

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 90842

Name: Raloxifene Hydrochloride Tablets USP, 60 mg

Sponsor: InvaGen Pharmaceuticals, Inc.

Approval Date: September 24, 2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90842

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APPLICATION NUMBER:

ANDA 90842

APPROVAL LETTER



ANDA 090842

InvaGen Pharmaceuticals, Inc.
Attention: Ram Mohan Kathuroju
Director-Regulatory Affairs
7 Oser Avenue
Hauppauge, NY 11788

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated October 2, 2008, 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 letter issued by this office on March 4, 2014, and to your amendments dated July 14, August 19, September 8, and September 22, 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, 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"):

<u>U.S. Patent Number</u>	<u>Expiration Date</u>
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 InvaGen Pharmaceuticals, Inc. (InvaGen) complied with the requirements of section 505(j)(2)(B) of the Act, and litigation for infringement of the '811, '719, and '064 patents was brought against InvaGen within the statutory 45-day period in the United States District Court for the Southern District of Indiana, Indianapolis Division [Eli Lilly and Company v. InvaGen Pharmaceuticals, Inc., Civil Action No. 1:09-CV-0087-DFH-TAB]. You have also notified the agency that Lilly has voluntarily dismissed its litigation against InvaGen. With respect to the '330 patent, you have notified the agency that no action for infringement was brought against InvaGen.

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

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

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

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

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

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

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

failure to self-identify or pay facility fees are subject to being denied entry into the United States.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

CAPT Jason J.Y. Woo, M.D., M.P.H.
Acting Director, Office of Regulatory Operations
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

09/24/2014

Associate Director for Review Quality, for
Jason Woo, M.D., M.P.H.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90842

OTHER ACTION LETTERS



ANDA 090842

InvaGen Pharmaceuticals, Inc.
Attention: Ram Mohan Kathuroju
Director-Regulatory Affairs
7 Oser Avenue
Hauppauge, NY 11788

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated October 2, 2008, 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 made to the tentative approval letter issued by this office on June 21, 2012, and to your amendment dated December 23, 2013.

We have completed the review of this ANDA as amended, 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 remain unable to grant final approval to your ANDA at this time because of the exclusivity issue noted below. Therefore, the ANDA remains **tentatively approved**. This determination is based upon information available to the agency at this time (i.e., information in your ANDA and the status of current good manufacturing practice (cGMP) at the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to our attention.

The reference listed drug (RLD) upon which you have based your ANDA, Evista Tablets, of Eli Lilly (Lilly), 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"):

<u>U.S. Patent Number</u>	<u>Expiration Date</u>
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 the patents are 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 InvaGen Pharmaceuticals, Inc. (InvaGen) complied with the requirements of section 505(j)(2)(B) of the Act, and litigation for infringement of the '811, '719, and '064 patents was brought against InvaGen within the statutory 45-day period in the United States District Court for the Southern District of Indiana, Indianapolis Division [Eli Lilly and Company v. InvaGen Pharmaceuticals, Inc., Civil Action No. 1:09-CV-0087-DFH-TAB]. You have also notified the agency that litigation was dismissed.

However, we are unable at this time to grant final approval to your ANDA. Prior to the submission of your ANDA, other applicants submitted substantially complete ANDAs providing for Raloxifene Hydrochloride Tablets USP, 60 mg, and containing paragraph IV certifications to the '811, '719, '064 and '330 patents. Your ANDA will be eligible for final approval on the date that is 180 days after the date the agency receives notice, with respect to one of the other ANDAs, of the commercial marketing or court decision dates identified in section 505(j)(5)(B)(iv) of the Act.¹

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

To reactivate your ANDA prior to final approval, please submit a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your ANDA will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval and should include a

¹ Because one of the other ANDAs 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, this reference to the 180-day exclusivity provision is to the section of the Act as in effect prior to December 8, 2003. See MMA § 1102(b)(1).

copy of a court decision, or a settlement or licensing agreement, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a MINOR AMENDMENT - FINAL APPROVAL REQUESTED.

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

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

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

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.

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.

For further information on the status of this ANDA, or prior to submitting additional amendments, please contact Bic Nguyen, Project Manager, at (240)276-9661.

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.



ANDA 090842

InvaGen Pharmaceuticals, Inc.
Attention: Sudhakar Vidiyala
President
7 Oser Avenue
Hauppauge, NY 11788

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated October 2, 2008, 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 your amendments dated January 20, 2008; July 7, and July 22, 2009; March 24, June 14, June 17, and December 6, 2010; May 16, and August 12, 2011; and February 16, 2012. We also acknowledge receipt of your correspondences dated December 29, 2008; February 23, and April 2, 2009; November 18, November 22, and November 28, 2011; and January 16, 2012, addressing patent issues associated with this ANDA.

We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your ANDA at this time because of the 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 practice (cGMP) of the facilities used in the manufacturing and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention.

The reference listed drug (RLD) upon which you have based your ANDA, Evista Tablets of Eli Lilly (Lilly), 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"):

<u>U.S. Patent Number</u>	<u>Expiration Date</u>
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
8,030,330 (the '330 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

With respect to the '120, '383, '811, '719, '064, and '330 patents, your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Raloxifene Hydrochloride Tablets USP, 60 mg, under this ANDA. You have notified the agency that InvaGen Pharmaceuticals, Inc. (InvaGen) complied with the requirements of section 505(j)(2)(B) of the Act, and litigation for infringement of the '811, '719, and '064 patents was brought against InvaGen within the statutory 45-day period in the United States District Court for the Southern District of Indiana, Indianapolis Division [Eli Lilly and Company v. InvaGen Pharmaceuticals, Inc., Civil Action No. 1:09-CV-0087-DFH-TAB]. You have also notified the agency that Lilly has voluntarily dismissed its litigation against InvaGen without prejudice. With respect to the '120, '383, and '330¹ patents, you have notified the agency that no action for infringement was brought against InvaGen.

With respect to the '763, '117, '847, '086, '968, '049, and '050 patents, your ANDA contains paragraph III certifications under section 505(j)(2)(A)(vii)(III) of the Act stating that InvaGen will not market Raloxifene Hydrochloride Tablets USP, 60 mg, prior to the expiration of these patents. Therefore, final approval of your ANDA may not be made effective pursuant to section 505(j)(5)(B)(ii) of the Act until the '847 and the '050 patents have expired, currently, March 2, 2014.

¹We note that the '330 patent was listed in the Orange Book after receipt of your ANDA.

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

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

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

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

This drug product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the Act. Also, until the agency issues the final approval letter, this drug product will not be deemed approved for marketing under section 505 of the Act, and will not be listed in the "Orange Book." Should you believe that there are grounds for issuing the final approval letter prior to March 2, 2014, you should amend your ANDA accordingly.

For further information on the status of this ANDA or upon submitting an amendment to the ANDA, please contact Christina Kirby, Pharm.D, Regulatory Project Manager, at 240-276-8573.

Sincerely yours,

{See appended electronic signature page}

Keith Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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

/s/

ROBERT L WEST

06/21/2012

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90842

LABELING

Raloxifene Hydrochloride Tablets USP 60 mg 30s count
Final Printed Container Label: Bottle Size: 50 / 60 cc

Each film-coated tablet contains 60 mg raloxifene hydrochloride, USP.
Store at 20°-25°C (68°-77°F). [See USP controlled room temperature.]

Dispense in a tight container.

Usual Adult Dosage
See accompanying package literature.

Rev.: 05/10

NDC 67787-256-30

Raloxifene Hydrochloride

Tablets, USP

60 mg

PHARMACIST: Dispense the Medication Guide provided separately to each patient.

30 TABLETS **Rx only**

 **InvaGen**

LOT

EXP



3 67787-256-30 4

Manufactured By :
InvaGen Pharmaceuticals, Inc.
Hauppauge, NY 11788

No Varnish

Size (In inches) : 1.312" x 3.5"



Raloxifene Hydrochloride Tablets USP 60 mg 1000s Count
Final Printed Container Label: Bottle Size: 150 cc

NDC 67787-256-10

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

Store at 20°–25°C (68°–77°F).
[See USP controlled room
temperature.]

Dispense in a tight container.

Usual Adult Dosage :
See accompanying package
literature.

Rev.: 05/10

**Raloxifene Hydrochloride
Tablets, USP**

60 mg

**PHARMACIST: Dispense the Medication Guide
provided separately to each patient.**

1000 TABLETS Rx only

 **InvaGen**

LOT :

No Varnish

EXP :



N
3 6 7 7 8 7 - 2 5 6 - 1 0 6

Manufactured By :
InvaGen Pharmaceuticals, Inc.
Hauppauge, NY 11788

Size (In inches) : 3 x 8





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 tablets (5.1). Women with active or past history of venous thromboembolism should not take raloxifene hydrochloride tablets (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).	
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 tablet, USP is an estrogen agonist/antagonist indicated for: Treatment 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)	

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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 tablets (see Warnings and Precautions (5.1)). Women with active or past history of venous thromboembolism should not take raloxifene hydrochloride tablets [see Contraindications (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 [see Warnings and Precautions (5.2) and Clinical Studies (14.5)].	
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1 INDICATIONS AND USAGE
1.1 Treatment of Osteoporosis in Postmenopausal Women

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

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosing

The recommended dosage is one 60 mg raloxifene hydrochloride tablet 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 osteoporosis treatment, 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 400-800 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 film coated round biconvex tablets (not scored) de-bossed with **IG** on one side and **256** 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 Warnings 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/m²), and hydrocephaly was observed in fetuses at doses ≥10 mg/kg (≥4 times the human dose based on surface area, mg/m²). 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/m²). 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/m²) during gestation and lactation resulted in decreased litter size, decreased birth weight, 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

WARNING: INCREASED RISK OF VENOUS THROMBOEMBOLISM AND DEATH FROM STROKE	
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 tablet, USP is an estrogen agonist/antagonist indicated for: Treatment 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)	

WARNING: INCREASED RISK OF VENOUS THROMBOEMBOLISM AND DEATH FROM STROKE	
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See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

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

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 tablets 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 tablets should be discontinued at least 72 hours prior to and during prolonged immobilization (e.g., post-surgical recovery, prolonged bed rest), and raloxifene hydrochloride tablets therapy should be resumed only after the patient is fully ambulatory. In addition, women taking raloxifene hydrochloride tablets 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 tablets. During an average follow-up of 5.6 years, 59 (1.2%) raloxifene hydrochloride tablets -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, 1.00-2.24; p=0.0499). There was no statistically significant difference between treatment groups in the incidence of stroke (249 in raloxifene hydrochloride tablets [4.9%] versus 224 placebo [4.4%]). Raloxifene hydrochloride tablets 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 tablets 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 tablets. Safety of raloxifene hydrochloride tablets in premenopausal women has not been established and its use is not recommended.

5.5 Hepatic Impairment

Raloxifene hydrochloride tablets 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 tablets 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 tablets. Women with this medical history should have serum triglycerides monitored when taking raloxifene hydrochloride tablets.

5.8 Renal Impairment

Raloxifene hydrochloride tablets 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 tablets have 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 tablets in men. Raloxifene hydrochloride tablets have 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 tablets-treated and placebo-treated groups had similar incidences of endometrial proliferation [see Clinical Studies (14.1)].

5.12 Breast Abnormalities

Any unexplained breast abnormality occurring during raloxifene hydrochloride tablets therapy should be investigated.

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 tablets 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 — 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 tablets-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 tablets-treated women and 8.8% of placebo-treated women.

Venous Thromboembolism: The most serious adverse reaction related to raloxifene hydrochloride tablets 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 tablets. Twenty-six raloxifene hydrochloride tablets-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 tablets therapy were hot flashes and leg cramps. Hot flashes occurred in about one in 10 patients on raloxifene hydrochloride tablets 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 tablets.

Table 1 lists adverse reactions occurring in osteoporosis treatment and placebo-controlled clinical trials at a frequency ≥2.0% in the 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 Tablets-Treated (60 mg Once Daily) Women than Placebo-Treated Women*

	Treatment	
	Raloxifene hydrochloride tablets N=2557 %	Placebo N=2576 %
Body as a Whole		
Infection	A	A
Flu Syndrome	13.5	11.4
Headache	9.2	8.5
Leg Cramps	7.0	3.7
Chest Pain	A	A
Fever	3.9	3.8
Cardiovascular System		
Hot Flashes	9.7	6.4
Migraine	A	A
Syncope	2.3	2.1
Varicose Vein	2.2	1.5
Digestive System		
Nausea	8.3	7.8
Diarrhea	7.2	6.9
Dyspepsia	A	A
Vomiting	4.8	4.3
Flatulence	A	A
Gastrointestinal Disorder	A	A
Gastroenteritis	B	B
Metabolic and Nutritional		
Weight Gain	A	A
Peripheral Edema	5.2	4.4
Musculoskeletal System		
Arthralgia	15.5	14.0
Myalgia	A	A
Arthritis	A	A
Tendon Disorder	3.6	3.1
Nervous System		
Depression	A	A
Insomnia	A	A
Vertigo	4.1	3.7
Neuralgia	2.4	1.9
Hypesthesia	2.1	2.0
Respiratory System		
Sinusitis	7.9	7.5
Rhinitis	10.2	10.1
Bronchitis	9.5	8.6
Pharyngitis	5.3	5.1
Cough Increased	9.3	9.2
Pneumonia	A	A
Laryngitis	B	B
Skin and Appendages		
Rash	A	A
Sweating	2.5	2.0
Special Senses		
Conjunctivitis	2.2	1.7
Urogenital System		
Vaginitis	A	A
Urinary Tract Infection	A	A
Cystitis	4.6	4.5
Leukorrhea	A	A
Uterine Disorder, †	3.3	2.3
Endometrial Disorder†	B	B
Vaginal Hemorrhage	2.5	2.4
Urinary Tract Disorder	2.5	2.1

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

† Includes only patients with an intact uterus: raloxifene hydrochloride tablets treatment trial; Treatment Trial: n=1948, Placebo, n=1999.

‡ Actual terms most frequently referred to endometrial fluid.

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

Gynecologic Cancers — Raloxifene-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 — The safety of raloxifene (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. Therapy was discontinued due to an adverse reaction in 25% of 5044 raloxifene-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-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 tablets is not recommended. Although not specifically studied, it is anticipated that other anion exchange resins would have a similar effect. Raloxifene hydrochloride tablets should not be co-administered with other anion exchange resins [see Clinical Pharmacology (12.3)].

7.2 Warfarin

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

7.3 Other Highly Protein-Bound Drugs

Raloxifene hydrochloride tablets should be used with caution with certain other highly protein-bound drugs such as diazepam, diazoxide, and lidocaine. Although not examined, raloxifene hydrochloride tablets 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 tablets with systemic estrogens has not been established and its use is not recommended.

7.5 Other Concomitant Medications

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

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

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 a osteoporosis treatment trial, raloxifene hydrochloride tablets 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 tablets 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 tablets 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 tablets 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 trial 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 tablets 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 1-acid glycoprotein, but not to sex-steroid binding globulin. Metabolism — Biotransformation and disposition of raloxifene in humans have been determined following oral administration of 14C-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 2: Summary of Raloxifene Pharmacokinetic Parameters in a Healthy Postmenopausal Woman

	C _{max} •† (ng/mL)/ (mg/kg)	t _{1/2} (hr)*	AUC _{0-∞} •† (ng•hr/mL)/ (mg/kg)	CL/F* (L/kg•hr)	V/F* (L/kg)
Single Dose	0.50	27.7	27.2	44.1	2348
Mean CV* (%)	52	10.7 to 273‡	44	46	52
Multiple Dose	1.36	32.5	24.2	47.4	2853
Mean CV* (%)	37	15.8 to 86.6‡	36	41	56

* 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. † Data normalized for dose in mg and body weight in kg.

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

Renal Impairment — In a osteoporosis treatment trial, 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 – 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-∞}) 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 total 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 (8.7)].

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 tablets 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 a single-dose study. In a osteoporosis treatment trial, there were no clinically relevant effects of warfarin co-administration on plasma concentrations of raloxifene [see Drug Interactions (7.2)].

Other Highly Protein-Bound Drugs — In a osteoporosis treatment trial, there were no clinically relevant effects of co-administration 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 co-administration 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 a osteoporosis treatment trial, co-administration of amoxicillin had no discernible effect on the pharmacokinetics of raloxifene [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 tablets with cyclosporine has not been studied.

Lipid-Lowering Agents — Concomitant administration of raloxifene hydrochloride tablets 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 unscheduled 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/m²) 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/m²) 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/m²), 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/m²), 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 tablets as a skeletal antiresorptive agent.

14 CLINICAL STUDIES

14.1 Treatment of Postmenopausal Osteoporosis

Effect on Fracture Incidence.

The effects of raloxifene hydrochloride tablets 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. 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 tablets, 60 mg administered once daily, increased spine and hip BMD by 2 to 3%. Raloxifene hydrochloride tablets decreased the incidence of the first vertebral fracture from 4.3% for placebo to 1.9% for raloxifene hydrochloride tablets (relative risk reduction = 55%) and subsequent vertebral fractures from 20.2% for placebo to 14.1% for raloxifene hydrochloride tablets (relative risk reduction = 30%) (see Table 4). All women in a study received calcium (500 mg/day) and vitamin D (400 to 600 IU/day). Raloxifene hydrochloride tablets 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.

	Number of Patients		Absolute Risk Reduction (ARR)	Relative Risk Reduction (95% CI)
	Raloxifene hydrochloride tablets	Placebo		
Fractures diagnosed radiographically				
Patients with no baseline fracture*	n=1401	n=1457		
Number (%) of patents with ≥1 new vertebral fracture	27 (1.9%)	62 (4.3%)	2.4%	55% (29%, 71%)
Patients with ≥1 baseline fracture*	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%)

* Includes all patients with baseline and at least one follow-up radiograph.

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

Table 4: Raloxifene hydrochloride tablets - (60 mg Once Daily) Related Increases in BMD* for the Osteoporosis Treatment Study Expressed as Mean Percentage Increase vs. Placebo†‡

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

* Note: all BMD increases were significant (p<0.001).

† Intent-to-treat analysis; last observation carried forward.

‡ All patients received calcium and vitamin 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 tablets 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 tablets-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 tablets-treated women had a 0.06 mm mean increase. Patients in a osteoporosis treatment study were not screened at baseline or excluded for pre-existing 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 tablets-treated women, and in 31 of 2010 women treated with raloxifene HCl 120 mg/day. There was no difference between raloxifene hydrochloride tablets- and placebo-treated women in the incidences of endometrial carcinoma, vaginal bleeding, or vaginal discharge.

14.5 Effects on Cardiovascular Disease

In a randomized, placebo-controlled, double-blind, multinational clinical trial 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 tablets 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 tablets was observed: 59 (1.2%) raloxifene hydrochloride tablets-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, 1.00-2.24; p=0.0499). The incidence of stroke did not differ significantly between treatment groups (249 with raloxifene hydrochloride tablets [4.9%] versus 224 with placebo [4.4%]; hazard ratio 1.10; 95% confidence interval 0.92-1.32; 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 60 mg are white film coated round biconvex, de-bossed with **IG** on one side and **256** on the other, supplied in bottles of 30 (NDC 67787-256-30) and 1000 (NDC 67787-256-10).

16.2 Storage and Handling

Store at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP]. 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 tablets and to reread it each time the prescription is renewed.

17.1 Osteoporosis Recommendations, Including Calcium and Vitamin D Supplementation

For osteoporosis treatment, 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 tablets 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 tablets 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 tablets therapy.

Medication Guide
Raloxifene Hydrochloride Tablets, USP for Oral Use
Read the Medication Guide that comes with raloxifene hydrochloride tablets before you start taking it 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 it 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 is raloxifene hydrochloride?

Raloxifene hydrochloride is a type of prescription medicine called a Selective Estrogen Receptor Modulator (SERM). Raloxifene hydrochloride is for women after menopause, and has more than one use:

- Osteoporosis: raloxifene hydrochloride tablets treat 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 tablets 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 it 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 it 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 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. Call your doctor for medical advice about side effects. You may report side effects to InvaGen Pharmaceuticals, Inc. at 1-877-354-3380 or FDA at 1-800-FDA-1088.

Medication Guide

Raloxifene Hydrochloride Tablets, USP for Oral Use

Read the Medication Guide that comes with raloxifene hydrochloride tablets before you start taking it 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 it and at regular checkups.

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

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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?”)

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Raloxifene hydrochloride is a type of prescription medicine called a Selective Estrogen Receptor Modulator (SERM). Raloxifene hydrochloride is for women after menopause, and has more than one use:

- Osteoporosis: raloxifene hydrochloride tablets treat 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:

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- 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

tablets passes into breast milk or what effect it might have on the baby.

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- 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*:

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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.

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- 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 it 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 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. Call your doctor for medical advice about side effects. You may report side effects to InvaGen Pharmaceuticals, Inc. at 1-877-354-3380 or FDA at 1-800-FDA-1088.

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 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 may make them worse 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.
- 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 tablets for up to eight years.

How should I store raloxifene hydrochloride tablets?

- Store raloxifene hydrochloride tablets at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP].
- 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 it was not prescribed. Do not give your raloxifene hydrochloride tablets to other people, even if they have the same symptoms you have. It 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.

What are the ingredients in raloxifene hydrochloride tablets?

Active Ingredient: raloxifene hydrochloride

Inactive Ingredients: mannitol, crospovidone, hydroxypropyl cellulose, poloxamer 407, magnesium stearate and opadry white (titanium Dioxide, hypromellose 2910 (3cP), hypromellose 2910 (6cP), macrogol/PEG 400 and polysorbate 80).

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

* Coumadin® is a registered trademark of Bristol-Myers Squibb Pharma Company and Jantoven® is a registered trademark of USL Pharma, Inc.

Manufactured By:

InvaGen Pharmaceuticals, Inc.

Hauppauge, NY 11788

Rev: 05/10

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 90842

LABELING REVIEWS

APPROVAL SUMMARY

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

ANDA Number: 090842

Dates of Submission: June 14, 2010 (amendment)

Applicant's Name: Invagen Pharmaceuticals, Inc.

Established Name: Raloxifene Hydrochloride Tablets USP, 60 mg

APPROVAL SUMMARY:

REMS required? (checked November 8, 2010)

☐ Yes ☒ No

REMS acceptable?

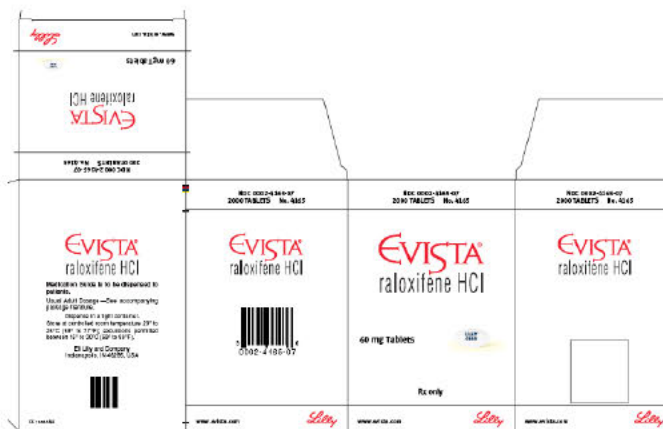
☐ Yes ☐ No ☒ n/a

1. Do you have Final Printed Labels and Labeling? Yes
2. CONTAINER (Bottles of 30s and 1000s):
Satisfactory in final print as submitted June 14, 2010.
3. PHYSICIAN INSERT
Satisfactory in final print as submitted June 14, 2010.
4. Stand-alone MEDICATION GUIDE
Satisfactory in final print as submitted June 14, 2010.
5. Revisions required post-approval: No.

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for Evista® Tablets (NDA 020815/S-025 approved September 13, 2007). NDA 020815/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 022042. NDA 022042 is a type 6 NDA and therefore not be listed in the OB. All exclusivity and updates are filed under the parent NDA 020815, 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 022042] should be addressed to the original NDA 020815 for this drug product, not to this NDA [NDA 22-042]. In the future, do not make submissions to this NDA [NDA 022042] except for the final printed labeling requested above."



USP: (checked October 13, 2010)

Raloxifene Hydrochloride Tablets

Packaging and storage— Preserve in tight containers, and store at controlled room temperature.

PF: (checked October 13, 2010)

ADDITIONAL REQUIREMENTS

- Packaging and Storage: Preserve in tight containers, and store at controlled room temperature.

2. PATENTS/EXCLUSIVITIES:

Information pertaining to the use of raloxifene hydrochloride tablets for prevention of osteoporosis in postmenopausal women and prevention of breast cancer has been carved out of Invagen's labeling. Invagen's product will only be indicated for the treatment of osteoporosis in postmenopausal women.

Patent Data for NDA 20-815 (current as of 5/15/09)

Patent No	Patent Expiration	Patent Use Code	How filed	Impact
5393763	JUL 28,2012	U-114	PIII	None
5457117	JUL 28,2012	U-114	PIII	None
5478847	MAR 02,2014	U-114	PIII	None
5811120	MAR 02,2014		PIV	None
5972383	MAR 02,2014	U-287	PIV	None
6458811	MAR 10,2017	U-825	Split Certification: PIV MOU for U-825	Carveout for U-825 (USE FOR PREVENTION OF BREAST CANCER)
6797719	MAR 10,2017		PIV	None
6894064	MAR 10,2017	U-657	Split Certification: PIV MOU for U-657	Carveout for U-657 (PREVENTION OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN)
6906086	JUL 28,2012	U-657	PIII	None
6906086	JUL 28,2012	U-662	PIII	None
RE38968	JUL 28,2012	U-662	PIII	None
RE38968	JUL 28,2012	U-657	PIII	None
RE39049	JUL 28,2012	U-662	PIII	None
RE39049	JUL 28,2012	U-657	PIII	None
RE39050	MAR 02,2014	U-662	PIII	None
RE39050	MAR 02,2014	U-657	PIII	None

Code Definition

U-114 USE FOR INHIBITING BONE RESORPTION

U-287 TREATMENT OR PREVENTION OF OSTEOPOROSIS

Reference ID: 2862990 OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

U-662 TREATMENT OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

U-825 USE FOR PREVENTION OF BREAST CANCER

InvaGen Pharmaceuticals, Inc., filed Paragraph IV certification for U.S patents 5811120, 5972383, 6458811, 6797719 and 6894064. Eli Lilly and company filed the patent infringement case against InvaGen Pharmaceuticals, Inc., in United States district court for the southern district of Indiana, Indianapolis Division. The patents-in-suit are U.S patents 6458811, 6797719 and 6894064.

Information on Split Certification from 12/29/08 XP Amendment:

The '811 patent has two independent claims (*i.e.*, claim 1 and 7) and fifteen dependent claims that depend directly or indirectly from claims 1 and 7. The '811 patent contains both composition and method claims.

Independent composition claims 1 and 7

Method claims 12-17

The '064 patent has one independent claims (*i.e.*, claim 1) and 11 dependent claims that depend directly or indirectly from claim 1. The '064 patent contains both composition and method claims.

Master Que Notes:

- 04/10/2009: SD 04/02/2009 & LD 04/03/09. Suit notice from innovator asking to stop approval until at least end of 30 month stay. tp
- 03/10/2009: LD 02/23/2009 & SD 02/26/2009. suit filed on 1/28/2009 in Southern D of IN for infringement of '811, '719, and '064. tp
- 01/08/2009: LD 12/29/2008 & SD 01/02/2009. Notice provided to patent holders. RR dated 12/22/2008.tp

Exclusivity Data

Exclusivity Code	Exclusivity Expiration	How filed
I-539	SEP 13, 2010	expired
ODE	SEP 13, 2014	Carve-out

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>

Due to Eli Lilly's marketing exclusivity rights for Evista[®] as an Orphan Drug, InvaGen's Raloxifene Hydrochloride drug product package insert label does not claim the Orphan Drug indication "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" and it intends to market its product before the Orphan Drug indication exclusivity expires.

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

InvaGen Pharmaceuticals Inc,
7 Oser Avenue,
Hauppauge, New York 11788
USA

4. CONTAINER/CLOSURE

RLD: 30s, 100s, 2000
ANDA: 30s and 1000s

Reference ID: 2862390

Bottle: white HDPE

Closure: 30s CRC; 1000s non-CRC

The proposed container/closure comply with USP <661> and USP <671> requirements.

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling is consistent with the composition statement.
Drug substance specification: "off white to pale yellow solid"

Item #	Ingredient	60 mg (mg/tablet)
1	Raloxifene Hydrochloride	60.0
2	Mannitol, USP (b) (4)	(b) (4)
3	Crospovidone, NF (b) (4)	
4	Hydroxy Propyl Cellulose, NF (b) (4)	
5	Polaxomer 407, NF (b) (4)	
6	(b) (4)	
7	(b) (4)	
8	Magnesium stearate, NF	
	(b) (4)	
9	Opadry White, (b) (4) (Titanium Dioxide, Hypromellose, Polyethylene glycol 400, Polysorbate 80)	
10	(b) (4)	
Total Tablet Weight		288.0
(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.

8. FINISHED PRODUCT COA -

RLD: White, elliptical and film coated tablets

ANDA: White, film coated round biconvex tablets de-bossed with IG on one side and 256 on the other.

9. MEDICATION GUIDE:

"Considering one month supply i.e., 30 tablets, firm will supply 34 medication guides for 1000's package size. The medication guides will be kept in shipping boxes and supplied to pharmacists."

10. SPL Statement provided in the October 2, 2008 submission:

Firm is committed to submit the Raloxifene Hydrochloride Tablets, 60 mg

package insert label in SPL format upon completion of labeling review.

Date of Review: November 10, 2010

Date of Submission: June 14, 2010

Primary Reviewer: Ruby Wu

Team Leader: Koung Lee

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

/s/

CHI-ANN Y WU
11/10/2010

KOUNG U LEE
11/16/2010
For Wm Peter Rickman

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

ANDA Number: 090842

Dates of Submission: July 7, 2009 (amendment)

Applicant's Name: Invagen Pharmaceuticals, Inc.

Established Name: Raloxifene Hydrochloride Tablets USP, 60 mg

Labeling Deficiencies:

1. GENERAL COMMENT:

Please respond to the following question on your cover letter: please comment on how many Medication Guides will be provided for each packaging configuration.

2. CONTAINER (Bottles of 30s and 1000s):

a. "Each film-coated tablet..."

b. Please revise the "PHARMACIST" statement to read:

"PHARMACIST: Dispense the enclosed Medication Guide to each patient." or

"PHARMACIST: Dispense the accompanying Medication Guide to each patient." Or

"PHARMACIST: Dispense the Medication Guide provided separately to each patient."

Please note that if the medication guides are not physically attached to the bottle of 1000s, please use the last statement.

3. PHYSICIAN INSERT

a. "CONTENTS" and "FULL PRESCRIBING INFORMATION" should be separated by a horizontal line [refer to 21 CFR 201.57(d)(2)].

b. The Agency recommends two-column format for the "HIGHLIGHTS" and "CONTENTS" sections.

c. HIGHLIGHTS, "To report SUSPECTED ADVERSE REACTIONS" subsection: To be in accord with 21 CFR 201.57(a)(11)(ii), please include the name and phone number of the manufacturer.

d. FULL PRESCRIBING INFORMATION

i. Throughout the insert, revise "in the" to read "in a" whenever you are referring to a study or trial conducted by the RLD.

ii. 6.1, third paragraph, subtitle: delete "(MORE)"

iii. Table 1, Title: "Table 1: Adverse Reactions Occurring in Placebo-Controlled Osteoporosis Clinical Trials at a Frequency $\geq 2.0\%$ and in more Raloxifene Hydrochloride Tablets -Treated (60 mg Once Daily) Women than Placebo-Treated Women"

iv. 12.3, third sentence: "...in systemic..." [add a space]

v. 14.1, first paragraph, first sentence: delete "(MORE)"

3. Stand-alone MEDICATION GUIDE

Revise to be consistent with the Medication Guide attached to the insert labeling.

Revise your labeling, as instructed above, and submit final printed labeling electronically.

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

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the previously submitted labeling with all differences annotated and explained.

NOTE TO CHEMIST:

REMS required?

☐ Yes ☒ No

REMS acceptable?

☐ Yes ☐ No ☒ n/a**FOR THE RECORD:****1. MODEL LABELING**

This review was based on the labeling for Evista® Tablets (NDA 020815/S-025 approved September 13, 2007). NDA 020815/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 022042. NDA 022042 is a type 6 NDA and therefore not be listed in the OB. All exclusivity and updates are filed under the parent NDA 020815, 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 022042] should be addressed to the original NDA 020815 for this drug product, not to this NDA [NDA 22-042]. In the future, do not make submissions to this NDA [NDA 022042] except for the final printed labeling requested above."



USP: The drug product is now subject to a USP 32 monograph (checked May 6, 2010)

Raloxifene Hydrochloride Tablets

Packaging and storage— Preserve in tight containers, and store at controlled room temperature.

REMS: none (checked May 6, 2010)

2. PATENTS/EXCLUSIVITIES:

Information pertaining to the use of raloxifene hydrochloride tablets for prevention of osteoporosis in postmenopausal women and prevention of breast cancer has been carved out of Invagen's labeling. Invagen's product will only be indicated for the treatment of osteoporosis in postmenopausal women.

Patent Data for NDA 20-815 (current as of 5/15/09)

Patent No	Patent Expiration	Patent Use Code	How filed	Impact
5393763	JUL 28,2012	U-114	PIII	None
5457117	JUL 28,2012	U-114	PIII	None
5478847	MAR 02,2014	U-114	PIII	None
5811120	MAR 02,2014		PIV	None
5972383	MAR 02,2014	U-287	PIV	None
6458811	MAR 10,2017	U-825	Split Certification: PIV MOU for U-825	Carveout for U-825 (USE FOR PREVENTION OF BREAST CANCER)
6797719	MAR 10,2017		PIV	None
6894064	MAR 10,2017	U-657	Split Certification: PIV MOU for U-657	Carveout for U-657 (PREVENTION OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN)

6906086	JUL 28,2012	U-657	PIII	None
6906086	JUL 28,2012	U-662	PIII	None
RE38968	JUL 28,2012	U-662	PIII	None
RE38968	JUL 28,2012	U-657	PIII	None
RE39049	JUL 28,2012	U-662	PIII	None
RE39049	JUL 28,2012	U-657	PIII	None
RE39050	MAR 02,2014	U-662	PIII	None
RE39050	MAR 02,2014	U-657	PIII	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

InvaGen Pharmaceuticals, Inc., filed Paragraph IV certification for U.S patents 5811120, 5972383, 6458811, 6797719 and 6894064. Eli Lilly and company filed the patent infringement case against InvaGen Pharmaceuticals, Inc., in United States district court for the southern district of Indiana, Indianapolis Division. The patents-in-suit are U.S patents 6458811, 6797719 and 6894064.

Information on Split Certification from 12/29/08 XP Amendment:

The '811 patent has two independent claims (*i.e.*, claim 1 and 7) and fifteen dependent claims that depend directly or indirectly from claims 1 and 7. The '811 patent contains both composition and method claims.

Independent composition claims 1 and 7

Method claims 12-17

The '064 patent has one independent claims (*i.e.*, claim 1) and 11 dependent claims that depend directly or indirectly from claim 1. The '064 patent contains both composition and method claims.

Master Que Notes:

- 04/10/2009: SD 04/02/2009 & LD 04/03/09. Suit notice from innovator asking to stop approval until at least end of 30 month stay. tp
- 03/10/2009: LD 02/23/2009 & SD 02/26/2009. suit filed on 1/28/2009 in Southern D of IN for infringement of '811, '719, and '064. tp
- 01/08/2009: LD 12/29/2008 & SD 01/02/2009. Notice provided to patent holders. RR dated 12/22/2008.tp

Exclusivity Data

Exclusivity Code	Exclusivity Expiration	How filed
I-539	SEP 13, 2010	Carve-out
ODE	SEP 13, 2014	Carve-out

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>

Due to Eli Lilly's marketing exclusivity rights for Evista[®] as an Orphan Drug, InvaGen's Raloxifene Hydrochloride drug product package insert label does not claim the Orphan Drug indication "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" and it intends to market its product before the Orphan Drug indication exclusivity expires.

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

InvaGen Pharmaceuticals Inc,
7 Oser Avenue,
Hauppauge, New York 11788
USA

4. CONTAINER/CLOSURE

RLD: 30s, 100s, 2000
ANDA: 30s and 1000s

Bottle: White HDPE

Closure: 30s CRC; 1000s non-CRC

The proposed container/closure comply with USP <661> and USP <671> requirements.

of medication guides per packaging configuration?

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling is consistent with the composition statement.
Drug substance specification: "off white to pale yellow solid"

Item #	Ingredient	60 mg (mg/tablet)
1	Raloxifene Hydrochloride	60.0
2	Mannitol, USP (b) (4)	(b) (4)
3	Crospovidone, NF (b) (4)	(b) (4)
4	Hydroxy Propyl Cellulose, NF (b) (4)	(b) (4)
5	Polaxomer 407, NF (b) (4)	(b) (4)
6	(b) (4)	(b) (4)
7	(b) (4)	(b) (4)
8	Magnesium stearate, NF	(b) (4)
	(b) (4)	(b) (4)
9	Opadry White, (b) (4) (Titanium Dioxide, Hypromellose, Polyethylene glycol 400, Polysorbate 80)	(b) (4)
10	(b) (4)	(b) (4)
Total Tablet Weight		288.0
	(b) (4)	(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.

8. FINISHED PRODUCT COA -

RLD: White, elliptical and film coated tablets
ANDA: White , film coated round biconvex tablets de-bossed with IG on one side and 256 on the other.

9. SPL Statement provided in the October 2, 2008 submission:

Firm is committed to submit the Raloxifene Hydrochloride Tablets, 60 mg
package insert label in SPL format upon completion of labeling review.

Date of Review: May 10, 2010

Date of Submission: July 7, 2009

Primary Reviewer: Ruby Wu

Team Leader: Koung Lee

ANDA: 090842
Review

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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ANDA-90842	ORIG-1	INVAGEN PHARMACEUTICA LS INC	RALOXIFENE HYDROCHLORIDE

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

/s/

CHI-ANN Y WU
05/10/2010
for Wm Peter Rickman

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

ANDA Number: 90-842

Dates of Submission: October 2, 2008 (original)

Applicant's Name: Invagen Pharmaceuticals, Inc.

Established Name: Raloxifene Hydrochloride Tablets USP, 60 mg

Labeling Deficiencies:

1. GENERAL COMMENT:

The drug product is now subject of a USP monograph titled "Raloxifene Hydrochloride Tablets". We encourage you to use "USP" in the established name of your drug product.

2. CONTAINER (Bottles of 30s and 1000s):

- a. Correct the spelling of the established name.
- b. Add "Each tablet contains 60 mg raloxifene hydrochloride, USP."
- c. Include a statement instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed, and state how the Medication Guide is provided. These statements shall appear on the label in a prominent and conspicuous manner. 21 CFR 208.24 (d)
For example:
- "PHARMACIST: PLEASE DISPENSE WITH ATTACHED MEDICATION GUIDE"
or
- "PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY"

3. PHYSICIAN INSERT

- a. GENERAL COMMENT: revise "Raloxifene hydrochloride Tablets" to read "raloxifene hydrochloride tablets" unless "Raloxifene" appears at the beginning of a sentence.
- b. HIGHLIGHTS
 - i. Title: "Initial" should appear on the next line and it should read "Initial U.S. Approval: 1997"
 - ii. Recent Major Changes: please delete "Indications and Usage, Invasive Breast Cancer Risk Reduction (1) 9/2007"
 - iii. Indications and usage: "Raloxifene hydrochloride tablet is..."
 - iv. "To report SUSPECTED ADVERSE REACTIONS" subsection: To be in accord with 21 CFR 201.57(a)(11)(ii), please include the name and phone number of the manufacturer.
- c. CONTENTS: Renumber (b) (4) to read "14.5". You should keep the same number system as the RLD.
- d. FULL PRESCRIBING INFORMATION
 - i. 1.1: Delete (b) (4)
 - ii. 2.2: "For osteoporosis treatment..."
 - iii. 5.11: Delete (b) (4)
 - iv. 5.12: Delete "Raloxifene hydrochloride tablets do not eliminate the risk of breast cancer [see Clinical Studies (14.4)]."
 - v. 6.1, sixth paragraph, first sentence: "Table 1 lists adverse reactions occurring in osteoporosis treatment and placebo-controlled clinical trials at a frequency $\geq$ 2.0% in the raloxifene hydrochloride-treated women than in placebo-treated women."
 - vi. Table 1, Title: "Table 1: Adverse Reactions Occurring in Placebo–Controlled Osteoporosis Clinical Trials at a Frequency $\geq$ 2.0%"
 - vii. Table 1: "† Includes only patients with an intact uterus: raloxifene hydrochloride tablets treatment trial: Treatment Trial: n=1948, Placebo, n=1999."
 - viii. 6.1: add at the end of this section
Breast Pain — Across all placebo-controlled trials, raloxifene was indistinguishable from placebo with regard to frequency and severity of breast pain and tenderness. Raloxifene was associated with less breast pain and tenderness than reported by women receiving estrogens

with or without added progestin.

Gynecologic Cancers — Raloxifene-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 — The safety of raloxifene (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. Therapy was discontinued due to an adverse reaction in 25% of 5044 raloxifene-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-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)].

- ix. 11: revise "HPMC" to read "hypromellose"
- x. 12.2, second paragraph, first sentence: "In the osteoporosis treatment trial, raloxifene..."
- xi. 12.3, first paragraph, first sentence: "...osteoporosis treatment trial using..."
- xii. 12.3, Special Populations, Renal Impairment, first sentence: "...In the osteoporosis treatment trial, raloxifene..."
- xiii. Renumeral (b) (4) to read "14.5". You should keep the same number system as the RLD.
- xiv. (b) (4) delete (b) (4)
- xv. 16.1: use lower case "w" for "white" and replace the colon with a period.
- xvi. 16.2: to be consistent with the RLD, please add "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."
- e. Medication Guide
 - i. What is raloxifene hydrochloride, bullet: "...tablets treat osteoporosis..."
 - ii. What is raloxifene hydrochloride: Delete "You and your doctor should talk about whether the possible benefit of raloxifene hydrochloride tablets in lowering your chance of getting invasive breast cancer is greater than its possible risks."
 - iii. How should I take raloxifene hydrochloride tablets: Delete "It is not known how long you should keep taking raloxifene hydrochloride tablets to lower your chance of getting invasive breast cancers."
 - iv. What else should I know about raloxifene hydrochloride tablets, fourth bullet: Delete "Because raloxifene hydrochloride tablets do not eliminate the chance of developing breast cancers"
 - v. Inactive Ingredients: revise "HPMC" to read "hypromellose"
 - vi. Replace "The brands listed are trademarks of their respective owners and are not trademarks of Eli Lilly and Company. The makers of these brands are not affiliated with and do not endorse Eli Lilly and Company or its products." with registered trademark statements for Coumadin and Jantoven."
 - vii. To facilitate reporting adverse events, add the following text and toll free number to the end of the "What are the possible or reasonably likely side effects" subsection of the Medication Guide: "Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088." (refer to 21 CFR 208.20(b)(7)(iii))

3. Stand-alone MEDICATION GUIDE

Please comment on how many medication guide will be provided for each packaging configuration.

Revise your labeling, as instructed above, and submit final printed labeling electronically.

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

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the previously submitted labeling with all differences annotated and explained.

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."



USP: The drug product is now subject to a USP 32 monograph (checked 5/18/09)

Raloxifene Hydrochloride Tablets

Packaging and storage— Preserve in tight containers, and store at controlled room temperature.

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

2. PATENTS/EXCLUSIVITIES:

Information pertaining to the use of raloxifene hydrochloride tablets for prevention of osteoporosis in postmenopausal women and prevention of breast cancer has been carved out of Invagen's labeling.

Patent Data for NDA 20-815 (current as of 5/15/09)

Patent No	Patent Expiration	Patent Use Code	How filed	Impact
5393763	JUL 28,2012	U-114	PIII	None
5457117	JUL 28,2012	U-114	PIII	None
5478847	MAR 02,2014	U-114	PIII	None
5811120	MAR 02,2014		PIV	None
5972383	MAR 02,2014	U-287	PIV	None
6458811	MAR 10,2017	U-825	Split Certification: PIV MOU for U-825	Carveout for U-825 (USE FOR PREVENTION OF BREAST CANCER)
6797719	MAR 10,2017		PIV	None
6894064	MAR 10,2017	U-657	Split Certification: PIV MOU for U-657	Carveout for U-657 (PREVENTION OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN)
6906086	JUL 28,2012	U-657	PIII	None
6906086	JUL 28,2012	U-662	PIII	None
RE38968	JUL 28,2012	U-662	PIII	None
RE38968	JUL 28,2012	U-657	PIII	None
RE39049	JUL 28,2012	U-662	PIII	None

RE39049	JUL 28,2012	U-657	PIII	None
RE39050	MAR 02,2014	U-662	PIII	None
RE39050	MAR 02,2014	U-657	PIII	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

InvaGen Pharmaceuticals, Inc., filed Paragraph IV certification for U.S patents 5811120, 5972383, 6458811, 6797719 and 6894064. Eli Lilly and company filed the patent infringement case against InvaGen Pharmaceuticals, Inc., in United States district court for the southern district of Indiana, Indianapolis Division. The patents-in-suit are U.S patents 6458811, 6797719 and 6894064.

