone mass versus calcium supplementation alone, as reflected by dual-energy x-ray absorptiometric (DXA) measurements of hip, spine, and total body BMD.

Effect on Bone Mineral Density

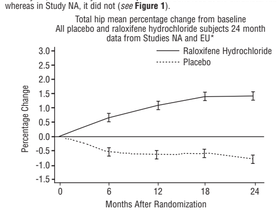
Compared with placebo, the increases in BMD for each of the three studies were statistically significant at 12 months and were maintained at 24 months (*see* **Table 6**). The placebo groups lost approximately 1% of BMD over 24 months.

Table 6: Raloxifene Hydrochloride- (60 mg Once Daily) Related Increases in BMD[a] for the Three Osteoporosis Prevention Studies Expressed as Mean Percentage Increase vs. Placebo[b] at 24 Months[c]

	Study		
	NA[d]	EU[d]	INT[d,e]
Site	%	%	%
Total Hip	2.0	2.4	1.3
Femoral Neck	2.1	2.5	1.6
Trochanter	2.2	2.7	1.3
Intertrochanter	2.3	2.4	1.3
Lumbar Spine	2.0	2.4	1.8

[a] Note: all BMD increases were significant ($p \leq 0.001$).
[b] All patients received calcium.
[c] Intent-to-treat analysis; last observation carried forward.
[d] Abbreviations: NA = North American, EU = European, INT = International.
[e] All women in the study had previously undergone hysterectomy.

Raloxifene hydrochloride also increased BMD compared with placebo in the total body by 1.3% to 2.0% and in Ward's Triangle (hip) by 3.1% to 4.0%. The effects of raloxifene hydrochloride on forearm BMD were inconsistent between studies. In Study EU, raloxifene hydrochloride prevented bone loss at the ultradistal radius, whereas in Study NA, it did not (*see* **Figure 1**).



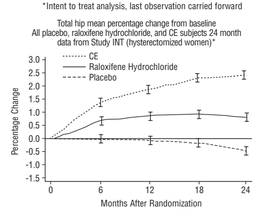


Figure 1: Total Hip Bone Mineral Density Mean Percentage Change From Baseline

Effect on Endometrium

In placebo-controlled osteoporosis prevention trials, endometrial thickness was evaluated every 6 months (for 24 months) by transvaginal ultrasonography (TVU). A total of 2978 TVU measurements were collected from 831 women in all dose groups. Placebo-treated women had a 0.04 mm mean decrease from baseline in endometrial thickness over 2 years, whereas the raloxifene hydrochloride-treated women had a 0.09 mm mean increase. Endometrial thickness measurements in raloxifene-treated women were indistinguishable from placebo. There were no differences between the raloxifene and placebo groups with respect to the incidence of reported vaginal bleeding.

14.5 Effects on Cardiovascular Disease

In a randomized, placebo-controlled, double-blind, multinational clinical trial (RUTH) of 10,101 postmenopausal women with documented coronary heart disease or at increased risk for coronary events, no cardiovascular benefit was demonstrated after treatment with raloxifene hydrochloride 60 mg once daily for a median follow-up of 5.6 years. No significant increase or decrease was observed for coronary events (death from coronary causes, nonfatal myocardial infarction, or hospitalization for an acute coronary syndrome). An increased risk of death due to stroke after treatment with raloxifene hydrochloride was observed: 59 (1.2%) raloxifene hydrochloride-treated women died due to a stroke compared to 39 (0.8%) placebo-treated women (2.2 versus 1.5 per 1000 women-years; hazard ratio 1.49; 95% confidence interval, 1.00 to 2.24; p = 0.0499). The incidence of stroke did not differ significantly between treatment groups (249 with raloxifene hydrochloride [4.9%] versus 224 with placebo [4.4%]; hazard ratio 1.10; 95% confidence interval 0.92 to 1.32; p = 0.30; 9.5 versus 8.6 per 1000 women-years) [*see Warnings and Precautions (5.2, 5.3)*].

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Raloxifene hydrochloride tablets USP are available as follows:

60 mg - white to off-white, film-coated, capsule-shaped tablets, debossed with "7290" on one side of the tablet, and "93" on the other side, in bottles of 30, 100, and 1000.

16.2 Storage and Handling

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. The USP defines controlled room temperature as a temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Medication Guide.

Physicians should instruct their patients to read the Medication Guide before starting therapy with raloxifene hydrochloride and to reread it each time the prescription is renewed.

17.1 Osteoporosis Recommendations, Including Calcium and Vitamin D Supplementation

For osteoporosis treatment or prevention, patients should be instructed to take supplemental calcium and/or vitamin D if intake is inadequate. Patients at increased risk for vitamin D insufficiency (e.g., over the age of 70 years, nursing home bound, chronically ill, or with gastrointestinal malabsorption syndromes) should be instructed to take additional vitamin D if needed. Weight-bearing exercises should be considered along with the modification of certain behavioral factors, such as cigarette smoking and/or excessive alcohol consumption, if these factors exist.

17.2 Patient Immobilization

Raloxifene hydrochloride should be discontinued at least 72 hours prior to and during prolonged immobilization (e.g., post-surgical recovery, prolonged bed rest), and patients should be advised to avoid prolonged restrictions of movement during travel because of the increased risk of venous thromboembolic events [*see Warnings and Precautions (5.1)*].

17.3 Hot Flashes or Flushes

Raloxifene hydrochloride may increase the incidence of hot flashes and is not effective in reducing hot flashes or flushes associated with estrogen deficiency. In some asymptomatic patients, hot flashes may occur upon beginning raloxifene hydrochloride therapy.

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MEDICATION GUIDE

Raloxifene Hydrochloride Tablets USP for Oral Use

Read the Medication Guide that comes with raloxifene hydrochloride tablets before you start taking them and each time you refill your prescription. The information may have changed. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment. Talk with your doctor about raloxifene hydrochloride tablets when you start taking them and at regular checkups.

What is the most important information I should know about raloxifene hydrochloride tablets?

Serious and life-threatening side effects can occur while taking raloxifene hydrochloride tablets. These include blood clots and dying from stroke:

- Increased risk of blood clots in the legs (deep vein thrombosis) and lungs (pulmonary embolism) have been reported with raloxifene hydrochloride tablets. Women who have or have had blood clots in the legs, lungs, or eyes should not take raloxifene hydrochloride tablets.
- Women who have had a heart attack or are at risk for a heart attack may have an increased risk of dying from stroke when taking raloxifene hydrochloride tablets.

1. Before starting raloxifene hydrochloride tablets, tell your doctor if you have had blood clots in your legs, lungs, or eyes, a stroke, mini-stroke (transient ischemic attack), or have an irregular heartbeat.
2. Stop taking raloxifene hydrochloride tablets and call your doctor if you have:
   - leg pain or a feeling of warmth in the lower leg (calf).
   - swelling of the legs, hands, or feet.
   - sudden chest pain, shortness of breath, or coughing up blood.
   - sudden change in your vision, such as loss of vision or blurred vision.
3. Being still for a long time (such as sitting still during a long car or airplane trip or being in bed after surgery) can increase your risk of blood clots (see **"What should I avoid if I am taking raloxifene hydrochloride tablets?"**).

What are raloxifene hydrochloride tablets?

Raloxifene hydrochloride tablets are a type of prescription medicine called a Selective Estrogen Receptor Modulator (SERM). Raloxifene hydrochloride tablets are for women after menopause.

Osteoporosis: Raloxifene hydrochloride tablets treat and prevent osteoporosis by helping make your bones stronger and less likely to break.

Raloxifene hydrochloride tablets are not for use in premenopausal women (women who have not passed menopause).

Who should not take raloxifene hydrochloride tablets?

Do not take raloxifene hydrochloride tablets if you:

- have or have had blood clots in your legs, lungs, or eyes. Taking raloxifene hydrochloride tablets may increase the risk of getting blood clots.
- are pregnant or could become pregnant. Raloxifene hydrochloride tablets could harm your unborn child.
- are nursing a baby. It is not known if raloxifene hydrochloride passes into breast milk or what effect it might have on the baby.

What should I tell my doctor before taking raloxifene hydrochloride tablets?

Raloxifene hydrochloride tablets may not be right for you. Before taking raloxifene hydrochloride tablets, tell your doctor about all your medical conditions, including if you:

- have had blood clots in your legs, lungs, or eyes, a stroke, mini-stroke (TIA/transient ischemic attack), or a type of irregular heartbeat (atrial fibrillation).
- have had breast cancer. Raloxifene hydrochloride tablets have not been fully studied in women who have a history of breast cancer.
- have liver or kidney problems.
- have taken estrogen in the past and had a high increase of triglycerides (a kind of fat in the blood).
- are pregnant, planning to become pregnant, or breast-feeding (see **"Who should not take raloxifene hydrochloride tablets?"**).

Tell your doctor about all medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine. Especially tell your doctor if you take:

- warfarin (Coumadin®, Jantoven®)

If you are taking warfarin or other coumarin blood thinners, your doctor may need to do a blood test when you first start or if you need to stop taking raloxifene hydrochloride tablets. Names for this test include "prothrombin time," "pro-time," or "INR." Your doctor may need to adjust the dose of your warfarin or other coumarin blood thinner.

- cholestyramine
- estrogens

Raloxifene hydrochloride tablets should not be taken with cholestyramine or estrogens.

How should I take raloxifene hydrochloride tablets?

- Take raloxifene hydrochloride tablets exactly how your doctor tells you to.
- Keep taking raloxifene hydrochloride tablets for as long as your doctor prescribes them for you.
- It is important to get your refills on time so you do not run out of the medicine.
- Take one raloxifene hydrochloride tablet each day.
- Take raloxifene hydrochloride tablets at any time of the day, with or without food.
- To help you remember to take raloxifene hydrochloride tablets, it may be best to take them at about the same time each day.
- Calcium and vitamin D may be taken at the same time as raloxifene hydrochloride tablets. It is important to take calcium and vitamin D, as directed by your physician, to prevent or treat osteoporosis.
- If you miss a dose, take it as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and take only your next regularly scheduled dose. Do not take two doses at the same time.

What should I avoid while taking raloxifene hydrochloride tablets?

- Being still for a long time (such as during long trips or being in bed after surgery) can increase the risk of blood clots. Raloxifene hydrochloride tablets may add to this risk. If you will need to be still for a long time, talk with your doctor about ways to reduce the risk of blood clots. On long trips, move around periodically. Stop taking raloxifene hydrochloride tablets at least 3 days before a planned surgery or before you plan on being still for a long time. You should start taking raloxifene hydrochloride tablets again when you return to your normal activities.
- Some medicines should not be taken with raloxifene hydrochloride tablets (see **"What should I tell my doctor before taking raloxifene hydrochloride tablets?"**).

What are the possible side effects of raloxifene hydrochloride tablets?

Serious and life-threatening side effects can occur while taking raloxifene hydrochloride tablets. These include blood clots and dying from stroke:

- Increased risk of blood clots in the legs (deep vein thrombosis) and lungs (pulmonary embolism) have been reported with raloxifene hydrochloride tablets. Women who have or have had blood clots in the legs, lungs, or eyes should not take raloxifene hydrochloride tablets.
- Women who have had a heart attack or are at risk for a heart attack may have an increased risk of dying from stroke when taking raloxifene hydrochloride tablets.

See **"What is the most important information I should know about raloxifene hydrochloride tablets?"**

The most common side effects of raloxifene hydrochloride tablets are hot flashes, leg cramps, swelling of the feet, ankles, and legs, flu syndrome, joint pain, and sweating. Hot flashes are more common during the first 6 months after starting treatment.

These are not all the side effects of raloxifene hydrochloride tablets. Tell your doctor about any side effect that bothers you or that does not go away. If you have any problems or questions that concern you while taking raloxifene hydrochloride tablets, ask your doctor or pharmacist for more information.

What else should I know about raloxifene hydrochloride tablets?

- Do not use raloxifene hydrochloride tablets to prevent heart disease, heart attack, or strokes.
- To get the calcium and vitamin D you need, your doctor may advise you to change your diet and/or take supplemental calcium and vitamin D. Your doctor may suggest other ways to help treat or prevent osteoporosis, in addition to taking raloxifene hydrochloride tablets and getting the calcium and vitamin D you need. These may include regular exercise, stopping smoking, and drinking less alcohol.
- Women who have hot flashes can take raloxifene hydrochloride tablets. Raloxifene hydrochloride tablets do not treat hot flashes, and they may cause hot flashes in some women (see **"What are the possible side effects of raloxifene hydrochloride tablets?"**).
- Raloxifene hydrochloride tablets have not been found to cause breast tenderness or enlargement. If you notice any changes in your breasts, call your doctor to find out the cause. Before starting and while taking raloxifene hydrochloride tablets you should have breast exams and mammograms, as directed by your doctor. Because raloxifene hydrochloride tablets do not eliminate the chance of developing breast cancers, you need these examinations to find any breast cancers as early as possible.
- Raloxifene hydrochloride tablets should not cause spotting or menstrual-type bleeding. If you have any vaginal bleeding, call your doctor to find out the cause. Raloxifene hydrochloride tablets have not been found to increase the risk for cancer of the lining of the uterus.
- Women in clinical trials have taken raloxifene hydrochloride for up to eight years.

How should I store raloxifene hydrochloride tablets?

- Store raloxifene hydrochloride tablets at 20° to 25°C (68° to 77°F).
- **Keep raloxifene hydrochloride tablets and all medicines out of the reach of children.**

General Information about the safe and effective use of raloxifene hydrochloride tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use raloxifene hydrochloride tablets for a condition for which they were not prescribed. Do not give your raloxifene hydrochloride tablets to other people, even if they have the same symptoms you have. They may harm them.

This Medication Guide is a summary of the most important information about raloxifene hydrochloride tablets. If you would like more information about raloxifene hydrochloride tablets, talk with your doctor. You can ask your doctor or pharmacist for information about raloxifene hydrochloride tablets that is written for health professionals. For more information, call 1-888-838-2872, MEDICAL AFFAIRS.

What are the ingredients in raloxifene hydrochloride tablets?

Active Ingredient: raloxifene hydrochloride

Inactive Ingredients: colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, povidone, pregelatinized starch, and titanium dioxide.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

All brand names listed are the registered trademarks of their respective owners and are not trademarks of Teva Pharmaceuticals USA.

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel
Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Rev. C 6/2012

MEDICATION GUIDE
Raloxifene Hydrochloride Tablets USP for Oral Use

Read the Medication Guide that comes with raloxifene hydrochloride tablets before you start taking them and each time you refill your prescription. The information may have changed. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment. Talk with your doctor about raloxifene hydrochloride tablets when you start taking them and at regular checkups.

What is the most important information I should know about raloxifene hydrochloride tablets?

Serious and life-threatening side effects can occur while taking raloxifene hydrochloride tablets. These include blood clots and dying from stroke:

- Increased risk of blood clots in the legs (deep vein thrombosis) and lungs (pulmonary embolism) have been reported with raloxifene hydrochloride tablets. Women who have or have had blood clots in the legs, lungs, or eyes should not take raloxifene hydrochloride tablets.
- Women who have had a heart attack or are at risk for a heart attack may have an increased risk of dying from stroke when taking raloxifene hydrochloride tablets.

1. Before starting raloxifene hydrochloride tablets, tell your doctor if you have had blood clots in your legs, lungs, or eyes, a stroke, mini-stroke (transient ischemic attack), or have an irregular heartbeat.
2. Stop taking raloxifene hydrochloride tablets and call your doctor if you have:
   - leg pain or a feeling of warmth in the lower leg (calf).
   - swelling of the legs, hands, or feet.
   - sudden chest pain, shortness of breath, or coughing up blood.
   - sudden change in your vision, such as loss of vision or blurred vision.
3. Being still for a long time (such as sitting still during a long car or airplane trip or being in bed after surgery) can increase your risk of blood clots (see "**What should I avoid if I am taking raloxifene hydrochloride tablets?**").

What are raloxifene hydrochloride tablets?

Raloxifene hydrochloride tablets are a type of prescription medicine called a Selective Estrogen Receptor Modulator (SERM). Raloxifene hydrochloride tablets are for women after menopause.

Osteoporosis: Raloxifene hydrochloride tablets treat and prevent osteoporosis by helping make your bones stronger and less likely to break.

Raloxifene hydrochloride tablets are not for use in premenopausal women (women who have not passed menopause).

Who should not take raloxifene hydrochloride tablets?

Do not take raloxifene hydrochloride tablets if you:

- have or have had blood clots in your legs, lungs, or eyes. Taking raloxifene hydrochloride tablets may increase the risk of getting blood clots.
- are pregnant or could become pregnant. Raloxifene hydrochloride tablets could harm your unborn child.
- are nursing a baby. It is not known if raloxifene hydrochloride passes into breast milk or what effect it might have on the baby.

What should I tell my doctor before taking raloxifene hydrochloride tablets?

Raloxifene hydrochloride tablets may not be right for you. Before taking raloxifene hydrochloride tablets, tell your doctor about all your medical conditions, including if you:

- have had blood clots in your legs, lungs, or eyes, a stroke, mini-stroke (TIA/transient ischemic attack), or a type of irregular heartbeat (atrial fibrillation).
- have had breast cancer. Raloxifene hydrochloride tablets have not been fully studied in women who have a history of breast cancer.
- have liver or kidney problems.
- have taken estrogen in the past and had a high increase of triglycerides (a kind of fat in the blood).
- are pregnant, planning to become pregnant, or breast-feeding (see "**Who should not take raloxifene hydrochloride tablets?**").

Tell your doctor about all medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine. Especially tell your doctor if you take:

- warfarin (Coumadin®, Jantoven®)

If you are taking warfarin or other coumarin blood thinners, your doctor may need to do a blood test when you first start or if you need to stop taking raloxifene hydrochloride tablets. Names for this test include "prothrombin time," "pro-time," or "INR." Your doctor may need to adjust the dose of your warfarin or other coumarin blood thinner.

- cholestyramine
- estrogens

Raloxifene hydrochloride tablets should not be taken with cholestyramine or estrogens.

How should I take raloxifene hydrochloride tablets?

- Take raloxifene hydrochloride tablets exactly how your doctor tells you to.
- Keep taking raloxifene hydrochloride tablets for as long as your doctor prescribes them for you.
- It is important to get your refills on time so you do not run out of the medicine.
- Take one raloxifene hydrochloride tablet each day.
- Take raloxifene hydrochloride tablets at any time of the day, with or without food.
- To help you remember to take raloxifene hydrochloride tablets, it may be best to take them at about the same time each day.
- Calcium and vitamin D may be taken at the same time as raloxifene hydrochloride tablets. It is important to take calcium and vitamin D, as directed by your physician, to prevent or treat osteoporosis.
- If you miss a dose, take it as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and take only your next regularly scheduled dose. Do not take two doses at the same time.

℞ only

Rev. C 6/2012

RALOXIFENE HYDROCHLORIDE TABLETS USP 7290

What should I avoid while taking raloxifene hydrochloride tablets?

- Being still for a long time (such as during long trips or being in bed after surgery) can increase the risk of blood clots. Raloxifene hydrochloride tablets may add to this risk. If you will need to be still for a long time, talk with your doctor about ways to reduce the risk of blood clots. On long trips, move around periodically. Stop taking raloxifene hydrochloride tablets at least 3 days before a planned surgery or before you plan on being still for a long time. You should start taking raloxifene hydrochloride tablets again when you return to your normal activities.
- Some medicines should not be taken with raloxifene hydrochloride tablets (see "**What should I tell my doctor before taking raloxifene hydrochloride tablets?**").

What are the possible side effects of raloxifene hydrochloride tablets?

Serious and life-threatening side effects can occur while taking raloxifene hydrochloride tablets. These include blood clots and dying from stroke:

- Increased risk of blood clots in the legs (deep vein thrombosis) and lungs (pulmonary embolism) have been reported with raloxifene hydrochloride tablets. Women who have or have had blood clots in the legs, lungs, or eyes should not take raloxifene hydrochloride tablets.
- Women who have had a heart attack or are at risk for a heart attack may have an increased risk of dying from stroke when taking raloxifene hydrochloride tablets.

See **"What is the most important information I should know about raloxifene hydrochloride tablets?"**

The most common side effects of raloxifene hydrochloride tablets are hot flashes, leg cramps, swelling of the feet, ankles, and legs, flu syndrome, joint pain, and sweating. Hot flashes are more common during the first 6 months after starting treatment.

These are not all the side effects of raloxifene hydrochloride tablets. Tell your doctor about any side effect that bothers you or that does not go away. If you have any problems or questions that concern you while taking raloxifene hydrochloride tablets, ask your doctor or pharmacist for more information.

What else should I know about raloxifene hydrochloride tablets?

- Do not use raloxifene hydrochloride tablets to prevent heart disease, heart attack, or strokes.
- To get the calcium and vitamin D you need, your doctor may advise you to change your diet and/or take supplemental calcium and vitamin D. Your doctor may suggest other ways to help treat or prevent osteoporosis, in addition to taking raloxifene hydrochloride tablets and getting the calcium and vitamin D you need. These may include regular exercise, stopping smoking, and drinking less alcohol.
- Women who have hot flashes can take raloxifene hydrochloride tablets. Raloxifene hydrochloride tablets do not treat hot flashes, and they may cause hot flashes in some women (see "**What are the possible side effects of raloxifene hydrochloride tablets?**").
- Raloxifene hydrochloride tablets have not been found to cause breast tenderness or enlargement. If you notice any changes in your breasts, call your doctor to find out the cause. Before starting and while taking raloxifene hydrochloride tablets you should have breast exams and mammograms, as directed by your doctor. Because raloxifene hydrochloride tablets do not eliminate the chance of developing breast cancers, you need these examinations to find any breast cancers as early as possible.
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- Women in clinical trials have taken raloxifene hydrochloride for up to eight years.

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Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured In Israel By:
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Jerusalem, 91010, Israel
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Sellersville, PA 18960
Rev. C 6/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78193

LABELING REVIEWS

Office of Generic Drugs

REVIEW OF PROFESSIONAL LABELING (Sixth Cycle)

APPROVAL SUMMARY (Supersedes TA Summary dated October 25, 2013)

ANDA Number:	078193
Date of Submission:	January 27, 2014
Applicant:	TEVA Pharmaceuticals USA
Established Name and Strength:	Raloxifene Hydrochloride Tablets USP, 60 mg
Proposed Proprietary Name:	NA

Labeling Comments below are considered:

☐ Minor Deficiency *

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

☒ No Comments (Approval Summary)

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

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated January 27, 2014.

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

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

Note RPM - Labeling comments end here

REVISIONS NEEDED POST APPROVAL?

- **Include the phonetic spelling of the drug where it appears in the Medication Guide Title.**
- **Encourage NDC numbers with the listing of packages in HOW SUPPLIED.**

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

Review Summary

Labeling Submitted (Zagreb and Israel versions)	Date submitted	Final or Draft	Recommendation

CONTAINER (30's, 100's, 1000's)	January 27, 2014	FPL	Satisfactory in FPL
INSERT	January 27, 2014	FPL (6 pt type)	Satisfactory in FPL
MEDICATION GUIDE	January 27, 2014	FPL (10 pt type)	Satisfactory in FPL
SPL	None submitted	NA	NA

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

FOR THE RECORD (Some from previous review):

1. **MODEL LABELING**

Model Labeling - This review is based on the labeling of Evista Tablets by Lilly NDA 020815/S-025, approved September 13, 2007. See Note:

NDA 20-815/S-025 provided for new indications (reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and women at high risk for invasive cancer). These indications were approved under NDA 22-042. NDA 22-042 is a type 6 NDA and therefore not be listed in the OB. All exclusivity and updates are filed under the parent NDA 20-815, and according to the approval letter, "All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions [for NDA 22-042] should be addressed to the original NDA 20-815 for this drug product, not to this NDA [NDA 22-042]. In the future, do not make submissions to this NDA [NDA 22-042] except for the final printed labeling requested above."
Teva has requested to carve-out information pertaining to the new indication because it is protected by exclusivity. Teva's insert labeling has been revised accordingly.

2. **USP & PF**

Raloxifene Hydrochloride Tablets

DEFINITION

Raloxifene Hydrochloride Tablets contain NLT 93.0% and NMT 107.0% of the labeled amount of raloxifene hydrochloride ($C_{28}H_{27}NO_4S \cdot HCl$).

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, and store at controlled room temperature.

3. **PATENT AND EXCLUSIVITY**

Patent No	Patent Expiration	Patent Use Code	How filed	Impact
5393763	JUL 28,2012	U-114	PIV (3/2/06 submission)	None
5457117	JUL 28,2012	U-114	PIV (3/2/06 submission)	None
5478847	MAR 02,2014	U-114	PIV (3/2/06 submission)	None
5811120	MAR 02,2014		PIV (3/2/06 submission)	None
5972383	MAR 02,2014	U-287	PIV (3/2/06 submission)	None
6458811	MAR 10,2017	U-825	PIV (3/2/06 submission)	None
6797719	MAR 10,2017		PIV (3/2/06 submission)	None
6894064	MAR 10,2017	U-657	PIV (3/2/06 submission)	None
6906086	JUL 28,2012	U-657	PIV (3/2/06 submission)	None
6906086	JUL 28,2012	U-662	PIV (3/2/06 submission)	None
RE38968	JUL 28,2012	U-662	PIV (3/2/06 submission)	None
RE38968	JUL 28,2012	U-657	PIV (3/2/06 submission)	None
RE39049	JUL 28,2012	U-662	PIV (4/6/06 amendment)	None
RE39049	JUL 28,2012	U-657	PIV (4/6/06 amendment)	None
RE39050	MAR 02,2014	U-662	PIV (4/6/06 amendment)	None
RE39050	MAR 02,2014	U-657	PIV (4/6/06 amendment)	None

Code	Definition
U-114	USE FOR INHIBITING BONE RESORPTION
U-287	TREATMENT OR PREVENTION OF OSTEOPOROSIS
U-657	PREVENTION OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN
U-662	TREATMENT OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN
U-825	USE FOR PREVENTION OF BREAST CANCER

7/25/2006-1:06-cv-1017-SEB-VSS filed in Southern Distric of IN for infringement of '050, '968, '049, and '086/mhs

Exclusivity Data

Exclusivity Code	Exclusivity Expiration	How filed
I-539	SEP 13, 2010	**Carve-out (1/25/08 submission)**
ODE	SEP 13, 2014	**Carve-out (6/27/08 submission)**

Code	Definition
I-539	REDUCTION IN RISK OF INVASIVE BREAST CANCER IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS AND WOMEN AT HIGH RISK FOR INVASIVE CANCER
ODE	Designation approved: Reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and reduction in risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer http://www.fda.gov/orphan/designat/list.htm

Teva's Exclusivity statement:

The indication protected by exclusivity I-539 and the ODE is not included in our labeling and will not appear in labeling for commercial distribution before expiration of the Orphan Drug Exclusivity on September 13, 2014.

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, October 16, 2008 4:20 PM
To: Shimer, Martin
Cc: Danso, Benjamin; Rickman, William P; Lee, Koung U
Subject: RE: TEVA's ANDA 78-193 for Raloxifene Tablets

Hi Marty,

There are only 3 indications for Evista:
EVISTA® is an estrogen agonist/antagonist indicated for:
• Treatment and prevention of osteoporosis in postmenopausal women. (1.1)
• Reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis. (1.2)
• Reduction in risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer. (1.3)

If a use code does not necessarily have to be linked to a particular indication & usage in the insert, then we'll leave the patent certification as is.

Thanks,

Ruby

From: Shimer, Martin
Sent: Thursday, October 16, 2008 2:22 PM
To: Wu, Ruby (Chi-Ann)
Cc: Danso, Benjamin; Rickman, William P
Subject: RE: TEVA's ANDA 78-193 for Raloxifene Tablets

Ruby,

Does the labeling for Evista include sections that appear to be attributable to both the I-539 exclusivity and to the U-825 method of use? I can see where the definitions REDUCTION IN RISK OF INVASIVE BREAST CANCER IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS AND WOMEN AT HIGH RISK FOR INVASIVE CANCER would not be considered synonymous with USE FOR PREVENTION OF BREAST CANCER. The former definition is rather specific for certain groups of females('postmenopausal women with osteoporosis and women at high risk'-other women outside of these groups are susceptible to osteoporosis) whereas the second definition is quite broad. I also don't necessarily see REDUCTION IN RISK as being the same as PREVENTION. For these reasons I'm of the opinion that TEVA can maintain address the exclusivity and the patent incongruously.

If the labeling doesn't appear to permit this sort of analysis let me know.

Marty

From: *Wu, Ruby (Chi-Ann)*
Sent: *Wednesday, October 15, 2008 4:33 PM*
To: *Shimer, Martin*

Cc: *Danso, Benjamin*
Subject: *RE: TEVA's ANDA 78-193 for Raloxifene Tablets*

Hi Marty,

According to Teva's 6/27/08 submission:

The indication protected by exclusivity I-539 and the ODE is not included in our labeling and will not appear in labeling for commercial distribution before expiration of the Orphan Drug Exclusivity on September 13, 2014.

I-539 and ODE provide for REDUCTION IN RISK OF INVASIVE BREAST CANCER IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS AND WOMEN AT HIGH RISK FOR INVASIVE CANCER and Teva has carved out this indication.

U-825 "USE FOR PREVENTION OF BREAST CANCER" has been added to '811 patent. Teva originally filed PIV. To be consistent with the exclusivity statement, does Teva need to revise their patent certification for '811 from PIV to MOU?

Ruby

In the letter dated January 27, 2014, TEVA explains that some of the patent certifications originally filed as Paragraph IV have been revised to Paragraph III:

> * All certifications in Teva's original ANDA, submitted on March 2, 2006, were PIV, as were the later-submitted certifications to the '049, '050 and '330. Certifications to the '763, '117, '847, '120, '383, '086, '968, '049 and '050 were later revised from P4 to P3 in a Patent Amendment dated February 9, 2011 (all expire on or before March 2, 2014).

As can be seen in the table above, four patents will remain in force after March 2, 2014, the date upon which Teva requests issuance of final approval for ANDA 078193: the '811, '719, '064 and '330 patents. It is our understanding that while the (b) (4) ANDA holds entitlement to exclusivity for the '811, '719 and '064 patents, Teva and (b) (4) share first-to-file status for the '330 patent.

4. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling is consistent with the composition statement.

(b) (4)

- Pregelatinized Starch NF (b) (4)
- Raloxifene Hydrochloride
- Magnesium Stearate NF
- (b) (4)
- Povidone USP (b) (4)
- Colloidal Silicon Dioxide NF (b) (4)
- Microcrystalline Cellulose NF (b) (4)

(b) (4)

- Hydroxypropyl Methylcellulose
- Polydextrose;
- Titanium Dioxide USP;
- Polyethylene Glycol (b) (4)

5. MANUFACTURING FACILITY

Original Site:
TEVA Pharmaceutical Industries
Hashikma Street, Industrial Zone Kfar-Saba 44102
ISRAEL Registration no. 3002721084

Additional site proposed in the March 31, 2008 amendment:
TEVA Pharmaceuticals USA
650 Cathill RD
Sellersville, PA 18960

See note from sponsor's current submission:

> Teva hereby acknowledges that the Division of Labeling had no further comments at the time of issuance of the May 15, 2013 complete response letter. However, please note that the draft package insert, medication guide and container labels for Teva's Kfar Saba facility have been updated to include format-related changes in accord with Teva's standard format. In addition, the draft labeling for Teva's Zagreb, Croatia facility, which incorporates the above-noted changes for the Kfar Saba facility, is being provided herein for completeness of the file.
>
> All draft labeling items for both proposed manufacturing facilities are provided **herein** as follows:

Zagreb, Croatia:

- Draft package insert (Rev. C 6/2012) in Word and PDF formats
- Comparison of current package insert for Zagreb, Croatia (Rev. C 6/2012) to current package insert for Kfar Saba, Israel (Rev. C 6/2012) in PDF format
- Draft medication guide (Rev. C 6/2012) in Word and PDF formats
- Comparison of current medication guide for Zagreb, Croatia (Rev. C 6/2012) to current medication guide for Kfar Saba, Israel medication guide (Rev. C 6/2012) in PDF format
- Draft container labels (Rev. B 6/2012) in Word and PDF formats
- Comparison of current container labels for Zagreb, Croatia (Rev. B 6/2012) to current containers labels for Kfar Saba, Israel (Rev. B 6/2012) in PDF format

Kfar Saba, Israel:

- Draft package insert (Rev. C 6/2012) in Word and PDF formats
- Comparison of current package insert (Rev. C 6/2012) to previously submitted package insert (Rev. A 10/2008) in PDF format
- Draft medication guide (Rev. C 6/2012) in Word and PDF formats
- Comparison of current medication guide (Rev. C 6/2012) to previously submitted medication guide (Rev. A 10/2008) in PDF format
- Draft container labels (Rev. B 6/2012) in Word and PDF formats
- Comparison of current container labels (Rev. B 6/2012) to previously submitted container labels (Rev. A 10/2008) in PDF format

Please note that Teva's Sellersville, PA site is not currently manufacturing Raloxifene Hydrochloride Tablets, USP. In the event that we decide to resume manufacturing at this facility in the future, we commit to update Teva's draft labeling for the Sellersville, PA site to reflect the above-noted changes.

6. FINISHED PRODUCT DESCRIPTION

RLD: White, elliptical and film coated tablets

ANDA: White to off white, film coated capsule shaped tablet, debossed with "7290" on one side of the tablet, and "93" on the other.

7. STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS

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

DISPENSING STATEMENTS COMPARISON
RLD: Dispense in a tight container.
ANDA: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

8. PRODUCT LINE

RLD: 30s, 100s, 2000
ANDA: Container: white round HDPE; Closure: 30s-CRC; 100s-CRC and non-CRC, 1000s- nonCRC

(b) (4)

9. **CONTAINER/CLOSURE**

ANDA: Container: white round HDPE; Closure: 30s-CRC; 100s-CRC and non-CRC, 1000s- nonCRC

(b) (4)

10. **MEDICATION GUIDES**

According to Philip Erickson of Teva on 10/16/08:
30s: 1 medication guide will be provided.
100s: 4 medication guides will be provided.
1000s: 34 medication guides will be provided.

11. **RELATED APPLICATIONS** None

12. **SPL DATA ELEMENTS** None submitted this review cycle

13. **CITIZENS PETITION/PROPRIETARY NAME/CONSULTS** None

Date of Review:	February 3, 2014
Primary Reviewer:	Charlie Hoppes
Team Leader:	John Grace

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

/s/

CHARLES V HOPPES
02/04/2014

JOHN F GRACE
02/04/2014

Office of Generic Drugs

REVIEW OF PROFESSIONAL LABELING (Fifth Cycle)

TENTATIVE APPROVAL SUMMARY

ANDA Number:	078193
Date of Submission:	August 6, 2013
Applicant:	TEVA Pharmaceuticals USA
Established Name and Strength:	Raloxifene Hydrochloride Tablets USP, 60 mg
Proposed Proprietary Name:	NA

Labeling Comments below are considered:

☐ Minor Deficiency *

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

☒ No Comments (Tentative Approval Summary)

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

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated August 6, 2013.

Prior to the submission of your final printed labeling, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

Note RPM - Labeling comments end here

REVISIONS NEEDED POST APPROVAL?

- **Include the phonetic spelling of the drug where it appears in the Medication Guide Title.**
- **Encourage NDC numbers with the listing of packages in HOW SUPPLIED.**

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

Review Summary

Labeling Submitted	Date submitted	Final or Draft	Recommendation
CONTAINER (30's, 100's, 1000's)	8/6/2013	Draft	Satisfactory in draft

INSERT	8/6/2013	Draft	Satisfactory in draft
MEDICATION GUIDE	8/6/2013	Draft	Satisfactory in draft
SPL	None submitted	NA	NA

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

FOR THE RECORD (Some from previous review):

1. **MODEL LABELING**

Model Labeling - This review is based on the labeling of Evista Tablets by Lilly NDA 020815/S-025, approved September 13, 2007. See Note:

NDA 20-815/S-025 provided for new indications (reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and women at high risk for invasive cancer). These indications were approved under NDA 22-042. NDA 22-042 is a type 6 NDA and therefore not be listed in the OB. All exclusivity and updates are filed under the parent NDA 20-815, and according to the approval letter, "All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions [for NDA 22-042] should be addressed to the original NDA 20-815 for this drug product, not to this NDA [NDA 22-042]. In the future, do not make submissions to this NDA [NDA 22-042] except for the final printed labeling requested above."
Teva has requested to carve-out information pertaining to the new indication because it is protected by exclusivity. Teva's insert labeling has been revised accordingly.

2. **USP & PF**

Raloxifene Hydrochloride Tablets

DEFINITION

Raloxifene Hydrochloride Tablets contain NLT 93.0% and NMT 107.0% of the labeled amount of raloxifene hydrochloride ($C_{28}H_{27}NO_4S \cdot HCl$).

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, and store at controlled room temperature.

3. **PATENT AND EXCLUSIVITY**

Patent No	Patent Expiration	Patent Use Code	How filed	Impact
5393763	JUL 28,2012	U-114	PIV (3/2/06 submission)	None
5457117	JUL 28,2012	U-114	PIV (3/2/06 submission)	None
5478847	MAR 02,2014	U-114	PIV (3/2/06 submission)	None
5811120	MAR 02,2014		PIV (3/2/06 submission)	None
5972383	MAR 02,2014	U-287	PIV (3/2/06 submission)	None
6458811	MAR 10,2017	U-825	PIV (3/2/06 submission)	None
6797719	MAR 10,2017		PIV (3/2/06 submission)	None
6894064	MAR 10,2017	U-657	PIV (3/2/06 submission)	None
6906086	JUL 28,2012	U-657	PIV (3/2/06 submission)	None
6906086	JUL 28,2012	U-662	PIV (3/2/06 submission)	None
RE38968	JUL 28,2012	U-662	PIV (3/2/06 submission)	None
RE38968	JUL 28,2012	U-657	PIV (3/2/06 submission)	None
RE39049	JUL 28,2012	U-662	PIV (4/6/06 amendment)	None
RE39049	JUL 28,2012	U-657	PIV (4/6/06 amendment)	None
RE39050	MAR 02,2014	U-662	PIV (4/6/06 amendment)	None
RE39050	MAR 02,2014	U-657	PIV (4/6/06 amendment)	None

Code	Definition
U-114	USE FOR INHIBITING BONE RESORPTION
U-287	TREATMENT OR PREVENTION OF OSTEOPOROSIS
U-657	PREVENTION OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN
U-662	TREATMENT OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN
U-825	USE FOR PREVENTION OF BREAST CANCER

7/25/2006-1:06-cv-1017-SEB-VSS filed in Southern Distric of IN for infringement of '050, '968, '049, and '086/mhs

Exclusivity Data

Exclusivity Code	Exclusivity Expiration	How filed
I-539	SEP 13, 2010	**Carve-out (1/25/08 submission)**
ODE	SEP 13, 2014	**Carve-out (6/27/08 submission)**

Code	Definition
I-539	REDUCTION IN RISK OF INVASIVE BREAST CANCER IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS AND WOMEN AT HIGH RISK FOR INVASIVE CANCER
ODE	Designation approved: Reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and reduction in risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer http://www.fda.gov/orphan/designat/list.htm

Teva's Exclusivity statement:

The indication protected by exclusivity I-539 and the ODE is not included in our labeling and will not appear in labeling for commercial distribution before expiration of the Orphan Drug Exclusivity on September 13, 2014.

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, October 16, 2008 4:20 PM
To: Shimer, Martin
Cc: Danso, Benjamin; Rickman, William P; Lee, Koung U
Subject: RE: TEVA's ANDA 78-193 for Raloxifene Tablets

Hi Marty,

There are only 3 indications for Evista:
EVISTA® is an estrogen agonist/antagonist indicated for:
- *Treatment and prevention of osteoporosis in postmenopausal women. (1.1)*
- *Reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis. (1.2)*
- *Reduction in risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer. (1.3)*

If a use code does not necessarily have to be linked to a particular indication & usage in the insert, then we'll leave the patent certification as is.

Thanks,

Ruby

From: Shimer, Martin
Sent: Thursday, October 16, 2008 2:22 PM
To: Wu, Ruby (Chi-Ann)
Cc: Danso, Benjamin; Rickman, William P
Subject: RE: TEVA's ANDA 78-193 for Raloxifene Tablets

Ruby,

Does the labeling for Evista include sections that appear to be attributable to both the I-539 exclusivity and to the U-825 method of use? I can see where the definitions REDUCTION IN RISK OF INVASIVE BREAST CANCER IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS AND WOMEN AT HIGH RISK FOR INVASIVE CANCER would not be considered synonymous with USE FOR PREVENTION OF BREAST CANCER. The former definition is rather specific for certain groups of females('postmenopausal women with osteoporosis and women at high risk'-other women outside of these groups are susceptible to osteoporosis) whereas the second definition is quite broad. I also don't necessarily see REDUCTION IN RISK as being the same as PREVENTION. For these reasons I'm of the opinion that TEVA can maintain address the exclusivity and the patent incongruously.

If the labeling doesn't appear to permit this sort of analysis let me know.

Marty

From: *Wu, Ruby (Chi-Ann)*
Sent: *Wednesday, October 15, 2008 4:33 PM*
To: *Shimer, Martin*

Cc: *Danso, Benjamin*
Subject: *RE: TEVA's ANDA 78-193 for Raloxifene Tablets*

Hi Marty,

According to Teva's 6/27/08 submission:

The indication protected by exclusivity I-539 and the ODE is not included in our labeling and will not appear in labeling for commercial distribution before expiration of the Orphan Drug Exclusivity on September 13, 2014.

I-539 and ODE provide for REDUCTION IN RISK OF INVASIVE BREAST CANCER IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS AND WOMEN AT HIGH RISK FOR INVASIVE CANCER and Teva has carved out this indication.

U-825 "USE FOR PREVENTION OF BREAST CANCER" has been added to '811 patent. Teva originally filed PIV. To be consistent with the exclusivity statement, does Teva need to revise their patent certification for '811 from PIV to MOU?

Ruby

4. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling is consistent with the composition statement.

(b) (4)

- Pregelatinized Starch NF (b) (4)
- Raloxifene Hydrochloride
- Magnesium Stearate NF
- (b) (4)
- Povidone USP (b) (4)
- Colloidal Silicon Dioxide NF (b) (4)
- Microcrystalline Cellulose NF (b) (4)

(b) (4)

- Hydroxypropyl Methylcellulose
- Polydextrose;
- Titanium Dioxide USP;
- Polyethylene Glycol (b) (4)

5. MANUFACTURING FACILITY

Original Site:
TEVA Pharmaceutical Industries
Hashikma Street, Industrial Zone Kfar-Saba 44102
ISRAEL Registration no. 3002721084

Additional site proposed in the March 31, 2008 amendment:
TEVA Pharmaceuticals USA
650 Cathill RD
Sellersville, PA 18960

See note from sponsor's current submission:

Teva hereby acknowledges that the Division of Labeling had no further comments at the time of issuance of the May 15, 2013 complete response letter. However, please note that the draft package insert, medication guide and container labels for Teva's Kfar Saba facility have been updated to include format-related changes in accord with Teva's standard format. In addition, the draft labeling for Teva's Zagreb, Croatia facility, which incorporates the above-noted changes for the Kfar Saba facility, is being provided herein for completeness of the file.

All draft labeling items for both proposed manufacturing facilities are provided **herein** as follows:

Zagreb, Croatia:

- Draft package insert (Rev. C 6/2012) in Word and PDF formats
- Comparison of current package insert for Zagreb, Croatia (Rev. C 6/2012) to current package insert for Kfar Saba, Israel (Rev. C 6/2012) in PDF format
- Draft medication guide (Rev. C 6/2012) in Word and PDF formats
- Comparison of current medication guide for Zagreb, Croatia (Rev. C 6/2012) to current medication guide for Kfar Saba, Israel medication guide (Rev. C 6/2012) in PDF format
- Draft container labels (Rev. B 6/2012) in Word and PDF formats
- Comparison of current container labels for Zagreb, Croatia (Rev. B 6/2012) to current containers labels for Kfar Saba, Israel (Rev. B 6/2012) in PDF format

Kfar Saba, Israel:

- Draft package insert (Rev. C 6/2012) in Word and PDF formats
- Comparison of current package insert (Rev. C 6/2012) to previously submitted package insert (Rev. A 10/2008) in PDF format
- Draft medication guide (Rev. C 6/2012) in Word and PDF formats
- Comparison of current medication guide (Rev. C 6/2012) to previously submitted medication guide (Rev. A 10/2008) in PDF format
- Draft container labels (Rev. B 6/2012) in Word and PDF formats
- Comparison of current container labels (Rev. B 6/2012) to previously submitted container labels (Rev. A 10/2008) in PDF format

Please note that Teva's Sellersville, PA site is not currently manufacturing Raloxifene Hydrochloride Tablets, USP. In the event that we decide to resume manufacturing at this facility in the future, we commit to update Teva's draft labeling for the Sellersville, PA site to reflect the above-noted changes.

6. FINISHED PRODUCT DESCRIPTION

RLD: White, elliptical and film coated tablets

ANDA: White to off white, film coated capsule shaped tablet, debossed with "7290" on one side of the tablet, and "93" on the other.

7. STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS

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

DISPENSING STATEMENTS COMPARISON
RLD: Dispense in a tight container.
ANDA: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

8. PRODUCT LINE

RLD: 30s, 100s, 2000
ANDA: Container: white round HDPE; Closure: 30s-CRC; 100s-CRC and non-CRC, 1000s- nonCRC

(b) (4)

9. **CONTAINER/CLOSURE**

ANDA: Container: white round HDPE; Closure: 30s-CRC; 100s-CRC and non-CRC, 1000s- nonCRC

(b) (4)

10. **MEDICATION GUIDES**

According to Philip Erickson of Teva on 10/16/08:
30s: 1 medication guide will be provided.
100s: 4 medication guides will be provided.
1000s: 34 medication guides will be provided.

11. **RELATED APPLICATIONS** None

12. **SPL DATA ELEMENTS** None submitted this review cycle

13. **CITIZENS PETITION/PROPRIETARY NAME/CONSULTS** None

Date of Review:	October 18, 2013
Primary Reviewer:	Charlie Hoppes
Team Leader:	John Grace

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

/s/

CHARLES V HOPPES
10/24/2013

JOHN F GRACE
10/25/2013

Supersedes review signed off 10/20/08

APPROVAL SUMMARY

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

ANDA Number: 78-193

Dates of Submission: January 21, 2009 (amendment)

Applicant's Name: TEVA Pharmaceuticals USA

Established Name: Raloxifene Hydrochloride Tablets USP, 60 mg

---

APPROVAL SUMMARY:

Do you have Final Printed Labels and Labeling? Yes.

1. CONTAINER (Bottles of 30s, 100s, and 1000s):
   Satisfactory in final print as submitted January 21, 2009.

2. PHYSICIAN INSERT
   Satisfactory in final print as submitted January 21, 2009.

3. Stand-alone MEDICATION GUIDE
   Satisfactory in final print as submitted January 21, 2009.

Revisions needed post-approval: No.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Evista

NDA Number: 20-815

NDA Drug Name: Raloxifene Hydrochloride Tablets

NDA Firm: Eli Lilly

Date of Approval of NDA Insert and supplement: NDA 20-815/S-025 approved Sept. 13, 2007

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels.

NOTE TO CHEMIST:

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for Evista® Tablets (Eli Lilly; NDA 20-815/S-025 approved September 13, 2007).

NDA 20-815/S-025 provided for new indications (reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and women at high risk for invasive cancer). These indications were approved under NDA 22-042. NDA 22-042 is a type 6 NDA and therefore not be listed in the OB. All exclusivity and updates are filed under the parent NDA 20-815, and according to the approval letter, "All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions [for NDA 22-042] should be addressed to the original NDA 20-815 for this drug product, not to this NDA [NDA 22-042]. In the future, do not make submissions to this NDA [NDA 22-042] except for the final printed labeling requested above."
Teva has requested to carve-out information pertaining to the new indication because it is protected by exclusivity. Teva's insert labeling has been revised accordingly.

USP: The drug product is now subject to a USP 31 monograph (added in the second supplement). (checked 1/29/09)
Raloxifene Hydrochloride Tablets
Packaging and storage— Preserve in tight containers, and store at controlled room temperature.

January 21, 2009 amendment:

> USP Monograph Reference RTS-C47067. Specifically, Teva requested that USP publish our finished product dissolution test method in the official monograph. It is our belief that USP intends to include Teva's method in the compendial monograph upon final approval of ANDA #78-193.
>
> The enclosed summary and accompanying supporting documents are provided as a result of January 13, 2009 communications with Dr. Paul Schwartz of the Division of Chemistry I. Also, as a result of communications with Lillie Golson of the Labeling Review Branch, the statement "USP Dissolution Test Pending" has been added to the Description section of our package insert.

MedWatch: no new labeling issues in Medwatch since the labeling approved 9/13/07 (checked 1/29/09)

2. PATENTS/EXCLUSIVITIES:

Patent Data for NDA 20-815 (current as of 1/29/09)

Patent No	Patent Expiration	Patent Use Code	How filed	Impact
5393763	JUL 28,2012	U-114	PIV (3/2/06 submission)	None
5457117	JUL 28,2012	U-114	PIV (3/2/06 submission)	None
5478847	MAR 02,2014	U-114	PIV (3/2/06 submission)	None
5811120	MAR 02,2014		PIV (3/2/06 submission)	None
5972383	MAR 02,2014	U-287	PIV (3/2/06 submission)	None
6458811	MAR 10,2017	U-825	PIV (3/2/06 submission)	None
6797719	MAR 10,2017		PIV (3/2/06 submission)	None
6894064	MAR 10,2017	U-657	PIV (3/2/06 submission)	None
6906086	JUL 28,2012	U-657	PIV (3/2/06 submission)	None
6906086	JUL 28,2012	U-662	PIV (3/2/06 submission)	None
RE38968	JUL 28,2012	U-662	PIV (3/2/06 submission)	None
RE38968	JUL 28,2012	U-657	PIV (3/2/06 submission)	None
RE39049	JUL 28,2012	U-662	PIV (4/6/06 amendment)	None
RE39049	JUL 28,2012	U-657	PIV (4/6/06 amendment)	None
RE39050	MAR 02,2014	U-662	PIV (4/6/06 amendment)	None
RE39050	MAR 02,2014	U-657	PIV (4/6/06 amendment)	None

Code	Definition
U-114	USE FOR INHIBITING BONE RESORPTION
U-287	TREATMENT OR PREVENTION OF OSTEOPOROSIS
U-657	PREVENTION OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN
U-662	TREATMENT OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

U-825 USE FOR PREVENTION OF BREAST CANCER

7/25/2006-1:06-cv-1017-SEB-VSS filed in Southern Distric of IN for infringement of '050, '968, '049, and '086/mhs

Exclusivity Data

Exclusivity Code	Exclusivity Expiration	How filed
I-539	SEP 13, 2010	Carve-out (1/25/08 submission)
ODE	SEP 13, 2014	Carve-out (6/27/08 submission)

Code	Definition
I-539	REDUCTION IN RISK OF INVASIVE BREAST CANCER IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS AND WOMEN AT HIGH RISK FOR INVASIVE CANCER
ODE	Designation approved: Reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and reduction in risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer http://www.fda.gov/orphan/designat/list.htm

Teva's Exclusivity statement:

The indication protected by exclusivity I-539 and the ODE is not included in our labeling and will not appear in labeling for commercial distribution before expiration of the Orphan Drug Exclusivity on September 13, 2014.