Information on Split Certification from 12/29/08 XP Amendment:

The '811 patent has two independent claims (*i.e.*, claim 1 and 7) and fifteen dependent claims that depend directly or indirectly from claims 1 and 7. The '811 patent contains both composition and method claims.

Independent composition claims 1 and 7

Method claims 12-17

The '064 patent has one independent claims (*i.e.*, claim 1) and 11 dependent claims that depend directly or indirectly from claim 1. The '064 patent contains both composition and method claims.

Master Que Notes:

- 04/10/2009: SD 04/02/2009 & LD 04/03/09. Suit notice from innovator asking to stop approval until at least end of 30 month stay. tp
- 03/10/2009: LD 02/23/2009 & SD 02/26/2009. suit filed on 1/28/2009 in Southern D of IN for infringement of '811, '719, and '064. tp
- 01/08/2009: LD 12/29/2008 & SD 01/02/2009. Notice provided to patent holders. RR dated 12/22/2008.tp

Exclusivity Data

Exclusivity Code	Exclusivity Expiration	How filed
I-539	SEP 13, 2010	Carve-out
ODE	SEP 13, 2014	Carve-out

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>

Due to Eli Lilly's marketing exclusivity rights for Evista[®] as an Orphan Drug, InvaGen's Raloxifene Hydrochloride drug product package insert label does not claim the Orphan Drug indication "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" and it intends to market its product before the Orphan Drug indication exclusivity expires.

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

InvaGen Pharmaceuticals Inc,
7 Oser Avenue,
Hauppauge, New York 11788
USA

4. CONTAINER/CLOSURE

RLD: 30s, 100s, 2000

ANDA: 30s and 1000s

Type	Description (Capsule Count)
Bottle	50/60 CC, white HDPE, (30 Tablets)
Bottle	500 CC, white HDPE, (1000 Tablets)
Closure	33 mm, CRC Cap (b) (4)
Closure	53 mm, White, RS Cap (b) (4)

of medication guides per packaging configuration?

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling is consistent with the composition statement.
Drug substance specification: "off white to pale yellow solid"

Item #	Ingredient	60 mg (mg/tablet)
1	Raloxifene Hydrochloride	60.0
2	Mannitol, USP (b) (4)	(b) (4)
3	Crospovidone, NF (b) (4)	
4	Hydroxy Propyl Cellulose, NF (b) (4)	
5	Polaxomer 407, NF (b) (4)	
6	(b) (4)	
7	(b) (4)	
8	Magnesium stearate, NF	
	(b) (4)	
9	Opadry White, (b) (4) (Titanium Dioxide, Hypromellose, Polyethylene glycol 400, Polysorbate 80)	
10	(b) (4)	
Total Tablet Weight		288.0
(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.

8. FINISHED PRODUCT COA -

RLD: White, elliptical and film coated tablets

ANDA: White , film coated round biconvex tablets de-bossed with IG on one side and 256 on the other.

9. SPL Statement provided in the October 2, 2008 submission:

Firm is committed to submit the Raloxifene Hydrochloride Tablets, 60 mg
package insert label in SPL format upon completion of labeling review.

Date of Review: May 19, 2009

Date of Submission: October 2, 2008

Primary Reviewer: Ruby Wu

Team Leader: Koung Lee

ANDA: 90-842
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
5/19/2009 03:54:23 PM
LABELING REVIEWER
for Wm Peter Rickman

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 90842

CHEMISTRY REVIEWS



CHEMISTRY REVIEW



First Generic: No

Approvable from CMC perspective (CR#4)-Previously TAed-03/04/14

No RPN

Monday, September 08, 2014

Pending DMF review (b) (4) (SD#30 dated 8/28/14)

ANDA 090842

(Review #4)

Raloxifene Hydrochloride Tablets USP, 60 mg

InvaGen Pharmaceuticals, Inc.

**Yingxu Peng, Ph.D.
Chemistry Division I**

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Chemistry Review Data Sheet

1. ANDA 090842
2. REVIEW #: 4
3. REVIEW DATE: August 01, 2014
4. REVIEWER: Yingxu Peng, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents:	Document Date
Original submission	10/2/2008
Patent (AM)	12/29/2008
CMC (AM)	1/20/2009
CMC (AM)	7/22/2009
CMC (AM)	3/24/2010
CMC (T-AM)	6/17/2010
CMC (T-AM)	2/16/2012
Tentative Approval	3/4/2014

Previous CMC Reviews:

CR#01: Not Approvable 05/01/2009 Ramnarayan S. Randad

CR#02: Not Approvable 10/19/2009 Ramnarayan S. Randad

CR#03: CMC Adequate 08/04/2010 Ramnarayan S. Randad

CR#03 T-AM: CMC Adequate 04/03/2012 Ramnarayan S. Randad

(Review response to telephone deficiencies)

CR#03A (Addendum): CMC Adequate 06/14/2012 Ramnarayan S. Randad.

(This review is essentially same as review #3 dated 4/3/2012. Only changes made in this review are the following: (1) updated the status of EES and DMF in section #18. (2) updated the review for any editorial and /or minor revisions to review #3)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission/Request for Final Approval; Patent & Exclusivity/Patent Information (SD#20, eCTD sequence # 0017)	12/23/2013
Response to ECD/Quality (SD#22, eCTD sequence # 0019)	08/19/2014

7. NAME & ADDRESS OF APPLICANT:

Name:	InvaGen Pharmaceuticals, Inc. Attention: Ram Mohan Kathuroju
Address:	7 Oser Avenue Hauppauge, NY 11788
US Representative:	N/A
Telephone/Fax	Tel: 631-231-3233 Fax: 631-231-4248
email	ramk@invagen.com

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS FOR SUBMISSION: 505(j)

Reference Product: Evista® Tablets, 60 mg
Manufacturer: Eli Lilly
NDA # 20-815

Certification	Patent #	Expiration Date	Use Code
III	5393763	7/28/2012	
	5457117	7/28/2012	
	5478847	3/2/2014	
	6906086	7/28/2012	
	RE38968	7/28/2012	
	RE39050	3/2/2014	
IV	5811120	3/2/2014	
	5972383	3/2/2014	
	6458811	3/10/2017	
	6797719	3/10/2017	
	6894064	3/10/2017	
MOU	6458811	3/10/2017	U-825
	6894064	3/10/2017	U-657
Exclusivity	I-539	9/13/10	
--	ODE*	9/13/14	

*ODE= does not apply. Labeling indication is carved out.

Patent certification and exclusivity, Basis of submission: See review #01

10. PHARMACOL. CATEGORY: Treatment of osteoporosis in postmenopausal women.

11. DOSAGE FORM: Tablets

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:

Chemical Name:

1) Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]-, hydrochloride.

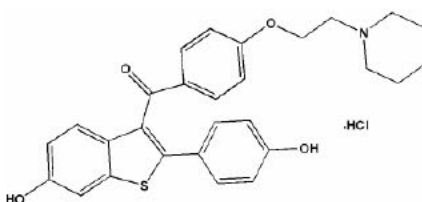
2) 6-Hydroxy-2-(p-hydroxyphenyl)benzo[b]thien-3-yl-p-(2-peridinoethoxy)phenyl ketone, hydrochloride.

CAS # 82640-04-8

USAN: Raloxifene Hydrochloride

Molecular Weight: 510.04

Molecular formula: $C_{28}H_{27}NO_4S.HCl$



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item referenced	Code ¹	Status ²	Date review completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate with IR/S.Sanders*	1/22/14	IR amendment pending review w/ DMF team
	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		

Supporting Document # 30 dated 08/28/2014 needs review per DARRTS.

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. * STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
Methods Validation	Not required per OGD policy	--	
Labeling	Acceptable	11/16/10	C.Y. Wu
Bioequivalence	Acceptable	8/19/11	K. M. Kitchens
DBE Dissolution	Acceptable	1/9/09	C. Lee
EA	Adequate per CFR 21 § 25.31 (a)	See review #01 (05/01/2009)	Ramnarayan S. Randad
Radiopharmaceutical	N/A		

* DARRTS checked on 09/08/ 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: Minor Amendment (Resubmission/Request for Final Approval)

20. EES INFORMATION (Last checked 09/04/2014)

Overall Recommendation: Acceptable , on 01-JULY-2014, by T. Sharp			
Drug Substance			
Function	Site Information	FEI#	Status
(b) (4)			
Drug Product			
Function	Site Information	FEI#	Status
INVAGEN PHARMACEUTICALS INC FINISHED DOSAGE MANUFACTURER	7 OSER AVE HAUPPAUGE, NY 11788-3811	3003950641	Acceptable 08-APR-2014, OC- SAFAALJAZIR

The Chemistry Review for ANDA 90-842

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable from CMC perspective

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

N/A

II. Summary of Chemistry Assessments

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

The drug substance Raloxifene Hydrochloride is off-white to pale yellow solid. It is very slightly soluble in water. The manufacturer of the drug substance used by the ANDA applicant is (b) (4)

Each tablet contains 60 mg of Raloxifene Hydrochloride, which is the molar equivalent of 55.71 mg of free base. Inactive ingredients include mannitol, crospovidone, hydroxypropyl cellulose, poloxamer 407, magnesium stearate and opadry white (titanium Dioxide, HPMC 2910 (3cP), HPMC 2910 (6cP), macrogol/PEG 400 and polysorbate 80.

DP is labeled for an oral use and is dispensed in HDPE bottles.

Both the drug substance (DS) and DP have USP monograph.

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

Raloxifene hydrochloride is an estrogen agonist/antagonist that belongs to the benzothiophene class of compounds. 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.

The dose for the Raloxifene Hydrochloride tablets is 1-tablet/day (60 mg/day).

DS: IT = 0.10% QT = 0.15%

DP: IT = 0.2% QT = (b) (4) %

Raloxifene hydrochloride 60 mg tablets are white film coated round biconvex, de-bossed with **IG** on one side and **256** on the other, supplied in bottles of 30 (NDC 67787-256-30) and 1000 (NDC 67787-256-10):

Store at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP].

The proposed expiration for the product is (b) (4) months.

C. Basis for Approvability or Not-Approval Recommendation

Label: Adequate

BE: Adequate

CMC: Adequate

A APPENDICES

A.1 Facilities and Equipment (biotech only): N/A

A.2 Adventitious Agents Safety Evaluation: N/A

A.3 Novel Excipients: N/A

R REGIONAL INFORMATION

R1 Executed Batch Records: Provided

R2 Comparability Protocols: None

Part V. Review of Common Technical Document-Quality (Ctd-Q) Module 1***Documents***

Patent Certification Provided: ☒ Yes ☐ No

Exclusivity Provided: ☒ Yes ☐ No

Debarment Certification Provided: ☒ Yes ☐ No

cGMP Statement Provided: ☒ Yes ☐ No

Reprocessing Statement Provided: ☒ Yes ☐ No

Letters of Authorization Provided: ☒ Yes ☐ No

Request for Bio-waiver provided: ☐ Yes ☒ No

Citizen Petition and/or Control Request Linked to the Application: N/A

Environmental Impact Considerations/Categorical Exclusions Provided:

☒ Yes ☐ No

The product is adequate from CMC perspective. No further deficiencies.

ADMINISTRATIVE

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: HFD-620/Yingxu Peng, Ph.D./Review Chemist /08/01/2014; 09/04/2014

Chemistry Team Leader Name/Date: HFD-620/Raj Bykadi, Ph.D./ Sept 8, 2014

Project Manager Name/Date: HFD-617/Ankara (Nikki) Yokum/09/08/14, 09/12/14

DD/DDD Name/Date: HFD-620/Bing Cai, Ph.D./September 12, 2014

TYPE OF LETTER: Adequate

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

/s/

YINGXU PENG

09/12/2014

ANKARA N YOKUM

09/13/2014

GURURAJ BYKADI

09/15/2014

BING CAI on behalf of ANDRE S RAW

09/15/2014

**CHEM COMPLETE
LABELING, BIO, EER OK**

ANDA 090842

Raloxifene Hydrochloride Tablets USP, 60 mg

InvaGen Pharmaceuticals Inc.

**Ramnarayan S. Randad, Ph.D.
Chemistry Division I**

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Chemistry Review Data Sheet

1. ANDA 090842
2. REVIEW #: 03A (ADDENDUM)
3. REVIEW DATE: May 11, 2010; June 29, 2010;
11/22/11; 3/7/2012; 6/6/12
4. REVIEWER: Ramnarayan S. Randad, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents:</u>	<u>Document Date</u>
Original submission	10/2/2008
Patent (AM)	12/29/2008
CMC (AM)	1/20/2009
CMC (AM)	7/22/2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
CMC (AM)	3/24/2010
CMC (T-AM)	6/17/2010
CMC (T-AM)	2/16/2012

7. NAME & ADDRESS OF APPLICANT:

Name:	InvaGen Pharmaceuticals, Inc. Attention: Sudhakar Vidiyala
Address:	7 Oser Avenue Hauppauge, NY 11788
US Representative:	N/A
Telephone/Fax	Tel: 631-231-3233 Fax: 631-231-4248

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS FOR SUBMISSION: 505(j)

Chemistry Review Data Sheet

Reference Product: Evista® Tablets, 60 mg
 Manufacturer: Eli Lilly
 NDA # 20-815

Certification	Patent #	Expiration Date	Use Code
III	5393763	7/28/2012	
	5457117	7/28/2012	
	5478847	3/2/2014	
	6906086	7/28/2012	
	RE38968	7/28/2012	
	RE39050	3/2/2014	
IV	5811120	3/2/2014	
	5972383	3/2/2014	
	6458811	3/10/2017	
	6797719	3/10/2017	
	6894064	3/10/2017	
MOU	6458811	3/10/2017	U-825
	6894064	3/10/2017	U-657
Exclusivity	I-539	9/13/10	
	ODE*	9/13/14	

*ODE= does not apply. Labeling indication is carved out.

Patent certification and exclusivity, Basis of submission:

See review #01

10. PHARMACOL. CATEGORY: Treatment of osteoporosis in postmenopausal women.
11. DOSAGE FORM: Tablets
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:

Chemical Name:

1) Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl] [4-[2-(1-

Chemistry Review Data Sheet

piperidinyl)ethoxy]phenyl]-, hydrochloride.

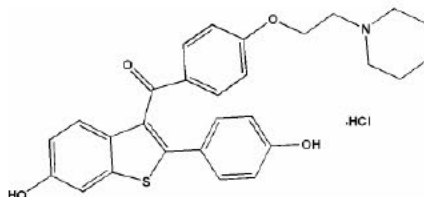
2) 6-Hydroxy-2-(p-hydroxyphenyl)benzo[b]thien-3-yl-p-(2-peridinoethoxy)phenyl ketone, hydrochloride.

CAS # 82640-04-8

USAN: Raloxifene Hydrochloride

Molecular Weight: 510.04

Molecular formula: $C_{28}H_{27}NO_4S \cdot HCl$



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item referenced	Code ¹	Status ²	Date review completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	6/6/12	Rev #5 by Dr. Randad
	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		

* DARRTS checked. No new amendments as of June 8, 2012

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)

Chemistry Review Data Sheet

B. Related NDA/ANDA (s):

Following is a representative list of TA'ed ANDA:

FIRM NAME	ANDA #
Teva	78-193

C. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. * STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
CMC	Acceptable		
DMF	Acceptable		
Microbiology	N/A		
EES	Acceptable	5/21/12	
Methods Validation	Will not submitted	--	
Labeling	Acceptable	11/16/10	DARRTS
Bioequivalence	Acceptable	8/19/11	DARRTS
DBE Dissolution	Acceptable	1/9/09	C. Lee
EA	N/A		
Radiopharmaceutical	N/A		

* DARRTS checked on June 8, 2012

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: Minor AM (DMF rev)

The Chemistry Review for ANDA 90-842

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC, labeling, Bio are AC.

The ANDA #90842 is 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)

The drug substance Raloxifene Hydrochloride is off-white to pale yellow solid. It is very slightly soluble in water. The manufacturer of the drug substance used by the ANDA applicant is (b) (4)

Each tablet contains 60 mg of Raloxifene Hydrochloride, which is the molar equivalent of 55.71 mg of free base. Inactive ingredients include mannitol, crospovidone, hydroxypropyl cellulose, poloxamer 407, magnesium stearate and opadry white (titanium Dioxide, HPMC 2910 (3cP), HPMC 2910 (6cP), macrogol/PEG 400 and polysorbate 80.

DP is labeled for an oral use and is dispensed in HDPE bottles.

Both the drug substance (DS) and DP have USP monograph.

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

Raloxifene hydrochloride is an estrogen agonist/antagonist that belongs to the benzothiophene class of compounds.

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.

The dose for the Raloxifene Hydrochloride tablets is 1-tablet/day (60 mg/day).

<u>DS:</u>	IT = 0.10%	QT = 0.15%
<u>DP:</u>	IT = 0.2%	QT = (b) (4) %

Raloxifene hydrochloride 60 mg tablets are white film coated round biconvex, de-bossed with IG on one side and 256 on the other, supplied in bottles of 30 (NDC 67787-256-30) and 1000 (NDC 67787-256-10):

Store at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP].

The proposed expiration for the product is (b) (4) months.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is approvable; see section 18.

III. Administrative

A. Reviewer Ramnarayan S. Randad

A APPENDICES

A.1 Facilities and Equipment (biotech only): N/A

A.2 Adventitious Agents Safety Evaluation: N/A

A.3 Novel Excipients: N/A

R REGIONAL INFORMATION

R1 Executed Batch Records : Provided

R2 Comparability Protocols : None

30. MICROBIOLOGY: N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

Method validation will not be requested (see review #01).

32. LABELING: See section #18

Items Reviewed by Chemist: Satisfactory review #01

2. How Supplied Section:

a. Packaging: Satisfactory

Raloxifene hydrochloride 60 mg tablets are White film coated round biconvex, de-bossed with IG on one side and 256 on the other, supplied in bottles of 30 (NDC 67787-256-30) and 1000 (NDC 67787-256-10):

b. Storage Conditions: Satisfactory

Store at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP].

The expiration dating for the product is (b) (4) months.

NOTES/QUESTIONS FROM THE LABELING REVIEW: None

33. **ESTABLISHMENT INSPECTION:** *See section #18*

34. **BIOEQUIVALENCE:** *See section #18*

35. **ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:** *Satisfactory review #01*

36. **CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT**

None. CMC acceptable.

cc: ANDA 90842
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-620/Ramnarayan S. Randad, Ph.D./
June 3, 2010; 6/29/10, Nov 28, 2011; 3/7/2012; 6/7/12

HFD-620/Raj Bykadi, Team Leader/June 3, June 30, July 1 2010,
Nov 29, 2011, 3/12/2012, June 8, 2012

HFD-617/Ben Danso, Pharm. D./10-7-09; 7-22-10; 12-8-11;
3-6-2012; 3-13-2012; 6-11-12

F/T by

CMC APPROVABLE

EES, Bio, labeling acceptable

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

/s/

RAMNARAYAN S RANDAD

06/11/2012

090842CR03.A.doc

GURURAJ BYKADI

06/14/2012

BENJAMIN DANSO

06/14/2012

CHEM COMP., PN EER ONLY

ANDA 090842

Raloxifene Hydrochloride Tablets USP, 60 mg

InvaGen Pharmaceuticals Inc.

Ramnarayan S. Randad, Ph.D.
Chemistry Division I

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III. Administrative	8
A. Reviewer Ramnarayan S. Randad	8
Chemistry Assessment	9
30. MICROBIOLOGY: N/A.....	33
31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS.....	34
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34. BIOEQUIVALENCE: Review pending.....	34
35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:	34

Chemistry Review Data Sheet

1. ANDA 090842
2. REVIEW #: 03
3. REVIEW DATE: May 11, 2010; June 29, 2010;
11/22/11; 3/7/2012
4. REVIEWER: Ramnarayan S. Randad, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents:</u>	<u>Document Date</u>
Original submission	10/2/2008
Patent (AM)	12/29/2008
CMC (AM)	1/20/2009
CMC (AM)	7/22/2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
CMC (AM)	3/24/2010
CMC (T-AM)	6/17/2010
CMC (T-AM)	2/16/2012

7. NAME & ADDRESS OF APPLICANT:

Name:	InvaGen Pharmaceuticals, Inc. Attention: Sudhakar Vidiyala
Address:	7 Oser Avenue Hauppauge, NY 11788
US Representative:	N/A
Telephone/Fax	Tel: 631-231-3233 Fax: 631-231-4248

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS FOR SUBMISSION: 505(j)

Chemistry Review Data Sheet

Reference Product: Evista® Tablets, 60 mg
 Manufacturer: Eli Lilly
 NDA # 20-815

Certification	Patent #	Expiration Date	Use Code
III	5393763	7/28/2012	
	5457117	7/28/2012	
	5478847	3/2/2014	
	6906086	7/28/2012	
	RE38968	7/28/2012	
	RE39050	3/2/2014	
IV	5811120	3/2/2014	
	5972383	3/2/2014	
	6458811	3/10/2017	
	6797719	3/10/2017	
	6894064	3/10/2017	
MOU	6458811	3/10/2017	U-825
	6894064	3/10/2017	U-657
Exclusivity	I-539	9/13/10	
	ODE*	9/13/14	

*ODE= does not apply. Labeling indication is carved out.

Patent certification and exclusivity, Basis of submission:

See review #01

10. PHARMACOL. CATEGORY: Treatment of osteoporosis in postmenopausal women.
11. DOSAGE FORM: Tablets
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:

Chemical Name:

1) Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl] [4-[2-(1-

Chemistry Review Data Sheet

piperidinyl)ethoxy]phenyl]-, hydrochloride.

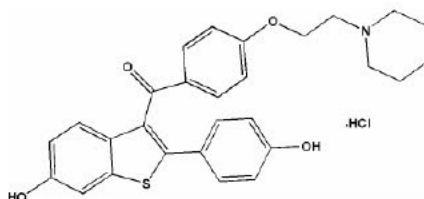
2) 6-Hydroxy-2-(p-hydroxyphenyl)benzo[b]thien-3-yl-p-(2-peridinoethoxy)phenyl ketone, hydrochloride.

CAS # 82640-04-8

USAN: Raloxifene Hydrochloride

Molecular Weight: 510.04

Molecular formula: $C_{28}H_{27}NO_4S \cdot HCl$



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item referenced	Code ¹	Status ²	Date review completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	12/05/2011	Rev #4 by Dr. Randad
	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		

* DARRTS checked. No new amendments as of March 9, 2012

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)

Chemistry Review Data Sheet

B. Related NDA/ANDA (s):

Following is a representative list of TA'ed ANDA:

FIRM NAME	ANDA #
Teva	78-193

C. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. * STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	PENDING	//	
Methods Validation	Will not submitted	--	
Labeling	Acceptable	11/16/10	DARRTS
Bioequivalence	Acceptable	8/19/11	DARRTS
DBE Dissolution	Acceptable	1/9/09	C. Lee
EA	N/A		
Radiopharmaceutical	N/A		

* DARRTS checked on March 9, 2012

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: Minor AM (DMF rev)

The Chemistry Review for ANDA 90-842

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA #90842 is approvable, **PN EES ONLY**.

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)

The drug substance Raloxifene Hydrochloride is off-white to pale yellow solid. It is very slightly soluble in water. The manufacturer of the drug substance used by the ANDA applicant is (b) (4)

Each tablet contains 60 mg of Raloxifene Hydrochloride, which is the molar equivalent of 55.71 mg of free base. Inactive ingredients include mannitol, crospovidone, hydroxypropyl cellulose, poloxamer 407, magnesium stearate and opadry white (titanium Dioxide, HPMC 2910 (3cP), HPMC 2910 (6cP), macrogol/PEG 400 and polysorbate 80.

DP is labeled for an oral use and is dispensed in HDPE bottles.

Both the drug substance (DS) and DP have USP monograph.

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

Raloxifene hydrochloride is an estrogen agonist/antagonist that belongs to the benzothiophene class of compounds. 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.

The dose for the Raloxifene Hydrochloride tablets is 1-tablet/day (60 mg/day).

<u>DS:</u>	IT = 0.10%	QT = 0.15%
<u>DP:</u>	IT = 0.2%	QT = (b) (4) %

Raloxifene hydrochloride 60 mg tablets are white film coated round biconvex, de-bossed with IG on one side and 256 on the other, supplied in bottles of 30 (NDC 67787-256-30) and 1000 (NDC 67787-256-10):

Store at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP].

The proposed expiration for the product is (b) (4) months.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is approvable; see section 18.

III. Administrative

A. Reviewer

Ramnarayan S. Randad

A APPENDICES

A.1 Facilities and Equipment (biotech only): N/A

A.2 Adventitious Agents Safety Evaluation: N/A

A.3 Novel Excipients: N/A

R REGIONAL INFORMATION

R1 Executed Batch Records : Provided

R2 Comparability Protocols : None

30. **MICROBIOLOGY:** *N/A*

31. **SAMPLES AND RESULTS/METHODS VALIDATION STATUS**

Method validation will not be requested (see review #01).

32. **LABELING:** *See section #18*

Items Reviewed by Chemist: Satisfactory review #01

2. How Supplied Section:

a. Packaging: Satisfactory

Raloxifene hydrochloride 60 mg tablets are White film coated round biconvex, de-bossed with IG on one side and 256 on the other, supplied in bottles of 30 (NDC 67787-256-30) and 1000 (NDC 67787-256-10):

b. Storage Conditions: Satisfactory

Store at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP].

The expiration dating for the product is (b) (4) months.

NOTES/QUESTIONS FROM THE LABELING REVIEW: None

33. **ESTABLISHMENT INSPECTION:** *See section #18*

34. **BIOEQUIVALENCE:** *See section #18*

35. **ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:** *Satisfactory review #01*

36. **CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT**

None. CMC acceptable.

cc: ANDA 90-842
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-620/Ramnarayan S. Randad, Ph.D./ June 3, 2010; 6/29/10,
Nov 28, 2011; 3/7/2012
HFD-620/Raj Bykadi, Team Leader/June 3, June 30, July 1 2010,
Nov 29, 2011, 3/12/2012
HFD-617/Ben Danso, Pharm. D./10-7-09; 7-22-10; 12-8-11;
3-6-2012; 3-13-2012

F/T by

CMC APPROVABLE

EES PENDING

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

/s/

RAMNARAYAN S RANDAD
04/03/2012
90842.CR03.NA

GURURAJ BYKADI
04/03/2012

BENJAMIN DANSO
04/03/2012

CHEM COMPLETE, PN LBL, BIO AND EES

ANDA 090842

Raloxifene Hydrochloride Tablets USP, 60 mg

InvaGen Pharmaceuticals Inc.

Ramnarayan S. Randad, Ph.D.
Chemistry Division I

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A. Reviewer Ramnarayan S. Randad	8
Chemistry Assessment	9
30. MICROBIOLOGY: N/A.....	32
31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS.....	33
32. LABELING: Pending review of amendment dated 07/23/04.....	33
33. ESTABLISHMENT INSPECTION: EER Pending	33
34. BIOEQUIVALENCE: Review pending.....	33
35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:	33

Chemistry Review Data Sheet

1. ANDA 090842
2. REVIEW #: 03
3. REVIEW DATE: May 11, 2010; June 29, 2010
4. REVIEWER: Ramnarayan S. Randad, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents:</u>	<u>Document Date</u>
Original submission	10/2/2008
Patent (AM)	12/29/2008
CMC (AM)	1/20/2009
CMC (AM)	7/22/2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
CMC (AM)	3/24/2010
CMC (T-AM)	6/17/2010

7. NAME & ADDRESS OF APPLICANT:

Name:	InvaGen Pharmaceuticals, Inc. Attention: Sudhakar Vidiyala
Address:	7 Oser Avenue Hauppauge, NY 11788
US Representative:	N/A
Telephone/Fax	Tel: 631-231-3233 Fax: 631-231-4248

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS FOR SUBMISSION: 505(j)

Reference Product: Evista® Tablets, 60 mg
Manufacturer: Lilly

Chemistry Review Data Sheet

NDA # 20-815

Certification	Patent #	Expiration Date	Use Code
III	5393763	7/28/2012	
	5457117	7/28/2012	
	5478847	3/2/2014	
	6906086	7/28/2012	
	RE38968	7/28/2012	
	RE39050	3/2/2014	
IV	5811120	3/2/2014	
	5972383	3/2/2014	
	6458811	3/10/2017	
	6797719	3/10/2017	
	6894064	3/10/2017	
MOU	6458811	3/10/2017	U-825
	6894064	3/10/2017	U-657
Exclusivity	I-539	9/13/10	
	ODE*	9/13/14	

ODE= does not apply. Labeling indication is carved out.

Patent certification and exclusivity, Basis of submission:

See review #01

10. PHARMACOL. CATEGORY: Treatment of osteoporosis in postmenopausal women.
11. DOSAGE FORM: Tablets
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:

Chemical Name:

1) Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl] [4-[2-(1-piperidinyloxy)ethoxy]phenyl]-, hydrochloride.

Chemistry Review Data Sheet

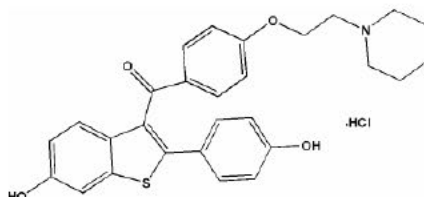
2) 6-Hydroxy-2-(p-hydroxyphenyl)benzo[b]thien-3-yl-p-(2-peridinoethoxy)phenyl ketone, hydrochloride.

CAS # 82640-04-8

USAN: Raloxifene Hydrochloride

Molecular Weight: 510.04

Molecular formula: $C_{28}H_{27}NO_4S \cdot HCl$



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	6/29/2010	Rev #3 by Dr. Randad
	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		

* DARRTS checked. No new amendments as of June 30, 2010

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. Related NDA/ANDA (s):

Following is a representative list of TA'ed ANDA:

Chemistry Review Data Sheet

FIRM NAME	ANDA #
Teva	78-193

C. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. *STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending (Need overall recommendation)	--	
Methods Validation	Will not submitted	--	
Labeling	Deficient	5/10/10	DARRTS
Bioequivalence	Pending		
DBE Dissolution	Acceptable	1/9/09	C. Lee
EA	N/A		
Radiopharmaceutical	N/A		

* DARRTS checked on 6-30-2010

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: Minor AM

The Chemistry Review for ANDA 90-842

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA #90-842 is 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)

The drug substance Raloxifene Hydrochloride is off-white to pale yellow solid. It is very slightly soluble in water. The manufacturer of the drug substance used by the ANDA applicant is (b) (4)

Each tablet contains 60 mg of Raloxifene Hydrochloride, which is the molar equivalent of 55.71 mg of free base. Inactive ingredients include mannitol, crospovidone, hydroxypropyl cellulose, poloxamer 407, magnesium stearate and opadry white (titanium Dioxide, HPMC 2910 (3cP), HPMC 2910 (6cP), macrogol/PEG 400 and polysorbate 80.

DP is labeled for an oral use and is dispensed in HDPE bottles.

Both the drug substance (DS) and DP have USP monograph.

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

Raloxifene hydrochloride is an estrogen agonist/antagonist that belongs to the benzothiophene class of compounds. 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.

The dose for the Raloxifene Hydrochloride tablets is 1-tablet/day (60 mg/day).

<u>DS:</u>	IT = 0.10%	QT = 0.15%
<u>DP:</u>	IT = 0.2%	QT = (b) (4) %

Raloxifene hydrochloride 60 mg tablets are White film coated round biconvex, de-bossed with IG on one side and 256 on the other, supplied in bottles of 30 (NDC 67787-256-30) and 1000 (NDC 67787-256-10):

Store at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP].

The proposed expiration for the product is (b) (4) months.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is not approvable at this time for the following reasons:

- CMC adequate
- Labeling deficient
- Pending Bioequivalence review
- EER Pending

III. Administrative

A. Reviewer

Ramnarayan S. Randad

A APPENDICES

A.1 Facilities and Equipment (biotech only): N/A

A.2 Adventitious Agents Safety Evaluation: N/A

A.3 Novel Excipients: N/A

R REGIONAL INFORMATION

R1 Executed Batch Records : Provided

R2 Comparability Protocols : None

30. **MICROBIOLOGY:** *N/A*

31. **SAMPLES AND RESULTS/METHODS VALIDATION STATUS**

Method validation will not be requested (see review #01).

32. **LABELING:** *See section #18*

Items Reviewed by Chemist: Satisfactory review #01

2. How Supplied Section:

a. Packaging: Satisfactory

Raloxifene hydrochloride 60 mg tablets are White film coated round biconvex, de-bossed with IG on one side and 256 on the other, supplied in bottles of 30 (NDC 67787-256-30) and 1000 (NDC 67787-256-10):

b. Storage Conditions: Satisfactory

Store at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP].

The expiration dating for the product is (b) (4) months.

NOTES/QUESTIONS FROM THE LABELING REVIEW: None

33. **ESTABLISHMENT INSPECTION:** *See section #18*

34. **BIOEQUIVALENCE:** *See section #18*

35. **ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:** *Satisfactory review #01*

36. **CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT**

None. CMC acceptable.

cc: ANDA 90-842
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-620/Ramnarayan S. Randad, Ph.D./ June 3, 2010; 6/29/10
HFD-620/Raj Bykadi, Team Leader/ June 3, June 30, July 1 2010
HFD-617/Ben Danso, Pharm. D./ 10-7-09; 7-22-2010

F/T by

NOT APPROVABLE

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
-----	-----	-----	-----
ANDA-90842	ORIG-1	INVAGEN PHARMACEUTICA LS INC	RALOXIFENE HYDROCHLORIDE

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

/s/

RAMNARAYAN S RANDAD
07/28/2010

GURURAJ BYKADI
07/28/2010

BENJAMIN DANSO
08/04/2010

ANDA 90-842

Raloxifene Hydrochloride Tablets,
60 mg

InvaGen Pharmaceuticals Inc.

Ramnarayan S. Randad, Ph.D.
Chemistry Division I

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II. Summary of Chemistry Assessments	7
III. Administrative	8
A. Reviewer Ramnarayan S. Randad	8
Chemistry Assessment	9
30. MICROBIOLOGY: N/A.....	33
31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS.....	33
32. LABELING: Pending review of amendment dated 07/23/04.....	33
33. ESTABLISHMENT INSPECTION: EER Pending	34
34. BIOEQUIVALENCE: Review pending.....	34
35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:	34

Chemistry Review Data Sheet

1. ANDA 90-842
2. REVIEW #: 02
3. REVIEW DATE: September 22, 2009
4. REVIEWER: Ramnarayan S. Randad, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents:</u>	<u>Document Date</u>
Original submission	10/2/2008
Patent (AM)	12/29/2008
CMC (AM)	1/20/2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
CMC (AM)	7/22/2009

7. NAME & ADDRESS OF APPLICANT:

Name:	InvaGen, Inc. Attention: Sudhakar Vidiyala
Address:	7 Oser Avenue Hauppauge, NY 11788 Tel: 631-231-3233
US Representative:	N/A
Telephone/Fax	Tel: 631-231-3233 Fax: 631-231-4248

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS FOR SUBMISSION: 505(j)

Reference Product: Evista® Tablets, 60 mg
Manufacturer: Lilly
NDA # 20-815

Chemistry Review Data Sheet

Certification	Patent #	Expiration Date	Use Code
III	5393763	7/28/2012	
	5457117	7/28/2012	
	5478847	3/2/2014	
	6906086	7/28/2012	
	RE38968	7/28/2012	
	RE39050	3/2/2014	
IV	5811120	3/2/2014	
	5972383	3/2/2014	
	6458811	3/10/2017	
	6797719	3/10/2017	
	6894064	3/10/2017	
MOU	6458811	3/10/2017	U-825
	6894064	3/10/2017	U-657
Exclusivity	I-539	9/13/10	
	ODE*	9/13/14	

ODE= does not apply. Labeling indication is carved out.

Patent certification and exclusivity, Basis of submission:

See review #01

10. PHARMACOL. CATEGORY: Treatment of osteoporosis in postmenopausal women.

11. DOSAGE FORM: Tablets

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:

Chemical Name:

1) Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl] [4-[2-(1-piperidinyloxy)ethoxy]phenyl]-, hydrochloride.

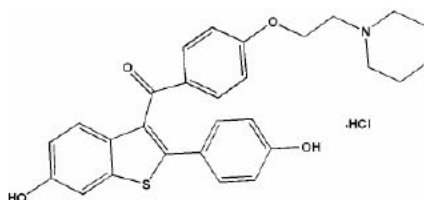
2) 6-Hydroxy-2-(p-hydroxyphenyl)benzo[b]thien-3-yl-p-(2-peridinoethoxy)phenyl ketone, hydrochloride.

Chemistry Review Data Sheet

CAS # 82640-04-8

USAN: Raloxifene Hydrochloride

Molecular Weight: 510.04

Molecular formula: $C_{28}H_{27}NO_4S \cdot HCl$ 

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item referenced	Code ¹	Status ²	Date review completed	Comments
(b) (4)	II	(b) (4)		1	Inadequate	9/22/09	Rev #2 by Dr. Randad
	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		
	III			4	N/A		

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. **Related NDA/ANDA (s):**

Following is a representative list of TA'ed ANDA:

FIRM NAME	ANDA #
Teva	78-193

Chemistry Review Data Sheet

C. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		As of 9/9/09
Methods Validation	Will not submitted		
Labeling	Deficient	5/19/09	DARRTS
Bioequivalence	Pending		
DBE Dissolution	acceptable	1/9/09	C. Lee
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: Minor AM

The Chemistry Review for ANDA 90-842

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA #90-842 is 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)

The drug substance Raloxifene Hydrochloride is off-white to pale yellow solid. It is very slightly soluble in water. The manufacturer of the drug substance used by the ANDA applicant is (b) (4)

Each tablet contains 60 mg of Raloxifene Hydrochloride, which is the molar equivalent of 55.71 mg of free base. Inactive ingredients include mannitol, crospovidone, hydroxypropyl cellulose, poloxamer 407, magnesium stearate and opadry white (titanium Dioxide, HPMC 2910 (3cP), HPMC 2910 (6cP), macrogol/PEG 400 and polysorbate 80).

DP is labeled for an oral use and is dispensed in HDPE bottles.

Both the drug substance (DS) and DP have USP monograph.

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

Raloxifene hydrochloride is an estrogen agonist/antagonist that belongs to the benzothiophene class of compounds. 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.

The dose for the Raloxifene Hydrochloride tablets is 1-tablet/day (60 mg/day).

<u>DS:</u>	IT = 0.10%	QT = 0.15%
<u>DP:</u>	IT = 0.2%	QT = 0.5%

Raloxifene hydrochloride 60 mg tablets are White film coated round biconvex, de-bossed with IG on one side and 256 on the other, supplied in bottles of 30 (NDC 67787-256-30) and 1000 (NDC 67787-256-10):

Store at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP].

The proposed expiration for the product is (b) (4) months.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is not approvable at this time for the following reasons:

- Minor CMC deficiencies
- Labeling deficient
- Pending Bioequivalence review
- EER Pending

III. Administrative

A. Reviewer

Ramnarayan S. Randad

A APPENDICES

A.1 Facilities and Equipment (biotech only): N/A

A.2 Adventitious Agents Safety Evaluation: N/A

A.3 Novel Excipients: N/A

R REGIONAL INFORMATION

R1 Executed Batch Records : Provided

R2 Comparability Protocols : None

30. MICROBIOLOGY: N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

Method validation will not be requested (see review #01).

32. LABELING: See section #18

Items Reviewed by Chemist: Satisfactory review #01

2. How Supplied Section:

a. Packaging: Satisfactory

Raloxifene hydrochloride 60 mg tablets are White film coated round biconvex, de-bossed with IG on one side and 256 on the other, supplied in bottles of 30 (NDC 67787-256-30) and 1000 (NDC 67787-256-10):

b. Storage Conditions: Satisfactory

Store at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP].

The expiration dating for the product is (b) (4) months.

NOTES/QUESTIONS FROM THE LABELING REVIEW: None

33. ESTABLISHMENT INSPECTION: *See section #18*

34. BIOEQUIVALENCE: *See section #18*

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
Satisfactory review #01

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-842

APPLICANT: Invagen Inc.

DRUG PRODUCT: Raloxifene Hydrochloride Tablets, 60 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. The Drug Master File (b) (4) which describes the manufacture of the drug substance, has been found deficient. The DMF holder has been notified by a separate letter. Please respond to these deficiencies only after you have learned that the DMF holder has responded.

2.

(b) (4)

3.

4. Please provide any additional long term stability data that may be available.

Sincerely yours,

{See appended electronic signature page}

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

cc: ANDA 90-842
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-620/Ramnarayan S. Randad, Ph.D./9/22/09; 9/28/09
HFD-620/Raj Bykadi, Team Leader/ September 24,29, 2009
HFD-617/Ben Danso, Pharm. D./ 10-7-09

F/T by

TYPE OF LETTER: NOT APPROVABLE - MINOR

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
-----	-----	-----	-----
ANDA-90842	ORIG-1	INVAGEN PHARMACEUTICA LS INC	RALOXIFENE HYDROCHLORIDE

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

/s/

RAMNARAYAN S RANDAD
10/19/2009

GURURAJ BYKADI
10/19/2009

BENJAMIN DANSO
10/19/2009

ANDA 90-842

Raloxifene Hydrochloride Tablets,
60 mg

InvaGen Pharmaceuticals, Inc.

Ramnarayan S. Randad, Ph.D.
Chemistry Division I

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Chemistry Review Data Sheet

1. ANDA 90-842
2. REVIEW #: 01
3. REVIEW DATE: February 18, 2009; March 12, 2009
4. REVIEWER: Ramnarayan S. Randad, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents:</u>	<u>Document Date</u>

<u>FDA:</u>	<u>Document Date</u>
Acknowledgement letter (Acceptable for filling: 10/6/08)	12/5/2008

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original submission	10/2/2008
Patent Amendment (XP)	12/29/2008
CMC Amendment (AM)	1/20/2009

7. NAME & ADDRESS OF APPLICANT:

Name:	InvaGen, Inc. Attention: Sudhakar Vidiyala
Address:	7 Oser Avenue Hauppauge, NY 11788 Tel: 631-231-3233
US Representative:	N/A
Telephone/Fax	Tel: 631-231-3233 Fax: 631-231-4248

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS FOR SUBMISSION: 505(j)

Chemistry Review Data Sheet

Reference Product: Evista® Tablets, 60 mg
Manufacturer: Lilly
NDA # 20-815

Certification	Patent #	Expiration Date	Use Code
III	5393763	7/28/2012	
	5457117	7/28/2012	
	5478847	3/2/2014	
	6906086	7/28/2012	
	RE38968	7/28/2012	
	RE39050	3/2/2014	
IV	5811120	3/2/2014	
	5972383	3/2/2014	
	6458811	3/10/2017	
	6797719	3/10/2017	
	6894064	3/10/2017	
MOU	6458811	3/10/2017	U-825
	6894064	3/10/2017	U-657
Exclusivity	I-539	9/13/10	
	ODE*	9/13/14	

ODE= does not apply. Labeling indication is carved out.

Patent certification and exclusivity: The firm has provided a paragraph III and IV certification and has listed the above patents with expiry dates. 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 paragraph IV patents are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

The exclusivity statement is provided. Firm states that the since the labeling is carved out for orphan drug indication, the product will be marketed before the expiry of ODE on 9/13/14.

Basis of submission: The basis of submission is RLD, Evista® Tablets, manufactured by Lilly. The DP from InvaGen has the same active ingredient, route of the administration, dosage form, and the strength as the RLD. The side-by-side comparison of the RLD and the proposed DP is provided.

10. PHARMACOL. CATEGORY: Treatment of osteoporosis in postmenopausal women.

Chemistry Review Data Sheet

11. DOSAGE FORM: Tablets
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:

Chemical Name:

1) Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl] [4-[2-(1-piperidinyl)ethoxy]phenyl]-, hydrochloride.

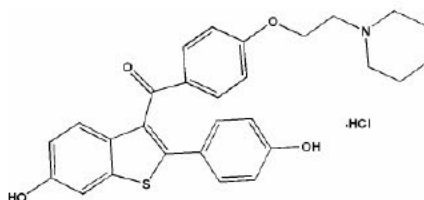
2) 6-Hydroxy-2-(p-hydroxyphenyl)benzo[b]thien-3-yl-p-(2-peridinoethoxy)phenyl ketone, hydrochloride.