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, October 16, 2008 4:20 PM
To: Shimer, Martin
Cc: Danso, Benjamin; Rickman, William P; Lee, Koung U
Subject: RE: TEVA's ANDA 78-193 for Raloxifene Tablets

Hi Marty,

There are only 3 indications for Evista:
EVISTA® is an estrogen agonist/antagonist indicated for:
• Treatment and prevention of osteoporosis in postmenopausal women. (1.1)
• Reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis. (1.2)
• Reduction in risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer. (1.3)

If a use code does not necessarily have to be linked to a particular indication & usage in the insert, then we'll leave the patent certification as is.

Thanks,

Ruby

From: Shimer, Martin
Sent: Thursday, October 16, 2008 2:22 PM
To: Wu, Ruby (Chi-Ann)
Cc: Danso, Benjamin; Rickman, William P
Subject: RE: TEVA's ANDA 78-193 for Raloxifene Tablets

Ruby,

Does the labeling for Evista include sections that appear to be attributable to both the I-539 exclusivity and to the U-825 method of use? I can see where the definitions REDUCTION IN RISK OF INVASIVE BREAST CANCER IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS AND WOMEN AT HIGH RISK FOR INVASIVE CANCER would not be considered synonymous with USE FOR PREVENTION OF BREAST CANCER. The former definition is rather specific for certain groups of females('postmenopausal women with osteoporosis and women at high risk'-other women outside of these groups are susceptible to osteoporosis) whereas the second definition is quite broad. I also don't necessarily see REDUCTION IN RISK as being the same as PREVENTION. For these reasons I'm of the opinion that TEVA can maintain address the exclusivity and the patent incongruously.

If the labeling doesn't appear to permit this sort of analysis let me know.

Marty

From: *Wu, Ruby (Chi-Ann)*
Sent: *Wednesday, October 15, 2008 4:33 PM*
To: *Shimer, Martin*

Cc: *Danso, Benjamin*
Subject: *RE: TEVA's ANDA 78-193 for Raloxifene Tablets*

Hi Marty,

According to Teva's 6/27/08 submission:

The indication protected by exclusivity I-539 and the ODE is not included in our labeling and will not appear in labeling for commercial distribution before expiration of the Orphan Drug Exclusivity on September 13, 2014.

I-539 and ODE provide for REDUCTION IN RISK OF INVASIVE BREAST CANCER IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS AND WOMEN AT HIGH RISK FOR INVASIVE CANCER and Teva has carved out this indication.

U-825 "USE FOR PREVENTION OF BREAST CANCER" has been added to '811 patent. Teva originally filed PIV. To be consistent with the exclusivity statement, does Teva need to revise their patent certification for '811 from PIV to MOU?

Ruby

2. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM
Original Site:
TEVA Pharmaceutical Industries
Hashikma Street, Industrial Zone Kfar-Saba 44102
ISRAEL Registration no. 3002721084

Additional site proposed in the March 31, 2008 amendment:
TEVA Pharmaceuticals USA
650 Cathill RD
Sellersville, PA 18960

Please note that the changes proposed for the additional site do not include any changes to the drug product composition.

4. CONTAINER/CLOSURE
RLD: 30s, 100s, 2000
ANDA: Container: white round HDPE; Closure: 30s-CRC; 100s-CRC and non-CRC, 1000s- nonCRC
(b) (4)

According to Philip Erickson of Teva on 10/16/08:
30s: 1 medication guide will be provided.
100s: 4 medication guides will be provided.
1000s: 34 medication guides will be provided.

On October 20, 2008, Virginia Hogan of Teva confirmed that the type size for the content of labeling is 6 points and the MedGuide is 10 points.

5. INACTIVE INGREDIENTS
The description of the inactive ingredients in the insert labeling is consistent with the composition statement.
(b) (4)
- Pregelatinized Starch NF (b) (4)
- Raloxifene Hydrochloride
- Magnesium Stearate NF
- (b) (4)
- Povidone USP (b) (4)
- Colloidal Silicon Dioxide NF (b) (4)
- Microcrystalline Cellulose NF (b) (4)

(b) (4)
- Hydroxypropyl Methylcellulose
- Polydextrose;
- Titanium Dioxide USP;
- Polyethylene Glycol (b) (4)

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
RLD: Store at CRT 20-25 C(68-77F) excursions permitted to 15^{o}-30^{o}C (59^{o}-86^{o}F)
ANDA: Store at 20°-25°C (68°-77°F)[see USP Controlled Room Temperature]"

7. DISPENSING STATEMENTS COMPARISON
RLD: Dispense in a tight container.
ANDA: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

8. FINISHED PRODUCT COA -
RLD: White, elliptical and film coated tablets

ANDA: White to off white, film coated capsule shaped tablet, debossed with “7290” on one side of the tablet, and “93” on the other.

Date of Review: January 29, 2009 Date of Submission: January 21, 2009
Primary Reviewer: Ruby Wu
Team Leader: Koung Lee

ANDA: 78-193
V:\FIRMSNZ\TEVA\LTRS&REV\78193.ap2.L.doc
Review

Following this page, 14 Pages of Draft Labeling have been Withheld in Full as (b)(4)

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

/s/

Ruby Wu
2/2/2009 12:19:42 PM
LABELING REVIEWER

Koung Lee
2/9/2009 08:56:14 AM
LABELING REVIEWER
For Wm Peter Rickman

APPROVAL SUMMARY

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

ANDA Number: 78-193

Dates of Submission: October 3, 2008 (amendment)

Applicant's Name: TEVA Pharmaceuticals USA

Established Name: Raloxifene Hydrochloride Tablets, 60 mg

APPROVAL SUMMARY:

Do you have Final Printed Labels and Labeling? Yes.

1. CONTAINER (Bottles of 30s, 100s, and 1000s):
   Satisfactory in final print as submitted October 3, 2008.

2. PHYSICIAN INSERT
   Satisfactory in final print as submitted October 3, 2008.

3. Stand-alone MEDICATION GUIDE
   Satisfactory in final print as submitted October 3, 2008.

Revisions needed post-approval: No.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Evista

NDA Number: 20-815

NDA Drug Name: Raloxifene Hydrochloride Tablets

NDA Firm: Eli Lilly

Date of Approval of NDA Insert and supplement: NDA 20-815/S-025 approved Sept. 13, 2007

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels.

NOTE TO CHEMIST:

FOR THE RECORD:

1. MODEL LABELING
This review was based on the labeling for Evista® Tablets (Eli Lilly; NDA 20-815/S-025 approved September 13, 2007).

NDA 20-815/S-025 provided for new indications (reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and women at high risk for invasive cancer). These indications were approved under NDA 22-042. NDA 22-042 is a type 6 NDA and therefore not be listed in the OB. All exclusivity and updates are filed under the parent NDA 20-815, and according to the approval letter, "All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions [for NDA 22-042] should be addressed to the original NDA 20-815 for this drug product, not to this NDA [NDA 22-042]. In the future, do not make submissions to this NDA [NDA 22-042] except for the final printed labeling requested above."
Teva has requested to carve-out information pertaining to the new indication because it is protected by exclusivity. Teva's insert labeling has been revised accordingly.

USP: The drug product is not subject to a USP 31 monograph. (checked 10/15/08)

MedWatch: no new labeling issues in Medwatch since the labeling approved 9/13/07 (checked 10/15/08)

2. PATENTS/EXCLUSIVITIES:

Patent Data for NDA 20-815 (current as of 10/15/08)

Patent No	Patent Expiration	Patent Use Code	How filed	Impact
5393763	JUL 28,2012	U-114	PIV (3/2/06 submission)	None
5457117	JUL 28,2012	U-114	PIV (3/2/06 submission)	None
5478847	MAR 02,2014	U-114	PIV (3/2/06 submission)	None
5811120	MAR 02,2014		PIV (3/2/06 submission)	None
5972383	MAR 02,2014	U-287	PIV (3/2/06 submission)	None
6458811	MAR 10,2017	U-825	PIV (3/2/06 submission)	None
6797719	MAR 10,2017		PIV (3/2/06 submission)	None
6894064	MAR 10,2017	U-657	PIV (3/2/06 submission)	None
6906086	JUL 28,2012	U-657	PIV (3/2/06 submission)	None
6906086	JUL 28,2012	U-662	PIV (3/2/06 submission)	None
RE38968	JUL 28,2012	U-662	PIV (3/2/06 submission)	None
RE38968	JUL 28,2012	U-657	PIV (3/2/06 submission)	None
RE39049	JUL 28,2012	U-662	PIV (4/6/06 amendment)	None
RE39049	JUL 28,2012	U-657	PIV (4/6/06 amendment)	None
RE39050	MAR 02,2014	U-662	PIV (4/6/06 amendment)	None
RE39050	MAR 02,2014	U-657	PIV (4/6/06 amendment)	None

Code	Definition
U-114	USE FOR INHIBITING BONE RESORPTION
U-287	TREATMENT OR PREVENTION OF OSTEOPOROSIS
U-657	PREVENTION OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN
U-662	TREATMENT OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN
U-825	USE FOR PREVENTION OF BREAST CANCER

7/25/2006-1:06-cv-1017-SEB-VSS filed in Southern Distric of IN for infringement of '050, '968, '049, and '086/mhs

Exclusivity Data

Exclusivity Code	Exclusivity Expiration	How filed
I-539	SEP 13, 2010	Carve-out (1/25/08 submission)
ODE	SEP 13, 2014	Carve-out (6/27/08 submission)

Code	Definition
I-539	REDUCTION IN RISK OF INVASIVE BREAST CANCER IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS AND WOMEN AT HIGH RISK FOR INVASIVE CANCER

ODE Designation approved: Reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and reduction in risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer

http://www.fda.gov/orphan/designat/list.htm

Teva's Exclusivity statement:

The indication protected by exclusivity I-539 and the ODE is not included in our labeling and will not appear in labeling for commercial distribution before expiration of the Orphan Drug Exclusivity on September 13, 2014.

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, October 16, 2008 4:20 PM
To: Shimer, Martin
Cc: Danso, Benjamin; Rickman, William P; Lee, Koung U
Subject: RE: TEVA's ANDA 78-193 for Raloxifene Tablets

Hi Marty,

There are only 3 indications for Evista:
EVISTA® is an estrogen agonist/antagonist indicated for:
• Treatment and prevention of osteoporosis in postmenopausal women. (1.1)
• Reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis. (1.2)
• Reduction in risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer. (1.3)

If a use code does not necessarily have to be linked to a particular indication & usage in the insert, then we'll leave the patent certification as is.

Thanks,

Ruby

From: Shimer, Martin
Sent: Thursday, October 16, 2008 2:22 PM
To: Wu, Ruby (Chi-Ann)
Cc: Danso, Benjamin; Rickman, William P
Subject: RE: TEVA's ANDA 78-193 for Raloxifene Tablets

Ruby,

Does the labeling for Evista include sections that appear to be attributable to both the I-539 exclusivity and to the U-825 method of use? I can see where the definitions REDUCTION IN RISK OF INVASIVE BREAST CANCER IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS AND WOMEN AT HIGH RISK FOR INVASIVE CANCER would not be considered synonymous with USE FOR PREVENTION OF BREAST CANCER. The former definition is rather specific for certain groups of females('postmenopausal women with osteoporosis and women at high risk'-other women outside of these groups are susceptible to osteoporosis) whereas the second definition is quite broad. I also don't necessarily see REDUCTION IN RISK as being the same as PREVENTION. For these reasons I'm of the opinion that TEVA can maintain address the exclusivity and the patent incongruously.

If the labeling doesn't appear to permit this sort of analysis let me know.

Marty

From: *Wu, Ruby (Chi-Ann)*
Sent: *Wednesday, October 15, 2008 4:33 PM*
To: *Shimer, Martin*
Cc: *Danso, Benjamin*
Subject: *RE: TEVA's ANDA 78-193 for Raloxifene Tablets*

Hi Marty,

According to Teva's 6/27/08 submission:

The indication protected by exclusivity I-539 and the ODE is not included in our labeling and will not appear in labeling for commercial distribution before expiration of the Orphan Drug Exclusivity on September 13, 2014.

I-539 and ODE provide for REDUCTION IN RISK OF INVASIVE BREAST CANCER IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS AND WOMEN AT HIGH RISK FOR INVASIVE CANCER and Teva has carved out this indication.

U-825 "USE FOR PREVENTION OF BREAST CANCER" has been added to '811 patent. Teva originally filed PIV. To be consistent with the exclusivity statement, does Teva need to revise their patent certification for '811 from PIV to MOU?

Ruby

2. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM
   Original Site:
   TEVA Pharmaceutical Industries
   Hashikma Street, Industrial Zone Kfar-Saba 44102
   ISRAEL Registration no. 3002721084

   Additional site proposed in the March 31, 2008 amendment:
   TEVA Pharmaceuticals USA
   650 Cathill RD
   Sellersville, PA 18960

   Please note that the changes proposed for the additional site do not include any changes to the drug product composition.

4. CONTAINER/CLOSURE
   RLD: 30s, 100s, 2000
   ANDA: Container: white round HDPE; Closure: 30s-CRC; 100s-CRC and non-CRC, 1000s- nonCRC
   (b) (4)

   According to Philip Erickson of Teva on 10/16/08:
   30s: 1 medication guide will be provided.
   100s: 4 medication guides will be provided.
   1000s: 34 medication guides will be provided.

5. INACTIVE INGREDIENTS
   The description of the inactive ingredients in the insert labeling is consistent with the composition statement.
   (b) (4)
   - Pregelatinized Starch NF (b) (4)
   - Raloxifene Hydrochloride
   - Magnesium Stearate NF
   - (b) (4)
   - Povidone USP (b) (4)
   - Colloidal Silicon Dioxide NF (b) (4)
   - Microcrystalline Cellulose NF (b) (4)

   (b) (4)
   - Hydroxypropyl Methylcellulose
   - Polydextrose;
   - Titanium Dioxide USP;
   - Polyethylene Glycol (b) (4)

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   RLD: Store at CRT 20-25 C(68-77F) excursions permitted to 15°-30°C (59°-86°F)
   ANDA: Store at 20°-25°C (68°-77°F)[see USP Controlled Room Temperature]"

7. DISPENSING STATEMENTS COMPARISON
   RLD: Dispense in a tight container.
   ANDA: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

8. FINISHED PRODUCT COA -
   RLD: White, elliptical and film coated tablets
   ANDA: White to off white, film coated capsule shaped tablet, debossed with “7290” on one side of the tablet, and “93” on the other.

Date of Review: October 17, 2008 Date of Submission: October 3, 2008
Primary Reviewer: Ruby Wu
Team Leader: Koung Lee

ANDA: 78-193
V:\FIRMSNZ\TEVA\LTRS&REV\78193.ap.L.doc
Review

Following this page, 14 Pages of Draft Labeling have been Withheld in Full as (b)(4)

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

/s/

Ruby Wu
10/17/2008 02:04:11 PM
LABELING REVIEWER

Koung Lee
10/20/2008 04:05:53 PM
LABELING REVIEWER
On October 20, 2008, Virginia Hogan of Teva confirmed that the type size for the content of labeling is 6 points and the MedGuide is 10 points.

This supersedes the review signed off 2/6/07

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

ANDA Number: 78-193
Dates of Submission: January 25, 2008 (amendment)
Applicant's Name: TEVA Pharmaceuticals USA
Established Name: Raloxifene Hydrochloride Tablets, 60 mg

TENTATIVE APPROVAL:

Do you have Final Printed Labels and Labeling? No. – The firm submitted draft copies of their labels and labeling, which is acceptable for a Tentative Approval. Final Printed Labeling will be submitted by the firm prior to full approval of this application.

1. CONTAINER (Bottles of 30s, 100s, and 1000s):
   Satisfactory in draft as submitted in the January 25, 2008 e-amendment.

2. PHYSICIAN INSERT
   Satisfactory in draft as submitted in the January 25, 2008 e-amendment.

3. Stand-alone MEDICATION GUIDE
   Satisfactory in draft as submitted in the January 25, 2008 e-amendment.

Revisions needed post-tentative approval: Yes.

From: Wu, Ruby (Chi-Ann)
Sent: Wednesday, February 06, 2008 9:17 AM
To: 'philip.erickson@TevaUSA.com'
Subject: 78-193 Raloxifene

Good morning Philip,

Please address the following labeling comments post-tentative approval (i.e., when you are requesting full approval):

INSERT: Please retain the same numbering system as the RLD for the sections, subsections, and tables throughout the insert (you do not need to renumber).

MEDICATION GUIDE: Please comment on how many medication guides will be provided with each packaging configuration.

Thanks,
Ruby

BASIS OF TENTATIVE APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Evista

NDA Number: 20-815

NDA Drug Name: Raloxifene Hydrochloride Tablets

NDA Firm: Eli Lilly

Date of Approval of NDA Insert and supplement: NDA 20-815/S-025 approved Sept. 13, 2007

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels.

NOTE TO CHEMIST:

FOR THE RECORD:

1. MODEL LABELING
This review was based on the labeling Evista (NDA 20-815; Raloxifene HCL tablets; Eli Lilly). NDA 20-815/S-025 approved September 13, 2007 provides for a new indication. The indication for invasive breast cancer was approved under NDA 22-042. NDA 22-042 is a type 6 NDA and will not be listed in the OB. All exclusivity and updates will be filed under the parent NDA 20-815: "All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions [for NDA 22-042] should be addressed to the original NDA 20-815 for this drug product, not to this NDA. In the future, do not make submissions to this NDA except for the final printed labeling requested above." Teva has requested to carve-out information pertaining to the new indication because it is protected by exclusivity. Teva's insert labeling has been revised accordingly.

The drug product is not subject to a USP 30 monograph. (checked 2/6/08)

2. PATENTS/EXCLUSIVITIES:

Patent Data for NDA 20-815 (current as of 2/6/08)

Patent No	Patent Expiration	Patent Use Code	How filed	Impact
5393763	JUL 28,2012	U-114	PIV (3/2/06 submission)	None
5457117	JUL 28,2012	U-114	PIV (3/2/06 submission)	None
5478847	MAR 02,2014	U-114	PIV (3/2/06 submission)	None
5811120	MAR 02,2014		PIV (3/2/06 submission)	None
5972383	MAR 02,2014	U-287	PIV (3/2/06 submission)	None
6458811	MAR 10,2017		PIV (3/2/06 submission)	None
6797719	MAR 10,2017		PIV (3/2/06 submission)	None
6894064	MAR 10,2017	U-657	PIV (3/2/06 submission)	None
6906086	JUL 28,2012	U-657	PIV (3/2/06 submission)	None
6906086	JUL 28,2012	U-662	PIV (3/2/06 submission)	None
RE38968	JUL 28,2012	U-662	PIV (3/2/06 submission)	None
RE38968	JUL 28,2012	U-657	PIV (3/2/06 submission)	None
RE39049	JUL 28,2012	U-662	PIV (4/6/06 amendment)	None
RE39049	JUL 28,2012	U-657	PIV (4/6/06 amendment)	None
RE39050	MAR 02,2014	U-662	PIV (4/6/06 amendment)	None
RE39050	MAR 02,2014	U-657	PIV (4/6/06 amendment)	None

Code	Definition
U-114	USE FOR INHIBITING BONE RESORPTION
U-287	TREATMENT OR PREVENTION OF OSTEOPOROSIS
U-657	PREVENTION OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN
U-662	TREATMENT OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

Exclusivity Data

Exclusivity Code	Exclusivity Expiration	How filed
I-539	SEP 13,2010	Carve-out (1/25/08 submission)

Code	Definition
I-539	REDUCTION IN RISK OF INVASIVE BREAST CANCER IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS AND WOMEN AT HIGH RISK FOR INVASIVE CANCER

7/25/2006-1:06-cv-1017-SEB-VSS filed in Southern Distric of IN for infringement of '050, '968, '049, and '086/mhs

2. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM
TEVA Pharmaceutical Industries
Hashikma Street
Industrial Zone Kfar-Saba 44102
ISRAEL Registration no. 3002721084

4. CONTAINER/CLOSURE
RLD: 30s u-of-u, 100s u-of-u, 2000
ANDA: Container: white round HDPE; Closure: 30s-CRC; 100s-CRC and non-CRC, 1000s- nonCRC

(b) (4)

5. INACTIVE INGREDIENTS
The description of the inactive ingredients in the insert labeling is consistent with the composition statement.

(b) (4)

- Pregelatinized Starch NF (b) (4)
- Raloxifene Hydrochloride
- Magnesium Stearate NF
- (b) (4)
- Povidone USP (b) (4)
- Colloidal Silicon Dioxide NF (b) (4)
- Microcrystalline Cellulose NF (b) (4)

(b) (4)

- Hydroxypropyl Methylcellulose
- Polydextrose;
- Titanium Dioxide USP;
- Polyethylene Glycol (b) (4)

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
RLD: Store at CRT 20-25 C(68-77F) excursions permitted to 15°-30°C (59°-86°F)
ANDA: Store at 20°-25°C (68°-77°F)[see USP Controlled Room Temperature]"

7. DISPENSING STATEMENTS COMPARISON
RLD: Dispense in a tight container.
ANDA: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

8. BIOAVAILABILITY/BIOEQUIVALENCE: 1/10/2007 - Bio deficiencies given to document room for faxing/sm

9. FINISHED PRODUCT COA -
RLD: White, elliptical and film coated tablets
ANDA: White to off white, film coated capsule shaped tablet, debossed with "7290" on one side of the tablet, and "93" on the other.

Date of Review: February 6, 2008 Date of Submission: January 25, 2008

Primary Reviewer: Ruby Wu

Team Leader: John Grace

ANDA: 78-193
V:\FIRMSNZ\TEVA\LTRS&REV\78193.tap2.L.doc
Review

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/s/

Ruby Wu
2/6/2008 09:24:30 AM
LABELING REVIEWER

John Grace
2/6/2008 11:24:13 AM
LABELING REVIEWER

TENTATIVE APPROVAL SUMMARY

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

ANDA Number: 78-193

Dates of Submission: January 29, 2007 (amendment)

Applicant's Name: TEVA Pharmaceuticals USA

Established Name: Raloxifene Hydrochloride Tablets, 60 mg

TENTATIVE APPROVAL:

Do you have Final Printed Labels and Labeling? No. – The firm submitted draft copies of their labels and labeling, which is acceptable for a Tentative Approval. Final Printed Labeling will be submitted by the firm prior to full approval of this application.

1. CONTAINER (Bottles of 30s, 100s, and 1000s):
   Satisfactory in draft as submitted in the August 4, 2006 e-amendment.

2. PHYSICIAN INSERT
   Satisfactory in draft as submitted in the August 4, 2006 e-amendment.

3. PATIENT PACKAGE INSERT
   Satisfactory in draft as submitted in the August 4, 2006 e-amendment.

Revisions needed post-tentative approval: No.

BASIS OF TENTATIVE APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Evista

NDA Number: 20-815

NDA Drug Name: Raloxifene Hydrochloride Tablets

NDA Firm: Eli Lilly

Date of Approval of NDA Insert and supplement: NDA 20-815/S-010 Approved June 13, 2002

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels.

NOTE TO CHEMIST:

FOR THE RECORD:

1. MODEL LABELING
   This review was based on the labeling Evista (NDA 20-815; Raloxifene HCL tablets; Eli Lilly).
   - Physician Insert: NDA 20-815/S-010 Approved June 13, 2002 [Revised March 19, 2001 identifer #PV 3085AMP)]
     - Patient Package Insert: NDA 20-815/S-006, approved June 27, 2000 [FPL submitted on October 23, 2000, Identifier PV 3380 AMP, Dated June 26, 2000]

   Additionally, please note that the statement "Raloxifene hydrochloride tablets do not contain enough lactose to cause symptoms in women who have lactose intolerance" has been removed from the patient package insert. Lactose is not used in the manufacture of Teva's Raloxifene Hydrochloride Tablets, 60 mg.

   The drug product is not subject to a USP 29 monograph. (checked 2/5/07)

2. PATENTS/EXCLUSIVITIES:

Patent Data for NDA 20-815 (current as of 2/5/07)

Patent No	Patent Expiration	Patent Use Code	How filed	Impact
5393763	JUL 28,2012	U-114	PIV (3/2/06 submission)	None
5457117	JUL 28,2012	U-114	PIV (3/2/06 submission)	None
5478847	MAR 02,2014	U-114	PIV (3/2/06 submission)	None
5811120	MAR 02,2014		PIV (3/2/06 submission)	None
5972383	MAR 02,2014	U-287	PIV (3/2/06 submission)	None
6458811	MAR 10,2017		PIV (3/2/06 submission)	None
6797719	MAR 10,2017		PIV (3/2/06 submission)	None
6894064	MAR 10,2017	U-657	PIV (3/2/06 submission)	None
6906086	JUL 28,2012	U-657	PIV (3/2/06 submission)	None
6906086	JUL 28,2012	U-662	PIV (3/2/06 submission)	None
RE38968	JUL 28,2012	U-662	PIV (3/2/06 submission)	None
RE38968	JUL 28,2012	U-657	PIV (3/2/06 submission)	None
RE39049	JUL 28,2012	U-662	PIV (4/6/06 amendment)	None
RE39049	JUL 28,2012	U-657	PIV (4/6/06 amendment)	None
RE39050	MAR 02,2014	U-662	PIV (4/6/06 amendment)	None
RE39050	MAR 02,2014	U-657	PIV (4/6/06 amendment)	None

Code	Definition
U-114	USE FOR INHIBITING BONE RESORPTION
U-287	TREATMENT OR PREVENTION OF OSTEOPOROSIS
U-657	PREVENTION OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN
U-662	TREATMENT OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

Exclusivity Data
There is no unexpired exclusivity for this product.

7/25/2006-1:06-cv-1017-SEB-VSS filed in Southern Distric of IN for infringement of '050, '968, '049, and '086/mhs

2. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM
   TEVA Pharmaceutical Industries
   Hashikma Street
   Industrial Zone
   Kfar-Saba 44102
   ISRAEL
   Registration no. 3002721084

4. CONTAINER/CLOSURE
   RLD: 30s u-of-u, 100s u-of-u, 2000
   ANDA: Container: white round HDPE; Closure: 30s-CRC; 100s-CRC and non-CRC, 1000s- nonCRC

(b) (4)

5. INACTIVE INGREDIENTS
   The description of the inactive ingredients in the insert labeling is consistent with the composition statement.

(b) (4)

- Pregelatinized Starch NF (b) (4)
- Raloxifene Hydrochloride
- Magnesium Stearate NF
- (b) (4)
- Povidone USP (b) (4)
- Colloidal Silicon Dioxide NF (b) (4)
- Microcrystalline Cellulose NF (b) (4)

(b) (4)

- Hydroxypropyl Methylcellulose
- Polydextrose;
- Titanium Dioxide USP;
- Polyethylene Glycol (b) (4)

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   RLD: Store at CRT 20-25 C(68-77F) excursions permitted to 15^{o}-30^{o}C (59^{o}-86^{o}F)
   ANDA: Store at 20°-25°C (68°-77°F)[see USP Controlled Room Temperature]"

7. DISPENSING STATEMENTS COMPARISON
   RLD: Dispense in a tight container.
   ANDA: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

8. BIOAVAILABILITY/BIOEQUIVALENCE: 1/10/2007 - Bio deficiencies given to document room for faxing/sm

9. FINISHED PRODUCT COA -
   RLD: White, elliptical and film coated tablets
   ANDA: White to off white, film coated capsule shaped tablet, debossed with “7290” on one side of the tablet, and “93” on the other.

Date of Review: February 5, 2007 Date of Submission: January 29, 2007

Primary Reviewer: Ruby Wu

Team Leader: John Grace

ANDA: 78-193
V:\FIRMSNZ\TEVA\LTRS&REV\78193.tap.L.doc
Review

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

/s/

Ruby Wu
2/5/2007 10:30:29 AM
MEDICAL OFFICER

John Grace
2/6/2007 09:57:11 AM
MEDICAL OFFICER

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

ANDA Number: 78-193
Dates of Submission: August 4, 2006 (amendment-electronic)
Applicant's Name: TEVA Pharmaceuticals USA
Established Name: Raloxifene Hydrochloride Tablets, 60 mg

Labeling Deficiencies:

1. CONTAINER (Bottles of 30s, 100s, and 1000s):
   Satisfactory in draft as submitted in the August 4, 2006 e-amendment.

2. PHYSICIAN INSERT
   Due to changes in the insert labeling for the reference listed drug, (Evista- Procter & Gamble Pharmaceuticals, Inc.; NDA 20-815/S-022 & S-023 approved August 11, 2006) please revise your labeling to be in accord with the attached labeling.

3. PATIENT PACKAGE INSERT
   Refer to Physician Insert Comment.

Please revise your labeling as described above and submit electronically.

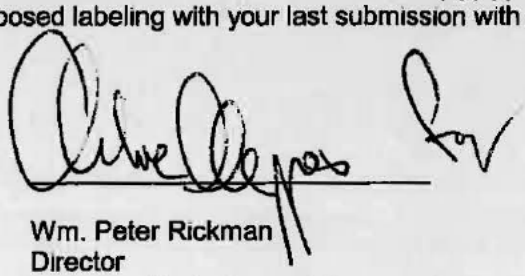
The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format. For additional information, please refer to 21 CFR 314.94(d)(ii), SPL Implementation Guide for FDA Content of Labeling Submissions at http://www.fda.gov/cder/regulatory/ersr/SPL2aIG_v20051006_r1.pdf and Docket 92S-0251, Memorandum 32.

Although Docket 92S-0251, Memorandum 32 states that as of October 31, 2005, Structured Product Labeling (SPL) in XML format is the only acceptable format for the submission of the content of labeling in electronic format, abbreviated new drug applications not listed as the referenced listed drug (RLD) may be submitted in PDF and MS Word until the SPL for the RLD is posted on the DailyMed website at http://dailymed.nlm.nih.gov/dailymed/about.cfm. Should you decide to take the option of waiting until the SPL for the RLD is posted on the website, you will be responsible for submitting your content of labeling in SPL within 30 days after the SPL for the RLD is posted on the DailyMed website. If you have any questions on SPL submissions, please call Mr. Koung Lee at 301-827-7336.

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://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

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.



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

Attachment: RLD labeling

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 29		X	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR. Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label)		X	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e. Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported		X	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?			X
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	

Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling		X	
Bioequivalence Issues: (Compare bioequivalency values insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity List expiration date for all patents, exclusivities, etc. or if none, please state. **NONE**	X		

NOTE TO CHEMIST:

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling Evista (NDA 20-815; Raloxifene HCL tablets; Eli Lilly). Most recently approved labeling is NDA 20-815/S-022 & S-023 approved August 11, 2006.

These supplemental new drug applications provide for:

- NDA 20-835/S-022: A new indication to support the use of Actonel 35 mg once a week for the treatment of osteoporosis in men.
- NDA 20-835/S-023 An updated patient package insert (PPI) to align the Actonel PPI with the Actonel With Calcium PPI.

The drug product is not subject to a USP 29 monograph. (checked 8/16/06)

2. PATENTS/EXCLUSIVITIES:

Patent Data for NDA 20-815 (current as of 8/14/06)

Patent No	Patent Expiration	Patent Use Code	How filed	Impact
5393763	JUL 28,2012	U-114	PIV (3/2/06 submission)	None
5457117	JUL 28,2012	U-114	PIV (3/2/06 submission)	None
5478847	MAR 02,2014	U-114	PIV (3/2/06 submission)	None
5811120	MAR 02,2014		PIV (3/2/06 submission)	None
5972383	MAR 02,2014	U-287	PIV (3/2/06 submission)	None
6458811	MAR 10,2017		PIV (3/2/06 submission)	None
6797719	MAR 10,2017		PIV (3/2/06 submission)	None
6894064	MAR 10,2017	U-657	PIV (3/2/06 submission)	None
6906086	JUL 28,2012	U-657	PIV (3/2/06 submission)	None
6906086	JUL 28,2012	U-662	PIV (3/2/06 submission)	None
RE38968	JUL 28,2012	U-662	PIV (3/2/06 submission)	None
RE38968	JUL 28,2012	U-657	PIV (3/2/06 submission)	None
RE39049	JUL 28,2012	U-662	PIV (4/6/06 amendment)	None
RE39049	JUL 28,2012	U-657	PIV (4/6/06 amendment)	None
RE39050	MAR 02,2014	U-662	PIV (4/6/06 amendment)	None
RE39050	MAR 02,2014	U-657	PIV (4/6/06 amendment)	None

Code	Definition
U-114	USE FOR INHIBITING BONE RESORPTION
U-287	TREATMENT OR PREVENTION OF OSTEOPOROSIS
U-657	PREVENTION OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN
U-662	TREATMENT OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

Exclusivity Data
There is no unexpired exclusivity for this product.

7/25/2006-1:06-cv-1017-SEB-VSS filed in Southern Distric of IN for infringement of '050, '968, '049, and '086/mhs

2. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM
TEVA Pharmaceutical Industries
Hashikma Street
Industrial Zone
Kfar-Saba 44102
ISRAEL
Registration no. 3002721084

4. CONTAINER/CLOSURE
RLD: 30s u-of-u, 100s u-of-u, 2000
ANDA: Container: white round HDPE; Closure: 30s-CRC; 100s-CRC and non-CRC, 1000s- nonCRC
(need clarification on the closure of the marketed bottles of 100s)

5. INACTIVE INGREDIENTS
The description of the inactive ingredients in the insert labeling is not consistent with the composition statement. Firm needs to add "hypromellose".

(b) (4)

- Pregelatinized Starch NF (b) (4)
- Raloxifene Hydrochloride
- Magnesium Stearate NF
- (b) (4)
- Povidone USP (b) (4)
- Colloidal Silicon Dioxide NF (b) (4)
- Microcrystalline Cellulose NF (b) (4)

(b) (4)

- Hydroxypropyl Methylcellulose
- Polydextrose,
- Titanium Dioxide USP,
- Polyethylene Glycol (b) (4)

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
RLD: Store at CRT 20-25 C(68-77F) excursions permitted to 15°-30°C (59°-86°F)
ANDA: Store at 20°-25°C (68°-77°F)[see USP Controlled Room Temperature]"

7. DISPENSING STATEMENTS COMPARISON
RLD: Dispense in a tight container.
ANDA: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

8. BIOAVAILABILITY/BIOEQUIVALENCE: 7/13/2006 - Bio dissolution prereview complete IC (repeat dissolution)/AS

9. FINISHED PRODUCT COA -
RLD: White, elliptical and film coated tablets
ANDA: White to off white, film coated capsule shaped tablet, debossed with "7290" on one side of the tablet, and "93" on the other.

Date of Review: August 16, 2006 Date of Submission: August 4, 2006

Primary Reviewer: Ruby Wu Date: 8/16/06

Team Leader: John Grace Date: 8/24/2006

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cc:

ANDA: 78-193
DUP/DIVISION FILE
HFD-613/Rwu/JGrace (no cc)
V:\FIRMSNZ\TEVA\LTRS&REV\78193.na2.L.doc
Review

A3.1

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

ANDA Number: 78-193
Dates of Submission: March 2, 2006 (original-electronic)
Applicant's Name: TEVA Pharmaceuticals USA
Established Name: Raloxifene Hydrochloride Tablets, 60 mg

Labeling Deficiencies:

1. CONTAINER (Bottles of 30s, 100s. and 1000s):
   a. Please clarify if the closure for the bottles of 100s that will be marketed will have CRC or non-CRC caps.
   b. The container states: "Each tablet contains raloxifene hydrochloride equivalent to 60 mg raloxifene". However, the DESCRIPTION section of the insert labeling states. "Each raloxifene hydrochloride tablet contains 60 mg of raloxifene hydrochloride, which is the molar equivalent of 55.71 mg of free base." Please clarify.

2. PHYSICIAN INSERT
   DESCRIPTION: Hypromellose is one the ingredients in [redacted] (b) (4) Please include hypromellose in the list of inactive ingredients. Please delete [redacted] (b) (4) since the individual components are already listed.

3. PATIENT PACKAGE INSERT
   Last paragraph - Please include the inactive ingredients in the tablets.

Please revise your labeling as described above and submit electronically. The immediate container labels may be submitted either electronically or in hard copy.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format. For additional information, please refer to 21 CFR 314.94(d)(ii), SPL Implementation Guide for FDA Content of Labeling Submissions at http://www.fda.gov/cder/regulatory/ersr/SPL2aIG_v20051006_r1.pdf and Docket 92S-0251, Memorandum 32.

Although Docket 92S-0251, Memorandum 32 states that as of October 31, 2005, Structured Product Labeling (SPL) in XML format is the only acceptable format for the submission of the content of labeling in electronic format, abbreviated new drug applications not listed as the referenced listed drug (RLD) may be submitted in PDF and MS Word until the SPL for the RLD is posted on the DailyMed website at http://dailymed.nlm.nih.gov/dailymed/about.cfm. Should you decide to take the option of waiting until the SPL for the RLD is posted on the website, you will be responsible for submitting your content of labeling in SPL within 30 days after the SPL for the RLD is posted on the DailyMed website. If you have any questions on SPL submissions, please call Mr. Koung Lee at 301-827-7336.

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://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

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.

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

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured **USP 29**		X	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR. Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label)		X	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult, Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by ..." statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?			X
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	

Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. **NONE**	X		

NOTE TO CHEMIST:

FOR THE RECORD:

1. MODEL LABELING

   This review was based on the labeling Evista (NDA 20-815; Raloxifene HCL tablets; Eli Lilly).

   - Physician Insert: NDA 20-815/S-010 Approved June 13, 2002 [Revised March 19, 2001 identifer #PV 3085AMP)]
   - Patient Package Insert: NDA 20-815/S-006, approved June 27, 2000 [FPL submitted on October 23, 2000, Identifier PV 3380 AMP, Dated June 26, 2000]

   The drug product is not subject to a USP 29 monograph.

2. PATENTS/EXCLUSIVITIES:

   Patent Data for NDA 20-815 (current as of 6/23/06)

Patent No	Patent Expiration	Patent Use Code	How filed	Impact
5393763	JUL 28,2012	U-114	PIV (3/2/06 submission)	None
5457117	JUL 28,2012	U-114	PIV (3/2/06 submission)	None
5478847	MAR 02,2014	U-114	PIV (3/2/06 submission)	None
5811120	MAR 02,2014		PIV (3/2/06 submission)	None
5972383	MAR 02,2014	U-287	PIV (3/2/06 submission)	None
6458811	MAR 10,2017		PIV (3/2/06 submission)	None
6797719	MAR 10,2017		PIV (3/2/06 submission)	None
6894064	MAR 10,2017	U-657	PIV (3/2/06 submission)	None
6906086	JUL 28,2012	U-657	PIV (3/2/06 submission)	None
6906086	JUL 28,2012	U-662	PIV (3/2/06 submission)	None
RE38968	JUL 28,2012	U-662	PIV (3/2/06 submission)	None
RE38968	JUL 28,2012	U-657	PIV (3/2/06 submission)	None
R E39049	JUL 28,2012	U-662	PIV (4/6/06 amendment)	None
RE39049	JUL 28,2012	U-657	PIV (4/6/06 amendment)	None
RE39050	MAR 02,2014	U-662	PIV (4/6/06 amendment)	None
RE39050	MAR 02,2014	U-657	PIV (4/6/06 amendment)	None

Code	Definition
U-114	USE FOR INHIBITING BONE RESORPTION
U-287	TREATMENT OR PREVENTION OF OSTEOPOROSIS
U-657	PREVENTION OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN
U-662	TREATMENT OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

Exclusivity Data
There is no unexpired exclusivity for this product.

2. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM
TEVA Pharmaceutical Industries
Hashikma Street
Industrial Zone
Kfar-Saba 44102
ISRAEL
Registration no. 3002721084

4. CONTAINER/CLOSURE
RLD: 30s u-of-u, 100s u-of-u, 2000
ANDA: Container: white round HDPE; Closure: 30s-CRC; 100s-CRC and non-CRC, 1000s- nonCRC
(need clarification on the closure of the marketed bottles of 100s)

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The description of the inactive ingredients in the insert labeling is not consistent with the composition statement. Firm needs to add "hypromellose".

(b) (4)

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- Raloxifene Hydrochloride
- Magnesium Stearate NF
- (b) (4)
- Povidone USP (b) (4)
- Colloidal Silicon Dioxide NF (b) (4)
- Microcrystalline Cellulose NF (b) (4)

(b) (4)

- Hydroxypropyl Methylcellulose
- Polydextrose,
- Titanium Dioxide USP,
- Polyethylene Glycol (b) (4)

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
RLD: Store at CRT 20-25 C(68-77F) excursions permitted to 15°-30°C (59°-86°F)
ANDA: Store at 20°-25°C (68°-77°F)[see USP Controlled Room Temperature]"

7. DISPENSING STATEMENTS COMPARISON
RLD: Dispense in a tight container.
ANDA: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

8. BIOAVAILABILITY/BIOEQUIVALENCE: pending as of 6/29/06

9. FINISHED PRODUCT COA -
RLD: White, elliptical and film coated tablets
ANDA: White to off white, film coated capsule shaped tablet, debossed with "7290" on one side of the tablet, and "93" on the other.

Date of Review: June 29, 2006 Date of Submission: March 2, 2006 (original-electronic)

Primary Reviewer: Ruby Wu Rw Date: 6/29/06

Team Leader: John Grace John J Grace Date: 6.30.06

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cc:
ANDA: 78-193
DUP/DIVISION FILE
HFD-613/Rwu/JGrace (no cc)
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Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78193

CHEMISTRY REVIEWS

ANDA 078193

Raloxifene Hydrochloride Tablets USP, 60 mg

Teva Pharmaceutical USA

Aijin Shen, Ph.D.

Office of Generic Drugs
Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 078193

2. REVIEW: #4

3. REVIEW DATE: 09/20/2013, 11/18/2013, 01/08/2014

4. REVIEWER: Aijin Shen

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	3/2/2006
Quality Information(minor amendments)	2/22/2007 (DL response to FDA ltr dt 10/25/06) 9/6/2007 (Tele amendment for t-con dt 8/27/07) 2/14/2008 (Tele amendment for t-con dt 02/07/08)
Quality Information (minor amendments)	3/31/2008 (Additional site for DP mfg); 7/8/2008 (DS particle size spec and method)
Quality Information (Facility Info)	6/28/2012 (Add site for DP mfg - Zagreb, Croatia)
Tentative Approval	4/16/2008
Previous CMC Reviews	
CMC Review #1 (Pendse) (Submission reviewed: original ANDA 3/2/2006))	10/25/2006
CMC Review #2 (Pendse/Randad) Submission reviewed: Amendments dt 2/22/07; t-con amendment 9/6/07; Tecon request 2/14/18	4/17/2008
CMC Review #3 (Shen) (Submission reviewed: Amendment: dt 6/28/13)	4/12/2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission/Quality/Response to Information Request	August 06, 2013
ECD	11/08/2013
ECD	12/27/2013

7. NAME & ADDRESS OF APPLICANT:

Name: TEVA Pharmaceuticals USA

Address: 425 Privet Road
Horsham, PA 19044

Representative: Jill Pastore

Telephone: 215-591-3142
Fax: 215-591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Raloxifene Hydrochloride Tablets

9. LEGAL BASIS FOR SUBMISSION: Referenced Listed Drug: Evista® Tablets, 60 mg manufactured by Eli Lily and Company (NDA 20-815).

Paragraph IV Certification

The firm certifies that to the best of their knowledge there are 10 listed patents which claim the reference drug EVISTA® Tablets.

U.S. Patent #	Expiration Date	U.S. Patent #	Expiration Date
5393763	7/28/2012	5811120	3/2/2014
5457117	7/28/2012	5972383	3/2/2014
5478847	3/2/2014	6458811	3/10/2017
6797719	3/10/2017	6894064	3/10/2017
6906086	7/28/2012	RE38968	7/28/2012

The firm hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that all of the above listed patents, which have been filed for EVIST A@ Tablets, are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted. TEVA Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Eli Lilly as the holder of NDA #20-815 for EVISTA® Tablets and owner of the patents. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patents are invalid, unenforceable, or will not be infringed.

10. PHARMACOL. CATEGORY: Anti-osteoporotic

Raloxifene hydrochloride tablets are used by women after menopause to treat or prevent a condition called osteoporosis.

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 60 mg

13. ROUTE OF ADMINISTRATION: Oral

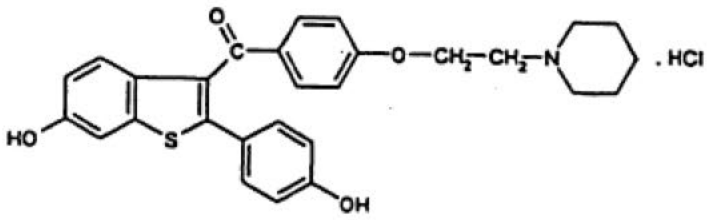
14. Rx/OTC DISPENSED: _X__Rx ___OTC

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:



The chemical designation is: [6-Hydroxy-2-(4-hydroxyfenyl)benzo[*b*] thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl- methanone hydrochloride.

Raloxifene HCl has the empirical formula

$C_{28}H_{27}NO_4S \cdot HCl$, which corresponds to a molecular weight 510.05.

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	12/04/13	Reviewed by Aijin Shen
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

* Checked DARRTS, January 08, 2014

[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: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS*	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A	--	--
EES	Acceptable	01-03-2014	E. Hany
Methods Validation	Not needed	--	--
Labeling	Tentative AP	10/24/2013	C. Hoppes
Bioequivalence	Acceptable	04/05/2011	D. Nhu
EA	N/A		
Radiopharmaceutical	N/A		

*DARRTS checked on January 08, 2014

19. ORDER OF REVIEW

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

The Executive Summary

The Chemistry Review for ANDA 078193

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable

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)

Drug Product

Raloxifene hydrochloride (RLD Evista®) is supplied in a tablet dosage form for oral administration. Each Raloxifene hydrochloride tablet contains 60 mg of Raloxifene hydrochloride, which is the molar equivalent of 55.71 mg of free base. Inactive ingredients include (b) (4) colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, (b) (4) poly dextrose, polyethylene glycol, povidone, pregelatinized starch, (b) (4) and titanium dioxide.

(b) (4)

Drug substance

The chemical designation is methanone, [6-hydroxy-2-(4-hydroxyphenyl) benzo [b] thien-3-yl]-[4[2-(l-piperidinyl) ethoxy]phenyl]-, hydrochloride. Raloxifene hydrochloride is off-white to pale-yellow solid that is very slightly soluble in water. Mol wt = 510.05.

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

Raloxifene hydrochloride tablets are a prescription medicine used by women after menopause to treat or prevent a condition called osteoporosis. One should take calcium and vitamin D along with Raloxifene hydrochloride tablets if enough calcium and vitamin D is not included in the diet.

Raloxifene hydrochloride tablets treat osteoporosis by helping make bones stronger and less likely to break. It helps prevent osteoporosis [redacted] after menopause.
Raloxifene hydrochloride tablets, 60 mg are white to off-white, film-coated, capsule-shaped tablets, debossed with "7290" on one side of the tablet, and "93" on the other in bottles of 30, 100, and 1000.
Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

MDD is 60 mg.
DS IT = 0.10% QT = 0.15%
DP IT = 0.2% QT = [redacted]%*

[redacted]

C. Basis for Approvability or Not-Approval Recommendation
This ANDA is approvable.

********** **END** **********

30. MICROBIOLOGY: N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS: N/A

32. LABELING: Acceptable by C. Hoppes 11/2013

33. ESTABLISHMENT INSPECTION: Acceptable, 01/03/2014

34. BIOEQUIVALENCE: Acceptable 04/05/2011

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: Can be granted

cc: ANDA78-193
ANDA DUP
DIV FILE
Field Copy

Endorsement Block

HFD-627/Review chemist/Aijin Shen, Ph.D./ Sept 30, December 04, 2013, January 08, 2014

HFD-627/Team leader/RBykadi, Ph.D./ October 11, 15, December 5, 2013, January 09, 2014

HFD-617/Project manager/Danbi Lee, Pharm.D./ Hany S Edward, 1/10/14

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APPROVABLE

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

/s/

AIJIN SHEN
01/10/2014

DANBI LEE
01/13/2014

GURURAJ BYKADI
01/13/2014

BING CAI
01/13/2014

ANDA 078193

Raloxifene Hydrochloride Tablets, 60 mg

Teva Pharmaceutical USA

Aijin Shen, Ph.D.

Office of Generic Drugs
Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 078193

2. REVIEW #3

3. REVIEW DATE: 02/09/2013

4. REVIEWER: Aijin Shen

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original submission	3/2/06
Labeling amendment (AF)	8/4/06
Minor amendment (AM)	2/22/07
Telephone amendment	9/6/07
Telephone request	2/14/08
CMC Review #2	4/17/2008
CMC Review #1	10/25/2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Quality /Response to Information Request (CMC amendment)	6/28/2012

7. NAME & ADDRESS OF APPLICANT:

Name: TEVA Pharmaceuticals USA

Address: 1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Representative: Jean Zwicker

Telephone: 215-591-8725
Fax: 215-591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Raloxifene Hydrochloride Tablets

9. LEGAL BASIS FOR SUBMISSION: Referenced Listed Drug: Evista® Tablets, 60 mg manufactured by Eli Lily and Company (NDA 20-815).

Paragraph IV Certification
The firm certifies that to the best of their knowledge there are 10 listed patents which claim the reference drug EVISTA® Tablets.

U.S. Patent #	Expiration Date	U.S. Patent #	Expiration Date
5393763	7/28/2012	5811120	3/2/2014
5457117	7/28/2012	5972383	3/2/2014
5478847	3/2/2014	6458811	3/10/2017
6797719	3/10/2017	6894064	3/10/2017
6906086	7/28/2012	RE38968	7/28/2012

The firm hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that all of the above listed patents, which have been filed for EVIST A@ Tablets, are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted. TEVA Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Eli Lilly as the holder of NDA #20-815 for EVISTA® Tablets and owner of the patents. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patents are invalid, unenforceable, or will not be infringed.

10. PHARMACOL. CATEGORY: Anti-osteoporotic

Raloxifene hydrochloride tablets are used by women after menopause to treat or prevent a condition called osteoporosis.

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 60 mg

13. ROUTE OF ADMINISTRATION: Oral

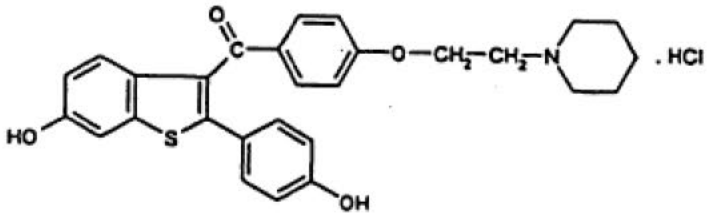
14. Rx/OTC DISPENSED: _X__Rx ___OTC

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:



The chemical designation is: [6-Hydroxy-2-(4-hydroxyfenyl)benzo[*b*] thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl- methanone hydrochloride.

Raloxifene HCl has the empirical formula

$C_{28}H_{27}NO_4S \cdot HCl$, which corresponds to a molecular weight 510.05.

17. RELATED/SUPPORTING DOCUMENTS:

Executive Summary Section

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	11/17/11	Reviewed by Aijin Shen
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

* Checked DARRTS, No new amendments as of Feb 22, 2013

[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: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending	9/1/2012	EES_Prod
Methods Validation	No needed		

Labeling	Tentative AP	02/09/2009	R. Wu
Bioequivalence	Acceptable	04/05/2011	D. NHU
EA	N/A		
Radiopharmaceutical	N/A		

DARRTS checked, Feb 22, 2013

19. ORDER OF REVIEW

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

The Executive Summary

The Chemistry Review for ANDA 078193

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable

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)

Drug Product

Raloxifene hydrochloride (RLD Evista) is supplied in a tablet dosage form for oral administration. Each Raloxifene hydrochloride tablet contains 60 mg of raloxifene hydrochloride, which is the molar equivalent of 55.71 mg of free base. Inactive ingredients include (b) (4) colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, (b) (4) poly dextrose, polyethylene glycol, povidone, pregelatinized starch, (b) (4) and titanium dioxide.

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The chemical designation is methanone, [6-hydroxy-2-(4-hydroxyphenyl) benzo [b] thien-3-yl]-[4[2-(l-piperidinyl) ethoxy]phenyl]-, hydrochloride. Raloxifene hydrochloride is off-white to pale-yellow solid that is very slightly soluble in water.

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Raloxifene hydrochloride tablets treat osteoporosis by helping make bones stronger and less likely to break. It helps prevent osteoporosis (b) (4) (b) (4) after menopause.

Raloxifene hydrochloride tablets, 60 mg are white to off-white, film-coated, capsule-shaped tablets, debossed with "7290" on one side of the tablet, and "93" on the other in bottles of 30, 100, and 1000.
Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

MDD is 60 mg.
DS IT = 0.10% QT = 0.15%
DP IT = 0.2% QT = 0.5%

C. Basis for Approvability or Not-Approval Recommendation

This application is not approvable due to minor CMC issues.

****

(b) (4)

30. MICROBIOLOGY: N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS: N/A

32. LABELING: Acceptable by RWu on 2/2/2009

33. ESTABLISHMENT INSPECTION: Pending

34. BIOEQUIVALENCE: Acceptable 04/05/2011

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: Can be granted

III. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 078193 APPLICANT: TEVA Pharmaceuticals USA

DRUG PRODUCT: Raloxifene Hydrochloride Tablets USP, 60 mg

The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.

9. (b) (4)

Sincerely yours,

{See appended electronic signature page}

Andre Raw, Ph. D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA78-193
ANDA DUP
DIV FILE
Field Copy

Endorsement Block

HFD-627/Review chemist/Aijin Shen, Ph.D./ 2/14, April 4, 2013

HFD-627/Team leader/RBykadi, Ph.D./ Feb 22, 27, April 4, 2013

HFD-617/Project manager/Rinku Patel, Pharm.D./4/8/2013

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NOT APPROVABLE

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/s/

AIJIN SHEN
04/09/2013

RINKU PATEL
04/09/2013

GURURAJ BYKADI
04/10/2013

BING CAI
04/12/2013

ANDA 78-193

Raloxifene Hydrochloride Tablets, 60 mg

Teva Pharmaceutical USA

Anil D. Pendse, Ph.D.

Office of Generic Drugs
Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 78-193

2. REVIEW #:2

3. REVIEW DATE: 7/19/07, 10/8/07, 2/27/08

4. REVIEWER: Anil D. Pendse

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original submission	3/2/06
Labeling amendment (AF)	8/4/06

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor amendment (AM)	2/22/07
Telephone amendment	9/6/07
Telephone request	2/14/08

7. NAME & ADDRESS OF APPLICANT:

Name: TEVA Pharmaceuticals USA

Address: 1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Representative: Phillip Erickson

Telephone: 215-591-3000

Fax: 215-591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Raloxifene Hydrochloride Tablets

9. LEGAL BASIS FOR SUBMISSION: Referenced Listed Drug: Evista® Tablets, 60 mg manufactured by Eli Lily and Company (NDA 20-815).

Paragraph IV Certification
The firm certifies that to the best of their knowledge there are 10 listed patents which claim the reference drug EVISTA® Tablets.

U.S. Patent #	Expiration Date	U.S. Patent #	Expiration Date
5393763	7/28/2012	5811120	3/2/2014
5457117	7/28/2012	5972383	3/2/2014
5478847	3/2/2014	6458811	3/10/2017
6797719	3/10/2017	6894064	3/10/2017
6906086	7/28/2012	RE38968	7/28/2012

The firm hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that all of the above listed patents, which have been filed for EVIST A@ Tablets, are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted. TEVA Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Eli Lilly as the holder of NDA #20-815 for EVISTA® Tablets and owner of the patents. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patents are invalid, unenforceable, or will not be infringed.

10. PHARMACOL. CATEGORY: Anti-osteoporotic
Raloxifene hydrochloride tablets are used by women after menopause to treat or prevent a condition called osteoporosis.

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 60 mg

13. ROUTE OF ADMINISTRATION: Oral

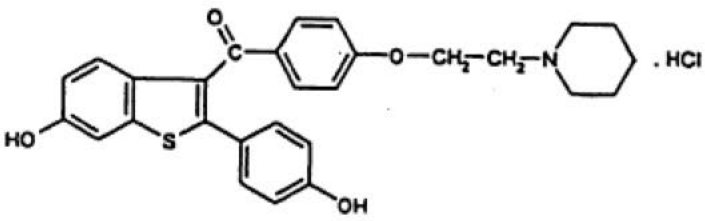
14. Rx/OTC DISPENSED: _X__Rx ___OTC

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:



The chemical designation is: [6-Hydroxy-2-(4-hydroxyfenyl)benzo[*b*] thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl- methanone hydrochloride.

Raloxifene HCl has the empirical formula

$C_{28}H_{27}NO_4S \cdot HCl$, which corresponds to a molecular weight 510.05.

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	7/20/07*	Reviewed by ADPendse
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

* Checked COMIS, No new amendments as of Oct 10, 2007

[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: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	6/1/2006	Adams
Methods Validation	No needed		

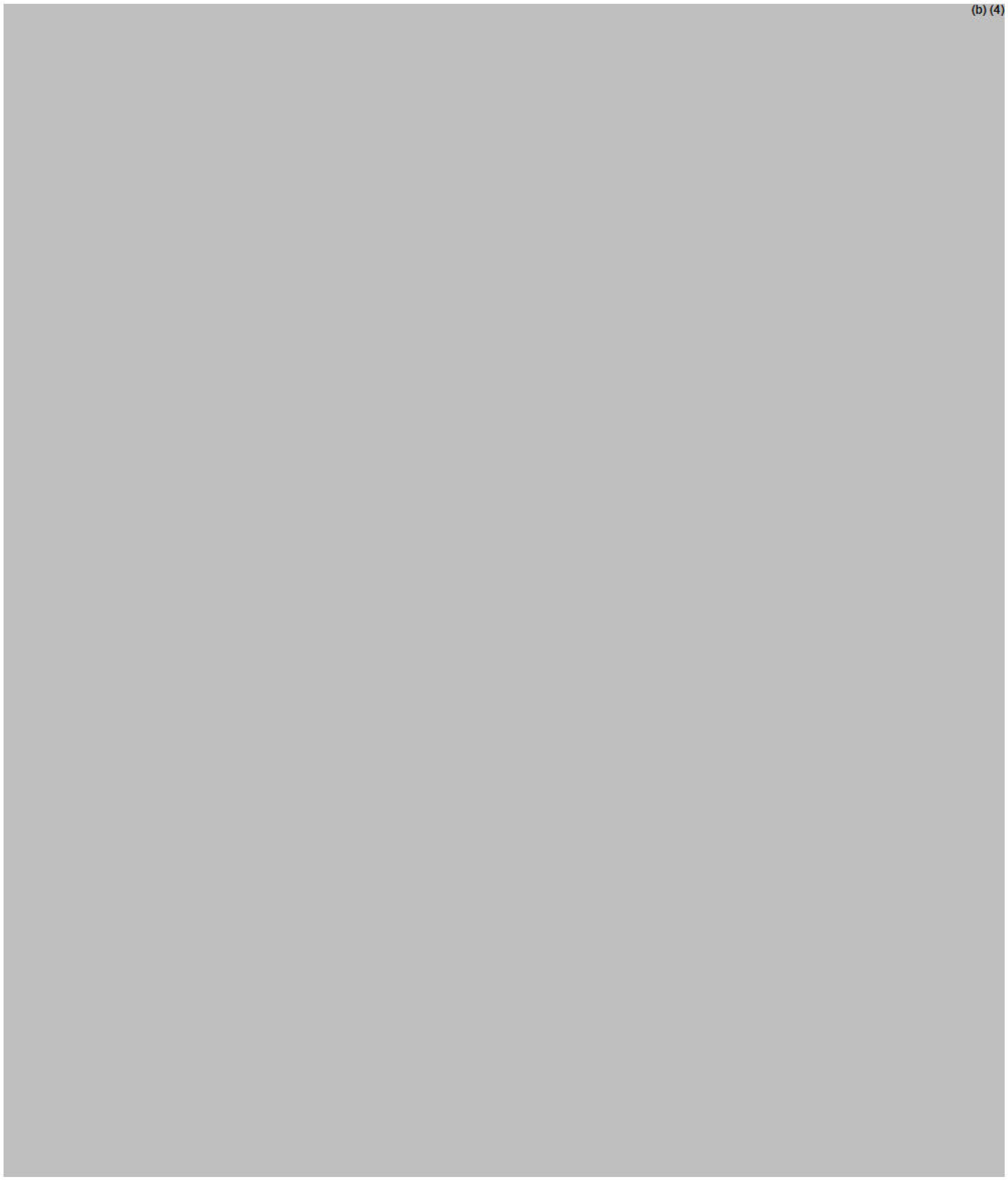
Labeling	Tentative AP	2/5/2007	R. Wu
Bioequivalence	Acceptable	7/26/2007	SM
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

Chemistry Review Data Sheet

(b) (4)



The Chemistry Review for ANDA 78-193

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable

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)

Drug Product

Raloxifene hydrochloride (RLD Evista) is supplied in a tablet dosage form for oral administration. Each Raloxifene hydrochloride tablet contains 60 mg of raloxifene hydrochloride, which is the molar equivalent of 55.71 mg of free base. Inactive ingredients include (b) (4) colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, (b) (4) poly dextrose, polyethylene glycol, povidone, pregelatinized starch, (b) (4) and titanium dioxide.

Drug substance

The chemical designation is methanone, [6-hydroxy-2-(4-hydroxyphenyl) benzo [b] thien-3-yl]-[4[2-(l-piperidinyl) ethoxy]phenyl]-, hydrochloride. Raloxifene hydrochloride is an off-white to pale-yellow solid that is very slightly soluble in water.

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

Raloxifene hydrochloride tablets are a prescription medicine used by women after menopause to treat or prevent a condition called osteoporosis. One should take calcium and vitamin D along with Raloxifene hydrochloride tablets if enough calcium and vitamin D is not included in the diet.

Raloxifene hydrochloride tablets treat osteoporosis by helping make bones stronger and less likely to break. It helps prevent osteoporosis (b) (4) (b) (4) after menopause.

Raloxifene hydrochloride tablets, 60 mg are white to off-white, film-coated, capsule-shaped tablets, debossed with "7290" on one side of the tablet, and "93" on the other in bottles of 30, 100, and 1000.

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

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

MDD is 60 mg.

DS IT = 0.10% QT = 0.15%

DP IT = 0.2% QT = 0.5%

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable.

Following this page, 10 Pages Withheld in Full as (b)(4)

(b) (4)

[redacted]

30. MICROBIOLOGY: N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS: N/A

32. LABELING: Acceptable by RWu on 2/6/2007

33. ESTABLISHMENT INSPECTION: Acceptable on 6/1/06 by Adams

34. BIOEQUIVALENCE: Acceptable by SM on 7/26/07

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: Can be granted

cc: ANDA78-193
ANDA DUP
DIV FILE
Field Copy

Endorsement Block

HFD-627/Review chemist/ADPendse, Ph.D/10/8/07, 2/27/08

HFD-627/Team leader/RBykadi, Ph.D./ 10/10/07, 2/27/08

HFD-617/Project manager/BDanso, Pharm.D./1-28-08,2/27/08

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APPROVABLE

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

/s/

Ramnarayan Randad
4/17/2008 07:34:35 AM
CHEMIST
for Dr. Anil Pendse

Gururaj Bykadi
4/17/2008 08:14:43 AM
CHEMIST
Ram Randad signed for Anil Pendse as Anil iPendse is on vacation
Ram Randad signed for Anil Pendse as Anil iPendse is on vacation

Simon Eng
4/17/2008 08:29:53 AM
CSO

ANDA 78-193

Raloxifene Hydrochloride Tablets, 60 mg

Teva Pharmaceutical USA

Anil D. Pendse, Ph.D.

Office of Generic Drugs
Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 78-193

2. REVIEW #:1

3. REVIEW DATE: 8/1/06

4. REVIEWER: Anil D. Pendse

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission Labeling amendment	3/2/06 8/4/06

7. NAME & ADDRESS OF APPLICANT:

Name: TEVA Pharmaceuticals USA

Address: 1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Representative: Phillip Erickson

Telephone: 215-591-3000
Fax: 215-591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None

b) Non-Proprietary Name (USAN): Raloxifene Hydrochloride Tablets

9. LEGAL BASIS FOR SUBMISSION: Referenced Listed Drug: Evista® Tablets, 60 mg manufactured by Eli Lily and Company (NDA 20-815).

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6797719	3/10/2017	6894064	3/10/2017
6906086	7/28/2012	RE38968	7/28/2012

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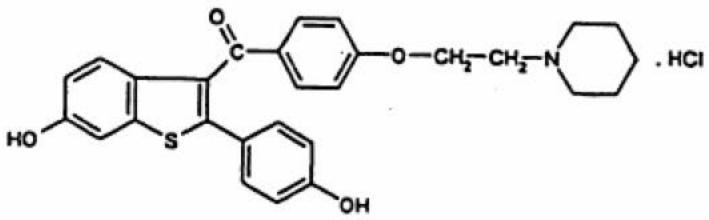

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A. DMFs:

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(b) (4)	II	(b) (4)		1	Deficient	9/5/06	Reviewed by ADPendse
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

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[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

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	6/1/06	Adams
Methods Validation	No needed		
Labeling	Not Acceptable	8/16/06	R. Wu
Bioequivalence	Pending Dissolution review - Not Acceptable (Nguyen//7-11-06)		
EA	N/A		
Radiopharmaceutical	N/A		

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:

The Chemistry Review for ANDA 78-193

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable at this time

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)

Drug Product

Raloxifene hydrochloride is supplied in a tablet dosage form for oral administration. Each Raloxifene hydrochloride tablet contains 60 mg of raloxifene hydrochloride, which is the molar equivalent of 55.71 mg of free base. Inactive ingredients include (b) (4) colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, (b) (4) poly dextrose, polyethylene glycol, povidone, pregelatinized starch, (b) (4) and titanium dioxide.

Drug substance

The chemical designation is methanone, [6-hydroxy-2-(4-hydroxyphenyl) benzo [b] thien-3-yl]-[4[2-(l-piperidinyl) ethoxy]phenyl]-, hydrochloride. Raloxifene hydrochloride is an off-white to pale-yellow solid that is very slightly soluble in water.

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

Raloxifene hydrochloride tablets are a prescription medicine used by women after menopause to treat or prevent a condition called osteoporosis. One should take calcium and vitamin D along with Raloxifene hydrochloride tablets if enough calcium and vitamin D is not included in the diet.

Raloxifene hydrochloride tablets treat osteoporosis by helping make bones stronger and less likely to break. It helps prevent osteoporosis (b) (4) (b) (4) after menopause.

Raloxifene hydrochloride tablets, 60 mg are white to off-white, film-coated, capsule-shaped tablets, debossed with "7290" on one side of the tablet, and "93" on the other in bottles of 30, 100, and 1000.

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

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

MDD is 60 mg.

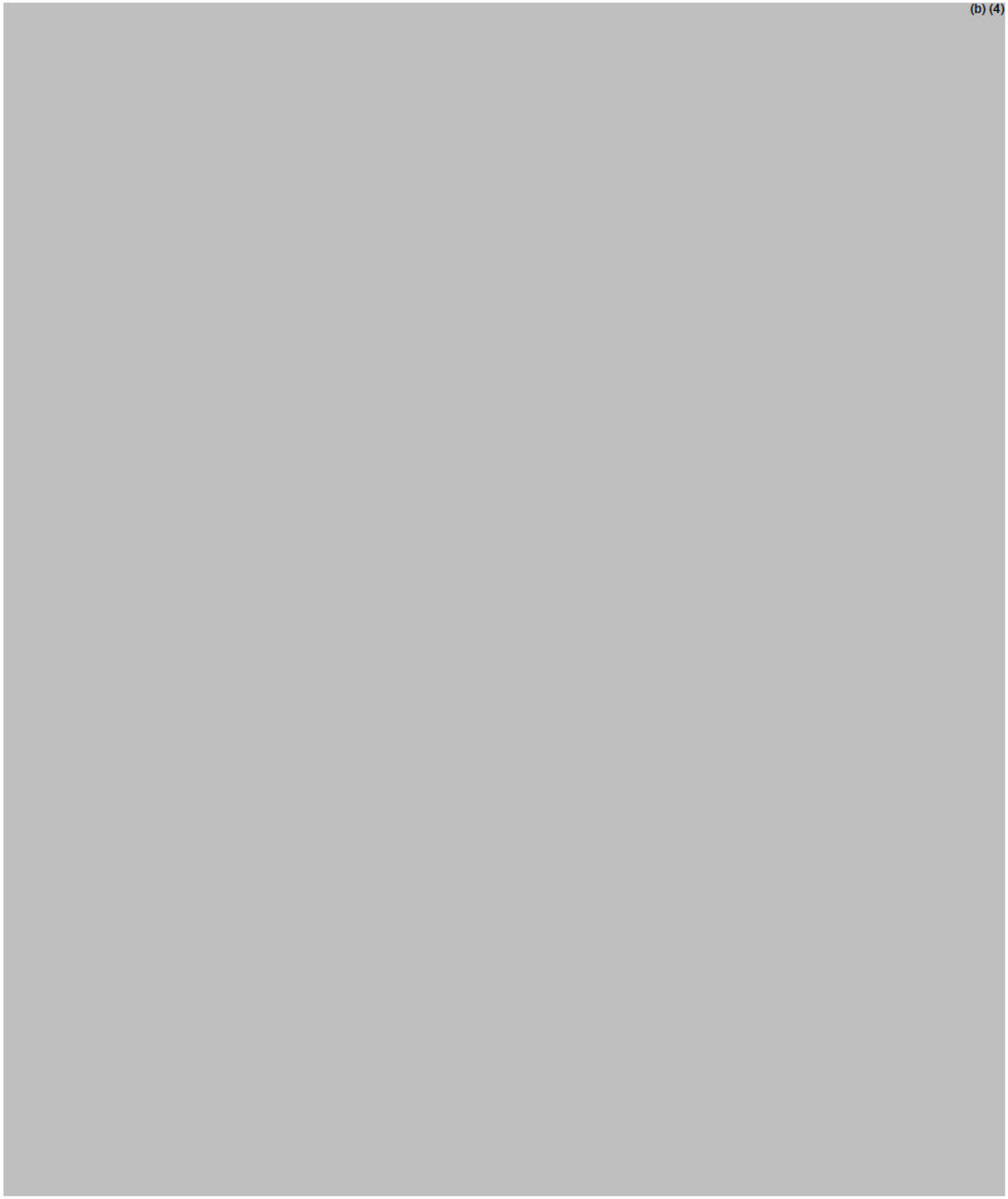
DS IT = 0.10% QT = 0.15%
DP IT = 0.2% QT = 0.5%

C. Basis for Approvability or <u>Not-Approval</u> Recommendation

DMF (b) (4) is deficient, Bioequivalence and Labeling information is not acceptable.

Following this page, 12 Pages Withheld in Full as (b)(4)

(b) (4)



30. MICROBIOLOGY: N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS: N/A

32. LABELING: Not acceptable on 8/16/06, R.Wu.

33. ESTABLISHMENT INSPECTION: Acceptable on 6/1/06 by Adams

34. BIOEQUIVALENCE: DBE has not finalized the dissolution limits. Not acceptable on 7/11/06, Nguyen

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: Can be granted

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-193 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Raloxifene Hydrochloride Tablets, 60 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. DMF (b) (4) has been found inadequate. The DMF holder has been notified. Please do not respond to this letter until the DMF holder has informed you that a complete response to the DMF deficiencies has been submitted to the agency.

2. (b) (4)

3.

4.

5.

6.

7.

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

1. Your reply should also address the labeling deficiencies provided to you by the Division of Labeling.

2. Your reply should also address the bioequivalence deficiencies provided to you by the Division of Bioequivalence.

3. Please provide any additional long term stability data for all strengths of the drug product.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA78-193
ANDA DUP
DIV FILE
Field Copy

Endorsement Block

HFD-627/Review chemist/ADPendse, Ph.D/9/8/06

HFD-627/Team leader/RBykadi, Ph.D./06

HFD-617Project manager/BDanso, Pharm.D./10-5-06

F/T by: ard/ / /06

V:\Chemistry Division I\Team 5\Final Version For DFS Folder\78193.REV1.doc

TYPE OF LETTER: NOT APPROVABLE – **MINOR**

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/s/

Anil Pendse
10/23/2006 03:33:45 PM
CHEMIST

Benjamin Danso
10/24/2006 03:36:34 PM
CSO

NA review

Gururaj Bykadi
10/25/2006 01:00:48 PM
CHEMIST
For R. Patel

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78193

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE DISSOLUTION ACKNOWLEDGEMENT REVIEW

ANDA No.	78-193
Drug Product Name	Raloxifene Hydrochloride Tablets
Strength	60 mg
Applicant Name	Teva Pharmaceuticals USA
Submission Date	July 12, 2007
Reviewer	Beth Fabian-Fritsch, R.Ph.

EXECUTIVE SUMMARY

This is a review of the dissolution specification acknowledgement from the firm.

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

The application is complete.

COMMENTS:

None

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 and the application is approvable.

ANDA 78-193

BIOEQUIVALENCE - ACCEPTABLE

Submission date: July 12, 2007

1. Study Amendment (STA) — Strengths: All; Outcome: AC

Outcome Decisions: **AC** - Acceptable

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/s/

Beth Fabian-Fritsch
7/20/2007 01:17:37 PM
BIOPHARMACEUTICS

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/s/

DUONG NHU
04/05/2011

DIVISION OF BIOEQUIVALENCE DISSOLUTION ACKNOWLEDGEMENT REVIEW

ANDA No.	78-193
Drug Product Name	Raloxifene Hydrochloride Tablets
Strength	60 mg
Applicant Name	Teva Pharmaceuticals USA
Submission Date	July 12, 2007
Reviewer	Beth Fabian-Fritsch, R.Ph.

EXECUTIVE SUMMARY

This is a review of the dissolution specification acknowledgement from the firm.

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

The application is complete.

COMMENTS:

None

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 and the application is approvable.

ANDA 78-193

BIOEQUIVALENCE - ACCEPTABLE

Submission date: July 12, 2007

1. Study Amendment (STA) Strengths: All
Outcome: AC

Outcome Decisions: **AC** - Acceptable

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/s/

Beth Fabian-Fritsch
7/20/2007 01:17:37 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW OF AN AMENDMENT

ANDA No.	78-193
Drug Product Name	Raloxifene Hydrochloride Tablet
Strength(s)	60 mg
Applicant Name	Teva Pharmaceuticals USA
Address	1090 Horsham Rd, PO Box 1090, North Wales, PA 19454
Applicant's Point of Contact	Philip Erickson
Contact's Telephone Number	215-591-3000
Contact's Fax Number	215-591-8812
Original Submission Date(s)	March 2, 2006
Amendment Date	March 22, 2007
Reviewer	Christina H. Lee, Pharm.D.

EXECUTIVE SUMMARY

This amendment has been submitted in response to the deficiency letters from the Agency dated July 14, 2006 and January 12, 2007 regarding the firm's pending ANDA# 78-193. Both letters addressed the firm's dissolution method comparing its test product, Raloxifene HCl, 60 mg tablets with the RLD Evista® Tablet 60 mg manufactured by Eli Lilly. The firm was requested to conduct its dissolution testing using the DBE recommended method—*1000 mL of 0.1% Polysorbate 80 in water (@ 37°C) , USP Apparatus II (paddle) at 50 rpm,* sampling time points 10, 15, 20 and 30 minutes.

In the current amendment, Teva has submitted comparative dissolution testing comparing its test product, Raloxifene HCl, 60 mg tablets (Lot# K-35052, Biobatch) with the RLD Evista® Tablet 60 mg (Lot# A198352) using the DBE-suggested method. In addition, Teva also included dissolution testing data (using DBE-recommended method) on two development batches of Raloxifene HCl Tablets (Lot# K344/01/1 and Lot# K34534/1), which previously failed in pilot bioequivalence studies versus Evista®. Based on the resubmitted dissolution data using the DBE method, Teva proposes reconsideration of its dissolution method—*900 mL, 1% SLS in 0.05 M sodium phosphate buffer, Apparatus II at 75 rpm- submitted in the original application*.

The DBE concurs with the firm's proposal on the dissolution method for its test product. However, the firm's proposed specification of NLT (b)(4)%(Q) in (b)(4) minutes is not acceptable. Based on the data submitted, the DBE recommends dissolution specification of NLT 80%(Q) in 45 minutes. The application is incomplete pending the firm's acknowledgment of the DBE-recommended specification.

TABLE OF CONTENTS

DEFICIENCY COMMENTS, FIRM'S RESPONSES, AND REVIEWER'S COMMENTS

Deficiency Comment:

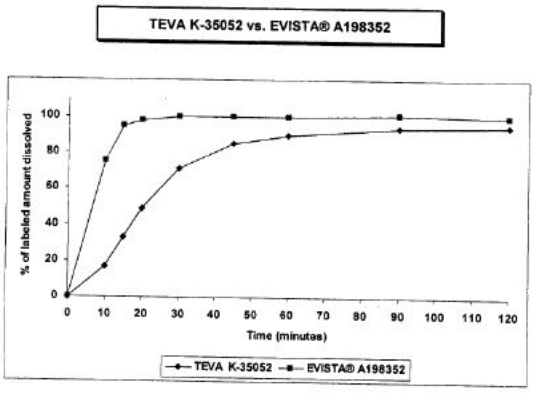
Please conduct dissolution testing on the test and reference products (12 units each) using the following FDA-recommended method and resubmit the results with individual data as well as mean, range and CV%. The dissolution testing should be conducted in 1000mL of 0.1% Polysorbate 80 in water (@ 37°C) using USP Apparatus II (paddle) at 50 rpm. The recommended sampling time points are 10, 15, 20 and 30 minutes. The test product should meet the following specification: NLT 80%(Q)in 30 minutes.

Firm's Response:

Comparative dissolution profiles were generated using the method and parameters noted above (The DBE recommended method -- *1000mL of 0.1% Polysorbate 80 in water (@ 37°C) using USP Apparatus II (paddle) at 50 rpm. The recommended sampling time points are 10, 15, 20 and 30 minutes. The test product should meet the following specification--NLT 80%(Q)in 30 minutes)* for Teva ANDA Lot# K-35053 (Bio-batch) and innovator Lot# A198352 (Evista®), the lots for which passing bioequivalence study results were presented in the original ANDA.

Table 1. Dissolution profile, Raloxifene HCl

Product ID/Batch No.	Dosage Form	No. of Dosage Units	Collection Times (Minutes) Mean % Dissolved (Range), % RSD							
			10	15	20	30	45	60	90	120
Raloxifene HCl K-35052	60 mg Tablets	12	17	33	49	71	85	90	94	95 (b) (4)
			19.4%	14.2%	10.8%	5.4%	2.5%	2.1%	2.1%	1.7%
Evista® Tablet 60 mg A198352			75	95	98	100	100	100	101	100 (b) (4)
			7.6%	1.9%	2.1%	2.0%	1.7%	1.7%	1.9%	2.1%

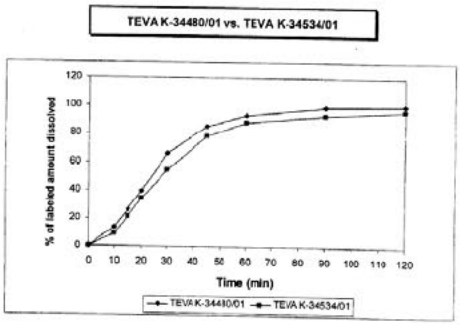


These dissolution profiles for the Teva lot and innovator lot were not comparable; therefore, further testing was performed.

Two development batches of Raloxifene HCl Tablets, 60 mg (K-344801/1 and K-34534/1), which previously failed in pilot bioequivalence studies versus Evista®, were tested using the DBE recommended dissolution method. See below table for dissolution data for these two batches.

Table 2. Dissolution profile, Raloxifene HCl (Batch K-344801/1 and K-34534/1)

Product ID/Batch No.	Dosage Form	No. of Dosage Units	Collection Times (Minutes) Mean % Dissolved (Range), % RSD							
			10	15	20	30	45	60	90	120
Raloxifene HCl K-344801/1	60 mg Tablets	6	13	26	39	66	85	93 (b) (4)	99 (b) (4)	100 (b) (4)
			6.5%	2.7%	2.0%	2.6%	3.5%	1.8%	1.5%	1.8%
Raloxifene HCl K-34534/1			9	21	34	54	78	88	93 (b) (4)	96 (b) (4)
			17.5%	17.8%	15.6%	17.5%	5.7%	3.8%	2.5%	2.9%



The results, which showed slow dissolution, were not consistent with the plasma results from the pilot biostudies. The following table summarizes the test/reference ratios of mean values from these studies, as well as the bioequivalence study results for the pivotal study (ANDA Lot# K-35052):

Table 3. Comparative bioequivalence study results from the biobatch and two development batches:

Batch #	Cmax ratio (%) CI (%)		AUCt ratio (%) CI (%)	
	Fasting Study	Postprandial Study	Fasting Study	Postprandial Study
K-35052	91.1 (81.0-102.4)	101.7 (93.9-110.1)	92.8 (86.3-99.8)	100.0 (93.8-106.6)
K-344801/1	106.0 (90.3-124.5)	103.4 (87.6-122.0)	86.3 (76.3-97.5)	99.0 (93.0-105.4)
K-34534/1	129.0	116.2	100.5	102.1

	(109.9-151.3)	(98.3-137.3)	(88.9-113.6)	(95.9-108.8)

Reviewer's comments on dissolution:

In the current amendment, Teva has submitted two comparative dissolution testing comparing its test product, Raloxifene HCl, 60 mg tablets (Lot# K-35052, Biobatch) with the RLD Evista® Tablet 60 mg (Lot# A198352) using the DBE-suggested method. In addition, Teva also included dissolution testing data using DBE-recommended method on two development batches of Raloxifene HCl Tablets (Lot# K344/01/1 and Lot# K34534/1), which previously failed in pilot bioequivalence studies versus Evista® using the DBE recommended dissolution method.

Based on the resubmitted dissolution data using the DBE method, Teva proposes reconsideration of its dissolution method—900 mL, 1% SLS in 0.05 M sodium phosphate buffer, Apparatus II at 75 rpm- submitted in the original application.

Based on review of the data submitted, the DBE found that the firm's-proposed dissolution method is better reflective of its test product's in vitro performance. Therefore, the DBE concurs with the firm's proposed dissolution method (see Table below). However, the firm's proposed specification of NLT (b)(4)%(Q) in (b)(4) minutes is not acceptable as the results achieve a specification of NLT80%(Q) in 45 minutes at the S1 level. Therefore, the DBE recommends a dissolution specification of NLT 80%(Q) in 45 minutes.

Dissolution Data-firm proposed method in the Original ANDA submission

Study Ref. No.	Product ID/Batch No.	Dosage form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)				Study Report Location
					15 min	30 min	45 min	60 min	
CDP-1240/01	Raloxifene HCl K-35052	60 mg Tablets	Dissolution: Apparatus 2 (Paddles) Speed of Rotation: 75 rpm Medium: 1% SLS in 0.05M sodium phosphate buffer volume: 900 mL Temperature: 37°C± 0.5°C Tolerance: NLT (b)(4)% (Q) dissolved in (b)(4) minutes.	12	63	97	100	100 (b) (4)	Teva Pharmaceutical Industries, Ltd., Hashikma Street, Industrial Area, Kfar-Saba 44102, ISRAEL
	Evista ® 8EF35A	60 mg Tablets		12	62	84	92	96 (b) (4)	

DEFICIENCY COMMENTS FOR THE CURRENT SUBMISSION

The firm's proposed specification of NLT (b)(4)%(Q) in (b)(4) minutes is not acceptable. Based on the data submitted, the DBE recommends dissolution specification of NLT 80%(Q) in 45 minutes. The application is incomplete pending the firm's acknowledgment of the DBE-recommended specification. The firm is requested to acknowledge its acceptance of the DBE recommended dissolution method and specification.

RECOMMENDATION

The dissolution testing conducted by Teva on its test product, Raloxifene HCl, 60 mg tablets (Lot# K-35052, Biobatch) comparing with the RLD Evista® Tablet 60 mg (Lot# A198352) using the firm proposed method is acceptable. The dissolution testing should be conducted in *900 mL, 1% SLS in 0.05 M sodium phosphate buffer, Apparatus II at 75 rpm as proposed by the firm*. However, the firm's proposed specification of NLT (b)(4)%(Q) in (b)(4) minutes is not acceptable. Based on the data submitted, the DBE recommends dissolution specification of NLT 80%(Q) in 45 minutes. The application is incomplete pending the firm's acknowledgment of the DBE-recommended specification.

The firm should be informed of the above recommendation.

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BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA: 78193

APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Raloxifene Hydrochloride Tablet, 60 mg

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

Your proposed dissolution method, using 900 mL of 1% SLS in 0.05 M sodium phosphate buffer, Apparatus II at 75 rpm, is acceptable. However, based on the data submitted in your original application, DBE recommends the following specification:

Not less than 80% (Q) of the labeled amount of drug in the dosage form is dissolved in 45 minutes.

Please acknowledge your acceptance of the above dissolution method and specification.

Sincerely Yours,

Dale P. Connor, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 78193A0307: Raloxifene Hydrochloride Tablet 60 mg, Teva Pharmaceuticals USA

1.	Amendment (STA)	Strength:	60 mg
	(STA)	Outcome:	**AC**
	Submission Date(s)	**March 22, 2007**	

BIOEQUIVALENCE OUTCOME DECISIONS:	AC – Acceptable IC – Incomplete UN – Unacceptable WC – Without Credit

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/s/

Christina Lee
4/27/2007 08:12:45 AM
BIOPHARMACEUTICS

Chandra S. Chaurasia
4/27/2007 11:01:41 AM
BIOPHARMACEUTICS

Barbara Davit
4/27/2007 12:00:25 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-193
Drug Product Name	Raloxifene Hydrochloride Tablet
Strength	60 mg
Applicant Name	Teva Pharmaceuticals USA
Address	1090 Horsham Rd, PO Box 1090, North Wales, PA 19454
Contact Information	Philip Erickson
Phone Number	215-591-3000
Fax Number	215-591-8812
Submission Date(s)	March 2, 2006
Amendment Date(s)	NA
Reviewer	Christina Lee, Pharm.D.
First Generic	No

Executive Summary

Teva conducted two randomized, two-way crossover studies in healthy postmenopausal females comparing its 60 mg of the test product with the RLD Evista® Tablet 60 mg manufactured by Eli Lilly and Company under a fasting (n=59) and non-fasting (n=44) conditions. In addition, the firm has also submitted comparative dissolution data. Statistical analysis of the plasma concentration data for raloxifene HCl demonstrates bioequivalence.

The results (point estimate, 90% CI) of the **fasting BE study** for Raloxifene are LAUCt of 0.93, 86.36 -99.7%; LAUCI of 0.94, 87.24 - 101.12%; and LCmax of 0.91, 80.51 – 102.35%; raloxifene 4ß-glucuronide: LAUCt of 0.94, 87.9 – 100.7%; LAUCi of 0.94, 87.5 – 100.0%; and LCmax of 0.80, 75.1 – 85.3%; raloxifene 6ß-glucuronide: LAUCt of 0.93, 87.1 – 99.8%; LAUCi of 0.94, 87.2 – 100.5%; and LCmax of 0.89, 82.7 – 95.0%. The study appears to be adequately powered to take into account of the high variability of the parent moiety. Per DBE recommendation, the firm has measured plasma metabolites level, however, the 90% CI outside the acceptable range for the 4ß-glucuronide is presumably due to the study not being adequately powered to establish bioequivalence based on the metabolite levels. In light of this, the relatively low plasma metabolite concentrations (compared to plasma parent concentrations), and coupled with the fact that the PK measures for the parent moiety and for raloxifene 6ß-glucuronide are within the acceptable range, the DBE concludes that the 4ß-glucuronide data supports a conclusion of bioequivalence for this product.

The results (point estimate, 90% CI) of the **fed BE study** for Raloxifene are LAUCt of 1.01, 93.84 -108.60%; LAUCI of 1.01, 93.40 – 109.78%; and LCmax of 1.02, 92.82 – 111.59%; raloxifene 4ß-glucuronide: LAUCt of 1.03, 85.13 – 112.05%; LAUCi of 1.03, 93.94 – 112.43%; and LCmax of 0.98, 90.53 – 106.76%; raloxifene 6ß-glucuronide: LAUCt of 1.00, 93.94 – 106.71%; LAUCi of 1.00, 93.87 – 107.43%; and LCmax of 1.02, 94.00 – 110.15%.

The firm performed dissolution testing using its own proposed method (900 ml, 1% SLS in 0.05 M sodium phosphate buffer, Apparatus II at 75 rpm) instead of the FDA-recommended method (1000 mL, 0.1% polysorbate 80 aq. solution, Apparatus II at 50

rpm). The dissolution method was reviewed by DBE, and a deficiency letter was issued on July 14, 2006. The firm has been recommended to conduct and submit dissolution testing using the FDA-recommended method.

The fasting and fed *in vivo* BE study meets the bioequivalence criteria, however due to incomplete dissolution testing, the application is incomplete.

Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Raloxifene HCl Tablets, 60 mg
Reference Product	Evista® Tablets 60 mg (also available in 5 mg)
RLD Manufacturer	Eli Lilly and Company
NDA No.	20-815
RLD Approval Date	12/09/1997
Indication	Treatment and prevention of osteoporosis in postmenopausal women.

B. PK/PD Information (Sources: Electronic Clinical Pharmacology, 2007 PDR and Micromedex)

Bioavailability	Although 60% of an oral dose is absorbed, raloxifene accounts for only 2% of plasma circulating compounds due to extensive first-pass metabolism.
Food Effect	High-fat meals increase the Cmax and AUC of raloxifene by 28% and 16%, respectively but does not lead to clinically meaningful changes in systemic exposure. May be administered without regard to meals.
Tmax	Varies depending on systemic interconversion and enterohepatic cycling of parent drug and its glucuronide metabolites
Metabolism	Extensive first-pass metabolism to the following glucuronide conjugates: raloxifene-4'-glucuronide, raloxifene-6-glucuronide, and raloxifene-6, 4'-diglucuronide; Raloxifene and its glucuronide metabolites undergo enterohepatic cycling which affects bioavailability and time to peak plasma concentration. Raloxifene and its glucuronide conjugates are interconverted by reversible systemic metabolism and enterohepatic cycling.
Excretion	Less than 0.2% is excreted unchanged in urine and less than 6% is eliminated in urine as glucuronide conjugates.
Half-life	Elimination T1/2 of raloxifene is highly variable; mean T1/2 after multiple oral doses is 32.5 hours (range: 15.8—86.6 h).
Relevant OGD or DBE History	Only two ANDAs [redacted] 78193, Teva) have been submitted for this drug product. DBE has finished [redacted] ANDA [redacted] review and the application has been found complete. The OGD has reviewed several control documents (01-318, [redacted]; 02-015, [redacted]; 01546, [redacted]; 02-110, [redacted]; 03-155, [redacted]; 03757, [redacted] 03936, [redacted]; 04504, [redacted]; 041177, [redacted]; 050957, [redacted]; 050993, [redacted]; 051263, [redacted] and 060639, [redacted]) regarding the Agency requirements for demonstration of in vivo bioequivalence and dissolution for raloxifene, the DBE recommends the following: 1. The following studies are recommended to establish bioequivalence for raloxifene hydrochloride tablets: • A 2-way crossover fasting *in-vivo* BE study

comparing Raloxifene HCl Tablets, 60 mg, to the RLD, Evista® (Raloxifene Hydrochloride) Tablets, 60 mg.

- A 2-way crossover fed in-vivo BE study comparing Raloxifene HCl Tablets, 60 mg, to the RLD.

2. Measure raloxifene and its metabolites, raloxifene-4'-glucuronide and raloxifene-6'-glucuronide. Please analyze raloxifene using the 90% CI approach. Based on BA/BE Guidance (2003), the assessment of bioequivalence was based on the parent raloxifene. The data of the metabolites were presented for information purposes only. For the metabolites, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax.
3. There is no USP dissolution method available for this drug. A comparative dissolution testing on 12 dosage units of the test and RLD products using the following FDA method is recommended:

Apparatus: USP Apparatus II (paddle)
Speed: 50 rpm
Medium: 0.1% polysorbate 80 aqueous solution
Volume: 1000 mL
Sampling times: 10, 20, 30, and 45 min. or until $\geq$ 80% of the labeled content is dissolved.