CAS # 82640-04-8

USAN: Raloxifene Hydrochloride

Molecular Weight: 510.04

Molecular formula: $C_{28}H_{27}NO_4S \cdot HCl$



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item referenced	Code ¹	Status ²	Date review completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	1	Inadequate	2/17/09	Rev #1 by Dr. Randad
	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		

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. **Related NDA/ANDA (s) :**

Following is a representative list of tentatively approved ANDA's for Raloxifene Hydrochloride:

FIRM NAME	ANDA #
Teva	78-193

C. **Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. **STATUS:**

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		

Chemistry Review Data Sheet

EES	Pending		
Methods Validation	Will not submitted		
Labeling	Pending		
Bioequivalence	Pending		
DBE Dissolution	Acceptable	1/9/09	C. Lee
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 ☐ No
If no, explain reason(s) below:

The Chemistry Review for ANDA 90-842

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA #90-842 is 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)

The drug substance Raloxifene Hydrochloride is off-white to pale yellow solid. It is very slightly soluble in water. The manufacturer of the drug substance used by the ANDA applicant is (b) (4)

Each tablet contains 60 mg of Raloxifene Hydrochloride, which is the molar equivalent of 55.71 mg of free base. Inactive ingredients include mannitol, crospovidone, hydroxypropyl cellulose, poloxamer 407, magnesium stearate and opadry white (titanium Dioxide, HPMC 2910 (3cP), HPMC 2910 (6cP), macrogol/PEG 400 and polysorbate 80.

DP is labeled for an oral use and is dispensed in HDPE bottles.

Both the drug substance (DS) and DP have USP monograph.

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

Raloxifene hydrochloride is an estrogen agonist/antagonist that belongs to the benzothiophene class of compounds. 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

Chemistry Review

incidence.

The dose for the Raloxifene Hydrochloride tablets is 1-tablet/day (60 mg/day).

<u>DS</u>	IT = 0.10%	QT = 0.15%
<u>DP</u>	IT = 0.2%	QT = (b) (4) %

Raloxifene hydrochloride 60 mg tablets are white film coated round biconvex, de-bossed with IG on one side and 256 on the other, supplied in bottles of 30 (NDC 67787-256-30) and 1000 (NDC 67787-256-10):

Store at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP].

The proposed expiration for the product is (b) (4) months.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is not approvable at this time for the following reasons:

- MINOR Chemistry Issues
- Labeling review pending
- Pending Bioequivalence review
- EER Pending

III. Administrative

A. Reviewer

Ramnarayan S. Randad

A APPENDICES**A.1 Facilities and Equipment (biotech only): N/A****A.2 Adventitious Agents Safety Evaluation: N/A****A.3 Novel Excipients: N/A****R REGIONAL INFORMATION****R1 Executed Batch Records : Provided****R2 Comparability Protocols : None****30. MICROBIOLOGY: N/A****31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS**

Firm states that the samples of DP, DS, RS will be made available to the agency upon request. Method validation will not be requested based on the current OGD guideline for method validation.

The method validation request selection criteria:

	DS	DP
USP item	Yes	Yes
First generic	No	No
New technology	No	No
Low dose drug		No
Multiple drug components		No
Multiple drug impurities or degradants		No

32. LABELING: Pending

Items Reviewed by Chemist: satisfactory

1. Description Section

Chemistry Review

a. Structures:	Satisfactory
b. Chemical names:	Satisfactory
c. Empirical formulas:	Satisfactory
d. Name of the inactive's:	Satisfactory
e. Physical and Chemical properties of DS:	Satisfactory

2. How Supplied Section:

a. Packaging: Satisfactory

Raloxifene hydrochloride 60 mg tablets are White film coated round biconvex, de-bossed with IG on one side and 256 on the other, supplied in bottles of 30 (NDC 67787-256-30) and 1000 (NDC 67787-256-10):

b. Storage Conditions: Satisfactory

Store at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP].

The expiration dating for the product is (b) (4) months.

NOTES/QUESTIONS FROM THE LABELING REVIEW: None

33. ESTABLISHMENT INSPECTION: EER Pending

34. BIOEQUIVALENCE: Review pending (dissolution acceptable)

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL

EXCLUSION: Satisfactory

The firm stated that they are subject to a categorical exclusion.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-842

APPLICANT: InvaGen Pharmaceuticals, Inc.

DRUG PRODUCT: Raloxifene Hydrochloride Tablets, 60 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. The Drug master file (b) (4) which describes the manufacture of the drug substance, has been found deficient. The DMF holder has been notified by a separate letter. Please respond to this deficiency only after you have learned that the DMF holder has responded.

2.

3.

4.

5.

6.

7.

8.

9.

(b) (4)

10.

11.

12.

13.

14.

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

1. All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval. We have requested an evaluation from the Office of Compliance.
2. Your labeling information is pending review. Deficiencies, if any, will be communicated separately.
3. Your bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.

4. Please provide any additional long term stability data that may be available.

Sincerely yours,

{See appended electronic signature page}

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

cc: ANDA 90-842
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-620/Ramnarayan S. Randad, Ph.D./2/18/09; 3/11/09; 4/8/09
HFD-620/Raj Bykadi, Team Leader/ April 8, 2009
HFD-617/Benjamin Danso, Pharm. D./4-2-09

V:\Chemistry Division I\Team 5\Final Version For DFS
(Original)\90842.CR01.NA.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

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

/s/

Ramnarayan Randad
4/29/2009 11:28:45 AM
CHEMIST

Gururaj Bykadi
4/29/2009 01:29:19 PM
CHEMIST

Benjamin Danso
5/1/2009 04:19:53 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 90842

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE AMENDMENT REVIEW

ANDA No.	090842	
Drug Product Name	Raloxifene Hydrochloride Tablets, USP	
Strength(s)	60 mg	
Applicant Name	InvaGen Pharmaceuticals, Inc.	
Address	7 Oser Avenue, Hauppauge, New York 11788	
Applicant's Point of Contact	Dr. Sudhakar Rao Vidiyala, President	
Contact's Telephone Number	631-231-3233	
Contact's Fax Number	631-231-4248	
Original Submission Date(s)	October 2, 2008 (Original submission) December 6, 2010 (telephone amendment in response to request for bioequivalence information) May 16, 2011 (response to bioequivalence deficiencies)	
Submission Date(s) of Amendment(s) Under Review	August 12, 2011	
Reviewer	Kelly M. Kitchens, Ph.D.	
Study Number (s)	BA0818122-01	BA0818123-01
Study Type (s)	Fasting	Fed
Strength (s)	60 mg	60 mg
Clinical Site	BA Research India Limited,	
Clinical Site Address	1 st Floor, Silver Arcade, Near Ashwamegh III, Samrajya, Mujmahuda Road, Akota, Vadodara -390 020, Gujarat, India	
DSI Inspection Status	A routine inspection was requested for ANDA 090175 on 6/30/2008. The inspection was completed on 8/6/2009 and the outcome was VAI. The DSI findings were specific to ANDA 090175 and do not impact the validity of the clinical results in the current ANDA.	
Analytical Site	(b) (4)	
Analytical Site Address	(b) (4)	
DSI Inspection Status	A routine inspection was requested for ANDA 090228 on (b) (4). The inspection was completed on (b) (4) and the outcome was (b) (4). One of the DSI findings may impact the analytical results of the current ANDA. The firm addressed this DSI finding in the previous bioequivalence amendment. Based on the firm's response, the reviewer determined that the DSI finding does not impact the analytical results in the current ANDA. In addition, the other DSI findings were specific to ANDA 090228 and do not impact the analytical results in the current ANDA.	

OVERALL REVIEW RESULT	ADEQUATE		
WAIVER REQUEST RESULT	Not applicable		
DSI REPORT RESULT	ADEQUATE		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
13	AMENDMENT	60 mg	ADEQUATE

1 EXECUTIVE SUMMARY

On October 2, 2008, InvaGen Pharmaceuticals, Inc. submitted an abbreviated new drug application (ANDA) with the results of fasting and fed bioequivalence (BE) studies comparing the test product Raloxifene Hydrochloride Tablets (60 mg) to the reference listed drug (RLD) EVISTA® (Raloxifene Hydrochloride) Tablets (60 mg) manufactured by Eli Lilly. The fasting and fed BE studies were designed as single-dose, two-way crossover BE studies in healthy male subjects. The fasting study did not pass BE acceptance criteria (lnCmax 90% CI: 65.27, 101.56) using analytically valid assay results, and the fasting study had bioanalytical deficiencies. The fed BE study passed BE acceptance criteria, yet the fed study was incomplete due to clinical and bioanalytical deficiencies.

The firm submitted an amendment dated May 16, 2011 that contained the firm's responses to the deficiencies of the original submission. Most of the deficiencies were satisfactorily addressed. In the firm's bioanalytical report, sample S27P1 9.0 Hour (raloxifene) was reanalyzed because it was considered high compared to the preceding and succeeding time points. The Division of Bioequivalence I (DBI) considers this a pharmacokinetic repeat. As a result, the DBI considered the original value (7218.021 pg/mL) to be analytically valid, and the 90% C.I. for lnCmax of raloxifene did not meet bioequivalence acceptance criteria using the original value for this sample. Therefore, fasting study no. BA0818122-01 was considered unacceptable.

This is a review of the firm's bioequivalence amendment submitted August 12, 2011. The firm indicated that the reason for reanalysis of sample S27P1 9.0 Hour should have been reported as "Over the Calibration Curve (OCC)" since the original value for this sample was greater than the upper limit of quantitation (6648.402 pg/mL) for raloxifene. In the original submission, this sample was reanalyzed as an analytical repeat per the firm's SOP, and the firm acknowledged that the reanalysis of this sample should not have been reported as a pharmacokinetic repeat. The firm also submitted revised SOPs for sample reanalysis and chromatographic integration. The firm's responses to the deficiencies are acceptable.

The firm used BA Research India Limited and (b) (4) for the clinical site and analytical sites, respectively. A routine inspection was requested for the clinical site on 6/30/2008 for ANDA 090175. The inspection was completed on 8/6/2009 and the outcome was VAI. The Division of Scientific Investigations (DSI) findings of the clinical site were determined

by the reviewer to be specific to ANDA 090175. A routine inspection was requested for the analytical site on (b) (4) for ANDA 090228. The inspection was completed on (b) (4) and the outcome was (b) (4). One DSI finding of the analytical site may impact the analytical results of the current ANDA. Therefore, the Division of Bioequivalence I (DBI) requested the firm to address this finding, and the firm submitted its response in the previous bioequivalence amendment (May 16, 2011). Based on the firm's response, the reviewer determined that the DSI finding does not impact the analytical results in the current ANDA. In addition, the other DSI findings were specific to ANDA 090228 and do not impact the analytical results in the current ANDA.

ANDA 090842 is **ADEQUATE**.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information

See original review [DARRTS: ANDA 090842, KITCHENS, KELLY, M, Submit/Final Date 01/28/2011, REV-BIOEQ-01(General Review)].

3.2 PK/PD Information

See original review [DARRTS: ANDA 090842, KITCHENS, KELLY, M, Submit/Final Date 01/28/2011, REV-BIOEQ-01(General Review)].

3.3 OGD Recommendations for Drug Product

See original review [DARRTS: ANDA 090842, KITCHENS, KELLY, M, Submit/Final Date 01/28/2011, REV-BIOEQ-01(General Review)].

3.4 Deficiencies, Firm's Response and Conclusion

DEFICIENCY #1:

SOP (b) (4) (Criteria for sample reanalysis and reporting) does not include objective criteria for repeating the analysis of sample S27P1 9.0 Hour, of which the original analysis was found to be analytically valid. Therefore, the original value (7218.021 pg/mL) should be used in the statistical analysis. When using the original assay value for said sample, the 90% confidence interval (C.I.) for $\ln C_{\max}$ of raloxifene was [65.27;101.56] and did not meet bioequivalence acceptance criteria. As a result, fasting study no. BA0818122-01 is unacceptable.

Firm's Response:

We acknowledge the comment and find the response received from the (b) (4) as follows:

“Originally, sample S27P1 9.0 hour was selected for reassay based on analyte interference. However, upon receipt of the DBE Deficiency Letter of July 7, 2011, we retained the services of an independent consultant to review the sample in question and advise us on the validity of our approach. The consultant agreed with the Agency's interpretation (from (b) (4)). The consultant also noted that the sample in question had a value on original assay of 7218.021 pg/mL while the assay calibration curve upper limit of quantitation was 6648.402 pg/mL, thus the value obtained was extrapolated and therefore; not analytically valid. The sample should have been diluted and reassayed in singlet as over the calibration curve (OCC) as per (b) (4) SOP (b) (4) applicable at the time of study (copy attached). The sample was not reassayed as a dilution but was reassayed in singlet according to (b) (4) SOP on AI samples. The reassay value was well within the calibration range (64.831 pg/ml) and was reported. Subsequently, at the InvaGen's request, the sample was reassayed in duplicate (73.489 and 74.646 pg/mL) and these reassay values agreed with the first reassay value. (b) (4) investigated the discrepancy between the original value and the reassay values and could find no assignable cause for the difference other than the possible interference of the sample during the original sample preparation process.

Since the original value was not analytically valid, the original reassay value was reported as per (b) (4) SOPs.

We regret the confusion surrounding the reanalysis. In the future, (b) (4) will ensure that analytically valid values are obtained for all samples prior to selection for reassay for other reasons”.

In reference to the above,

- Please find the Memo from (b) (4) in section **M5.3.1.2 Comparative BA and Bioequivalence study reports (Attachment 1)**.

- Please find SOP for Criteria for Sample Reanalysis and Reporting, (b) (4)
(applicable at the time of study) in section **M5.3.1.2 Comparative BA and Bioequivalence study reports (Attachment 2)**.

(b) (4)

Reviewer's Comments:

- Per the Memo from (b) (4) the firm was advised that it should have reported the reassay for sample S27P1 9.0 Hour as “concentration outside the calibration curve (OCC).”
- In the memo, the firm was also advised to investigate the cause of the discrepancy between the original value and the reassay value of 64.831 pg/mL. The firm suggested analytical interference or contamination during original sample processing.
- The firm has acknowledged that the reason for reanalysis for this sample should have been reported as OCC since the original value was not within the standard curve range for raloxifene. In the original submission, this sample was reanalyzed as an analytical repeat per the firm's SOP, and the firm acknowledged that the reanalysis of this sample should not have been reported as a pharmacokinetic repeat.
- To further justify the reanalysis result for this sample, in the amendment dated May 16, 2011, the firm reported the results of the sample reanalyzed in duplicate with a set of freshly prepared calibration curve standards, two sets of quality control (QC) samples, and the QC samples prepared during the original analysis (July 15, 2008). The concentrations for replicate 1 and 2 were 73.489 pg/mL and 74.646 pg/mL, respectively. There is a 12.5% difference between the average of the duplicate reassay samples (74.068 pg/mL) and the reassay value obtained in the original study (64.831 pg/mL).

Table 1: Concentration data of Raloxifene in Clinical Samples (pg/mL)

SUBJECT/ PERIOD/HOUR	Replicate 1	Replicate 2	Mean
	pg/mL		pg/mL
S27\P1\9.00 HR	73.489	74.646	74.068

**Table 2: Summary of calibration curve performed during this analysis for
Raloxifene**

Batch ID	Date Batch	STD A	STD B	STD C	STD D	STD E	STD F	STD G	STD H	Slope	Intercept	r
	Injected	30.822	61.645	123.290	308.224	770.560	1541.121	3082.241	6164.483			
		(pg/mL)	(pg/mL)	(pg/mL)	(pg/mL)	(pg/mL)	(pg/mL)	(pg/mL)	(pg/mL)			
002_011	3-May-11	30.038	65.087	123.866	296.622	767.453	1547.124	3193.039	5959.549	0.000181	-0.000432	0.9993
% ACCURACY		97.5	105.6	100.5	96.2	99.6	100.4	103.6	96.7			

Table 3: Summary of Fresh Quality Control Samples analyzed during this analysis:

Batch ID	Date Batch	LQC	MQC	HQC
	Injected	88.687	2463.521	4927.041
		(pg/mL)	(pg/mL)	(pg/mL)
002_011	3-May-11	87.664	2505.693	4670.547
		83.392	2441.302	4768.922
Mean		85.528	2473.498	4719.735
% Accuracy		96.4	100.4	95.8

Table 4: Summary of Quality Control Samples stored for 1021 days and analyzed during this analysis:

Batch ID	Date Batch	LQC	MQC	HQC
	Injected	95.737	2659.361	5318.721
		(pg/mL)	(pg/mL)	(pg/mL)
002_011	3-May-11	91.400	2670.948	5363.181
		101.708	2545.285	5470.363
Mean		96.554	2608.117	5416.772
% Accuracy		100.9	98.1	101.8

- The firms' response is **satisfactory**.

DEFICIENCY #2:

Please revise your SOP (b) (4) for future studies to include objective criteria for reanalysis of samples with anomalous values, otherwise known as pharmacokinetic (PK) repeats.

Firm's Response:

We acknowledge the comment and (b) (4) (Bio Analytical site) has revised SOP# (b) (4) to include objective criteria for reanalysis of samples with anomalous values and a copy of the same (SOP# (b) (4)) is included in section **M5.3.1.2 Comparative BA and Bioequivalence study reports (Attachment 3).**

Reviewer's Comments:

- The firm submitted SOP # (b) (4) "Criteria for Sample Reanalysis and Reporting" with effective date (b) (4)
- The firm revised the criteria for samples reanalyzed due to **Sample Anomalies** as follows:

4.3 Second Category: Sample Anomalies:

4.3.1 Samples will be considered sample anomalies for any of the following reasons. These samples will be re-assayed in **duplicate** (sample volume permitting).

A. Analytical Interference (AI): Predose sample having interference more than LLOQ standard (Std A).

Note: Upon re-assay of AI sample, if one of two values obtained is above LLOQ, then report the median of three values i.e. BLQ and two measurable values.

B. Suspected Mix up (SM) of individual samples during analysis such as swapping of samples from identical time points from 2 different subjects. E.g. 2 hour sample from subject A are analyzed with subject B and vice versa or same time point samples switched between different periods (SM):

C. Double Peak (DP): When the concentration of a specific sample (Css) is greater than both the previous sample (Cps) and the next sample (Cns) concentrations and both of the following conditions are met:

1. $C_{ss}/C_{ps} \text{ \& } C_{ss}/C_{ns} \geq 2.0$
2. C_{ss} concentration is greater than LQC concentration.

Note: In case C_{ps} or C_{ns} values are Below Limit of Quantitation (BLQs) the corresponding ratios will be considered greater than 2.0.

- The firm's response is **acceptable**.

DEFICIENCY #3:

Please revise your SOP (b) (4) (Chromatographic integration) to include objective criteria for performing manual integration of chromatogram peaks. Please be advised to implement pre-established SOPs for your analytical procedures in future studies.

Firm's Response:

We acknowledge the comment and (b) (4) (Bio Analytical site) has revised SOP# (b) (4) to include objective criteria for performing manual integration of chromatogram peaks and a copy of the same (SOP# (b) (4)) is included in section **M5.3.1.2 Comparative BA and Bioequivalence study reports (Attachment 4)**.

Reviewer's Comments:

- The firm submitted SOP # (b) (4), "Chromatographic Integration" with effective date (b) (4).
- The firm revised the criteria for manual integration of chromatogram peaks as follows:
4.9 For all manually integrated peaks, if the resulting change in the peak area is less than 5%, then the peak should not be re-integrated.
- The firm's response is **acceptable**.

3.5 Deficiency Comments

There are no deficiencies.

3.6 Recommendations

1. The Division of Bioequivalence I (DBI) **accepts** the fasting study no. BA0818122-01 conducted by InvaGen Pharmaceuticals, Inc. on its Raloxifene Hydrochloride Tablets, 60 mg (lot #ID080510), comparing it to Eli Lilly's EVISTA® (Raloxifene Hydrochloride) Tablets, 60 mg (lot # A489455).
2. The DBI **accepts** the fed study no. BA0818123-01 conducted by InvaGen Pharmaceuticals, Inc. on its Raloxifene Hydrochloride Tablets, 60 mg (lot #ID080510), comparing it to Eli Lilly's EVISTA® (Raloxifene Hydrochloride) Tablets, 60 mg (lot # A489455).
3. The firm's in vitro dissolution testing is **acceptable**. The dissolution testing should be conducted in 1000 mL of 0.1% Polysorbate 80 in water at 37°C ± 0.5°C using USP apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

NLT 80% (Q) in 30 minutes

3.7 Comments for Other OGD Disciplines

Discipline	Comment
None	None

APPEARS THIS WAY ON
ORIGINAL

BIOEQUIVALENCE COMMENTS TO BE COMMUNICATED TO THE FIRM

ANDA: 090842

APPLICANT: InvaGen Pharmaceuticals, Inc.

DRUG PRODUCT: Raloxifene Hydrochloride Tablets USP, 60 mg

The Division of Bioequivalence I (DBI) has completed its review acknowledged on the cover page and has no further questions at this time.

We acknowledge that you will conduct dissolution testing for your test product using the USP dissolution method and specification:

Medium: 0.1% Polysorbate 80 in water
Volume: 1000 mL
Temperature: 37°C±0.5°C
USP Apparatus: II (Paddle)
Speed: 50 rpm
Specification: NLT 80% (Q) in 30 minutes

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

Sincerely yours,

{See appended electronic signature page}

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

3.8 Outcome Page

COMPLETED ASSIGNMENT FOR 90842 ID: 14816

Reviewer: Kitchens, Kelly

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Raloxifene Hydrochloride Tablets, USP, 60 mg

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
14816	8/12/2011	Other	Study Amendment	1	1
				Bean Total:	1

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

/s/

KELLY M KITCHENS
08/19/2011

YIH CHAIN HUANG
08/19/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
08/19/2011

DIVISION OF BIOEQUIVALENCE AMENDMENT REVIEW

ANDA No.	090842	
Drug Product Name	Raloxifene Hydrochloride Tablets, USP	
Strength(s)	60 mg	
Applicant Name	InvaGen Pharmaceuticals, Inc.	
Address	7 Oser Avenue, Hauppauge, New York 11788	
Applicant's Point of Contact	Dr. Sudhakar Rao Vidiyala, President	
Contact's Telephone Number	631-231-3233	
Contact's Fax Number	631-231-4248	
Original Submission Date(s)	October 2, 2008 (Original submission) December 6, 2010 (telephone amendment in response to request for bioequivalence information)	
Submission Date(s) of Amendment(s) Under Review	May 16, 2011	
Reviewer	Kelly M. Kitchens, Ph.D.	
Study Number (s)	BA0818122-01	BA0818123-01
Study Type (s)	Fasting	Fed
Strength (s)	60 mg	60 mg
Clinical Site	BA Research India Limited,	
Clinical Site Address	1 st Floor, Silver Arcade, Near Ashwamegh III, Samrajya, Mujmahuda Road, Akota, Vadodara -390 020, Gujarat, India	
DSI Inspection Status	A routine inspection was requested for ANDA 090175 on 6/30/2008. The inspection was completed on 8/6/2009 and the outcome was VAI. The DSI findings were specific to ANDA 090175 and do not impact the validity of the clinical results in the current ANDA.	
Analytical Site	(b) (4)	
Analytical Site Address	(b) (4)	
DSI Inspection Status	A routine inspection was requested for ANDA 090228 on (b) (4). The inspection was completed on (b) (4) and the outcome was (b) (4). One of the DSI findings may impact the analytical results of the current ANDA. The firm addressed this DSI finding in the current bioequivalence amendment. Based on the firm's response, the reviewer determined that the DSI finding does not impact the analytical results in the current ANDA. In addition, the other DSI findings were specific to ANDA 090228 and do not impact the analytical results in the current ANDA.	
OVERALL REVIEW RESULT	INADEQUATE	

WAIVER REQUEST RESULT	Not applicable		
DSI REPORT RESULT	ADEQUATE		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
12	AMENDMENT	60 mg	INADEQUATE

1 EXECUTIVE SUMMARY

On October 2, 2008, InvaGen Pharmaceuticals, Inc. submitted an abbreviated new drug application (ANDA) with the results of fasting and fed bioequivalence (BE) studies comparing the test product Raloxifene Hydrochloride Tablets (60 mg) to the reference listed drug (RLD) EVISTA® (Raloxifene Hydrochloride) Tablets (60 mg) manufactured by Eli Lilly. The fasting and fed BE studies were designed as single-dose, two-way crossover BE studies in healthy male subjects. The fasting study did not pass BE acceptance criteria (lnCmax 90% CI: 65.27, 101.56) using analytically valid assay results, and the fasting study had bioanalytical deficiencies. The fed BE study passed BE acceptance criteria, yet the fed study was incomplete due to clinical and bioanalytical deficiencies.

This is a review of the bioequivalence amendment submitted May 16, 2011 that contains the firm's responses to the deficiencies for the original submission. The deficiencies #1-3 and 5-7 have been satisfactorily addressed. Regarding deficiency #4, the firm's SOP (b) (4) (Criteria for sample reanalysis and reporting) does not include objective criteria for repeating sample S27P1 9.0 Hour. As a result, the 90% C.I. for lnCmax of raloxifene does not meet bioequivalence acceptance criteria using the original value (7218.021 pg/mL) for this sample. Therefore, fasting study no. BA0818122-01 remains unacceptable.

The firm used BA Research India Limited and (b) (4) for the clinical site and analytical sites, respectively. A routine inspection was requested for the clinical site on 6/30/2008 for ANDA 090175. The inspection was completed on 8/6/2009 and the outcome was VAI. A routine inspection was requested for the analytical site on (b) (4) for ANDA 090228. The inspection was completed on (b) (4) and the outcome was (b) (4). The Division of Scientific Investigations (DSI) findings of the clinical site were determined by the reviewer to be specific to ANDA 090175. One DSI finding of the analytical site may impact the analytical results of the current ANDA. Therefore, the DBE requested the firm to address this finding, and the firm submitted its response in the current bioequivalence amendment (May 16, 2011). The other DSI findings of the analytical site are specific to ANDA 090228 and do not impact the study outcome in the current ANDA [see DARRTS: ANDA 090842, KITCHENS, KELLY, M, Submit/Final Date 01/28/2011, REV-BIOEQ-01(General Review)].

ANDA 090842 remains **INADEQUATE**.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information

See original review [DARRTS: ANDA 090842, KITCHENS, KELLY, M, Submit/Final Date 01/28/2011, REV-BIOEQ-01(General Review)].

3.2 PK/PD Information

See original review [DARRTS: ANDA 090842, KITCHENS, KELLY, M, Submit/Final Date 01/28/2011, REV-BIOEQ-01(General Review)].

3.3 OGD Recommendations for Drug Product

See original review [DARRTS: ANDA 090842, KITCHENS, KELLY, M, Submit/Final Date 01/28/2011, REV-BIOEQ-01(General Review)].

3.4 Deficiencies, Firm's Response and Conclusion

DEFICIENCY #1:

Please explain the term "No Intercept" used to assign to the original values of the raloxifene-4'-glucuronide samples which were reanalyzed for the reason "Concentration Over the Calibration Curve (OCC)" in fasting study no. BA0818122-01. The same term was also used for the raloxifene-4'-glucuronide QC samples in fasting study no. BA0818122-01.

Firm's Response:

We acknowledge the comment and find the response received from the (b) (4) as follows:

“For calculating Raloxifene-4’-glucuronide concentration in samples, quadratic regression was used. Due to the nature of the quadratic equation, the curve cannot extrapolate the analyte to internal standard peak area ratios beyond a certain point after highest calibration standard (Std. H or Std. H’). Hence, some of the sample concentrations higher than highest calibration standard values were reported either as a numerical value or as “No Intercept”. Hence, for samples reported as “No Intercept” by the analyst software, original values in the repeat table were identified as “No Intercept”. Therefore, all the “No Intercept” samples were over the calibration curve and were repeated as OCC samples.

As an example, in subjects 19 & 20 result table Raloxifene-4’-glucuronide to internal standard peak area ratio for highest calibration standard (std. H’) is 10.214. For samples having peak area ratio higher than 10.333 the concentration is reported as “No Intercept”. Hence, in this batch, for samples having peak area ratio higher than 10.333, the analyst software cannot extrapolate the calibration curve to calculate a numerical value using the quadratic regression and thus assigns “No Intercept” value to these samples”.

In reference to the above,

- Please find the subjects 19 & 20 Raloxifene-4’-glucuronide result table in section **M5.3.1.2 Comparative BA and Bioequivalence study reports (Attachment 1).**

	Sample Name	Sample ID	Sample Type	Acquisition Date	Vial Position	Plate Position	File Name	Analyte Peak Area (counts)	Analyte Concentration (ng/mL)	Area Ratio	IS Peak Area (counts)	UR	Calculated Concentration (ng/mL)	Accuracy (%)
1	REF LLOQ	SUB19&20_1	Unknown	7/22/2008 7:51:35 AM	1	7	001_005	54906	N/A	0.050	1105009	☐	0.635	N/A
2	REF LLOQ	SUB19&20_2	Unknown	7/22/2008 8:02:41 AM	1	7	001_005	47894	N/A	0.043	1124881	☐	0.541	N/A
3	STD A	SUB19&20_3	Unknown	7/22/2008 8:12:14 AM	3	10	001_005	67583	N/A	0.085	795031	☐	1.105	N/A
4	STD H	SUB19&20_4	Unknown	7/22/2008 8:23:10 AM	11	10	001_005	8571687	N/A	11.321	757178	☐	No Intercept	N/A
5	REF BLANK	SUB19&20_5	Unknown	7/22/2008 8:32:55 AM	2	7	001_005	0	N/A	#DIV/0!	0	☐	#DIV/0!	N/A
6	BLANK	SUB19&20_6	Unknown	7/22/2008 8:44:03 AM	1	10	001_005	0	N/A	#DIV/0!	0	☐	#DIV/0!	N/A
7	BLANK IS	SUB19&20_7	Unknown	7/22/2008 8:55:07 AM	2	10	001_005	0	N/A	0.000	754639	☐	No Peak	N/A
8	STD A	SUB19&20_8	Standard	7/22/2008 9:04:44 AM	3	10	001_005	66473	1.072	0.084	793275	☒	1.089	102
9	STD A'	SUB19&20_9	Unknown	7/22/2008 9:14:16 AM	4	10	001_005	64738	N/A	0.083	781640	☐	1.076	N/A
10	STD B	SUB19&20_10	Standard	7/22/2008 9:23:53 AM	5	10	001_005	125301	2.145	0.158	794485	☒	2.075	97
11	STD C	SUB19&20_11	Standard	7/22/2008 9:33:29 AM	6	10	001_005	253612	4.290	0.323	785159	☒	4.292	100
12	STD D	SUB19&20_12	Standard	7/22/2008 9:43:02 AM	7	10	001_005	623122	10.725	0.789	789813	☒	10.635	99
13	STD E	SUB19&20_13	Standard	7/22/2008 9:52:36 AM	8	10	001_005	1554364	26.812	1.970	769173	☒	27.379	102
14	STD F	SUB19&20_14	Standard	7/22/2008 10:02:11 AM	9	10	001_005	2853460	53.025	3.706	769577	☒	54.142	101
15	STD G	SUB19&20_15	Standard	7/22/2008 10:11:39 AM	10	10	001_005	5168383	107.250	6.626	780041	☒	107.483	100
16	STD H	SUB19&20_16	Unknown	7/22/2008 10:21:06 AM	11	10	001_005	814041	N/A	11.978	67960	☐	No Intercept	N/A
17	STD H'	SUB19&20_17	Standard	7/22/2008 10:30:38 AM	12	10	001_005	8145555	214.499	10.214	797480	☒	211.088	98
18	S19P1 0.0 HR	SUB19&20_18	Unknown	7/22/2008 10:40:09 AM	13	10	001_005	995	N/A	0.001	722332	☐	< 0	N/A
19	S19P1 0.5 HR	SUB19&20_19	Unknown	7/22/2008 10:49:44 AM	14	10	001_005	8083712	N/A	8.554	712392	☐	153.373	N/A
20	S19P1 1.0 HR	SUB19&20_20	Unknown	7/22/2008 10:59:20 AM	15	10	001_005	9610111	N/A	12.044	714605	☐	No Intercept	N/A
21	S19P1 2.0 HR	SUB19&20_21	Unknown	7/22/2008 11:08:54 AM	16	10	001_005	5406986	N/A	7.492	721694	☐	126.545	N/A
22	S19P1 3.0 HR	SUB19&20_22	Unknown	7/22/2008 11:18:29 AM	17	10	001_005	4339085	N/A	5.836	743445	☐	91.666	N/A
23	S19P1 4.0 HR	SUB19&20_23	Unknown	7/22/2008 11:28:02 AM	18	10	001_005	4521191	N/A	6.387	707623	☐	102.559	N/A
24	S19P1 5.0 HR	SUB19&20_24	Unknown	7/22/2008 11:37:34 AM	19	10	001_005	5885833	N/A	8.401	700623	☐	149.201	N/A
25	HQC	SUB19&20_25	Quality Co	7/22/2008 11:47:09 AM	20	10	001_005	7056737	171.599	8.495	830711	☒	151.749	88
26	S19P1 6.0 HR	SUB19&20_26	Unknown	7/22/2008 11:56:44 AM	21	10	001_005	4606119	N/A	5.986	772103	☐	94.170	N/A
27	S19P1 7.0 HR	SUB19&20_27	Unknown	7/22/2008 12:06:15 PM	22	10	001_005	4494125	N/A	5.943	755185	☐	93.731	N/A
28	S19P1 8.0 HR	SUB19&20_28	Unknown	7/22/2008 12:15:50 PM	23	10	001_005	3263193	N/A	4.197	777498	☐	62.229	N/A
29	S19P1 9.0 HR	SUB19&20_29	Unknown	7/22/2008 12:25:23 PM	24	10	001_005	4001060	N/A	5.196	775880	☐	78.963	N/A
30	S19P1 10.0 HR	SUB19&20_30	Unknown	7/22/2008 12:34:55 PM	25	10	001_005	4194659	N/A	5.674	739282	☐	88.562	N/A

Printing Time: 6:36:43 PM
Printing Date: July 23, 2008

Operator:

(b) (4)

Page 1 of 4

	Sample Name	Sample ID	Sample Type	Acquisition Date	Vial Position	Plate Position	File Name	Analyte Peak Area (counts)	Analyte Concentration (ng/mL)	Area Ratio	IS Peak Area (counts)	UR Sec Rec	Calculated Concentration (ng/mL)	Accuracy (%)
31	S19P1 12.0 HR	SUB19&20_31	Unknown	7/22/2008 12:44:30 PM	26	10	001_005	4570268	N/A	6.035	757293		95.526	N/A
32	S19P1 16.0 HR	SUB19&20_32	Unknown	7/22/2008 12:54:01 PM	27	10	001_005	3678848	N/A	4.868	755764		73.797	N/A
33	MQC	SUB19&20_33	Quality Co	7/22/2008 1:03:35 PM	28	10	001_005	3889135	85.800	5.094	755454	X	77.837	91
34	S19P1 20.0 HR	SUB19&20_34	Unknown	7/22/2008 1:13:09 PM	29	10	001_005	3945878	N/A	5.536	716370		85.440	N/A
35	S19P1 24.0 HR	SUB19&20_35	Unknown	7/22/2008 1:22:42 PM	30	10	001_005	3801453	N/A	5.118	703744		78.265	N/A
36	S19P1 48.0 HR	SUB19&20_36	Unknown	7/22/2008 1:32:13 PM	31	10	001_005	415571	N/A	0.554	749626		7.424	N/A
37	S19P1 72.0 HR	SUB19&20_37	Unknown	7/22/2008 1:41:49 PM	32	10	001_005	35811	N/A	0.051	703281		0.654	N/A
38	S19P1 96.0 HR	SUB19&20_38	Unknown	7/22/2008 1:51:23 PM	33	10	001_005	6686	N/A	0.009	751024		0.092	N/A
39	S19P1 120.0 HR	SUB19&20_39	Unknown	7/22/2008 2:00:58 PM	34	10	001_005	1542	N/A	0.002	673606		0.006	N/A
40	LQC	SUB19&20_40	Quality Co	7/22/2008 2:10:33 PM	35	10	001_005	174094	3.089	0.233	747424	X	3.082	100
41	S19P2 0.0 HR	SUB19&20_41	Unknown	7/22/2008 2:20:08 PM	36	10	001_005	877	N/A	0.001	759550		< 0	N/A
42	S19P2 0.5 HR	SUB19&20_42	Unknown	7/22/2008 2:29:40 PM	37	10	001_005	6169855	N/A	7.973	776396		138.114	N/A
43	S19P2 1.0 HR	SUB19&20_43	Unknown	7/22/2008 2:39:14 PM	38	10	001_005	5979200	N/A	7.710	758251		131.665	N/A
44	S19P2 2.0 HR	SUB19&20_44	Unknown	7/22/2008 2:48:49 PM	39	10	001_005	4451511	N/A	5.856	790122		92.046	N/A
45	S19P2 3.0 HR	SUB19&20_45	Unknown	7/22/2008 2:58:23 PM	40	10	001_005	3743854	N/A	5.259	711920		80.831	N/A
46	S19P2 4.0 HR	SUB19&20_46	Unknown	7/22/2008 3:08:00 PM	41	10	001_005	3922017	N/A	5.337	734854		82.268	N/A
47	S19P2 5.0 HR	SUB19&20_47	Unknown	7/22/2008 3:17:35 PM	42	10	001_005	4863859	N/A	6.430	752902		104.049	N/A
48	HQC	SUB19&20_48	Quality Co	7/22/2008 3:27:09 PM	43	10	001_005	7006834	171.599	9.315	752171	X	176.303	103
49	S19P2 6.0 HR	SUB19&20_49	Unknown	7/22/2008 3:36:42 PM	44	10	001_005	4380126	N/A	5.712	768593		89.282	N/A
50	S19P2 7.0 HR	SUB19&20_50	Unknown	7/22/2008 3:46:16 PM	45	10	001_005	4381061	N/A	5.722	765701		89.468	N/A
51	S19P2 8.0 HR	SUB19&20_51	Unknown	7/22/2008 3:55:51 PM	46	10	001_005	4234217	N/A	5.446	777423		84.290	N/A
52	S19P2 9.0 HR	SUB19&20_52	Unknown	7/22/2008 4:05:26 PM	47	10	001_005	4818565	N/A	6.084	759186		96.486	N/A
53	S19P2 10.0 HR	SUB19&20_53	Unknown	7/22/2008 4:14:59 PM	48	10	001_005	5481851	N/A	7.313	750946		122.437	N/A
54	S19P2 12.0 HR	SUB19&20_54	Unknown	7/22/2008 4:24:35 PM	49	10	001_005	5422936	N/A	7.347	738095		123.209	N/A
55	S19P2 16.0 HR	SUB19&20_55	Unknown	7/22/2008 4:34:10 PM	50	10	001_005	4142587	N/A	5.690	731844		88.305	N/A
56	MQC	SUB19&20_56	Quality Co	7/22/2008 4:43:45 PM	51	10	001_005	3916103	85.800	5.535	703652	X	88.512	101
57	S19P2 20.0 HR	SUB19&20_57	Unknown	7/22/2008 4:53:18 PM	52	10	001_005	4403831	N/A	6.096	722342		96.734	N/A
58	S19P2 24.0 HR	SUB19&20_58	Unknown	7/22/2008 5:02:50 PM	53	10	001_005	2561115	N/A	3.696	692888		53.955	N/A
59	S19P2 48.0 HR	SUB19&20_59	Unknown	7/22/2008 5:12:26 PM	54	10	001_005	283014	N/A	0.417	679025		5.558	N/A
60	S19P2 72.0 HR	SUB19&20_60	Unknown	7/22/2008 5:21:59 PM	1	11	001_005	83790	N/A	0.119	703175		1.530	N/A

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	Sample Name	Sample ID	Sample Type	Acquisition Date	Vial Position	Plate Position	File Name	Analyte Peak Area (counts)	Analyte Concentration (ng/mL)	Area Ratio	IS Peak Area (counts)	UR Sec Rec	Calculated Concentration (ng/mL)	Accuracy (%)
51	S19P2 96.0 HR	SUB19&20_61	Unknown	7/22/2008 5:33:11 PM	2	11	001_005	9063	N/A	0.013	712696		0.144	N/A
52	S19P2 120.0 HR	SUB19&20_62	Unknown	7/22/2008 5:42:46 PM	3	11	001_005	2700	N/A	0.004	723371		0.025	N/A
53	LQC	SUB19&20_63	Quality Co	7/22/2008 5:52:21 PM	4	11	001_005	175589	3.089	0.234	751625	X	3.091	100
54	S20P1 0.0 HR	SUB19&20_64	Unknown	7/22/2008 6:01:55 PM	5	11	001_005	0	N/A	0.030	720814		No Peak	N/A
55	S20P1 0.5 HR	SUB19&20_65	Unknown	7/22/2008 6:11:27 PM	6	11	001_005	2915540	N/A	3.946	738945		58.037	N/A
56	S20P1 1.0 HR	SUB19&20_66	Unknown	7/22/2008 6:21:00 PM	7	11	001_005	5434446	N/A	7.328	741623		122.767	N/A
57	S20P1 2.0 HR	SUB19&20_67	Unknown	7/22/2008 6:30:32 PM	8	11	001_005	6206031	N/A	8.210	755906		144.161	N/A
58	S20P1 3.0 HR	SUB19&20_68	Unknown	7/22/2008 6:40:07 PM	9	11	001_005	6818840	N/A	9.007	757062		166.520	N/A
59	S20P1 4.0 HR	SUB19&20_69	Unknown	7/22/2008 6:49:42 PM	10	11	001_005	8408314	N/A	11.578	726211		No Intercep	N/A
70	S20P1 5.0 HR	SUB19&20_70	Unknown	7/22/2008 6:59:17 PM	11	11	001_005	9099866	N/A	12.397	705570		No Intercep	N/A
71	HQC	SUB19&20_71	Quality Co	7/22/2008 7:08:51 PM	12	11	001_005	9885357	171.599	9.293	751682	X	175.552	102
72	S20P1 6.0 HR	SUB19&20_72	Unknown	7/22/2008 7:18:24 PM	13	11	001_005	8861450	N/A	9.117	752639		169.906	N/A
73	S20P1 7.0 HR	SUB19&20_73	Unknown	7/22/2008 7:27:56 PM	14	11	001_005	5253508	N/A	6.714	732421		109.343	N/A
74	S20P1 8.0 HR	SUB19&20_74	Unknown	7/22/2008 7:37:31 PM	15	11	001_005	4804011	N/A	6.431	736909		104.051	N/A
75	S20P1 9.0 HR	SUB19&20_75	Unknown	7/22/2008 7:47:05 PM	16	11	001_005	6312408	N/A	8.750	721391		158.917	N/A
76	S20P1 10.0 HR	SUB19&20_76	Unknown	7/22/2008 7:56:37 PM	17	11	001_005	6343487	N/A	8.653	733109		156.139	N/A
77	S20P1 12.0 HR	SUB19&20_77	Unknown	7/22/2008 8:06:10 PM	18	11	001_005	5589226	N/A	7.951	702917		137.589	N/A
78	S20P1 16.0 HR	SUB19&20_78	Unknown	7/22/2008 8:15:41 PM	19	11	001_005	4208863	N/A	5.603	730324		88.910	N/A
79	MQC	SUB19&20_79	Quality Co	7/22/2008 8:25:19 PM	20	11	001_005	3657483	85.800	4.779	765306	X	72.235	84
80	S20P1 20.0 HR	SUB19&20_80	Unknown	7/22/2008 8:34:59 PM	21	11	001_005	4241800	N/A	5.853	723493		92.180	N/A
81	S20P1 24.0 HR	SUB19&20_81	Unknown	7/22/2008 8:44:31 PM	22	11	001_005	4609883	N/A	6.796	707814		111.032	N/A
82	S20P1 48.0 HR	SUB19&20_82	Unknown	7/22/2008 8:54:06 PM	23	11	001_005	1317320	N/A	1.844	714400		25.547	N/A
83	S20P1 72.0 HR	SUB19&20_83	Unknown	7/22/2008 9:03:41 PM	24	11	001_005	472371	N/A	0.695	680106		9.338	N/A
84	S20P1 96.0 HR	SUB19&20_84	Unknown	7/22/2008 9:13:14 PM	25	11	001_005	139600	N/A	0.193	721613		2.552	N/A
85	S20P1 120.0 HR	SUB19&20_85	Unknown	7/22/2008 9:22:47 PM	26	11	001_005	42406	N/A	0.061	690162		0.792	N/A
86	LQC	SUB19&20_86	Quality Co	7/22/2008 9:32:22 PM	27	11	001_005	172609	3.089	0.218	791788	X	2.882	93
87	S20P2 0.0 HR	SUB19&20_87	Unknown	7/22/2008 9:41:55 PM	28	11	001_005	946	N/A	0.001	733695		< 0	N/A
88	S20P2 0.5 HR	SUB19&20_88	Unknown	7/22/2008 9:51:31 PM	29	11	001_005	1157663	N/A	1.547	748306		21.268	N/A
89	S20P2 1.0 HR	SUB19&20_89	Unknown	7/22/2008 10:01:04 PM	30	11	001_005	4221357	N/A	5.822	725033		91.394	N/A
90	S20P2 2.0 HR	SUB19&20_90	Unknown	7/22/2008 10:10:37 PM	31	11	001_005	5487308	N/A	9.213	704155		172.953	N/A

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	Sample Name	Sample ID	Sample Type	Acquisition Date	Vial Position	Plate Position	File Name	Analyte Peak Area (counts)	Analyte Concentration (ng/mL)	Area Ratio	IS Peak Area (counts)	UR e C R e d	Calculated Concentration (ng/mL)	Accuracy (%)
91	S20P2 3.0 HR	SUB19&20_91	Unknown	7/22/2008 10:20:09 PM	32	11	001_005	9443187	N/A	12.845	735153	☐	No Intercept	N/A
92	S20P2 4.0 HR	SUB19&20_92	Unknown	7/22/2008 10:29:43 PM	33	11	001_005	10036635	N/A	14.096	712079	☐	No Intercept	N/A
93	S20P2 5.0 HR	SUB19&20_93	Unknown	7/22/2008 10:39:19 PM	34	11	001_005	12375372	N/A	16.717	740292	☐	No Intercept	N/A
94	HQC	SUB19&20_94	Quality Co	7/22/2008 10:48:39 PM	35	11	001_005	8529569	171.599	8.453	772446	☒	150.512	88
95	S20P2 6.0 HR	SUB19&20_95	Unknown	7/22/2008 10:58:11 PM	36	11	001_005	11351452	N/A	15.203	746653	☐	No Intercept	N/A
96	S20P2 7.0 HR	SUB19&20_96	Unknown	7/22/2008 11:07:43 PM	37	11	001_005	9350542	N/A	12.537	745831	☐	No Intercept	N/A
97	S20P2 8.0 HR	SUB19&20_97	Unknown	7/22/2008 11:17:16 PM	38	11	001_005	7400255	N/A	10.065	735226	☐	204.396	N/A
98	S20P2 9.0 HR	SUB19&20_98	Unknown	7/22/2008 11:26:52 PM	39	11	001_005	7202017	N/A	9.963	722887	☐	200.066	N/A
99	S20P2 10.0 HR	SUB19&20_99	Unknown	7/22/2008 11:36:27 PM	40	11	001_005	7378036	N/A	10.333	714014	☐	215.855	N/A
100	S20P2 12.0 HR	SUB19&20_100	Unknown	7/22/2008 11:46:03 PM	41	11	001_005	8159448	N/A	11.618	702078	☐	No Intercept	N/A
101	S20P2 16.0 HR	SUB19&20_101	Unknown	7/22/2008 11:55:36 PM	42	11	001_005	5539071	N/A	8.957	618401	☐	165.007	N/A
102	MQC	SUB19&20_102	Quality Co	7/23/2008 12:05:09 AM	43	11	001_005	3770942	85.600	5.119	736661	☒	78.290	91
103	S20P2 20.0 HR	SUB19&20_103	Unknown	7/23/2008 12:14:44 AM	44	11	001_005	5045851	N/A	7.519	671042	☐	127.182	N/A
104	S20P2 24.0 HR	SUB19&20_104	Unknown	7/23/2008 12:24:16 AM	45	11	001_005	5393687	N/A	8.110	665085	☐	141.578	N/A
105	S20P2 48.0 HR	SUB19&20_105	Unknown	7/23/2008 12:33:49 AM	46	11	001_005	1779556	N/A	2.505	710465	☐	35.324	N/A
106	S20P2 72.0 HR	SUB19&20_106	Unknown	7/23/2008 12:43:25 AM	47	11	001_005	576879	N/A	1.057	640662	☐	14.342	N/A
107	S20P2 96.0 HR	SUB19&20_107	Unknown	7/23/2008 12:53:00 AM	48	11	001_005	116981	N/A	0.165	706270	☐	2.179	N/A
108	S20P2 120.0 HR	SUB19&20_108	Unknown	7/23/2008 1:03:33 AM	49	11	001_005	47099	N/A	0.071	661067	☐	0.922	N/A
109	LQC	SUB19&20_109	Quality Co	7/23/2008 1:13:31 AM	50	11	001_005	168366	3.089	0.235	717639	☒	3.104	100

CHROMATOGRAMS REVIEWED

BATCH ACCEPTED

(b) (4)

Data reviewed

(b) (4)

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Reviewer's Comments:

- The firm indicated that the software could not extrapolate the calibration curve to calculate a numerical value for samples with a R4G:IS peak ratio that exceeded the R4G ULOQ:IS peak ratio. Hence, the term "No Intercept" was assigned as the value for such samples. The raw data for subjects 19 and 20 was submitted as an example to this approach. The ULOQ: IS peak ratio was 8145555:797480, or 10.214, and any sample whose R4G:IS ratio was greater than 10.214 was reported as having the original value "No Intercept," and repeated for the reason "Concentration over the Calibration Curve (OCC)" per the firm's SOP on repeat analysis.
- The samples with original value "No Intercept" were repeated for the reason OCC. In the original submission for this ANDA, the firm followed the pre-established SOP pertaining to samples repeated for the reason OCC [see DARRTS: ANDA 090842, KITCHENS, KELLY, M, Submit/Final Date 01/28/2011, REV-BIOEQ-01(General Review)].
- The firms' response is **acceptable**.