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Agency Guidance 2003 CDER BA/BE guidance

Drug Specific Issues (if any) None

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	
In vitro dissolution	Yes	1
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	No	

D. Pre-Study Bioanalytical Method Validation

Raloxifene:

Information requested	Data
Bioanalytical method validation report location	(b) (4)
Analyte	Raloxifene
Internal standard (IS)	(b) (4)
Method description	High performance liquid chromatographic mass spectrometric method, (b) (4)
Limit of quantitation	5.20 pg/mL Validation Report Page 10
Average recovery of drug (%)	Low QC: 67.0% Validation Report Page 43 High QC: 77.2%
Average recovery of IS (%)	72.0% Validation Report Page 44
Standard curve concentrations (pg/mL)	5.20, 10.4, 26.0, 65.0, 130, 260, 520, 1040 and 1300 pg/mL Validation Report Page 39
QC concentrations (pg/mL)	5.20, 15.0, 50.0, 500 and 1000 pg/mL Validation Report Pages 28,33
QC Intraday precision range (%)	**Batch:** **05CMY** Validation Report Page 28 LLOQ QC: 7.0% Low QC: 4.1% Medium-Low QC: 2.8% Medium-High QC: 6.4% High QC: 5.1%
QC Intraday accuracy range (%)	**Batch:** **05CMY** Validation Report Page 28 LLOQ QC: 98.7% Low QC: 104.7% Medium-Low QC: 101.8% Medium-High QC: 107.8% High QC: 102.0%
QC Interday precision range (%)	LLOQ QC: 12.6%, Low QC: 8.6%, Medium-Low QC: 5.7%, Medium-High QC: 4.6%, High QC: 4.4% Validation Report Page 33
QC Interday accuracy range (%)	LLOQ QC: 85.8%, Low QC: 98.0%, Medium-Low QC: 101.0%, Medium-High QC: 102.0%, High QC: 101.0% Validation Report Page 33
Bench-top stability (hrs)	48 hours at Ambient Temperature Validation Report Page 52
Stock Solution Stability (days)	231 days at 100 mcg/mL in Methanol at –80°C 32 days at 0.520 ng/mL in Methanol at –80°C Validation Report Pages 63,64
Post-preparative Stability	99.5 hours at Ambient Temperature Validation Report Page 60
Freeze-thaw stability (cycles)	6 cycles at -80°C Validation Report Page 57
Long-term storage stability (days)	465 days at –80°C Validation Report Page 49
Processed Sample Integrity	124.5 hours at Ambient Temperature Validation Report Page 78
Dilution integrity	up to 2000 pg/mL Validation Report Page 75
Selectivity	No interfering peaks noted in any of the 6 human plasma (EDTA) lots screened Validation Report Page 20

Raloxifene-4β-Glucuronide:

Information requested	Data
Bioanalytical method validation report location	(b) (4)
Analyte	Raloxifene 4-β-Glucuronide
Internal standard (IS)	(b) (4)
Method description	High performance liquid chromatographic mass spectrometric method, (b) (4)
Limit of quantitation	2.00 ng/mL Validation Report Page 12
Average recovery of drug (%)	Low QC: 92.0% Validation Report Page 45 Medium-Low QC: 97.7% Medium-High QC: 93.1% High QC: 93.3%
Average recovery of IS (%)	86.3% Validation Report Page 47
Standard curve concentrations (ng/mL)	2.00, 4.00, 10.0, 20.0, 50.0, 100, 200, 400 and 500 ng/mL Validation Report Page 40
QC concentrations (ng/mL)	2.10, 6.00, 30.0, 150 and 375 ng/mL Validation Report Pages 29,34
QC Intraday precision range (%)	**Batch: 15CTG 16CTG 18CTG** LLOQ QC: 3.9% 1.8% 2.7% Low QC: 8.9% 2.7% 3.5% Medium-Low QC: 2.8% 7.3% 3.2% Medium-High QC: 2.9% 13.1% 5.0% High QC: 2.5% 4.7% 6.4% Validation Report Page 29
QC Intraday accuracy range (%)	**Batch: 15CTG 16CTG 18CTG** LLOQ QC: 107.1% 94.8% 109.0% Low QC: 96.5% 99.8% 102.0% Medium-Low QC: 105.0% 108.3% 100.0% Medium-High QC: 98.7% 111.3% 99.3% High QC: 100.5% 103.5% 96.0% Validation Report Page 29
QC Interday precision range (%)	LLOQ QC: 6.8%, Low QC: 5.8%, Medium-Low QC: 5.8%, Medium-High QC: 10.1%, High QC: 5.5% Validation Report Page 34
QC Interday accuracy range (%)	LLOQ QC: 103.8%, Low QC: 99.5%, Medium-Low QC: 104.7%, Medium-High QC: 103.3%, High QC: 100.0% Validation Report Page 34
Bench-top stability (hrs)	28 hours at Ambient Temperature Validation Report Page 53
Stock Solution Stability (days)	203 days at 106 mcg/mL in Methanol at –80°C 15 days at 0.200 mcg/mL in Methanol at –80°C Validation Report Pages 65,66
Post-preparative Stability	193 hours at Ambient Temperature Validation Report Page 61
Freeze-thaw stability (cycles)	6 cycles at -80°C Validation Report Page 58
Long-term storage stability (days)	465 days at –80°C Validation Report Page 50
Processed Sample Integrity	127.0 hours at Ambient Temperature Validation Report Page 80
Dilution integrity	up to 750 ng/mL Validation Report Page 76
Selectivity	No interfering peaks noted in any of the 10 human plasma (EDTA) lots screened Validation Report Page 20

Raloxifene-6β-Glucuronide:

Information requested	Data
Bioanalytical method validation report location	(b) (4)
Analyte	Raloxifene 6-β-Glucuronide
Internal standard (IS)	(b) (4)
Method description	High performance liquid chromatographic mass spectrometric method, (b) (4)
Limit of quantitation	0.286 ng/mL Validation Report Page 14
Average recovery of drug (%)	Low QC: 94.8% Medium-Low QC: 104.8% Medium-High QC: 98.0% High QC: 97.5% Validation Report Page 46
Average recovery of IS (%)	94.3% Validation Report Page 48
Standard curve concentrations (ng/mL)	0.286, 0.572, 1.43, 2.86, 7.15, 14.3, 28.5, 57.0 and 71.3 ng/mL Validation Report Page 41
QC concentrations (ng/mL)	0.300, 0.856, 4.28, 21.4 and 53.5 ng/mL Validation Report Pages 31,35
QC Intraday precision range (%)	**Batch: 15CTG 16CTG 18CTG** LLOQ QC: 4.1% 3.2% 3.2% Low QC: 9.3% 4.4% 5.6% Medium-Low QC: 4.2% 8.2% 2.0% Medium-High QC: 4.0% 13.3% 3.0% High QC: 2.3% 4.4% 7.5% Validation Report Page 31
QC Intraday accuracy range (%)	**Batch: 15CTG 16CTG 18CTG** LLOQ QC: 112.0% 108.7% 113.3% Low QC: 96.5% 99.4% 97.8% Medium-Low QC: 101.9% 102.3% 100.8% Medium-High QC: 98.6% 102.8% 98.1% High QC: 99.3% 102.2% 96.4% Validation Report Page 31
QC Interday precision range (%)	LLOQ QC: 3.8%, Low QC: 6.4%, Medium-Low QC: 5.2%, Medium-High QC: 8.2%, High QC: 5.4% Validation Report Page 35
QC Interday accuracy range (%)	LLOQ QC: 111.3%, Low QC: 97.9%, Medium-Low QC: 101.6%, Medium-High QC: 100.0%, High QC: 99.3% Validation Report Page 35
Bench-top stability (hrs)	28 hours at Ambient Temperature Validation Report Page 55
Stock Solution Stability (days)	203 days at 113 mcg/mL in Methanol at –80°C 4 days at 0.0285 mcg/mL in Methanol at –80°C Validation Report Pages 67,68
Post-preparative Stability	193 hours at Ambient Temperature Validation Report Page 62
Freeze-thaw stability (cycles)	6 cycles at -80°C Validation Report Page 59
Long-term storage stability (days)	465 days at –80°C Validation Report Page 51
Processed Sample Integrity	127.0 hours at Ambient Temperature Validation Report Page 82
Dilution integrity	up to 107 ng/mL Validation Report Page 77
Selectivity	No interfering peaks noted in any of the 10 human plasma (EDTA) lots screened Validation Report Page 20

E. In Vivo Study

1. Single-dose Fasting Bioequivalence Study **No. AA 27246**

Study Summary, Fasting Bioequivalence Study	
Study No.	AA27246
Study Design	Randomized, open label, single-dose, two-treatment, two-period, crossover fasted bioequivalence study of Raloxifene 60 mg Tablets in healthy volunteers
No. of subjects enrolled	60
No. of subjects completing	59
No. of subjects analyzed	59 (Subject #59 withdrew from the study for personal reasons) **(Section 10.2 Protocol Deviations)**
Subjects (Healthy or Patients?)	Healthy
Sex (es) included (how many?)	**Male:** 0 **Female:** 59 (postmenopausal)
Test product	Raloxifene HCl Tablets
Reference product	Evista® Tablets
Strength tested	60 mg
Dose	1 x 60 mg

Raloxifene					
	Geometric Means			90% CI	
Parameter	**Test**	**Reference**	**T/R Ratio**	**Lower CI**	**Upper CI**
LAUCT	16008.89	17236.87	0.929	86.4	99.9
LAUCI	16925.39	18027.71	0.939	87.3	101.0
LCMAX	402.4061	442.3204	0.91	80.9	102.4

Raloxifene-4 β-glucuronide					
	Geometric Means			90% CI	
Parameter	**Test**	**Reference**	**T/R Ratio**	**Lower CI**	**Upper CI**
LAUCT	2685.99	2853.34	0.941	87.9	100.8
LAUCI	2805.12	2996.66	0.936	87.5	100.1
LCMAX	143.2153	178.7188	0.801	75.3	85.3

Raloxifene-6 β-glucuronide					
	Geometric Means			90% CI	
Parameter	**Test**	**Reference**	**T/R Ratio**	**Lower CI**	**Upper CI**
LAUCT	652.97	700.43	0.932	87.0	99.8
LAUCI	678.20	724.26	0.936	87.2	100.5
LCMAX	23.95860	26.99021	0.888	83.0	95.0

Reanalysis of study Samples (Raloxifene)

AA27246 – Fasted Bioequivalence Study Appendix 16.4, Analytical Report, Pages 321 - 323								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Above the Accepted Range	2	2	0.05	0.05	2	2	0.05	0.05
Diluted Concentration Unreliable	4	8	0.10	0.21	4	7	0.10	0.18
Insufficient Sample for Analysis	1	0	0.03	0.00	0	0	0.00	0.00
Incongruous Value, Inversion suspected	0	2	0.00	0.05	0	0	0.00	0.00
Lost in Processing	31	31	0.80	0.80	25	24	0.64	0.62
Lowest Standard Removed	3	3	0.08	0.08	3	3	0.08	0.08
Reassayed in Error	1	0	0.03	0.00	1	0	0.03	0.00
Total	42	46	1.08	1.19	35	36	0.90	0.93

Reanalysis of study Samples (Raloxifene-4 β-glucuronide)

AA27246 – Fasted Bioequivalence Study Appendix 16.4, Analytical Report, Pages 324,325,326 and 330								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Incongruous Value Inversion Suspected	0	2	0.00	0.05	0	2	0.00	0.05
Lost in Processing	26	29	0.67	0.75	26	29	0.67	0.75
Reassayed in Error	14	14	0.36	0.36	14	13	0.36	0.34
Unacceptable Chromatography	1	0	0.03	0.00	1	0	0.03	0.00
Total	41	45	1.06	1.16	41	44	1.06	1.13

Reanalysis of study Samples (Raloxifene-6 β-glucuronide)

AA27246 – Fasted Bioequivalence Study Appendix 16.4, Analytical Report, Pages 327,328,329 and 331								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Incongruous Value Inversion Suspected	0	2	0.00	0.05	0	2	0.00	0.05
Lost in Processing	27	28	0.70	0.72	27	28	0.70	0.72
Reassayed in Error	1	0	0.03	0.00	0	0	0.00	0.00
Total	28	30	0.72	0.77	27	30	0.70	0.77

Total sample analyzed = 3879

Did use of recalculated plasma concentration data change study outcome? N/A (No PK repeats)

Comments on Fasting Study: The study appears to be adequately powered to take into account of the high variability of the parent moiety. Per DBE recommendation, the firm has measured plasma metabolites level, however, the 90% CI outside the acceptable range for the 4ß-glucuronide is presumably due to the study not being adequately powered to establish bioequivalence based on the metabolite levels. In light of this, the relatively low plasma metabolite concentrations (compared to plasma parent concentrations), and coupled with the fact that the PK measures for the parent moiety and for raloxifene 6ß-glucuronide are within the acceptable range, the DBE concludes that the 4ß-glucuronide data supports a conclusion of bioequivalence for this product.
The fasting BE study is **acceptable.**

2. Single-dose Fed Bioequivalence Study **No. AA 28757**

Study Summary, Fed Bioequivalence Study	
Study No.	AA28757
Study Design	Randomized, open label, single-dose, two-treatment, two-period, crossover fed bioequivalence study of Raloxifene 60 mg Tablets in healthy volunteers
No. of subjects enrolled	45
No. of subjects completing	44
No. of subjects analyzed	44 (Subject 21 was excluded from PK analysis due to a positive pre-dose >5% Cmax) (Section 11.4.1.4 Non-Zero-Pre-Dose Concentrations)
Subjects (Healthy or Patients?)	Healthy
Sex (es) included (how many?)	**Male:** 0 **Female:** 45 (postmenopausal)
Test product	Raloxifene HCl Tablets
Reference product	Evista® Tablets
Strength tested	60 mg
Dose	1 x 60 mg

Raloxifene					
	Geometric Means			**90% CI**	
Parameter	**Test**	**Reference**	**T/R Ratio**	**Lower CI**	**Upper CI**
LAUCT	20648.76	20625.23	100.1	93.9%	106.7%
LAUCI	22507.73	22387.73	100.5	94.1%	107.4%
LCMAX	527.032	517.887	101.8	94.0%	110.1%

Raloxifene-4 β-glucuronide					
	Geometric Means			**90% CI**	
Parameter	**Test**	**Reference**	**T/R Ratio**	**Lower CI**	**Upper CI**
LAUCT	3309.52	3278.80	100.9	93.8%	108.6%
LAUCI	3533.72	3485.65	101.4	93.8%	109.5%
LCMAX	318.1625	312.6049	101.8	92.8%	111.7%

Raloxifene-6 β-glucuronide					
	Geometric Means			**90% CI**	
Parameter	**Test**	**Reference**	**T/R Ratio**	**Lower CI**	**Upper CI**
LAUCT	800.47	775.38	103.2	95.1%	112.1%
LAUCI	849.93	826.22	102.9	94.3%	112.2%
LCMAX	38.38052	39.03804	98.3	90.5%	106.9%

Reanalysis of study Samples (Raloxifene)

AA28757 – Fed Bioequivalence Study Appendix 16.4, Analytical Report, Pages 202,203,204 and 211								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Above Accepted Range	0	2	0.00	0.09	0	0	0.00	0.00
Diluted Concentration Unreliable	0	2	0.00	0.09	0	2	0.00	0.09
Incongruous Value Positive Predose	1	0	0.04	0.00	0	0	0.00	0.00
Lost in Processing	3	4	0.13	0.17	3	4	0.13	0.17
Lowest Standard Removed	6	2	0.26	0.09	6	2	0.26	0.09
Unacceptable Chromatography	0	1	0.00	0.04	0	1	0.00	0.04
Unacceptable Internal Standard Response	12	3	0.51	0.13	12	3	0.51	0.13
Total	22	14	0.94	0.60	21	12	0.90	0.51

Reanalysis of study Samples (Raloxifene-4 β-glucuronide)

AA28757 – Fed Bioequivalence Study Appendix 16.4, Analytical Report, Pages 205,206,207,212 and 213								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Above Accepted Range	9	10	0.38	0.43	0	1	0.00	0.04
Diluted Concentration Unreliable	10	8	0.43	0.34	10	8	0.43	0.34
Incongruous value Positive Predose	1	0	0.04	0.00	0	0	0.00	0.00
Incongruous value Unexpected Concentration	0	2	0.00	0.09	0	2	0.00	0.09
Lost in Processing	11	6	0.47	0.26	11	6	0.47	0.26
Unacceptable Internal Standard Response	2	0	0.09	0.00	2	0	0.09	0.00
Total	33	26	1.41	1.11	23	17	0.98	0.73

Reanalysis of study Samples (Raloxifene-6 β-glucuronide)

AA28757 – Fed Bioequivalence Study Appendix 16.4, Analytical Report, Pages 208,209,210,214,215 and 216								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Above Accepted Range	5	6	0.21	0.26	0	2	0.00	0.09
Diluted Concentration Unreliable	10	4	0.43	0.17	10	4	0.43	0.17
Incongruous Value Positive Predose	2	1	0.09	0.04	0	0	0.00	0.00
Incongruous Value Unexpected Concentration	0	2	0.00	0.09	0	2	0.00	0.09
Lost in Processing	11	6	0.47	0.26	11	6	0.47	0.26
Unacceptable Internal Standard Response	2	1	0.09	0.04	2	1	0.09	0.04
Total	30	20	1.28	0.85	23	15	0.98	0.64

Total sample analyzed = 2340

Did use of recalculated plasma concentration data change study outcome? N/A (No PK repeats)

Comments on Fasting Study: Acceptable

F. Formulation

Location in appendix	Section IV. B. Page 30
Are inactive ingredients within IIG limits?	Yes
If no, list ingredients outside of limits	N/A
If a tablet, is the product scored?	No
If yes, which strengths are scored?	N/A
Is scoring of RLD the same as test?	N/A
Is the formulation acceptable?	Yes
If not acceptable, why?	N/A

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	Firm
Medium	1% SLS in 0.05M sodium phosphate buffer
Volume (mL)	900 mL
USP Apparatus type	USP Apparatus II (Paddle)
Rotation (rpm)	75 rpm
Firm's proposed specifications	NLT (b)(4)% (Q) in (b)(4) minutes
FDA-recommended specifications	NLT 80% (Q) in 30 minutes
F2 metric calculated?	No
If no, reason why F2 not calculated	(b)(4)% of the test drug was dissolved in (b)(4) minutes
Is method acceptable?	No
If not then why?	The FDA dissolution method is recommended

Comments on Dissolution: Since there is an FDA-recommended dissolution method available, the firm proposed dissolution method is not acceptable. The firm should conduct and submit its dissolution testing using the FDA-recommended method.

H. Waiver Request(s): NA

I. Deficiency Comment: The firm submitted its own proposed dissolution testing method described above. On July 17, 2006, DBE completed its review of Teva's submission of dissolution testing method, recommended the firm to repeat dissolution testing using the FDA-recommended method, and submit the data for review.

J. Recommendations

1. The randomized, open label, single-dose, two-treatment, two-period, crossover **fasting** bioequivalence study conducted by Teva Pharmaceuticals USA, on its Raloxifene HCl 60mg tablets, lot #K35052, comparing to Evista® 60 mg tablets, lot #8EF35A manufactured by Eli Lilly and Company is acceptable.

2. The randomized, open label, single-dose, two-treatment, two-period, crossover **fed** bioequivalence study conducted by Teva Pharmaceuticals USA, on its Raloxifene HCl 60mg tablets, lot #K35052, comparing to Evista® 60 mg tablets, lot #8EF35A manufactured by Eli Lilly and Company is acceptable.

3. The dissolution testing conducted by Teva on its Raloxifene HCl Tablets 60 mg is not acceptable. The dissolution testing should be conducted on the test and reference products (12 units each) using the FDA-recommended method (1000 mL 0.1% Polysorbate 80 Aqueous Solution using Apparatus II (Paddle) at 50 rpm). The test product should meet the following specification:

NLT 80% (Q) in 30 minutes

Overall, the application is incomplete and the firm should be informed of the deficiency comments and recommendations.

Christina Lee, Pharm.D.	Team III	Date
Chandra S. Chaurasia, Ph.D. Team Leader	Team III	Date
Dale P. Conner, Pharm. D. Director, Division of Bioequivalence Office of Generic Drugs		Date

IV. Appendix

A. Individual Study Reviews

2. Single-dose Fasting Bioequivalence Study **No. AA27246**

a) Study Design

Study Information	
Study Number	AA27246
Study Title	Randomized, open label, single-dose, two-treatment, two-period, crossover fasted bioequivalence study of Raloxifene 60 mg Tablets in healthy volunteers
Clinical Site	MDS Pharma Services 4705 Dobrin St. ST. Laurent, Montreal, Quebec, Canada
Principal Investigator	Gaetano Morelli, MD
Study/Dosing Dates	Group 1: Period I: 06/03/05; Period II: 06/17/05 Group 2: Period I: 06/18/05; Period II: 07/02/05
Analytical Site	(b) (4)
Analytical Director	(b) (6)
Analysis Dates	Raloxifene: began on 07/11/05; completed on 11/17/05; Raloxifene-4β-Glucuronide and Raloxifene-6β-Glucuronide: began on 07/11/05; completed on 08/30/05
Storage Period	164 days (First day of sample collection: Jun 3, 2005; last day of sample analysis: Nov 17, 2005)

Reviewer's Note: Subjects were recruited in two groups. However, the study was conducted at the same center, and the subject population was homogenous. In addition, the reviewer analyzed the PK data using group by treatment interaction, and no significant group effect (p>0.1) was observed.

Treatment ID	**Test**	**Reference**
Test or Reference	A	B
Product Name	Raloxifene HCl	Evista®
Manufacturer	Teva Pharmaceuticals	Eli Lilly
Batch/Lot No.	K35052	8EF35A
Manufacture Date	04/13/05	N/A
Expiration Date	NA	06/01/2006
Strength	60 mg	60 mg
Dosage Form	Tablet	Tablet
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	100.6%	100.7%
Content Uniformity (mean, %CV)	100.3% (RSD=1.3%)	97.5% (RSD=1.2%)
Formulation	See Appendix Section IV	
Dose Administered	1 x 60 mg	
Route of Administration	Orally	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	2 (Group 1: Subject Nos. 1-30; Group 2: Subject Nos. 31-60)
Washout Period	14 days
Randomization Scheme	**AB**:2, 3, 6, 7, 11, 12, 15, 17, 18, 20, 22, 23, 24, 27, 28, 31, 32, 34, 35, 37, 39, 41, 42, 44, 48, 50, 51, 53, 56, 57 **BA**:1, 4, 5, 8, 9, 10, 13, 14, 16, 19, 21, 25, 26, 29, 30, 33, 36, 38, 40, 43, 45, 46, 47, 49, 52, 54, 55, 58, 59, 60
Blood Sampling Times	0, 0.333, 0.667, 1, 1.333, 1.667, 2, 2.333, 2.667, 3, 3.333, 3.667, 4, 4.333, 4.667, 5, 5.333, 5.667, 6, 6.333, 6.667, 7, 8, 9, 10, 12, 16, 24, 36, 48, 72, 96 and 144 hours post-dose
Blood Volume Collected/Sample	7 mL were collected in blood collection tubes containing EDTA. After collection, blood samples were centrifuged at 3500 rpm for 8 minutes at 0ºC. The resulting plasma was split into two approximately equal aliquots, transferred into polypropylene tubes, and within one hour of collection. The samples were then flash frozen within 20 minutes of collection and stored at -80ºC (±15ºC) until analysis.
Blood Sample Processing/Storage	At a nominal temperature of -80°C
IRB Approval	Yes (Approval dated 05/03/05; amendment approval dated 05/10/05)
Informed Consent	Yes (Approval dated 05/03/05; final revised approval dated 05/13/05)
Subjects Demographics	See Table 1
Length of Fasting	10 hours
Length of Confinement	From at least 10 hours before dosing until after the 24-hour blood draw. Subjects were to return for the 36-, 48, 72, 96- and 144-hour blood draws.
Safety Monitoring	Vital signs taken 24 hours post-dosing

Comments on Study Design: Acceptable.

b) Clinical Results

Table 1 Demographics of Study Subjects

	Test Product N=59	Reference Product N=59
Age (Years)		
Mean±SD	59.9 ± 3.6	59.9 ± 3.6
Range	51 - 65	51 - 65
Age Groups (Years)		
40-64	53 (89.8%)	53 (89.8%)
65-75	6 (10.2%)	6 (10.2%)
Sex		
Female	59 (100%)	59 (100%)
Race		
Caucasian	59 (100%)	59 (100%)

Table 2 Dropout Information

Subject No	Reason	Period	Replaced?
59	Personal reason	II	No

Table 3 Study Adverse Events

Adverse Event (Classified according to MedDRA Version 8.1) System Organ Class Preferred Term	Test	Reference	Total
General disorders and administration site conditions	4 (6.8%)	4 (6.7%)	7 (11.7%)
Vessel puncture site bruise	1 (1.7%)	2 (3.3%)	2 (3.3%)
Asthenia	1 (1.7%)	0 (0%)	1 (1.7%)
Catheter site erythema	0 (0%)	1 (1.7%)	1 (1.7%)
Catheter site pain	0 (0%)	1 (1.7%)	1 (1.7%)
Catheter site related reaction	0 (0%)	1 (1.7%)	1 (1.7%)
Chest pain	0 (0%)	1 (1.7%)	1 (1.7%)
Face oedema	1 (1.7%)	0 (0%)	1 (1.7%)
Facial pain	1 (1.7%)	0 (0%)	1 (1.7%)
Swelling	1 (1.7%)	0 (0%)	1 (1.7%)
Venipuncture site swelling	0 (0%)	1 (1.7%)	1 (1.7%)
Nervous system disorders	3 (5.1%)	3 (5%)	5 (8.3%)
Headache	1 (1.7%)	3 (5%)	3 (5%)
Somnolence	2 (3.4%)	0 (0%)	2 (3.3%)
Disturbance in attention	1 (1.7%)	0 (0%)	1 (1.7%)
Dizziness	1 (1.7%)	0 (0%)	1 (1.7%)

Respiratory, thoracic and mediastinal disorders	1	(1.7%)	1	(1.7%)	2	(3.3%)
Pharyngolaryngeal pain	1	(1.7%)	1	(1.7%)	2	(3.3%)
Cough	0	(0%)	1	(1.7%)	1	(1.7%)
Musculoskeletal and connective tissue disorders	0	(0%)	2	(3.3%)	2	(3.3%)
Back pain	0	(0%)	1	(1.7%)	1	(1.7%)
Muscle spasms	0	(0%)	1	(1.7%)	1	(1.7%)
Skin and subcutaneous tissue disorders	0	(0%)	1	(1.7%)	1	(1.7%)
Erythema	0	(0%)	1	(1.7%)	1	(1.7%)
Pruritus	0	(0%)	1	(1.7%)	1	(1.7%)
Gastrointestinal disorders	1	(1.7%)	0	(0%)	1	(1.7%)
Diarrhoea	1	(1.7%)	0	(0%)	1	(1.7%)

Table 4 Protocol Deviations

- The freezer at the clinical site was out-of-range for less than 3 hours on 07/08/2005 and 07/10/2005 for sampling time points 36 to 144 hours of period II. This should have no impact since the short-term stability of 48 hours for raloxifene and 228 hours for raloxifene-4β-glucuronide and raloxifene-6β-glucuronide at ambient temperature have been proven.
- Subject 19 had a concomitant medication (Advil®) for continuous cheek pain that was unrelated to the study drug; subject 37 had multivitamin during both periods of the study; subject 53 administered one dose of Advil and Acetaminophen during treatment B. All concomitant medication intakes were under the supervision of the study director.
- Forty-one late blood draws were reported (< 20 minutes), six subjects exhibited protocol deviations with "no show" and one subject had no blood sample obtained for the 144-hour in period I and 4-, 5.67-, 6- and 16-hour blood draws in period II due to difficulties with venipuncture (For details of protocol deviation, please see Appendix 5.3 of the Clinical Conduct of Study Report in Appendix 16.2). These deviations were minor and had no effect on the outcome of the study. For late blood draws, actual draw times were used for PK analysis.

Comments on Dropouts/Adverse Events/Protocol Deviations:

a) Twenty-five (25) cases of adverse events reported for both study periods – 15 were related to treatment A and 20 related to treatment B. All adverse events were resolved with no serious adverse events reported in this study.
b) The adverse events and protocol deviations did not compromise the integrity of the study.

c) Bioanalytical Results

Table 5 Assay Quality Control – Within Study

	Raloxifene
QC Conc.	15.0, 50.0, 500 and 1000 pg/mL
Inter day Precision (%CV)	4.1% to 7.5%
Inter day Accuracy (%)	93.5% – 104.7%
Cal. Standards Conc.	5.20, 10.4, 26.0, 65.0, 130, 260, 520, 1040 and1300 pg/mL
Inter day Precision (%CV)	2.6% -- 9.5%
Inter day Accuracy (%)	96.2% – 102.6%
Linearity Range (range of R^2 values)	0.9935 – 0.9999

	Raloxifene-4β-Glucuronide
QC Conc.	6.00, 30.0, 150 and 375 ng/mL
Inter day Precision (%CV)	4.6% to 6.5%
Inter day Accuracy (%)	97.7% – 104.0%
Cal. Standards Conc.	2.00, 4.00, 10.0, 20.0, 50.0, 100, 200, 400 and 500 ng/mL
Inter day Precision (%CV)	3.2% - 6.9%
Inter day Accuracy (%)	98.4% – 102.5%
Linearity Range (range of R^2 values)	0.9916 – 0.9997

	Raloxifene-6β-Glucuronide
QC Conc.	0.836, 4.18, 20.9 and 52.3 ng/mL
Inter day Precision (%CV)	4.4% to 13.2%
Inter day Accuracy (%)	92.1% – 99.0%
Cal. Standards Conc.	0.280, 0.560, 1.40, 2.80, 7.00, 14.0, 27.9, 55.7 and 69.6 ng/mL
Inter day Precision (%CV)	2.9% - 6.6%
Inter day Accuracy (%)	93.2% – 103.4%
Linearity Range (range of R^2 values)	0.9917 – 0.9999

Comments on Study Assay Quality Control: Acceptable. The selection of QC concentrations is appropriate, relative to the concentrations in the study samples. All study samples are within the standard curve limits.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms: Acceptable

Table 6 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
[redacted]	(b) (4)	Chromatographic and Spectrometric Methods: Calibration curve Preparation, Specifications and Acceptance Criteria
		Reporting of Data Generated from the Analysis of Biological Matrices and the Reassay of Samples

Table 7 Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays: Acceptable

d) Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters for raloxifene (N=59)

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	pg*hr/mL	17644.96	44.03	18740.68	42.73	0.94
AUC∞	pg*hr/mL	18718.79	45.03	19658.22	45.11	0.95
Cmax	pg/mL	470.15	66.92	502.32	54.49	0.94
Tmax	hr	8.33	97.46	6.92	84.70	1.20
Kel	hr^{-1}	0.03	28.26	0.03	29.18	0.98
T1/2	hr	26.57	34.11	25.91	33.12	1.03

Table 9 Geometric Means and 90% Confidence Intervals for raloxifene (N=59)

Parameter	Test	Reference	T/R	Lower CI	Upper CI
	Mean	Mean			
AUC0-t	16039.23	17279.75	0.93	86.36	99.77
AUC∞	16957.21	18054.06	0.94	87.24	101.12
Cmax	402.50	443.39	0.91	80.51	102.35

Table 10 Additional Study Information

Root mean square error, AUC_{0-t}	Raloxifene: 0.23 Raloxifene-4 β-glucuronide: 0.22 Raloxifene-6 β-glucuronide: 0.22
Root mean square error, AUC_{∞}	Raloxifene: 0.23 Raloxifene-4 β-glucuronide: 0.21 Raloxifene-6 β-glucuronide: 0.22
Root mean square error, C_{max}	Raloxifene: 0.39 Raloxifene-4 β-glucuronide: 0.21 Raloxifene-6 β-glucuronide: 0.23
K_{el} and AUC_{∞} determined for how many subjects?	59 subjects
Do you agree or disagree with firm's decision?	Agree
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	Subject 19 (Period II, Test drug: C1= 17.20 pg/mL; Cmax = 392.0 pg/mL, % of Cmax = 4.39)
-first measurable drug concentration as C_{max}	None
Were the subjects dosed as more than one group?	Yes

Comments on Pharmacokinetic and Statistical Analysis: The reviewer agreed that subject 19 should not be excluded from the PK analysis because the pre-dose value was less than 5% of the corresponding Cmax values. The reviewer's calculated 90% confidence intervals for the test and reference ratios for the LAUCT, LAUCI and LCmax are in agreement with the firm's reported values and are within acceptable limits of 80-125%.

The firm has submitted the plasma concentrations and pharmacokinetic parameters for metabolites (raloxifene 4ß-glucuronide and raloxifene 6ß-glucuronide). Per CDER BA/BE guidance, issued March 2003, "for BE studies, measurement of only the parent drug released from the dosage form, rather than the metabolite, is generally recommended". The study appears to be adequately powered to take into account of the high variability of the parent moiety. Per DBE recommendation, the firm has measured plasma metabolites level, however, the 90% CI outside the acceptable range for the 4ß-glucuronide is presumably due to the study not being adequately powered to establish bioequivalence based on the metabolite levels. In light of this, the relatively low plasma metabolite concentrations (compared to plasma parent concentrations), and coupled with the fact that the PK measures for the parent moiety and for raloxifene 6ß-glucuronide are within the acceptable range, the DBE concludes that the 4ß-glucuronide data supports a conclusion of bioequivalence for this product.

In addition, because of enterohepatic recycling, high variability in plasma concentrations of raloxifene should be considered when evaluating plasma raloxifene 6ß-glucuronide and raloxifene 4ß-glucuronide data.

The following are the firm's PK parameters and 90% C.I. calculation for metabolite(s)

Geometric Means and 90% Confidence Intervals for Raloxifene-4 β-glucuronide

Raloxifene-4 β-glucuronide					
	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUCT	2685.99	2853.34	0.941	87.9	100.8
LAUCI	2805.12	2996.66	0.936	87.5	100.1
LCMAX	143.2153	178.7188	0.801	75.3	85.3

Arithmetic Mean Pharmacokinetic Parameters for Raloxifene-4 β-glucuronide

PARAMETER	Units	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
AUCT	ng*hr/mL	2999.60	49.48	3131.04	43.38	0.96
AUCI	ng*hr/mL	3182.29	48.00	3305.33	43.43	0.96
CMAX	ng/mL	152.40	34.46	192.64	39.49	0.79
TMAX	hr	2.22	79.28	2.01	161.43	1.10
KE	hr^{-1}	0.04	48.28	0.04	49.62	1.04
THALF	hr	21.77	51.71	22.00	41.26	0.99

Geometric Means and 90% Confidence Intervals for Raloxifene-6 β-glucuronide

Raloxifene-6 β-glucuronide					
	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUCT	652.97	700.43	0.932	87.0	99.8
LAUCI	678.20	724.26	0.936	87.2	100.5
LCMAX	23.95860	26.99021	0.888	83.0	95.0

Arithmetic Mean Pharmacokinetic Parameters for Raloxifene-6 β-glucuronide

PARAMETER	Units	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
AUCT	ng*hr/mL	726.75	47.14	763.61	41.61	0.95
AUCI	ng*hr/mL	759.61	48.38	797.52	41.88	0.95
CMAX	ng/mL	25.82	37.94	28.84	35.38	0.90
TMAX	hr	5.89	88.36	4.59	113.10	1.28
KE	hr^{-1}	0.04	39.98	0.04	41.53	0.93

PARAMETER	Units	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
THALF	hr	22.24	44.20	20.59	39.52	1.08

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: Acceptable

Table 11 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

For raloxifene:

Time	Test (n=59)		Reference (n=59)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.29	768.11	0.00	.	.
0.333	42.12	93.50	83.00	87.49	0.51
0.667	117.75	46.77	163.71	34.59	0.72
1	124.86	37.93	160.38	33.93	0.78
1.333	130.33	43.56	162.84	36.80	0.80
1.667	144.31	45.81	169.65	40.73	0.85
2	142.71	48.76	169.03	39.68	0.84
2.333	154.88	46.97	174.17	42.44	0.89
2.667	158.61	48.59	173.63	45.32	0.91
3	162.18	51.50	175.62	43.65	0.92
3.333	167.23	53.15	172.73	45.54	0.97
3.667	173.75	55.97	185.46	60.96	0.94
4	178.22	63.51	186.72	55.45	0.95
4.333	200.13	57.83	221.68	49.69	0.90
4.667	277.73	49.32	315.43	58.31	0.88
5	347.18	55.61	398.20	59.23	0.87
5.333	340.86	52.37	403.94	59.85	0.84
5.667	347.81	74.44	364.83	63.25	0.95
6	336.71	76.44	348.99	67.15	0.96
6.333	329.10	69.16	330.50	67.40	1.00
6.667	316.43	65.22	316.98	56.27	1.00
7	305.54	60.19	301.42	55.13	1.01
8	267.96	55.92	281.43	55.55	0.95
9	270.97	61.56	283.17	57.68	0.96
10	306.92	76.07	301.31	55.10	1.02
12	253.84	59.56	258.50	52.91	0.98

16	233.25	45.57	241.39	44.49	0.97
24	256.69	43.79	264.93	41.27	0.97
36	200.47	43.41	212.47	43.07	0.94
48	171.58	45.35	186.72	49.61	0.92
72	101.65	59.39	109.00	63.13	0.93
96	53.98	76.51	62.99	76.67	0.86
144	17.42	112.38	19.68	128.13	0.89

For raloxifene-4 β-glucuronide

Time (hr)	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
0	0.00	.	0.00	.	.
0.333	24.76	100.83	48.64	99.99	0.51
0.667	100.12	53.50	154.79	46.06	0.65
1	120.73	44.79	161.32	43.07	0.75
1.333	119.61	45.30	151.77	46.69	0.79
1.667	120.16	45.71	144.13	50.75	0.83
2	112.80	48.44	133.89	51.68	0.84
2.333	107.97	48.21	119.58	50.93	0.90
2.667	100.05	46.73	112.49	53.33	0.89
3	90.98	47.92	98.23	51.65	0.93
3.333	86.24	50.55	89.32	52.62	0.97
3.667	82.38	53.64	82.48	53.78	1.00
4	78.72	56.44	77.47	52.74	1.02
4.333	83.68	56.62	82.87	51.33	1.01
4.667	100.10	49.12	100.62	49.46	0.99
5	98.68	46.19	103.34	49.71	0.95
5.333	87.64	44.80	97.54	47.73	0.90
5.667	81.92	43.05	87.46	48.99	0.94
6	76.97	47.24	78.49	47.47	0.98
6.333	71.36	45.78	73.03	47.33	0.98
6.667	67.63	46.13	65.97	44.15	1.03
7	62.49	43.26	60.86	43.40	1.03
8	50.49	43.65	49.56	38.40	1.02
9	48.72	58.19	50.76	43.21	0.96

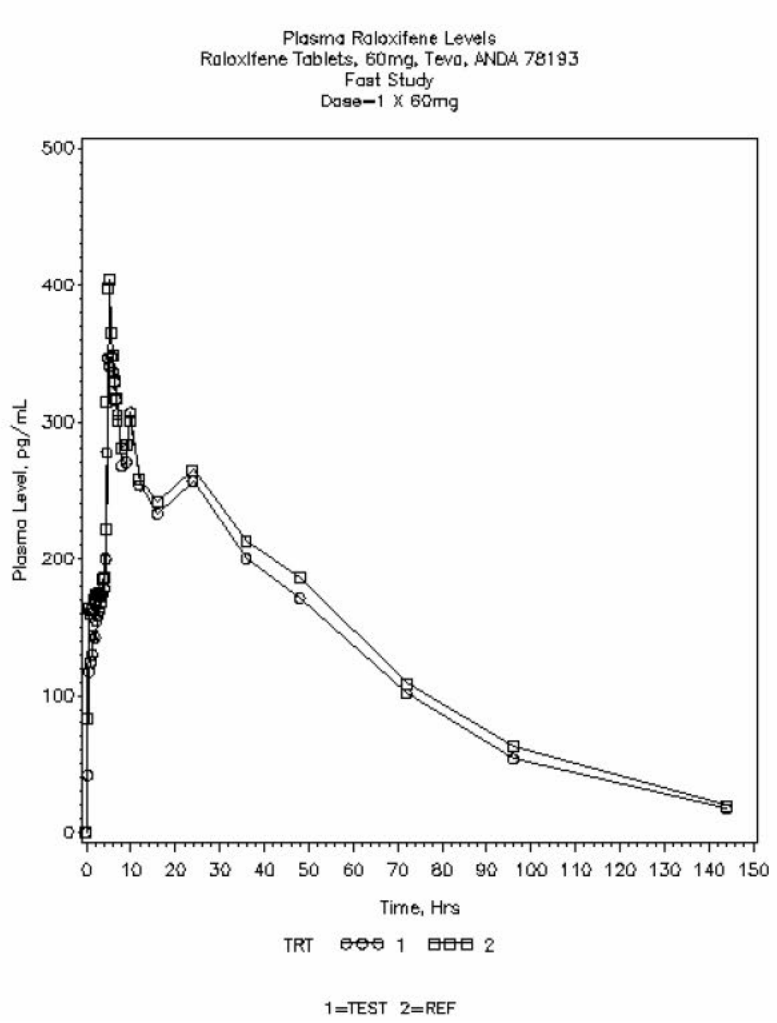
10	54.08	64.14	57.73	57.23	0.94
12	43.30	61.99	47.56	48.08	0.91
16	38.78	50.68	42.84	50.55	0.91
24	48.06	45.90	49.30	47.49	0.97
36	31.14	73.98	31.19	59.32	1.00
48	27.56	67.63	26.47	59.59	1.04
72	11.42	96.42	12.87	84.70	0.89
96	5.29	117.64	6.17	116.65	0.86
144	1.32	180.63	1.16	228.56	1.14

For raloxifene-6 β-glucuronide

Time (hr)	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
0	0.00	.	0.00	.	.
0.333	2.13	100.58	4.09	100.25	0.52
0.667	11.21	55.66	17.71	46.18	0.63
1	14.54	43.09	20.26	36.49	0.72
1.333	14.96	42.38	19.49	38.68	0.77
1.667	15.25	42.71	18.65	46.24	0.82
2	14.68	43.61	17.67	49.29	0.83
2.333	14.50	43.77	16.05	50.24	0.90
2.667	13.63	42.24	15.28	50.02	0.89
3	12.56	42.02	13.86	50.15	0.91
3.333	12.18	43.14	12.45	47.54	0.98
3.667	11.82	46.31	11.80	44.40	1.00
4	11.72	48.69	11.57	47.86	1.01
4.333	13.22	50.84	12.92	49.59	1.02
4.667	17.97	45.35	18.09	43.10	0.99
5	20.15	40.91	21.30	44.09	0.95
5.333	19.63	44.26	21.77	48.56	0.90
5.667	19.23	44.35	20.53	48.64	0.94
6	19.05	49.15	19.18	48.09	0.99
6.333	18.05	45.90	18.12	49.24	1.00
6.667	17.30	44.75	17.14	48.37	1.01
7	16.12	43.08	15.91	45.69	1.01

8	13.30	39.52	13.41	44.68	0.99
9	12.70	48.67	13.60	43.37	0.93
10	14.82	50.20	15.67	47.01	0.95
12	11.64	46.43	12.92	41.03	0.90
16	10.53	47.85	11.35	44.45	0.93
24	11.78	43.23	12.26	46.32	0.96
36	8.00	63.03	8.25	54.92	0.97
48	7.15	65.42	6.93	59.53	1.03
72	3.03	92.54	3.41	82.32	0.89
96	1.48	116.34	1.65	106.73	0.90
144	0.39	187.37	0.37	169.65	1.05

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



2. Single-dose Fed Bioequivalence Study **No. AA28757**

a) Study Design

Study Information	
Study Number	MDS ID: AA28757; PMRI ID: 2005-974
Study Title	Randomized, open label, single-dose, two-treatment, two-period, crossover fed bioequivalence study of Raloxifene 60 mg Tablets in healthy volunteers
Clinical Site	Pharma Medica Research Inc. (PMRI) 966 Pantera Drive, Unit 31, Mississauge, Ontario, Canada
Principal Investigator	Xueyu (Eric) Chen, MD, Ph.D., FRCE(C)
Study/Dosing Dates	Group 1: Period I: 09/28/05 (1-24); Period II: 10/12/05 (25-45) Group 2: Period I: 10/02/05 (1-24); Period II: 10/06/05 (25-45)
Analytical Site	(b) (4)
Analytical Director	(b) (6)
Analysis Dates (page 455)	Between Nov 30, 2005 to Feb 8, 2006
Storage Period (page 457)	133 days (First day of sample collection: Sept 28, 2005; last day of sample analysis: Feb 8, 2005)

Reviewer's Note: Subjects were recruited in two groups. However, the study was conducted at the same center, and the subject population was homogenous. In addition, the reviewer analyzed the PK data using group by treatment interaction, and no significant group effect ($p>0.1$) was observed.

Treatment ID	**Test**	**Reference**
Test or Reference	A	B
Product Name	Raloxifene HCl	Evista®
Manufacturer	Teva Pharmaceuticals	Eli Lilly
Batch/Lot No.	K35052	8EF35A
Manufacture Date	04/13/05	N/A
Expiration Date	NA	06/01/2006
Strength	60 mg	60 mg
Dosage Form	Tablet	Tablet
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	100.6%	100.7%
Content Uniformity (mean, %CV)	100.3% (RSD=1.3%)	97.5% (RSD=1.2%)
Formulation	See Appendix Section IV	
Dose Administered	1 x 60 mg	
Route of Administration	Orally	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	2 (Group 1: Subject Nos. 1-24; Group 2: Subject Nos. 25-45)*
Washout Period	14 days
Randomization Scheme (page 16)	**AB**: 3, 4, 6, 8, 9, 10, 15, 16, 17, 18, 21, 22, 25, 26, 30, 31, 33, 34, 37, 38, 42, 43, 46, 48 **BA**: 1, 2, 5, 7, 11, 12, 13, 14, 19, 20, 23, 24, 27, 28, 29, 32, 35, 36, 39, 40, 41, 44, 45, 47
Blood Sampling Times	0, 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 24, 36, 48, 72, 96 and 120 hours post-dose
Blood Volume Collected/Sample	6 mL were collected in blood collection tubes containing EDTA. After collection, blood samples were centrifuged at 3500 rpm for 8 minutes at 0ºC. The resulting plasma was split into two approximately equal aliquots. The samples were then flash frozen within 20 minutes of collection and stored at -80ºC (±15ºC) until analysis.
Blood Sample Processing/Storage	At a nominal temperature of -80°C
IRB Approval	Yes (Approval dated 09/01/05)
Informed Consent	Yes (Approval dated 01/24/05
Subjects Demographics	See **Table 12**
Length of Fasting	10 hours
Length of Confinement	From at least 10.5 hours before dosing until after the 24-hour blood draw. Subjects were to return for the 36-, 48, 72, 96- and 144-hour blood draws.
Safety Monitoring	Vital signs taken 24 hours post-dosing
Standard FDA Meal Used?	Yes
If no, then meal is listed in table below	N/A

*The original protocol was planned for 48 subjects, but only 45 subjects were recruited. Therefore, there was a discrepancy between the Randomization Scheme (#48) and the number of subjects included in the study (#45).

Comments on Study Design: Acceptable

b) Clinical Results

Table 12 Demographics of Study Subjects

Study No. 2005-974, Fed	
	Treatment Groups
	Test & Reference Products* N = 45
Age (years)	
Mean ± SD	54 ± 5
Range	42 - 64
Groups	
< 18	0 (0%)
18 - 40	0 (0%)
41 - 64	45 (100%)
65 - 75	0 (0%)
> 75	0 (0%)
Sex	
Female	45 (100%)
Male	0 (0%)
Race	
Asian	5 (11%)
Black	6 (13%)
Caucasian	34 (76%)
Hispanic	0 (0%)
Other	0 (0%)
Other Factors	

* *Crossover design = Subjects completing the study received both treatments*

Table 13 Dropout Information: None (Subject 21 was excluded from PK analysis. See additional notes for excluded subject for Pharmacokinetic and statistical analysis under Table 21- Additional Study Information)

Table 14 Study Adverse Events

Body System/Adverse Event	**Reported Incidence by Treatment Groups** Fed Bioequivalence Study Study No. 2005-974	
	Test (n = 45)	**Reference (n = 45)**
Body as a Whole		
Headache	3 (6.67%)	2 (4.44%)
Infect		1 (2.22%)
Pain abdo		1 (2.22%)
Malaise		1 (2.22%)
Pain neck		1 (2.22%)
Pain	1 (2.22%)	
Asthenia		2 (4.44%)
Cardiovascular System		
Hypertens		1 (2.22%)
Digestive System		
Constip		2 (4.44%)
Diarrhea	1 (2.22%)	2 (4.44%)

Metabolic and Nutritional Disorders		
Bun Inc	1 (2.22%)	4 (8.89%)
Hyperglycem	2 (4.44%)	
GGTP Inc	1 (2.22%)	
Hyperlipem	1 (2.22%)	2 (4.44%)
Bilirubinem		1 (2.22%)
Hyperkalem		1 (2.22%)
Edema Periph	1 (2.22%)	
HDL Dec		1 (2.22%)
Hypercholesterem	1 (2.22%)	3 (6.67%)
Creatinine Inc		1 (2.22%)
Musculoskeletal System		
Myalgia	1 (2.22%)	1 (2.22%)
Nervous System		
Somnolence	1 (2.22%)	
Vasodilat	1 (2.22%)	
Dizziness	2 (4.44%)	
Respiratory System		
Cough Inc		1 (2.22%)
Rhinitis	2 (4.44%)	
Respirat Dis	1 (2.22%)	
Pharyngitis	2 (4.44%)	2 (4.44%)
Skin and Appendages		
Rash		1 (2.22%)
Urogenital System		
Dysuria	1 (2.22%)	
Hematuria	2 (4.44%)	3 (6.67%)
Urin Abnorm	2 (4.44%)	8 (17.78%)
Urin Frequency	1 (2.22%)	
Kidney Func Abnorm		1 (2.22%)
Total	28 (62.22%)	43 (95.56%)

Table 15 Protocol Deviations

Subject No.	Period	Deviation
25, 35 and 42	Both	The age limit was changed to 18 to 65 inclusive to allow subjects who are under the age of 45 but surgically sterile to participate in the study.
22, 24, 39 and 44	Both	These subjects have used or use more than 10 cigarettes per day.
07-09, 11 and 13-14	1	Within 20 minutes from the end of sample collection, the plasma samples were to be flash frozen. Samples from these subjects at
		Draw 22 were longer than 20 minutes.
N/A	Both	45 subjects were dosed in Period 1.
28	1	Subject 28 had coffee prior to Period 1 dosing.
42	1	Subject 42 had a chocolate chip cookie prior to Period 1 Dosing.
25-30	1	Within 20 minutes from the end of sample collection, the plasma samples were to be flash frozen. It cannot be verified if samples from these subjects were flash frozen within 20 minutes.
40	Screening	Subject 40 was transferred from another study which used CML HealthCare Inc. as the clinical laboratory for her screening lab tests.
09	1	Subject 09 took a caplet of Tylenol® 500 mg prior to Period 2.
ALL	Screening and Period 2	The fasting times for cholesterol, LDL & HDL cholesterol and triglycerides tests were not documented on the lab requisition forms for all the subjects during screening or post clinical test.
26	Screening	Subject 26 did not have her urine microscopic test repeated as requested by the investigator.

- Sixty-nine (69) subjects exhibited protocol deviations related to blood draw time (All but two subjects had more than 30 minutes delay: subject 22, delayed for 79 minutes at 72-hour draw, period I and 66 minutes for 120-hour draw, period II; subject 14, delayed for 40 minutes at 48-hour draw, period II). (For details please see Section 16.3). Actual sampling times were used for PK analyses. These deviations were minor and had no effect on the outcome of the study.