R4G – Raloxifene-4'-Glucuronide

IS – Internal Standard

ULOQ – Upper Limit of Quantitation

DEFICIENCY #2:

Please provide objective justifications for manually integrating the peaks for samples S3P2 96.0 HR SUB3&4_61 (raloxifene), S3P2 96.0 HR SUB3&4_61 (raloxifene-4'-glucuronide), S3P2 96.0 HR SUB3&4_61 (raloxifene-6-glucuronide), and S5P2 96.0 HR SUB5&6_60 (raloxifene-4'-glucuronide) in fasting study no. BA0818122-01. Please also provide the standard operating procedure (SOP) detailing the reintegration method.

Firm's Response:

We acknowledge the comment and find the response received from the (b) (4) as follows:

“The chromatograms for S3P2 96.0 HR SUB3&4_61 were manually integrated due to shift in the Retention Time (RT) of the analytes and the internal standard for this sample. The RT of analytes (raloxifene, raloxifene-4'-glucuronide and raloxifene-6-glucuronide) and the internal standard shifted by about 0.6 minutes as shown below:

Analyte	Raloxifene	Raloxifene-4'-glucuronide	Raloxifene-6-glucuronide	Internal Standard
Approximate RT (RRT) in the batch	5.07 min (0.97)	4.71 min (0.90)	4.28 min (0.82)	5.23 min (1.00)
Approximate RT (RRT) for sample S3P2 96.0 HR	5.65 min (0.97)	5.31 min (0.91)	4.87 min (0.84)	5.83 min (1.00)

RRT: Relative Retention Time with respect to internal standard

In the above batch, the RT window was selected as 0.5 min. However, the RT shifted by about 0.6 min for all the analytes in this sample. Hence, these peaks were manually integrated without changing any other integration parameters except for the RT window.

The raloxifene-4'-glucuronide chromatogram for S5P2 96.0 HR SUB5&6_60 was misidentified by the analyst software at the RT of 4.85 min (RRT 0.93) instead of 4.68 min (RRT 0.90).

Hence, this peak was manually integrated at 4.68 min without changing any other integration parameters.

(b) (4) did not have a Standard Operating Procedure (SOP) for reintegration at the time of the study. A Standard Operating Procedure (SOP) (b) (4) detailing chromatographic integration (reintegration) was implemented on (b) (4)

In reference to the above,

- Please find the SOP for detailing chromatographic integration (reintegration) (b) (4) effective date (b) (4) (Sop No. (b) (4)) in section **M5.3.1.2 Comparative BA and Bioequivalence study reports (Attachment 2)**.

Reviewer's Comments:

- The firm indicated that the chromatograms of the above-mentioned samples were manually integrated due to a shift in the retention times of about 0.6 minutes, which was outside of the retention time window of 0.5 minutes for that batch. This retention time window was not mentioned in a pre-established SOP since the analytical site did not have an SOP for chromatographic integration at the time of the study.
- The analytical site developed SOP (b) (4) for chromatographic integration (effective date (b) (4)), and the firm submitted the most current version of SOP (b) (4) (effective date (b) (4)) in response to this deficiency. Both versions of the SOP are effective after the time of the fasting BE study (July 17-28, 2008).
- Section 4.8 of the SOP states that “In some cases, the integration parameters required to accurately integrate high concentration samples may not provide accurate results for low concentration samples. The reverse may also be true. This situation may arise from a concentration dependent change in peak shape, closely eluting interfering peaks, slight interferences with low concentration samples or increased baseline noise due to lower signal to noise ratios. In these cases and others such as retention time shift (with out changing relative retention time), unintegrated peak or misidentified peak, manual integration of some peaks may be necessary.” The reviewer does not consider these reasons for performing manual integration to be objective criteria.
- The manual integration for the above-mentioned chromatograms are acceptable per the comparable integration of raloxifene and metabolite samples (since there is currently no SOP for chromatographic integration with objective integration criteria). The reviewer does not consider the manually integrated chromatograms to affect the study outcome since the shifts in retention times were minimal (i.e. 0.6 minutes). However, the firm will be requested to revise its SOP (b) (4) to include objective criteria for performing manual integration of chromatogram peaks. The firm will also be advised to implement *pre-established* SOPs for its analytical procedures in future studies.

DEFICIENCY #3:

Please explain why subject 11 had no measurable raloxifene concentrations at all time points after receiving the test product treatment in the fasting study no. BA0818122-01, considering that this subject had measurable concentrations for both glucuronide metabolites under the same treatment. This subject also had measurable concentrations of raloxifene and raloxifene glucuronide metabolites after receiving the reference product.

Firm's Response:

We acknowledge the comment and find the response received from the (b) (4) as follows:

“For subject 11, raloxifene concentration was between 36.217 pg/mL to 511.949 pg/mL for reference product. For test product, the concentration varied between 0.872 pg/mL to 12.369

pg/mL. However, all these concentrations are Below Limit of Quantitation (BLQ) and were reported as BLQs.

For subject 11, raloxifene-4'-glucuronide concentration was between 1.132 ng/mL to 139.737 ng/mL for reference product. For test product, the concentration varied between 1.080 ng/mL to 7.657 ng/mL. The ratio of C_{max} between reference and test product for raloxifene-4'-glucuronide is about 18.

For subject 11, raloxifene-6-glucuronide concentration was between 0.400 ng/mL to 44.199 ng/mL for reference product. For test product, the concentration varied between 0.416 ng/mL to 1.844 ng/mL. The ratio of C_{max} between reference and test product for raloxifene-4'-glucuronide is about 24.

The ratio of glucuronide metabolites in test to reference product is between $1/18^{th}$ to $1/24^{th}$. The C_{max} for raloxifene in the reference product is 511.949 pg/mL. Considering the ratio of glucuronide metabolites between test and reference products, the relative Raloxifene concentration should be between 21.331 pg/mL to 28.442 pg/mL, which is Below the Limit of Quantitation (BLQ) of Raloxifene (33.242 pg/mL). Hence, the analytical concentrations obtained for Raloxifene are in line with the glucuronide metabolites concentrations observed for this subject”.

In reference to the above,

- Please find the result table for Raloxifene, raloxifene-4'-glucuronide and raloxifene-6'-glucuronide subjects 11 & 12 section **M5.3.1.2 Comparative BA and Bioequivalence study reports (Attachment 3)**.

Reviewer's Note: the reviewer is only including the results for raloxifene:

	Sample Name	Sample ID	Sample Type	Acquisition Date	Vial Position	Plate Position	File Name	Analyte Peak Area (counts)	Analyte Concentration (pg/mL)	Area Ratio	IS Peak Area (counts)	Use Score	Calculated Concentration (pg/mL)	Accuracy (%)
1	REF LLOQ	SUB11&12_1	Unknown	7/19/2008 9:20:26 PM	1	7	001_003	4742	N/A	0.005	951913		37.230	N/A
2	REF LLOQ	SUB11&12_2	Unknown	7/19/2008 9:31:36 PM	1	7	001_003	5026	N/A	0.005	100393		37.443	N/A
3	STD A	SUB11&12_3	Unknown	7/19/2008 9:41:11 PM	5	7	001_003	3121	N/A	0.004	727573		31.392	N/A
4	STD H	SUB11&12_4	Unknown	7/19/2008 9:50:46 PM	13	7	001_003	585857	N/A	0.799	733395		6738.241	N/A
5	REF BLANK	SUB11&12_5	Unknown	7/19/2008 10:00:21 PM	2	7	001_003	0	N/A	0.000	1494		No Peak	N/A
6	BLANK	SUB11&12_6	Unknown	7/19/2008 10:09:54 PM	3	7	001_003	0	N/A	0.000	961		No Peak	N/A
7	BLANK IS	SUB11&12_7	Unknown	7/19/2008 10:19:29 PM	4	7	001_003	0	N/A	0.000	720201		No Peak	N/A
8	STD A	SUB11&12_8	Standard	7/19/2008 10:29:02 PM	5	7	001_003	3343	33.242	0.005	740774	☒	33.272	100
9	STD A'	SUB11&12_9	Unknown	7/19/2008 10:38:37 PM	6	7	001_003	3051	N/A	0.004	749729		29.527	N/A
10	STD B	SUB11&12_10	Standard	7/19/2008 10:48:09 PM	7	7	001_003	6343	66.484	0.009	730222	☒	68.502	103
11	STD C	SUB11&12_11	Standard	7/19/2008 10:57:42 PM	8	7	001_003	11310	132.968	0.015	737938	☒	124.556	94
12	STD D	SUB11&12_12	Standard	7/19/2008 11:07:20 PM	9	7	001_003	27809	332.420	0.039	712552	☒	324.611	98
13	STD E	SUB11&12_13	Standard	7/19/2008 11:16:52 PM	10	7	001_003	73378	831.050	0.103	710522	☒	866.933	104
14	STD F	SUB11&12_14	Standard	7/19/2008 11:26:25 PM	11	7	001_003	148822	1662.100	0.200	744255	☒	1683.084	101
15	STD G	SUB11&12_15	Standard	7/19/2008 11:36:01 PM	12	7	001_003	295473	3324.201	0.402	734453	☒	3391.093	102
16	STD H	SUB11&12_16	Standard	7/19/2008 11:45:33 PM	13	7	001_003	561305	6648.402	0.772	726993	☒	6512.536	98
17	STD H'	SUB11&12_17	Unknown	7/19/2008 11:55:09 PM	14	7	001_003	578337	N/A	0.808	715487		6818.281	N/A
18	S11P1 0.0 HR	SUB11&12_18	Unknown	7/20/2008 12:04:41 AM	15	7	001_003	0	N/A	0.000	719849		No Peak	N/A
19	S11P1 0.5 HR	SUB11&12_19	Unknown	7/20/2008 12:14:14 AM	16	7	001_003	7103	N/A	0.010	730852		77.219	N/A
20	S11P1 1.0 HR	SUB11&12_20	Unknown	7/20/2008 12:23:49 AM	17	7	001_003	12788	N/A	0.018	723581		144.338	N/A
21	S11P1 2.0 HR	SUB11&12_21	Unknown	7/20/2008 12:33:21 AM	18	7	001_003	13075	N/A	0.019	704499		151.839	N/A
22	S11P1 3.0 HR	SUB11&12_22	Unknown	7/20/2008 12:42:53 AM	19	7	001_003	12135	N/A	0.017	705750		140.324	N/A
23	S11P1 4.0 HR	SUB11&12_23	Unknown	7/20/2008 12:52:25 AM	20	7	001_003	20958	N/A	0.029	726391		238.722	N/A
24	S11P1 5.0 HR	SUB11&12_24	Unknown	7/20/2008 1:02:01 AM	21	7	001_003	27542	N/A	0.038	731104		313.171	N/A
25	HQC	SUB11&12_25	Quality C	7/20/2008 1:11:36 AM	22	7	001_003	454249	5318.721	0.615	738961	☒	5184.086	97
26	S11P1 6.0 HR	SUB11&12_26	Unknown	7/20/2008 1:21:11 AM	23	7	001_003	43812	N/A	0.061	723786		506.145	N/A
27	S11P1 7.0 HR	SUB11&12_27	Unknown	7/20/2008 1:30:46 AM	24	7	001_003	44594	N/A	0.061	733096		508.660	N/A
28	S11P1 8.0 HR	SUB11&12_28	Unknown	7/20/2008 1:40:18 AM	25	7	001_003	45039	N/A	0.061	735694		511.949	N/A

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	Sample Name	Sample ID	Sample Type	Acquisition Date	Vial Position	Plate Position	File Name	Analyte Peak Area (counts)	Analyte Concentration (pg/mL)	Area Ratio	IS Peak Area (counts)	Use Score	Calculated Concentration (pg/mL)	Accuracy (%)
9	S11P1 9.0 HR	SUB11&12_29	Unknown	7/20/2008 1:49:48 AM	26	7	001_003	41690	N/A	0.054	765435		454.939	N/A
0	S11P1 10.0 HR	SUB11&12_30	Unknown	7/20/2008 1:59:16 AM	27	7	001_003	38393	N/A	0.052	738391		434.085	N/A
1	S11P1 12.0 HR	SUB11&12_31	Unknown	7/20/2008 2:08:46 AM	28	7	001_003	34458	N/A	0.048	712726		403.287	N/A
2	S11P1 16.0 HR	SUB11&12_32	Unknown	7/20/2008 2:18:20 AM	29	7	001_003	19251	N/A	0.027	717470		221.669	N/A
3	MQC	SUB11&12_33	Quality C	7/20/2008 2:27:54 AM	30	7	001_003	229217	2659.361	0.319	719546	☒	2684.178	101
4	S11P1 20.0 HR	SUB11&12_34	Unknown	7/20/2008 2:37:28 AM	31	7	001_003	16859	N/A	0.022	750152		184.890	N/A
5	S11P1 24.0 HR	SUB11&12_35	Unknown	7/20/2008 2:47:01 AM	32	7	001_003	15156	N/A	0.021	720449		172.756	N/A
6	S11P1 48.0 HR	SUB11&12_36	Unknown	7/20/2008 2:56:36 AM	33	7	001_003	3430	N/A	0.005	705539		36.217	N/A
7	S11P1 72.0 HR	SUB11&12_37	Unknown	7/20/2008 3:06:06 AM	34	7	001_003	850	N/A	0.001	689401		5.586	N/A
8	S11P1 96.0 HR	SUB11&12_38	Unknown	7/20/2008 3:15:41 AM	35	7	001_003	338	N/A	0.001	651072		< 0	N/A
9	S11P1 120.0 HR	SUB11&12_39	Unknown	7/20/2008 3:25:14 AM	36	7	001_003	0	N/A	0.000	715857		No Peak	N/A
0	LQC	SUB11&12_40	Quality C	7/20/2008 3:34:47 AM	37	7	001_003	7986	95.737	0.011	740328	☒	86.231	90
1	S11P2 0.0 HR	SUB11&12_41	Unknown	7/20/2008 3:44:21 AM	38	7	001_003	0	N/A	0.000	717305		No Peak	N/A
2	S11P2 0.5 HR	SUB11&12_42	Unknown	7/20/2008 3:53:55 AM	39	7	001_003	0	N/A	0.000	735035		No Peak	N/A
3	S11P2 1.0 HR	SUB11&12_43	Unknown	7/20/2008 4:03:37 AM	40	7	001_003	484	N/A	0.001	717759		0.872	N/A
4	S11P2 2.0 HR	SUB11&12_44	Unknown	7/20/2008 4:13:21 AM	41	7	001_003	782	N/A	0.001	733784		4.175	N/A
5	S11P2 3.0 HR	SUB11&12_45	Unknown	7/20/2008 4:22:59 AM	42	7	001_003	1186	N/A	0.002	718356		9.120	N/A
6	S11P2 4.0 HR	SUB11&12_46	Unknown	7/20/2008 4:32:35 AM	43	7	001_003	905	N/A	0.001	721823		5.765	N/A
7	S11P2 5.0 HR	SUB11&12_47	Unknown	7/20/2008 4:42:09 AM	44	7	001_003	1284	N/A	0.002	729952		10.024	N/A
8	HQC	SUB11&12_48	Quality C	7/20/2008 4:51:46 AM	45	7	001_003	456874	5318.721	0.624	732524	☒	5259.925	99
9	S11P2 6.0 HR	SUB11&12_49	Unknown	7/20/2008 5:01:22 AM	46	7	001_003	1619	N/A	0.002	739400		13.660	N/A
0	S11P2 7.0 HR	SUB11&12_50	Unknown	7/20/2008 5:10:58 AM	47	7	001_003	1239	N/A	0.002	728388		9.540	N/A
1	S11P2 8.0 HR	SUB11&12_51	Unknown	7/20/2008 5:20:32 AM	48	7	001_003	1369	N/A	0.002	696325		11.776	N/A
2	S11P2 9.0 HR	SUB11&12_52	Unknown	7/20/2008 5:30:09 AM	49	7	001_003	1513	N/A	0.002	751762		12.165	N/A
3	S11P2 10.0 HR	SUB11&12_53	Unknown	7/20/2008 5:39:45 AM	50	7	001_003	1467	N/A	0.002	720360		12.369	N/A
4	S11P2 12.0 HR	SUB11&12_54	Unknown	7/20/2008 5:49:20 AM	51	7	001_003	1152	N/A	0.002	749146		8.160	N/A
5	S11P2 16.0 HR	SUB11&12_55	Unknown	7/20/2008 5:58:57 AM	52	7	001_003	917	N/A	0.001	700538		6.230	N/A
6	MQC	SUB11&12_56	Quality C	7/20/2008 6:08:36 AM	53	7	001_003	217052	2659.361	0.299	725260	☒	2521.418	95

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	Sample Name	Sample ID	Sample Type	Acquisition Date	Vial Position	Plate Position	File Name	Analyte Peak Area (counts)	Analyte Concentration (pg/mL)	Area Ratio	IS Peak Area (counts)	Usecor	Calculated Concentration (pg/mL)	Accuracy (%)
i7	S11P2 20.0 HR	SUB11&12_57	Unknown	7/20/2008 6:18:11 AM	54	7	001_003	887	N/A	0.001	721613	☐	5.559	N/A
i8	S11P2 24.0 HR	SUB11&12_58	Unknown	7/20/2008 6:27:27 AM	1	8	001_003	854	N/A	0.001	683673	☐	5.727	N/A
i9	S11P2 48.0 HR	SUB11&12_59	Unknown	7/20/2008 6:38:24 AM	2	8	001_003	208	N/A	0.000	707430	☐	< 0	N/A
i0	S11P2 72.0 HR	SUB11&12_60	Unknown	7/20/2008 6:47:55 AM	3	8	001_003	0	N/A	0.000	725820	☐	No Peak	N/A
i1	S11P2 96.0 HR	SUB11&12_61	Unknown	7/20/2008 6:57:29 AM	4	8	001_003	0	N/A	0.000	708918	☐	No Peak	N/A
i2	S11P2 120.0 HR	SUB11&12_62	Unknown	7/20/2008 7:07:06 AM	5	8	001_003	0	N/A	0.000	695370	☐	No Peak	N/A
i3	LQC	SUB11&12_63	Quality C	7/20/2008 7:16:40 AM	6	8	001_003	8507	95.737	0.012	731202	☒	93.384	98
i4	S12P1 0.0 HR	SUB11&12_64	Unknown	7/20/2008 7:26:12 AM	7	8	001_003	0	N/A	0.000	711775	☐	No Peak	N/A
i5	S12P1 0.5 HR	SUB11&12_65	Unknown	7/20/2008 7:35:47 AM	8	8	001_003	8046	N/A	0.012	696911	☐	92.634	N/A
i6	S12P1 1.0 HR	SUB11&12_66	Unknown	7/20/2008 7:45:18 AM	9	8	001_003	6443	N/A	0.009	716686	☐	71.068	N/A
i7	S12P1 2.0 HR	SUB11&12_67	Unknown	7/20/2008 7:54:50 AM	10	8	001_003	7755	N/A	0.011	710885	☐	87.261	N/A
i8	S12P1 3.0 HR	SUB11&12_68	Unknown	7/20/2008 8:04:22 AM	11	8	001_003	7679	N/A	0.011	716311	☐	85.677	N/A
i9	S12P1 4.0 HR	SUB11&12_69	Unknown	7/20/2008 8:13:58 AM	12	8	001_003	6795	N/A	0.010	704515	☐	76.593	N/A
i0	S12P1 5.0 HR	SUB11&12_70	Unknown	7/20/2008 8:23:31 AM	13	8	001_003	7254	N/A	0.010	698749	☐	82.814	N/A
i1	HQC	SUB11&12_71	Quality C	7/20/2008 8:33:02 AM	14	8	001_003	439319	5318.721	0.614	715808	☒	5175.858	97
i2	S12P1 6.0 HR	SUB11&12_72	Unknown	7/20/2008 8:42:33 AM	15	8	001_003	8151	N/A	0.012	694620	☐	94.236	N/A
i3	S12P1 7.0 HR	SUB11&12_73	Unknown	7/20/2008 8:52:08 AM	16	8	001_003	8970	N/A	0.013	697393	☐	103.757	N/A
i4	S12P1 8.0 HR	SUB11&12_74	Unknown	7/20/2008 9:01:41 AM	17	8	001_003	11481	N/A	0.016	702128	☐	133.205	N/A
i5	S12P1 9.0 HR	SUB11&12_75	Unknown	7/20/2008 9:11:16 AM	18	8	001_003	13586	N/A	0.019	700161	☐	158.979	N/A
i6	S12P1 10.0 HR	SUB11&12_76	Unknown	7/20/2008 9:20:47 AM	19	8	001_003	10842	N/A	0.015	718101	☐	122.622	N/A
i7	S12P1 12.0 HR	SUB11&12_77	Unknown	7/20/2008 9:30:19 AM	20	8	001_003	12277	N/A	0.017	717140	☐	139.692	N/A
i8	S12P1 16.0 HR	SUB11&12_78	Unknown	7/20/2008 9:39:54 AM	21	8	001_003	11798	N/A	0.017	708962	☐	135.650	N/A
i9	MQC	SUB11&12_79	Quality C	7/20/2008 9:49:28 AM	22	8	001_003	211994	2659.361	0.302	702664	☒	2541.887	96
i0	S12P1 20.0 HR	SUB11&12_80	Unknown	7/20/2008 9:59:03 AM	23	8	001_003	14082	N/A	0.020	714912	☐	161.454	N/A
i1	S12P1 24.0 HR	SUB11&12_81	Unknown	7/20/2008 10:08:37 AM	24	8	001_003	12328	N/A	0.017	731710	☐	137.397	N/A
i2	S12P1 48.0 HR	SUB11&12_82	Unknown	7/20/2008 10:18:12 AM	25	8	001_003	3797	N/A	0.006	679380	☐	42.360	N/A
i3	S12P1 72.0 HR	SUB11&12_83	Unknown	7/20/2008 10:27:43 AM	26	8	001_003	712	N/A	0.001	677865	☐	4.046	N/A
i4	S12P1 96.0 HR	SUB11&12_84	Unknown	7/20/2008 10:37:18 AM	27	8	001_003	350	N/A	0.001	670900	☐	< 0	N/A

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	Sample Name	Sample ID	Sample Type	Acquisition Date	Vial Position	Plate Position	File Name	Analyte Peak Area (counts)	Analyte Concentration (pg/mL)	Area Ratio	IS Peak Area (counts)	Usecor	Calculated Concentration (pg/mL)	Accuracy (%)
35	S12P1 120.0 HR	SUB11&12_85	Unknown	7/20/2008 10:46:52 AM	28	8	001_003	0	N/A	0.000	705286	☐	No Peak	N/A
36	LQC	SUB11&12_86	Quality C	7/20/2008 10:56:27 AM	29	8	001_003	8273	95.737	0.012	705299	☒	94.050	98
37	S12P2 0.0 HR	SUB11&12_87	Unknown	7/20/2008 11:05:59 AM	30	8	001_003	0	N/A	0.000	704210	☐	No Peak	N/A
38	S12P2 0.5 HR	SUB11&12_88	Unknown	7/20/2008 11:15:34 AM	31	8	001_003	598	N/A	0.001	673460	☐	2.671	N/A
39	S12P2 1.0 HR	SUB11&12_89	Unknown	7/20/2008 11:25:09 AM	32	8	001_003	2559	N/A	0.004	699665	☐	26.052	N/A
40	S12P2 2.0 HR	SUB11&12_90	Unknown	7/20/2008 11:34:41 AM	33	8	001_003	3242	N/A	0.005	690390	☐	34.823	N/A
41	S12P2 3.0 HR	SUB11&12_91	Unknown	7/20/2008 11:44:14 AM	34	8	001_003	5222	N/A	0.008	674474	☐	60.538	N/A
42	S12P2 4.0 HR	SUB11&12_92	Unknown	7/20/2008 11:53:49 AM	35	8	001_003	5834	N/A	0.008	703909	☐	65.146	N/A
43	S12P2 5.0 HR	SUB11&12_93	Unknown	7/20/2008 12:03:21 PM	36	8	001_003	7891	N/A	0.011	693789	☐	91.190	N/A
44	HQC	SUB11&12_94	Quality C	7/20/2008 12:12:53 PM	37	8	001_003	433967	5318.721	0.615	705679	☒	5186.199	98
45	S12P2 6.0 HR	SUB11&12_95	Unknown	7/20/2008 12:22:26 PM	38	8	001_003	11147	N/A	0.016	684865	☐	132.570	N/A
46	S12P2 7.0 HR	SUB11&12_96	Unknown	7/20/2008 12:31:59 PM	39	8	001_003	9071	N/A	0.014	649073	☐	113.153	N/A
47	S12P2 8.0 HR	SUB11&12_97	Unknown	7/20/2008 12:41:34 PM	40	8	001_003	13693	N/A	0.019	709286	☐	158.144	N/A
48	S12P2 9.0 HR	SUB11&12_98	Unknown	7/20/2008 12:51:09 PM	41	8	001_003	21755	N/A	0.031	711108	☐	253.424	N/A
49	S12P2 10.0 HR	SUB11&12_99	Unknown	7/20/2008 1:00:42 PM	42	8	001_003	20029	N/A	0.029	697847	☐	237.452	N/A
100	S12P2 12.0 HR	SUB11&12_100	Unknown	7/20/2008 1:10:17 PM	43	8	001_003	15933	N/A	0.023	695658	☐	188.516	N/A
101	S12P2 16.0 HR	SUB11&12_101	Unknown	7/20/2008 1:19:51 PM	44	8	001_003	9927	N/A	0.014	688445	☐	116.900	N/A
102	MQC	SUB11&12_102	Quality C	7/20/2008 1:29:22 PM	45	8	001_003	217035	2659.361	0.311	697133	☒	2623.124	99
103	S12P2 20.0 HR	SUB11&12_103	Unknown	7/20/2008 1:38:55 PM	46	8	001_003	9211	N/A	0.013	711280	☐	104.491	N/A
104	S12P2 24.0 HR	SUB11&12_104	Unknown	7/20/2008 1:48:33 PM	47	8	001_003	8309	N/A	0.012	670535	☐	99.786	N/A
105	S12P2 48.0 HR	SUB11&12_105	Unknown	7/20/2008 1:58:08 PM	48	8	001_003	2068	N/A	0.003	691966	☐	20.402	N/A
106	S12P2 72.0 HR	SUB11&12_106	Unknown	7/20/2008 2:07:40 PM	49	8	001_003	671	N/A	0.001	675644	☐	3.570	N/A
107	S12P2 96.0 HR	SUB11&12_107	Unknown	7/20/2008 2:17:13 PM	50	8	001_003	0	N/A	0.000	684037	☐	No Peak	N/A
108	S12P2 120.0 HR	SUB11&12_108	Unknown	7/20/2008 2:26:49 PM	51	8	001_003	0	N/A	0.000	648095	☐	No Peak	N/A
109	LQC	SUB11&12_109	Quality C	7/20/2008 2:36:27 PM	52	8	001_003	7992	95.737	0.011	713822	☒	89.690	94

CHROMATOGRAMS REVIEW
BATCH ACCEPTED

(b) (4)

Data Reviewed.

(b) (4)

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Reviewer's Comments:

- The firm reported the range of raloxifene test product concentrations from subject 11, which were BLQ of 33.242 pg/mL. The firm did not have reanalysis procedures for samples that were BLQ in its SOP for sample reanalysis. Therefore, the firm reported the raloxifene sample concentrations as BLQ. This does not necessarily explain *why* subject 11 had no measurable raloxifene concentrations after receiving the test product treatment in the fasting bioequivalence (BE) study.
- The 90% C.I. values for the least squares geometric means of raloxifene AUC_{0-t}, AUC_∞ and C_{max} in the fasting BE study were calculated using the data from subject 11, and the data from subject 11 did not affect the study outcome using either analytically valid assay results or re-calculated assay results (see Deficiency #4), despite the BLQ raloxifene concentrations for subject 11 [see DARRTS: ANDA 090842, KITCHENS, KELLY, M, Submit/Final Date 01/28/2011, REV-BIOEQ-01(General Review)].

DEFICIENCY #4:

You repeated the sample S27P1 9.0 Hour in your fasting study using the following reason: "S27P1 9.0 Hour had a concentration of 7218.021pg/mL and the analyte peak area also was very high (~100 times) when compared to the preceding and succeeding time points. No such abnormality was found in RA4G and RA6G for this particular time point. Hence S27P1 9.0 Hour was repeated under AI, suspected analytical interference from the analyst during processing." However, per your SOP No. (b) (4) "Analytical Interference (AI)" is defined as "Predose sample having interference more than LOQ standard (Std A)." Therefore, your repeat of the above-mentioned was a violation of your SOP, and is not valid. Rather, the DBE considers such repeat as "PK repeat" and biased. In such case, only the original value for this sample (S27P1 9.0 Hour) of your fasting study should be used in the data analysis of the study. The DBE reanalyzed the data using the original value of the above sample and the 90% C.I. for lnC_{max} of raloxifene, [65.27;101.56], failed to meet the acceptable bioequivalence limits of [80.00;125.00]. In addition, the point estimate for lnC_{max} of raloxifene-4'-glucuronide was outside the limits of [80.00;125.00] and did not support the bioequivalence of test product. Therefore, your fasting bioequivalence study no. BA0818122-01 is unacceptable.

Firm's Response:

We acknowledge the comment and find the response received from the (b) (4) (b) (4) as follows:

"(b) (4) agrees with the agency that as per SOP (b) (4), "Analytical Interference" is defined as interference from the predose samples. However, in the same SOP section 4.5, also defines "In situations where none of the above criteria or codes may apply. In such special cases, different criteria for repeats and reports may be used, which will be decided by the Director of (b) (4) or designee. A written authorization or approval from the Director of (b) (4) is required which must remain as a part of raw data for the particular study."

Measurable analyte concentrations are not expected in predose samples and when measurable concentrations are seen in these samples they might be due to analytical interference (AI). In the current sample (S27P1 9.0 Hour) the Raloxifene concentration was found to be ~100 times higher than the preceding (71.441 pg/mL) and succeeding (68.975 pg/mL) time points with no observed unusual concentrations for either metabolite. Moreover, in the entire study, maximum peak plasma concentration observed for Raloxifene was 893.694 pg/mL (except for the original concentration value observed in the above sample). Therefore, S27P1 9.0 Hour original concentration value (7218.021 pg/mL) was about eight times higher than the highest C_{max} observed during the entire study and about 60 times higher than the highest sample concentration (115.623 pg/mL) for this subject. Hence, as per SOP (b) (4) section 4.5, this sample was identified as AI due to suspected analytical interference from the analyst during the processing. Hence, the sample was repeated and the repeat value (64.831pg/mL) confirmed that the original value was due to analytical interference.

InvaGen requested (b) (4) on (b) (4), to re-analyse the plasma sample S27P1 at 9.0 hours to re-confirm that the data generated from the original repeat analysis.

It is observed that repeat analysis data done on 02 May 2011 is replicates exhibited concentrations of 73.489 pg/mL and 74.646 pg/mL is comparable to the original repeat analysis data presented in original ANDA. This further confirms that original data is through the contamination during the processing”.

In reference to the above,

- Please find the Analytical report “the determination of Raloxifene in human plasma in subject 27, period 1, 9.0 hour sample using a liquid chromatographic method with MS/MS detection in section **M5.3.1.2 Comparative BA and Bioequivalence study reports (Attachment 4)**.

Reviewer’s Comments:

- The firm’s SOP section 4.3 describes the category of Sample Anomalies, where “Individual samples with questionable concentrations such as mix up of individual samples or samples whose concentrations are not consistent with PK data or any other reason making the sample concentration a suspect will be coded as Pharmacokinetic (PK) repeats.” and section 4.3.1 states “These samples will be repeated in duplicate if sample volume allows.” The firm treated sample S27P1 9.0 Hour as an analytical repeat (analytical interference) and only repeated sample analysis once. Yet the sample should have been treated as a PK repeat and reanalyzed in duplicate per the firm’s SOP.
- The SOP does not include objective criteria for repeating sample S27P1 9.0 Hour in either section 4.3 or section 4.5. Per the firm’s SOP, the original value for sample S27P1 9.0 Hour is analytically valid, and therefore the original value (7218.021 pg/mL) is the reportable value. The lack of objective criteria for PK repeats make the original value the only acceptable value for inclusion in PK analysis, and the 90% C.I. for $\ln C_{max}$ of raloxifene does not meet bioequivalence acceptance criteria when using the original value for the sample in question.
- The firm will be advised to revise its SOP (b) (4) to include objective criteria for reanalysis of sample anomalies, otherwise known as PK repeats.

- The firm's response is **incomplete**. Fasting study no. BA0818122-01 remains unacceptable.

DEFICIENCY #5:

Please indicate what medical interventions were used to resolve the adverse events experienced by subject 13 (headache) and subject 26 (fever) in the fed study no. BA0818123-01.

Firm's Response:

We acknowledge the comment and find the response received from the **BA Research India Limited Analytical** (Clinical study site) as follows:

“As per raw data, **Subject# 13** had adverse event - **Fever** and **Subject# 26** had adverse event- **Headache** in project# BA0818123-01 provided in original ANDA.

Subject no. 13 had complaint of Fever on 22 Aug 08 at approximately 1700 hours (After dosing of period II) which he reported at 1720 hours. Subject was prescribed **Metacin tablets (Paracetamol IP 0.5 gm)** for resolution of event. The subject got completely resolved on 23 Aug 08 at 0710 hours. The relationship of adverse event with Investigational product was declared as ‘Possible’ by the Co-investigator and the severity of the event was declared as ‘Mild’ by the duty physician.

Subject no. 26 had complaint of Headache on 22 Aug 08 at approximately 1700 hours (After dosing of period II) which reported at 1718 hours. Subject was prescribed **Vicks VapoRub (Decongestant ointment)** for resolution of event. The subject got completely resolved on 22 Aug 08 at 2140 hours. The relationship of adverse event with Investigational product was declared as ‘Possible’ by the Co-investigator and the severity of the event was declared as ‘Mild’ by the duty physician”.

Reviewer's Comments:

- Raloxifene is not reported to have drug interactions with Paracetamol (acetaminophen) or Vicks VapoRub.
- The firm's response is **acceptable**.

DEFICIENCY #6:

Please submit chromatograms from at least 20% of the total number of subjects that completed fed study no. BA0818123-01 (i.e. 20% of 41 subjects, or at least 8 subjects).

Firm's Response:

We acknowledge the comment and find the response received from the (b) (4) as follows:

“Chromatograms for 20% of the total number of subjects (subjects 1 through 8) for Fed

study no. BA0818123-01 in section **M5.3.1.2 Comparative BA and Bioequivalence study Reports (Attachment 5)**".

Reviewer's Comments:

- The firm submitted chromatograms from subjects 1-8. There were no interfering peaks in the chromatograms.
- The firm's response is **acceptable**.

DEFICIENCY #7:

In 2009, following the inspection by the FDA Division of Scientific Investigations (DSI) of the analytical site (b) (4) Form FDA-483 was issued. One of the DSI's objectable findings was (b) (4) The analytical site's response to this DSI Finding was that the SOP was revised to require (b) (4) for preparation of calibrators and QCs.

The sample analysis of the bioequivalence studies of your current application was conducted at (b) (4) prior to the above DSI inspection and (b) (4) response stating its commitment to revise the SOP for the preparation of calibration curve standards and quality control samples. Please indicate if (b) (4) in the current ANDA. Also, please submit (u) (4) revised and current SOP for the preparation of calibration curve standards and quality control samples.

Firm's Response:

We acknowledge the comment and find the response received from the (b) (4) as follows:

(b) (4)

In reference to the above,
Please find the revised current SOP for the preparation of calibration curve standards and quality control samples (SOP, (b) (4)) in section **M5.3.1.2 Comparative BA and Bioequivalence study reports (Attachment 6)**.

Reviewer's Comments:

- The analytical site revised its SOP (b) (4) Preparation and Acceptance Criteria for Calibration Curve Standards and Quality Control Samples (effective date (b) (4)), which was after the dates of analysis for the fasting and fed BE studies (July 17-28, 2008,

and September 2-15, 2008, respectively). In the revised SOP, section 4.1 states (b) (4) to prepare calibration standards and quality control samples.” The SOP that was effective at the time of the BE studies (b) (4) (effective date (b) (4)).

- Per the firm’s Bioanalytical Method and the response to deficiency #7, the firm (b) (4) (b) (4) in the current ANDA. (b) (4) do not affect the acceptability of the analytical results.
- The firm’s response is **satisfactory**.

3.5 Deficiency Comments

1. SOP (b) (4) (Criteria for sample reanalysis and reporting) does not include objective criteria that justify the repeat of sample S27P1 9.0 Hour. Therefore, the original value (7218.021 pg/mL) for this sample is the only acceptable result for use in the statistical analysis. When using the original result, the 90% C.I. for lnCmax of raloxifene does not meet bioequivalence acceptance criteria. As a result, fasting study no. BA0818122-01 remains unacceptable. The firm will be advised to revise its SOP (b) (4) for future studies to include objective criteria for reanalysis of sample anomalies, otherwise known as pharmacokinetic (PK) repeats.
2. The firm will be requested to revise its SOP (b) (4) (Chromatographic integration) to include objective criteria for performing manual integration of chromatogram peaks. The firm will also be advised to implement *pre-established* SOPs for its analytical procedures in future studies.

3.6 Recommendations

1. The Division of Bioequivalence (DBE) finds the fasting study no. BA0818122-01 conducted by InvaGen Pharmaceuticals, Inc. on its Raloxifene Hydrochloride Tablets, 60 mg (lot #ID080510), comparing it to Eli Lilly's EVISTA® (Raloxifene Hydrochloride) Tablets, 60 mg (lot # A489455) **unacceptable**.
2. The DBE **accepts** the fed study no. BA0818123-01 conducted by InvaGen Pharmaceuticals, Inc. on its Raloxifene Hydrochloride Tablets, 60 mg (lot #ID080510), comparing it to Eli Lilly's EVISTA® (Raloxifene Hydrochloride) Tablets, 60 mg (lot # A489455).
3. The firm's in vitro dissolution testing is **acceptable**. The dissolution testing should be conducted in 1000 mL of 0.1% Polysorbate 80 in water at 37°C ± 0.5°C using USP apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

NLT 80% (Q) in 30 minutes

3.7 Comments for Other OGD Disciplines

Discipline	Comment
None	None

BIOEQUIVALENCE DEFICIENCIES

ANDA: 090842
APPLICANT: InvaGen Pharmaceuticals, Inc.
DRUG PRODUCT: Raloxifene Hydrochloride Tablets USP, 60 mg

The Division of Bioequivalence (DBE) has completed its review of the submission acknowledged on the cover page and has identified the following deficiencies:

1. SOP (b) (4) (Criteria for sample reanalysis and reporting) does not include objective criteria for repeating the analysis of sample S27P1 9.0 Hour, of which the original analysis was found to be analytically valid. Therefore, the original value (7218.021 pg/mL) should be used in the statistical analysis. When using the original assay value for said sample, the 90% confidence interval (C.I.) for lnCmax of raloxifene was [65.27;101.56] and did not meet bioequivalence acceptance criteria. As a result, fasting study no. BA0818122-01 is **unacceptable**.
2. Please revise your SOP (b) (4) for future studies to include objective criteria for reanalysis of samples with anomalous values, otherwise known as pharmacokinetic (PK) repeats.
3. Please revise your SOP (b) (4) (Chromatographic integration) to include objective criteria for performing manual integration of chromatogram peaks. Please be advised to implement **pre-established** SOPs for your analytical procedures in future studies.