Comments on Dropouts/Adverse Events/Protocol Deviations:

a) There were 104 adverse events (AEs) in this study. All adverse events (AEs) were listed as mild in severity. Overall, 4 subject (9% of the study population experienced at least 1 AE that was possibly or probably related to Treatment A, and 6 subjects (13% of the study population) experienced at least 1 AE that was possibly or probably related to Treatment B. There were no serious adverse events reported in this study.
b) The adverse events and protocol deviations did not compromise the integrity of the study.

c) Bioanalytical Results

Table 16 Assay Quality Control – Within Study

	Raloxifene
QC Conc.	29.9, 49.9, 499 and 998 pg/mL
Inter day Precision (%CV)	8.3% to 11.0%
Inter day Accuracy (%)	100.7% – 105.0%
Cal. Standards Conc.	10.4, 20.8, 42.3, 65.0, 130, 260, 520, 1040 and 1300 pg/mL

Inter day Precision (%CV)	5.1% -- 11.1%
Inter day Accuracy (%)	97.1% – 102%
Linearity Range (range of R^2 values)	0.9904 – 0.9998

	Raloxifene-4β-Glucuronide
QC Conc.	6.00, 30.0, 150 and 375 ng/mL
Inter day Precision (%CV)	2.9% to 4.4%
Inter day Accuracy (%)	98.7% – 101.3%
Cal. Standards Conc.	2.00, 4.00, 10.0, 20.0, 50.0, 100, 200, 400 and 500 ng/mL
Inter day Precision (%CV)	2.0% -- 4.1%
Inter day Accuracy (%)	97.6% – 104%
Linearity Range (range of R^2 values)	0.9951 – 0.9999

	Raloxifene-6β-Glucuronide
QC Conc.	0.836, 4.18, 20.9 and 52.3 ng/mL
Inter day Precision (%CV)	3.7% to 4.5%
Inter day Accuracy (%)	95.5% – 96.9%
Cal. Standards Conc.	0.280, 0.560, 1.40, 2.80, 7.00, 14.0, 27.9, 55.7 and 69.6 ng/mL
Inter day Precision (%CV)	2.3% -- 4.7%
Inter day Accuracy (%)	96.1% – 101.8%
Linearity Range (range of R^2 values)	0.9961 – 1.0000

Comments on Study Assay Quality Control: Acceptable. The selection of QC concentrations is appropriate, relative to the concentrations in the study samples. All study samples are within the standard curve limits.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms: Acceptable

Table 17 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
(b) (4)		Chromatographic and Spectrometric Methods: Calibration curve Preparation, Specifications and Acceptance Criteria
		Reporting of Data Generated from the Analysis of Biological Matrices and the Reassay of Samples

Table 18 Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays: Acceptable

d) Pharmacokinetic Results

Table 19 Arithmetic Mean Pharmacokinetic Parameters for raloxifene (N=44)

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	pg*hr/mL	3599.89	45.31	3551.05	42.02	1.01
AUC∞	pg*hr/mL	3845.07	43.96	3792.71	42.34	1.01
Cmax	pg/mL	352.77	48.98	333.59	36.01	1.06
Tmax	hr	1.84	52.80	1.91	57.97	0.97
Kel	hr^{-1}	0.04	60.69	0.04	56.57	0.98
T1/2	hr	24.39	62.20	22.40	49.38	1.09

Table 20 Geometric Means and 90% Confidence Intervals for raloxifene (N=44)

Parameter	Test	Reference	T/R	Lower CI	Upper CI
	Mean	Mean			
AUC0-t	3316.15	3285.02	1.01	93.84	108.60
AUC∞	3539.23	3495.23	1.01	93.40	109.78
Cmax	318.29	312.75	1.02	92.82	111.59

Table 21 Additional Study Information

Root mean square error, AUC_{0-t}	Raloxifene: 0.20 Raloxifene-4 β-glucuronide: 0.23 Raloxifene-6 β-glucuronide: 0.18
Root mean square error, AUC_{∞}	Raloxifene: 0.21 Raloxifene-4 β-glucuronide: 0.23 Raloxifene-6 β-glucuronide: 0.18
Root mean square error, C_{max}	Raloxifene: 0.26 Raloxifene-4 β-glucuronide: 0.23 Raloxifene-6 β-glucuronide: 0.22
K_{el} and AUC_{∞} determined for how many subjects?	44 subjects
Do you agree or disagree with firm's decision?	Agree
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	See the **Reviewer's Notes** below
-first measurable drug concentration as C_{max}	None
Were the subjects dosed as more than one group?	No

Reviewer's Notes(See section 11.4.1.4 Non-zero Pre-dose Concentrations for details):

- Subject 21 had positive pre-dose of raloxifene, raloxifen-4β-glucuronide and raloxifen-6β-glucuronide in Period I (Formulation A: Test). This subject was excluded from the pharmacokinetic and statistical analysis for raloxifene, raloxifen-4β-glucuronide, raloxifene-6β-glucuronide since the pre-dose value for the parent compound was greater than 5% of the corresponding Cmax value (Per the FDA Guidance for Industry):

Analyte	Concentration	Cmax	Pre-dose concentration as a percentage of Cmax (%)
Raloxifene (pg/mL)	32.3	637	5.07
Raloxifene-4ß-glucuronide (ng/mL)	2.23	312	0.71
Raloxifene-6ß-glucuronide (ng/mL)	0.424	31.6	1.34

- The following subjects had positive pre-doses for raloxifene-6β-glucuronide. These subjects were not excluded from the pharmacokinetic and statistical analysis since the pre-dose value was less than 5% of the corresponding Cmax value (Per the FDA Guidance for Industry):

Subject	Formulation	Period	Concentration (ng/mL)	Cmax (ng/mL)	Pre-dose concentration as a percentage of Cmax (%)
9	B	2	0.405	53.3	0.76
28	A	2	0.461	31.7	1.45

Comments on Pharmacokinetic and Statistical Analysis: The reviewer calculated 90% confidence intervals for the test and reference ratios for the LAUCT, LAUCI and LCmax are in agreement with the firm's reported values and are within acceptable limits of 80-125%. The firm has submitted the plasma concentrations and pharmacokinetic parameters for the metabolites (raloxifene 4ß-glucuronide and raloxifene 6ß-glucuronide). Per CDER BA/BE guidance, issued March 2003, "for BE studies, measurement of only the parent drug released from the dosage form, rather than the metabolite, is generally recommended". Therefore, the results on the metabolites

(raloxifene 4ß-glucuronide and raloxifene 6ß-glucuronide) are for information purposes only. The following are the firm's PK parameters and 90% C.I. calculation for metabolites:

Geometric Means and 90% Confidence Intervals for Raloxifene-4 β-glucuronide

Raloxifene-4 β-glucuronide					
	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUCT	3309.52	3278.80	100.9	93.8%	108.6%
LAUCI	3533.72	3485.65	101.4	93.8%	109.5%
LCMAX	318.1625	312.6049	101.8	92.8%	111.7%

Arithmetic Mean Pharmacokinetic Parameters for Raloxifene-4 β-glucuronide

PARAMETER	Units	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
AUCT	ng*hr/mL	868.75	43.12	834.56	38.66	1.04
AUCI	ng*hr/mL	926.06	42.77	890.26	40.03	1.04
CMAX	ng/mL	41.96	47.63	41.85	35.99	1.00
TMAX	hr	2.63	110.19	2.81	114.37	0.94
KE	hr^{-1}	0.04	54.90	0.04	53.96	1.00
THALF	hr	23.64	61.70	22.34	47.99	1.06

Geometric Means and 90% Confidence Intervals for Raloxifene-6 β-glucuronide

Raloxifene-6 β-glucuronide					
	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUCT	800.47	775.38	103.2	95.1%	112.1%
LAUCI	849.93	826.22	102.9	94.3%	112.2%
LCMAX	38.38052	39.03804	98.3	90.5%	106.9%

Arithmetic Mean Pharmacokinetic Parameters for Raloxifene-6 β-glucuronide

PARAMETER	Units	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
AUCT	ng*hr/mL	21886.44	31.30	22033.05	34.24	0.99
AUCI	ng*hr/mL	23857.80	30.96	24013.02	33.84	0.99

PARAMETER	Units	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
CMAX	ng/mL	559.30	35.10	558.05	40.38	1.00
TMAX	hr	7.05	91.46	6.01	134.66	1.17
KE	hr^{-1}	0.03	36.61	0.03	31.35	0.99
THALF	hr	30.54	51.92	28.44	44.72	1.07

Summary and Conclusions, Single-Dose Fed Bioequivalence Study: Acceptable

Table 22 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

For raloxifene:

Time	Test (n= 44)		Reference (n=44)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.00	.	0.00	.	.
0.33	19.28	232.59	39.99	179.10	0.48
0.67	133.98	150.97	160.26	101.22	0.84
1	213.66	89.84	223.72	70.88	0.96
1.5	265.08	63.11	254.90	53.33	1.04
2	240.01	50.14	233.50	43.99	1.03
2.5	210.03	44.38	206.35	41.77	1.02
3	174.87	51.29	180.96	52.57	0.97
3.5	139.13	57.22	142.01	53.94	0.98
4	119.05	64.45	123.63	62.70	0.96
4.5	110.45	58.64	118.09	66.74	0.94
5	80.40	57.45	83.55	74.45	0.96
5.5	67.30	60.07	67.41	77.50	1.00
6	62.52	63.37	60.07	86.90	1.04
6.5	61.13	64.61	56.58	86.96	1.08
7	61.84	61.77	57.05	81.67	1.08
8	65.31	60.53	62.38	69.08	1.05
10	73.95	43.61	73.49	50.25	1.01
12	59.93	47.04	60.30	46.10	0.99
16	58.04	57.80	56.87	53.14	1.02
24	59.60	56.55	56.29	56.61	1.06
36	30.39	63.18	30.05	57.62	1.01

48	25.53	77.88	24.24	63.49	1.05
72	12.85	70.76	11.87	72.86	1.08
96	6.16	99.12	6.60	110.89	0.93
120	2.79	148.53	3.45	129.62	0.81

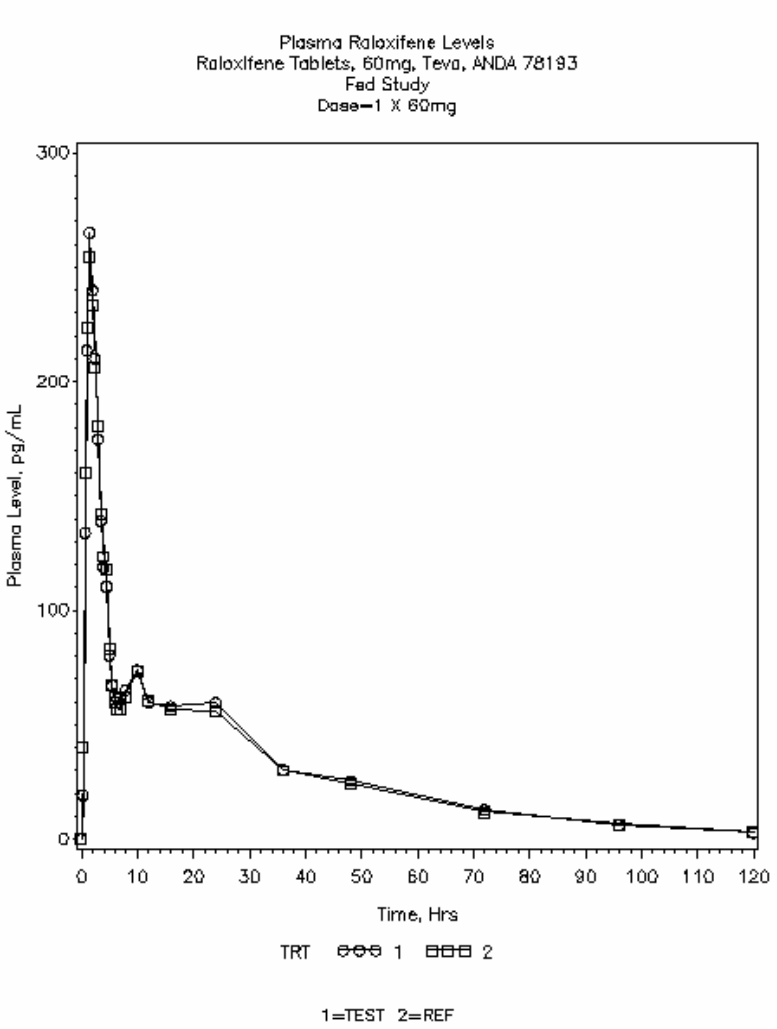
For raloxifene-4 β-glucuronide:

Time (hr)	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
0	0.01	663.32	0.01	663.32	1.14
0.33	1.63	202.85	3.46	170.02	0.47
0.67	14.48	148.71	17.79	98.18	0.81
1	26.10	94.98	27.66	70.92	0.94
1.5	33.53	65.23	32.98	55.66	1.02
2	31.60	54.21	30.94	48.64	1.02
2.5	28.29	46.58	27.84	43.77	1.02
3	24.07	48.28	24.33	47.63	0.99
3.5	19.73	49.28	19.75	51.59	1.00
4	16.97	55.29	17.40	56.80	0.98
4.5	16.82	54.02	17.26	59.92	0.97
5	14.32	60.83	14.14	68.48	1.01
5.5	13.07	66.00	12.39	74.97	1.05
6	13.01	70.50	11.68	81.47	1.11
6.5	13.55	73.98	11.53	78.64	1.18
7	14.26	68.40	12.40	74.57	1.15
8	15.66	60.79	14.21	65.27	1.10
10	19.94	40.30	19.50	44.56	1.02
12	17.59	42.48	17.35	41.05	1.01
16	17.53	54.29	16.87	48.53	1.04
24	15.45	48.91	14.42	48.62	1.07
36	8.24	60.32	8.14	53.78	1.01
48	6.95	86.51	6.31	56.63	1.10
72	3.44	69.05	3.18	72.04	1.08
96	1.73	96.18	1.74	104.74	0.99
120	0.85	133.87	1.00	120.53	0.85

For Raloxifene-6 β-glucuronide:

Time (hr)	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
0	0.00	.	0.00	.	.
0.33	47.32	189.98	86.58	177.68	0.55
0.67	215.19	136.61	231.38	95.43	0.93
1	280.40	77.64	303.14	71.44	0.92
1.5	356.14	52.56	349.49	50.87	1.02
2	373.60	42.96	368.50	41.47	1.01
2.5	363.75	32.91	366.95	37.22	0.99
3	339.34	32.34	360.61	36.25	0.94
3.5	322.27	34.62	323.14	36.93	1.00
4	315.11	37.15	302.80	36.80	1.04
4.5	336.98	35.74	332.23	33.34	1.01
5	313.18	36.89	306.89	41.16	1.02
5.5	305.98	42.66	284.43	37.28	1.08
6	294.34	37.69	274.75	39.50	1.07
6.5	299.77	38.29	281.70	44.06	1.06
7	311.09	36.48	290.11	39.96	1.07
8	321.39	32.59	307.98	37.36	1.04
10	396.07	30.62	414.77	48.13	0.95
12	386.16	35.10	396.59	47.85	0.97
16	367.11	37.72	373.86	54.75	0.98
24	361.05	36.96	390.30	49.18	0.93
36	270.30	42.12	266.83	44.36	1.01
48	206.41	45.10	202.68	42.82	1.02
72	108.09	44.14	105.91	46.14	1.02
96	61.74	59.16	58.51	61.56	1.06
120	32.53	80.00	34.04	75.37	0.96

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



B. **Formulation Data** (CMC review V:\FIRMSNZ\TEVA\LTRS&REV\78193.REV1.doc)

(b) (4)

(b) (4)

[redacted]

C. Dissolution Data-firm proposed method

Study Ref. No.	Product ID/Batch No.	Dosage form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)				Study Report Location
					15 min	30 min	45 min	60 min	
CDP-1240/01	Raloxifene HCl K-35052	60 mg Tablets	Dissolution: Apparatus 2 (Paddles) Speed of Rotation: 75 rpm Medium: 1% SLS in 0.05M sodium phosphate buffer volume: 900 mL Temperature: 37°C± 0.5°C Tolerance: NLT (b) (4)% (Q) dissolved in (b) (4) minutes.	12	63	97	100	100 (b) (4)	Teva Pharmaceutical Industries, Ltd., Hashikma Street, Industrial Area, Kfar-Saba 44102, ISRAEL
	Evista ® 8EF35A	60 mg Tablets		12	62	84	92	96 (b) (4)	

Reviewer's Notes: The dissolution review was completed on July 7, 2006. A deficiency letter was issued and the following dissolution method and specification were recommended:

> 1000 mL, 0.1% polysorbate 80 aqueous solution, USP Apparatus II (paddle), 50 rpm with specification [NLT 80% (Q) in 30 mins]
> (V:\firmsnz\teva\ltrs&rev\78193d0306 .doc)

Comments on Dissolution: Incomplete. The firm was suggested by the FDA to conduct the dissolution testing using the FDA-recommended method described above and resubmit the results for further evaluation.

D. Consult Reviews: None

E. Additional Attachments: SAS data

a. SAS data for fasting study:

Obs	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15	C16
1	0.0	29.80	192.0	165.0	192.0	253.0	244.0	261.0	247.0	187.0	168.0	150.0	153.0	190.0	379.0	524.0
2	0.0	34.80	179.0	150.0	169.0	131.0	127.0	114.0	93.1	92.7	114.0	190.0	128.0	175.0	222.0	174.0
3	0.0	13.10	65.0	130.0	173.0	190.0	161.0	197.0	252.0	334.0	341.0	273.0	254.0	246.0	297.0	335.0
4	0.0	150.00	252.0	231.0	211.0	150.0	192.0	146.0	160.0	145.0	165.0	214.0	185.0	206.0	218.0	265.0
5	0.0	38.80	75.9	67.3	64.7	65.1	52.0	70.5	88.9	83.8	76.9	78.8	80.8	103.0	101.0	79.6
6	0.0	94.60	241.0	169.0	159.0	185.0	178.0	167.0	190.0	201.0	189.0	178.0	196.0	199.0	208.0	186.0
7	0.0	74.90	238.0	208.0	297.0	289.0	256.0	213.0	266.0	245.0	262.0	319.0	324.0	394.0	744.0	615.0
8	0.0	22.60	162.0	151.0	161.0	180.0	171.0	247.0	217.0	169.0	186.0	146.0	137.0	167.0	258.0	278.0
9	0.0	13.50	117.0	83.5	84.6	98.0	105.0	101.0	113.0	147.0	174.0	152.0	155.0	175.0	286.0	278.0
10	0.0	19.30	150.0	97.9	106.0	87.0	94.3	84.5	86.2	85.0	91.3	87.3	85.9	110.0	150.0	157.0
11	0.0	45.90	112.0	119.0	112.0	150.0	147.0	132.0	138.0	135.0	130.0	171.0	182.0	204.0	216.0	215.0
12	0.0	153.00	157.0	198.0	195.0	187.0	165.0	181.0	162.0	158.0	161.0	161.0	152.0	173.0	195.0	257.0
13	0.0	16.60	165.0	128.0	96.4	105.0	89.7	93.5	103.0	96.1	124.0	154.0	140.0	199.0	312.0	267.0
14	0.0	58.20	120.0	157.0	114.0	105.0	97.2	88.8	102.0	73.1	86.6	64.4	78.8	146.0	324.0	198.0
15	0.0	58.30	143.0	113.0	113.0	114.0	127.0	155.0	129.0	120.0	114.0	115.0	111.0	129.0	139.0	149.0
16	0.0	35.80	143.0	111.0	101.0	84.9	94.0	113.0	106.0	113.0	153.0	116.0	138.0	248.0	286.0	226.0
17	0.0	71.00	135.0	137.0	146.0	164.0	141.0	159.0	137.0	142.0	150.0	146.0	139.0	183.0	177.0	152.0
18	0.0	26.00	73.3	71.5	82.2	84.2	93.7	132.0	125.0	156.0	143.0	165.0	202.0	207.0	189.0	226.0
19	0.0	159.00	198.0	263.0	279.0	373.0	364.0	362.0	406.0	350.0	291.0	338.0	352.0	351.0	395.0	433.0
20	0.0	118.00	153.0	174.0	244.0	311.0	358.0	385.0	334.0	297.0	340.0	414.0	378.0	533.0	499.0	522.0
21	0.0	110.00	144.0	130.0	158.0	145.0	137.0	124.0	151.0	120.0	134.0	148.0	181.0	181.0	291.0	235.0
22	0.0	348.00	193.0	147.0	148.0	145.0	135.0	137.0	146.0	193.0	199.0	198.0	244.0	272.0	370.0	296.0
23	0.0	33.30	183.0	136.0	110.0	94.5	93.7	96.6	95.0	81.3	82.8	87.3	79.7	103.0	120.0	251.0
24	0.0	46.30	132.0	202.0	145.0	144.0	130.0	120.0	137.0	134.0	121.0	130.0	132.0	183.0	197.0	304.0
25	0.0	42.50	244.0	205.0	285.0	198.0	163.0	158.0	146.0	145.0	150.0	190.0	187.0	327.0	315.0	303.0
26	0.0	66.50	210.0	151.0	148.0	212.0	163.0	169.0	174.0	187.0	145.0	143.0	142.0	170.0	191.0	202.0
27	0.0	242.00	232.0	231.0	212.0	221.0	223.0	394.0	395.0	260.0	279.0	347.0	281.0	305.0	815.0	1070.0
28	0.0	70.50	160.0	222.0	173.0	226.0	189.0	205.0	162.0	171.0	201.0	179.0	242.0	214.0	482.0	911.0
29	0.0	0.00	46.4	81.0	105.0	173.0	194.0	211.0	206.0	211.0	200.0	179.0	162.0	167.0	223.0	302.0
30	0.0	119.00	278.0	251.0	283.0	297.0	270.0	243.0	210.0	242.0	182.0	179.0	193.0	189.0	241.0	269.0
31	0.0	11.40	83.7	129.0	143.0	171.0	170.0	143.0	173.0	178.0	165.0	157.0	162.0	165.0	314.0	518.0
32	0.0	11.30	78.9	73.8	79.6	77.3	76.7	96.2	107.0	121.0	110.0	148.0	167.0	272.0	520.0	684.0
33	0.0	13.10	164.0	120.0	158.0	144.0	168.0	173.0	216.0	278.0	247.0	223.0	245.0	217.0	230.0	250.0
34	0.0	0.00	105.0	99.9	114.0	138.0	160.0	169.0	193.0	198.0	245.0	245.0	231.0	280.0	267.0	251.0
35	0.0	0.00	109.0	122.0	146.0	122.0	143.0	152.0	170.0	202.0	242.0	347.0	406.0	563.0	547.0	611.0
36	0.0	91.10	171.0	171.0	179.0	216.0	200.0	266.0	228.0	242.0	161.0	335.0	384.0	561.0	494.0	399.0

ORIGINAL DATA SUBMITTED

Obs	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15	C16
37	0.0	222.00	278.0	189.0	161.0	229.0	183.0	175.0	168.0	188.0	247.0	181.0	204.0	244.0	299.0	470.0
38	17.2	77.70	196.0	132.0	119.0	136.0	118.0	155.0	167.0	178.0	183.0	147.0	155.0	230.0	203.0	232.0
39	0.0	11.90	189.0	174.0	233.0	155.0	111.0	92.4	90.7	87.2	83.9	90.7	88.4	91.2	439.0	379.0
40	0.0	69.30	194.0	153.0	141.0	170.0	130.0	155.0	126.0	142.0	137.0	131.0	145.0	144.0	132.0	163.0
41	0.0	22.80	130.0	113.0	98.9	76.5	88.7	78.8	58.8	79.7	75.7	78.5	85.6	87.8	217.0	309.0
42	0.0	10.10	81.6	71.4	77.5	72.1	69.9	67.4	71.0	62.7	61.4	64.2	60.5	82.3	338.0	292.0
43	0.0	0.00	43.0	62.4	66.9	88.8	97.8	126.0	134.0	156.0	226.0	235.0	192.0	173.0	437.0	824.0
44	0.0	22.80	164.0	137.0	134.0	137.0	148.0	244.0	215.0	193.0	156.0	144.0	148.0	142.0	248.0	458.0
45	0.0	0.00	40.8	114.0	138.0	139.0	172.0	183.0	200.0	152.0	135.0	133.0	169.0	153.0	265.0	704.0
46	0.0	23.00	202.0	181.0	212.0	345.0	249.0	220.0	217.0	193.0	163.0	163.0	189.0	187.0	391.0	354.0
47	0.0	144.00	114.0	211.0	253.0	253.0	297.0	191.0	149.0	127.0	117.0	116.0	159.0	150.0	607.0	632.0
48	0.0	114.00	152.0	166.0	189.0	224.0	235.0	175.0	144.0	138.0	156.0	114.0	120.0	137.0	516.0	557.0
49	0.0	28.20	223.0	345.0	286.0	227.0	228.0	253.0	293.0	281.0	292.0	314.0	316.0	359.0	642.0	818.0
50	0.0	108.00	218.0	156.0	181.0	230.0	251.0	283.0	232.0	241.0	239.0	270.0	277.0	308.0	547.0	478.0
51	0.0	0.00	170.0	154.0	160.0	146.0	155.0	237.0	217.0	248.0	229.0	256.0	256.0	255.0	255.0	265.0
52	0.0	0.00	103.0	156.0	146.0	145.0	146.0	155.0	201.0	205.0	238.0	275.0	275.0	299.0	342.0	375.0
53	0.0	55.80	78.4	67.6	76.3	106.0	95.0	79.0	98.3	116.0	151.0	158.0	206.0	320.0	321.0	296.0
54	0.0	40.00	75.8	61.3	107.0	103.0	107.0	97.9	101.0	108.0	104.0	143.0	206.0	363.0	320.0	233.0
55	0.0	67.30	117.0	106.0	96.1	93.6	92.0	106.0	97.6	85.8	83.8	87.1	89.3	102.0	97.6	239.0
56	0.0	106.00	92.1	86.9	84.6	96.8	93.7	107.0	96.0	100.0	93.6	92.4	108.0	111.0	134.0	257.0
57	0.0	32.90	170.0	132.0	124.0	115.0	113.0	140.0	137.0	148.0	162.0	164.0	145.0	160.0	310.0	988.0
58	0.0	59.20	186.0	122.0	135.0	148.0	116.0	136.0	148.0	112.0	101.0	84.9	92.6	92.4	92.5	110.0
59	0.0	60.10	157.0	77.7	80.9	80.9	64.0	64.5	61.8	72.5	66.0	67.1	77.5	91.9	164.0	242.0
60	0.0	95.70	140.0	72.2	55.3	60.4	47.0	55.8	51.2	53.9	46.6	47.2	57.1	58.2	69.5	123.0
61	0.0	51.10	73.6	149.0	120.0	93.6	68.9	82.9	96.5	100.0	110.0	99.8	116.0	131.0	158.0	153.0
62	0.0	48.90	152.0	146.0	115.0	127.0	81.9	77.1	75.5	82.7	88.8	94.4	84.2	131.0	338.0	255.0
63	0.0	7.54	99.6	130.0	92.1	110.0	117.0	126.0	114.0	89.6	103.0	88.9	97.6	118.0	137.0	169.0
64	0.0	12.70	62.9	99.1	231.0	246.0	266.0	267.0	241.0	250.0	197.0	127.0	195.0	211.0	250.0	314.0
65	0.0	162.00	120.0	87.4	69.7	54.6	52.5	46.0	45.0	55.7	52.4	47.2	51.8	83.5	149.0	206.0
66	0.0	0.00	59.8	148.0	192.0	149.0	124.0	85.7	92.0	95.8	102.0	75.6	74.6	106.0	96.2	116.0
67	0.0	0.00	11.1	48.0	73.3	178.0	172.0	191.0	198.0	208.0	254.0	240.0	248.0	249.0	266.0	410.0
68	0.0	9.43	146.0	165.0	157.0	158.0	189.0	178.0	202.0	196.0	192.0	195.0	182.0	189.0	270.0	370.0
69	0.0	46.20	103.0	90.8	119.0	84.4	103.0	105.0	122.0	117.0	131.0	118.0	128.0	117.0	262.0	281.0
70	0.0	31.50	107.0	128.0	81.4	100.0	123.0	113.0	126.0	168.0	128.0	161.0	192.0	188.0	257.0	397.0
71	0.0	232.00	168.0	133.0	151.0	126.0	139.0	122.0	121.0	134.0	140.0	147.0	131.0	242.0	160.0	179.0
72	0.0	120.00	106.0	84.9	83.8	108.0	137.0	188.0	217.0	212.0	220.0	183.0	183.0	186.0	357.0	658.0
73	0.0	8.51	152.0	170.0	221.0	241.0	230.0	337.0	336.0	412.0	486.0	439.0	760.0	674.0	639.0	788.0
74	0.0	85.30	295.0	209.0	207.0	227.0	285.0	260.0	346.0	446.0	352.0	393.0	507.0	395.0	411.0	654.0
75	0.0	6.54	141.0	229.0	197.0	163.0	147.0	160.0	154.0	171.0	167.0	167.0	158.0	195.0	211.0	302.0

Obs	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15	C16
76	0.0	5.23	92.9	157.0	194.0	204.0	180.0	215.0	202.0	167.0	166.0	203.0	186.0	187.0	242.0	623.0
77	0.0	106.00	110.0	181.0	203.0	284.0	284.0	275.0	354.0	265.0	247.0	269.0	281.0	262.0	350.0	313.0
78	0.0	144.00	144.0	210.0	275.0	223.0	260.0	239.0	225.0	270.0	202.0	208.0	202.0	217.0	784.0	533.0
79	0.0	51.10	172.0	126.0	112.0	117.0	140.0	166.0	116.0	150.0	129.0	173.0	129.0	142.0	190.0	583.0
80	0.0	21.90	80.2	64.8	69.7	80.5	77.2	89.1	91.4	93.2	95.1	91.5	80.6	80.9	159.0	319.0
81	0.0	15.10	165.0	132.0	137.0	146.0	96.7	91.4	95.8	93.4	97.1	90.9	80.2	152.0	305.0	206.0
82	0.0	19.20	128.0	116.0	129.0	166.0	148.0	203.0	172.0	192.0	201.0	232.0	201.0	166.0	396.0	370.0
83	0.0	82.30	145.0	116.0	92.0	83.0	78.8	115.0	112.0	111.0	119.0	115.0	109.0	119.0	158.0	221.0
84	0.0	99.20	146.0	181.0	147.0	153.0	132.0	99.8	116.0	98.0	108.0	111.0	101.0	135.0	248.0	299.0
85	0.0	103.00	133.0	133.0	120.0	115.0	93.1	87.3	87.1	87.6	75.5	91.7	178.0	294.0	197.0	228.0
86	0.0	88.80	112.0	114.0	131.0	133.0	139.0	116.0	104.0	98.2	90.5	111.0	106.0	118.0	282.0	264.0
87	0.0	52.40	130.0	100.0	90.6	96.7	112.0	120.0	125.0	119.0	109.0	84.6	72.1	77.7	94.5	317.0
88	0.0	74.60	116.0	115.0	86.5	95.6	76.8	69.4	60.3	60.5	48.5	51.4	54.8	54.0	74.4	80.8
89	0.0	248.00	263.0	207.0	172.0	215.0	230.0	250.0	279.0	271.0	247.0	261.0	219.0	233.0	231.0	265.0
90	0.0	99.30	115.0	146.0	142.0	112.0	112.0	207.0	236.0	252.0	293.0	328.0	256.0	229.0	225.0	291.0
91	0.0	53.60	125.0	99.0	104.0	99.9	133.0	135.0	119.0	116.0	123.0	129.0	120.0	137.0	206.0	307.0
92	0.0	8.49	44.1	57.3	66.7	94.5	118.0	113.0	114.0	157.0	128.0	122.0	171.0	150.0	175.0	300.0
93	0.0	124.00	236.0	223.0	247.0	285.0	312.0	320.0	323.0	333.0	367.0	501.0	479.0	545.0	898.0	973.0
94	0.0	52.60	240.0	273.0	327.0	340.0	298.0	250.0	281.0	270.0	325.0	323.0	.	283.0	394.0	418.0
95	0.0	6.03	43.4	76.3	66.6	61.3	69.8	79.7	101.0	159.0	121.0	112.0	123.0	194.0	297.0	460.0
96	0.0	113.00	131.0	139.0	154.0	163.0	167.0	187.0	179.0	152.0	168.0	167.0	162.0	297.0	719.0	1080.0
97	0.0	42.10	103.0	80.7	91.8	106.0	148.0	141.0	138.0	133.0	128.0	127.0	124.0	152.0	268.0	529.0
98	0.0	0.00	20.4	39.7	52.7	76.9	61.8	128.0	142.0	157.0	199.0	335.0	293.0	250.0	330.0	494.0
99	0.0	90.80	193.0	146.0	173.0	190.0	155.0	155.0	166.0	154.0	139.0	144.0	160.0	162.0	306.0	462.0
100	0.0	92.60	233.0	189.0	194.0	236.0	257.0	287.0	281.0	301.0	459.0	722.0	567.0	534.0	503.0	586.0
101	0.0	88.90	142.0	107.0	105.0	128.0	107.0	136.0	130.0	94.8	102.0	101.0	86.0	136.0	272.0	554.0
102	0.0	174.00	187.0	144.0	149.0	156.0	161.0	118.0	126.0	120.0	109.0	101.0	106.0	152.0	219.0	639.0
103	0.0	69.80	218.0	167.0	157.0	157.0	164.0	208.0	166.0	188.0	246.0	234.0	182.0	325.0	258.0	216.0
104	0.0	51.20	177.0	228.0	194.0	283.0	325.0	307.0	398.0	336.0	286.0	354.0	274.0	375.0	344.0	307.0
105	0.0	0.00	81.9	151.0	131.0	153.0	145.0	170.0	175.0	227.0	256.0	219.0	220.0	227.0	289.0	268.0
106	0.0	0.00	46.8	263.0	273.0	298.0	239.0	229.0	225.0	218.0	180.0	173.0	185.0	192.0	183.0	237.0
107	0.0	175.00	187.0	175.0	194.0	200.0	264.0	201.0	184.0	162.0	159.0	133.0	142.0	171.0	226.0	746.0
108	0.0	56.30	100.0	105.0	111.0	189.0	165.0	126.0	102.0	107.0	102.0	117.0	109.0	120.0	134.0	138.0
109	0.0	68.80	127.0	115.0	165.0	119.0	146.0	149.0	150.0	142.0	145.0	121.0	116.0	112.0	144.0	183.0
110	0.0	6.61	26.0	81.6	43.5	81.7	125.0	125.0	86.6	111.0	80.6	96.5	129.0	163.0	181.0	220.0
111	0.0	16.10	135.0	210.0	175.0	197.0	210.0	219.0	185.0	166.0	150.0	135.0	153.0	203.0	414.0	455.0
112	0.0	20.30	95.7	191.0	169.0	145.0	145.0	175.0	181.0	139.0	138.0	131.0	136.0	183.0	205.0	480.0
113	0.0	5.82	192.0	136.0	134.0	213.0	249.0	316.0	309.0	441.0	383.0	427.0	374.0	319.0	361.0	310.0
114	0.0	44.40	155.0	128.0	124.0	161.0	174.0	184.0	208.0	248.0	268.0	267.0	239.0	330.0	518.0	529.0

Obs	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15	C16
115	0.0	42.80	155.0	177.0	151.0	113.0	100.0	108.0	132.0	136.0	114.0	111.0	105.0	179.0	248.0	232.0
116	0.0	9.12	29.4	107.0	97.0	110.0	94.0	83.3	84.9	110.0	98.6	107.0	93.5	108.0	123.0	237.0
117	0.0	45.30	126.0	131.0	106.0	85.8	84.9	85.4	91.9	89.8	115.0	98.9	108.0	185.0	143.0	140.0
118	0.0	83.30	87.8	137.0	88.6	84.6	101.0	161.0	124.0	136.0	147.0	164.0	202.0	173.0	143.0	122.0

Obs	C17	C18	C19	C20	C21	C22	C23	C24	C25	C26	C27	C28	C29	C30
1	401.0	343.0	466.0	279.0	242.0	235.0	197.0	192.0	224.0	181.0	197.0	229.0	186.0	184.0
2	211.0	199.0	179.0	208.0	158.0	148.0	125.0	121.0	146.0	105.0	178.0	174.0	186.0	162.0
3	387.0	430.0	360.0	318.0	327.0	339.0	264.0	244.0	288.0	235.0	209.0	304.0	156.0	175.0
4	321.0	259.0	245.0	234.0	246.0	240.0	240.0	271.0	260.0	231.0	225.0	193.0	164.0	201.0
5	74.1	100.0	80.3	73.6	85.5	83.7	71.9	73.9	105.0	80.5	79.3	123.0	133.0	122.0
6	163.0	157.0	159.0	154.0	145.0	136.0	144.0	164.0	173.0	164.0	163.0	154.0	115.0	99.0
7	503.0	525.0	479.0	489.0	560.0	540.0	428.0	489.0	348.0	407.0	267.0	324.0	259.0	212.0
8	265.0	271.0	254.0	235.0	241.0	245.0	195.0	198.0	236.0	212.0	245.0	247.0	201.0	217.0
9	229.0	233.0	188.0	171.0	186.0	169.0	119.0	137.0	126.0	158.0	181.0	200.0	151.0	151.0
10	149.0	192.0	145.0	237.0	230.0	221.0	178.0	146.0	154.0	127.0	110.0	109.0	61.8	67.6
11	221.0	239.0	241.0	249.0	207.0	207.0	185.0	204.0	298.0	234.0	243.0	320.0	282.0	259.0
12	301.0	235.0	221.0	262.0	431.0	225.0	203.0	217.0	242.0	240.0	267.0	297.0	324.0	297.0
13	228.0	196.0	179.0	166.0	157.0	174.0	159.0	172.0	268.0	211.0	232.0	330.0	205.0	217.0
14	178.0	158.0	156.0	151.0	146.0	137.0	160.0	152.0	151.0	140.0	185.0	256.0	190.0	183.0
15	170.0	192.0	153.0	158.0	156.0	188.0	160.0	163.0	225.0	207.0	158.0	187.0	257.0	207.0
16	265.0	243.0	196.0	192.0	242.0	235.0	344.0	274.0	235.0	250.0	227.0	221.0	233.0	188.0
17	180.0	158.0	198.0	214.0	245.0	253.0	197.0	168.0	238.0	177.0	158.0	185.0	153.0	126.0
18	197.0	188.0	184.0	199.0	249.0	244.0	205.0	177.0	199.0	192.0	192.0	188.0	201.0	161.0
19	408.0	513.0	424.0	378.0	391.0	380.0	385.0	392.0	370.0	314.0	231.0	340.0	180.0	120.0
20	753.0	1070.0	1290.0	1160.0	1220.0	902.0	691.0	575.0	521.0	421.0	256.0	223.0	127.0	93.7
21	247.0	180.0	183.0	163.0	186.0	217.0	194.0	164.0	196.0	170.0	200.0	169.0	108.0	66.0
22	287.0	302.0	262.0	215.0	224.0	212.0	231.0	182.0	200.0	202.0	198.0	270.0	249.0	296.0
23	492.0	505.0	541.0	696.0	530.0	406.0	308.0	.	416.0	325.0	311.0	375.0	215.0	213.0
24	529.0	332.0	339.0	330.0	286.0	269.0	249.0	246.0	487.0	381.0	294.0	274.0	264.0	228.0
25	234.0	257.0	221.0	197.0	234.0	207.0	225.0	224.0	229.0	186.0	169.0	174.0	140.0	161.0
26	277.0	211.0	222.0	227.0	205.0	191.0	248.0	220.0	203.0	178.0	162.0	169.0	216.0	191.0
27	1040.0	781.0	604.0	519.0	475.0	649.0	630.0	553.0	611.0	410.0	416.0	439.0	296.0	230.0
28	835.0	890.0	769.0	725.0	693.0	664.0	602.0	529.0	579.0	430.0	364.0	371.0	410.0	275.0
29	268.0	297.0	420.0	394.0	373.0	383.0	305.0	267.0	282.0	224.0	198.0	213.0	168.0	156.0
30	252.0	256.0	224.0	221.0	202.0	229.0	252.0	374.0	342.0	229.0	186.0	226.0	.	212.0
31	386.0	329.0	331.0	260.0	356.0	366.0	256.0	311.0	291.0	211.0	231.0	204.0	215.0	162.0
32	679.0	495.0	425.0	402.0	393.0	410.0	413.0	537.0	413.0	346.0	264.0	314.0	.	271.0
33	232.0	215.0	395.0	343.0	354.0	380.0	290.0	350.0	367.0	298.0	282.0	387.0	311.0	256.0

Obs	C17	C18	C19	C20	C21	C22	C23	C24	C25	C26	C27	C28	C29	C30
34	277.0	237.0	258.0	282.0	280.0	240.0	309.0	379.0	295.0	295.0	291.0	428.0	288.0	258.0
35	464.0	400.0	531.0	412.0	497.0	385.0	371.0	978.0	1740.0	1030.0	653.0	727.0	507.0	402.0
36	398.0	376.0	350.0	455.0	416.0	357.0	292.0	294.0	299.0	263.0	361.0	434.0	242.0	242.0
37	754.0	643.0	836.0	851.0	726.0	424.0	460.0	387.0	376.0	368.0	312.0	398.0	348.0	268.0
38	244.0	268.0	288.0	308.0	351.0	329.0	244.0	261.0	206.0	253.0	240.0	392.0	283.0	254.0
39	318.0	259.0	246.0	307.0	240.0	285.0	172.0	161.0	195.0	156.0	131.0	174.0	164.0	168.0
40	257.0	326.0	275.0	328.0	426.0	347.0	246.0	234.0	227.0	173.0	179.0	195.0	253.0	216.0
41	264.0	252.0	234.0	232.0	215.0	188.0	178.0	339.0	213.0	224.0	217.0	333.0	229.0	243.0
42	245.0	205.0	165.0	178.0	209.0	263.0	231.0	255.0	287.0	236.0	193.0	267.0	218.0	158.0
43	587.0	1670.0	1550.0	1290.0	996.0	1080.0	789.0	633.0	651.0	560.0	403.0	408.0	146.0	102.0
44	538.0	374.0	445.0	307.0	256.0	233.0	304.0	512.0	430.0	337.0	468.0	497.0	216.0	154.0
45	435.0	395.0	367.0	322.0	383.0	278.0	250.0	211.0	359.0	314.0	270.0	272.0	215.0	150.0
46	545.0	423.0	358.0	410.0	398.0	359.0	286.0	257.0	340.0	289.0	252.0	233.0	244.0	189.0
47	379.0	334.0	255.0	229.0	226.0	253.0	268.0	192.0	219.0	211.0	196.0	182.0	147.0	104.0
48	510.0	358.0	368.0	269.0	256.0	245.0	210.0	228.0	272.0	188.0	158.0	172.0	139.0	146.0
49	659.0	609.0	619.0	518.0	564.0	435.0	429.0	427.0	642.0	491.0	427.0	414.0	347.0	240.0
50	467.0	468.0	430.0	413.0	523.0	501.0	398.0	535.0	501.0	404.0	368.0	406.0	348.0	265.0
51	258.0	253.0	241.0	234.0	226.0	241.0	270.0	312.0	374.0	306.0	293.0	406.0	357.0	282.0
52	398.0	404.0	423.0	443.0	448.0	450.0	356.0	393.0	540.0	479.0	398.0	462.0	361.0	291.0
53	344.0	231.0	218.0	222.0	196.0	173.0	170.0	341.0	348.0	322.0	236.0	291.0	248.0	240.0
54	225.0	167.0	197.0	202.0	204.0	199.0	192.0	236.0	427.0	296.0	277.0	290.0	254.0	262.0
55	279.0	215.0	200.0	226.0	199.0	223.0	191.0	172.0	166.0	156.0	148.0	175.0	116.0	166.0
56	238.0	206.0	194.0	197.0	229.0	199.0	215.0	195.0	191.0	183.0	161.0	213.0	.	183.0
57	983.0	1210.0	888.0	756.0	689.0	611.0	628.0	541.0	438.0	478.0	460.0	304.0	182.0	127.0
58	141.0	116.0	139.0	147.0	230.0	235.0	225.0	286.0	180.0	150.0	166.0	188.0	122.0	83.6
59	282.0	202.0	185.0	189.0	194.0	164.0	214.0	181.0	206.0	192.0	172.0	212.0	206.0	203.0
60	104.0	91.2	83.2	82.9	120.0	113.0	99.4	106.0	124.0	131.0	133.0	166.0	197.0	202.0
61	168.0	167.0	160.0	196.0	181.0	182.0	158.0	132.0	193.0	148.0	114.0	111.0	77.7	66.2
62	265.0	234.0	203.0	200.0	199.0	189.0	189.0	168.0	198.0	176.0	129.0	194.0	196.0	170.0
63	282.0	242.0	209.0	195.0	186.0	177.0	147.0	157.0	171.0	141.0	165.0	159.0	205.0	159.0
64	490.0	395.0	402.0	357.0	323.0	315.0	325.0	282.0	285.0	245.0	267.0	279.0	193.0	328.0
65	159.0	159.0	131.0	127.0	116.0	136.0	101.0	125.0	72.9	70.4	122.0	153.0	90.2	95.3
66	99.4	94.7	90.5	79.5	73.3	75.4	55.5	59.4	89.5	66.9	158.0	108.0	71.3	49.7
67	433.0	384.0	475.0	479.0	501.0	455.0	416.0	365.0	377.0	311.0	272.0	233.0	252.0	179.0
68	329.0	309.0	316.0	266.0	267.0	254.0	272.0	242.0	246.0	217.0	190.0	195.0	162.0	127.0
69	278.0	168.0	161.0	202.0	174.0	170.0	161.0	175.0	154.0	159.0	189.0	211.0	221.0	136.0
70	251.0	212.0	248.0	228.0	243.0	168.0	193.0	200.0	217.0	202.0	173.0	240.0	184.0	117.0
71	189.0	177.0	173.0	163.0	168.0	154.0	177.0	183.0	181.0	174.0	219.0	200.0	173.0	166.0
72	387.0	494.0	594.0	543.0	537.0	589.0	697.0	515.0	542.0	422.0	419.0	355.0	211.0	174.0

Obs	C17	C18	C19	C20	C21	C22	C23	C24	C25	C26	C27	C28	C29	C30
73	912.0	672.0	529.0	498.0	441.0	421.0	364.0	209.0	289.0	316.0	346.0	334.0	167.0	95.6
74	838.0	607.0	601.0	589.0	615.0	486.0	397.0	352.0	302.0	240.0	240.0	244.0	96.7	45.3
75	461.0	499.0	362.0	303.0	281.0	261.0	219.0	211.0	195.0	138.0	143.0	162.0	149.0	103.0
76	645.0	573.0	535.0	486.0	331.0	304.0	270.0	246.0	176.0	160.0	124.0	158.0	102.0	122.0
77	413.0	448.0	377.0	488.0	540.0	527.0	416.0	403.0	528.0	484.0	452.0	.	332.0	368.0
78	446.0	424.0	373.0	383.0	357.0	402.0	365.0	416.0	393.0	403.0	377.0	487.0	463.0	481.0
79	633.0	527.0	500.0	431.0	357.0	322.0	249.0	233.0	232.0	195.0	168.0	157.0	131.0	110.0
80	521.0	401.0	329.0	290.0	258.0	241.0	187.0	232.0	209.0	196.0	136.0	170.0	131.0	103.0
81	163.0	195.0	149.0	107.0	133.0	124.0	142.0	123.0	143.0	148.0	171.0	281.0	251.0	210.0
82	260.0	217.0	188.0	173.0	172.0	181.0	157.0	154.0	175.0	160.0	195.0	200.0	143.0	117.0
83	215.0	258.0	255.0	230.0	202.0	215.0	169.0	172.0	154.0	144.0	159.0	216.0	117.0	104.0
84	322.0	273.0	228.0	237.0	221.0	217.0	202.0	208.0	222.0	187.0	184.0	309.0	189.0	133.0
85	248.0	203.0	203.0	204.0	257.0	227.0	229.0	231.0	305.0	261.0	235.0	260.0	211.0	165.0
86	333.0	287.0	251.0	249.0	279.0	301.0	234.0	276.0	310.0	242.0	194.0	236.0	188.0	167.0
87	309.0	252.0	194.0	143.0	148.0	136.0	104.0	105.0	131.0	107.0	76.9	89.3	65.5	56.6
88	70.5	67.8	64.6	59.3	66.9	54.6	52.1	46.2	53.4	44.0	54.2	72.0	63.5	60.4
89	334.0	372.0	352.0	333.0	321.0	343.0	308.0	267.0	301.0	249.0	214.0	281.0	244.0	137.0
90	338.0	320.0	289.0	235.0	210.0	261.0	231.0	217.0	370.0	215.0	265.0	261.0	205.0	153.0
91	214.0	172.0	195.0	201.0	173.0	186.0	217.0	166.0	162.0	134.0	108.0	113.0	70.8	44.7
92	254.0	224.0	261.0	463.0	306.0	287.0	363.0	487.0	431.0	336.0	311.0	431.0	200.0	121.0
93	914.0	883.0	709.0	895.0	657.0	647.0	624.0	533.0	647.0	517.0	443.0	451.0	315.0	316.0
94	466.0	.	.	481.0	372.0	374.0	371.0	399.0	390.0	349.0	.	348.0	332.0	290.0
95	487.0	474.0	474.0	380.0	366.0	319.0	296.0	232.0	232.0	232.0	206.0	167.0	167.0	129.0
96	1040.0	730.0	579.0	616.0	511.0	484.0	471.0	372.0	396.0	336.0	263.0	202.0	151.0	105.0
97	379.0	351.0	290.0	316.0	324.0	389.0	388.0	317.0	433.0	338.0	294.0	353.0	420.0	375.0
98	465.0	434.0	383.0	328.0	329.0	352.0	324.0	330.0	329.0	248.0	269.0	305.0	250.0	287.0
99	293.0	521.0	420.0	471.0	388.0	338.0	286.0	281.0	281.0	231.0	264.0	357.0	305.0	262.0
100	707.0	1150.0	1520.0	1410.0	1070.0	1080.0	991.0	1160.0	1130.0	958.0	688.0	632.0	489.0	475.0
101	521.0	387.0	334.0	271.0	240.0	263.0	222.0	177.0	261.0	192.0	289.0	214.0	194.0	161.0
102	669.0	496.0	405.0	366.0	338.0	248.0	193.0	192.0	250.0	215.0	214.0	243.0	158.0	136.0
103	198.0	215.0	251.0	255.0	251.0	255.0	201.0	184.0	183.0	184.0	212.0	154.0	141.0	137.0
104	260.0	286.0	246.0	243.0	241.0	220.0	198.0	219.0	244.0	250.0	298.0	303.0	247.0	225.0
105	216.0	216.0	232.0	224.0	233.0	211.0	192.0	182.0	210.0	208.0	221.0	287.0	130.0	83.7
106	255.0	279.0	315.0	291.0	275.0	340.0	255.0	264.0	346.0	265.0	230.0	219.0	94.7	54.0
107	885.0	568.0	562.0	476.0	449.0	428.0	347.0	329.0	320.0	278.0	233.0	172.0	137.0	108.0
108	132.0	157.0	126.0	129.0	127.0	144.0	134.0	127.0	153.0	123.0	117.0	136.0	108.0	85.0
109	234.0	230.0	164.0	160.0	173.0	417.0	162.0	211.0	211.0	171.0	174.0	185.0	192.0	128.0
110	203.0	164.0	136.0	136.0	132.0	135.0	104.0	104.0	107.0	101.0	91.5	138.0	167.0	126.0
111	344.0	300.0	312.0	319.0	317.0	301.0	246.0	216.0	256.0	222.0	192.0	182.0	123.0	59.4

Obs	C17	C18	C19	C20	C21	C22	C23	C24	C25	C26	C27	C28	C29	C30
112	573.0	489.0	515.0	429.0	374.0	361.0	305.0	257.0	349.0	287.0	254.0	250.0	164.0	106.0
113	431.0	721.0	662.0	664.0	653.0	598.0	434.0	478.0	534.0	454.0	420.0	341.0	206.0	151.0
114	364.0	315.0	342.0	284.0	282.0	255.0	453.0	398.0	425.0	416.0	371.0	386.0	324.0	311.0
115	181.0	166.0	154.0	142.0	123.0	135.0	113.0	128.0	152.0	127.0	132.0	156.0	132.0	105.0
116	229.0	232.0	230.0	211.0	206.0	165.0	232.0	202.0	258.0	191.0	172.0	199.0	177.0	155.0
117	154.0	139.0	127.0	143.0	134.0	172.0	140.0	121.0	148.0	143.0	162.0	201.0	186.0	179.0
118	128.0	124.0	157.0	109.0	96.4	124.0	114.0	120.0	164.0	139.0	150.0	211.0	139.0	169.0

Obs	C31	C32	C33	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16
1	86.2	55.20	20.50	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
2	99.4	46.50	18.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
3	82.7	46.50	8.91	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
4	164.0	133.00	32.20	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
5	81.3	48.00	11.50	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
6	63.2	22.40	9.04	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
7	150.0	104.00	37.60	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
8	171.0	115.00	74.50	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
9	87.7	42.00	9.76	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
10	30.1	18.00	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
11	179.0	99.60	24.60	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
12	278.0	179.00	71.90	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
13	.	.	20.60	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
14	119.0	67.70	16.80	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
15	214.0	91.00	141.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
16	128.0	92.20	35.30	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
17	143.0	159.00	72.60	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
18	93.5	58.00	27.20	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
19	41.5	21.00	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
20	32.6	14.60	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
21	36.4	12.40	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
22	179.0	107.00	18.40	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
23	133.0	78.00	32.30	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
24	131.0	66.20	18.10	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
25	98.3	55.00	17.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
26	139.0	65.60	21.20	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
27	100.0	36.20	9.62	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
28	149.0	93.10	17.50	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
29	76.8	38.10	8.92	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
30	86.8	41.70	7.33	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5

Obs	C31	C32	C33	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16
31	86.6	37.70	.	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
32	133.0	.	13.80	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
33	157.0	94.80	29.20	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
34	142.0	82.40	23.60	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
35	227.0	145.00	41.80	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
36	139.0	78.00	24.30	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
37	83.5	33.30	6.55	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
38	132.0	63.40	15.70	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
39	129.0	66.40	28.70	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
40	154.0	105.00	30.40	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
41	83.4	40.10	7.28	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
42	65.7	28.60	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
43	46.8	16.50	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
44	39.9	22.70	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
45	59.7	27.50	6.15	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
46	106.0	56.60	17.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
47	58.9	30.40	12.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
48	116.0	83.10	22.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
49	130.0	61.40	13.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
50	120.0	.	.	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
51	143.0	73.60	21.70	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
52	144.0	74.50	17.10	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
53	106.0	54.10	13.70	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
54	132.0	86.60	17.30	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
55	157.0	82.70	42.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
56	183.0	96.50	43.50	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
57	44.5	16.50	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
58	28.9	9.79	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
59	207.0	168.00	82.40	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
60	177.0	107.00	40.20	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
61	38.2	19.40	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
62	84.1	40.00	10.60	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
63	74.7	39.60	8.55	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
64	48.5	21.40	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
65	38.5	13.50	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
66	21.2	9.52	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
67	119.0	39.00	5.46	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
68	104.0	36.00	6.67	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
69	82.6	25.40	6.09	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5

Obs	C31	C32	C33	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16
70	53.2	27.30	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
71	128.0	74.40	21.80	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
72	107.0	61.80	33.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
73	47.3	23.00	5.86	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
74	21.3	8.30	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
75	49.5	20.10	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
76	34.8	16.70	.	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
77	240.0	.	27.60	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
78	325.0	201.00	61.40	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
79	84.4	59.10	22.30	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
80	84.9	57.20	26.80	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
81	128.0	52.60	16.50	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
82	61.1	17.30	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
83	50.8	23.80	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
84	66.0	29.70	8.23	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
85	72.5	34.30	8.96	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
86	92.2	37.10	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
87	26.6	12.20	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
88	33.9	28.30	9.87	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
89	63.3	26.20	6.32	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
90	87.8	29.90	6.50	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
91	25.9	14.20	5.77	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
92	50.2	.	5.95	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
93	197.0	149.00	.	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
94	254.0	187.00	87.20	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
95	54.9	19.30	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
96	47.3	24.10	7.19	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
97	146.0	75.50	13.80	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
98	120.0	64.90	15.20	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
99	280.0	181.00	65.50	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
100	346.0	184.00	35.40	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
101	124.0	54.80	12.60	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
102	104.0	64.40	13.20	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
103	118.0	75.00	17.30	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
104	116.0	79.90	27.70	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
105	42.9	12.30	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
106	21.3	5.97	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
107	46.1	20.10	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
108	30.3	8.35	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5

Obs	C31	C32	C33	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16
109	52.9	26.10	8.08	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
110	55.1	22.20	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
111	19.7	6.21	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
112	26.3	9.57	0.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
113	89.0	45.60	11.00	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
114	126.0	50.40	10.10	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
115	83.4	40.50	9.85	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
116	86.9	51.10	11.50	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
117	126.0	119.00	53.90	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5
118	164.0	109.00	58.80	0	0.33	0.67	1	1.33	1.67	2	2.33	2.67	3	3.33	3.67	4	4.33	4.67	5

Obs	T17	T18	T19	T20	T21	T22	T23	T24	T25	T26	T27	T28	T29	T30	T31	T32	T33	SUB	SEQ	PER
1	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	1	2	1
2	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	1	2	2
3	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	2	1	1
4	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	2	1	2
5	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	3	1	1
6	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	3	1	2
7	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	4	2	1
8	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	4	2	2
9	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	5	2	1
10	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	5	2	2
11	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	6	1	1
12	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	6	1	2
13	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	7	1	1
14	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	7	1	2
15	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	8	2	1
16	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	8	2	2
17	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	9	2	1
18	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	9	2	2
19	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	10	2	1
20	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	10	2	2
21	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	11	1	1
22	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	11	1	2
23	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	12	1	1
24	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	12	1	2
25	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	13	2	1
26	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	13	2	2
27	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	14	2	1

Obs	T17	T18	T19	T20	T21	T22	T23	T24	T25	T26	T27	T28	T29	T30	T31	T32	T33	SUB	SEQ	PER
28	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	14	2	2
29	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	15	1	1
30	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	15	1	2
31	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	16	2	1
32	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	16	2	2
33	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	17	1	1
34	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	17	1	2
35	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	18	1	1
36	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	18	1	2
37	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	19	2	1
38	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	19	2	2
39	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	20	1	1
40	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	20	1	2
41	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	21	2	1
42	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	21	2	2
43	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	22	1	1
44	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	22	1	2
45	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	23	1	1
46	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	23	1	2
47	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	24	1	1
48	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	24	1	2
49	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	25	2	1
50	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	25	2	2
51	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	26	2	1
52	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	26	2	2
53	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	27	1	1
54	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	27	1	2
55	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	28	1	1
56	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	28	1	2
57	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	29	2	1
58	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	29	2	2
59	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	30	2	1
60	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	30	2	2
61	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	31	1	1
62	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	31	1	2
63	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	32	1	1
64	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	32	1	2
65	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	33	2	1
66	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	33	2	2

Obs	T17	T18	T19	T20	T21	T22	T23	T24	T25	T26	T27	T28	T29	T30	T31	T32	T33	SUB	SEQ	PER
67	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	34	1	1
68	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	34	1	2
69	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	35	1	1
70	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	35	1	2
71	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	36	2	1
72	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	36	2	2
73	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	37	1	1
74	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	37	1	2
75	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	38	2	1
76	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	38	2	2
77	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	39	1	1
78	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	39	1	2
79	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	40	2	1
80	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	40	2	2
81	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	41	1	1
82	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	41	1	2
83	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	42	1	1
84	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	42	1	2
85	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	43	2	1
86	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	43	2	2
87	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	44	1	1
88	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	44	1	2
89	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	45	2	1
90	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	45	2	2
91	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	46	2	1
92	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	46	2	2
93	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	47	2	1
94	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	47	2	2
95	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	48	1	1
96	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	48	1	2
97	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	49	2	1
98	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	49	2	2
99	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	50	1	1
100	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	50	1	2
101	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	51	1	1
102	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	51	1	2
103	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	52	2	1
104	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	52	2	2
105	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	53	1	1

Obs	T17	T18	T19	T20	T21	T22	T23	T24	T25	T26	T27	T28	T29	T30	T31	T32	T33	SUB	SEQ	PER
106	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	53	1	2
107	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	54	2	1
108	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	54	2	2
109	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	55	2	1
110	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	55	2	2
111	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	56	1	1
112	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	56	1	2
113	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	57	1	1
114	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	57	1	2
115	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	58	2	1
116	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	58	2	2
117	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	60	2	1
118	5.33	5.67	6	6.33	6.67	7	8	9	10	12	16	24	36	48	72	96	144	60	2	2

Obs	TREAT	AUCT	AUCI	CMAX	TMAX	KE	THALF	KE_FIRST	KE_LAST	CLAST	NEWCMAX
1	B	16677.77	17700.41	524	5.00	0.02	34.58	0	0	20.50	524
2	A	14342.52	15115.62	222	4.67	0.02	29.77	0	0	18.00	222
3	A	16754.01	17043.26	430	5.67	0.03	22.50	0	0	8.91	430
4	B	21515.16	22879.50	321	5.33	0.02	29.37	0	0	32.20	321
5	A	10567.15	10984.79	133	36.00	0.03	25.17	0	0	11.50	133
6	B	10543.21	10906.82	241	0.67	0.02	27.88	0	0	9.04	241
7	B	25466.10	27394.33	744	4.67	0.02	35.55	0	0	37.60	744
8	A	23142.57	29700.83	278	5.00	0.01	61.02	0	0	74.50	278
9	B	13528.58	13848.77	286	4.67	0.03	22.74	0	0	9.76	286
10	A	6545.07	7198.02	237	6.33	0.03	25.14	0	0	0.00	237
11	A	23973.97	24859.23	320	24.00	0.03	24.94	0	0	24.60	320
12	B	31669.00	35490.64	431	6.67	0.02	36.84	0	0	71.90	431
13	A	22345.92	23260.56	330	24.00	0.02	30.78	0	0	20.60	330
14	B	16857.63	17469.55	324	4.67	0.03	25.25	0	0	16.80	324
15	B	23716.96	.	257	36.00	.	.	0	0	141.00	257
16	A	19936.21	21987.85	344	8.00	0.02	40.29	0	0	35.30	344
17	B	20280.10	.	253	7.00	.	.	0	0	72.60	253
18	A	15743.59	17196.23	249	6.67	0.02	37.02	0	0	27.20	249
19	B	15224.02	15795.70	513	5.67	0.04	18.87	0	0	0.00	513
20	A	15363.11	15748.75	1290	6.00	0.04	18.31	0	0	0.00	1290
21	A	8821.85	9175.90	291	4.67	0.04	19.79	0	0	0.00	291
22	B	23741.00	24310.25	370	4.67	0.03	21.44	0	0	18.40	370
23	A	22815.34	24452.98	696	6.33	0.02	35.14	0	0	32.30	696
24	B	21643.21	22322.72	529	5.33	0.03	26.02	0	0	18.10	529

Obs	TREAT	AUCT	AUCI	CMAX	TMAX	KE	THALF	KE_FIRST	KE_LAST	CLAST	NEWCMAX
25	B	14968.25	15688.46	327	4.33	0.02	29.37	0	0	17.00	327
26	A	17537.44	18360.79	277	5.33	0.03	26.92	0	0	21.20	277
27	B	25249.63	25539.07	1070	5.00	0.03	20.86	0	0	9.62	1070
28	A	29414.23	30030.00	911	5.00	0.03	24.39	0	0	17.50	911
29	A	14897.30	15196.56	420	6.00	0.03	23.25	0	0	8.92	420
30	B	17091.30	17301.96	374	9.00	0.03	19.92	0	0	7.33	374
31	B	14782.02	16086.37	518	5.00	0.03	23.98	0	0	.	518
32	A	24545.89	24989.35	684	5.00	0.03	22.27	0	0	13.80	684
33	A	25582.70	26869.20	395	6.00	0.02	30.54	0	0	29.20	395
34	B	24585.63	25535.27	428	24.00	0.02	27.89	0	0	23.60	428
35	A	45546.43	47362.27	1740	10.00	0.02	30.11	0	0	41.80	1740
36	B	24586.12	25598.87	561	4.33	0.02	28.89	0	0	24.30	561
37	B	23426.61	23612.99	851	6.33	0.04	19.72	0	0	6.55	851
38	A	22246.34	22785.12	392	24.00	0.03	23.79	0	0	15.70	392
39	A	16234.61	17738.10	439	4.67	0.02	36.31	0	0	28.70	439
40	B	20972.60	22294.07	426	6.67	0.02	30.13	0	0	30.40	426
41	B	17942.69	18156.13	339	9.00	0.03	20.32	0	0	7.28	339
42	A	13835.88	14668.11	338	4.67	0.03	20.17	0	0	0.00	338
43	A	19194.95	19651.23	1670	5.67	0.04	19.17	0	0	0.00	1670
44	B	18536.23	19107.01	538	5.33	0.04	17.43	0	0	0.00	538
45	A	15869.23	16055.65	704	5.00	0.03	21.01	0	0	6.15	704
46	B	19128.68	19803.94	545	5.33	0.03	27.53	0	0	17.00	545
47	A	12663.73	13179.75	632	5.00	0.02	29.81	0	0	12.00	632
48	B	16472.84	17399.25	557	5.00	0.02	29.19	0	0	22.00	557
49	B	27037.56	27443.40	818	5.00	0.03	21.64	0	0	13.00	818
50	A	21991.22	25982.45	547	4.67	0.03	23.05	0	0	.	547
51	B	25403.84	26235.84	406	24.00	0.03	26.58	0	0	21.70	406
52	A	28148.06	28728.19	540	10.00	0.03	23.52	0	0	17.10	540
53	A	19696.86	20160.75	348	10.00	0.03	23.47	0	0	13.70	348
54	B	22171.00	22789.15	427	10.00	0.03	24.77	0	0	17.30	427
55	A	16893.00	19264.03	279	5.33	0.02	39.13	0	0	42.00	279
56	B	19960.58	22194.18	257	5.00	0.02	35.59	0	0	43.50	257
57	B	17729.43	18117.51	1210	5.67	0.04	16.30	0	0	0.00	1210
58	A	8879.78	9109.45	286	9.00	0.04	16.26	0	0	0.00	286
59	B	24488.53	30785.31	282	5.33	0.01	52.97	0	0	82.40	282
60	A	18887.35	20842.62	202	48.00	0.02	33.71	0	0	40.20	202
61	A	7037.58	7796.25	196	6.33	0.03	27.11	0	0	0.00	196
62	B	14147.38	14513.65	338	4.67	0.03	23.95	0	0	10.60	338

Obs	TREAT	AUCT	AUCI	CMAX	TMAX	KE	THALF	KE_FIRST	KE_LAST	CLAST	NEWCMAX
63	A	13331.56	13613.98	282	5.33	0.03	22.90	0	0	8.55	282
64	B	17657.88	18034.19	490	5.33	0.06	12.19	0	0	0.00	490
65	B	7442.70	7774.27	206	5.00	0.04	17.02	0	0	0.00	206
66	A	5552.71	5834.46	192	1.33	0.03	20.51	0	0	0.00	192
67	A	18853.62	18981.97	501	6.67	0.04	16.29	0	0	5.46	501
68	B	14403.85	14580.70	370	5.00	0.04	18.38	0	0	6.67	370
69	A	13514.59	13696.40	281	5.00	0.03	20.69	0	0	6.09	281
70	B	11953.79	12854.23	397	5.00	0.03	22.86	0	0	0.00	397
71	B	16972.83	17854.48	242	4.33	0.02	28.03	0	0	21.80	242
72	A	22860.71	24732.96	697	8.00	0.02	39.33	0	0	33.00	697
73	A	16461.62	16663.01	912	5.33	0.03	23.82	0	0	5.86	912
74	B	11486.66	11721.42	838	5.33	0.04	19.61	0	0	0.00	838
75	B	10351.59	10957.28	499	5.67	0.03	20.89	0	0	0.00	499
76	A	10106.93	10510.03	645	5.33	0.04	16.73	0	0	.	645
77	A	35304.67	36301.51	540	6.67	0.03	25.03	0	0	27.60	540
78	B	42742.80	45370.36	784	4.67	0.02	29.66	0	0	61.40	784
79	B	14113.77	15303.38	633	5.33	0.02	36.98	0	0	22.30	633
80	A	13260.89	14937.63	521	5.33	0.02	43.37	0	0	26.80	521
81	A	17879.77	18487.85	305	4.67	0.03	25.54	0	0	16.50	305
82	B	11123.24	11557.67	396	4.67	0.04	17.41	0	0	0.00	396
83	A	10020.84	10795.50	258	5.67	0.03	22.56	0	0	0.00	258
84	B	14302.32	14583.71	322	5.33	0.03	23.70	0	0	8.23	322
85	B	15599.80	15909.98	305	10.00	0.03	24.00	0	0	8.96	305
86	A	14481.20	15664.94	333	5.33	0.03	22.12	0	0	0.00	333
87	A	5676.68	6058.28	317	5.00	0.03	21.68	0	0	0.00	317
88	B	5793.05	6333.92	116	0.67	0.02	37.98	0	0	9.87	116
89	B	15871.97	16068.41	372	5.67	0.03	21.55	0	0	6.32	372
90	A	16054.06	16246.35	370	10.00	0.03	20.51	0	0	6.50	370
91	B	6837.86	7108.10	307	5.00	0.02	32.46	0	0	5.77	307
92	A	17182.64	17374.74	487	9.00	0.03	22.38	0	0	5.95	487
93	B	30677.26	40190.49	973	5.00	0.02	44.26	0	0	.	973
94	A	34551.16	40365.16	481	6.33	0.01	46.22	0	0	87.20	481
95	A	11945.88	12433.54	487	5.33	0.04	17.51	0	0	0.00	487
96	B	14727.71	15003.97	1080	5.00	0.03	26.63	0	0	7.19	1080
97	B	27580.61	27997.02	529	5.00	0.03	20.92	0	0	13.80	529
98	A	22061.82	22589.68	494	5.00	0.03	24.07	0	0	15.20	494
99	A	31874.44	35097.92	521	5.67	0.02	34.11	0	0	65.50	521
100	B	51849.80	52954.49	1520	6.00	0.03	21.63	0	0	35.40	1520

Obs	TREAT	AUCT	AUCI	CMAX	TMAX	KE	THALF	KE_FIRST	KE_LAST	CLAST	NEWCMAX
101	A	17242.61	17641.39	554	5.00	0.03	21.94	0	0	12.60	554
102	B	16404.53	16855.19	669	5.33	0.03	23.66	0	0	13.20	669
103	B	15671.07	16306.58	325	4.33	0.03	25.46	0	0	17.30	325
104	A	21675.29	22975.20	398	2.67	0.02	32.53	0	0	27.70	398
105	A	11170.26	11492.06	289	4.67	0.04	18.13	0	0	0.00	289
106	B	9773.11	9904.91	346	10.00	0.05	15.30	0	0	0.00	346
107	B	12418.13	12991.94	885	5.33	0.04	19.79	0	0	0.00	885
108	A	7487.84	7660.57	189	1.67	0.05	14.34	0	0	0.00	189
109	B	12390.56	12701.84	417	7.00	0.03	26.70	0	0	8.08	417
110	A	9327.58	9941.34	220	5.00	0.04	19.16	0	0	0.00	220
111	A	9315.52	9447.52	455	5.00	0.05	14.73	0	0	0.00	455
112	B	12471.16	12667.20	573	5.33	0.05	14.20	0	0	0.00	573
113	A	21068.90	21446.63	721	5.67	0.03	23.80	0	0	11.00	721
114	B	25277.17	25560.40	529	5.00	0.04	19.44	0	0	10.10	529
115	B	11418.60	11750.94	248	4.67	0.03	23.39	0	0	9.85	248
116	A	14507.78	14911.07	258	10.00	0.03	24.31	0	0	11.50	258
117	B	18842.76	23300.27	201	24.00	0.01	57.32	0	0	53.90	201
118	A	18827.08	23012.76	211	24.00	0.01	49.34	0	0	58.80	211

ORIGINAL DATA SUBMITTED

The GLM Procedure

Class Level Information		
Class	**Levels**	**Values**
SUB	59	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 60
TRT	2	1 2
PER	2	1 2
SEQ	2	1 2

Number of observations	118

Dependent Variables With Equivalent Missing Value Patterns		
Pattern	**Obs**	**Dependent Variables**
1	118	AUCT CMAX LAUCT LCMAX
2	116	AUCI LAUCI

NOTE: Variables in each group are consistent with respect to the presence or absence of missing values.

ORIGINAL DATA SUBMITTED

The GLM Procedure

Dependent Variable: AUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	60	6221145989	103685766	5.71	<.0001
Error	57	1035452308	18165830		
Corrected Total	117	7256598297			

R-Square	Coeff Var	Root MSE	AUCT Mean
0.857309	23.42759	4262.139	18192.82

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	20478136	20478136	1.13	0.2928
SUB(SEQ)	57	6154065800	107966067	5.94	<.0001
PER	1	11865582	11865582	0.65	0.4223
TRT	1	34736472	34736472	1.91	0.1721

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	20478136	20478136	1.13	0.2928
SUB(SEQ)	57	6154065800	107966067	5.94	<.0001
PER	1	11184050	11184050	0.62	0.4359
TRT	1	34736472	34736472	1.91	0.1721

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	20478135.84	20478135.84	0.19	0.6648

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-1085.28608	784.836160	-1.38	0.1721

ORIGINAL DATA SUBMITTED

The GLM Procedure

Dependent Variable: CMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	60	6407537.25	106792.29	1.64	0.0308
Error	57	3709532.10	65079.51		
Corrected Total	117	10117069.36			

R-Square	Coeff Var	Root MSE	CMAX Mean
0.633339	52.46551	255.1069	486.2373

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	63527.109	63527.109	0.98	0.3273
SUB(SEQ)	57	6254928.247	109735.583	1.69	0.0254
PER	1	57112.000	57112.000	0.88	0.3528
TRT	1	31969.896	31969.896	0.49	0.4862

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	63527.109	63527.109	0.98	0.3273
SUB(SEQ)	57	6254928.247	109735.583	1.69	0.0254
PER	1	58553.049	58553.049	0.90	0.3469
TRT	1	31969.896	31969.896	0.49	0.4862

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	63527.10938	63527.10938	0.58	0.4499

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-32.9247126	46.9757282	-0.70	0.4862

ORIGINAL DATA SUBMITTED

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	60	18.44208643	0.30736811	5.59	<.0001
Error	57	3.13489531	0.05499816		
Corrected Total	117	21.57698174			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.854711	2.412669	0.234517	9.720226

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.01399180	0.01399180	0.25	0.6159
SUB(SEQ)	57	18.24703906	0.32012349	5.82	<.0001
PER	1	0.01738060	0.01738060	0.32	0.5762
TRT	1	0.16367497	0.16367497	2.98	0.0899

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.01399180	0.01399180	0.25	0.6159
SUB(SEQ)	57	18.24703906	0.32012349	5.82	<.0001
PER	1	0.01561487	0.01561487	0.28	0.5962
TRT	1	0.16367497	0.16367497	2.98	0.0899

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.01399180	0.01399180	0.04	0.8351

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.07449764	0.04318426	-1.73	0.0899

ORIGINAL DATA SUBMITTED

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	60	22.14819186	0.36913653	2.43	0.0005
Error	57	8.65991341	0.15192831		
Corrected Total	117	30.80810526			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.718908	6.445985	0.389780	6.046862

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.25155023	0.25155023	1.66	0.2034
SUB(SEQ)	57	21.51038164	0.37737512	2.48	0.0004
PER	1	0.11023415	0.11023415	0.73	0.3979
TRT	1	0.27602584	0.27602584	1.82	0.1830

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.25155023	0.25155023	1.66	0.2034
SUB(SEQ)	57	21.51038164	0.37737512	2.48	0.0004
PER	1	0.11619396	0.11619396	0.76	0.3855
TRT	1	0.27602584	0.27602584	1.82	0.1830

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.25155023	0.25155023	0.67	0.4176

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.09674449	0.07177459	-1.35	0.1830

ORIGINAL DATA SUBMITTED

The GLM Procedure
Least Squares Means

TRT	AUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	17643.1158	554.9630	<.0001	-1.38	0.1721
2	18728.4019	554.9630	<.0001		

TRT	CMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	469.381609	33.216856	<.0001	-0.70	0.4862
2	502.306322	33.216856	<.0001		

TRT	LAUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	9.68279300	0.03053588	<.0001	-1.73	0.0899
2	9.75729064	0.03053588	<.0001		

TRT	LCMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	5.99770676	0.05075230	<.0001	-1.35	0.1830
2	6.09445125	0.05075230	<.0001		

ORIGINAL DATA SUBMITTED

The GLM Procedure
Least Squares Means

SEQ	AUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	18602.4042	550.2398	<.0001	1.06	0.2928
2	17769.1134	559.6463	<.0001		

SEQ	CMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	509.050000	32.934154	<.0001	0.99	0.3273
2	462.637931	33.497172	<.0001		

SEQ	LAUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	9.73093257	0.03027600	<.0001	0.50	0.6159
2	9.70915106	0.03079357	<.0001		

SEQ	LCMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	6.09225686	0.05032036	<.0001	1.29	0.2034
2	5.99990115	0.05118060	<.0001		

PER	AUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	17877.8509	554.9630	<.0001	-0.78	0.4359
2	18493.6668	554.9630	<.0001		

PER	CMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	508.122989	33.216856	<.0001	0.95	0.3469
2	463.564943	33.216856	<.0001		

ORIGINAL DATA SUBMITTED

The GLM Procedure
Least Squares Means

PER	LAUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	9.70853671	0.03053588	<.0001	-0.53	0.5962
2	9.73154692	0.03053588	<.0001		

PER	LCMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	6.07746336	0.05075230	<.0001	0.87	0.3855
2	6.01469465	0.05075230	<.0001		

TRT	AUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	17643.1158	554.9630	<.0001	-1.38	0.1721
2	18728.4019	554.9630	<.0001		

TRT	CMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	469.381609	33.216856	<.0001	-0.70	0.4862
2	502.306322	33.216856	<.0001		

TRT	LAUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	9.68279300	0.03053588	<.0001	-1.73	0.0899
2	9.75729064	0.03053588	<.0001		

TRT	LCMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	5.99770676	0.05075230	<.0001	-1.35	0.1830
2	6.09445125	0.05075230	<.0001		

ORIGINAL DATA SUBMITTED

The GLM Procedure

Dependent Variable: AUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	60	7490990239	124849837	6.48	<.0001
Error	55	1060098977	19274527		
Corrected Total	115	8551089216			

R-Square	Coeff Var	Root MSE	AUCI Mean
0.876028	22.88939	4390.276	19180.40

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	5208711	5208711	0.27	0.6053
SUB(SEQ)	57	7439383498	130515500	6.77	<.0001
PER	1	22007092	22007092	1.14	0.2899
TRT	1	24390938	24390938	1.27	0.2655

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	4524088	4524088	0.23	0.6300
SUB(SEQ)	57	7439476822	130517137	6.77	<.0001
PER	1	19578299	19578299	1.02	0.3179
TRT	1	24390938	24390938	1.27	0.2655

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	4524088.455	4524088.455	0.03	0.8530

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-926.390664	823.515511	-1.12	0.2655

ORIGINAL DATA SUBMITTED

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	60	19.35345349	0.32255756	6.04	<.0001
Error	55	2.93634452	0.05338808		
Corrected Total	115	22.28979800			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.868265	2.365594	0.231059	9.767468

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.00168410	0.00168410	0.03	0.8597
SUB(SEQ)	57	19.20382706	0.33690925	6.31	<.0001
PER	1	0.03628980	0.03628980	0.68	0.4132
TRT	1	0.11165252	0.11165252	2.09	0.1538

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.00021098	0.00021098	0.00	0.9501
SUB(SEQ)	57	19.20990115	0.33701581	6.31	<.0001
PER	1	0.02980742	0.02980742	0.56	0.4581
TRT	1	0.11165252	0.11165252	2.09	0.1538

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.00021098	0.00021098	0.00	0.9801

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.06267786	0.04334131	-1.45	0.1538

ORIGINAL DATA SUBMITTED

The GLM Procedure
Least Squares Means

TRT	AUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	18722.4380	571.6474	<.0001	-1.12	0.2655
2	19648.8287	592.7875	<.0001		

TRT	LAUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	9.73844822	0.03008559	<.0001	-1.45	0.1538
2	9.80112608	0.03119819	<.0001		

ORIGINAL DATA SUBMITTED

The GLM Procedure
Least Squares Means

SEQ	AUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	19385.1208	566.7822	<.0001	0.48	0.6300
2	18986.1460	597.4409	<.0001		

SEQ	LAUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	9.77114944	0.02982954	<.0001	0.06	0.9501
2	9.76842486	0.03144309	<.0001		

PER	AUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	18770.6436	592.7875	<.0001	-1.01	0.3179
2	19600.6231	571.6474	<.0001		

PER	LAUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	9.75359472	0.03119819	<.0001	-0.75	0.4581
2	9.78597958	0.03008559	<.0001		

TRT	AUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	18722.4380	571.6474	<.0001	-1.12	0.2655
2	19648.8287	592.7875	<.0001		

TRT	LAUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	9.73844822	0.03008559	<.0001	-1.45	0.1538
2	9.80112608	0.03119819	<.0001		

Mean Plasma Raloxifene Levels for Test & Reference Products

	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
Time (hr)					
0	0.29	768.11	0.00	.	.
0.333	42.12	93.50	83.00	87.49	0.51
0.667	117.75	46.77	163.71	34.59	0.72
1	124.86	37.93	160.38	33.93	0.78
1.333	130.33	43.56	162.84	36.80	0.80
1.667	144.31	45.81	169.65	40.73	0.85
2	142.71	48.76	169.03	39.68	0.84
2.333	154.88	46.97	174.17	42.44	0.89
2.667	158.61	48.59	173.63	45.32	0.91
3	162.18	51.50	175.62	43.65	0.92
3.333	167.23	53.15	172.73	45.54	0.97
3.667	173.75	55.97	185.46	60.96	0.94
4	178.22	63.51	186.72	55.45	0.95
4.333	200.13	57.83	221.68	49.69	0.90
4.667	277.73	49.32	315.43	58.31	0.88
5	347.18	55.61	398.20	59.23	0.87
5.333	340.86	52.37	403.94	59.85	0.84
5.667	347.81	74.44	364.83	63.25	0.95
6	336.71	76.44	348.99	67.15	0.96
6.333	329.10	69.16	330.50	67.40	1.00
6.667	316.43	65.22	316.98	56.27	1.00
7	305.54	60.19	301.42	55.13	1.01
8	267.96	55.92	281.43	55.55	0.95
9	270.97	61.56	283.17	57.68	0.96
10	306.92	76.07	301.31	55.10	1.02
12	253.84	59.56	258.50	52.91	0.98
16	233.25	45.57	241.39	44.49	0.97
24	256.69	43.79	264.93	41.27	0.97
36	200.47	43.41	212.47	43.07	0.94
48	171.58	45.35	186.72	49.61	0.92
72	101.65	59.39	109.00	63.13	0.93
96	53.98	76.51	62.99	76.67	0.86
144	17.42	112.38	19.68	128.13	0.89

UNIT: Plasma Level=pg/mL Time=hrs

ARITHMETIC MEANS AND RATIOS

	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
PARAMETER					
AUCT	17644.96	44.03	18740.68	42.73	0.94
AUCI	18718.79	45.03	19658.22	45.11	0.95
CMAX	470.15	66.92	502.32	54.49	0.94
TMAX	8.33	97.46	6.92	84.70	1.20
KE	0.03	28.26	0.03	29.18	0.98
THALF	26.57	34.11	25.91	33.12	1.03
LAUCT	16039.06	0.00	17286.31	0.00	0.93
LAUCI	16952.95	0.00	17993.52	0.00	0.94
LCMAX	403.03	0.13	443.50	0.11	0.91

UNIT: AUC=pg hr/mL CMAX=pg/mL TMAX=hr
Log-transformed Data Were Converted To Anti-log In The Table

ORIGINAL DATA SUBMITTED

	Test LS Mean	Ref LS Mean	Ratio LS Means	Lower 90% CI	Upper 90% CI
PARAMETER					
AUCT	17643.12	18728.40	0.94	87.20	101.21
AUCI	18722.44	19648.83	0.95	88.15	102.42
CMAX	469.38	502.31	0.93	77.81	109.08
LAUCT	16039.23	17279.75	0.93	86.36	99.77
LAUCI	16957.21	18054.06	0.94	87.24	101.12
LCMAX	402.50	443.39	0.91	80.51	102.35

b. SAS data for fed study:

Obs	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15	C16
1	0	82.20	295.00	330.00	261.00	222.0	200.0	144.0	116.0	94.0	95.7	60.6	39.4	41.0	51.7	54.1
2	0	8.81	132.00	236.00	256.00	214.0	182.0	150.0	111.0	92.1	88.8	66.6	72.8	75.8	72.2	67.8
3	0	3.39	37.20	77.50	92.50	119.0	326.0	389.0	232.0	168.0	133.0	67.8	50.4	37.8	28.2	24.2
4	0	80.20	327.00	361.00	328.00	216.0	149.0	94.3	54.8	49.7	47.0	40.3	36.7	52.3	61.0	58.9
5	0	0.00	4.86	11.00	48.90	246.0	266.0	212.0	171.0	120.0	126.0	83.7	62.2	64.4	57.7	57.1
6	0	0.00	5.47	43.90	102.00	211.0	179.0	166.0	174.0	122.0	126.0	69.6	47.3	38.0	32.4	35.3
7	0	0.00	7.86	25.40	58.70	98.4	101.0	90.8	76.2	69.3	109.0	65.7	52.7	37.9	27.9	21.6
8	0	16.50	148.00	225.00	227.00	148.0	104.0	65.1	50.2	37.5	29.1	20.3	16.5	14.1	17.8	28.5
9	0	3.88	120.00	242.00	309.00	351.0	266.0	205.0	135.0	101.0	77.0	48.8	37.4	35.4	43.3	49.5
10	0	0.00	17.90	78.40	257.00	311.0	261.0	205.0	173.0	150.0	96.5	59.6	41.8	35.2	29.4	27.5
11	0	12.00	220.00	323.00	209.00	146.0	102.0	66.0	44.0	32.6	32.9	21.5	26.1	34.1	31.9	29.7
12	0	195.00	433.00	321.00	205.00	140.0	112.0	70.8	50.9	38.4	29.6	17.7	14.2	15.0	25.9	28.8
13	0	0.00	7.12	105.00	293.00	187.0	134.0	116.0	86.4	60.9	54.6	29.5	21.2	14.5	11.9	12.8
14	0	0.00	0.00	0.00	7.47	39.5	102.0	124.0	133.0	121.0	131.0	89.5	62.5	56.0	46.4	43.8
15	0	0.00	2.88	15.20	254.00	354.0	334.0	280.0	219.0	165.0	140.0	110.0	96.7	78.6	70.5	72.4
16	0	3.13	51.40	132.00	282.00	263.0	232.0	181.0	140.0	104.0	110.0	74.4	59.1	55.1	56.3	51.2
17	0	3.23	103.00	268.00	352.00	295.0	217.0	153.0	103.0	80.3	71.3	62.0	61.6	57.2	47.9	41.6
18	0	49.00	246.00	337.00	378.00	260.0	160.0	114.0	90.6	83.9	129.0	126.0	115.0	105.0	93.1	115.0
19	0	187.00	679.00	602.00	435.00	341.0	247.0	157.0	124.0	111.0	112.0	117.0	123.0	119.0	132.0	142.0
20	0	24.10	194.00	384.00	434.00	414.0	413.0	406.0	307.0	266.0	231.0	170.0	137.0	107.0	101.0	100.0
21	0	0.00	13.30	77.60	160.00	278.0	384.0	423.0	303.0	228.0	193.0	128.0	83.7	70.6	49.5	45.6
22	0	3.23	738.00	523.00	324.00	276.0	240.0	180.0	140.0	127.0	105.0	73.8	55.6	38.2	31.3	31.0
23	0	34.30	104.00	150.00	261.00	305.0	279.0	342.0	285.0	224.0	167.0	114.0	72.5	60.4	46.2	43.7
24	0	0.00	0.00	5.60	22.80	51.8	127.0	211.0	216.0	205.0	173.0	97.8	66.5	48.8	43.2	41.8
25	0	164.00	449.00	510.00	502.00	416.0	346.0	269.0	214.0	182.0	169.0	117.0	101.0	79.9	77.0	77.0
26	0	219.00	921.00	996.00	735.00	495.0	349.0	243.0	190.0	159.0	166.0	162.0	150.0	142.0	148.0	168.0
27	0	26.90	126.00	131.00	150.00	144.0	133.0	163.0	158.0	135.0	115.0	83.3	68.7	86.8	94.7	88.6
28	0	8.84	27.00	37.70	109.00	258.0	218.0	151.0	136.0	142.0	146.0	125.0	93.6	83.0	85.4	80.6

ORIGINAL DATA SUBMITTED

Obs	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15	C16
29	0	0.00	38.20	60.40	123.00	147.0	178.0	211.0	204.0	195.0	216.0	133.0	118.0	118.0	105.0	95.4
30	0	0.00	2.93	44.00	182.00	181.0	190.0	128.0	113.0	120.0	202.0	141.0	104.0	80.6	75.4	59.1
31	0	0.00	13.40	99.50	170.00	165.0	138.0	114.0	79.9	53.0	51.4	32.5	24.4	29.1	34.7	41.9
32	0	77.20	208.00	202.00	132.00	96.0	84.5	57.3	42.9	34.9	32.7	22.6	18.5	13.2	12.9	14.6
33	0	0.00	18.80	194.00	413.00	460.0	341.0	256.0	193.0	154.0	114.0	76.3	54.9	41.5	42.9	48.3
34	0	0.00	25.90	251.00	461.00	417.0	303.0	234.0	182.0	136.0	108.0	78.5	54.2	38.6	30.5	26.4
35	0	0.00	0.00	0.00	0.00	2.8	141.0	377.0	413.0	434.0	344.0	205.0	156.0	146.0	129.0	129.0
36	0	0.00	0.00	0.00	2.43	39.8	85.6	215.0	164.0	313.0	332.0	210.0	182.0	199.0	205.0	202.0
37	0	0.00	20.60	124.00	249.00	273.0	210.0	147.0	121.0	97.4	90.0	53.4	38.7	29.8	33.2	55.6
38	0	58.60	301.00	322.00	258.00	163.0	106.0	71.4	47.9	37.3	34.0	21.8	17.2	17.0	16.5	22.4
39	0	328.00	613.00	467.00	322.00	252.0	172.0	110.0	85.5	66.3	53.3	34.4	32.3	30.3	30.8	38.3
40	0	37.50	94.70	152.00	286.00	362.0	426.0	344.0	298.0	241.0	206.0	139.0	103.0	79.5	61.4	54.8
41	0	0.00	5.76	191.00	264.00	242.0	274.0	240.0	185.0	150.0	142.0	102.0	86.8	90.0	119.0	128.0
42	0	0.00	18.90	123.00	235.00	234.0	220.0	200.0	185.0	165.0	149.0	107.0	88.7	66.6	48.3	47.5
43	0	2.58	129.00	555.00	618.00	427.0	294.0	218.0	169.0	135.0	133.0	114.0	117.0	159.0	150.0	156.0
44	0	0.00	15.20	290.00	672.00	441.0	302.0	236.0	159.0	125.0	115.0	102.0	109.0	124.0	125.0	126.0
45	0	0.00	4.14	38.30	116.00	143.0	144.0	138.0	122.0	125.0	146.0	110.0	80.9	66.2	47.2	42.3
46	0	0.00	91.20	212.00	172.00	146.0	135.0	118.0	110.0	90.7	83.7	57.3	39.6	32.3	30.4	26.2
47	0	0.00	0.00	51.10	260.00	179.0	122.0	91.1	60.5	42.1	43.0	22.9	18.2	15.5	17.2	22.4
48	0	216.00	445.00	384.00	240.00	132.0	90.2	64.0	37.7	31.2	35.1	39.0	47.2	47.5	45.6	47.0
49	0	2.37	7.81	41.30	430.00	304.0	219.0	153.0	106.0	79.9	74.7	51.0	38.5	33.1	32.6	32.3
50	0	2.26	31.80	86.10	234.00	244.0	206.0	143.0	133.0	97.0	73.2	45.8	38.3	29.5	25.5	24.7
51	0	35.60	296.00	321.00	247.00	179.0	150.0	128.0	92.7	75.9	65.8	43.7	35.0	29.7	27.3	24.6
52	0	25.80	260.00	308.00	192.00	155.0	122.0	103.0	79.0	75.6	108.0	84.9	80.5	87.2	80.7	89.2
53	0	65.00	305.00	363.00	271.00	219.0	135.0	101.0	64.3	59.4	57.4	42.0	37.4	32.5	26.3	26.5
54	0	4.61	27.40	138.00	274.00	215.0	140.0	97.4	73.5	79.1	70.1	43.9	25.4	20.0	15.3	20.1
55	0	0.00	5.94	38.00	165.00	236.0	234.0	265.0	302.0	349.0	374.0	351.0	290.0	279.0	258.0	234.0
56	0	35.00	192.00	400.00	538.00	402.0	346.0	265.0	212.0	183.0	195.0	164.0	138.0	138.0	128.0	106.0
57	0	2.90	30.60	60.90	76.50	159.0	209.0	155.0	151.0	121.0	133.0	88.9	62.9	44.9	36.0	33.7
58	0	19.60	118.00	142.00	152.00	186.0	195.0	197.0	133.0	112.0	138.0	119.0	103.0	66.7	48.9	42.2
59	0	0.00	77.80	316.00	252.00	182.0	122.0	84.1	56.3	44.8	42.4	42.6	50.3	53.6	59.0	61.0
60	0	0.00	22.20	81.40	177.00	189.0	193.0	228.0	176.0	148.0	130.0	80.2	60.4	42.1	36.4	30.2
61	0	186.00	366.00	344.00	270.00	219.0	147.0	89.6	56.0	41.8	34.6	30.2	31.6	31.3	32.9	40.0
62	0	0.00	23.40	39.70	113.00	269.0	332.0	338.0	250.0	215.0	203.0	119.0	87.0	69.0	56.7	53.1
63	0	2.32	27.60	113.00	342.00	381.0	293.0	230.0	169.0	153.0	148.0	165.0	176.0	170.0	170.0	137.0
64	0	0.00	168.00	444.00	523.00	469.0	341.0	252.0	161.0	127.0	116.0	99.8	117.0	130.0	115.0	105.0
65	0	2.03	40.40	324.00	493.00	381.0	248.0	156.0	99.0	66.0	49.4	37.9	33.6	28.5	31.7	49.0
66	0	0.00	5.62	90.50	288.00	303.0	293.0	234.0	158.0	122.0	87.1	51.0	34.7	27.0	26.1	28.7
67	0	5.60	19.80	78.40	167.00	161.0	131.0	84.9	59.2	43.5	41.5	29.1	18.7	18.2	20.9	25.6
68	0	5.47	54.40	97.90	129.00	143.0	120.0	93.2	65.3	51.4	45.6	43.0	35.3	34.6	37.3	38.8

ORIGINAL DATA SUBMITTED

Obs	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15	C16
69	0	0.00	0.00	60.00	168.00	218.0	320.0	329.0	317.0	295.0	270.0	163.0	123.0	93.9	86.6	76.3
70	0	0.00	189.00	438.00	574.00	465.0	400.0	448.0	307.0	277.0	218.0	159.0	112.0	102.0	92.7	87.0
71	0	18.40	152.00	335.00	303.00	230.0	141.0	92.2	62.3	46.6	35.5	22.0	19.4	18.7	25.1	31.9
72	0	8.05	300.00	309.00	180.00	113.0	72.9	51.8	36.6	26.7	26.7	18.9	14.2	13.4	19.1	35.1
73	0	8.18	85.10	183.00	248.00	185.0	163.0	123.0	100.0	91.3	96.8	79.1	61.0	52.7	48.3	51.3
74	0	5.35	141.00	249.00	284.00	204.0	164.0	101.0	86.5	69.0	69.8	45.3	33.1	29.6	35.7	41.6
75	0	96.40	316.00	367.00	256.00	200.0	138.0	109.0	80.8	65.5	52.1	31.3	23.7	22.8	30.4	37.4
76	0	13.40	202.00	314.00	265.00	110.0	144.0	94.7	67.1	50.7	42.5	27.3	24.1	18.6	18.0	17.9
77	0	0.00	195.00	213.00	158.00	140.0	122.0	84.9	78.1	60.1	60.5	53.3	49.8	46.6	53.5	53.6
78	0	22.00	85.20	145.00	200.00	159.0	97.2	78.7	53.6	48.0	45.7	35.4	37.1	40.8	51.7	62.6
79	0	22.80	519.00	623.00	632.00	487.0	273.0	195.0	147.0	111.0	91.8	66.6	47.1	34.6	35.9	33.2
80	0	0.00	74.20	303.00	405.00	358.0	272.0	193.0	154.0	129.0	111.0	81.8	58.2	49.8	49.3	55.8
81	0	71.50	368.00	301.00	203.00	127.0	79.0	51.3	40.5	33.9	32.0	20.6	17.8	19.5	28.7	39.0
82	0	4.09	102.00	150.00	209.00	232.0	194.0	201.0	158.0	135.0	139.0	89.7	63.7	52.5	46.5	49.1
83	0	0.00	10.70	45.90	100.00	148.0	283.0	232.0	189.0	159.0	144.0	89.7	80.3	70.2	71.4	62.3
84	0	0.00	0.00	5.76	35.70	128.0	303.0	291.0	204.0	164.0	127.0	75.2	56.0	44.7	37.7	34.3
85	0	43.20	207.00	333.00	303.00	248.0	181.0	127.0	83.1	70.3	66.2	40.0	30.6	24.7	19.2	14.8
86	0	9.78	136.00	214.00	202.00	185.0	139.0	129.0	94.8	80.7	80.2	45.8	31.8	24.6	19.3	20.3
87	0	39.40	236.00	291.00	282.00	246.0	225.0	185.0	158.0	199.0	235.0	164.0	132.0	103.0	99.6	110.0
88	0	6.06	92.80	229.00	309.00	353.0	314.0	202.0	151.0	107.0	91.2	70.5	63.3	59.8	72.2	94.4

Obs	C17	C18	C19	C20	C21	C22	C23	C24	C25	C26	T1	T2	T3	T4	T5	T6	T7	T8
1	72.00	80.0	54.0	64.8	46.40	32.50	22.10	10.70	6.40	5.89	0	0.33	0.67	1	1.5	2	2.5	3
2	60.30	46.3	48.7	42.8	40.90	14.80	16.20	8.67	3.25	0.00	0	0.33	0.67	1	1.5	2	2.5	3
3	30.50	62.3	48.6	39.1	28.30	29.40	21.90	18.40	3.89	0.00	0	0.33	0.67	1	1.5	2	2.5	3
4	54.00	48.2	39.2	35.1	32.10	18.90	18.90	17.40	7.39	2.05	0	0.33	0.67	1	1.5	2	2.5	3
5	58.70	69.0	50.7	56.2	52.60	27.40	18.60	5.85	0.00	0.00	0	0.33	0.67	1	1.5	2	2.5	3
6	48.40	54.7	40.1	42.2	37.80	27.00	6.79	2.19	0.00	0.00	0	0.33	0.67	1	1.5	2	2.5	3
7	24.50	57.7	45.4	30.1	35.10	28.80	40.80	21.80	23.20	7.19	0	0.33	0.67	1	1.5	2	2.5	3
8	49.50	70.7	46.7	32.6	34.50	19.90	16.40	9.15	5.74	3.06	0	0.33	0.67	1	1.5	2	2.5	3
9	60.10	53.5	47.9	39.7	22.10	18.70	20.20	11.30	3.55	0.00	0	0.33	0.67	1	1.5	2	2.5	3
10	26.80	28.0	24.5	18.7	7.18	5.80	6.25	3.42	2.92	0.00	0	0.33	0.67	1	1.5	2	2.5	3
11	27.40	35.1	24.6	26.7	32.10	24.20	15.80	7.59	2.62	0.00	0	0.33	0.67	1	1.5	2	2.5	3
12	36.00	52.2	41.6	41.7	39.20	62.70	36.80	15.50	4.97	0.00	0	0.33	0.67	1	1.5	2	2.5	3
13	20.10	28.8	27.0	37.6	52.00	4.40	2.61	0.00	0.00	0.00	0	0.33	0.67	1	1.5	2	2.5	3
14	26.40	44.0	38.5	44.3	49.30	26.30	28.10	18.80	3.18	3.10	0	0.33	0.67	1	1.5	2	2.5	3
15	86.60	95.0	77.3	87.9	92.10	35.90	34.60	25.30	8.52	3.97	0	0.33	0.67	1	1.5	2	2.5	3
16	55.40	88.4	61.8	45.2	47.20	46.60	35.30	21.30	8.58	5.67	0	0.33	0.67	1	1.5	2	2.5	3
17	37.90	78.7	50.5	44.6	32.70	16.60	23.50	24.70	20.40	14.00	0	0.33	0.67	1	1.5	2	2.5	3
18	84.50	61.6	43.0	44.6	38.20	18.40	14.40	15.30	16.80	15.10	0	0.33	0.67	1	1.5	2	2.5	3

ORIGINAL DATA SUBMITTED

Obs	C17	C18	C19	C20	C21	C22	C23	C24	C25	C26	T1	T2	T3	T4	T5	T6	T7	T8
19	160.00	134.0	151.0	168.0	148.00	34.70	29.80	8.80	0.00	0.00	0	0.33	0.67	1	1.5	2	2.5	3
20	102.00	109.0	98.1	156.0	67.90	20.70	17.10	4.36	0.00	0.00	0	0.33	0.67	1	1.5	2	2.5	3
21	37.60	22.2	57.6	72.7	94.40	21.70	26.10	12.30	8.04	6.58	0	0.33	0.67	1	1.5	2	2.5	3
22	33.50	24.5	24.9	56.3	81.10	36.50	30.30	19.90	9.86	0.00	0	0.33	0.67	1	1.5	2	2.5	3
23	41.80	63.9	51.0	49.0	45.20	33.30	20.00	9.38	4.61	2.02	0	0.33	0.67	1	1.5	2	2.5	3
24	41.90	48.7	41.2	35.4	38.20	21.80	19.20	9.77	2.58	0.00	0	0.33	0.67	1	1.5	2	2.5	3
25	111.00	128.0	102.0	98.6	94.80	41.50	53.00	34.60	36.20	11.20	0	0.33	0.67	1	1.5	2	2.5	3
26	165.00	180.0	142.0	177.0	171.00	97.00	57.20	21.70	7.61	3.60	0	0.33	0.67	1	1.5	2	2.5	3
27	88.20	84.7	86.8	87.1	67.10	41.00	19.30	3.39	0.00	0.00	0	0.33	0.67	1	1.5	2	2.5	3
28	68.80	83.6	65.4	48.7	41.20	14.70	11.80	2.46	0.00	0.00	0	0.33	0.67	1	1.5	2	2.5	3
29	95.30	96.3	53.1	37.4	51.90	10.70	2.96	0.00	0.00	0.00	0	0.33	0.67	1	1.5	2	2.5	3
30	53.70	58.2	48.0	21.1	32.00	12.40	10.60	3.22	0.00	0.00	0	0.33	0.67	1	1.5	2	2.5	3
31	64.30	56.9	60.8	56.2	55.10	24.90	28.60	7.20	0.00	0.00	0	0.33	0.67	1	1.5	2	2.5	3
32	32.20	40.2	40.8	41.2	52.80	26.70	25.00	17.00	9.85	5.12	0	0.33	0.67	1	1.5	2	2.5	3
33	45.20	64.9	59.2	57.7	74.40	33.30	27.60	12.20	6.70	0.00	0	0.33	0.67	1	1.5	2	2.5	3
34	18.40	52.3	54.8	51.2	55.20	22.30	23.60	9.79	2.97	0.00	0	0.33	0.67	1	1.5	2	2.5	3
35	186.00	149.0	114.0	104.0	102.00	67.00	49.00	11.30	0.00	0.00	0	0.33	0.67	1	1.5	2	2.5	3
36	190.00	169.0	136.0	107.0	107.00	78.00	46.80	25.40	15.10	4.22	0	0.33	0.67	1	1.5	2	2.5	3
37	61.80	118.0	81.3	34.6	60.70	31.60	21.70	12.00	4.36	0.00	0	0.33	0.67	1	1.5	2	2.5	3
38	38.10	90.0	52.8	42.0	48.70	21.00	14.10	3.10	0.00	0.00	0	0.33	0.67	1	1.5	2	2.5	3
39	49.90	67.0	53.4	58.3	58.10	31.20	32.10	22.40	12.40	5.01	0	0.33	0.67	1	1.5	2	2.5	3
40	45.80	70.5	55.1	83.7	68.40	20.20	28.60	15.50	9.00	4.82	0	0.33	0.67	1	1.5	2	2.5	3
41	132.00	88.7	68.9	62.0	47.60	2.84	3.30	0.00	0.00	0.00	0	0.33	0.67	1	1.5	2	2.5	3
42	49.80	57.8	37.8	36.9	57.00	15.70	7.93	0.00	0.00	0.00	0	0.33	0.67	1	1.5	2	2.5	3
43	165.00	136.0	108.0	104.0	127.00	66.40	82.70	34.40	16.40	8.14	0	0.33	0.67	1	1.5	2	2.5	3
44	113.00	126.0	113.0	106.0	126.00	80.20	130.00	38.90	11.40	4.53	0	0.33	0.67	1	1.5	2	2.5	3
45	36.20	47.5	55.2	47.4	48.90	28.50	29.40	22.60	11.20	6.62	0	0.33	0.67	1	1.5	2	2.5	3
46	23.90	44.9	53.2	47.7	66.40	35.00	35.70	21.80	9.95	9.13	0	0.33	0.67	1	1.5	2	2.5	3
47	38.60	63.8	38.6	30.5	40.30	37.90	20.00	10.90	7.11	2.59	0	0.33	0.67	1	1.5	2	2.5	3
48	39.70	59.5	49.9	50.4	63.00	58.70	35.70	12.60	3.09	2.29	0	0.33	0.67	1	1.5	2	2.5	3
49	42.30	54.1	49.0	32.6	35.10	35.30	15.20	3.47	0.00	0.00	0	0.33	0.67	1	1.5	2	2.5	3
50	29.40	41.1	31.0	28.1	31.70	9.60	24.30	2.41	0.00	0.00	0	0.33	0.67	1	1.5	2	2.5	3
51	39.60	45.7	42.4	58.4	43.00	22.00	17.20	6.99	0.00	0.00	0	0.33	0.67	1	1.5	2	2.5	3
52	79.90	90.9	56.0	40.6	29.40	18.00	22.70	12.00	3.63	0.00	0	0.33	0.67	1	1.5	2	2.5	3
53	33.20	65.8	59.5	46.1	42.10	44.40	34.80	22.00	16.00	15.60	0	0.33	0.67	1	1.5	2	2.5	3
54	32.60	78.3	49.9	46.6	27.80	35.90	29.20	24.00	20.00	16.20	0	0.33	0.67	1	1.5	2	2.5	3
55	212.00	205.0	124.0	138.0	191.00	59.70	34.30	10.80	6.16	0.00	0	0.33	0.67	1	1.5	2	2.5	3
56	129.00	99.9	78.4	70.1	119.00	49.90	25.20	5.57	3.17	0.00	0	0.33	0.67	1	1.5	2	2.5	3
57	20.90	34.5	45.4	67.5	60.60	20.00	17.00	7.45	0.00	0.00	0	0.33	0.67	1	1.5	2	2.5	3
58	36.50	36.0	51.6	50.1	45.90	11.20	8.08	2.46	0.00	0.00	0	0.33	0.67	1	1.5	2	2.5	3