Sincerely yours,

{See appended electronic signature page}

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

3.8 Outcome Page

COMPLETED ASSIGNMENT FOR 90842 ID: 14299

Reviewer: Kitchens, Kelly

Date Completed:

Verifier:

Date Verified:

Division: Division of Bioequivalence

Description: Raloxifene Hydrochloride Tablets, 60 mg

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
14299	5/16/2011	Other	Study Amendment	1	1
				Bean Total:	1

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

/s/

KELLY M KITCHENS

06/28/2011

YIH CHAIN HUANG

06/28/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER

06/28/2011

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	090842		
Drug Product Name	Raloxifene Hydrochloride Tablets, USP		
Strength(s)	60 mg		
Applicant Name	InvaGen Pharmaceuticals, Inc.		
Address	7 Oser Avenue, Hauppauge, New York 11788		
Applicant's Point of Contact	Dr.Sudhakar Rao Vidiyala, President		
Contact's Telephone Number	631-231-3233		
Contact's Fax Number	631-231-4248		
Original Submission Date(s)	October 2, 2008		
Submission Date(s) of Amendment(s) Under Review	December 6, 2010 (telephone amendment in response to request for bioequivalence information)		
Reviewer	Kelly M. Kitchens, Ph.D.		
Study Number (s)	BA0818122-01	BA0818123-01	
Study Type (s)	Fasting	Fed	
Strength (s)	60 mg	60 mg	
Clinical Site	BA Research India Limited,		
Clinical Site Address	1 st Floor, Silver Arcade, Near Ashwamegh III, Samrajya, Mujmahuda Road, Akota, Vadodara -390 020, Gujarat, India		
DSI Inspection Status	A routine inspection was requested for ANDA 090175 on 6/30/2008. The inspection was completed on 8/6/2009 and the outcome was VAI. The DSI findings were specific to ANDA 090175 and should not impact the study outcome in the current ANDA.		
Analytical Site	(b) (4)		
Analytical Site Address	(b) (4)		
DSI Inspection Status	A routine inspection was requested for ANDA 090228 on (b) (4). The inspection was completed on (b) (4) and the outcome was (b) (4). The DSI findings were specific to ANDA 090228 and do not impact the validity of the analytical results in the current ANDA.		
OVERALL REVIEW RESULT	INADEQUATE		
WAIVER REQUEST RESULT	Not applicable		
DSI REPORT RESULT	ADEQUATE		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1	FASTING STUDY	60 mg	INADEQUATE

1	FED STUDY	60 mg	INADEQUATE
1	DISSOLUTION	60 mg	ADEQUATE
N/A	DSI REPORT	60 mg	ADEQUATE
N/A	DSI REPORT	60 mg	ADEQUATE

1 EXECUTIVE SUMMARY

InvaGen Pharmaceuticals, Inc. submitted an abbreviated new drug application (ANDA) with the results of fasting and fed bioequivalence (BE) studies comparing the test product Raloxifene Hydrochloride Tablets (60 mg) to the reference listed drug (RLD) EVISTA® (Raloxifene Hydrochloride) Tablets (60 mg) manufactured by Eli Lilly. The fasting and fed BE studies were designed as single-dose, two-way crossover BE studies in healthy male subjects. The fasting study is incomplete due to bioanalytical and pharmacokinetic/statistical deficiencies, and the fed study is incomplete due to clinical and bioanalytical deficiencies. The results of the fasting and fed BE studies are summarized in the following tables:

Raloxifene Hydrochloride Tablets Dose (1 x 60 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Study No. BA0818122-01 Raloxifene (N=32)					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (pg *hr/mL)	11416.02	11289.49	1.01	91.90	111.26
AUC _∞ (pg *hr/mL)	13490.21	13911.86	0.97	89.60	104.95
C _{max} (pg/mL)	366.78	392.51	0.93	84.56	103.27

The reviewer recalculated the PK parameters for Raloxifene using the original value for sample S27P1 9.0 Hour, since the original value was analytically valid, and the firm reanalyzed this sample for a non-objective reason. The 90% C.I. for lnC_{max} do not meet acceptable bioequivalence criteria using the original value for this sample:

LSMEANS AND 90% CONFIDENCE INTERVALS

Parameter	Least Squares Geometric Mean		Ratio (T/R)	90% Confidence Intervals	
	Test	Reference		Lower	Upper
LAUCT	11389.92	11683.87	0.97	87.99	108.00
LAUCI	13490.21	13911.86	0.97	89.60	104.95
LCMAX	363.64	446.63	0.81	65.27	101.56

Fasting Study No. BA0818122-01 Raloxifene-4'-Glucuronide (N=27 for Test, N=26 for Reference)					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (ng *hr/mL)	2228.01	2552.54	0.87	67.05	113.63
AUC _∞ (ng *hr/mL)	2754.41	2688.58	1.02	91.33	114.92
C _{max} (ng/mL)	148.12	188.71	0.78	62.81	98.09
Fasting Study No. BA0818122-01 Raloxifene-6-Glucuronide (N=32)					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (ng *hr/mL)	612.21	664.82	0.92	76.33	111.10
AUC _∞ (ng *hr/mL)	700.06	686.19	1.02	94.11	110.60
C _{max} (ng/mL)	30.98	37.33	0.83	69.09	99.68

Raloxifene Hydrochloride Tablets Dose (1 x 60 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Study No. BA0818123-01 Raloxifene (N=41)					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (pg *hr/mL)	14505.38	15007.53	0.97	85.53	109.23
AUC _∞ (pg *hr/mL)	17152.70	18229.64	0.94	83.46	106.08
C _{max} (pg/mL)	491.74	493.52	1.00	91.02	109.08
Fed Study No. BA0818123-01 Raloxifene-4'-Glucuronide (N=41)					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (ng *hr/mL)	3044.00	3035.41	1.00	90.91	110.62
AUC _∞ (ng *hr/mL)	3092.31	3077.77	1.00	91.22	110.67
C _{max} (ng/mL)	298.58	291.42	1.02	94.46	111.14
Fed Study No. BA0818123-01 Raloxifene-6-Glucuronide (N=41)					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (ng *hr/mL)	534.88	540.97	0.99	88.68	110.24
AUC _∞ (ng *hr/mL)	558.87	560.85	1.00	89.46	110.99
C _{max} (ng/mL)	38.09	37.23	1.02	95.27	109.86

The dissolution testing was previously reviewed for the 60 mg strength [see DARRTS: ANDA 090842, LEE, CHRISTINA H, Submit/Final Date: 01/09/2009, REV-BIOEQ-02 (Dissolution Review)]. The test product met the USP specification of NLT 80% (Q) in 30 minutes at the S1 level.

The firm used BA Research India Limited and (b) (4) for the clinical site and analytical sites, respectively. A routine inspection was requested for the clinical site on 6/30/2008 for ANDA 090175. The inspection was completed on 8/6/2009 and the outcome was VAI. The DSI findings were determined by the reviewer to be specific to ANDA 090175 and should not impact the study outcome in the current ANDA (see Section 3.10 Review of DSI Report for Clinical Site and Firm's Response to the Form-483 Observations). A routine inspection was requested for the analytical site on (b) (4) for ANDA 090228. The inspection was completed on (b) (4) and the outcome was (b) (4). The DSI findings were also determined by the reviewer to be specific to ANDA 090228 and do not impact the validity of the analytical results in the current ANDA (see Section 3.11 Review of DSI Report for Analytical Site and Firm's Response to the Form-483 Observations).

ANDA 090842 is INADEQUATE.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information¹

Test Product	Raloxifene Hydrochloride Tablets, 60 mg
Reference Product	EVISTA® (Raloxifene Hydrochloride) Tablets, 60 mg
RLD Manufacturer	Eli Lilly
NDA No.*	020815
RLD Approval Date	December 9, 1997
Indication^{2,3}	• Treatment and prevention of osteoporosis in postmenopausal women. • Reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis.[†] • Reduction in risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer.[†] Important Limitations: [†] EVISTA is not indicated for the treatment of invasive breast cancer, reduction of the risk of recurrence of breast cancer, or reduction risk of noninvasive breast cancer.

*Drugs@FDA and DARRTS also lists NDA 022042 for EVISTA®, approved September 13, 2007, manufactured by Eli Lilly. Indications[†] were added to the label for NDA 022042 in September 2007, along with a box warning (see the Drug Specific Issues in the following table).

3.2 PK/PD Information^{4,5}

Bioavailability	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%.
Food Effect	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. EVISTA can be administered without regard to meals.
T_{max}	The time to reach average maximum plasma concentration and bioavailability are functions of systemic interconversion and enterohepatic cycling of raloxifene and its glucuronide metabolites.
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

¹ Online-Orange Book, keyword search by active ingredient: raloxifene, accessed December 2, 2010.

² RLD label for NDA 020815 according to Drugs@FDA, approved July 17, 2007

³ RLD label for NDA 022042 according to Drugs@FDA, approved September 13, 2007

⁴ RLD label for NDA 020815 according to Drugs@FDA, approved July 17, 2007

⁵ RLD label for NDA 022042 according to Drugs@FDA, approved September 13, 2007

	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.
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.
Half-life	27.7 hours
Drug Specific Issues (if any)	BOXED WARNING: INCREASED RISK OF VENOUS THROMBOEMBOLISM AND DEATH FROM STROKE - Increased risk of deep vein thrombosis and pulmonary embolism have been reported with EVISTA. Women with active or past history of venous thromboembolism should not take EVISTA. - 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.

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2, fasting and fed
---------------------------------------	--------------------

1.	Type of study:	Fasting
	Design:	Single-dose, two way crossover in vivo
	Strength:	60 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	

2.	Type of study:	Fed
	Design:	Single-dose, two way crossover in vivo
	Strength:	60 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	

Analytes to measure (in plasma/serum/blood):	Raloxifene and the metabolites, raloxifene-4'-glucuronide and raloxifene-6'-glucuronide in plasma.
Bioequivalence based on:	(90% CI) Raloxifene
Waiver request of in-vivo testing:	Not applicable

Source of most recent recommendations:	Guidance for Industry: Individual Product Bioequivalence Recommendations, Guidance on Raloxifene Hydrochloride (finalized May 2008). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm089554.pdf
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Summary of OGD or DBE History	At the time of this review, the Orange Book does not list any approved ANDAs for Raloxifene Hydrochloride Tablets. The following Raloxifene applications are under review by the OGD (at the time of this review, only ANDA 078193 has been reviewed by the DBE): • [REDACTED] (b) (4) • ANDA 078193 (Teva Pharmaceuticals USA) – pending as of 10/24/2008 • ANDA 200825 (Watson Laboratories) – pending as of 12/23/2009 List of Controls: • 01-318 [REDACTED] (b) (4) • 01-546 [REDACTED] • 02-015 [REDACTED] • 02-110 [REDACTED] • 03-155 [REDACTED] • 03-757 [REDACTED] • 03-936 [REDACTED] • 04-1177 [REDACTED] (b) (4) • 04-504 (Teva) • 05-0993 [REDACTED] (b) (4) • 05-1263 [REDACTED] (b) (4) • 06-0639 [REDACTED] • 06-0986 [REDACTED] • 06-1396 [REDACTED] • 06-1613 [REDACTED] • 07-0165 [REDACTED] • 07-0288 (InvaGen) • 07-0446 [REDACTED] (b) (4) • 07-0685 [REDACTED] • 07-0732 [REDACTED]
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3.4 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	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	Yes	1

3.5 Pre-Study Bioanalytical Method Validation

Raloxifene
BA0818122-01 and BA0818123-01

Information Requested	Data
Bioanalytical method validation report location	Raloxifene Validation Report No: (b) (4) (b) (4)
Analyte	Raloxifene
Internal standard (IS)	(b) (4)
Method description	Type of Extraction: Precipitation Analytical Method: LC/MS/MS
Limit of quantitation	31.820 pg/mL for Raloxifene
Average recovery of drug (%)	88% for Raloxifene
Average recovery of IS (%)	115%
Standard curve concentrations (units/mL)	Standard curve range: 31.820 to 6364.039 pg/mL
QC concentrations (units/mL)	LQC: 91.642 pg/mL, MQC: 2545.616 pg/mL and HQC: 5091.231 pg/mL
QC Intraday precision range (%)	2-6%
QC Intraday accuracy range (%)	94-104%
QC Interday precision range (%)	2-5%
QC Interday accuracy range (%)	98-100%
Bench-top stability (hrs)	6 hours @ room temperature
Stock stability (days)	25 days in Refrigerator
Processed stability (hrs)	83 hours @ 4°C and 6 hours @ room temperature
Freeze-thaw stability (cycles)	3 cycles
Long-term storage stability (days)	64 days @ -80°C
Dilution integrity	Concentration diluted 10-fold
Selectivity	No interfering peaks noted in blank plasma samples at the retention times of analyte & IS.

RALOFIXENE-4'-GLUCURONIDE
BA0818122-01 and BA0818123-01

Information Requested	Data
Bioanalytical method validation report location	Raloxifene Validation Report No: (b) (4) (b) (4)
Analyte	Raloxifene-4'-Glucuronide
Internal standard (IS)	(b) (4)
Method description	Type of Extraction: Precipitation Analytical Method: LC/MS/MS
Limit of quantitation	0.978 ng/mL
Average recovery of drug (%)	80%
Average recovery of IS (%)	115%
Standard curve concentrations (units/mL)	Standard curve range: 0.978 to 195.594 ng/mL
QC concentrations (units/mL)	LQC: 2.817 ng/mL, MQC: 78.237 ng/mL and HQC: 156.475 ng/mL
QC Intraday precision range (%)	1-9%
QC Intraday accuracy range (%)	90-102%
QC Interday precision range (%)	4-6%
QC Interday accuracy range (%)	96-97%
Bench-top stability (hrs)	6 hours @ room temperature
Stock stability (days)	30 days in Refrigerator
Processed stability (hrs)	83 hours @ 4°C and 6 hours @ room temperature
Freeze-thaw stability (cycles)	3 cycles
Long-term storage stability (days)	64 days @ -80°C
Dilution integrity	Concentration diluted 10-fold
Selectivity	No interfering peaks noted in blank plasma samples at the retention times of analyte & IS.

RALOXIFENE-6-GLUCURONIDE
BA0818122-01 and BA0818123-01

Information Requested	Data
Bioanalytical method validation report location	Raloxifene Validation Report No: (b) (4) (b) (4)
Analyte	Raloxifene-6-Glucuronide
Internal standard (IS)	(b) (4)
Method description	Type of Extraction: Precipitation Analytical Method: LC/MS/MS
Limit of quantitation	0.415 ng/mL
Average recovery of drug (%)	81%
Average recovery of IS (%)	115%
Standard curve concentrations (units/mL)	Standard curve range: 0.415 to 82.951 ng/mL
QC concentrations (units/mL)	LQC: 1.194 ng/mL, MQC: 33.180 ng/mL and HQC: 66.361 ng/mL
QC Intraday precision range (%)	2-9%
QC Intraday accuracy range (%)	92-100%
QC Interday precision range (%)	1-4%
QC Interday accuracy range (%)	96-98%
Bench-top stability (hrs)	6 hours @ room temperature
Stock stability (days)	30 days in Refrigerator
Processed stability (hrs)	83 hours @ 4°C and 6 hours @ room temperature
Freeze-thaw stability (cycles)	3 cycles
Long-term storage stability (days)	64 days @ -80°C
Dilution integrity	Concentration diluted 10-fold
Selectivity	No interfering peaks noted in blank plasma samples at the retention times of analyte & IS.

SOPs submitted	- SOP (b) (4) Preparation and acceptance criteria for CC's and QC's - SOP (b) (4) Criteria for sample reanalysis and reporting
Bioanalytical method is acceptable	Acceptable

Comments on the Pre-Study Method Validation:

- All three analytes (raloxifene, raloxifene-4'-glucuronide, and raloxifene-6-glucuronide) were measured by a single assay.
- The firm used K₃EDTA as the anticoagulant, which is the same anticoagulant used in the bio-study sample analysis.
- In the Validation Report Part-1 (report date June 18, 2008), the firm demonstrated long term stability of raloxifene and its metabolites for 30 days at -80°C. In the Addendum Report-1 Part-2 (report date June 30, 2008), the firm demonstrated

long term stability for 45 days at -80°C. And in Addendum Report-2 Part-3, the firm demonstrated long term stability for 64 days at -80°C.

- The long-term storage stability of 64 days at -80°C is sufficient to cover the maximum storage time of the study samples (38 days).
- The pre-study method validation is **acceptable**.

APPEARS THIS WAY ON
ORIGINAL

3.6 In Vivo Studies

Table 1. Summary of all *in vivo* Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (range)	Mean Parameters (%CV)						Study Report Location
					Cmax (pg/mL)	Tmax (hr)	AUCt (pg*hr/mL)	AUCi (pg*hr/mL)	tHalf (hr)	Kel (1/hr)	
Study # BA0818 122-01	To compare oral bioavailability of Raloxifene Hydrochloride tablets 60 mg with that of 'EVISTA' (Raloxifene Hydrochloride) tablets 60 mg in healthy adult human subjects under fasting conditions and to monitor safety of subjects.	An open label, randomized, two-period, two-treatment, two-sequence, single-dose, crossover, balanced, fasting, study design	Raloxifene Hydrochloride Tablets 1x60 mg, Oral, [Lot #: ID080510]	36 Enrolled, 32 dosed, 32 completed study, (32 males, 0 females) Age: 29.0 (20.0-42.0) years Healthy male subjects.	381.886 (45.591)	12.000 (5.000-24.000)	12322.241 (53.155)	14675.670 (42.855)	18.742 (49.055)	0.043 (34.900)	Section 11.4
			'EVISTA' Tablets (Raloxifene HCl Tablets) 1x60 mg, Oral, [Lot #: A489455]		423.759 (38.365)	8.000 (1.000-24.000)	13086.590 (53.870)	15229.321 (45.704)	20.321 (39.790)	0.039 (35.235)	
Study # BA0818 123-01	To compare oral bioavailability of Raloxifene Hydrochloride tablets 60 mg with that of 'EVISTA' (Raloxifene	An open label, randomized, two-period, two-treatment, two-sequence,	Raloxifene Hydrochloride Tablets 1x60 mg, Oral, [Lot #: ID080510]	46 Enrolled, 42 dosed, 41 completed study, (41 males, 0 females)	561.048 (57.935)	24.000 (1.000-9.000)	18071.725 (77.677)	19733.967 (70.784)	16.561 (32.400)	0.045 (22.625)	Section 11.4

	Hydrochloride) tablets 60 mg in healthy adult human subjects under non-fasting conditions and to monitor safety of subjects.	single-dose, crossover , balanced, non-fasting, study design	‘EVISTA’ Tablets (Raloxifene HCl Tablets) 1×60 mg, Oral, [Lot #: A489455]	Age: 29.0 (18.0-41.0) years Healthy male subjects.	554.854 (51.410)	24.000 (1.000-10.000)	18156.137 (61.404)	20162.008 (57.177)	16.377 (27.611)	0.045 (22.633)	
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Note: The mean age is calculated based on completed subjects. Tmax is presented as Median (Range).

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

Raloxifene Hydrochloride Tablets Dose (1 x 60 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Study No. BA0818122-01 Raloxifene (N=32)					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (pg *hr/mL)	11416.02	11289.49	1.01	91.90	111.26
AUC _∞ (pg *hr/mL)	13490.21	13911.86	0.97	89.60	104.95
C _{max} (pg/mL)	366.78	392.51	0.93	84.56	103.27
Fasting Study No. BA0818122-01 Raloxifene-4'-Glucuronide (N=27 for Test, N=26 for Reference)					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (ng *hr/mL)	2228.01	2552.54	0.87	67.05	113.63
AUC _∞ (ng *hr/mL)	2754.41	2688.58	1.02	91.33	114.92
C _{max} (ng/mL)	148.12	188.71	0.78	62.81	98.09
Fasting Study No. BA0818122-01 Raloxifene-6-Glucuronide (N=32)					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (ng *hr/mL)	612.21	664.82	0.92	76.33	111.10
AUC _∞ (ng *hr/mL)	700.06	686.19	1.02	94.11	110.60
C _{max} (ng/mL)	30.98	37.33	0.83	69.09	99.68

Raloxifene Hydrochloride Tablets Dose (1 x 60 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Study No. BA0818123-01 Raloxifene (N=41)					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (pg *hr/mL)	14505.38	15007.53	0.97	85.53	109.23
AUC _∞ (pg *hr/mL)	17152.70	18229.64	0.94	83.46	106.08
C _{max} (pg/mL)	491.74	493.52	1.00	91.02	109.08
Fed Study No. BA0818123-01 Raloxifene-4'-Glucuronide (N=41)					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (ng *hr/mL)	3044.00	3035.41	1.00	90.91	110.62
AUC _∞ (ng *hr/mL)	3092.31	3077.77	1.00	91.22	110.67
C _{max} (ng/mL)	298.58	291.42	1.02	94.46	111.14
Fed Study No. BA0818123-01 Raloxifene-6-Glucuronide (N=41)					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (ng *hr/mL)	534.88	540.97	0.99	88.68	110.24
AUC _∞ (ng *hr/mL)	558.87	560.85	1.00	89.46	110.99
C _{max} (ng/mL)	38.09	37.23	1.02	95.27	109.86

Table 3a. Reanalysis of Study Samples (Fasting)

Bioequivalence FASTING Study No. BA0818122-01 Raloxifene Analytical Report Page No. 37 Analyte: Raloxifene								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic ¹	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Reason - LIS	1	2	0.1	0.2	1	2	0.1	0.2
Reason - AI	0	1	0	0.1	0	1	0	0.1
Total	1	3	0.1	0.2	1	3	0.1	0.2

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

LIS- LOW INTERNAL STANDARD
AI- ANALYTICAL INTERFERENCE

Did use of recalculated plasma concentration data change study outcome?

Per the firm's SOP, Analytical Interference (AI) is defined as "Predose sample having interference more than LOQ standard (Std A)." However, the firm repeated one sample for the reason AI because "S27P1 9.0 Hour had a concentration of 7218.021pg/mL and the analyte peak area also was very high (≈ 100 times) when compared to the preceding and succeeding time points. No such abnormality was found in RA4G and RA6G for this particular time point. Hence S27P1 9.0 Hour was repeated under AI, suspected analytical interference from the analyst during processing." Therefore, the reviewer recalculated the PK parameters for Raloxifene using this original value. The following results show that the 90% C.I. for $\ln C_{max}$ do not meet acceptable bioequivalence criteria using the original value for this sample:

LSMEANS AND 90% CONFIDENCE INTERVALS

Parameter	Least Squares Geometric Mean		Ratio (T/R)	90% Confidence Intervals	
	Test	Reference		Lower	Upper
LAUCT	11389.92	11683.87	0.97	87.99	108.00
LAUCI	13490.21	13911.86	0.97	89.60	104.95
LCMAX	363.64	446.63	0.81	65.27	101.56

Comments from the Reviewer:

- The sample repeated for S27P1 9.0 Hour should have been coded as a pharmacokinetic repeat since it was repeated for a subjective reason (i.e. suspected analytical interference). Since the original value was analytically valid, and the firm reanalyzed this sample for a non-objective reason, the reviewer analyzed the data using the original value and concluded that the fasting bioequivalence study for raloxifene failed to meet acceptable bioequivalence criteria for $\ln C_{max}$.

Bioequivalence FASTING Study No. BA0818122-01 Raloxifene-4'-Glucuronide Analytical Report Page No. 38 Analyte: Raloxifene-4'-Glucuronide								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic ¹	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Reason - LIS	1	2	0.1	0.2	1	2	0.1	0.2
Reason - OCC	17	29	1.3	2.3	17	28	1.3	2.4
Reason - RBE	1	0	0.1	0.0	0	0	0.0	0.0
Total	19	31	1.5	2.4	18	30	1.4	2.3

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

LIS-- LOW INTERNAL STANDARD

OCC-- CONCENTRATION OVER THE CALIBRATION CURVE

RBE- REPEATED BY ERROR

Did use of recalculated plasma concentration data change study outcome?

The firm followed the pre-established SOP.

Comments from the Reviewer:

- One sample was Repeated by Error (RBE); therefore, the original value was reported.
- Nineteen of the samples repeated for Concentration Over the Calibration Curve (OCC) had the original value “No Intercept.” The firm will be requested to explain what is meant by the term “No Intercept.”

Bioequivalence FASTING Study No. BA0818122-01 Raloxifene-6-Glucuronide Analytical Report Page No. 40 Analyte: Raloxifene-6-Glucuronide								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic ¹	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Reason - LIS	1	2	0.1	0.2	1	2	0.1	0.2
Reason - OCC	1	1	0.1	0.1	1	1	0.1	0.1
Total	2	3	0.2	0.2	2	3	0.2	0.2

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

LIS- LOW INTERNAL STANDARD

OCC-- CONCENTRATION OVER THE CALIBRATION CURVE

Did use of recalculated plasma concentration data change study outcome?

The firm followed the pre-established SOP.

Comments from the Reviewer:

None

Table 4b. Reanalysis of Study Samples (Fed)

Bioequivalence FED Study No. BA0818123-01 Raloxifene Analytical Report Page No. 41 Analyte: Raloxifene								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic ¹	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Reason - LIS	1	1	0.1	0.1	1	1	0.1	0.1
Reason - LP	2	1	0.1	0.1	2	1	0.1	0.1
Total	3	2	0.2	0.1	3	2	0.2	0.1

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

LIS- LOW INTERNAL STANDARD
LP- LOST IN PROCESSING

Did use of recalculated plasma concentration data change study outcome?

The firm followed the pre-established SOP.

Comments from the Reviewer:

None

Bioequivalence Study No. BA0818123-01 Raloxifene-4'-Glucuronide Analytical Report Page No. 42 Analyte: Raloxifene-4'-Glucuronide								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic ¹	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Reason - LP	2	1	0.1	0.1	2	1	0.1	0.1
Reason - LIS	1	1	0.1	0.0	1	1	0.0	0.1
Reason - OCC	141	119	8.5	7.1	140	118	8.4	7.1
Reason - RBE	0	1	0	0.1	0	0	0	0.0
Total	144	122	8.6	7.3	143	120	8.6	7.2

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

LP- LOST IN PROCESSING
LIS- LOW INTERNAL STANDARD
OCC- CONCENTRATION OVER THE CALIBRATION CURVE
RBE- REPEATED BY ERROR

Did use of recalculated plasma concentration data change study outcome?

The firm followed the pre-established SOP.

Comments from the Reviewer:

- One hundred and thirty (130) of the samples repeated for Concentration Over the Calibration Curve (OCC) had the original value "No Intercept." The firm will be requested to explain what is meant by the term "No Intercept."
- Although the preceding table indicates that 140 values of the 141 reanalyzed test samples and 118 values of the 119 reanalyzed reference samples were reported after reanalysis, all the 141 test and 119 reference recalculated values were reported per the firm's repeat list of the study for raloxifene-4'-glucuronide.

Bioequivalence Study No. BA0818123-01 Raloxifene-6-Glucuronide Analytical Report Page No. 52 Analyte: Raloxifene-6-Glucuronide								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic ¹	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Reason - LP	2	1	0.1	0.1	2	1	0.1	0.1
Reason - LIS	1	1	0.1	0.1	1	1	0.1	0.1
Reason - OCC	6	2	0.4	0.1	6	2	0.4	0.1
Reason - RBE	0	1	0	0.1	0	0	0.0	0.0
Total	9	5	0.5	0.3	9	4	0.5	0.2

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

LP- LOST IN PROCESSING

LIS- LOW INTERNAL STANDARD

OCC- CONCENTRATION OVER THE CALIBRATION RANGE

RBE- REPEATED BY ERROR

Did use of recalculated plasma concentration data change study outcome?

The firm followed the pre-established SOP.

Comments from the Reviewer:

- One sample was Repeated by Error (RBE); therefore, the original value was reported.

Comments on the In Vivo studies:

- The 90% C.I. for lnCmax do not meet acceptable bioequivalence criteria using the original assay values for raloxifene in the fasting bioequivalence study.
- The 90% C.I. of raloxifene-4'-glucuronide and raloxifene-6-glucuronide are also outside of acceptable bioequivalence limits.
- The firm will be requested to explain the term "No Intercept" for the original values of the raloxifene-4'-glucuronide samples reanalyzed for the reason Concentration Over the Calibration Curve (OCC) in fasting study no. BA0818122-01.
- The in vivo studies are **incomplete**.

3.7 Formulation

Location in appendix	4.2, page 65
If a tablet, is the RLD scored?	No
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	ACCEPTABLE
If not acceptable, why?	

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DARRTS: ANDA 090842, LEE, CHRISTINA H, Submit/Final Date: 01/09/2009, REV-BIOEQ-02 (Dissolution Review)
Source of Method (USP, FDA or Firm)	USP
Medium	0.1% Polysorbate 80 in water
Volume (mL)	1000 mL
USP Apparatus type	Apparatus 2 (Paddle)
Rotation (rpm)	50
USP-recommended specifications	NLT 80% (Q) dissolved in 30 minutes
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	Rapidly dissolving
Is the dissolution testing acceptable?	ACCEPTABLE
If not then why?	

Reviewer's Comments:

- The dissolution testing was previously reviewed [see DARRTS: ANDA 090842, LEE, CHRISTINA H, Submit/Final Date: 01/09/2009, REV-BIOEQ-02 (Dissolution Review)].
- The firm conducted its dissolution testing per the USP method. The dissolution data meet the USP-recommended specification of NLT 80% in 30 minutes at the S1 level. The firm proposed a specification of NLT 80% (Q) in 30 minutes, which is the same as that recommended by USP.
- The dissolution testing is **acceptable**.

3.9 Waiver Request(s)

No waiver requests were submitted.

3.10 Review of DSI Report for Clinical Site and Firm's Response to the Form-483 Observations

At the request of the DBE, the DSI conducted an audit of the clinical portions of the fasting and fed bioequivalence studies for ANDA 090175. Following the inspection of the analytical site (September 15-19, 2008), a Form FDA-483 was issued. DSI received the firm's response to Form FDA-483 on November 24, 2008. The Form 483 observations of the clinical site, firm's responses, and DSI evaluations are as follows:

DSI FINDING #1:

Study Protocol Section 10.5 - Handling of Adverse Events and Adverse Drug Reactions states that subjects will be monitored throughout the study period for adverse events and reporting the events to the IEC and sponsor.

- a) Subject 21 (Period I (10/16-10/17/07)), experienced fever, chills, and rigors. On 10/24/07, subject was advised to "come for follow-up." The records did not indicate when subsequent follow-up was conducted, and/or result of follow-up with the subject.*

DSI Conclusion:

In their response letter, the firm provided documentation that they had tried to contact Subject 21 for follow up of the adverse event (upper respiratory tract infection) but the subject did not show up until the end of the study. Therefore, subject 21 was discontinued from the study. The adverse event was considered mild and declared resolved at the final visit by the clinical investigator.

Please note that this event of upper respiratory tract infection was discussed in the adverse event section of the study report. In their response letter, the firm mentioned that they will improve on the subject communication documentation for adverse event issues. This observation should not have a significant impact to the study outcome.

Reviewer's Comments:

The reviewer agrees with the DSI finding and conclusion that this observation should not impact the study outcome. In addition, there were no issues with adverse event reporting in the current ANDA. The firm documented the conditions and outcome of each adverse event observed in the fasting and fed bioequivalence studies.

DSI FINDING #2:

Study Protocol Section 7.3 - Subject Withdrawal or Discontinuation Criteria states that the subject's withdrawal during the study shall be adequately documented. Review of the study records indicated the following:

- a) In numerous occurrences, discontinued subjects were "advised to come for follow up." Records did not consistently include date of follow-up, and/or results of follow-up. Examples included Subject 14, 29, 30, and 36 respectively. (Protocol V-BA0786044).*

DSI Conclusion:

The firm stated that it was their common practice to inform the discontinued subjects to return for follow up visits. However, the correspondences with these subjects were not documented. In their response letter, the firm provided documentation to show that subjects 14, 29, 30 and 36 returned to the clinic on Nov 28, 2007 for final visit and checkup. This observation should not have an impact to the study outcome.

Reviewer's Comments:

The reviewer agrees with the DSI finding and conclusion that this observation should not impact the study outcome. The reviewer notes that there is no documentation of post study assessments for the subject that was discontinued from the current fed study (subject 26). However, this should not impact the outcome of the studies in the current ANDA.

DSI FINDING #3:

Study Protocol Section 1.7 - Safety Assessment states that subjects will be questioned for well being at the time of clinical examinations, during vital signs recording, and during ambulatory samples. In numerous instances, subjects' well being was not documented at the time ambulatory samples were performed.

DSI Conclusion:

The firm agreed with the findings and admitted that this was an oversight and promised to correct this issue in future studies. According to the firm, subject well being was a subjective assessment which included asking the subject "How are you feeling". For subject 13, the case record form showed that the firm failed to monitor the subject's well being in 1 out of the 9 sampling visits. For subject 15, the case record form showed that the firm failed to monitor the subject's well being in 2 out of the 9 sampling visits. For subject 20, the firm failed to monitor the subject's well being in 2 out of the 9 sampling visits. Although it was objectionable that the firm did not perform the subject well being checks for all the sampling visits, the number of such deviations was small when compared to the total number of sampling visits, and the subjects all reported "fine" in the remaining sampling visits. This observation should not have an impact to the study outcome.

Reviewer's Comments:

The reviewer agrees with the DSI conclusion that this observation should not impact the study outcome. In the current ANDA, the firm documented the well-being of the subjects throughout the fasting and fed bioequivalence studies.

DSI FINDING #4:

SOP V-CL004. 00, Section 5.6.2 - Informed Consent Form (ICF) for Study requires completing the subject's ICF, and in case of illiterate subjects to obtain their thumb impression. Subject's ICFs did not include obtaining consent of Legally Acceptable Representative (LA) / impartial witness for minor or illiterate subjects.

DSI Conclusion:

The firm acknowledged that this was an oversight on their part and had since revised the SOP to address this issue accordingly. This observation should not have an impact to the study outcome.

Reviewer's Comments:

The reviewer agrees with the DSI conclusion that this observation should not impact the study outcome.

3.11 Review of DSI Report for Analytical Site and Firm's Response to the Form-483 Observations

At the request of the DBE, the DSI conducted an audit of the clinical and analytical portions of the fasting and fed bioequivalence studies for ANDA 090228. Following the 'for cause' inspection of the clinical site (March 2-6, 2009), there were no significant findings and no FDA Form-483 was issued. Following the inspection of the analytical site (b) (4) Form FDA-483 was issued. The firm's response to Form FDA-483 was dated (b) (4). The 483 observations of the clinical site, firm's responses, and DSI evaluations are as follows:

DSI FINDING #1:

(b) (4)

Reviewer's Comments:

The reviewer agrees with the DSI finding and conclusion. However, this finding is specific to ANDA 090228 and does not impact the validity of the analytical results in the current ANDA. (b) (4)

3.12 Deficiency Comments

1. The firm will be requested to explain the term “No Intercept” for the original values of the raloxifene-4’-glucuronide samples reanalyzed for the reason Concentration Over the Calibration Curve (OCC) in fasting study no. BA0818122-01.
2. The firm will be requested to explain what is meant by the term No Intercept (NI) for the raloxifene-4’-glucuronide QC samples in fasting study no. BA0818122-01.
3. The firm will be requested to provide objectionable justifications for manually integrating the peaks for samples S3P2 96.0 HR SUB3&4_61 (raloxifene), S3P2 96.0 HR SUB3&4_61 (raloxifene-4’-glucuronide), S3P2 96.0 HR SUB3&4_61 (raloxifene-6-glucuronide), and S5P2 96.0 HR SUB5&6_60 (raloxifene-4’-glucuronide) in fasting study no. BA0818122-01.
4. Since subject 11 had measurable concentrations of raloxifene and both glucuronide metabolites after receiving the reference product, and measurable glucuronide metabolite concentrations after receiving the test product, it is not clear why this subject did not have any measurable concentrations of raloxifene after receiving the test product in fasting study no. BA0818122-01. It may be an issue of product failure. The firm will be requested to explain why subject 11 had no measurable raloxifene concentrations at each time point after receiving the test product in fasting study no. BA0818122-01
5. Since the original value for sample S27P1 9.0 Hour was analytically valid, and the firm reanalyzed this sample for a non-objective reason, the reviewer used the original value in the statistical analysis. The 90% C.I. values for raloxifene lnCmax failed to meet acceptable bioequivalence criteria (65.27, 101.56) in the fasting bioequivalence study. In addition, the 90% C.I. values for raloxifene-4’-glucuronide (lnAUCt: 67.05, 113.63; lnCmax: 62.81, 98.09) and raloxifene-6-glucuronide (lnAUCt: 76.33, 111.10; lnCmax: 69.09, 99.68) also failed to meet acceptable bioequivalence criteria. Therefore, the fasting bioequivalence study no. BA0818122-01 failed.
6. The firm will be requested to indicate what treatments were used to resolve adverse events experienced by subject 13 (headache) and subject 26 (fever) in fed study no. BA0818123-01.
7. The firm will be requested to submit chromatograms from at least 20% of the total number of subjects that completed fed study no. BA0818123-01 (i.e. 41 subjects).
8. The firm will be requested to [REDACTED] (b) (4) in the current ANDA.

3.13 Recommendations

1. The Division of Bioequivalence (DBE) finds the fasting study no. BA0818122-01 incomplete due to the deficiencies mentioned above. InvaGen Pharmaceuticals, Inc. conducted the fasting bioequivalence study on its Raloxifene Hydrochloride Tablets, 60 mg (lot #ID080510), comparing it to Eli Lilly's EVISTA® (Raloxifene Hydrochloride) Tablets, 60 mg (lot # A489455).
2. The DBE finds the fed study no. BA0818123-01 incomplete due to the deficiencies mentioned above. InvaGen Pharmaceuticals, Inc. conducted the fed bioequivalence study on its Raloxifene Hydrochloride Tablets, 60 mg (lot #ID080510), comparing it to Eli Lilly's EVISTA® (Raloxifene Hydrochloride) Tablets, 60 mg (lot # A489455).
3. The firm's in vitro dissolution testing is acceptable. The dissolution testing should be conducted in 1000 mL of 0.1% Polysorbate 80 in water at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ using USP apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

NLT 80% (Q) in 30 minutes

3.14 Comments for Other OGD Disciplines

Discipline	Comment
None	None

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 5. Study Information

Study Number	BA0818122
Study Title	An Open Label, Balanced, Randomized, Two Treatment, Two Sequence, Two Period, Crossover, Single Dose, Comparative Oral Bioavailability Study of Raloxifene Hydrochloride Tablets 60mg and 'EVISTA' (Raloxifene Hydrochloride) Tablets 60mg in Healthy Adult Human Subjects Under Fasting Conditions
Clinical Site (Name, Address, Phone #)	BA Research India Ltd Opposite Pushparaj Towers, Nr. Judges Bungalows, Bodakdev, Ahmedabad-380054, Gujarat, India
Principal Investigator	Dr. Pruthvi Puwar and Dr. Ronak Modi
Dosing Dates	Period 1: June 20, 2008 Period 2: July 4, 2008
Analytical Site (Name, Address, Phone #)	(b) (4) Ph.D., (b) (4)
Analysis Dates	17 July 2008 thru 28 July 2008
Analytical Director	(b) (4) Ph.D.,
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	June 20, 2008 to July 28, 2008 (38 days)

Table 6. Product information

Product	Test	Reference
Treatment ID*	A	B
Product Name	Raloxifene Hydrochloride Tablets, 60 mg	EVISTA (Raloxifene Hydrochloride Tablets, 60 mg)
Manufacturer	Invagen Pharmaceuticals Inc.,	Eli Lilly & Company
Batch No.	ID080510	A489455
Manufacture Date	05/28/2008	N/A
Expiration Date	N/A	02/2010
Strength	60 mg	60 mg
Dosage Form	Tablet	Tablet
Bio-batch Size	(b) (4)	N/A
Production Batch Size	(b) (4)	N/A
Potency	98.0 %	98.7 %
Content Uniformity (mean, %CV)	99.9 % , 1.8%	100.4 % , 2.8 %
Dose Administered	60 mg	60 mg
Route of Administration	Oral	Oral

*ID assigned by the reviewer

Table 7. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Planned: 36 Enrolled: 32 Completed: 32 Analyzed: 32
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme	AB: 2, 4, 6, 7, 10, 12, 14, 16, 17, 20, 22, 24, 25, 28, 30, 32 BA: 1, 3, 5, 8, 9, 11, 13, 15, 18, 19, 21, 23, 26, 27, 29, 31
Blood Sampling Times	Pre-dose, 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 12.0, 16.0, 20.0, 24.0, 48.0, 72.0, 96.0 and 120.0 hours post dose (20 time points).
Blood Volume Collected/Sample	5 mL, 10 mL for pre-dose sample
Blood Sample Processing/Storage	Blood samples were collected in labeled K ₃ EDTA-vacutainers/vacuettes through an indwelling cannula placed in the forearm vein of the subjects. The sample were placed in a refrigerated centrifuge, and then spun at 3000 ± 100 rpm at 4°C for 15 minutes. The plasma was separated, transferred to labeled RIA vials in duplicate and stored in the freezer set at -70 ± 20°C at clinical site (BA Research India Ltd., Vadodara) until shipment. The samples were stored at analytical site (b) (4) until analysis.

IRB Approval	Approved June 18, 2008
Informed Consent	Yes, in English and Gujarati
Length of Fasting	At least 10 hours prior to drug administration until 4 hours after drug administration.
Length of Confinement	At least 11 hours prior to dosing until 24 hours post dose.
Safety Monitoring	During screening safety parameters assessed were vital signs, physical examination, complete medical history, and clinical laboratory safety tests at baseline. Sitting blood pressure and radial pulse were recorded at the time of clinical examination, prior to dosing, and at 2, 6, 10 hours $\pm$ 40 minutes post dose. Subjects were asked for well being at the time of clinical examination, during vital signs recordings and during ambulatory samples. Safety was also evaluated by collection of adverse events however there were no adverse events reported during the study.

Comments on Study Design:

- The firm used K₃EDTA as the anticoagulant, which is the same anticoagulant used in the method validation.
- The study design is **acceptable**.

4.1.1.2 Clinical Results

Table 8. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. BA0818122-01			
		Treatment Groups	
		Test Product N = 32	Reference Product N =32
Age (years)	Mean $\pm$ SD	29 $\pm$ 6	29 $\pm$ 6
	Range	20-42	20-42
Age Groups	< 18	-	-
	18 – 45	32 (100%)	32 (100%)
	> 45	-	-
Sex	Male	32 (100%)	32 (100%)
	Female	-	-
Race	Asian	32 (100%)	32 (100%)
	Black	-	-
	Caucasian	-	-
	Hispanic	-	-
	Other	-	-
BMI	Mean $\pm$ SD	21.22 ($\pm$ 2.1)	21.22 ($\pm$ 2.1)

(Kg/m ²)	Range	18.54 – 24.65	18.54 – 24.65
Tobacco users	Yes	13 (40.63%)	13 (40.63%)
	No	19 (59.38%)	19 (59.38%)

Table 9. Dropout Information, Fasting Bioequivalence Study

Study No. BA0818122-01				
Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with
NONE				

Table 10. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasting Bioequivalence Study Study No. BA0818122-01	
	Test N ¹ (%) ²	Reference N ¹ (%) ²
	NONE	
Number of subjects dosed with study drug	32	32

Table 11. Protocol Deviations, Fasting Bioequivalence Study

Study No. BA0818122-01		
Type	Subject #s (Test)	Subject #s (Ref.)
+22 minutes sampling deviation at 96.0 hours during period I, as the subject arrived late to the clinical facility.	04	NA
No sample was collected at 120.0 hours during Period I, as he did not reported to clinical facility.	NA	05
+15 minutes sampling deviation at 72.0 hours during period I, as the subject arrived late to the clinical facility.	24	NA
+16 minutes sampling deviation at 72.0 hours during period I, as the subject arrived late to the clinical facility.	25	NA
+36 minutes sampling deviation at 48.0 hours during period I, as the subject arrived late to the clinical facility.	NA	31
+29 minutes sampling deviation at 96.0 hours during period I, as the subject arrived late to the clinical facility.	NA	31
+07 minutes sampling deviation at 48.0 hours during period II, as the subject arrived late to the clinical facility.	01	NA
+03 minutes sampling deviation at 120.0 hours during period II, as the subject had difficulty with vein.	NA	02

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+05minutes sampling deviation at 48.0 hours during period II, as the subject arrived late to the clinical facility.	05	NA
+31minutes sampling deviation at 72.0 hours during period II, as the subject arrived late to the clinical facility.	NA	10
+03 minutes sampling deviation at 96.0 hours during period II, as the subject arrived late to the clinical facility.	NA	10
+25 minutes sampling deviation at 48.0 hours during period II, as the subject arrived late to the clinical facility.	NA	20
+21 minutes sampling deviation at 96.0 hours during period II, as the subject arrived late to the clinical facility.	NA	22
+06 minutes sampling deviation at 96.0 hours during period II, as the subject arrived late to the clinical facility.	23	NA
+18 minutes sampling deviation at 48.0 hours during period II, as the subject arrived late to the clinical facility.	NA	24
+16 minutes sampling deviation at 48.0 hours during period II, as the subject arrived late to the clinical facility.	NA	25

Comments on Dropouts/Adverse Events/Protocol Deviations:

- The firm reported that there were no discontinued subjects and no adverse events. All the reported out-of-range laboratory measurements (see table below) were considered clinically insignificant.

Subject Number	Abnormal Laboratory Measurement*
1	High E.S.R. High glucose-random (repeated)
2	High monocytes High ES.R. High urea (repeated)
3	High monocytes High E.S.R.
4	High eosinophils High bilirubin (repeated)
5	High monocytes High eosinophils High RDW CV
6	High monocytes
8, 27	High eosinophils High E.S.R.
9	High monocytes High eosinophils High basophils
10, 17	High monocytes High RDW CV
14, 20	High E.S.R.

15	High basophils
18	High E.S.R. (repeated twice, subject had no clinical symptoms)
19, 29	High eosinophils
21	High RDW CV High eosinophils High monocytes
22	High RDW CV High eosinophils High monocytes
23	Low lymphocyte High monocytes
24	High bilirubin value (repeated)
28	High eosinophils High monocytes
30	High monocytes High basophils
32	High RDW CV

*The repeated measurements were considered clinically insignificant

- All the reported protocol deviations were time deviations, and a missing sample. The firm considered deviations beyond ± 2 minutes of the scheduled time as sampling time deviations. Since the time deviations occurred for sampling times in the terminal elimination phase, the reviewer will use the scheduled time points in the pharmacokinetic and statistical analysis. These time deviations are not expected to affect the study outcome.
- The clinical results are **acceptable**.

4.1.1.3 Bioanalytical Results

Table 12. Assay Validation – Within the Fasting Bioequivalence Study

Bioequivalence Study No. BA0818122-01 Analyte Name: Raloxifene								
Parameter	Standard Curve Samples							
Concentration (pg/mL)	33.242	66.484	132.968	332.420	831.05	1662.100	3324.201	6648.402
Inter day Precision (%CV)	2	3	3	2	2	4	2	2
Inter day Accuracy (%Actual)	99	102	98	100	101	100	101	98
Linearity	Range of r values: 0.9977- 0.9998							
Linearity Range (pg /mL)	33.242-6648.402 pg/ml							
Sensitivity/LOQ (pg /mL)	33.242 pg/mL							

Bioequivalence Study No. BA0818122-01 Analyte Name: Raloxifene			
Parameter	Quality Control Samples		
Concentration (pg/mL)	95.737	2659.361	5318.721
Inter day Precision (%CV)	5	3	3
Inter day Accuracy (%Actual)	96	97	96

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Bioequivalence Study No. BA0818122-01 Analyte Name: Raloxifene-4'-Glucuronide								
Parameter	Standard Curve Samples							
Concentration (ng/mL)	1.072	2.145	4.290	10.725	26.812	53.625	107.25	214.499
Inter day Precision (%CV)	1	3	2	2	3	4	4	4
Inter day Accuracy (%Actual)	100	101	99	100	101	99	99	101
Linearity	Range of r values: 0.9860- 0.9999							
Linearity Range (ng /mL)	1.072-214.499 ng/ml							
Sensitivity/LOQ (ng /mL)	1.072 ng/mL							

Bioequivalence Study No. BA0818122-01 Analyte Name: Raloxifene-4'-Glucuronide			
Parameter	Quality Control Samples		
Concentration (ng/mL)	3.089	85.800	171.599
Inter day Precision (%CV)	4	5	6
Inter day Accuracy (%Actual)	94	92	93

Bioequivalence Study No. BA0818122-01 Analyte Name: Raloxifene-6-Glucuronide								
Parameter	Standard Curve Samples							
Concentration (ng/mL)	0.388	0.775	1.550	3.876	9.691	19.381	38.762	77.524
Inter day Precision (%CV)	1	2	2	3	2	4	3	2
Inter day Accuracy (%Actual)	100	101	98	100	101	99	102	99
Linearity	Range of r values: 0.9976- 0.9999							
Linearity Range (ng /mL)	0.388-77.524 ng/ml							
Sensitivity/LOQ (ng /mL)	0.388 ng/mL							

Bioequivalence Study No. BA0818122-01 Analyte Name: Raloxifene-6-Glucuronide			
Parameter	Quality Control Samples		
Concentration (ng/mL)	1.116	31.010	62.019
Inter day Precision (%CV)	5	5	5
Inter day Accuracy (%Actual)	94	93	94

Comments on Study Assay Validation:

- The calibration curve standards and quality control samples were prepared on July 15, 2008, and stored at -80°C.
- The firm used human plasma with K₃EDTA as the anticoagulant in the preparation of the CC standards and the QC samples. K₃EDTA was also used as the anticoagulant in the sample collection.

- Two raloxifene-4'-glucuronide QC samples had values No Intercept (NI). The firm will be requested to explain what is meant by the term NI.
- The firm analyzed 24 samples as part of the incurred samples re-analysis (ISR). Four time points were selected from each of 6 subjects (one at or near the peak concentration and the second at the elimination phase near LQC level from both the periods of raloxifene). At least 2/3 of the sample concentrations were within $\pm 20\%$ of the original value: 23 out of 24 of the raloxifene samples were within $\pm 20\%$ of the original values; all the raloxifene-4'-glucuronide samples were within $\pm 20\%$ of the original values; and 23 out of 24 of the raloxifene-6-glucuronide samples were within $\pm 20\%$ of the original values.
- The study assay validation is incomplete.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially from subjects 1-6

Comments on Chromatograms:

- The firm manually integrated the peaks for the following samples: S3P2 96.0 HR SUB3&4_61 (raloxifene); S3P2 96.0 HR SUB3&4_61 (raloxifene-4'-glucuronide); S3P2 96.0 HR SUB3&4_61 (raloxifene-6-glucuronide); and S5P2 96.0 HR SUB5&6_60 (raloxifene-4'-glucuronide). The firm will be requested to provide objectionable justifications for manually integrating the peaks for these samples.
- The chromatograms are incomplete.

Table 13. SOPs Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4)	(b) (4)	Criteria for Sample Analysis and Reporting

Table 14. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes, with the exception of one PK repeat assigned the analytical repeat code of Analytical Interference (AI)
Did recalculation of PK parameters change the study outcome?	Yes
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	

Summary/Conclusions, Study Assays:

- The bioanalytical results are **incomplete** because:
 - The firm will be requested to explain what is meant by the term NI for the raloxifene-4'-glucuronide QC samples.

- The firm will be requested to provide objective justifications for manually integrating the peaks for samples S3P2 96.0 HR SUB3&4_61 (raloxifene), S3P2 96.0 HR SUB3&4_61 (raloxifene-4'-glucuronide), S3P2 96.0 HR SUB3&4_61 (raloxifene-6-glucuronide), and S5P2 96.0 HR SUB5&6_60 (raloxifene-4'-glucuronide).

4.1.1.4 Pharmacokinetic Results

Table 15. Arithmetic Mean Pharmacokinetic Parameters- Reviewer Calculated
Mean plasma concentrations are presented in [Table 18](#) and [Figure 1](#)

Raloxifene Hydrochloride Tablets Dose (1 x 60 mg) Fasting Study No. BA0818122-01									
Raloxifene									
	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC_{0-t} (hr *pg/ml)	12719.23	49.17	5044.54	29279.31	13078.41	53.88	2915.85	31302.90	0.97
AUC_∞ (hr *pg/ml)	15016.34	42.53	6023.93	30841.78	15806.41	42.28	7008.01	32471.54	0.95
C_{max} (pg/ml)	381.886	45.59	0.00	893.69	423.759	38.36	115.62	876.89	0.90
T_{max}* (hr)	14.000	.	5.00	120.00	8.000	.	1.00	24.00	1.75
Kel (hr⁻¹)	0.044	32.52	0.02	0.09	0.042	30.13	0.03	0.07	1.06
T_{1/2} (hr)	17.346	34.77	7.93	33.21	17.947	27.65	10.17	27.09	0.97
Raloxifene-4'-Glucuronide									
	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC_{0-t} (hr *ng/ml)	2697.009	42.72	63.79	5198.79	2809.332	50.80	1025.31	7435.41	0.96
AUC_∞ (hr *ng/ml)	2896.207	35.90	1163.12	5245.42	2912.783	50.12	1078.59	7477.37	0.99
C_{max} (ng/ml)	166.269	33.84	7.66	283.51	191.913	30.69	97.91	366.33	0.87
T_{max}* (hr)	1.000	.	0.50	7.00	1.000	.	0.50	7.00	1.00
Kel (hr⁻¹)	0.073	41.22	0.03	0.15	0.071	42.54	0.03	0.14	1.03
T_{1/2} (hr)	11.172	41.37	4.53	25.49	11.768	43.94	4.88	24.20	0.95

Raloxifene-6-Glucuronide									
	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC _{0-t} (hr *ng/ml)	710.277	41.79	18.29	1377.43	731.991	47.84	288.41	1886.49	0.97
AUC _∞ (hr *ng/ml)	749.586	36.44	347.68	1395.57	748.032	47.76	293.61	1902.09	1.00
C _{max} (ng/ml)	35.288	42.45	1.84	66.36	39.723	37.66	19.15	84.83	0.89
T _{max} * (hr)	5.000	.	1.00	24.00	5.000	.	1.00	24.00	1.00
K _{el} (hr ⁻¹)	0.074	45.35	0.04	0.18	0.070	42.28	0.03	0.13	1.07
T _{1/2} (hr)	10.909	36.62	3.87	18.62	11.836	42.77	5.14	24.95	0.92

* T_{max} values are presented as median, range.

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

Raloxifene Hydrochloride Tablets 1x60 mg Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study (BA0818122-01)				
Parameter	Test	Reference	Ratio	90%CI
AUC _t	11429.994	11296.142	101.18%	(91.98%; 111.32%)
AUC _i	13444.650	13817.596	97.30%	(90.53%; 104.58%)
C _{max}	366.023	392.507	93.25%	(84.42%; 103.00%)

Table 17. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Raloxifene Hydrochloride Tablets Dose (1 x 60 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Study No. BA0818122-01 Raloxifene (N=32)					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (pg *hr/mL)	11416.02	11289.49	1.01	91.90	111.26
AUC _∞ (pg *hr/mL)	13490.21	13911.86	0.97	89.60	104.95
C _{max} (pg/mL)	366.78	392.51	0.93	84.56	103.27
Fasting Study No. BA0818122-01 Raloxifene-4'-Glucuronide (N=27 for Test, N=26 for Reference)					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (ng *hr/mL)	2312.57	2550.58	0.91	75.36	109.09
AUC _∞ (ng *hr/mL)	2687.36	2660.45	1.01	92.79	109.96
C _{max} (ng/mL)	149.81	183.73	0.82	69.43	95.75
Fasting Study No. BA0818122-01 Raloxifene-6-Glucuronide (N=32)					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (ng *hr/mL)	612.21	664.82	0.92	76.33	111.10
AUC _∞ (ng *hr/mL)	700.06	686.19	1.02	94.11	110.60
C _{max} (ng/mL)	30.98	37.33	0.83	69.09	99.68

Note: the pharmacokinetic parameters were calculated by the reviewer using the SAS code "CALCKE" to verify the study.

Table 18. Additional Study Information, Fasting Study No. BA0818122-01

Root mean square error, AUC _{0-t}	Raloxifene: 0.2214 R4G: 0.4360 R6G: 0.4424	
Root mean square error, AUC _∞	Raloxifene: 0.1480 R4G: 0.1825 R6G: 0.1804	
Root mean square error, C _{max}	Raloxifene: 0.2315 R4G: 0.3788 R6G: 0.4319	
	Test	Reference
Kel and AUC _∞ determined for how many subjects?	Raloxifene: 29	Raloxifene: 31

	R4G: 32 R6G: 31	R4G: 32 R6G: 32
Do you agree or disagree with firm's decision?	Raloxifene: Disagree. The elimination rate constants could only be estimated for 26 subjects. R4G: Disagree. The elimination rate constants could only be estimated for 28 subjects. R6G: Disagree. The elimination rate constants could only be estimated for 30 subjects.	Raloxifene: Disagree. The elimination rate constants could only be estimated for 26 subjects. R4G: Disagree. The elimination rate constants could only be estimated for 30 subjects. R6G: Disagree. The elimination rate constants could only be estimated for 31 subjects.
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	Raloxifene: 0 R4G: 0 R6G: 0	Raloxifene: 0 R4G: 0 R6G: 0
first measurable drug concentration as C_{max}	Raloxifene: 0 R4G: 7 R6G: 0	Raloxifene: 0 R4G: 7 R6G: 0
Were the subjects dosed as more than one group?	No	

Ratio of AUC _{0-t} /AUC _∞ Raloxifene				
Treatment	n	Mean	Minimum	Maximum
Test	26	0.90	0.72	0.96
Reference	26	0.90	0.73	0.97
Ratio of AUC _{0-t} /AUC _∞ Raloxifene-4'-Glucuronide				
Treatment	n	Mean	Minimum	Maximum
Test	28	0.98	0.88	1.00
Reference	30	0.98	0.94	1.00
Ratio of AUC _{0-t} /AUC _∞ Raloxifene-6-Glucuronide				
Treatment	n	Mean	Minimum	Maximum
Test	30	0.97	0.82	0.99
Reference	31	0.97	0.91	0.99

Comments on Pharmacokinetic and Statistical Analysis:

- The reviewer used the SAS code CALCKE to verify the study results. CALCKE was used because the individual elimination phases are highly variable.
- The firm did not estimate raloxifene Kel constants for subjects 2 (reference), 11 (test, the sample concentrations were below the limit of quantitation at every time point), 16 (test), and 23 (reference). The reviewer agrees that raloxifene Kel constants could not be estimated for these subjects, as well as for subjects 1 (reference), 12 (reference), 17 (reference), 22 (reference), 25 (test), 26 (test), and 27 (test and reference).
- The firm will be requested to explain why subject 11 had no measurable raloxifene concentrations at each time point after receiving the test product. Subject 11 had measurable raloxifene and glucuronide metabolite concentrations after receiving the reference product, and measurable glucuronide metabolite concentrations after receiving the test product.
- The RLD label indicates “the time to reach average maximum plasma concentration and bioavailability are functions of systemic interconversion and enterohepatic cycling of raloxifene and its glucuronide metabolites,” which possibly explains the wide range of Tmax values observed (test: 005 – 120.00 hours; reference: 1.00 – 24.00 hours).
- The raloxifene-4'-glucuronide Kel constants for subjects 5 (test), 11 (test), 17 (reference), 24 (test and reference), and 31 (test) could not be estimated. Also, the firm did not estimate raloxifene-6-glucuronide Kel constants for subject 5 (test). The reviewer agrees that raloxifene-6-glucuronide Kel constants could not be estimated for this subject, as well as for subjects 11 (test) and 17 (reference).
- Subjects 3 (reference), 8 (test), 13 (reference), and 30 (test) had raloxifene AUC0-t/AUC ∞ ratios < 0.80. The reviewer observed that the semi-log concentration vs. time plots for these subjects cover the absorption and elimination phases.
- Although the 90% C.I. values for the least squares geometric means of raloxifene AUC0-t, AUC ∞ and Cmax meet the criteria for bioequivalence, the 90% C.I. values for the least squares geometric means of raloxifene Cmax failed to meet the criteria using the original analytically valid assay results.
- The pharmacokinetic and statistical analysis is **incomplete**.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The in vivo fasting bioequivalence study is **incomplete** due to bioanalytical and pharmacokinetic/statistical deficiencies.

Table 19. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Raloxifene					
Time (hr)	Test (n=32)		Reference (n=32)		T/R Ratio
	Mean (pg/mL)	% CV	Mean (pg/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.50	94.12	98.75	94.12	59.20	1.00
1.00	98.24	64.83	118.64	42.66	0.83
2.00	108.99	52.83	114.56	36.29	0.95
3.00	119.54	55.13	129.28	41.73	0.92
4.00	142.25	88.23	158.90	53.80	0.90
5.00	267.44	68.06	334.79	52.44	0.80
6.00	219.88	67.50	268.05	51.33	0.82
7.00	206.47	59.33	250.60	48.78	0.82
8.00	221.56	51.51	248.48	52.19	0.89
9.00	266.63	43.62	310.10	44.11	0.86
10.00	284.04	45.71	335.48	47.13	0.85
12.00	298.65	46.87	328.91	48.08	0.91
16.00	277.47	52.02	283.69	46.39	0.98
20.00	280.76	55.72	285.30	54.21	0.98
24.00	298.18	52.34	296.69	51.11	1.01
48.00	114.25	62.46	113.93	68.06	1.00
72.00	32.72	121.27	41.27	123.91	0.79
96.00	2.57	397.45	8.54	267.15	0.30
120.00	1.35	565.69	1.14	556.78	1.19

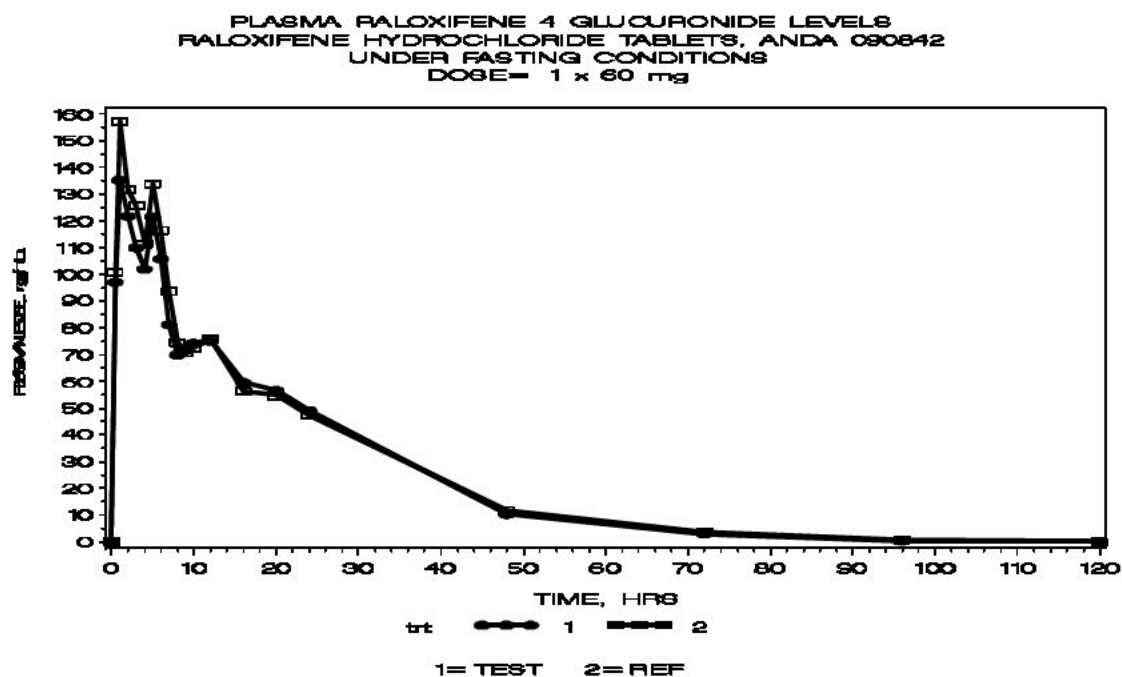
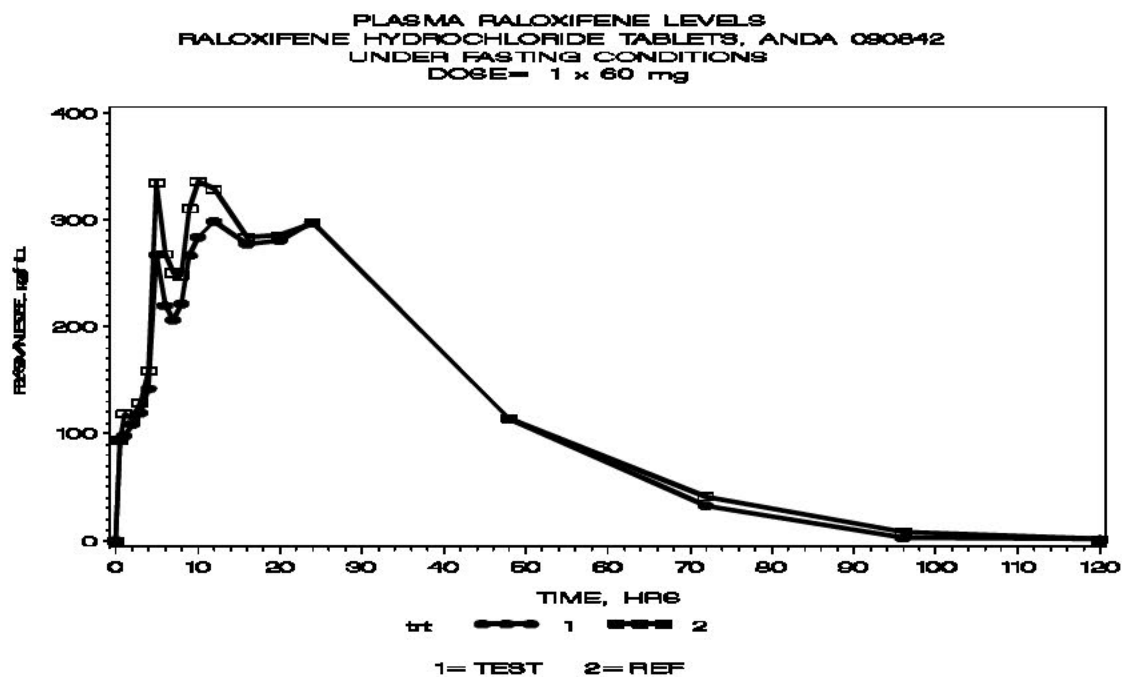
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Raloxifene-4'-Glucuronide					
Time (hr)	Test (n=32)		Reference (n=32)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.50	97.14	62.94	101.01	64.11	0.96
1.00	135.26	43.04	157.08	35.14	0.86
2.00	121.83	40.44	131.73	42.40	0.92
3.00	109.98	44.38	125.76	43.47	0.87
4.00	102.04	53.32	111.40	44.43	0.92
5.00	121.58	47.23	133.92	48.36	0.91
6.00	105.81	44.95	116.43	46.03	0.91
7.00	81.24	42.44	93.76	44.95	0.87
8.00	69.94	39.60	74.53	44.88	0.94
9.00	71.65	43.98	70.80	41.13	1.01
10.00	74.39	43.84	72.61	41.30	1.02
12.00	75.11	41.96	75.94	46.37	0.99
16.00	59.63	37.69	56.38	52.05	1.06
20.00	56.64	43.18	54.76	48.09	1.03
24.00	49.21	65.41	47.32	79.63	1.04
48.00	10.31	99.01	11.65	108.88	0.88
72.00	2.89	143.32	3.60	132.57	0.80
96.00	0.43	187.10	0.83	187.15	0.53
120.00	0.10	405.82	0.04	556.78	2.28

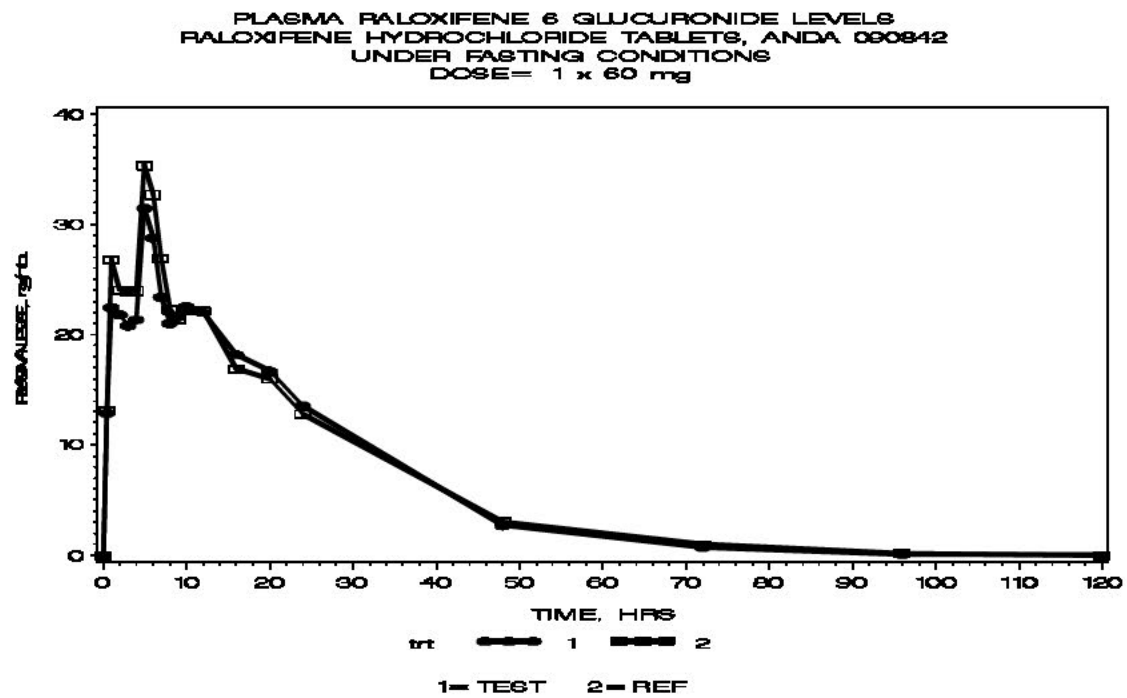
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Raloxifene-6-Glucuronide					
Time (hr)	Test (n=32)		Reference (n=32)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.50	12.88	79.05	13.15	69.16	0.98
1.00	22.47	52.00	26.81	40.09	0.84
2.00	21.79	43.65	24.09	41.48	0.90
3.00	20.81	44.33	23.81	41.52	0.87
4.00	21.35	54.63	23.99	48.50	0.89
5.00	31.45	50.79	35.34	46.55	0.89
6.00	28.75	43.05	32.69	39.10	0.88
7.00	23.40	41.54	26.90	39.17	0.87
8.00	21.01	41.33	22.24	40.49	0.94
9.00	21.65	42.40	21.40	35.13	1.01
10.00	22.57	41.96	22.27	38.37	1.01
12.00	21.99	39.56	22.18	40.32	0.99
16.00	18.18	41.78	16.87	46.92	1.08
20.00	16.69	47.35	15.97	51.90	1.04
24.00	13.55	61.49	12.81	76.60	1.06
48.00	2.69	94.92	3.02	108.19	0.89
72.00	0.72	142.79	0.97	136.69	0.74
96.00	0.09	214.81	0.20	200.75	0.44
120.00	0.02	565.69	0.00	.	.

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



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4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 20. Study Information

Study Number	BA0818123
Study Title	An Open Label, Balanced, Randomized, Two Treatment, Two Sequence, Two Period, Crossover, Single Dose, Comparative Oral Bioavailability Study of Raloxifene Hydrochloride Tablets 60mg and 'EVISTA' (Raloxifene Hydrochloride) Tablets 60mg in Healthy Adult Human Subjects Under Non-Fasting Conditions
Clinical Site (Name & Address)	BA Research India Ltd Opposite Pushparaj Towers, Nr. Judges Bungalows, Bodakdev, Ahmedabad-380054, Gujarat, India
Principal Investigator	Dr. Pruthvi Puwar and Dr. Ronak Modi
Dosing Dates	Period I: August 8, 2008 Period II: August 22, 2008
Analytical Site (Name & Address)	(b) (4) Ph.D., (b) (4)
Analysis Dates	2 Sep 2008 thru 15 Sep 2008
Analytical Director	(b) (4) Ph.D.,
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	August 8, 2008 to September 15, 2008 (38 days)

Table 21. Product Information

Product	Test	Reference
Treatment ID*	A	B
Product Name	Raloxifene Hydrochloride Tablets, 60 mg	EVISTA (Raloxifene Hydrochloride Tablets, 60 mg)
Manufacturer	Invagen Pharmaceuticals Inc.,	Eli Lilly & Company
Batch No.	ID080510	A489455
Manufacture Date	05/28/2008	N/A
Expiration Date	N/A	02/2010
Strength	60 mg	60 mg
Dosage Form	Tablet	Tablet
Bio-batch Size	(b) (4)	N/A
Production Batch Size	(b) (4)	N/A
Potency	98.0 %	98.7 %
Content Uniformity (mean, %CV)	99.9 % , 1.8%	100.4 % , 2.8 %
Dose Administered	60 mg	60 mg
Route of Administration	Oral	Oral

Table 22. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	Planned: 42 Enrolled: 46 Completed: 41 Analyzed: 41
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme	AB: 1, 4, 6, 7, 9, 12, 14, 16, 17, 19, 21, 23, 26, 27, 29, 32 BA: 2, 3, 5, 8, 10, 11, 13, 15, 18, 20, 22, 24, 25, 28, 30, 31
Blood Sampling Times	Pre-dose, 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 12.0, 16.0, 20.0, 24.0, 48.0, 72.0, 96.0 and 120.0 hours (20 time points)
Blood Volume Collected/Sample	5 mL
Blood Sample Processing/Storage	Blood samples were collected in labeled K ₃ EDTA-vacutainers/vacuettes through an indwelling cannula placed in the forearm vein of the subjects. The sample were placed in a refrigerated centrifuge, and then spun at 3000 ± 100 rpm at 4°C for 15 minutes. The plasma was separated, transferred to labeled RIA vials in duplicate and stored in the freezer set at -70 ± 20°C at clinical site (BA Research India Ltd., Vadodara) until shipment. The samples were stored at analytical site (b) (4) until analysis.
IRB Approval	Approved August 6, 2008
Informed Consent	Yes
Length of Fasting Before Meal	At least 10 hours
Length of Confinement	At least 11 hours prior to dosing until 24 hours post does.
Safety Monitoring	During screening safety parameters assessed were vital signs, physical examination, complete medical history, and clinical laboratory safety tests at baseline. Sitting blood pressure and radial pulse were recorded at the time of clinical examination, prior to dosing, and at 2, 6, 10 hours ± 40 minutes post dose. Subjects were asked for well being at the time of clinical examination, during vital signs recordings and during ambulatory samples. Safety was also evaluated by collection of adverse events however there were no adverse events reported during the study.
Was Standard FDA Meal Used?	Yes

Comments on Study Design:

- The firm used a high-fat (59.6% of total caloric content of the meal) and high-calorie (945.28 calories) meal in the fed BE study. The meal consisted of approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively, per the Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies (December 2002).

Composition of Meal Used in Fed Bioequivalence Study		
Composition	Percent of total Kcal	Kcal
Fat	59.60	0.5634
Carbohydrate	26.39	0.2495
Protein	14.01	0.1324
Total		0.9453

Item	Nos	Ingredients	Amount(gm)	Energy(Kcal)	CHO(gm)	Protein(gm)	Fat(gm)
Milk	1 Glass	Milk	200	232	10	8.4	17.6
		Sugar	5	20	5	0	0
Toast	1 No.	Bread	20	66	14.3	1.6	0.3
		Butter	5	35			3.8
Chana Chaat	1 Bowl	Desi Chana	20	66.6	11.3	5.3	0.3
		Onion	5	2.5	0.42	0.15	0.02
		Peanuts	10	66	2	2	5.6
		Oil	5	45	0	0	5
Vegetable Cutlet	2 Nos	Potatoes	75	78.75	18	1.5	0
		Onion	5	2.5	0.42	0.15	0.02
		Oil	15	135	0	0	15
		Paneer	75	194.7	0.93	14	15
TOTAL				944.05	62.37	33.1	62.64
Calories					249.48	132.4	563.4

- The firm used K₃EDTA as the anticoagulant, which is the same anticoagulant used in the method validation.
- The study design is **acceptable**.

4.1.2.2 Clinical Results

Table 23. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. BA0818123-01			
		Treatment Groups	
		Test Product N = 41	Reference Product N =41
Age (years)	Mean ± SD	29± 6	29± 6
	Range	18-41	18-41
Age Groups	< 18	-	-
	18 – 45	41 (100%)	41 (100%)

	> 45	-	-
Sex	Male	41 (100%)	41 (100%)
	Female	-	-
Race	Asian	41 (100%)	41 (100%)
	Black	-	-
	Caucasian	-	-
	Hispanic	-	-
	Other	-	-
BMI (Kg/m ²)	Mean ± SD	21.57 (± 2.39)	21.57 (± 2.39)
	Range	18.67 – 24.89	18.67 – 24.89
Tobacco users	Yes	6 (14.63%)	6 (14.63%)
	No	35 (85.37%)	35 (85.37%)

Table 24. Dropout Information, Fed Bioequivalence Study

Study No. BA0818123-01				
Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with
26 (b) (6)	Subject was discontinued from the study (on 08/26/08), as he did not report to facility for three consecutive ambulatory samples.	Period II	No	NA

Table 25. Study Adverse Events, Fed Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fed Bioequivalence Study Study No. BA0818123-01	
	Test N ¹ (% ²)	Reference N ¹ (% ²)
Body as a whole		
Fever	1(2.38%)	-
Headache	-	1(2.38%)
Number of subjects dosed with study drug	42	42

¹ The number of subjects that reported adverse event (AE).

² % (rate of occurrence) = N divided by number of subjects dosed with respective study drug.

Table 26. Protocol Deviations, Fed Bioequivalence Study

Study No. BA0818123-01		
Type	Subject #s (Test)	Subject #s (Ref.)
+39 minutes sampling deviation at 96.0 hours during period I, as the subject arrived late to the clinical facility.	NA	03
+36 minutes sampling deviation at 96.0 hours during period I, as the subject arrived late to the clinical facility.	NA	05
+30 minutes sampling deviation at 120.0 hours during	NA	05

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period I, as the subject arrived late to the clinical facility.		
As per protocol section # 1.13 and 9.2, subjects will be asked for well-being during ambulatory samples. In period I, well-being questionnaire was not done at 72.0 hours ambulatory sample.	NA	10
+23 minutes sampling deviation at 96.0 hours during period I, as the subject arrived late to the clinical facility.	NA	13
+23 minutes sampling deviation at 96.0 hours during period I, as the subject arrived late to the clinical facility.	14	NA
No sample at 96.0 hours during period I, as the subject did not report to the clinical facility.	NA	20
No sample at 120.0 hours during period I, as the subject did not report to the clinical facility.	NA	20
+11 minutes sampling deviation at 48.0 hours during period I, as the subject arrived late to the clinical facility.	23	NA
+37 minutes sampling deviation at 96.0 hours during period I, as the subject arrived late to the clinical facility.	NA	25
+35 minutes sampling deviation at 96.0 hours during period I, as the subject arrived late to the clinical facility.	27	NA
+15 minutes sampling deviation at 120.0 hours during period I, as the subject arrived late to the clinical facility.	27	NA
+24 minutes sampling deviation at 96.0 hours during period I, as the subject arrived late to the clinical facility.	34	NA
+10 minutes sampling deviation at 120.0 hours during period I, as the subject arrived late to the clinical facility.	NA	35
+19 minutes sampling deviation at 96.0 hours during period I, as the subject arrived late to the clinical facility.	38	NA
+58 minutes sampling deviation at 48.0 hours during period I, as the subject arrived late to the clinical facility.	39	NA
+14 minutes sampling deviation at 72.0 hours during period I, as the subject arrived late to the clinical facility.	39	NA
+62 minutes sampling deviation at 96.0 hours during period I, as the subject arrived late to the clinical facility.	39	NA
No sample at 120.0 hours during period I, as subject did not report to clinical facility.	39	NA
+37 minutes sampling deviation at 96.0 hours during	41	NA

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period I, as the subject arrived late to the clinical facility.		
+05 minutes sampling deviation at 72.0 hours during period II, as the subject arrived late to the clinical facility.	NA	06
No sample at 120.0 hours during period II, as subject did not report to clinical facility.	10	NA
+141 minutes sampling deviation at 72.0 hours during period II, as the subject arrived late to the clinical facility.	NA	16
+53 minutes sampling deviation at 72.0 hours during period II, as the subject arrived late to the clinical facility.	20	NA
+08 minutes sampling deviation at 96.0 hours during period II, as the subject arrived late to the clinical facility.	NA	23
+18 minutes sampling deviation at 120.0 hours during period II, as the subject arrived late to the clinical facility.	NA	27
No sample at 48.0 hours during period II, as subject did not report to clinical facility.	37	NA
+06 minutes sampling deviation at 48.0 hours during period II, as the subject arrived late to the clinical facility.	NA	38
+27 minutes sampling deviation at 48.0 hours during period II, as the subject arrived late to the clinical facility.	NA	39
No sample at 72.0 hours during period II, as subject did not report to clinical facility.	NA	39
+51 minutes sampling deviation at 96.0 hours during period II, as the subject arrived late to the clinical facility.	NA	39

Comments on Dropouts/Adverse Events/Protocol Deviations:

- Subject 13 experienced a mild headache in period II (test treatment) that was possibly related to the treatment drug. Subject 26 experienced a mild fever in period II (reference treatment) that was possibly related to the treatment drug. The adverse events (AE) were resolved with treatment. The firm will be requested to indicate what treatments were used to resolve these AEs
- All the reported protocol deviations were time deviations and missing samples. The firm considered deviations beyond ± 2 minutes of the scheduled time as sampling time deviations. Since the time deviations occurred for sampling times in the terminal elimination phase, the reviewer will use the scheduled time points in the pharmacokinetic and statistical analysis. These time deviations are not expected to affect the study outcome.
- The clinical results are **incomplete**.

4.1.2.3 Bioanalytical Results

Table 27. Assay Validation – Within the Fed Bioequivalence Study

Bioequivalence Study No. BA0818123-01 Analyte Name: Raloxifene								
Parameter	Standard Curve Samples							
Concentration (pg/mL)	31.991	63.982	127.963	319.908	799.770	1599.541	3199.081	6398.162
Inter day Precision (%CV)	2	4	4	4	2	3	3	2
Inter day Accuracy (%Actual)	100	100	100	101	100	100	100	100
Linearity	Range of r values: 0.9977- 0.9999							
Linearity Range (pg /mL)	31.991-6398.162 pg/ml							
Sensitivity/LOQ (pg /mL)	31.991 pg/mL							

Bioequivalence Study No. BA0818123-01 Analyte Name: Raloxifene			
Parameter	Quality Control Samples		
Concentration (pg/mL)	92.134	2559.265	5118.530
Inter day Precision (%CV)	6	4	5
Inter day Accuracy (%Actual)	97	97	97

Bioequivalence Study No. BA0818123-01 Analyte Name: Raloxifene-4'-Glucuronide								
Parameter	Standard Curve Samples							
Concentration (ng/mL)	1.004	2.008	4.017	10.042	25.106	50.212	100.425	200.849
Inter day Precision (%CV)	2	3	4	4	3	3	2	2
Inter day Accuracy (%Actual)	100	99	102	100	100	100	98	102
Linearity	Range of r values: 0.9975- 0.9999							
Linearity Range (ng /mL)	1.004-200.849 ng/ml							
Sensitivity/LOQ (ng /mL)	1.004 ng/mL							

Bioequivalence Study No. BA0818123-01 Analyte Name: Raloxifene-4'-Glucuronide			
Parameter	Quality Control Samples		
Concentration (ng/mL)	2.892	80.340	160.679
Inter day Precision (%CV)	6	6	6
Inter day Accuracy (%Actual)	98	98	100

Bioequivalence Study No. BA0818123-01 Analyte Name: Raloxifene-6-Glucuronide								
Parameter	Standard Curve Samples							
Concentration (ng/mL)	0.407	0.814	1.628	4.070	10.175	20.350	40.700	81.400
Inter day Precision (%CV)	2	3	4	6	3	4	3	1
Inter day Accuracy (%Actual)	100	101	100	98	100	100	100	100
Linearity	Range of r values: 0.9957- 0.9999							
Linearity Range (ng /mL)	0.407-81.400 ng/ml							
Sensitivity/LOQ (ng /mL)	0.407 ng/mL							

Bioequivalence Study No. BA0818123-01 Analyte Name: Raloxifene-6-Glucuronide			
Parameter	Quality Control Samples		
Concentration (ng/mL)	1.172	32.560	65.120
Inter day Precision (%CV)	6	5	6
Inter day Accuracy (%Actual)	98	101	101

Comments on Study Assay Validation:

- The calibration curve standards and quality control samples were prepared on August 14, 2008, and stored at -80°C.
- The firm used human plasma with K₃EDTA as the anticoagulant in the preparation of the CC standards and the QC samples. K₃EDTA was also used as the anticoagulant in the sample collection.
- The firm reported the results of the incurred samples re-analysis (ISR) from fasting study no. BA0818122-01 in the analytical report for fed study no. BA0818123-01, where at least 2/3 of the sample concentrations were within $\pm$ 20% of the original value.
- The study assay validation is acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	No
Were chromatograms serially or randomly selected?	Serially from subjects 1-6

Comments on Chromatograms:

- The firm did not submit chromatograms from at least 20% of the total number of subjects that completed the study (i.e. 41 subjects).
- The chromatograms are incomplete.

Table 28. SOPs Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4)	(b) (4)	Criteria for Sample Reanalysis and Reporting

Table 29. Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays:

- The bioanalytical results are **incomplete** because the firm did not submit chromatograms from at least 20% of the total number of subjects that completed the study.

4.1.2.4 Pharmacokinetic Results

Table 30. Arithmetic Mean Pharmacokinetic Parameters- Reviewer Calculated

Mean plasma concentrations are presented in [Table 33](#) and [Figure 2](#).

Raloxifene Hydrochloride Tablets Dose (1 x 60 mg) Fed Study No. BA0818123-01									
Raloxifene									
	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC _{0-t} (hr *pg/ml)	18061.42	77.70	4171.82	75070.20	18307.74	62.06	4010.78	50840.13	0.99
AUC _∞ (hr *pg/ml)	21163.36	68.79	7165.35	76683.88	21867.31	51.85	5066.10	52216.06	0.97
C _{max} (pg/ml)	561.048	57.93	232.00	1641.17	554.854	51.41	178.37	1580.62	1.01
T _{max} * (hr)	9.000	.	1.00	24.00	10.000	.	1.00	24.00	0.90
Kel (hr ⁻¹)	0.046	20.34	0.02	0.06	0.045	21.43	0.02	0.06	1.02
T _{1/2} (hr)	15.728	24.11	10.85	29.47	16.044	24.11	10.70	28.97	0.98

Raloxifene-4'-Glucuronide									
	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC _{0-t} (hr *ng/ml)	3410.191	51.20	1234.20	9443.90	3410.601	50.77	1284.75	8625.81	1.00
AUC _∞ (hr *ng/ml)	3454.816	50.60	1246.26	9468.77	3450.483	50.36	1323.16	8689.55	1.00
C _{max} (ng/ml)	327.617	46.65	145.55	737.90	321.554	48.11	151.49	768.89	1.02
T _{max} * (hr)	2.000	.	1.00	6.00	2.000	.	1.00	5.00	1.00
K _{el} (hr ⁻¹)	0.093	53.83	0.02	0.24	0.093	51.23	0.04	0.26	1.00
T _{1/2} (hr)	9.942	65.91	2.92	40.87	8.994	42.43	2.63	18.79	1.11
Raloxifene-6-Glucuronide									
	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC _{0-t} (hr *ng/ml)	615.950	60.05	214.90	1931.70	623.782	57.80	159.35	1943.12	0.99
AUC _∞ (hr *ng/ml)	640.145	58.48	224.01	1969.08	648.206	55.95	166.06	1956.60	0.99
C _{max} (ng/ml)	41.238	43.35	17.58	89.36	40.474	43.00	19.73	87.31	1.02
T _{max} * (hr)	3.000	.	1.00	12.00	3.000	.	1.00	12.00	1.00
K _{el} (hr ⁻¹)	0.098	58.99	0.02	0.26	0.095	53.38	0.03	0.29	1.03
T _{1/2} (hr)	9.492	58.09	2.68	27.79	8.906	45.41	2.42	20.66	1.07

*T_{max} values are presented as median, range.

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

Raloxifene Hydrochloride Tablets				
1x60 mg				
Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study (BA0818123-01)				
Parameter	Test	Reference	Ratio	90%CI
AUC _t	14512.346	14938.412	97.15%	(86.01%; 109.73%)
AUC _i	16591.929	16905.619	98.14%	(87.96%; 109.51%)
C _{max}	491.736	493.522	99.64%	(91.02%; 109.08%)

Table 32. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Raloxifene Hydrochloride Tablets Dose (1 x 60 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Study No. BA0818123-01 Raloxifene (N=41)					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (pg *hr/mL)	14505.38	15007.53	0.97	85.53	109.23
AUC _∞ (pg *hr/mL)	17152.70	18229.64	0.94	83.46	106.08
C _{max} (pg/mL)	491.74	493.52	1.00	91.02	109.08
Fed Study No. BA0818123-01 Raloxifene-4'-Glucuronide (N=41)					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (ng *hr/mL)	3044.00	3035.41	1.00	90.91	110.62
AUC _∞ (ng *hr/mL)	3092.31	3077.77	1.00	91.22	110.67
C _{max} (ng/mL)	298.58	291.42	1.02	94.46	111.14
Fed Study No. BA0818123-01 Raloxifene-6-Glucuronide (N=41)					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (ng *hr/mL)	534.88	540.97	0.99	88.68	110.24
AUC _∞ (ng *hr/mL)	558.87	560.85	1.00	89.46	110.99
C _{max} (ng/mL)	38.09	37.23	1.02	95.27	109.86

Note: the pharmacokinetic parameters were calculated by the reviewer using the SAS code "CALCKE" to verify the study.