ORIGINAL DATA SUBMITTED

Obs	C17	C18	C19	C20	C21	C22	C23	C24	C25	C26	T1	T2	T3	T4	T5	T6	T7	T8
59	58.40	49.1	36.6	43.8	43.20	34.70	26.80	10.20	3.65	0.00	0	0.33	0.67	1	1.5	2	2.5	3
60	40.10	36.5	24.7	49.7	68.90	42.60	25.80	7.77	3.20	0.00	0	0.33	0.67	1	1.5	2	2.5	3
61	54.10	59.1	42.0	40.1	23.40	11.40	15.60	11.40	5.14	2.58	0	0.33	0.67	1	1.5	2	2.5	3
62	65.00	82.6	56.5	38.4	46.60	32.20	37.10	31.00	9.79	3.64	0	0.33	0.67	1	1.5	2	2.5	3
63	77.30	80.6	77.8	86.1	54.20	23.50	15.20	8.72	3.23	0.00	0	0.33	0.67	1	1.5	2	2.5	3
64	107.00	70.5	63.2	49.3	42.50	33.20	13.10	2.57	0.00	0.00	0	0.33	0.67	1	1.5	2	2.5	3
65	58.70	70.6	59.1	38.7	48.20	14.60	9.73	3.45	2.40	0.00	0	0.33	0.67	1	1.5	2	2.5	3
66	50.50	57.7	38.1	30.4	35.70	17.30	18.20	11.00	7.89	3.19	0	0.33	0.67	1	1.5	2	2.5	3
67	46.90	56.4	31.6	24.1	35.80	27.70	17.60	15.90	20.10	14.50	0	0.33	0.67	1	1.5	2	2.5	3
68	53.00	67.0	46.5	27.0	38.10	49.70	14.10	22.50	14.90	9.60	0	0.33	0.67	1	1.5	2	2.5	3
69	77.40	86.6	92.5	85.0	36.90	15.80	9.46	3.73	0.00	0.00	0	0.33	0.67	1	1.5	2	2.5	3
70	83.20	115.0	108.0	107.0	116.00	74.90	38.20	16.10	8.13	0.00	0	0.33	0.67	1	1.5	2	2.5	3
71	43.00	65.5	42.9	43.2	34.10	13.60	19.20	12.60	7.02	4.01	0	0.33	0.67	1	1.5	2	2.5	3
72	51.40	69.9	45.2	26.2	44.60	25.70	38.20	17.80	15.50	8.41	0	0.33	0.67	1	1.5	2	2.5	3
73	54.40	48.2	41.5	41.4	38.60	22.60	13.30	5.12	3.13	0.00	0	0.33	0.67	1	1.5	2	2.5	3
74	53.10	56.9	38.4	40.7	34.90	5.83	5.06	0.00	0.00	0.00	0	0.33	0.67	1	1.5	2	2.5	3
75	46.80	80.7	60.6	45.5	37.20	7.48	5.85	2.80	0.00	0.00	0	0.33	0.67	1	1.5	2	2.5	3
76	30.60	70.4	57.5	37.6	48.00	9.99	3.86	0.00	0.00	0.00	0	0.33	0.67	1	1.5	2	2.5	3
77	52.70	92.4	97.9	92.5	22.20	8.52	3.43	0.00	0.00	0.00	0	0.33	0.67	1	1.5	2	2.5	3
78	79.50	68.5	67.7	74.2	61.80	13.70	12.50	0.00	0.00	0.00	0	0.33	0.67	1	1.5	2	2.5	3
79	60.90	94.1	68.2	52.4	86.70	43.70	48.20	13.30	6.42	3.45	0	0.33	0.67	1	1.5	2	2.5	3
80	82.30	97.7	81.1	57.1	69.40	31.10	34.70	26.90	17.70	11.30	0	0.33	0.67	1	1.5	2	2.5	3
81	62.70	84.3	54.0	44.4	51.30	33.60	22.80	13.40	8.35	3.57	0	0.33	0.67	1	1.5	2	2.5	3
82	50.70	96.3	66.6	47.1	54.20	28.30	14.70	13.80	6.32	4.61	0	0.33	0.67	1	1.5	2	2.5	3
83	48.90	39.7	37.1	61.2	70.90	34.70	23.60	14.30	8.92	5.31	0	0.33	0.67	1	1.5	2	2.5	3
84	26.10	40.8	36.5	55.4	67.70	33.00	29.80	16.60	9.49	4.61	0	0.33	0.67	1	1.5	2	2.5	3
85	9.51	44.6	40.9	30.0	42.60	34.10	36.90	20.90	13.50	10.70	0	0.33	0.67	1	1.5	2	2.5	3
86	28.40	42.0	29.3	20.4	27.20	29.80	19.30	15.20	11.40	8.70	0	0.33	0.67	1	1.5	2	2.5	3
87	133.00	132.0	127.0	110.0	113.00	51.30	38.60	12.90	6.68	3.09	0	0.33	0.67	1	1.5	2	2.5	3
88	89.40	91.0	70.2	76.8	68.30	22.80	32.70	16.20	9.74	5.61	0	0.33	0.67	1	1.5	2	2.5	3

Obs	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	T20	T21	T22	T23	T24	T25	T26	SUB	SEQ	PER
1	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	1	2	1
2	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	1	2	2
3	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	2	2	1
4	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	2	2	2
5	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	3	1	1
6	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	3	1	2
7	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	4	1	1
8	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	4	1	2

ORIGINAL DATA SUBMITTED

Obs	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	T20	T21	T22	T23	T24	T25	T26	SUB	SEQ	PER
9	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	5	2	1
10	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	5	2	2
11	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	6	1	1
12	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	6	1	2
13	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	7	2	1
14	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	7	2	2
15	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	8	1	1
16	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	8	1	2
17	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	9	1	1
18	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	9	1	2
19	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	10	1	1
20	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	10	1	2
21	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	11	2	1
22	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	11	2	2
23	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	12	2	1
24	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	12	2	2
25	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	13	2	1
26	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	13	2	2
27	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	14	2	1
28	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	14	2	2
29	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	15	1	1
30	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	15	1	2
31	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	16	1	1
32	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	16	1	2
33	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	17	1	1
34	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	17	1	2
35	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	18	1	1
36	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	18	1	2
37	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	19	2	1
38	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	19	2	2
39	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	20	2	1
40	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	20	2	2
41	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	22	1	1
42	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	22	1	2
43	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	23	2	1
44	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	23	2	2
45	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	24	2	1
46	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	24	2	2
47	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	25	1	1
48	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	25	1	2

ORIGINAL DATA SUBMITTED

Obs	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	T20	T21	T22	T23	T24	T25	T26	SUB	SEQ	PER
49	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	26	1	1
50	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	26	1	2
51	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	27	2	1
52	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	27	2	2
53	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	28	2	1
54	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	28	2	2
55	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	29	2	1
56	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	29	2	2
57	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	30	1	1
58	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	30	1	2
59	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	31	1	1
60	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	31	1	2
61	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	32	2	1
62	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	32	2	2
63	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	33	1	1
64	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	33	1	2
65	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	34	1	1
66	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	34	1	2
67	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	35	2	1
68	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	35	2	2
69	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	36	2	1
70	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	36	2	2
71	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	37	1	1
72	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	37	1	2
73	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	38	1	1
74	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	38	1	2
75	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	39	2	1
76	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	39	2	2
77	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	40	2	1
78	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	40	2	2
79	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	41	2	1
80	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	41	2	2
81	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	42	1	1
82	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	42	1	2
83	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	43	1	1
84	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	43	1	2
85	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	44	2	1
86	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	44	2	2

ORIGINAL DATA SUBMITTED

Obs	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	T20	T21	T22	T23	T24	T25	T26	SUB	SEQ	PER
87	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	45	2	1
88	3.5	4	4.5	5	5.5	6	6.5	7	8	10	12	16	24	36	48	72	96	120	45	2	2

Obs	TREAT	AUCT	AUCI	CMAX	TMAX	KE	THALF	KE_FIRST	KE_LAST	CLAST	NEWCMAX
1	B	3518.27	3777.09	330	1.00	0.02	30.46	0	0	5.89	330
2	A	2597.84	2694.96	256	1.50	0.03	20.71	0	0	0.00	256
3	B	2955.27	3079.44	389	3.00	0.03	22.12	0	0	0.00	389
4	A	2908.11	2954.12	361	1.00	0.04	15.56	0	0	2.05	361
5	A	2753.12	2883.47	266	2.50	0.04	15.44	0	0	0.00	266
6	B	2085.78	2120.69	211	2.00	0.06	11.05	0	0	0.00	211
7	A	3489.40	3824.75	109	4.50	0.02	32.33	0	0	7.19	109
8	B	2359.09	2496.40	227	1.50	0.02	31.10	0	0	3.06	227
9	B	2685.35	2783.36	351	2.00	0.04	19.14	0	0	0.00	351
10	A	1524.09	1745.44	311	2.00	0.01	52.54	0	0	0.00	311
11	A	2063.56	2135.45	323	1.00	0.04	19.02	0	0	0.00	323
12	B	3494.71	3614.34	433	0.70	0.04	16.68	0	0	0.00	433
13	B	1542.87	1563.81	293	1.50	0.12	5.56	0	0	0.00	293
14	A	2877.06	2978.78	133	3.50	0.03	22.75	0	0	3.10	133
15	A	5025.59	5151.23	354	2.00	0.03	21.94	0	0	3.97	354
16	B	4058.16	4275.19	282	1.50	0.03	26.53	0	0	5.67	282
17	A	3760.18	4943.81	352	1.50	0.01	58.60	0	0	14.00	352
18	B	3612.38	.	378	1.50	.	.	0	0	15.10	378
19	A	6162.84	6383.24	679	0.67	0.04	17.36	0	0	0.00	679
20	B	4689.24	4770.54	434	1.50	0.05	12.92	0	0	0.00	434
21	B	4170.99	4562.55	423	3.00	0.02	41.25	0	0	6.58	423
22	A	4186.13	4642.81	738	0.67	0.02	32.10	0	0	0.00	738
23	B	3429.68	3493.57	342	3.00	0.03	21.92	0	0	2.02	342
24	A	2416.01	2477.71	216	3.50	0.04	16.58	0	0	0.00	216
25	B	7264.90	7909.47	510	1.00	0.02	39.89	0	0	11.20	510
26	A	9136.48	9225.21	996	1.00	0.04	17.08	0	0	3.60	996
27	B	3473.57	3522.20	163	3.00	0.07	9.94	0	0	0.00	163
28	A	2454.80	2498.89	258	2.00	0.06	12.42	0	0	0.00	258
29	A	2367.82	2392.63	216	4.50	0.12	5.81	0	0	0.00	216
30	B	1987.83	2059.28	202	4.50	0.05	15.38	0	0	0.00	202
31	A	2704.06	2886.35	170	1.50	0.04	17.55	0	0	0.00	170
32	B	2966.61	3223.80	208	0.67	0.02	34.82	0	0	5.12	208
33	A	3931.33	4171.98	460	2.00	0.03	24.90	0	0	0.00	460
34	B	3272.84	3341.62	461	1.50	0.04	16.05	0	0	0.00	461
35	A	5655.25	5876.34	434	4.00	0.05	13.56	0	0	0.00	434

ORIGINAL DATA SUBMITTED

Obs	TREAT	AUCT	AUCI	CMAX	TMAX	KE	THALF	KE_FIRST	KE_LAST	CLAST	NEWCMAX
36	B	6669.45	6802.11	332	4.50	0.03	21.79	0	0	4.22	332
37	B	3268.63	3395.58	273	2.00	0.03	20.18	0	0	0.00	273
38	A	2336.91	2392.30	322	1.00	0.06	12.39	0	0	0.00	322
39	B	4279.59	4474.67	613	0.67	0.03	26.99	0	0	5.01	613
40	A	4387.40	4583.95	426	2.50	0.02	28.27	0	0	4.82	426
41	A	2608.57	2641.12	274	2.50	0.10	6.84	0	0	0.00	274
42	B	2273.32	2369.81	235	1.50	0.08	8.43	0	0	0.00	235
43	B	7998.18	8252.03	618	1.50	0.03	21.62	0	0	8.14	618
44	A	8695.40	8791.63	672	1.50	0.05	14.72	0	0	4.53	672
45	B	3518.94	3777.73	146	4.50	0.03	27.10	0	0	6.62	146
46	A	3814.05	4305.02	212	1.00	0.02	37.27	0	0	9.13	212
47	A	2639.18	2730.66	260	1.50	0.03	24.48	0	0	2.59	260
48	B	3832.49	3888.04	445	0.67	0.04	16.82	0	0	2.29	445
49	A	2409.76	2463.96	430	1.50	0.06	10.83	0	0	0.00	430
50	B	1986.74	.	244	2.00	.	.	0	0	0.00	244
51	B	2515.78	2701.85	321	1.03	0.04	18.45	0	0	0.00	321
52	A	2837.82	2932.87	308	1.00	0.04	18.15	0	0	0.00	308
53	B	4133.02	5428.11	363	1.00	0.01	57.54	0	0	15.60	363
54	A	3729.52	5723.58	274	1.50	0.01	85.32	0	0	16.20	274
55	B	7249.68	7409.19	374	4.50	0.04	17.95	0	0	0.00	374
56	A	5139.27	5201.02	538	1.50	0.05	13.50	0	0	0.00	538
57	A	2563.32	2825.43	209	2.50	0.03	24.39	0	0	0.00	209
58	B	2212.49	2269.47	197	3.00	0.04	16.06	0	0	0.00	197
59	A	2875.12	2963.00	316	1.00	0.04	16.69	0	0	0.00	316
60	B	3188.85	3262.27	228	3.00	0.04	15.90	0	0	0.00	228
61	B	2495.15	2595.10	366	0.67	0.03	26.85	0	0	2.58	366
62	A	4295.43	4377.00	338	3.00	0.04	15.53	0	0	3.64	338
63	A	3730.96	3832.03	381	2.00	0.03	21.69	0	0	0.00	381
64	B	3422.44	3458.83	523	1.50	0.07	9.82	0	0	0.00	523
65	A	2580.16	2656.84	493	1.50	0.03	22.15	0	0	0.00	493
66	B	2744.61	2882.39	303	2.00	0.02	29.94	0	0	3.19	303
67	B	2915.49	.	167	1.50	.	.	0	0	14.50	167
68	A	3247.64	3788.64	143	2.00	0.02	39.06	0	0	9.60	143
69	B	3124.31	3217.77	329	3.00	0.04	17.37	0	0	0.00	329
70	A	6438.85	6655.74	574	1.50	0.04	18.49	0	0	0.00	574
71	A	2666.88	2849.04	335	1.00	0.02	31.49	0	0	4.01	335
72	B	3396.23	3827.64	309	1.00	0.02	35.56	0	0	8.41	309
73	A	2377.71	2465.96	248	1.50	0.04	19.54	0	0	0.00	248
74	B	1746.73	1814.23	284	1.50	0.07	9.25	0	0	0.00	284

ORIGINAL DATA SUBMITTED

Obs	TREAT	AUCT	AUCI	CMAX	TMAX	KE	THALF	KE_FIRST	KE_LAST	CLAST	NEWCMAX
75	B	2111.12	2164.88	367	1.00	0.05	13.31	0	0	0.00	367
76	A	1854.42	1891.17	314	1.00	0.11	6.60	0	0	0.00	314
77	B	2109.12	2153.20	213	1.00	0.08	8.91	0	0	0.00	213
78	A	2328.56	2524.86	200	1.50	0.06	10.88	0	0	0.00	200
79	B	5090.16	5191.73	632	1.50	0.03	20.41	0	0	3.45	632
80	A	4915.25	5540.62	405	1.53	0.02	38.36	0	0	11.30	405
81	A	3210.54	3346.85	368	0.67	0.03	26.47	0	0	3.57	368
82	B	3330.27	3532.08	232	2.00	0.02	30.34	0	0	4.61	232
83	A	3655.11	3912.72	283	2.50	0.02	33.63	0	0	5.31	283
84	B	3614.80	3794.46	303	2.50	0.03	27.01	0	0	4.61	303
85	B	3689.23	4392.33	333	1.00	0.02	45.55	0	0	10.70	333
86	A	2725.67	3369.61	214	1.00	0.01	51.30	0	0	8.70	214
87	B	5761.72	5852.19	291	1.00	0.03	20.29	0	0	3.09	291
88	A	4318.03	4550.28	353	2.00	0.02	28.70	0	0	5.61	353

ORIGINAL DATA SUBMITTED

The GLM Procedure

Class Level Information		
Class	**Levels**	**Values**
SUB	44	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45
TRT	2	1 2
PER	2	1 2
SEQ	2	1 2

Number of observations	88

Dependent Variables With Equivalent Missing Value Patterns		
Pattern	**Obs**	**Dependent Variables**
1	88	AUCT CMAX LAUCT LCMAX
2	85	AUCI LAUCI

NOTE: Variables in each group are consistent with respect to the presence or absence of missing values.

ORIGINAL DATA SUBMITTED

The GLM Procedure

Dependent Variable: AUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	45	187945250.8	4176561.1	7.88	<.0001
Error	42	22273020.5	530310.0		
Corrected Total	87	210218271.3			

R-Square	Coeff Var	Root MSE	AUCT Mean
0.894048	20.36723	728.2239	3575.469

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	8920152.2	8920152.2	16.82	0.0002
SUB(SEQ)	42	178900332.4	4259531.7	8.03	<.0001
PER	1	66645.3	66645.3	0.13	0.7247
TRT	1	58120.9	58120.9	0.11	0.7422

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	8920152.2	8920152.2	16.82	0.0002
SUB(SEQ)	42	178900332.4	4259531.7	8.03	<.0001
PER	1	72279.8	72279.8	0.14	0.7138
TRT	1	58120.9	58120.9	0.11	0.7422

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	8920152.170	8920152.170	2.09	0.1553

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	51.4522013	155.418491	0.33	0.7422

ORIGINAL DATA SUBMITTED

The GLM Procedure

Dependent Variable: CMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	45	1486234.122	33027.425	3.25	<.0001
Error	42	426390.969	10152.166		
Corrected Total	87	1912625.091			

R-Square	Coeff Var	Root MSE	CMAX Mean
0.777065	29.35993	100.7580	343.1818

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	43980.606	43980.606	4.33	0.0435
SUB(SEQ)	42	1433820.484	34138.583	3.36	<.0001
PER	1	204.045	204.045	0.02	0.8879
TRT	1	8228.986	8228.986	0.81	0.3731

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	43980.606	43980.606	4.33	0.0435
SUB(SEQ)	42	1433820.484	34138.583	3.36	<.0001
PER	1	338.304	338.304	0.03	0.8560
TRT	1	8228.986	8228.986	0.81	0.3731

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	43980.60644	43980.60644	1.29	0.2628

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	19.3602484	21.5038949	0.90	0.3731

ORIGINAL DATA SUBMITTED

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	45	10.91396002	0.24253244	5.85	<.0001
Error	42	1.73996276	0.04142768		
Corrected Total	87	12.65392277			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.862496	2.511295	0.203538	8.104900

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.39660162	0.39660162	9.57	0.0035
SUB(SEQ)	42	10.49561844	0.24989568	6.03	<.0001
PER	1	0.01978728	0.01978728	0.48	0.4933
TRT	1	0.00195268	0.00195268	0.05	0.8292

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.39660162	0.39660162	9.57	0.0035
SUB(SEQ)	42	10.49561844	0.24989568	6.03	<.0001
PER	1	0.02031494	0.02031494	0.49	0.4876
TRT	1	0.00195268	0.00195268	0.05	0.8292

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.39660162	0.39660162	1.59	0.2147

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.00943090	0.04343933	0.22	0.8292

ORIGINAL DATA SUBMITTED

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	45	11.49193412	0.25537631	3.88	<.0001
Error	42	2.76410926	0.06581213		
Corrected Total	87	14.25604337			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.806110	4.456682	0.256539	5.756273

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.18526372	0.18526372	2.82	0.1008
SUB(SEQ)	42	11.28004377	0.26857247	4.08	<.0001
PER	1	0.01987042	0.01987042	0.30	0.5856
TRT	1	0.00675620	0.00675620	0.10	0.7503

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.18526372	0.18526372	2.82	0.1008
SUB(SEQ)	42	11.28004377	0.26857247	4.08	<.0001
PER	1	0.02089556	0.02089556	0.32	0.5761
TRT	1	0.00675620	0.00675620	0.10	0.7503

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.18526372	0.18526372	0.69	0.4109

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.01754240	0.05475083	0.32	0.7503

ORIGINAL DATA SUBMITTED

The GLM Procedure
Least Squares Means

TRT	AUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	3586.70825	109.89747	<.0001	0.33	0.7422
2	3535.25605	109.89747	<.0001		

TRT	CMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	351.844720	15.205550	<.0001	0.90	0.3731
2	332.484472	15.205550	<.0001		

TRT	LAUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	8.10656036	0.03071624	<.0001	0.22	0.8292
2	8.09712946	0.03071624	<.0001		

TRT	LCMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	5.76295595	0.03871469	<.0001	0.32	0.7503
2	5.74541355	0.03871469	<.0001		

ORIGINAL DATA SUBMITTED

The GLM Procedure
Least Squares Means

SEQ	AUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	3242.27346	112.36738	<.0001	-4.10	0.0002
2	3879.69085	107.37075	<.0001		

SEQ	CMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	319.785714	15.547290	<.0001	-2.08	0.0435
2	364.543478	14.855950	<.0001		

SEQ	LAUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	8.03464247	0.03140658	<.0001	-3.09	0.0035
2	8.16904734	0.03001003	<.0001		

SEQ	LCMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	5.70825406	0.03958479	<.0001	-1.68	0.1008
2	5.80011544	0.03782457	<.0001		

PER	AUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	3589.67121	109.89747	<.0001	0.37	0.7138
2	3532.29309	109.89747	<.0001		

PER	CMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	344.127329	15.205550	<.0001	0.18	0.8560
2	340.201863	15.205550	<.0001		

ORIGINAL DATA SUBMITTED

The GLM Procedure
Least Squares Means

PER	LAUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	8.11705443	0.03071624	<.0001	0.70	0.4876
2	8.08663539	0.03071624	<.0001		

PER	LCMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	5.76961009	0.03871469	<.0001	0.56	0.5761
2	5.73875941	0.03871469	<.0001		

TRT	AUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	3586.70825	109.89747	<.0001	0.33	0.7422
2	3535.25605	109.89747	<.0001		

TRT	CMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	351.844720	15.205550	<.0001	0.90	0.3731
2	332.484472	15.205550	<.0001		

TRT	LAUCT LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	8.10656036	0.03071624	<.0001	0.22	0.8292
2	8.09712946	0.03071624	<.0001		

TRT	LCMAX LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	5.76295595	0.03871469	<.0001	0.32	0.7503
2	5.74541355	0.03871469	<.0001		

ORIGINAL DATA SUBMITTED

The GLM Procedure

Dependent Variable: AUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	45	203265406.1	4517009.0	7.72	<.0001
Error	39	22809977.6	584871.2		
Corrected Total	84	226075383.7			

R-Square	Coeff Var	Root MSE	AUCI Mean
0.899105	20.02110	764.7687	3819.813

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	11569433.7	11569433.7	19.78	<.0001
SUB(SEQ)	42	191574099.7	4561288.1	7.80	<.0001
PER	1	38039.9	38039.9	0.07	0.8000
TRT	1	83832.8	83832.8	0.14	0.7070

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	10651619.5	10651619.5	18.21	0.0001
SUB(SEQ)	42	191516403.4	4559914.4	7.80	<.0001
PER	1	46527.0	46527.0	0.08	0.7794
TRT	1	83832.8	83832.8	0.14	0.7070

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	10651619.47	10651619.47	2.34	0.1339

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	64.1203170	169.363147	0.38	0.7070

ORIGINAL DATA SUBMITTED

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	45	11.11319521	0.24695989	5.64	<.0001
Error	39	1.70871509	0.04381321		
Corrected Total	84	12.82191029			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.866735	2.562340	0.209316	8.168942

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.47808573	0.47808573	10.91	0.0021
SUB(SEQ)	42	10.62128755	0.25288780	5.77	<.0001
PER	1	0.01063002	0.01063002	0.24	0.6251
TRT	1	0.00319191	0.00319191	0.07	0.7887

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.45250248	0.45250248	10.33	0.0026
SUB(SEQ)	42	10.61673344	0.25277937	5.77	<.0001
PER	1	0.01144034	0.01144034	0.26	0.6122
TRT	1	0.00319191	0.00319191	0.07	0.7887

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.45250248	0.45250248	1.79	0.1881

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.01251163	0.04635444	0.27	0.7887

ORIGINAL DATA SUBMITTED

The GLM Procedure
Least Squares Means

TRT	AUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	3829.72915	115.41251	<.0001	0.38	0.7070
2	3765.60883	123.95091	<.0001		

TRT	LAUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	8.17166588	0.03158823	<.0001	0.27	0.7887
2	8.15915425	0.03392518	<.0001		

ORIGINAL DATA SUBMITTED

The GLM Procedure
Least Squares Means

SEQ	AUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	3436.28691	124.06187	<.0001	-4.27	0.0001
2	4159.05107	115.29323	<.0001		

SEQ	LAUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	8.09092499	0.03395555	<.0001	-3.21	0.0026
2	8.23989514	0.03155558	<.0001		

PER	AUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	3821.55323	117.88971	<.0001	0.28	0.7794
2	3773.78475	121.59725	<.0001		

PER	LAUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	8.17725352	0.03226624	<.0001	0.51	0.6122
2	8.15356661	0.03328098	<.0001		

TRT	AUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	3829.72915	115.41251	<.0001	0.38	0.7070
2	3765.60883	123.95091	<.0001		

TRT	LAUCI LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2	
			Pr > |t|	t Value	Pr > |t|
1	8.17166588	0.03158823	<.0001	0.27	0.7887
2	8.15915425	0.03392518	<.0001		

Mean Plasma Raloxifene Levels for Test & Reference Products

	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
Time (hr)					
0	0.00	.	0.00	.	.
0.33	19.28	232.59	39.99	179.10	0.48
0.67	133.98	150.97	160.26	101.22	0.84
1	213.66	89.84	223.72	70.88	0.96
1.5	265.08	63.11	254.90	53.33	1.04
2	240.01	50.14	233.50	43.99	1.03
2.5	210.03	44.38	206.35	41.77	1.02
3	174.87	51.29	180.96	52.57	0.97
3.5	139.13	57.22	142.01	53.94	0.98
4	119.05	64.45	123.63	62.70	0.96
4.5	110.45	58.64	118.09	66.74	0.94
5	80.40	57.45	83.55	74.45	0.96
5.5	67.30	60.07	67.41	77.50	1.00
6	62.52	63.37	60.07	86.90	1.04
6.5	61.13	64.61	56.58	86.96	1.08
7	61.84	61.77	57.05	81.67	1.08
8	65.31	60.53	62.38	69.08	1.05
10	73.95	43.61	73.49	50.25	1.01
12	59.93	47.04	60.30	46.10	0.99
16	58.04	57.80	56.87	53.14	1.02
24	59.60	56.55	56.29	56.61	1.06
36	30.39	63.18	30.05	57.62	1.01
48	25.53	77.88	24.24	63.49	1.05
72	12.85	70.76	11.87	72.86	1.08
96	6.16	99.12	6.60	110.89	0.93
120	2.79	148.53	3.45	129.62	0.81

UNIT: Plasma Level=pg/mL Time=hrs

ARITHMETIC MEANS AND RATIOS

	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
PARAMETER					
AUCT	3599.89	45.31	3551.05	42.02	1.01
AUCI	3845.07	43.96	3792.71	42.34	1.01
CMAX	352.77	48.98	333.59	36.01	1.06
TMAX	1.84	52.80	1.91	57.97	0.97
KE	0.04	60.69	0.04	56.57	0.98
THALF	24.39	62.20	22.40	49.38	1.09
LAUCT	3324.00	0.01	3297.35	0.01	1.01
LAUCI	3549.33	0.01	3508.57	0.01	1.01
LCMAX	318.73	0.14	313.63	0.11	1.02

UNIT: AUC=pg hr/mL CMAX=pg/mL TMAX=hr
Log-transformed Data Were Converted To Anti-log In The Table

	Test LS Mean	Ref LS Mean	Ratio LS Means	Lower 90% CI	Upper 90% CI
PARAMETER					
AUCT	3586.71	3535.26	1.01	94.06	108.85
AUCI	3829.73	3765.61	1.02	93.86	109.55
CMAX	351.84	332.48	1.06	94.94	116.70
LAUCT	3316.15	3285.02	1.01	93.84	108.60
LAUCI	3539.23	3495.23	1.01	93.40	109.78
LCMAX	318.29	312.75	1.02	92.82	111.59

c. SAS Program for Fasting Study:

```
               *FOLLOW THE STEPS 1-14 TO RUN THIS PROGRAM;

       *STEP 1:       SELECT CALCKE.SAS IF YOU WANT TO CALCULATE KE AND OTHER PARAMETERS
               SELECT CONTINU.SAS IF YOU DO NOT WANT TO RECALCULATE KE.  SPONSOR'S KE WILL BE
USED FOR
               CALCULATION OF OTHER PARAMETERS WITH STATISTICS ON SPONSOR SUPPLIED PARAMETERS.
               SELECT CONTINU2.SAS FOR STATISTICS ON CALCULATED PARAMETERS;

%LET FNAME=%QUOTE(M:\My SAS Files\SAS Folder\continu.sas);
*%LET FNAME=%QUOTE(C:\SAS\CONTINU2.SAS);
*%LET FNAME=%QUOTE(C:\SAS\CALCKE.SAS);

       *STEP 2:       BLOOD LEVEL DATA: NEED FILE NAME, FIRST OBSERVATION AND VARIABLE LIST
               IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT LINE
               IF NO BLOOD DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 3
               IF MERGED DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 4;

*FILENAME ORGPLASM DDE 'EXCEL|Fast-IB!R2C1:R65C23';
*FILENAME ORGPLASM "&studydir.\&plasmadata";
*%LET FIRSTOBS=1;                                    /* FIRST OBSERVATION */
*%LET VARPLASM=SUB PER SEQ TREAT $ c_5 c_25 C1-C15;  /* VARIABLE LIST FOR THE PLASMA DATA FILE */
*%LET PLASMLS=256;                                   /* INCREASE LINE SIZE IF NEEDED */
*%READDATA(ORGPLASM,PLASMA,&FIRSTOBS,&VARPLASM,&PLASMLS)
*RUN;

       *IF INPUT FILE IS A SAS DATASET SPECIFIY LIBNAME WHERE THE SAS DATASET IS SAVED*;
*LIBNAME CONCDATA "P:\Data\Firms\Roxane\77262\Fast";

       *SPECIFY NAME OF THE CONCENTRATION SAS DATASET*;
*%let cdata=plconc;
*DATA PLASMA;
*       SET CONCDATA.&CDATA(rename=(seq=_seq trt=treat));
*       rename subj = sub;
*              if _seq = "AB" then seq = 1;
*              else if _seq = "BA" then seq = 2;
*              if treat = "A" then trt = 1;
*              else if treat = "B" then trt = 2;
*RUN;
*%SORTDS(PLASMA, &VARSORT)
*RUN;

       *STEP 3:       PK PARAMETER DATA: NEED FILE NAME, FIRST OBSERVATION AND VARIABLE LIST
               IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT LINE
               IF NO PK PARAMETER DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 4*;

*FILENAME ORGPARAM DDE 'EXCEL|Fast-IB!R2C25:R65C29';
*FILENAME ORGPARAM "&studydir.\&pkdata";
*%LET FIRSTOBS=1;                                    /* FIST OBSERVATION */
*%LET VARPARAM=SUB PER SEQ TREAT $ COHORT AUCT AUCI CMAX TMAX THALF KE; /* VARIABLE LIST */
```

```
*%LET PARAMLS=256;                                    /* INCREASE LINE SIZE IF NEEDED */
*%READDATA(ORGPARAM,PARAME,&FIRSTOBS,&VARPARAM,&PARAMLS)
*RUN;

       *IF INPUT FILE IS A SAS DATASET SPECIFIY LIBNAME WHERE THE SAS DATASET IS SAVED*;
*LIBNAME PKDATA "P:\Data\Firms\Ranbaxy\77143\Fast";

       *SPECIFY NAME OF THE PK SAS DATASET*;
*%let pdata=params;
*DATA PARAME;
*       SET CONCDATA.&PDATA(rename=(seq=_seq trt=treat));
*       sub = subj;
*       if _seq = "AB" then seq = 1;
*       else if _seq = "BA" then seq = 2;
*       if treat = "A" then trt = 1;
*       else if treat = "B" then trt = 2;
*       rename lambda_z = KE;
*RUN;
*%SORTDS(PARAME, &VARSORT)
*RUN;

       *STEP 4:       WRITE THE FILENAME OF THE MERGED DATA
              IF NO MERGED DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 2 OR 3
              IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT LINE*;

FILENAME ORGMERGE DDE 'EXCEL|Data!R2C1:R119C43';
*FILENAME ORGMERGE 'C:\Data\Firms\CorePharma\76634\Fasting\FDA.1';
%LET FIRSTOBS=1;                                      /* WRITE LINE NUMBER FOR THE FIRST
OBSERVATION */
%LET VARMERGE=SUB SEQ PER TREAT$ C1-C33 AUCT AUCI CMAX TMAX KE THALF;
%LET MERGELS=1000;                                    /* INCREASE LINE SIZE IF NEEDED */
%READDATA(ORGMERGE,MERGED,&FIRSTOBS,&VARMERGE,&MERGELS)
RUN;
%SORTDS(MERGED, &VARSORT)
RUN;

       *STEP 5:       ADD OR REDUCE THE BLOOD SAMPLE NUMBER TO FIT THE STUDY;

%LET   CONCENT=%STR(C1, C2, C3, C4, C5, C6, C7, C8, C9, C10, C11, C12, C13, C14, C15, C16, C17,
C18, c19, c20, c21, c22, c23, c24, c25, c26, c27, c28, c29, c30, c31, c32, c33);

       *STEP 6:       ADD OR REDUCE THE SAMPLING TIME POINTS AND CHANGE THE TIME;

%LET   TIME=%STR(T1=0; T2=0.333; T3=0.667; T4=1.0; T5=1.333; T6=1.667; T7=2.0; T8=2.333;
T9=2.667; T10=3.0; T11=3.333; T12=3.667;
       T13=4.0; T14=4.333; T15=4.667; T16=5.0; T17=5.333; T18=5.667; t19=6.0; t20=6.333;
t21=6.667; t22=7.0; t23=8.0; t24=9.0; t25=10.0; t26=12.0; t27=16.0; t28=24.0; t29=36.0; t30=48.0;
t31=72.0; t32=96.0; t33=144);

       *STEP 7:       WRITE THE TOTAL NUMBER OF SAMPLING TIME POINTS;

%LET NO_ASSAY=33;

       *STEP 8:       INITIALIZE KE_FIRST AND KE_LAST FOR KE CALCULATION IF THESE ARE NOT IN THE
DATA SUBMITTED;

%LET KE_FIRST=&NO_ASSAY-5;
%LET KE_LAST=&NO_ASSAY-1;

       *STEP 9:       SUBJECTS/RECORDS TO BE REMOVED FROM CALCULATION
              VARIOUS SCREENING CONDITIONS CAN BE APPLIED FOR SUBJECT REMOVAL
              LEAVE AS IT IS IF NO CHANGE IS DESIRED;

*%LET REMOVSUB=%STR(IF SUB^=26);
*       IF SUB^=15;
*       IF SUB^=34;
*       IF SUB^=37;
*       IF SUB^=49);
*%LET REMOVSUB=%STR(IF TMAX^=0.25);
```

```
       *STEP 10:      IF SEQ, PER, TRT OR OTHER VARIABLES TO BE ADDED OR MODIFIED
              CREATING NUMERIC VARIABLES FROM CHARACTER VARIABLES, ETC
              IF KE_FIRST AND KE_LAST ARE SUBMITTED IN THE DATA SET , KEEP THEM CLOSED;

%LET ADD_VAR=%STR(KE_FIRST=&KE_FIRST; KE_LAST=&KE_LAST; IF TREAT='A' THEN TRT=1; ELSE TRT=2);

       *PK REPEATS - USE ORIGINAL CONCENTRATIONS;
*DATA plasma;
*      set plasma;
*      if sub="S06" and peri="P2" then t8=123.256;
*      if sub="S17" and peri="P1" then t6=340.101;
*RUN;

       *STEP 11:      DATA STEP FOR ORIGIN (MASTER DATA SET) OPEN OR CLOSE LINES IF NEEDED;

DATA ORIGIN;
       ARRAY C(&NO_ASSAY) C1-C&NO_ASSAY;
       ARRAY T(&NO_ASSAY) T1-T&NO_ASSAY;
*      SET PLASMA;
*      SET PARAME;
       SET MERGED;
&TIME;
KE_FIRST=0;
KE_LAST=0;
CLAST=C&NO_ASSAY;
NEWCMAX=MAX(&CONCENT);
RUN;


       *STEP 12:      DESCRIBE TITLES FOR TABLES;

%LET TITLE1=Mean Plasma Raloxifene Levels;
%LET TITLE2=Mean Plasma Raloxifene Levels for Test & Reference Products;

       *DESCRIBE TITLES, FOOTNOTES AND LABELS FOR GRAPH;
%LET TITLE3=   Plasma Raloxifene Levels;
%LET TITLE4=   Raloxifene Tablets, 60mg, Teva, ANDA 78193;
%LET TITLE5=   Fast Study;
%LET TITLE6=   Dose=1 X 60mg;
%LET FOOTNOT1= 1=TEST  2=REF;
%LET FOOTNOT2= UNIT: Plasma Level=pg/mL  Time=hrs;
%LET FOOTNOT3= UNIT: AUC=pg hr/mL  CMAX=pg/mL  TMAX=hr;
%LET FOOTNOT4= Log-transformed Data Were Converted To Anti-log In The Table;
%LET LABEL1=   Plasma Level, pg/mL;
%LET LABEL2=   Time, Hrs;
%LET LABEL3=   Test;
%LET LABEL4=   Reference;

       *PRINT THE ORIGINAL DATASET SUBMITTED;
%PRINT(ORIGIN, ORIGINAL DATA SUBMITTED)
RUN;

       *TO CHECK >0 CONC FOR C1;
*PROC PRINT data=origin;
*      where c1 > 0;
*      var sub per seq c1 cmax;
*RUN;

%COPYDS(ORIGIN, NEW)
RUN;

       *STEP 13:      OPEN IF YOU WANT TO REMOVE, ADD OR EDIT;

*%REMUVSUB(NEW, NEW)
RUN;

%ADDVARIA(NEW, NEW)
RUN;
```

```
%RITEDATA(NEW, NEW, SUB TRT KE_FIRST KE_LAST)              /* TO EDIT KE-FIRST AND KE-LAST */
RUN;

%COPYDS(NEW, NEWCONC)
RUN;

DATA NEWCONC;
       ARRAY C(&NO_ASSAY) C1-C&NO_ASSAY;
       ARRAY T(&NO_ASSAY) T1-T&NO_ASSAY;
       NO_ASSAY=&NO_ASSAY;
SET NEWCONC;
        *TRANSVERSE THE C AND T DATA INTO COLUMNS WITH NEW VARIABLE NAMES;
DO I=1 TO NO_ASSAY;
TIME=T(I);
CONC=C(I);
I=I;
OUTPUT;
END;

        *STEP 14: CONGRATULATIONS!!! NOW YOU CAN SUBMIT THE PROGRAM;

/* DETERMINE NEWTMAX, KE_FIRST, KE_LAST, NEWAUCT AND AUCLST*/
DATA NEW;
       ARRAY C(&NO_ASSAY) C1-C&NO_ASSAY;
       ARRAY T(&NO_ASSAY) T1-T&NO_ASSAY;
       NO_ASSAY=&NO_ASSAY;
SET NEW;
CLAST=C&NO_ASSAY;
NEWCMAX=MAX(&CONCENT);
```

D. SAS Program for Fed Study:

```
               *FOLLOW THE STEPS 1-14 TO RUN THIS PROGRAM;

        *STEP 1:       SELECT CALCKE.SAS IF YOU WANT TO CALCULATE KE AND OTHER PARAMETERS
               SELECT CONTINU.SAS IF YOU DO NOT WANT TO RECALCULATE KE.  SPONSOR'S KE WILL BE
USED FOR
               CALCULATION OF OTHER PARAMETERS WITH STATISTICS ON SPONSOR SUPPLIED PARAMETERS.
               SELECT CONTINU2.SAS FOR STATISTICS ON CALCULATED PARAMETERS;

%LET FNAME=%QUOTE(M:\My SAS Files\SAS Folder\continu.sas);
*%LET FNAME=%QUOTE(C:\SAS\CONTINU2.SAS);
*%LET FNAME=%QUOTE(C:\SAS\CALCKE.SAS);

        *STEP 2:       BLOOD LEVEL DATA: NEED FILE NAME, FIRST OBSERVATION AND VARIABLE LIST
               IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT LINE
               IF NO BLOOD DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 3
               IF MERGED DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 4;

*FILENAME ORGPLASM DDE 'EXCEL|Fast-IB!R2C1:R65C23';
*FILENAME ORGPLASM "&studydir.\&plasmadata";
*%LET FIRSTOBS=1;                                    /* FIRST OBSERVATION */
*%LET VARPLASM=SUB PER SEQ TREAT $ c_5 c_25 C1-C15;  /* VARIABLE LIST FOR THE PLASMA DATA FILE */
*%LET PLASMLS=256;                                   /* INCREASE LINE SIZE IF NEEDED */
*%READDATA(ORGPLASM,PLASMA,&FIRSTOBS,&VARPLASM,&PLASMLS)
*RUN;

        *IF INPUT FILE IS A SAS DATASET SPECIFIY LIBNAME WHERE THE SAS DATASET IS SAVED*;
*LIBNAME CONCDATA "P:\Data\Firms\Roxane\77262\Fast";

        *SPECIFY NAME OF THE CONCENTRATION SAS DATASET*;
*%let cdata=plconc;
*DATA PLASMA;
*       SET CONCDATA.&CDATA(rename=(seq=_seq trt=treat));
*       rename subj = sub;
*               if _seq = "AB" then seq = 1;
```

```
*              else if _seq = "BA" then seq = 2;
*              if treat = "A" then trt = 1;
*              else if treat = "B" then trt = 2;
*RUN;
*%SORTDS(PLASMA, &VARSORT)
*RUN;

       *STEP 3:       PK PARAMETER DATA: NEED FILE NAME, FIRST OBSERVATION AND VARIABLE LIST
              IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT LINE
              IF NO PK PARAMETER DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 4*;

*FILENAME ORGPARAM DDE 'EXCEL|Fast-IB!R2C25:R65C29';
*FILENAME ORGPARAM "&studydir.\&pkdata";
*%LET FIRSTOBS=1;                                    /* FIST OBSERVATION */
*%LET VARPARAM=SUB PER SEQ TREAT $ COHORT AUCT AUCI CMAX TMAX THALF KE; /* VARIABLE LIST */
*%LET PARAMLS=256;                                   /* INCREASE LINE SIZE IF NEEDED */
*%READDATA(ORGPARAM,PARAME,&FIRSTOBS,&VARPARAM,&PARAMLS)
*RUN;

       *IF INPUT FILE IS A SAS DATASET SPECIFIY LIBNAME WHERE THE SAS DATASET IS SAVED*;
*LIBNAME PKDATA "P:\Data\Firms\Ranbaxy\77143\Fast";

       *SPECIFY NAME OF THE PK SAS DATASET*;
*%let pdata=params;
*DATA PARAME;
*      SET CONCDATA.&PDATA(rename=(seq=_seq trt=treat));
*      sub = subj;
*      if _seq = "AB" then seq = 1;
*      else if _seq = "BA" then seq = 2;
*      if treat = "A" then trt = 1;
*      else if treat = "B" then trt = 2;
*      rename lambda_z = KE;
*RUN;
*%SORTDS(PARAME, &VARSORT)
*RUN;

       *STEP 4:       WRITE THE FILENAME OF THE MERGED DATA
              IF NO MERGED DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 2 OR 3
              IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT LINE*;

FILENAME ORGMERGE DDE 'EXCEL|Data!R2C1:R89C36';
*FILENAME ORGMERGE 'C:\Data\Firms\CorePharma\76634\Fasting\FDA.1';
%LET FIRSTOBS=1;                                     /* WRITE LINE NUMBER FOR THE FIRST
OBSERVATION */
%LET VARMERGE=SUB SEQ PER TREAT$ C1-C26 AUCT AUCI CMAX TMAX KE THALF;
%LET MERGELS=1000;                                   /* INCREASE LINE SIZE IF NEEDED */
%READDATA(ORGMERGE,MERGED,&FIRSTOBS,&VARMERGE,&MERGELS)
RUN;
%SORTDS(MERGED, &VARSORT)
RUN;

       *STEP 5:       ADD OR REDUCE THE BLOOD SAMPLE NUMBER TO FIT THE STUDY;

%LET   CONCENT=%STR(C1, C2, C3, C4, C5, C6, C7, C8, C9, C10, C11, C12, C13, C14, C15, C16, C17,
C18, c19, c20, c21, c22, c23, c24, c25, c26);

       *STEP 6:       ADD OR REDUCE THE SAMPLING TIME POINTS AND CHANGE THE TIME;

%LET   TIME=%STR(T1=0; T2=0.33; T3=0.67; T4=1.0; T5=1.5; T6=2.0; T7=2.5; T8=3.0; T9=3.5;
T10=4.0; T11=4.5; T12=5.0;
       T13=5.5; T14=6.0; T15=6.5; T16=7.0; T17=8.0; T18=10.0; t19=12.0; t20=16.0; t21=24.0;
t22=36.0; t23=48.0; t24=72.0; t25=96.0; t26=120.0);

       *STEP 7:       WRITE THE TOTAL NUMBER OF SAMPLING TIME POINTS;

%LET NO_ASSAY=26;

       *STEP 8:       INITIALIZE KE_FIRST AND KE_LAST FOR KE CALCULATION IF THESE ARE NOT IN THE
DATA SUBMITTED;
```

```
%LET KE_FIRST=&NO_ASSAY-5;
%LET KE_LAST=&NO_ASSAY-1;

        *STEP 9:       SUBJECTS/RECORDS TO BE REMOVED FROM CALCULATION
                VARIOUS SCREENING CONDITIONS CAN BE APPLIED FOR SUBJECT REMOVAL
                LEAVE AS IT IS IF NO CHANGE IS DESIRED;

*%LET REMOVSUB=%STR(IF SUB^=26);
*       IF SUB^=15;
*       IF SUB^=34;
*       IF SUB^=37;
*       IF SUB^=49);
*%LET REMOVSUB=%STR(IF TMAX^=0.25);

        *STEP 10:      IF SEQ, PER, TRT OR OTHER VARIABLES TO BE ADDED OR MODIFIED
                CREATING NUMERIC VARIABLES FROM CHARACTER VARIABLES, ETC
                IF KE_FIRST AND KE_LAST ARE SUBMITTED IN THE DATA SET , KEEP THEM CLOSED;

%LET ADD_VAR=%STR(KE_FIRST=&KE_FIRST; KE_LAST=&KE_LAST; IF TREAT='A' THEN TRT=1; ELSE TRT=2);

        *PK REPEATS - USE ORIGINAL CONCENTRATIONS;
*DATA plasma;
*       set plasma;
*       if sub="S06" and peri="P2" then t8=123.256;
*       if sub="S17" and peri="P1" then t6=340.101;
*RUN;

        *STEP 11:      DATA STEP FOR ORIGIN (MASTER DATA SET) OPEN OR CLOSE LINES IF NEEDED;

DATA ORIGIN;
        ARRAY C(&NO_ASSAY) C1-C&NO_ASSAY;
        ARRAY T(&NO_ASSAY) T1-T&NO_ASSAY;
*       SET PLASMA;
*       SET PARAME;
        SET MERGED;
&TIME;
KE_FIRST=0;
KE_LAST=0;
CLAST=C&NO_ASSAY;
NEWCMAX=MAX(&CONCENT);
RUN;


        *STEP 12:      DESCRIBE TITLES FOR TABLES;

%LET TITLE1=Mean Plasma Raloxifene Levels;
%LET TITLE2=Mean Plasma Raloxifene Levels for Test & Reference Products;

        *DESCRIBE TITLES, FOOTNOTES AND LABELS FOR GRAPH;
%LET TITLE3=   Plasma Raloxifene Levels;
%LET TITLE4=   Raloxifene Tablets, 60mg, Teva, ANDA 78193;
%LET TITLE5=   Fed Study;
%LET TITLE6=   Dose=1 X 60mg;
%LET FOOTNOT1= 1=TEST  2=REF;
%LET FOOTNOT2= UNIT: Plasma Level=pg/mL  Time=hrs;
%LET FOOTNOT3= UNIT: AUC=pg hr/mL  CMAX=pg/mL  TMAX=hr;
%LET FOOTNOT4= Log-transformed Data Were Converted To Anti-log In The Table;
%LET LABEL1=   Plasma Level, pg/mL;
%LET LABEL2=   Time, Hrs;
%LET LABEL3=   Test;
%LET LABEL4=   Reference;

        *PRINT THE ORIGINAL DATASET SUBMITTED;
%PRINT(ORIGIN, ORIGINAL DATA SUBMITTED)
RUN;

        *TO CHECK >0 CONC FOR C1;
*PROC PRINT data=origin;
```

```
*       where c1 > 0;
*       var sub per seq c1 cmax;
*RUN;

%COPYDS(ORIGIN, NEW)
RUN;

        *STEP 13:      OPEN IF YOU WANT TO REMOVE, ADD OR EDIT;

*%REMUVSUB(NEW, NEW)
RUN;

%ADDVARIA(NEW, NEW)
RUN;

%RITEDATA(NEW, NEW, SUB TRT KE_FIRST KE_LAST)               /* TO EDIT KE-FIRST AND KE-LAST */
RUN;

%COPYDS(NEW, NEWCONC)
RUN;

DATA NEWCONC;
       ARRAY C(&NO_ASSAY) C1-C&NO_ASSAY;
       ARRAY T(&NO_ASSAY) T1-T&NO_ASSAY;
       NO_ASSAY=&NO_ASSAY;
SET NEWCONC;
        *TRANSVERSE THE C AND T DATA INTO COLUMNS WITH NEW VARIABLE NAMES;
DO I=1 TO NO_ASSAY;
TIME=T(I);
CONC=C(I);
I=I;
OUTPUT;
END;

        *STEP 14: CONGRATULATIONS!!! NOW YOU CAN SUBMIT THE PROGRAM;

/* DETERMINE NEWTMAX, KE_FIRST, KE_LAST, NEWAUCT AND AUCLST*/
DATA NEW;
       ARRAY C(&NO_ASSAY) C1-C&NO_ASSAY;
       ARRAY T(&NO_ASSAY) T1-T&NO_ASSAY;
       NO_ASSAY=&NO_ASSAY;
SET NEW;
CLAST=C&NO_ASSAY;
NEWCMAX=MAX(&CONCENT);
```

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-193 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Raloxifene Hydrochloride Tablet, 60 mg

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

Please conduct dissolution testing on the test and reference products (12 units each) using the following FDA-recommended method and resubmit the results with individual data as well as mean, range and CV%. The dissolution testing should be conducted in 1000mL of 0.1% Polysorbate 80 in water (@ 37°C) using USP Apparatus II (paddle) at 50 rpm. The recommended sampling time points are 10, 15, 20 and 30 minutes.