Table 33. Additional Study Information, Fed Study No. BA0818123-01

Root mean square error, AUC _{0-t}	Raloxifene: 0.3286 R4G: 0.2637 R6G: 0.2922	
Root mean square error, AUC _∞	Raloxifene: 0.2804 R4G: 0.2597 R6G: 0.2860	
Root mean square error, C _{max}	Raloxifene: 0.2432 R4G: 0.2185 R6G: 0.1913	
	Test	Reference
Kel and AUC _∞ determined for how many subjects?	Raloxifene: 41	Raloxifene: 40

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	R4G: 41 R6G: 41	R4G: 41 R6G: 41
Do you agree or disagree with firm's decision?	Raloxifene: Disagree. The elimination rate constants could only be estimated for 35 subjects. R4G: Agree R6G: Agree	Raloxifene: Disagree. The elimination rate constants could only be estimated for 35 subjects. R4G: Agree R6G: Disagree. The elimination rate constants could only be estimated for 40 subjects.
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	Raloxifene: 0 R4G: 0 R6G: 0	Raloxifene: 0 R4G: 0 R6G: 0
first measurable drug concentration as C_{max}	Raloxifene: 0 R4G: 0 R6G: 0	Raloxifene: 0 R4G: 2 R6G: 1
Were the subjects dosed as more than one group?	No	

Ratio of AUC _{0-t} /AUC _∞ Raloxifene				
Treatment	n	Mean	Minimum	Maximum
Test	35	0.92	0.84	0.98
Reference	35	0.92	0.83	0.98
Ratio of AUC _{0-t} /AUC _∞ Raloxifene-4'-Glucuronide				
Treatment	n	Mean	Minimum	Maximum
Test	41	0.98	0.95	1.00
Reference	41	0.99	0.96	1.00
Ratio of AUC _{0-t} /AUC _∞ Raloxifene-6-Glucuronide				
Treatment	n	Mean	Minimum	Maximum
Test	41	0.96	0.81	1.00
Reference	40	0.97	0.89	0.99

Comments on Pharmacokinetic and Statistical Analysis:

- The reviewer used the SAS code CALCKE to verify the study results. CALCKE was used because the individual elimination phases are highly variable.
- The firm did not estimate raloxifene Kel constants for subject 40 (reference). The reviewer agrees that raloxifene Kel constants could not be estimated for this subject, as well as for subjects 9 (test), 11 (test and reference), 12 (test and reference), 14 (reference), 23 (test and reference), 24 (test), 29 (test), and 38 (reference).
- The RLD label indicates “the time to reach average maximum plasma concentration and bioavailability are functions of systemic interconversion and enterohepatic cycling of raloxifene and its glucuronide metabolites,” which possibly explains the wide range of Tmax values observed (test: 0.05 – 120.00 hours; reference: 1.00 – 24.00 hours).
- The 90% C.I. values for the least squares geometric means of raloxifene AUC0-t, AUC ∞ and Cmax meet the criteria for bioequivalence.
- The pharmacokinetic and statistical analysis is **acceptable**.

Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

The in vivo fed bioequivalence study is **incomplete** due to clinical and bioanalytical deficiencies.

Table 34. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Raloxifene					
Time (hr)	Test (n=41)		Reference (n=41)		T/R Ratio
	Mean (pg/mL)	% CV	Mean (pg/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.50	27.81	175.35	33.76	254.60	0.82
1.00	115.72	105.42	133.15	126.97	0.87
2.00	230.82	48.30	229.80	58.52	1.00
3.00	255.06	37.25	248.37	51.16	1.03
4.00	268.07	45.05	249.38	44.20	1.07
5.00	335.03	59.35	303.83	48.56	1.10
6.00	334.72	64.35	302.81	46.61	1.11
7.00	369.04	59.59	340.44	46.18	1.08
8.00	419.46	60.94	383.87	46.61	1.09
9.00	459.38	57.82	441.43	47.62	1.04
10.00	477.45	57.15	455.57	49.22	1.05
12.00	489.87	65.48	462.44	48.23	1.06
16.00	414.47	59.71	433.85	63.41	0.96
20.00	402.03	63.47	427.78	53.55	0.94
24.00	402.56	68.17	434.55	58.52	0.93
48.00	147.68	114.88	148.99	74.66	0.99
72.00	44.64	161.77	42.17	129.42	1.06
96.00	10.35	293.50	9.37	266.34	1.10
120.00	1.56	624.50	2.32	443.40	0.67

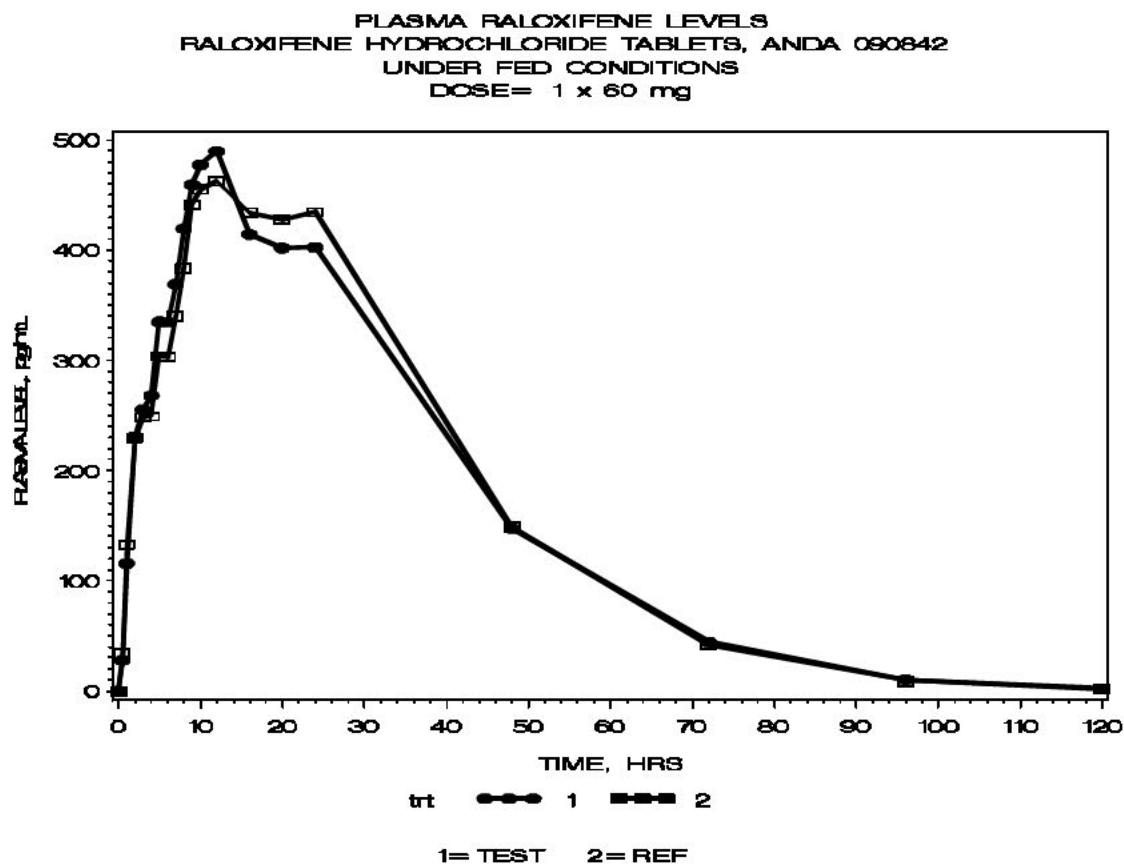
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Raloxifene-4'-Glucuronide					
Time (hr)	Test (n=41)		Reference (n=41)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.50	31.86	158.04	33.80	244.53	0.94
1.00	128.43	90.77	132.24	119.77	0.97
2.00	264.56	52.09	251.44	62.13	1.05
3.00	268.66	53.50	234.41	50.27	1.15
4.00	229.27	60.86	200.19	45.69	1.15
5.00	177.37	57.20	174.34	57.90	1.02
6.00	128.79	56.59	124.73	57.40	1.03
7.00	113.94	58.98	106.47	46.18	1.07
8.00	105.27	54.28	103.16	49.50	1.02
9.00	111.65	52.56	105.42	48.74	1.06
10.00	109.70	50.20	102.74	44.04	1.07
12.00	100.65	58.88	96.08	44.84	1.05
16.00	69.90	52.53	72.29	58.34	0.97
20.00	65.49	58.98	66.23	58.06	0.99
24.00	45.35	80.33	51.61	80.90	0.88
48.00	9.15	146.65	9.71	130.69	0.94
72.00	2.56	236.43	2.67	230.42	0.96
96.00	0.42	259.56	0.54	282.26	0.78
120.00	0.07	446.35	0.22	404.58	0.30

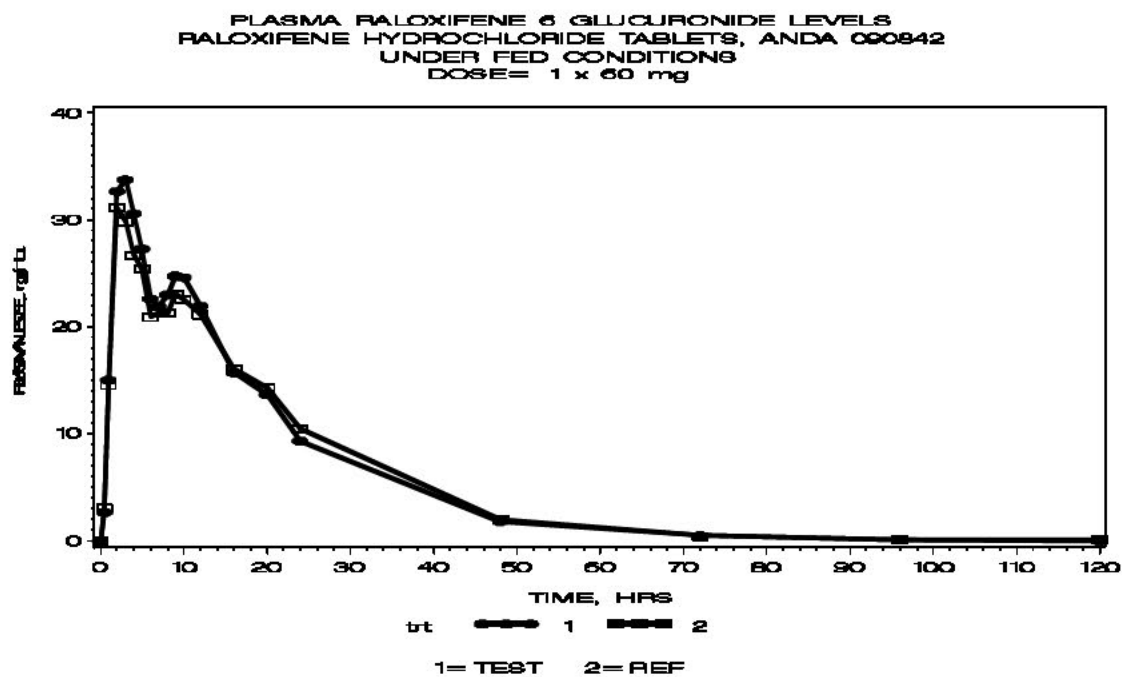
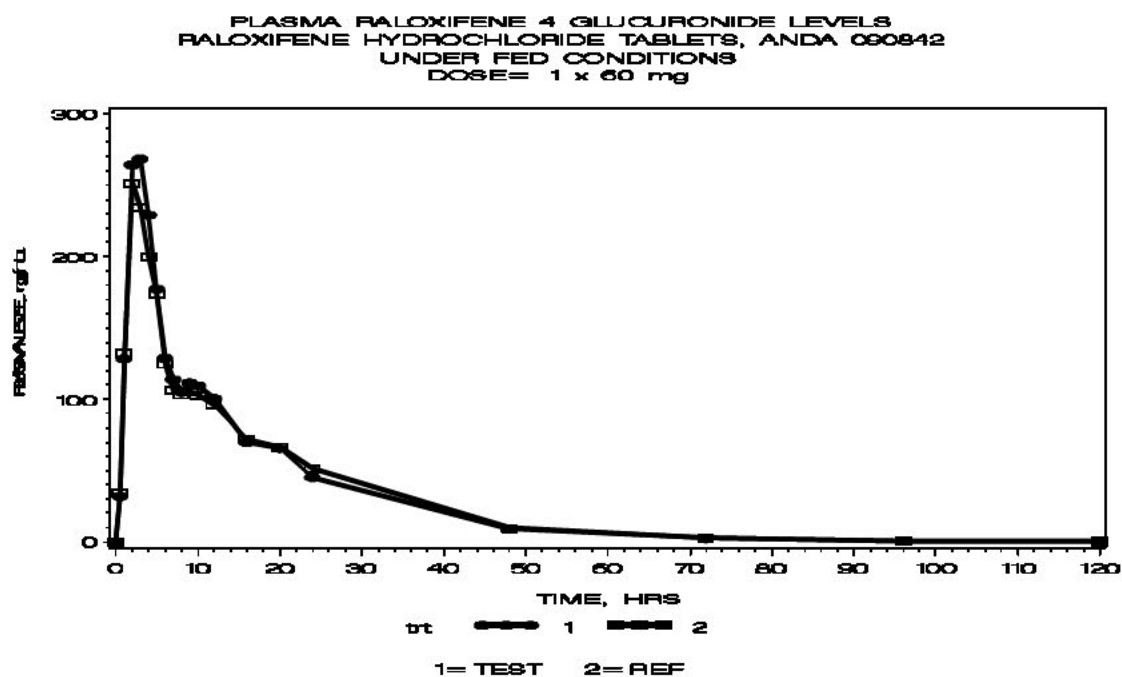
ANDA 090842
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Raloxifene-6-Glucuronide					
Time (hr)	Test (n=41)		Reference (n=41)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.50	2.65	163.62	3.04	264.50	0.87
1.00	15.01	109.37	14.54	120.61	1.03
2.00	32.66	54.58	31.16	57.66	1.05
3.00	33.76	46.85	29.82	44.99	1.13
4.00	30.58	59.32	26.74	46.47	1.14
5.00	27.28	56.68	25.41	59.53	1.07
6.00	22.60	63.52	20.91	70.48	1.08
7.00	21.88	62.34	21.27	59.33	1.03
8.00	22.98	60.05	21.31	58.16	1.08
9.00	24.75	55.76	23.05	54.02	1.07
10.00	24.62	50.88	22.56	53.41	1.09
12.00	21.95	56.09	21.13	50.91	1.04
16.00	15.70	50.54	16.12	57.51	0.97
20.00	13.65	54.43	14.30	61.10	0.95
24.00	9.33	81.34	10.45	79.57	0.89
48.00	1.80	182.80	1.98	139.09	0.91
72.00	0.49	272.39	0.44	264.64	1.12
96.00	0.06	453.26	0.10	371.54	0.57
120.00	0.00	.	0.05	365.62	0.00

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



ANDA 090842
Single-Dose Fed Bioequivalence Study Review



4.2 Formulation Data

Ingredient	Amount (mg) / Tablet	Amount (%) / Tablet
	60 mg	60 mg
Raloxifene Hydrochloride	60.00	(b) (4)
Mannitol, USP (b) (4)	(b) (4)	(b) (4)
Crospovidone, NF (b) (4)		(b) (4)
Hydroxy propyl Cellulose (b) (4)		(b) (4)
Poloxamer 407, NF (b) (4)		(b) (4)
(b) (4)		(b) (4)
(b) (4)		(b) (4)
(b) (4)		(b) (4)
Magnesium stearate, NF (b) (4)		(b) (4)
Opadry White (b) (4)		(b) (4)
(b) (4)		(b) (4)
TOTAL (b) (4)	288.0	N/A
(b) (4)		

(b) (4)

Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	• The inactive ingredient amounts are all within IIG levels based on the maximum daily dose (MDD) of 60 mg Raloxifene Hydrochloride per day. See Figure 3 (Formulation Calculation Worksheet). • The formulation is acceptable.

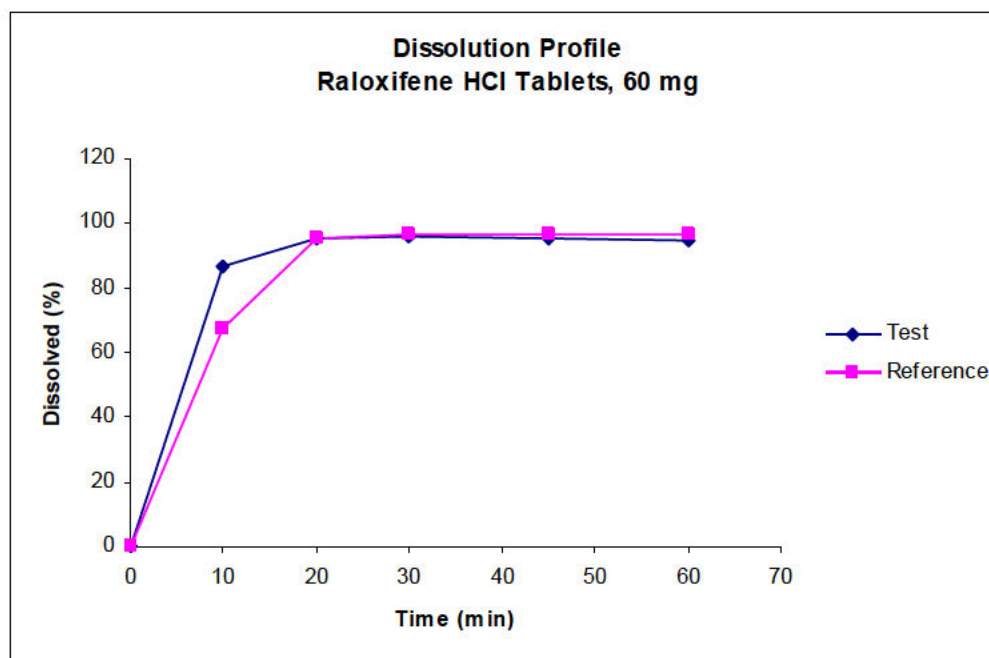
4.3 Dissolution Data

Dissolution Review Path	DARRTS: ANDA 090842, LEE, CHRISTINA H, Submit/Final Date: 01/09/2009, REV-BIOEQ-02 (Dissolution Review)
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Table 35. Dissolution Data

Dissolution Conditions		Apparatus:		USP Apparatus (II) Paddle							
		Speed of Rotation:		50 rpm							
		Medium:		0.1% Polysorbate 80 in water							
		Volume:		1000 ml							
		Temperature:		37.0 ± 0.5°C							
Firm's Proposed Specifications		NLT 80% (Q) in 30 minutes									
Dissolution Testing Site (Name, Address)		InvaGen Pharmaceuticals, Inc., Hauppauge, NY 11788									
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)					Study Report Location
						10 Min	20 Min	30 Min	45 Min	60 Min	
Study Report #: N/A	06/03/08	Test Product Raloxifene Hydrochloride Tablets, 60 mg Batch # ID080510 Mfg. Date: 05/28/2008	60 mg Tablet	12	Mean	86.4	95.2	96.0	95.4	94.4	N/A
					Range Min : Max:	(b) (4)					N/A
					%CV	4.2	2.1	1.7	1.6	1.7	N/A
Study Report #: N/A	06/03/08	Reference Product Evista® Tablets, 60 mg Batch # A489455 Exp. Date: 02/2010	60 mg Tablet	12	Mean	67.5	95.1	96.2	96.6	96.7	N/A
					Range Min : Max :	(b) (4)					N/A
					%CV	13.9	1.9	2.1	1.4	1.9	N/A

Figure 4. Dissolution Profile



4.4 SAS Output

4.4.1 Fasting (1 x 60 mg) Study Data (of Raloxifene)

FASTING CONCENTRATION DATASET

Obs	sub	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
1	1	2	1	1	B	0	140.633	90.441	122.824	84.281	182.779	558.943	191.863	160.319	159.651	156.874	182.258	156.931	140.245	147.456	170.763
2	1	2	2	1	A	0	105.961	75.237	59.541	44.046	43.574	403.355	155.740	123.045	134.214	166.444	169.982	162.039	130.511	117.250	136.349
3	2	1	1	1	A	0	62.853	138.225	107.356	85.364	68.193	173.437	105.481	129.171	215.689	200.926	181.688	173.971	154.652	157.831	237.836
4	2	1	2	1	B	0	35.137	143.384	136.376	137.294	129.359	120.005	149.446	152.516	158.084	265.761	330.173	316.125	398.416	336.830	428.766
5	3	2	1	1	B	0	140.857	137.410	110.080	95.563	205.251	295.246	207.417	276.533	246.867	270.828	265.569	230.424	182.700	181.090	196.342
6	3	2	2	1	A	0	92.003	115.027	104.929	111.111	89.679	216.904	158.604	133.795	177.161	195.363	208.787	166.875	160.939	147.085	171.958
7	4	1	1	1	A	0	39.225	88.924	99.072	109.678	125.303	166.258	152.098	198.255	229.907	228.950	270.315	226.692	236.339	165.226	179.348
8	4	1	2	1	B	0	0.000	37.785	35.303	97.138	101.410	328.094	185.591	160.697	156.498	174.408	176.196	163.749	133.742	135.742	167.032
9	5	2	1	1	B	0	86.351	81.057	97.419	117.216	134.519	225.480	184.499	172.346	164.743	331.663	341.427	309.562	236.456	233.545	276.991
10	5	2	2	1	A	0	65.236	45.407	64.448	66.970	64.285	129.202	110.031	127.422	100.959	198.757	189.750	181.843	228.325	205.316	276.880
11	6	1	1	1	A	0	140.987	110.769	84.953	101.094	102.651	196.879	155.926	142.399	164.332	206.602	261.885	297.988	279.010	296.407	421.344
12	6	1	2	1	B	0	108.481	57.735	51.432	54.640	86.952	194.443	150.925	147.575	142.025	206.773	294.995	255.009	227.521	242.955	348.513
13	7	1	1	1	A	0	0.000	82.311	90.343	113.361	144.320	450.251	561.850	447.457	498.387	419.601	430.217	380.607	323.063	326.135	213.542
14	7	1	2	1	B	0	116.403	177.670	158.835	193.955	199.768	481.611	558.360	506.112	573.678	437.038	398.004	550.313	301.393	262.692	212.432
15	8	2	1	1	B	0	54.330	59.100	68.026	94.866	105.643	417.549	228.554	180.999	153.772	185.678	263.167	203.763	181.327	205.962	198.772
16	8	2	2	1	A	0	127.386	89.227	93.623	59.316	87.322	464.083	270.137	212.306	264.721	245.984	208.247	205.561	192.534	168.928	176.836
17	9	2	1	1	B	0	46.381	178.196	158.579	158.194	153.379	343.886	209.908	190.284	186.398	246.665	522.628	497.395	399.541	360.896	372.381
18	9	2	2	1	A	0	142.354	117.612	132.104	134.113	133.938	300.591	209.296	210.757	195.273	213.570	274.004	294.769	256.657	240.904	342.599
19	10	1	1	1	A	0	150.808	98.523	195.918	114.644	133.222	448.104	366.202	332.821	262.862	293.468	397.661	450.141	540.897	581.172	555.977
20	10	1	2	1	B	0	145.881	84.341	98.288	78.846	90.660	348.224	243.739	206.077	204.502	411.948	359.260	352.081	392.900	459.945	466.714

Obs	sub	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
21	11	2	1	1	B	0	77.219	144.338	151.839	140.324	238.722	313.171	506.145	508.660	511.949	454.939	434.085	403.287	221.669	184.890	172.756
22	11	2	2	1	A	0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
23	12	1	1	1	A	0	92.634	71.068	87.261	85.677	76.593	82.814	94.236	103.757	133.205	158.979	122.622	139.692	135.650	161.454	137.397
24	12	1	2	1	B	0	0.000	0.000	34.823	60.538	65.146	91.190	132.570	113.153	158.144	253.424	237.452	188.516	116.900	104.491	99.786
25	13	2	1	1	B	0	53.366	98.300	84.495	90.055	90.768	156.994	124.126	134.239	130.933	243.067	286.876	254.287	160.333	178.677	209.130
26	13	2	2	1	A	0	36.426	48.461	60.528	54.203	68.111	132.682	99.252	103.142	104.607	295.986	225.043	227.898	156.810	162.911	268.415
27	14	1	1	1	A	0	44.035	72.352	72.379	112.002	136.426	204.009	176.656	191.035	176.832	167.475	185.387	216.131	191.508	194.239	304.348
28	14	1	2	1	B	0	92.855	87.304	118.134	120.876	125.959	127.841	113.381	118.905	107.512	139.055	169.292	225.151	210.084	186.424	277.627
29	15	2	1	1	B	0	120.802	147.354	145.541	130.471	172.199	267.608	306.708	428.375	377.404	410.731	358.914	359.354	362.337	394.829	385.754
30	15	2	2	1	A	0	84.743	98.473	110.233	133.375	137.526	353.573	338.947	228.491	267.641	381.823	351.718	425.441	398.126	384.545	430.531
31	16	1	1	1	A	0	46.710	92.176	94.119	134.431	134.906	150.037	130.837	138.318	138.662	187.192	210.404	318.071	315.275	274.582	291.671
32	16	1	2	1	B	0	59.399	184.751	126.267	106.323	88.035	177.037	140.016	137.012	174.597	166.562	172.528	176.708	191.956	194.710	198.071
33	17	1	1	1	A	0	37.915	58.179	109.255	87.570	121.341	224.471	187.974	178.300	171.874	256.217	400.313	423.146	431.470	445.501	456.606
34	17	1	2	1	B	0	0.000	172.517	107.136	151.904	154.365	387.664	405.980	271.271	260.733	421.186	473.448	545.271	477.728	534.247	546.631
35	18	2	1	1	B	0	58.846	87.043	106.875	152.221	232.655	876.894	388.221	302.282	300.296	551.334	711.636	727.666	574.556	777.388	721.265
36	18	2	2	1	A	0	161.130	123.411	124.641	139.960	225.025	356.791	231.475	209.712	220.593	402.824	425.081	436.309	407.153	513.798	678.952
37	19	2	1	1	B	0	201.197	189.854	151.166	159.151	265.992	537.956	297.318	335.942	279.824	402.276	462.031	567.606	437.993	496.868	525.253
38	19	2	2	1	A	0	128.841	82.820	96.274	112.442	137.234	343.599	259.767	266.102	272.551	373.302	430.377	499.761	464.576	504.334	485.668
39	20	1	1	1	A	0	36.558	57.358	64.724	75.503	196.421	294.257	196.764	190.497	230.611	263.581	243.361	238.215	232.003	246.697	283.586
40	20	1	2	1	B	0	0.000	69.144	87.712	131.901	182.613	443.627	272.414	244.704	282.680	403.067	321.615	306.114	326.893	309.681	353.721
41	21	2	1	1	B	0	144.439	124.454	146.365	173.481	135.606	372.285	315.823	275.298	264.752	358.742	387.848	400.825	382.301	345.013	367.196
42	21	2	2	1	A	0	103.717	98.571	123.438	142.714	150.292	178.642	210.128	176.400	241.653	464.766	461.905	465.511	343.851	309.092	346.476
43	22	1	1	1	A	0	0.000	57.384	107.612	218.212	198.935	648.605	426.104	361.898	317.630	263.903	271.892	258.772	214.212	209.294	185.961
44	22	1	2	1	B	0	76.657	164.447	119.137	123.096	276.401	309.279	202.777	198.293	176.073	224.966	193.336	187.439	163.924	127.655	118.003
45	23	2	1	1	B	0	108.369	112.043	106.567	134.772	151.389	409.300	307.977	274.425	241.066	234.726	251.581	253.303	235.848	261.937	200.854
46	23	2	2	1	A	0	102.031	92.307	100.271	116.225	106.614	152.746	148.793	127.346	121.771	171.218	196.559	176.061	200.938	221.219	249.044

Obs	sub	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
47	24	1	1	1	A	0	44.300	62.751	95.042	88.151	76.529	112.794	146.110	303.706	362.176	442.071	380.851	456.443	416.181	456.836	341.966
48	24	1	2	1	B	0	129.812	129.364	138.573	149.717	129.504	467.670	312.353	334.659	352.086	360.576	352.744	435.194	348.753	318.946	280.244
49	25	1	1	1	A	0	245.073	244.414	278.987	242.398	265.456	311.901	311.470	287.350	341.644	372.491	387.188	327.735	249.103	208.796	199.760
50	25	1	2	1	B	0	210.005	162.276	206.928	252.156	354.098	321.025	317.571	308.041	280.057	289.131	287.195	288.612	265.853	238.144	256.476
51	26	2	1	1	B	0	103.651	81.957	87.601	99.342	84.137	293.932	239.668	269.398	211.197	187.083	157.628	158.652	157.518	148.907	176.354
52	26	2	2	1	A	0	107.659	97.104	107.225	150.449	121.716	133.593	181.889	206.133	246.814	208.003	212.543	180.865	149.362	155.597	173.484
53	27	2	1	1	B	0	52.078	115.623	96.553	87.774	73.997	92.001	79.545	83.383	71.441	64.831	68.975	85.305	77.199	80.856	82.758
54	27	2	2	1	A	0	0.000	40.995	90.523	113.492	96.883	159.884	104.019	120.180	114.474	109.538	112.903	142.113	126.908	139.836	124.399
55	28	1	1	1	A	0	67.710	155.174	133.984	164.389	207.972	439.318	325.476	291.404	314.959	388.240	398.981	389.144	269.684	320.132	263.477
56	28	1	2	1	B	0	124.344	167.643	127.830	136.464	131.793	289.021	334.758	299.080	238.627	254.067	227.221	237.554	244.408	240.787	203.681
57	29	2	1	1	B	0	164.262	223.147	212.226	314.144	444.817	639.541	466.867	427.906	569.192	692.764	675.524	589.574	523.808	571.506	542.820
58	29	2	2	1	A	0	504.297	362.275	304.555	373.746	759.740	893.694	754.828	662.564	570.775	554.495	655.786	671.098	715.627	746.254	707.721
59	30	1	1	1	A	0	97.401	65.996	88.817	84.723	78.857	99.937	82.040	89.210	122.446	225.639	213.191	264.638	260.123	277.017	270.508
60	30	1	2	1	B	0	86.779	73.629	65.916	60.879	67.747	113.803	106.645	90.320	151.006	211.504	185.737	170.035	167.749	172.930	210.779
61	31	2	1	1	B	0	134.725	94.394	86.119	82.905	103.086	193.257	235.882	198.579	186.144	401.202	637.367	395.882	328.815	280.566	247.603
62	31	2	2	1	A	0	35.418	88.912	77.351	99.215	96.402	156.789	192.778	156.794	186.256	222.709	249.634	317.835	239.878	243.801	261.041
63	32	1	1	1	A	0	108.499	112.292	128.278	156.616	166.467	178.863	191.251	157.125	189.361	251.929	361.020	441.536	457.732	402.180	368.031
64	32	1	2	1	B	0	138.486	119.819	120.954	166.434	126.184	518.806	660.538	511.739	479.340	510.242	548.505	533.520	507.202	413.094	478.467

Obs	c17	c18	c19	c20	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	T20	trt
1	91.409	0.000	0.000	0.000	.	.	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
2	87.345	37.237	0.000	0.000	11	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
3	84.854	0.000	0.000	0.000	.	.	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
4	223.265	70.526	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
5	84.728	0.000	0.000	0.000	9	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
6	97.195	36.049	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1

Obs	c17	c18	c19	c20	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	T20	trt
7	43.983	0.000	0.000	0.000	14	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
8	45.426	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
9	90.604	39.109	0.000		16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
10	155.490	34.082	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
11	198.819	90.051	35.459	0.000	16	19	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
12	170.773	89.990	35.459	0.000	16	19	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
13	44.914	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
14	39.886	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
15	52.933	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
16	79.070	0.000	0.000	0.000	13	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
17	121.417	0.000	0.000	0.000	12	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
18	151.037	43.215	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
19	257.290	91.207	46.771	0.000	15	19	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
20	287.308	185.234	106.196	35.322	16	20	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
21	36.217	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
22	0.000	0.000	0.000	0.000	.	.	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
23	42.360	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
24	0.000	0.000	0.000	0.000	.	.	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
25	73.929	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
26	144.022	40.424	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
27	151.969	43.070	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
28	167.909	54.982	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
29	236.311	79.634	0.000	0.000	15	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
30	140.184	40.172	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
31	73.313	0.000	0.000	0.000	14	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
32	62.505	0.000	0.000	0.000	.	.	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2

Obs	c17	c18	c19	c20	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	T20	trt
33	205.872	65.500	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
34	56.255	170.917	0.000	0.000	.	.	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
35	261.350	114.029	44.365	0.000	15	19	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
36	316.193	164.670	0.000	43.231	17	20	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
37	139.506	38.956	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
38	132.027	37.887	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
39	146.927	53.217	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
40	165.838	78.965	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
41	110.058	34.683	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
42	99.500	0.000	0.000	0.000	13	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
43	50.249	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
44	0.000	0.000	0.000	0.000	.	.	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
45	70.618	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
46	102.119	0.000	0.000	0.000	.	.	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
47	41.935	0.000	0.000	0.000	16	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
48	57.500	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
49	0.000	0.000	0.000	0.000	.	.	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
50	41.713	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
51	116.337	51.650	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
52	168.357	81.614	0.000	0.000	.	.	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
53	55.268	0.000	0.000	0.000	.	.	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
54	58.379	0.000	0.000	0.000	.	.	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
55	76.789	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
56	101.411	34.966	0.000	0.000	15	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
57	168.095	47.488	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
58	158.405	59.231	0.000	0.000	15	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1

Obs	c17	c18	c19	c20	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	T20	trt
59	182.153	93.155	0.000	0.000	15	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
60	149.137	80.774	34.787	0.000	17	19	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
61	97.884	39.849	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
62	50.018	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
63	115.310	36.395	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
64	270.291	109.005	52.390	0.000	17	19	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2

FASTING PHARMACOKINETIC DATASET

Obs	sub	trt	seq	per	GRP	auct	auci	C _{MAX}	T _{MAX}	THALFR	KEL
1	1	1	2	2	1	7423.51	9106.61	403.355	5	31.3300	0.022124
2	1	2	2	1	1	7138.26	.	558.943	5	.	.
3	2	1	1	1	1	7613.04	.	237.836	24	.	.
4	2	2	1	2	1	17965.96	19841.52	428.766	24	18.4334	0.037603
5	3	1	2	2	1	8538.40	9645.92	216.904	5	21.2952	0.032549
6	3	2	2	1	1	8191.58	11238.08	295.246	5	24.9230	0.027812
7	4	1	1	1	1	7126.30	7979.08	270.315	10	13.4393	0.051576
8	4	2	1	2	1	5984.51	7008.01	328.094	5	15.6173	0.044383
9	5	1	2	2	1	11510.53	12291.47	276.880	24	15.8826	0.043642
10	5	2	2	1	1	11374.36	12333.29	341.427	10	16.9956	0.040784
11	6	1	1	1	1	18154.07	19189.72	421.344	24	20.2447	0.034238
12	6	2	1	2	1	15784.73	16919.95	348.513	24	22.1910	0.031236
13	7	1	1	1	1	10699.80	11352.93	561.850	6	10.0796	0.068767
14	7	2	1	2	1	11257.78	11843.07	573.678	8	10.1713	0.068147
15	8	1	2	2	1	7627.55	10553.23	464.083	5	25.6472	0.027026
16	8	2	2	1	1	7479.78	8521.18	417.549	5	13.6370	0.050828
17	9	1	2	2	1	13914.44	14916.35	342.599	24	16.0701	0.043133
18	9	2	2	1	1	13792.34	16987.17	522.628	10	18.2387	0.038004
19	10	1	1	1	1	25440.59	26797.32	581.172	20	20.1069	0.034473
20	10	2	1	2	1	27672.57	29049.26	466.714	24	27.0159	0.025657
21	11	1	2	2	1	.	.	0.000	120	.	.
22	11	2	2	1	1	9313.02	9910.46	511.949	8	11.4341	0.060621
23	12	1	1	1	1	5145.44	6023.93	161.454	20	14.3749	0.048219
24	12	2	1	2	1	2915.85	.	253.424	9	.	.
25	13	1	2	2	1	10972.64	11997.59	295.986	9	17.5748	0.039440
26	13	2	2	1	1	7519.27	9593.78	286.876	10	19.4503	0.035637
27	14	1	1	1	1	12207.53	13264.81	304.348	24	17.0154	0.040736
28	14	2	1	2	1	12175.37	13805.20	277.627	24	20.5469	0.033735
29	15	1	2	2	1	16876.33	17689.31	430.531	24	14.0275	0.049414
30	15	2	2	1	1	19082.68	21705.53	428.375	7	22.8297	0.030362
31	16	1	1	1	1	9793.39	11337.76	318.071	12	14.6015	0.047471
32	16	2	1	2	1	7142.75	.	198.071	24	.	.
33	17	1	1	1	1	18896.80	20515.94	456.606	24	17.1344	0.040454
34	17	2	1	2	1	19737.47	.	546.631	24	.	.
35	18	1	2	2	1	29279.31	30841.78	678.952	24	25.0520	0.027668
36	18	2	2	1	1	31302.90	32471.54	876.894	5	18.2586	0.037963
37	19	1	2	2	1	18430.94	19143.85	504.334	20	13.0428	0.053144

Obs	sub	trt	seq	per	GRP	auct	auci	CMAx	TMAx	THALFR	KEL
38	19	2	2	1	1	19977.08	20695.87	567.606	12	12.7894	0.054197
39	20	1	1	1	1	12703.20	14229.92	294.257	5	19.8854	0.034857
40	20	2	1	2	1	15927.42	18455.14	443.627	5	22.1881	0.031240
41	21	1	2	2	1	12559.65	14973.96	465.511	12	16.8188	0.041213
42	21	2	2	1	1	15099.75	15805.27	400.825	12	14.1000	0.049159
43	22	1	1	1	1	8670.56	9633.19	648.605	5	13.2787	0.052200
44	22	2	1	2	1	4046.33	.	309.279	5	.	.
45	23	1	2	2	1	8388.92	.	249.044	24	.	.
46	23	2	2	1	1	8786.23	10332.25	409.300	5	15.1748	0.045677
47	24	1	1	1	1	12419.21	12898.79	456.836	20	7.9270	0.087441
48	24	2	1	2	1	11525.98	12440.65	467.670	5	11.0261	0.062864
49	25	1	1	1	1	6512.65	.	387.188	10	.	.
50	25	2	1	2	1	9959.55	10582.96	354.098	4	10.3591	0.066912
51	26	1	2	2	1	11012.44	.	246.814	8	.	.
52	26	2	2	1	1	9404.59	11423.48	293.932	5	27.0936	0.025583
53	27	1	2	2	1	5044.54	.	159.884	5	.	.
54	27	2	2	1	1	3575.71	.	115.623	1	.	.
55	28	1	1	1	1	11151.29	12653.37	439.318	5	13.5587	0.051122
56	28	2	1	2	1	10698.81	11664.17	334.758	6	19.1369	0.036221
57	29	1	2	2	1	28663.33	29828.00	893.694	5	13.6295	0.050857
58	29	2	2	1	1	23383.83	24319.44	692.764	9	13.6564	0.050756
59	30	1	1	1	1	13508.77	17972.25	277.017	20	33.2118	0.020870
60	30	2	1	2	1	12004.07	13151.19	211.504	9	22.8569	0.030325
61	31	1	2	2	1	8790.15	9612.10	317.835	12	11.3906	0.060852
62	31	2	2	1	1	12500.40	13547.49	637.367	10	18.2135	0.038057
63	32	1	1	1	1	15220.76	15975.80	457.732	16	14.3798	0.048203
64	32	2	1	2	1	25788.17	27320.80	660.538	6	20.2775	0.034183

4.4.2 Fasting (1 x 60 mg) Study Output (of Raloxifene)

FASTING STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	32	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
trt	2	1 2
per	2	1 2
seq	2	1 2

Data for Analysis of AUCT LAUCT LCMAX	
Number of Observations Read	64
Number of Observations Used	63

Data for Analysis of AUCI LAUCI	
Number of Observations Read	64
Number of Observations Used	52

Data for Analysis of CMAX	
Number of Observations Read	64
Number of Observations Used	64

Note: Variables in each group are consistent with respect to the presence or absence of missing values.