The test product should meet the following specification:

NLT 80%(Q)in 30 minutes.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCE – Incomplete Submission Date: March 2, 2006

1. **FASTING STUDY** (STF) Strength: 60 mg
Outcome: IC

Clinical: MDS Pharma Services, St. Laurent, Quebec, Canada
Analytical: (b) (4)

2. **FED STUDY** (STP) Strength: 60 mg
Outcome: IC

Clinical: Pharma Medica Research Inc, Ontario Canada
Analytical: (b) (4)

Outcome Decisions: **IC** - Incomplete.

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

/s/

Christina Lee
1/5/2007 12:16:21 PM
BIOPHARMACEUTICS

Chandra S. Chaurasia
1/5/2007 12:57:28 PM
BIOPHARMACEUTICS

Barbara Davit
1/5/2007 04:34:17 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE DISSOLUTION CHECKLIST

ANDA No.	78-193
Drug Product Name	Raloxifene HCl Tablets
Strength	60 mg
Applicant Name	Teva Pharmaceuticals
Submission Date(s)	March 2, 2006
First Generic	No
Reviewer	Hoainhon Nguyen
File Location	**V:\firmsnz\teva\ltrs&rev\78193d0306 .doc**
Clinical Site	Pharma Medica Research, Ontario Canada (fed)
	MDS Pharma Services, St. Laurent, Canada (fasted)
Analytical Site	(b) (4)

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)			☒	☐	☐
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 all eight electronic summary biotables present			☒	☐	☐
Are electronic summary biotables in pdf format			☒	☐	☐

NOTE: The FDA method is as follows:

USP Apparatus:	II(paddle) @ 50 rpm
Dissolution Medium:	0.1% Polysorbate 80 in water
Volume of Dissolution Medium:	1000 mL

Specification: 80%(Q) in 30 minutes

7/6/06

Hoainhon Nguyen
Team I
Division of Bioequivalence
Office of Generic Drugs

Moheb H. Makary 7/7/06

Moheb H. Makary
Team I
Division of Bioequivalence
Office of Generic Drugs

CC: ANDA #78-193

V:\firmsnz\teva\ltrs&rev\78193d0306.doc
Endorsements: (Final with Dates)
HFD-650/HNguyen
HFD-650/MMakary 7/7/06

BIOEQUIVALENCE - INCOMPLETE Submission date: 03-02-2006

[NOTE: The in vitro testing is incomplete. The fasting and fed BE studies and waiver request are pending review]

1. DISSOLUTION (Dissolution Data) Strength: 60 mg
Outcome: IC

Outcome Decisions: IC – Acceptable or Incomplete
WinBio Comments: IC

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78193

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ROUTING SHEET

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

Division: I	Team: 14	PM: Bic Nguyen

Electronic ANDA: Yes ☒ No ☒

ANDA #:78193
Firm Name:TEVA Pharmaceuticals USA
ANDA Name:Raloxifen Hydrochloride Tablets 60mg
RLD Name:Evista (Eli Lilly)

Electronic AP Routing Summary Located:

V:\Chemistry Division I\Team 14\AP ROUTING SUMMARY\78193_Final_APRV_ROUT_SUMRY.doc

AP/TA Letter Located:

V:\Chemistry Division I\Team 14\Final Version For DARRTS (Original)\78193.AP_LTR.doc

Project Manager Evaluation: **Date:** **Initials:**

☒ Previously reviewed and tentatively approved --- Date 4/16/13
☐ Previously reviewed and CGMP Complete Response issued -- Date _____

Original Rec'd date 3/3/06	Date of Application 3/2/06	Date Acceptable for Filing 3/3/06
Patent Certification (type) IV	Date Patent/Excl. expires 3/2/14	Citizens' Petition/Legal Case? Yes☐ No ☐ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☐ **DMF#:** (b) (4) (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☐ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☐ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

GDUFA User Fee Obligation Status: ☒ Met ☐ Unmet**:** ☐ Facility Fee not paid, ☐ Backlog fee not paid
EER Status: ☐ Pending ☐☐ ☐ Acceptable ☐ OAI *EES Date Acceptable: 8/19/14* ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☐ Comment:
Date of Acceptable Quality (Chemistry) 1/13/14 Addendum Needed: Yes ☐ No ☐ Comment:
Date of Acceptable Bio 4/5/11 Bio reviews in DARRTS: Yes ☐ No ☐ (Volume location:)
Date of Acceptable Labeling 10/25/13 Attached labeling to Letter: Yes ☐ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) _____

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

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

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

Routing:

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

☒ Regulatory Support

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

☒ Division

☒ Bob West / Peter Rickman

☐ Kathleen Uhl

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

OGD APPROVAL ROUTING SUMMARY

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

Martin Shimer **Date: 1/8/2014**

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

Contains GDEA certification: Yes ☒ No ☐	Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD = Evista NDA# 20-815 Date Checked 2/27/14 Nothing Submitted ☒ Written request issued ☐ Study Submitted ☐
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☒ No ☐ Was applicant sued w/in 45 days:Yes ☒ No ☐ Has case been settled: Yes ☐ No ☒ Date settled: Is applicant eligible for 180 day Is a forfeiture memo needed: Yes ☐ No ☒ If yes, has it been completed	
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒	
Date of latest Labeling Review/Approval Summary _____	
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒☐	

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

Comments:ANDA previously TA'd on 4/16/2008. At the time the TA was issued the reason cited for TA was an unexpired 30 month stay of approval related to CA 06 CV 1017 pending in the Southern D of IN for infringement of the '086, '968, '049 and '050 patents(no suit filed on the '763(now exp.), '117(now exp.), '847, 120, '383, '811, '719, and '064 patents. It is noted that three of the patents ('086, '968 and '049) for which suit was brought expired on 7/28/2012. Of the patents for which suit was brought only the '050 patent remains unexpired and it is set to expire on 3/2/2014.

Patent Amendment rec'd on 7/8/2008-TEVA carving out ODE associated with "reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and reduction in risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer" which expires on 9/13/2014.
Patent Amendment rec'd on 9/9/2008- not really a patent amendment: statement from TEVA regarding the fact that their litigaiton remains pending in the SD of IN and that they do NOT believe a new in-vivo BE study is necessary related to a change in API supplier.
Patent Amendment rec'd on 11/12/2008-notice that the 30 month stay of approval was extended by the Court until 3/9/2009. Copy of Court's Order for CA 06 CV 1017 provided.
Patent Amendment rec'd on 10/4/2011: anticipatory PIV to the '330 patent, again: 10/5, 10/6, 10/7, 10/11, 10/12, 10/13, 10/14, 10/17, 10/18, 10/19, 10/20, 10/21, 10/24, 10/25, 10/26, 10/27, 10/28, 10/31, 11/1 and 11/2
Patent Amendment rec'd on 3/16/2012-documentation of notice for the '330 patent: notice sent via (b) (4) to Eli Lilly in Indianapolis IN with notice rec'd on 11/3/2011(X2). Cover letter of this amendment indicates that TEVA was not sued within 45 days.
As noted above the last patent for which suit was brought against TEVA will expire on 3/2/2014. There is no need to obtain a litigation status update from TEVA since they are currently blocked from Full Approval by the 180 day exclusivity period that is held by (b) (4) TEVA currently will not be eligible for Full Approval until after the '050 patent expires on 3/2/2014. This could change if (b) (4) ANDA is approved, they trigger their 180 day exclusivity period and then waive their exclusivity to this ANDA. However, if that happens it will either need to happen on or after 3/2/2014 or TEVA will need to provide an update on the status of CA 06 CV 1017.
ANDA currently is eligible for TA only as (b) (4) has not triggered and selectively waived their exclusivity to this ANDA.
Update 2/13/2014:
As noted 180 day exclusivity is held by (b) (4) because they hold the 180 day exclusivity seats outright to the '811, '719 and '064 patents and shared the 180 day seat with TEVA's ANDA 78-193 for the '330 patent. All four of these patents expires on March 10, 2017. TEVA submitted a correspondence to their ANDA 78-193 on January 27, 2014 asking the Agency to consider permitting relinquishment of the exclusivity seats on a patent-by-patent basis. As this drug product is governed under our pre-MMA regulations with respect to 180 day exclusivity each unexpired patent represents a potential exclusivity seat. TEVA's wish is to initially commercialize the product described in ANDA 78-193. However, the overall exclusivity seat for this product is held in ANDA (b) (4). That said, if the Agency were to permit relinquishment of the exclusivity seats for the '811, '719 and '064 patents then the only remaining exclusivity seat would

be for the '330 patent. Since this seat is shared between ANDAs (b) (4) and 78-193, approval of 78-193 would no longer be blocked by the 180 day seats for the '811, '719 and '064 patents. As the Agency had never before encountered relinquishment of exclusivity seats on a patent-by-patent basis this issue was discussed at a meeting on Wednesday the 12th of February (Martin Shimer, Dave Read, Cecelia Parise, Susan Levine, Mike Jones and Maryll Toufanian were present at OGD and Kim Dettelbach and Michael Stern from OCC participated via t-con). All in attendance at the meeting agreed that patent-by-patent relinquishment of 180 day exclusivity was permissible. Kim Dettelbach of OCC did also point out that the same effect could have been obtained by TEVA (b) (4) Ultimately the group agreed that TEVA could relinquish their exclusivity seats (b) (4) solely as it relates to the '811, '719 and '064 patents. TEVA also provided documentation to (b) (4) 78-193 to show that not only did they submit PIV certifications (b) (4) on 10/28/2011 but that notice was sent on 10/28/2011 as well.
This ANDA will be eligible for Full Approval on or after the expiration of the '847, '120, '383 and RE'050 patents on March 2, 2014. The Approval letter should grant TEVA shared 180 day exclusivity related to the '330 patent. A formal memo to the files of (b) (4) and 78-193 explaining the patent-by-patent relinquishment will be drafted and added to the ANDA records.

2. ***Labeling Endorsement***

Reviewer, CH
:
Date2/12/14

Labeling Team Leader, JG:
Date2/12/14

REMS required?
☐Yes ☒No

REMS acceptable?
☐Yes ☒No ☐n/a

Comments:
From: Grace, John F
Sent: Wednesday, February 12, 2014 4:05 PM
To: Hoppes, Charles V; Nguyen, Bic (CDER)
Subject: RE: 78193 Raloxifene

CONCUR.

From: Hoppes, Charles V
Sent: Wednesday, February 12, 2014 2:11 PM
To: Nguyen, Bic (CDER); Grace, John F
Subject: RE: 78193 Raloxifene

Thanks Bic,

Labeling for this application should still be OK as there have been no updates to the RLD labeling since the approval summary was signed.

Thanks,

Charlie.

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

David Read
OGD Regulatory Counsel

Date 26Feb2014
InitialsDTR

Pre-MMA Language included ☒
Post-MMA Language Included ☐
Comments:Changes to AP letter saved to V drive.

4. ***Quality Division Director /Deputy Director Evaluation***

Chemistry Div. **I (Raw)**

Date 2/27/14
Initials rlw/for

Comments: CMC Review #4 concluding that the CMC section of this ANDA is acceptable for final approval was endorsed by Bing Cai, Ph.D., Deputy Director, Division of Chemistry I for Andre Raw, Ph.D. on 1/13/14.

OGD Office Management Evaluation

5. Peter Rickman **Date 2/27/14**
Director, DLPS **Initials rlw/for**

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

Comments: This ANDA was gtanted tentative approval on April 16, 2008. Final approval was blocked at that time by ongoing patent litigation involving patents that have previously expired or will expire on March 2, 2014. Refer to the administrative summary created at the time of the tentative approval.

Final-printed labeling (FPL) found acceptable for approval 2/4/14, as endorsed 2/12/14. No REMS is required - MedGuide only. Teva has "carved-out" information from its labeling pertainig to the use of Tamoxifen Tablets USP, 60 mg for (1) Reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis, and (2) Women at high risk for invasive cancer. Both of these indications appear in the labeling for Lilly's Evista Tablets and are subject to orphan drug exclusivity. This "carve-out" is acceptable. Teva's product will be approved for the following indication - "Treatment and prevention of osteoporosis in post menopausal women". Lilly's ODE will expire on September 13, 2014.

CMC found acceptable for approval (Chemistry Review #4) 1/13/14.

OR

6. Robert L. West **Date 3/3/14**
Deputy Director, OGD **Initials RLWest**

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

Comments: Acceptable EES dated 1/3/14 (Verified 2/27/14). No "OAI" Alerts noted.

After March 2, 2014, there will only be 4 patents listed for this drug product in the "Orange Book". Those patents are the '811, '719, '064 and '330 patents. Teva provided a paragraph IV certification to each of these patens, but was not sued withinthe 45-day period. Teva has also successfully addressed the orphan drug exclusivity (ODE) listed in the "Orange Book".

Refer to the summary provided above for a discussion of 180-day generic drug exclusivity with respect to Raloxifene Hydrochloride Tablets USP, 60 mg. The agency has concluded that both Teva and (b) (4) are eligible to share 180-day exclusivity based upon their filings for the '330 patent. A memorandum summarizing the agency's findings has been completed and filed to DARRTS for both Teva's and (b) (4) ANDA.

This ANDA is recommended for final approval on or after March 2, 2014. As March 2, 2014 falls on a non workday, approval will be granted on the following workday - Monday, March 3, 2014. As the Federal government in the Washington, D.C. area was closed on Monday, March 3rd due to a snowstorm, final approval will be granted on March 4, 2014.

7. ***OGD Director Evaluation***

Kathleen Uhl

Comments: RLWest for Kathleen Uhl, M.D., Acting Director, Office of Generic Drugs 3/3/14.

First Generic Approval ☐

PD or Clinical for BE ☐

Special Scientific or Reg. Issue ☐

Press Release Acceptable ☐

Comments:

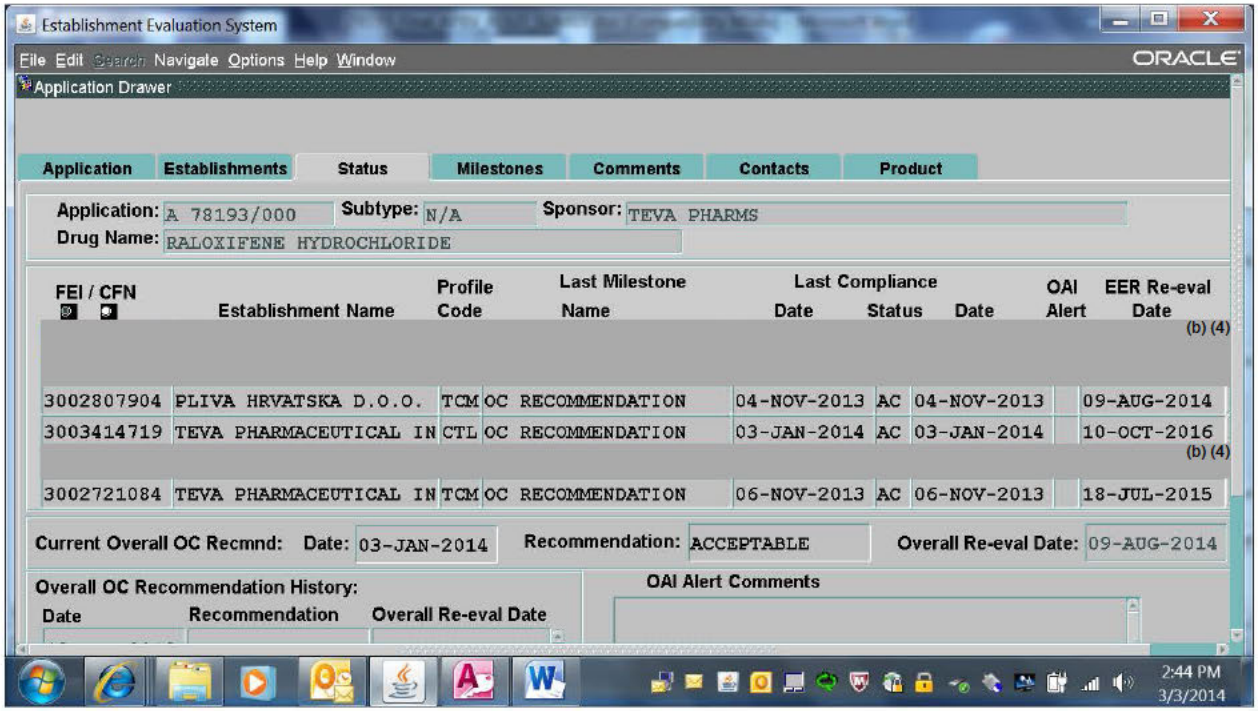
8. Project Manager **Date _____**

Initials _____

Comments:

Check Communication and Routing Summary into DARRTS

EES DATA:


Establishment Evaluation System
File Edit Search Navigate Options Help Window
ORACLE
Application Drawer
Application
Establishments
Status
Milestones
Comments
Contacts
Product
Application: A 78193/000
Subtype: N/A
Sponsor: TEVA PHARMS
Drug Name: RALOXIFENE HYDROCHLORIDE
FEI / CFN
Establishment Name
Profile Code
Last Milestone Name
Last Compliance Date
Status
Date
OAI Alert
EER Re-eval Date
(b) (4)
3002807904 PLIVA HRVATSKA D.O.O. TCM OC RECOMMENDATION 04-NOV-2013 AC 04-NOV-2013 09-AUG-2014
3003414719 TEVA PHARMACEUTICAL IN CTL OC RECOMMENDATION 03-JAN-2014 AC 03-JAN-2014 10-OCT-2016
(b) (4)
3002721084 TEVA PHARMACEUTICAL IN TCM OC RECOMMENDATION 06-NOV-2013 AC 06-NOV-2013 18-JUL-2015
Current Overall OC Recmnd: Date: 03-JAN-2014
Recommendation: ACCEPTABLE
Overall Re-eval Date: 09-AUG-2014
Overall OC Recommendation History:
Date
Recommendation
Overall Re-eval Date
OAI Alert Comments
2:44 PM
3/3/2014

Orange Book Report:

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Patent and Exclusivity Search Results from query on Appl No 020815 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
N020815	001	5478847	Mar 2, 2014			U - 114	Y
N020815	001	5811120	Mar 2, 2014				
N020815	001	5972383	Mar 2, 2014			U - 287	
N020815	001	6458811	Mar 10, 2017	Y	Y	U - 825	

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N020815	001	6797719	Mar 10, 2017		Y		
N020815	001	6894064	Mar 10, 2017		Y	U - 657	
N020815	001	8030330	Mar 10, 2017		Y		
N020815	001	RE39050	Mar 2, 2014			U - 657	
N020815	001	RE39050	Mar 2, 2014			U - 662	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N020815	**001**	**ODE**	**Sep 13, 2014**

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

/s/

BIC N NGUYEN
03/04/2014

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: March 3, 2014

FROM: Martin Shimer

Deputy Director, Division of Labeling and Program Support. Office of Generic Drugs

TO: ANDA (b) (4)

ANDA 78193: Teva Pharmaceuticals USA

SUBJECT: 180-day Exclusivity for Raloxifene Hydrochloride Tablets, 60 mg

---

This memorandum addresses 180-day exclusivity for raloxifene hydrochloride tablets, 60 mg, related to abbreviated new drug application (ANDA) (b) (4) submitted by (b) (4) (b) (4) and ANDA 78193 submitted by Teva Pharmaceuticals USA (TEVA).

I. STATUTORY BACKGROUND

A. Paragraph I-IV Certifications

Under the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. Law No. 98-417, 98 Stat. 1585 (1984) (Hatch-Waxman Amendments), a new drug application (NDA) applicant must submit information for each patent that claims the drug or method of using the drug that is the subject of the NDA (the listed drug, or RLD) and for which "a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug."[1] The U.S. Food and Drug Administration (FDA)

[1] Sections 505(b)(1) and (c)(2) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act).

publishes this patent information in FDA's publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly referred to as the Orange Book).

In its application, an ANDA sponsor generally must submit to FDA one of four specified certifications with respect to each patent (or patent claim) that claims a listed drug and is submitted by the sponsor for listing in the Orange Book. The certification must state one of the following:

(I) that the required patent information relating to such patent has not been filed (paragraph I certification)

(II) that such patent has expired (paragraph II certification)

(III) that the patent will expire on a particular date (paragraph III certification)

(IV) that such patent is invalid or will not be infringed by the drug for which approval is being sought (paragraph IV certification).

Section 505(j)(2)(A)(vii) of the FD&C Act.[2]

If an applicant files a paragraph I or II certification, the patent in question will not delay ANDA approval. If an applicant files a paragraph III certification, the applicant agrees to wait until the relevant patent has expired before seeking full approval of its ANDA.

If, however, an applicant wishes to seek approval of its ANDA before a listed patent has expired by challenging the validity of a patent or claiming that a patent would not be infringed by the product proposed in the ANDA, the applicant must submit a paragraph IV certification to FDA. The applicant filing a paragraph IV certification must also provide a notice to the NDA holder and the patent owner stating that the application has been submitted and explaining the factual and legal bases for the applicant's opinion that the patent is invalid or not infringed (see section 505 (j)(2)(B) of the FD&C Act).

As discussed in greater detail below, the first ANDA applicant that submits a valid paragraph IV certification to a patent is eligible for 180-day exclusivity as a reward for challenging a patent

[2] Congress amended section 505 of the Act in 2003 as part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (MMA) (Dec. 8, 2003). (b) (4) [redacted] *See* MMA § 1102(b)(1). See also *Letter to ANDA Applicant fr. G. Buehler, FDA Office of Generic Drugs re. Topiramate Sprinkle Capsules*, at 4 (April 15, 2009) (FDA Topiramate Letter) (concluding it is reasonable to apply pre-MMA scheme to exclusivity context in which at least one ANDA was filed prior to MMA, and for which first paragraph IV certification was submitted after date of enactment). References herein to the 180-day exclusivity provision are to the section of the Act as in effect prior to December 8, 2003.

and potentially clearing the way for generic competition. When an ANDA applicant with a valid paragraph IV certification is eligible for this exclusivity, the exclusivity generally prohibits FDA from approving any subsequent ANDA with a paragraph IV certification to that patent before the triggering of and during the exclusivity period.

B. 180-day Exclusivity

The 180-day exclusivity provisions of the pre-MMA Act give the first ANDA applicant to submit a substantially complete application that contains a paragraph IV certification challenging a patent an incentive in the form of the opportunity to be the only generic drug manufacturer to compete with the innovator for a 180-day period. The relevant statutory provision states:

> If the application contains a certification described in subclause IV of paragraph (j)(2)(A)(vii) and is for a drug for which a previous application has been submitted under this subsection [containing] such a certification, the application shall be made effective not earlier than one hundred and eighty days after -
>
> > (I) the date the Secretary receives notice from the applicant under the previous application of first commercial marketing of the drug under the previous application, or
> >
> > (I) the date of a decision of a court in action described in clause (ii) holding the patent which is the subject of the certification to be invalid or not infringed,
>
> whichever is earlier.

Section 505(j)(5)(B)(iv) of the FD&C Act.

The statute thus addresses the effect of an ANDA's exclusivity on *other* ANDAs; it delays the approval of an ANDA containing a paragraph IV certification for a drug for which a previous ANDA has been submitted containing a paragraph IV certification. In addition, the regulations require that, to be "the applicant submitting the first application" and therefore eligible for 180-day exclusivity, an ANDA applicant must submit an application that contains a paragraph IV certification (challenging a patent) and must be "substantially complete" (21 CFR § 314.107(c)).

C. Shared 180-day Exclusivity

In an August 2, 1999 response to citizen petitions from two generic drug firms addressing 180-day exclusivity for ANDAs for cisplatin, FDA stated that, the regulations governing 180-day exclusivity should be interpreted to award such exclusivity on a patent-by-patent basis.[3] That is,

[3] See Letter fr. J. Woodcock to R. Green, S. Sklar, and K. Beardsley, FDA Docket No. 99P-1271/PSA1 and PSA2, at 4 (Aug. 2, 1999) (concluding that the regulations at 21 CFR 314.107(c)(1) direct a patent-by-patent inquiry in

eligibility for 180-day exclusivity would be based on which company submitted the first paragraph IV certification challenging each listed patent. Therefore, in cases where multiple patents are listed, different applicants may have the first paragraph IV certification as to different patents and multiple ANDA applicants may simultaneously be eligible for 180-day exclusivity as to the particular patents on which they were first (mutually blocking).[4] Where different applicants are first on different patents, such that A blocks B and B blocks A, an exclusivity standoff occurs. In that limited situation, to avoid an absurd result where neither applicant can go to market because each blocks the other, FDA has determined that applicants will share a single exclusivity period.[5]

Similarly, exclusivity will be shared among multiple first applicants where all have certified to all relevant patents on the same first day or days. In other words, if there are multiple patents and there is a cohort of one or more applications that is not blocked by another applicant's exclusivity (because that cohort of one or more applicants is a first filer on *all* of the relevant patents), only that cohort of one or more applicants would be entitled to exclusivity for the drug product at issue.[6]

In either case, where there are multiple first applicants and each are blocked by the other (mutually blocking) or none is blocked by any other, a single period of exclusivity for all of the ANDAs eligible for 180-day exclusivity will be shared, and it will be triggered and begin to run by the earlier of either first commercial marketing of the product by any first applicant or a court decision on any one of the patents that qualified any first applicant for exclusivity. In addition, once an exclusivity is triggered by any first applicant, exclusivity is triggered for all first

---

determining 180 day exclusivity because they specify that an application will be delayed by 180 day exclusivity if it contains a paragraph IV certification and is for the same listed drug for which a previous paragraph IV certification for the same patent has been received).

[4] A recent district court decision disagreed with FDA's long-standing "patent-by-patent" approach to pre-MMA exclusivity. See *Watson Labs., Inc. v. Sebelius*, Civ. Action No. 12-1344, 2012 U.S. Dist. LEXIS 185685 (D.D.C. Oct. 22, 2012). This decision was vacated and dismissed as moot by the U.S. Court of Appeals for the D.C. Circuit, however. *Watson Labs., Inc. v. Sebelius*, No. 02-5332, 2013 U.S. App. LEXIS 117116 (D.C. Cir. June 10, 2013).

[5] See Letter fr. J. Woodcock to R. Green, S. Sklar, and K. Beardsley, FDA Docket No. 99P-1271/PSA1 and PSA2, at 4 (Aug. 2, 1999); (b) (4) We note that for ANDAs that are covered by the 2003 amendments in the MMA, this problem was rectified by Congress when it altered the statute to award exclusivity only to an ANDA applicant that submitted the first paragraph IV certification for any patent listed for the drug product.

[6] See, e.g., Letter fr. G. Buehler to Barr Laboratories, Inc., at 2-3 (Oct. 14, 2004) (re. approval of ANDA 76-863, concluding Barr Laboratories was the only applicant to be a first filer on two patents that were not listed at the same time); (b) (4) Letter to Ranbaxy Inc. fr. G. Buehler, FDA Office of Generic Drugs re ANDA 76413 for metformin extended-release tablets, 500 mg (June 18, 2004) (noting Ranbaxy not originally eligible for final approval because two other applicants were first to file paragraph IV certifications to the relevant patents) (Ranbaxy Metformin Letter).

applicants that share the exclusivity.[7] During that "shared" exclusivity period, FDA may approve any ANDA eligible for exclusivity and otherwise ready for approval, but no other ANDAs.[8] "First commercial marketing" under these provisions includes marketing under many different circumstances including marketing by a first applicant under its own ANDA, and marketing by a first applicant pursuant to an "authorized generic" agreement with the RLD sponsor, irrespective of whether the first applicant's own ANDA has been approved.[9]

To note, FDA has interpreted the Act and regulations to prohibit "rolling" exclusivity in many circumstances. For example, if the first applicant with a valid paragraph IV certification subsequently withdraws its application or changes or withdraws its paragraph IV certification, no subsequent ANDA applicant will be eligible for 180-day exclusivity.[10] In addition, FDA permits an ANDA applicant that is eligible for 180-day exclusivity to relinquish all claims to 180-day exclusivity prior to approval, which eliminates the bar to approval of a subsequent ANDA applicant based on that exclusivity.[11]

I. FACTUAL BACKGROUND

A. Evista NDA 20815

Evista (raloxifene hydrochloride) tablets, 60 mg was approved on December 9, 1997 for the prevention of osteoporosis in postmenopausal women. This indication was modified to include treatment of osteoporosis in postmenopausal women with approval of Supplement No. 3 on September 30, 1999. Evista was awarded five years of new chemical entity (NCE) exclusivity

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[7] Letter to B. Rein fr. W. Hubbard re. FDA Docket No. 2004-P-0227, at 3, note 3 (July 2, 2004) (Gabapentin CP Response); Ranbaxy Metformin Letter, at 2-3.

[8] Gabapentin CP Response, at 3. See also FDA Topiramate Letter, at 2.

[9] See, e.g., FDA Citizen Petition Response, at 7, FDA Docket No. 2000P-1446 (Feb. 6, 2001) (finding Mylan's marketing of an authorized generic of Pfizer's nifedipine product post-ANDA approval triggered Mylan's 180-day exclusivity period) (upheld in *Mylan Pharmaceuticals, Inc. v. Thompson*, 207 F. Supp. 2d 476 (N.D.W.Va. 2001); (b) (4)

[10] *180-Day Generic Drug Exclusivity for Abbreviated New Drug Application; Proposed Rule*, 64 FR 42873, 42875 (Aug. 6, 1999), *withdrawn on unrelated grounds*, *Withdrawal, 180-Day Generic Drug Exclusivity for Abbreviated New Drug Applications; Proposed rule*, 67 FR 66593, 66593 (Nov. 1, 2002).

[11] See Gabapentin CP Response, at 12 (agency concluding that waiver and relinquishment of 180-day exclusivity are permitted under section 505(j)(5)(B)(iv) of the FD&C Act; that practice is consistent with the Agency's permitting waiver and relinquishment of new chemical entity, new clinical investigation, and pediatric exclusivity; and that waiver and relinquishment of 180-day exclusivity advance a fundamental objective of the Hatch-Waxman amendments by promoting competition in the pharmaceutical marketplace).

upon approval with this exclusivity expiring on December 9, 2002. As of the date of this memo the following patents are listed in the Orange Book for Evista NDA 20815.

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
N020815	001	5478847	Mar 2, 2014			U - 114
N020815	001	5811120	Mar 2, 2014			
N020815	001	5972383	Mar 2, 2014			U - 287
N020815	001	6458811	Mar 10, 2017	Y	Y	U - 825
N020815	001	6797719	Mar 10, 2017		Y	
N020815	001	6894064	Mar 10, 2017		Y	U - 657
N020815	001	8030330	Mar 10, 2017		Y	
N020815	001	RE39050	Mar 2, 2014			U - 657
N020815	001	RE39050	Mar 2, 2014			U - 662

B. 180-day Exclusivity for ANDAs Referencing Evista

[redacted] (b) (4) then amended its ANDA on the following dates to provide PIV certifications to several later-listed patents:

- Patent No. 6458811 [redacted] (b) (4)

- Patent No. 6797719 (b) (4)
- Patent No. 6894064 (b) (4)
- Patent No. RE39050 (b) (4)
- Patent No. 8030330 (b) (4)

On March 2, 2014, four of the patents that protect Evista will expire. These four patents are Patent Nos. 5478847, 5811120, 5972383, and RE39050. With the expiration of these patents, all claims to 180-day exclusivity related to these patents will elapse. This will leave the possibility for 180-day exclusivity after March 2, 2014 related to Patent Nos. 6458811, 6797719, 6894064 and 8030330, all of which expire on March 10, 2017. (b) (4) PIV certifications and resulting notice on Patent Nos. 6458811, 6797719 and 6894064 predate the submission of the next ANDA submitted to FDA, that being TEVA's ANDA 78193 submitted on March 3, 2006. Therefore, it is undisputed (b) (4) is solely eligible for 180-day exclusivity related to Patent Nos. 6458811, 6797719 and 6894064.

Both (b) (4) and TEVA submitted a PIV certification to Patent No. 8030330 on October 28, 2011, which is the earliest possible date that a valid PIV certification could be made to the '330 patent because this date is the date that the '330 patent was submitted for listing in NDA 20815. Both TEVA and (b) (4) provided documentation to their respective ANDAs indicating that notice was submitted simultaneously with the submission of their PIV certifications to this patent. Under these circumstances, both (b) (4) and TEVA share eligibility for 180-day exclusivity with respect to the '330 patent.[12]

Under a pre-MMA patent-by-patent exclusivity analysis, (b) (4) is the only applicant eligible for 180-day exclusivity for raloxifene hydrochloride tablets, 60 mg because the company is solely eligible for exclusivity for the '811, '719 and '064 patents, and shares eligibility for 180-day exclusivity for the '330 patent. As (b) (4) ANDA is not blocked on or after March 2, 2014, by another applicant's eligibility for 180-day exclusivity, (b) (4) will be eligible for full approval on or after March 2, 2014. (b) (4)

[12] (b) (4) was also first to file on patent no. 5731327. FDA removed this patent from the Orange Book in January 2003 per the RLD holder's request. This was prior to the decision of the D.C. Circuit that directed FDA to maintain patent information in the Orange Book when ANDA sponsors had filed PIVs to the patent notwithstanding a request by the RLD to delist the patent. *Ranbaxy Labs. Ltd. v. Leavitt*, 469 F.3d 120 (D.C. Cir. 2006). Because the patent is not listed in the Orange Book, and neither (b) (4) nor TEVA are required to certify to it, the patent is not a potential bar to FDA approval.

On February 19, 2014, TEVA submitted a letter to ANDA 78193.[13] (b) (4) [redacted] (b) (4)[14]

C. Relinquishment of Exclusivity

Relinquishment of eligibility for 180-day exclusivity has been permitted by FDA since 1997.[15] Since 1997, there have been other instances of relinquishment of eligibility for 180-day exclusivity by applicants that are otherwise eligible for the 180-day exclusivity seat. However, in all previous case of relinquishment of eligibility for 180-day exclusivity, the relinquishment has been an outright relinquishment of eligibility for exclusivity as it relates to a given drug product as a whole, not a patent-by-patent relinquishment. (b) (4) [redacted]

Upon consideration of the relevant law and facts, FDA has determined that (b) (4) may relinquish its eligibility for exclusivity related to the '811, '719 and '064 patents. Under the patent-by-patent approach to exclusivity that is applied in the pre-MMA context, each patent is treated as a separate basis for 180-day exclusivity. It follows that under this approach, an ANDA applicant may relinquish its eligibility on a patent-by-patent basis as well. We note that relinquishment in this case furthers the goals of the Hatch-Waxman Amendments of facilitating the earliest approval and market entry of a generic version of Raloxifene Hydrochloride Tablets, 60 mg.

[13] Letter to K. Uhl, Acting Dir. FDA Office of Generic Drugs, fr. S. Tomsky, Vice President, Teva U.S. Generics, Reg. Affairs re. ANDA # 078193 (Jan. 27, 2014).

[14] Id., at 1.

[15] Gabapentin CP Response, at 4-5.

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/s/

MARTIN H Shimer
03/03/2014

EASILY CORRECTABLE DEFICIENCY EMAIL

ANDA 078193

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

APPLICANT: Teva Pharmaceuticals USA TEL: (215) 591-3142

ATTN: Scott D. Tomsky FAX: (215) 591-8812

FROM: Bic Nguyen FDA CONTACT PHONE: (240) 276-9661

Dear Sir:

This communication is in reference to your abbreviated new drug application (ANDA) dated March 2, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Raloxifene Hydrochloride Tablets USP, 60 mg.

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies within ten (10) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
CHEMISTRY

If you do not submit a complete response within ten (10) U.S. business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments.

If you are unable to submit a complete response within ten (10) U.S. business days, please contact the Regulatory Project Manager immediately so a complete response may be issued if appropriate.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review.

If you have questions regarding these deficiencies please contact the Regulatory Project Manager, Bic Nguyen at (240)-276-9661.

We have completed our review, as amended, and have the following comments:

PRODUCT QUALITY

(b) (4)

Sincerely yours,

{See appended electronic signature page}

Andre S. Raw, Ph.D.
Director
Division of Chemistry I
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/

GURURAJ BYKADI
12/23/2013

EASILY CORRECTABLE DEFICIENCY EMAIL

ANDA 078193

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

APPLICANT: Teva Pharmaceuticals USA TEL: 215-591-3142

ATTN: Scott D. Tomsky FAX: 215-591-8812

FROM: Danbi Lee FDA CONTACT PHONE: 240-276-8527

Dear Sir:

This communication is in reference to your abbreviated new drug application (ANDA) dated March 2, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Raloxifene Hydrochloride Tablets USP, 60 mg.

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies within ten (10) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFFICIENCY
CHEMISTRY

If you do not submit a complete response within ten (10) U.S. business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments.

If you are unable to submit a complete response within ten (10) U.S. business days, please contact the Regulatory Project Manager immediately so a complete response may be issued if appropriate.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review.

If you have questions regarding these deficiencies please contact the Regulatory Project Manager, Danbi Lee at 240-276-8527.

We have completed our review, as amended, and have the following comments:

PRODUCT QUALITY

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

Sincerely yours,

{See appended electronic signature page}

Andre S. Raw, Ph.D.
Director
Division of Chemistry I
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/

GURURAJ BYKADI
10/25/2013

COMPLETE RESPONSE

ANDA 078193

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

TO: TEVA Pharmaceuticals USA

TEL: 215-591-8725

ATTN: Jean W. Zwicker

FAX: 215-591-8812

FROM: Christina Kirby

FDA CONTACT PHONE: 240-276-8519

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated March 2, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Raloxifene Hydrochloride Tablets USP, 60 mg.

We have completed the review and have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (____ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 78193

COMPLETE RESPONSE

TEVA Pharmaceuticals USA
Attention: Jean W. Zwicker
425 Privet Road
Horsham, PA 19044

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated March 2, 2006, received March 3, 2006, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Raloxifene Hydrochloride Tablets USP, 60 mg.

Reference is also made to the tentative approval letter issued by this office on April 16, 2008, and to your amendments dated July 8, October 3, and October 20, 2008; January 21, 2009; and June 28, 2012.

We have completed our review of this ANDA and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

The deficiencies presented below represent MINOR deficiencies.

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

4. (b) (4)

5.

6.

7.

8.

9.

BIOEQUIVALENCE

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

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

LABELING

The Division of Labeling has completed its review of your last labeling amendment dated January 21, 2009 and has no further questions.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.
In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

OTHER

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle. The resubmission to this will be considered to represent a **MINOR AMENDMENT**. The designation as a **RESUBMISSION/AFTER ACTION MINOR COMPLETE RESPONSE AMENDMENT** should appear prominently in your cover letter. In addition, please designate in bold on your cover letter each review discipline (Product Quality (CMC), Labeling, Bioequivalence, Microbiology, Clinical) you are providing responses to.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.65. You may also request an extension of time in which to resubmit the ANDA. A resubmission response must fully address all the deficiencies listed.

The drug product may not be legally marketed until you have been notified in writing that this ANDA is approved.

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

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees

when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

If you have any questions, call Christina Kirby, Regulatory Project Manager, at (240) 276-8519.

Sincerely yours,

{See appended electronic signature page}

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

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/s/

ROBERT L WEST

05/15/2013

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

OGD APPROVAL ROUTING SUMMARY

ANDA # 78-193 Applicant TEVA Pharmaceuticals USA
Drug Raloxifen HCl Tablets Strength(s)60 mg

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

REVIEWER: **DRAFT Package** **FINAL Package**

1. **Martin Shimer** Date5 Feb 2008 Date_____
Chief, Reg. Support Branch Initials MHS Initials_____
Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☐
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD =_____ NDA#_____
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked _____
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☒ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☒ No ☐ Study Submitted ☐
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:TA
Comments:ANDA submitted on 3/3/2006 with PIV certs to the '763, '117, '847, '120, '383, '811, '719, '064, '086, and '968 patents. On 3/28/2006 TEVA submitted PIV certs to the '049 and '050 patents. According to a note on the MC rec'd by the Agency on 3/30/2006, the '049 and '050 patents were listed on 3/30/2006. ANDA was ACK for filing with PIV on 3/3/2006(LO dated 4/27/2006). On 7/17/2006, Finnegan, Henderson submitted a correspondence in which they informed FDA that CA # 1:06-cv-1017-SEB-VSS was filed in the Southern D of IN on 7/29/2006 for infringement of the '050, '968, '049 and '086 patents. TEVA notified OGD of same information on 7/21/2006. (b) (4) show deliver to Eli Lilly on 5/16/2006. Therefore, the 30 month stay of approval is 11/16/2008. On 1/28/2008 TEVA provided a revised exclusivity statement in which they expressed their intent to carve out claims associated with I-539.

ANDA eligible for TA only due to unexpired 30 month stay of approval.

2. Project Manager, Ben Danso Team5 Date1-31-08 Date_____
Review Support Branch Initials bd Initials_____

Original Rec'd date3-2-06
Date Acceptable for Filing3-3-06
Patent Certification (type)P4
Date Patent/Exclus.expires
Citizens' Petition/Legal Case Yes☐ No ☐
(If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐
Priority Approval Yes ☒ No ☐
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio review tabbed Yes ☒ No ☐
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 6-1-06
Date of Office Bio Review 2-20-07
Date of Labeling Approv. Sum 2-6-07
Date of Sterility Assur. App.
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☒
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement
Reviewer: Labeling Team Leader:
Date_____ Date_____
Name/Initials_____ Name/Initials_____

Comments:

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 3/5/08
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials DTR
Comments:Changes to TA ltr saved to V drive.

5. Div. Dir./Deputy Dir. Date 3/4/08
Chemistry Div. I II OR III Initials PS
Comments:CMC is OK current dissolution data provided

6. Frank Holcombe **First Generics Only** Date _____
Assoc. Dir. For Chemistry Initials _____
Comments: (First generic drug review)

7. Vacant Date _____
Deputy Dir., DLPS Initials _____

8. Peter Rickman Date 4/16/2008
Director, DLPS Initials wpr
Para.IV Patent Cert: Yes☒ No☐;Pending Legal Action: Yes ☒No ☐;Petition: Yes☐ No☒
Comments:applicant made PIVs to all listed patents and was sued on the '050, '968, '049 and '086 patents; 30 month stay expires 11/16/2008; W/H exclusivity I-539 indication has been caved-out of proposed labeling; Labeling acceptable 2/6/2007 per TA Summary; Bio accepatble 1/5/2007 (fasting & Fed studies acceptable) 7/20/2007 (diss acceptable); EER acceptable 6/1/2006

Okay for TA only

OR

8. Robert L. West Date _____
Deputy Director, OGD Initials _____
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Press Release Acceptable ☐
Comments:

9. Gary Buehler Date _____
Director, OGD Initials _____
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Team Ben Danso Date 4/16/08
Review Support Branch Initials se

_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
3:15pmTime notified of approval by phone
3:23pmTime approval letter faxed

FDA Notification:
4/16Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.

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

/s/

Simon Eng

4/17/2008 07:07:33 AM

BIOEQUIVALENCY AMENDMENT

ANDA 78-193

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: TEVA Pharmaceuticals USA TEL: 215.591.3141

ATTN: Philip Erickson FAX: 215.591.8812

FROM: Steven Mazzella PROJECT MANAGER: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on March 22, 2007, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Raloxifene HCl Tablets, 60 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **1** 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**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and 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 both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

ANDA: 78-193

APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Raloxifene Hydrochloride Tablet, 60 mg

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

Your proposed dissolution method, using 900 mL of 1% SLS in 0.05 M sodium phosphate buffer, Apparatus II at 75 rpm, is acceptable. However, based on the data submitted in your original application, DBE recommends the following specification:

Not less than 80% (Q) of the labeled amount of drug in the dosage form is dissolved in 45 minutes.

Please acknowledge your acceptance of the above dissolution method and specification.

Sincerely Yours,

{See appended electronic signature page}

Dale P. Connor, Pharm.D.
Director, Division of Bioequivalence
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 Davit
5/2/2007 03:56:52 PM
Signing for Dale P Conner

BIOEQUIVALENCY AMENDMENT

ANDA 78-193

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: TEVA Pharmaceuticals USA TEL: 215.591.3141

ATTN: Philip Erickson FAX: 215.591.8812

FROM: Steven Mazzella PROJECT MANAGER: (301) 827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on March 02, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Raloxifene HCl Tablets, 60 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **1** 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**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and 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 both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-193 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Raloxifene Hydrochloride Tablet, 60 mg

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

Please conduct dissolution testing on the test and reference products (12 units each) using the following FDA-recommended method and resubmit the results with individual data as well as mean, range and CV%. The dissolution testing should be conducted in 1000mL of 0.1% Polysorbate 80 in water (@ 37°C) using USP Apparatus II (paddle) at 50 rpm. The recommended sampling time points are 10, 15, 20 and 30 minutes.

The test product should meet the following specification:

NLT 80%(Q)in 30 minutes.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Barbara Davit
1/11/2007 04:03:48 PM
Signing for Dale P Conner

MINOR AMENDMENT

ANDA 78-193

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: TEVA Pharmaceuticals USA TEL: 215-591-3141

ATTN: Philip Erickson FAX: 215-591-8812

FROM: Benjamin Danso PROJECT MANAGER: (301) 827-5763

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated March 02, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Raloxifene HCl Tablets, 60 mg.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__1__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. 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. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS: Chemistry comments provided. Please include in response.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-193 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Raloxifene Hydrochloride Tablets, 60 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. DMF (b) (4) has been found inadequate. The DMF holder has been notified. Please do not respond to this letter until the DMF holder has informed you that a complete response to the DMF deficiencies has been submitted to the agency.

2. (b) (4)

3.

4.

5.

6.

7.

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

1. Your reply should also address the labeling deficiencies provided to you by the Division of Labeling.

2. Your reply should also address the bioequivalence deficiencies provided to you by the Division of Bioequivalence.

3. Please provide any additional long term stability data for all strengths of the drug product.

Sincerely yours,

{See appended electronic signature page}

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
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/

Gururaj Bykadi
10/25/2006 12:46:56 PM
for R. Patel

BIOEQUIVALENCY AMENDMENT

ANDA 78-193

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JUL 14 2006

APPLICANT: TEVA Pharmaceuticals USA TEL: 215.591.3141

ATTN: Philip Erickson FAX: 215.591.8812

FROM: Aaron Sigler PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on March 02, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Raloxifene HCl Tablets, 60 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. 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**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and 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 both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-193 APPLICANT: Teva Pharmaceuticals

DRUG PRODUCT: Raloxifene Hydrochloride Tablets, 60 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 conducted later. The following deficiency has been identified:

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

USP Apparatus:	II(paddle)@ 50 rpm
Dissolution Medium:	0.1% Polysorbate 80 in water (@ 37°C)
Volume of Dissolution Medium:	1000 mL
Sampling Times:	10, 15, 20, 30 minutes or until at least 80% of the labeled amount is dissolved.

The results should be submitted in electronic CTD format, with individual data as well as mean, range and CV% data included.

Sincerely yours,

Barbara Davit for

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 78-193

TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

APR 27 2006

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to your correspondence dated March 28, 29, 30 and March 31, 2006. Reference is also made to your correspondence dated April 3, 4, 5, 6 and 7, 2006.

NAME OF DRUG: Raloxifene Hydrochloride Tablets, 60 mg

DATE OF APPLICATION: March 2, 2006

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 3, 2006

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet " PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

You must submit a copy of a court order or judgement or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (301) 827-0503.

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:

Simon Eng
Project Manager
(301) 827-5765

Sincerely yours,

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

ANDA 78-193
cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-92

Endorsement:
HFD-615/M. Shimer, Chief, RSB _____ date 27 APR 06
HFD-615/S. Middleton, CSO _____ date 4/27/06
Word File
V:/FIRMSNZ\TEVA\LTRS&REV\78193.ACK
FT by StM 4/27/06
ANDA Acknowledgment Letter!