FASTING STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	33	14.87915661	0.45088353	9.20	<.0001
Error	29	1.42100307	0.04900011		
Corrected Total	62	16.30015969			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.912823	2.370025	0.221360	9.339972

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.01163002	0.01163002	0.24	0.6298
sub(seq)	30	14.86339615	0.49544654	10.11	<.0001
per	1	0.00220712	0.00220712	0.05	0.8334
trt	1	0.00192333	0.00192333	0.04	0.8443

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00696115	0.00696115	0.14	0.7090
sub(seq)	30	14.85716498	0.49523883	10.11	<.0001
per	1	0.00233968	0.00233968	0.05	0.8286
trt	1	0.00192333	0.00192333	0.04	0.8443

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	0.00696115	0.00696115	0.01	0.9064

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.01114519	0.05625469	0.20	0.8443

FASTING STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	33	8.74498703	0.26499961	4.94	<.0001
Error	29	1.55418013	0.05359242		
Corrected Total	62	10.29916715			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.849097	3.899829	0.231500	5.936168

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.05296057	0.05296057	0.99	0.3284
sub(seq)	30	8.53935007	0.28464500	5.31	<.0001
per	1	0.08152790	0.08152790	1.52	0.2273
trt	1	0.07114848	0.07114848	1.33	0.2586

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.05963661	0.05963661	1.11	0.3002
sub(seq)	30	8.50407859	0.28346929	5.29	<.0001
per	1	0.08642820	0.08642820	1.61	0.2142
trt	1	0.07114848	0.07114848	1.33	0.2586

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	0.05963661	0.05963661	0.21	0.6498

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	-0.06778648	0.05883177	-1.15	0.2586

FASTING STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	32	7.50099792	0.23440619	10.70	<.0001
Error	19	0.41608875	0.02189941		
Corrected Total	51	7.91708667			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.947444	1.547246	0.147984	9.564383

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.01573490	0.01573490	0.72	0.4072
sub(seq)	29	7.47509217	0.25776180	11.77	<.0001
per	1	0.00024708	0.00024708	0.01	0.9165
trt	1	0.00992377	0.00992377	0.45	0.5089

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00224157	0.00224157	0.10	0.7525
sub(seq)	29	7.41007708	0.25551990	11.67	<.0001
per	1	0.00012006	0.00012006	0.01	0.9418
trt	1	0.00992377	0.00992377	0.45	0.5089

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	0.00224157	0.00224157	0.01	0.9260

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	-0.03077774	0.04572087	-0.67	0.5089

AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS

Obs	sub	trt	AUCRATIO
1	1	1	0.82
2	2	1	.
3	3	1	0.89
4	4	1	0.89
5	5	1	0.94
6	6	1	0.95
7	7	1	0.94
8	8	1	0.72
9	9	1	0.93
10	10	1	0.95
11	11	1	.
12	12	1	0.85
13	13	1	0.91
14	14	1	0.92
15	15	1	0.95
16	16	1	0.86
17	17	1	0.92
18	18	1	0.95
19	19	1	0.96
20	20	1	0.89
21	21	1	0.84
22	22	1	0.90
23	23	1	.
24	24	1	0.96
25	25	1	.
26	26	1	.
27	27	1	.
28	28	1	0.88
29	29	1	0.96
30	30	1	0.75
31	31	1	0.91
32	32	1	0.95
33	1	2	.
34	2	2	0.91
35	3	2	0.73
36	4	2	0.85

Obs	sub	trt	AUCRATIO
37	5	2	0.92
38	6	2	0.93
39	7	2	0.95
40	8	2	0.88
41	9	2	0.81
42	10	2	0.95
43	11	2	0.94
44	12	2	.
45	13	2	0.78
46	14	2	0.88
47	15	2	0.88
48	16	2	.
49	17	2	.
50	18	2	0.96
51	19	2	0.97
52	20	2	0.86
53	21	2	0.96
54	22	2	.
55	23	2	0.85
56	24	2	0.93
57	25	2	0.94
58	26	2	0.82
59	27	2	.
60	28	2	0.92
61	29	2	0.96
62	30	2	0.91
63	31	2	0.92
64	32	2	0.94

TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
1	2	1.04	.	0.72	1.00	.	.
2	1	0.42	.	0.55	1.00	.	.
3	2	1.04	0.86	0.73	1.00	1.17	0.85
4	1	1.19	1.14	0.82	2.00	1.16	0.86
5	2	1.01	1.00	0.81	2.40	1.07	0.93
6	1	1.15	1.13	1.21	1.00	1.10	0.91
7	1	0.95	0.96	0.98	0.75	1.01	0.99
8	2	1.02	1.24	1.11	1.00	0.53	1.88
9	2	1.01	0.88	0.66	2.40	1.13	0.88
10	1	0.92	0.92	1.25	0.83	1.34	0.74
11	2	.	.	0.00	15.0	.	.
12	1	1.76	.	0.64	2.22	.	.
13	2	1.46	1.25	1.03	0.90	1.11	0.90
14	1	1.00	0.96	1.10	1.00	1.21	0.83
15	2	0.88	0.81	1.01	3.43	1.63	0.61
16	1	1.37	.	1.61	0.50	.	.
17	1	0.96	.	0.84	1.00	.	.
18	2	0.94	0.95	0.77	4.80	0.73	1.37
19	2	0.92	0.93	0.89	1.67	0.98	1.02
20	1	0.80	0.77	0.66	1.00	1.12	0.90
21	2	0.83	0.95	1.16	1.00	0.84	1.19
22	1	2.14	.	2.10	1.00	.	.
23	2	0.95	.	0.61	4.80	.	.
24	1	1.08	1.04	0.98	4.00	1.39	0.72
25	1	0.65	.	1.09	2.50	.	.
26	2	1.17	.	0.84	1.60	.	.
27	2	1.41	.	1.38	5.00	.	.
28	1	1.04	1.08	1.31	0.83	1.41	0.71
29	2	1.23	1.23	1.29	0.56	1.00	1.00
30	1	1.13	1.37	1.31	2.22	0.69	1.45
31	2	0.70	0.71	0.50	1.20	1.60	0.63
32	1	0.59	0.58	0.69	2.67	1.41	0.71

RATIO OF SPONSOR/REVIEWER CALCULATED PARAMETERS

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	1	2	1	1	2	7138.26	.	558.943	B	7138.26	11662.57	558.943	1.00000	.	1
2	1	2	2	1	1	7423.51	9106.61	403.355	A	7429.46	9114.35	403.355	1.00080	1.00085	1
3	2	1	1	1	1	7613.04	.	237.836	A	7613.04	.	237.836	1.00000	.	1
4	2	1	2	1	2	17965.96	19841.52	428.766	B	17965.96	19841.52	428.766	1.00000	1.00000	1
5	3	2	1	1	2	8191.58	11238.08	295.246	B	8191.58	11238.08	295.246	1.00000	1.00000	1
6	3	2	2	1	1	8538.40	9645.92	216.904	A	8538.40	9645.92	216.904	1.00000	1.00000	1
7	4	1	1	1	1	7126.30	7979.08	270.315	A	7126.30	7979.08	270.315	1.00000	1.00000	1
8	4	1	2	1	2	5984.51	7008.01	328.094	B	5984.52	7008.01	328.094	1.00000	1.00000	1
9	5	2	1	1	2	11374.36	12333.29	341.427	B	11374.36	12333.29	341.427	1.00000	1.00000	1
10	5	2	2	1	1	11510.53	12291.47	276.880	A	11520.24	12301.58	276.880	1.00084	1.00082	1
11	6	1	1	1	1	18154.07	19189.72	421.344	A	18154.07	19189.72	421.344	1.00000	1.00000	1
12	6	1	2	1	2	15784.73	16919.95	348.513	B	15784.73	16919.95	348.513	1.00000	1.00000	1
13	7	1	1	1	1	10699.80	11352.93	561.850	A	10699.80	11352.93	561.850	1.00000	1.00000	1
14	7	1	2	1	2	11257.78	11843.07	573.678	B	11257.78	11843.07	573.678	1.00000	1.00000	1
15	8	2	1	1	2	7479.78	8521.18	417.549	B	7479.78	8521.18	417.549	1.00000	1.00000	1
16	8	2	2	1	1	7627.55	10553.23	464.083	A	7627.55	10553.23	464.083	1.00000	1.00000	1
17	9	2	1	1	2	13792.34	16987.17	522.628	B	13792.34	16987.17	522.628	1.00000	1.00000	1
18	9	2	2	1	1	13914.44	14916.35	342.599	A	13914.44	14916.35	342.599	1.00000	1.00000	1
19	10	1	1	1	1	25440.59	26797.32	581.172	A	25440.59	26797.32	581.172	1.00000	1.00000	1
20	10	1	2	1	2	27672.57	29049.26	466.714	B	27723.40	29101.37	466.714	1.00184	1.00179	1
21	11	2	1	1	2	9313.02	9910.46	511.949	B	9313.03	9910.46	511.949	1.00000	1.00000	1
22	11	2	2	1	1	.	.	0.000	A	0.00	.	0.000	.	.	.
23	12	1	1	1	1	5145.44	6023.93	161.454	A	5145.44	6023.93	161.454	1.00000	1.00000	1
24	12	1	2	1	2	2915.85	.	253.424	B	2915.85	7959.02	253.424	1.00000	.	1

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUICI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
25	13	2	1	1	2	7519.27	9593.78	286.876	B	7519.27	9593.78	286.876	1.00000	1.00000	1
26	13	2	2	1	1	10972.64	11997.59	295.986	A	10972.64	11997.59	295.986	1.00000	1.00000	1
27	14	1	1	1	1	12207.53	13264.81	304.348	A	12207.53	13264.81	304.348	1.00000	1.00000	1
28	14	1	2	1	2	12175.37	13805.20	277.627	B	12175.37	13805.20	277.627	1.00000	1.00000	1
29	15	2	1	1	2	19082.68	21705.53	428.375	B	19082.68	21705.53	428.375	1.00000	1.00000	1
30	15	2	2	1	1	16876.33	17689.31	430.531	A	16876.33	17689.31	430.531	1.00000	1.00000	1
31	16	1	1	1	1	9793.39	11337.76	318.071	A	9793.39	11337.76	318.071	1.00000	1.00000	1
32	16	1	2	1	2	7142.75	.	198.071	B	7142.75	.	198.071	1.00000	.	1
33	17	1	1	1	1	18896.80	20515.94	456.606	A	18896.80	20515.94	456.606	1.00000	1.00000	1
34	17	1	2	1	2	19737.47	.	546.631	B	19737.47	26794.11	546.631	1.00000	.	1
35	18	2	1	1	2	31302.90	32471.54	876.894	B	31302.90	32471.55	876.894	1.00000	1.00000	1
36	18	2	2	1	1	29279.31	30841.78	678.952	A	29279.31	30841.78	678.952	1.00000	1.00000	1
37	19	2	1	1	2	19977.08	20695.87	567.606	B	19977.08	20695.87	567.606	1.00000	1.00000	1
38	19	2	2	1	1	18430.94	19143.85	504.334	A	18430.94	19143.85	504.334	1.00000	1.00000	1
39	20	1	1	1	1	12703.20	14229.92	294.257	A	12703.20	14229.92	294.257	1.00000	1.00000	1
40	20	1	2	1	2	15927.42	18455.14	443.627	B	15985.12	18512.94	443.627	1.00362	1.00313	1
41	21	2	1	1	2	15099.75	15805.27	400.825	B	15099.75	15805.27	400.825	1.00000	1.00000	1
42	21	2	2	1	1	12559.65	14973.96	465.511	A	12559.65	14973.96	465.511	1.00000	1.00000	1
43	22	1	1	1	1	8670.56	9633.19	648.605	A	8670.56	9633.19	648.605	1.00000	1.00000	1
44	22	1	2	1	2	4046.33	.	309.279	B	4046.33	7115.52	309.279	1.00000	.	1
45	23	2	1	1	2	8786.23	10332.25	409.300	B	8786.23	10332.25	409.300	1.00000	1.00000	1
46	23	2	2	1	1	8388.92	.	249.044	A	8388.92	.	249.044	1.00000	.	1
47	24	1	1	1	1	12419.21	12898.79	456.836	A	12419.21	12906.59	456.836	1.00000	1.00060	1
48	24	1	2	1	2	11525.98	12440.65	467.670	B	11576.64	12501.59	467.670	1.00440	1.00490	1
49	25	1	1	1	1	6512.65	.	387.188	A	6512.65	10644.59	387.188	1.00000	.	1
50	25	1	2	1	2	9959.55	10582.96	354.098	B	9999.81	10629.43	354.098	1.00404	1.00439	1

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
51	26	2	1	1	2	9404.59	11423.48	293.932	B	9404.59	11423.48	293.932	1.00000	1.00000	1
52	26	2	2	1	1	11012.44	.	246.814	A	11012.44	17590.18	246.814	1.00000	.	1
53	27	2	1	1	2	3575.71	.	115.623	B	3575.71	7331.25	115.623	1.00000	.	1
54	27	2	2	1	1	5044.54	.	159.884	A	5044.54	6909.06	159.884	1.00000	.	1
55	28	1	1	1	1	11151.29	12653.37	439.318	A	11151.29	12653.37	439.318	1.00000	1.00000	1
56	28	1	2	1	2	10698.81	11664.17	334.758	B	10698.81	11664.17	334.758	1.00000	1.00000	1
57	29	2	1	1	2	23383.83	24319.44	692.764	B	23383.83	24319.44	692.764	1.00000	1.00000	1
58	29	2	2	1	1	28663.33	29828.00	893.694	A	28663.34	29828.00	893.694	1.00000	1.00000	1
59	30	1	1	1	1	13508.77	17972.25	277.017	A	13508.77	17972.25	277.017	1.00000	1.00000	1
60	30	1	2	1	2	12004.07	13151.19	211.504	B	12004.07	13151.19	211.504	1.00000	1.00000	1
61	31	2	1	1	2	12500.40	13547.49	637.367	B	12562.73	13609.89	637.367	1.00499	1.00461	1
62	31	2	2	1	1	8790.15	9612.10	317.835	A	8790.15	9612.11	317.835	1.00000	1.00000	1
63	32	1	1	1	1	15220.76	15975.80	457.732	A	15220.76	15975.80	457.732	1.00000	1.00000	1
64	32	1	2	1	2	25788.17	27320.80	660.538	B	25788.17	27320.80	660.538	1.00000	1.00000	1

Note: The above table comparing the firm to reviewer ratio of PK parameters was generated using the SAS code “CALCKE.”

4.4.3 Fed (1 x 60 mg) Study Data (of Raloxifene)

FED CONCENTRATION DATASET

Obs	sub	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
1	1	1	1	1	A	0	0.000	129.553	363.740	327.934	318.921	236.00	209.78	195.72	209.61	266.62	356.65	228.41	161.67	145.42	165.02
2	1	1	2	1	B	0	243.130	610.188	482.195	567.217	485.072	476.47	461.39	462.26	507.51	688.61	853.61	674.93	603.61	558.83	851.52
3	2	2	1	1	B	0	0.000	0.000	148.885	193.451	253.114	328.51	278.98	281.06	290.98	735.40	660.31	698.51	697.66	670.02	718.41
4	2	2	2	1	A	0	43.242	70.801	150.393	205.186	280.134	477.69	342.83	345.77	469.45	724.22	931.96	975.16	783.18	765.35	811.78
5	3	2	1	1	B	0	0.000	191.548	370.892	263.233	196.106	292.01	407.03	504.27	539.60	572.61	566.26	532.28	461.59	571.61	568.29
6	3	2	2	1	A	0	0.000	53.025	388.100	304.074	240.066	485.14	640.78	684.89	713.37	686.15	702.27	646.59	542.17	477.27	429.21
7	4	1	1	1	A	0	0.000	0.000	69.624	158.330	162.704	340.68	437.12	547.34	739.33	762.31	739.97	711.97	698.68	587.36	734.23
8	4	1	2	1	B	0	0.000	0.000	55.940	105.942	149.742	200.95	205.29	219.05	268.54	457.76	440.76	456.30	448.11	463.59	514.38
9	5	2	1	1	B	0	0.000	173.859	384.001	283.330	204.545	229.03	246.69	435.40	554.55	600.19	563.58	517.16	450.52	465.57	516.54
10	5	2	2	1	A	0	0.000	41.160	392.033	306.222	229.529	262.00	315.92	540.70	534.88	716.96	676.94	624.27	534.13	516.16	501.58
11	6	1	1	1	A	0	0.000	43.821	271.362	265.468	291.547	409.98	351.47	329.18	299.23	325.39	325.00	252.27	174.32	140.73	147.93
12	6	1	2	1	B	0	58.978	163.261	287.668	257.498	271.647	406.75	390.07	391.71	334.35	375.80	372.25	446.17	355.80	378.20	439.41
13	7	1	1	1	A	0	126.411	567.330	482.873	442.593	465.725	414.54	444.24	444.67	453.63	428.53	465.12	494.16	404.47	415.88	470.20
14	7	1	2	1	B	0	0.000	0.000	149.393	251.457	339.009	535.64	391.76	379.08	327.88	282.69	272.41	239.22	187.31	180.61	198.51
15	8	2	1	1	B	0	37.923	308.538	284.191	239.104	228.237	310.03	323.56	569.42	584.80	635.56	623.84	582.96	541.44	542.35	507.18
16	8	2	2	1	A	0	79.757	459.136	445.381	345.034	403.837	644.12	703.42	636.81	686.95	794.90	918.82	871.01	660.44	798.18	612.62
17	9	1	1	1	A	0	0.000	210.489	271.986	221.152	211.237	193.56	200.29	206.25	229.69	247.14	244.17	258.86	279.09	260.15	238.99
18	9	1	2	1	B	0	0.000	324.232	343.909	230.293	214.114	191.27	206.49	228.46	289.65	338.28	334.48	299.23	308.79	303.85	262.26
19	10	2	1	1	B	0	35.541	150.093	198.263	175.422	161.972	200.59	308.20	417.87	584.00	692.37	741.92	720.77	616.30	634.72	501.34
20	10	2	2	1	A	0	0.000	113.289	139.973	137.370	130.148	147.03	135.92	271.15	315.53	466.41	407.86	498.05	347.59	353.57	410.41
21	11	2	1	1	B	0	0.000	0.000	88.467	158.656	245.920	399.84	349.85	298.24	287.65	253.09	233.11	215.07	155.21	134.14	105.59
22	11	2	2	1	A	0	0.000	0.000	224.728	430.080	473.434	376.97	283.15	262.96	244.14	238.30	247.17	221.51	155.42	135.16	119.61
23	12	1	1	1	A	0	0.000	0.000	169.059	223.470	279.193	225.80	230.59	193.37	193.54	208.06	216.30	238.86	242.40	187.31	169.29

Obs	sub	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
24	12	1	2	1	B	0	0.000	60.180	282.243	282.628	210.935	200.20	182.01	151.15	150.79	150.31	151.70	176.99	181.55	154.76	125.83
25	13	2	1	1	B	0	0.000	107.041	392.339	502.377	460.194	678.17	761.04	681.73	767.36	787.78	877.67	943.81	1580.62	916.41	917.02
26	13	2	2	1	A	0	62.144	214.522	388.192	407.302	403.654	511.03	581.18	773.14	961.61	1173.80	1211.54	1641.17	1156.14	1056.57	1177.50
27	14	1	1	1	A	0	0.000	0.000	115.664	192.406	173.258	504.95	421.63	350.33	315.59	326.14	318.20	297.20	265.00	280.32	245.44
28	14	1	2	1	B	0	0.000	0.000	176.039	162.902	134.503	118.39	124.35	166.84	198.47	241.97	235.78	190.64	144.75	232.86	163.90
29	15	2	1	1	B	0	0.000	0.000	339.986	339.762	299.671	263.24	231.03	280.09	326.84	357.05	411.41	518.26	465.93	457.30	308.94
30	15	2	2	1	A	0	0.000	0.000	172.619	204.945	202.484	257.17	229.85	260.68	407.51	317.11	318.03	338.75	339.74	312.62	324.38
31	16	1	1	1	A	0	0.000	252.774	456.882	340.811	290.713	227.56	243.51	239.50	312.33	373.48	380.29	432.71	326.60	342.33	381.38
32	16	1	2	1	B	0	0.000	473.893	457.269	407.365	414.070	509.34	440.88	714.43	750.71	875.87	767.74	757.97	553.59	561.42	552.15
33	17	1	1	1	A	0	0.000	72.464	202.301	227.143	273.091	269.41	359.01	564.05	691.84	717.42	783.06	826.89	647.24	609.29	622.41
34	17	1	2	1	B	0	0.000	0.000	86.121	115.726	182.787	206.25	228.34	341.15	558.54	626.44	552.64	557.00	552.24	613.67	610.09
35	18	2	1	1	B	0	0.000	50.557	82.567	97.091	106.717	166.79	157.87	141.87	149.69	241.81	272.56	264.19	254.42	292.98	261.14
36	18	2	2	1	A	0	0.000	32.933	75.121	88.392	135.962	227.89	157.81	144.58	157.37	204.72	255.49	247.78	201.73	227.79	261.05
37	19	1	1	1	A	0	0.000	41.951	266.251	203.075	171.611	248.69	354.91	421.44	748.52	690.20	637.02	664.12	598.20	619.31	629.10
38	19	1	2	1	B	0	0.000	0.000	219.415	229.942	207.343	206.36	182.04	227.51	278.63	386.39	403.06	481.46	487.19	558.68	649.06
39	20	2	1	1	B	0	266.417	432.215	573.635	567.568	437.823	363.72	442.44	491.65	680.03	877.68	930.94	683.56	725.55	512.32	627.36
40	20	2	2	1	A	0	0.000	102.878	230.294	302.206	398.555	460.42	376.72	404.41	407.95	472.99	488.58	476.57	494.35	473.36	381.55
41	21	1	1	1	A	0	0.000	123.704	310.362	298.166	210.459	202.39	190.78	184.23	191.18	198.69	229.40	245.20	231.01	219.73	180.54
42	21	1	2	1	B	0	0.000	0.000	197.274	215.264	230.680	192.84	176.82	160.04	165.98	232.99	249.39	288.02	253.88	243.60	241.34
43	22	2	1	1	B	0	43.092	209.011	175.389	159.717	207.482	423.83	395.26	352.17	339.45	292.00	260.49	254.79	191.00	165.56	130.77
44	22	2	2	1	A	0	32.754	136.446	201.265	229.351	225.554	328.71	306.15	299.21	406.37	303.35	319.21	300.61	270.91	214.60	175.89
45	23	1	1	1	A	0	86.263	161.813	220.186	231.460	234.519	225.48	190.95	212.21	229.79	276.54	270.76	235.45	222.03	235.63	273.68
46	23	1	2	1	B	0	98.527	215.010	193.189	168.202	152.304	129.52	128.42	142.01	168.15	151.41	167.55	147.98	139.13	165.78	170.17
47	24	2	1	1	B	0	0.000	183.801	339.198	352.761	379.394	420.23	382.50	336.50	345.33	382.78	371.33	380.36	277.93	346.92	340.41
48	24	2	2	1	A	0	0.000	0.000	187.206	182.120	247.208	312.28	266.71	248.27	228.08	225.50	212.79	175.83	141.10	147.65	136.39
49	25	2	1	1	B	0	0.000	0.000	110.420	98.440	115.307	154.54	125.45	134.49	164.26	260.55	215.47	244.16	235.14	247.77	209.95

Obs	sub	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
50	25	2	2	1	A	0	67.435	189.040	203.029	184.212	192.956	167.84	146.46	175.00	191.59	252.62	274.79	321.50	293.18	305.72	267.04
51	27	1	1	1	A	0	176.292	210.019	267.873	247.045	243.812	497.15	540.31	586.69	553.41	508.36	501.46	474.71	443.87	441.52	342.04
52	27	1	2	1	B	0	0.000	40.476	165.238	545.854	576.744	726.23	608.50	560.95	492.69	462.06	489.47	562.15	536.37	533.49	669.89
53	28	2	1	1	B	0	0.000	39.898	408.222	339.186	362.104	414.26	462.25	509.24	554.71	524.96	522.96	506.35	560.84	586.62	687.90
54	28	2	2	1	A	0	91.335	155.997	276.898	586.915	769.512	1288.50	1307.73	1166.39	1299.51	1182.04	1172.96	1148.98	746.35	586.44	522.55
55	29	1	1	1	A	0	0.000	46.553	89.795	109.071	127.153	154.32	193.57	237.12	246.55	252.58	279.44	297.96	234.44	295.76	248.71
56	29	1	2	1	B	0	0.000	0.000	148.383	122.053	126.548	154.67	334.93	290.05	295.82	292.63	260.76	298.61	213.57	236.64	234.13
57	30	2	1	1	B	0	0.000	0.000	0.000	79.922	105.474	178.37	128.69	142.47	142.67	136.38	137.40	120.06	135.38	127.68	103.29
58	30	2	2	1	A	0	178.261	192.247	232.000	226.352	190.860	187.45	177.88	169.67	181.73	179.68	197.88	168.40	186.77	188.67	158.96
59	31	2	1	1	B	0	0.000	186.758	194.015	187.542	172.487	150.15	170.02	223.21	261.63	241.56	242.11	294.94	204.09	164.13	150.36
60	31	2	2	1	A	0	0.000	105.142	223.719	231.010	213.635	175.13	145.51	153.61	166.31	221.06	250.92	320.55	289.61	246.09	250.94
61	32	1	1	1	A	0	45.678	169.643	274.165	270.072	231.210	348.24	324.82	294.43	392.23	349.54	470.99	401.74	336.43	345.93	322.52
62	32	1	2	1	B	0	216.447	385.814	295.639	288.592	260.329	272.41	282.39	387.51	530.64	638.24	590.99	643.30	549.64	591.71	466.91
63	33	2	1	1	B	0	0.000	0.000	61.972	121.361	182.232	223.36	170.30	182.82	166.85	172.63	251.50	302.70	314.28	366.43	338.01
64	33	2	2	1	A	0	0.000	77.981	0.000	138.162	131.911	190.11	171.46	164.57	160.88	153.02	158.48	240.21	260.52	269.51	297.89
65	34	1	1	1	A	0	52.214	145.487	183.932	188.056	186.511	174.72	181.97	255.07	376.76	514.69	486.33	487.79	469.80	435.27	444.60
66	34	1	2	1	B	0	0.000	57.911	124.612	144.842	167.882	193.60	164.15	163.32	189.37	245.24	363.43	412.63	414.37	396.42	428.49
67	35	2	1	1	B	0	0.000	69.850	156.878	230.465	276.033	454.87	344.04	423.63	558.45	529.68	537.19	605.70	481.06	376.03	430.98
68	35	2	2	1	A	0	98.442	312.039	363.386	345.720	405.585	350.79	298.62	439.57	422.97	429.73	387.67	383.15	322.85	293.95	316.95
69	36	1	1	1	A	0	0.000	70.285	189.604	250.865	286.079	369.20	287.01	301.20	327.74	421.29	550.28	499.91	421.68	480.57	444.59
70	36	1	2	1	B	0	384.180	608.795	474.989	361.089	373.887	432.53	454.45	513.48	466.50	538.06	564.20	548.38	476.36	508.06	611.97
71	37	2	1	1	B	0	0.000	41.298	173.627	205.505	232.646	245.01	284.76	345.30	428.29	391.97	465.80	507.96	412.79	488.22	425.28
72	37	2	2	1	A	0	0.000	44.157	168.958	241.510	314.482	299.20	304.81	311.01	339.93	515.95	554.27	636.32	617.65	606.57	562.35
73	38	1	1	1	A	0	0.000	140.152	174.856	196.328	146.889	135.28	146.32	190.37	187.24	255.04	232.54	228.74	253.83	211.49	196.85
74	38	1	2	1	B	0	0.000	203.189	203.596	202.910	194.388	199.10	199.28	200.50	260.34	242.52	271.87	254.66	188.41	176.28	158.62
75	39	1	1	1	A	0	0.000	0.000	205.558	268.972	266.851	287.18	250.87	355.06	451.60	431.28	502.28	548.73	526.04	416.95	579.66

Obs	sub	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
76	39	1	2	1	B	0	0.000	35.099	189.864	335.941	259.404	290.13	346.90	503.58	603.32	756.55	891.68	1026.21	851.64	864.43	817.17
77	40	2	1	1	B	0	0.000	0.000	156.475	188.192	176.963	174.92	158.19	146.51	207.08	333.98	308.86	320.62	319.99	350.73	358.40
78	40	2	2	1	A	0	0.000	57.693	215.286	239.937	201.258	198.46	162.91	159.85	197.87	307.91	317.10	216.37	164.37	166.32	143.61
79	41	1	1	1	A	0	0.000	0.000	102.686	220.380	359.357	546.62	653.76	812.86	682.13	694.51	530.97	544.82	360.59	300.29	347.87
80	41	1	2	1	B	0	0.000	136.740	177.881	230.914	268.567	449.15	450.20	439.50	468.29	509.76	433.83	377.29	246.27	231.86	232.57
81	42	2	1	1	B	0	0.000	0.000	71.436	173.293	200.093	293.66	328.56	417.70	498.31	584.97	816.02	906.54	1013.51	1166.90	1210.94
82	42	2	2	1	A	0	0.000	0.000	96.202	238.483	269.082	376.41	454.61	597.42	872.11	1020.25	1050.47	1261.48	1187.82	1370.34	1457.83

Obs	c17	c18	c19	c20	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	T20	trt
1	72.724	39.647	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
2	338.308	217.151	104.125	50.734	18	20	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
3	277.847	98.281	34.703	0.000	17	19	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
4	245.677	88.128	32.449	0.000	17	19	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
5	147.079	49.265	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
6	113.952	34.212	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
7	391.586	122.715	33.667	0.000	17	19	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
8	204.650	71.032	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
9	166.701	66.180	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
10	180.384	35.403	0.000	0.000	15	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
11	37.868	0.000	0.000	0.000	7	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
12	187.734	51.516	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
13	216.913	87.191	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
14	125.263	52.708	0.000	0.000	11	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
15	156.281	52.420	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
16	192.650	67.425	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
17	96.434	0.000	0.000	0.000	.	.	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1

Obs	c17	c18	c19	c20	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	T20	trt
18	85.390	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
19	139.447	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
20	150.279	49.915	0.000		16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
21	0.000	0.000	0.000	0.000			0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
22	0.000	0.000	0.000	0.000			0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
23	0.000	0.000	0.000	0.000			0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
24	0.000	0.000	0.000	0.000			0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
25	386.199	164.542	61.672	0.000	16	19	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
26	609.214	271.037	104.191	0.000	17	19	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
27	57.171	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
28	59.382	0.000	0.000	0.000			0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
29	84.148	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
30	92.062	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
31	124.045	39.775	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
32	156.107	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
33	210.019	56.954	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
34	292.186	84.827	0.000	0.000	15	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
35	169.110	44.968	0.000	0.000	15	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
36	106.848	56.378	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
37	235.451	83.448	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
38	236.081	99.670	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
39	109.046	0.000			14	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
40	88.464	33.347	0.000	0.000	14	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
41	56.166	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
42	53.135	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
43	32.317	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2

Obs	c17	c18	c19	c20	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	T20	trt
44	41.033	0.000	0.000	0.000	14	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
45	67.556	0.000	0.000	0.000	.	.	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
46	63.302	0.000	0.000	0.000	.	.	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
47	62.079	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
48	0.000	0.000	0.000	0.000	.	.	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
49	67.254	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
50	78.712	0.000	52.776	0.000	13	19	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
51	104.210	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
52	273.766	110.081	43.142	0.000	16	19	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
53	148.202	36.143	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
54	107.960	32.502	0.000	0.000	10	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
55	117.137	119.970	0.000	0.000	.	.	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
56	78.606	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
57	33.098	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
58	58.077	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
59	55.883	0.000	0.000	0.000	14	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
60	63.973	0.000	0.000	0.000	14	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
61	98.714	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
62	168.317	45.079	0.000	0.000	15	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
63	86.096	40.734	0.000	0.000	15	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
64	128.016	42.990	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
65	132.029	57.196	0.000	0.000	15	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
66	198.707	62.999	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
67	122.222	32.017	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
68	91.407	0.000	0.000	0.000	9	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
69	179.301	67.400	0.000	0.000	16	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1

Obs	c17	c18	c19	c20	KE_FIRST	KE_LAST	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	T20	trt
70	223.900	80.691	38.259	0.000	16	19	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
71	117.791	42.640	0.000	0.000	15	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
72		46.651	0.000	0.000	15	18	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
73	37.929	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
74	0.000	0.000	0.000	0.000			0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
75	315.163	36.495	49.520		16	19	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
76	362.979		0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
77	111.420	0.000	0.000	0.000			0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
78	33.627	0.000	0.000	0.000	15	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
79	53.623	0.000	0.000	0.000	9	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1
80	49.071	0.000	0.000	0.000	11	17	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
81	479.561	183.785	92.797	42.186	18	20	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	2
82	920.710	361.537	151.708	60.691	17	20	0	0.5	1	2	3	4	5	6	7	8	9	10	12	16	20	24	48	72	96	120	1

FED PHARMACOKINETIC DATASET

Obs	sub	trt	seq	per	GRP	auct	auci	C _{MAX}	T _{MAX}	THALFR	KEL
1	1	1	1	1	1	9205.48	10539.96	363.74	2	23.3307	0.029710
2	1	2	1	2	1	41025.01	42699.87	853.61	10	22.8825	0.030292
3	2	1	2	2	1	33353.59	34123.00	975.16	12	16.4354	0.042174
4	2	2	2	1	1	30568.29	31369.04	735.40	9	15.9938	0.043338
5	3	1	2	2	1	20407.63	21056.87	713.37	8	13.1539	0.052695
6	3	2	2	1	1	21945.50	22912.51	572.61	9	13.6055	0.050946
7	4	1	1	1	1	34633.94	35292.54	762.31	9	13.5596	0.051118
8	4	2	1	2	1	20305.33	22027.47	514.38	24	16.8050	0.041246
9	5	1	2	2	1	22194.72	22879.63	716.96	9	13.4097	0.051690
10	5	2	2	1	1	21155.91	22701.89	600.19	9	16.1921	0.042808
11	6	1	1	1	1	7606.41	8304.43	409.98	5	12.7768	0.054251
12	6	2	1	2	1	18975.83	20129.42	446.17	12	15.5216	0.044657
13	7	1	1	1	1	22362.06	24845.76	567.33	1	19.7448	0.035105
14	7	2	1	2	1	11672.86	13875.81	535.64	5	28.9703	0.023926
15	8	1	2	2	1	28879.77	30346.37	918.82	10	15.0771	0.045973
16	8	2	2	1	1	21925.27	23033.92	635.56	9	14.6596	0.047283
17	9	1	1	1	1	9742.08	.	279.09	16	.	.
18	9	2	1	2	1	10831.90	12695.16	343.91	2	15.1249	0.045828
19	10	1	2	2	1	16690.55	17827.76	498.05	12	15.7919	0.043893
20	10	2	2	1	1	19840.47	22430.34	741.92	10	12.8734	0.053843
21	11	1	2	2	1	4970.56	.	473.43	4	.	.
22	11	2	2	1	1	4445.17	.	399.84	5	.	.
23	12	1	1	1	1	4821.52	.	279.19	4	.	.
24	12	2	1	2	1	4010.78	.	282.63	3	.	.
25	13	1	2	2	1	59844.80	62676.81	1641.17	12	18.8404	0.036790
26	13	2	2	1	1	46043.52	47697.09	1580.62	16	18.5849	0.037296
27	14	1	1	1	1	10072.32	11055.46	504.95	5	11.9197	0.058152
28	14	2	1	2	1	6766.60	.	241.97	9	.	.
29	15	1	2	2	1	11801.12	13770.91	407.51	8	14.8308	0.046737
30	15	2	2	1	1	13637.44	15081.54	518.26	12	11.8954	0.058270
31	16	1	1	1	1	16012.32	16856.89	456.88	2	14.7181	0.047095
32	16	2	1	2	1	22414.21	25657.83	875.87	9	14.4024	0.048127
33	17	1	1	1	1	26477.66	27620.86	826.89	12	13.9130	0.049820
34	17	2	1	2	1	26080.56	28302.13	626.44	9	18.1531	0.038183
35	18	1	2	2	1	10956.73	12722.44	261.05	24	21.7087	0.031929
36	18	2	2	1	1	12827.51	14131.81	292.98	20	20.1047	0.034477

Obs	sub	trt	seq	per	GRP	auct	auci	CMAX	TMAX	THALFR	KEL
37	19	1	1	1	1	26413.72	28396.58	748.52	8	16.4703	0.042085
38	19	2	1	2	1	24118.98	26672.35	649.06	24	17.7572	0.039035
39	20	1	2	2	1	17029.12	17684.87	494.35	16	13.6303	0.050853
40	20	2	2	1	1	23382.04	25212.95	930.94	10	11.6381	0.059558
41	21	1	1	1	1	7963.31	9116.73	310.36	2	14.2345	0.048695
42	21	2	1	2	1	8816.32	9741.90	288.02	12	12.0741	0.057408
43	22	1	2	2	1	8696.24	9389.28	406.37	8	11.7071	0.059207
44	22	2	2	1	1	7323.47	7877.69	423.83	5	11.8871	0.058311
45	23	1	1	1	1	9570.89	.	276.54	9	.	.
46	23	2	1	2	1	6500.60	.	215.01	1	.	.
47	24	1	2	2	1	4171.82	.	312.28	5	.	.
48	24	2	2	1	1	12784.76	13743.50	420.23	5	10.7049	0.064751
49	25	1	2	2	1	11722.44	15068.93	321.50	12	29.4695	0.023521
50	25	2	2	1	1	7897.07	9331.90	260.55	9	14.7880	0.046872
51	27	1	1	1	1	15447.25	17496.54	586.69	7	13.6307	0.050852
52	27	2	1	2	1	29977.20	31110.16	726.23	5	18.2030	0.038079
53	28	1	2	2	1	28874.55	29428.25	1307.73	6	11.8083	0.058700
54	28	2	2	1	1	24119.32	24708.18	687.90	24	11.2930	0.061378
55	29	1	1	1	1	12611.79	.	297.96	12	.	.
56	29	2	1	2	1	9073.93	10968.34	334.93	6	16.7049	0.041494
57	30	1	2	2	1	7005.14	8386.73	232.00	2	16.4892	0.042036
58	30	2	2	1	1	4375.67	5066.10	178.37	5	14.4592	0.047938
59	31	1	2	2	1	9370.47	10686.36	320.55	12	14.2577	0.048615
60	31	2	2	1	1	7237.20	8636.55	294.94	12	17.3569	0.039935
61	32	1	1	1	1	12975.73	15104.50	470.99	10	14.9477	0.046371
62	32	2	1	2	1	21852.34	22779.65	643.30	12	14.2586	0.048612
63	33	1	2	2	1	12005.85	13939.49	297.89	24	17.1875	0.040329
64	33	2	2	1	1	12576.99	13499.09	366.43	20	15.6908	0.044175
65	34	1	1	1	1	18089.58	19479.05	514.69	9	16.8387	0.041164
66	34	2	1	2	1	17986.49	19563.80	428.49	24	17.3545	0.039941
67	35	1	2	2	1	13071.94	15546.69	439.57	7	18.7663	0.036936
68	35	2	2	1	1	18428.98	19020.11	605.70	12	12.7976	0.054162
69	36	1	1	1	1	19756.12	21471.04	550.28	10	17.6363	0.039302
70	36	2	1	2	1	27029.60	28012.96	611.97	24	17.8159	0.038906
71	37	1	2	2	1	25906.85	26884.18	636.32	12	14.5212	0.047733
72	37	2	2	1	1	17457.21	18349.14	507.96	12	14.4990	0.047807
73	38	1	1	1	1	7644.81	8238.39	255.04	9	10.8475	0.063899

Obs	sub	trt	seq	per	GRP	auct	auci	CMAX	TMAX	THALFR	KEL
74	38	2	1	2	1	4802.80	.	271.87	10	.	.
75	39	1	1	1	1	25838.28	27084.57	579.66	24	17.4447	0.039734
76	39	2	1	2	1	36922.17	42598.19	1026.21	12	21.6779	0.031975
77	40	1	2	2	1	6588.33	7165.35	317.10	10	11.8940	0.058277
78	40	2	2	1	1	12005.03	.	358.40	24	.	.
79	41	1	1	1	1	14660.43	15516.69	812.86	7	11.0683	0.062624
80	41	2	1	2	1	10636.68	11501.33	509.76	9	12.2135	0.056753
81	42	1	2	2	1	75070.20	76683.88	1457.83	24	18.4297	0.037610
82	42	2	2	1	1	50840.13	52216.06	1210.94	24	22.6076	0.030660

4.4.4 Fed (1 x 60 mg) Study Output (of Raloxifene)

FED STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	41	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 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42
trt	2	1 2
per	2	1 2
seq	2	1 2

Data for Analysis of AUCT CMAX LAUCT LCMAX	
Number of Observations Read	82
Number of Observations Used	82

Data for Analysis of AUCI LAUCI	
Number of Observations Read	82
Number of Observations Used	70

Note: Variables in each group are consistent with respect to the presence or absence of missing values.

FED STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	42	30.30049005	0.72144024	6.68	<.0001
Error	39	4.21021342	0.10795419		
Corrected Total	81	34.51070347			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.878003	3.422482	0.328564	9.600162

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.10453843	0.10453843	0.97	0.3312
sub(seq)	39	30.14485779	0.77294507	7.16	<.0001
per	1	0.02736449	0.02736449	0.25	0.6175
trt	1	0.02372934	0.02372934	0.22	0.6418

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.10453843	0.10453843	0.97	0.3312
sub(seq)	39	30.14485779	0.77294507	7.16	<.0001
per	1	0.02860499	0.02860499	0.26	0.6096
trt	1	0.02372934	0.02372934	0.22	0.6418

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	0.10453843	0.10453843	0.14	0.7150

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	-0.03403260	0.07258920	-0.47	0.6418

FED STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	42	17.01027826	0.40500663	6.85	<.0001
Error	39	2.30587285	0.05912494		
Corrected Total	81	19.31615111			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.880625	3.921175	0.243156	6.201106

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.25126203	0.25126203	4.25	0.0460
sub(seq)	39	16.74404471	0.42933448	7.26	<.0001
per	1	0.01470216	0.01470216	0.25	0.6208
trt	1	0.00026937	0.00026937	0.00	0.9465

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.25126203	0.25126203	4.25	0.0460
sub(seq)	39	16.74404471	0.42933448	7.26	<.0001
per	1	0.01479062	0.01479062	0.25	0.6198
trt	1	0.00026937	0.00026937	0.00	0.9465

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	0.25126203	0.25126203	0.59	0.4489

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	-0.00362596	0.05372020	-0.07	0.9465

FED STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	39	18.25752114	0.46814157	5.95	<.0001
Error	30	2.35888386	0.07862946		
Corrected Total	69	20.61640500			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.885582	2.853634	0.280409	9.826398

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.00681363	0.00681363	0.09	0.7705
sub(seq)	36	17.82206122	0.49505726	6.30	<.0001
per	1	0.37024642	0.37024642	4.71	0.0381
trt	1	0.05839986	0.05839986	0.74	0.3956

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00254515	0.00254515	0.03	0.8584
sub(seq)	36	17.83152211	0.49532006	6.30	<.0001
per	1	0.40184683	0.40184683	5.11	0.0312
trt	1	0.05839986	0.05839986	0.74	0.3956

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	0.00254515	0.00254515	0.01	0.9433

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	-0.06089276	0.07065654	-0.86	0.3956

AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS

Obs	sub	trt	AUCRATIO
1	1	1	0.87
2	2	1	0.98
3	3	1	0.97
4	4	1	0.98
5	5	1	0.97
6	6	1	0.92
7	7	1	0.90
8	8	1	0.95
9	9	1	.
10	10	1	0.94
11	11	1	.
12	12	1	.
13	13	1	0.95
14	14	1	0.91
15	15	1	0.86
16	16	1	0.95
17	17	1	0.96
18	18	1	0.86
19	19	1	0.93
20	20	1	0.96
21	21	1	0.87
22	22	1	0.93
23	23	1	.
24	24	1	.
25	25	1	0.84
26	27	1	0.88
27	28	1	0.98
28	29	1	.
29	30	1	0.84
30	31	1	0.88
31	32	1	0.86
32	33	1	0.92
33	34	1	0.93
34	35	1	0.84
35	36	1	0.92
36	37	1	0.96

Obs	sub	trt	AUCRATIO
37	38	1	0.93
38	39	1	0.95
39	40	1	0.92
40	41	1	0.94
41	42	1	0.98
42	1	2	0.96
43	2	2	0.97
44	3	2	0.96
45	4	2	0.92
46	5	2	0.93
47	6	2	0.94
48	7	2	0.84
49	8	2	0.95
50	9	2	0.85
51	10	2	0.88
52	11	2	.
53	12	2	.
54	13	2	0.97
55	14	2	.
56	15	2	0.90
57	16	2	0.87
58	17	2	0.92
59	18	2	0.91
60	19	2	0.90
61	20	2	0.93
62	21	2	0.90
63	22	2	0.93
64	23	2	.
65	24	2	0.93
66	25	2	0.85
67	27	2	0.96
68	28	2	0.98
69	29	2	0.83
70	30	2	0.86
71	31	2	0.84
72	32	2	0.96
73	33	2	0.93
74	34	2	0.92

Obs	sub	trt	AUCRATIO
75	35	2	0.97
76	36	2	0.96
77	37	2	0.95
78	38	2	.
79	39	2	0.87
80	40	2	.
81	41	2	0.92
82	42	2	0.97

TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS

sub	seq	RAUCT12	RAUC12	RCMAX12	RTMAX12	RKE12	RTHALF12
1	1	0.22	0.25	0.43	0.20	0.98	1.02
2	2	1.09	1.09	1.33	1.33	0.97	1.03
3	2	0.93	0.92	1.25	0.89	1.03	0.97
4	1	1.71	1.60	1.48	0.38	1.24	0.81
5	2	1.05	1.01	1.19	1.00	1.21	0.83
6	1	0.40	0.41	0.92	0.42	1.21	0.82
7	1	1.92	1.79	1.06	0.20	1.47	0.68
8	2	1.32	1.32	1.45	1.11	0.97	1.03
9	1	0.90	-	0.81	8.00	-	-
10	2	0.84	0.79	0.67	1.20	0.82	1.23
11	2	1.12	-	1.18	0.80	-	-
12	1	1.20	-	0.99	1.33	-	-
13	2	1.30	1.31	1.04	0.75	0.99	1.01
14	1	1.49	-	2.09	0.56	-	-
15	2	0.87	0.91	0.79	0.67	0.80	1.25
16	1	0.71	0.66	0.52	0.22	0.98	1.02
17	1	1.02	0.98	1.32	1.33	1.30	0.77
18	2	0.85	0.90	0.89	1.20	0.93	1.08
19	1	1.10	1.06	1.15	0.33	1.08	0.93
20	2	0.73	0.70	0.53	1.60	0.85	1.17
21	1	0.90	0.94	1.08	0.17	0.85	1.18
22	2	1.19	1.19	0.96	1.60	1.02	0.98
23	1	1.47	-	1.29	9.00	-	-
24	2	0.33	-	0.74	1.00	-	-
25	2	1.48	1.50	1.23	1.33	0.50	1.99
27	1	0.52	0.56	0.81	1.40	1.34	0.75
28	2	1.20	1.19	1.90	0.25	0.96	1.05
29	1	1.39	-	0.89	2.00	-	-
30	2	1.60	1.66	1.30	0.40	0.88	1.14
31	2	1.29	1.24	1.09	1.00	1.22	0.82
32	1	0.59	0.66	0.73	0.83	0.95	1.05
33	2	0.95	0.97	0.81	1.20	0.91	1.10
34	1	1.01	1.00	1.20	0.38	1.03	0.97
35	2	0.71	0.82	0.73	0.58	0.68	1.47
36	1	0.73	0.77	0.90	0.42	1.01	0.99
37	2	1.48	1.47	1.25	1.00	1.00	1.00

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
38	1	1.59	.	0.94	0.90	.	.
39	1	0.70	0.64	0.56	2.00	1.24	0.80
40	2	0.55	.	0.88	0.42	.	.
41	1	1.38	1.35	1.59	0.78	1.10	0.91
42	2	1.48	1.47	1.20	1.00	1.23	0.82

RATIO OF SPONSOR/REVIEWER CALCULATED PARAMETERS

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	1	1	1	1	1	9205.48	10539.96	363.74	A	9205.48	10539.96	363.74	1.00000	1.00000	1
2	1	1	2	1	2	41025.01	42699.87	853.61	B	41025.01	42699.87	853.61	1.00000	1.00000	1
3	2	2	1	1	2	30568.29	31369.04	735.40	B	30568.29	31369.04	735.40	1.00000	1.00000	1
4	2	2	2	1	1	33353.59	34123.00	975.16	A	33353.59	34123.00	975.16	1.00000	1.00000	1
5	3	2	1	1	2	21945.50	22912.51	572.61	B	21945.50	22912.51	572.61	1.00000	1.00000	1
6	3	2	2	1	1	20407.63	21056.87	713.37	A	20407.63	21056.87	713.37	1.00000	1.00000	1
7	4	1	1	1	1	34633.94	35292.54	762.31	A	34633.94	35292.54	762.31	1.00000	1.00000	1
8	4	1	2	1	2	20305.33	22027.47	514.38	B	20305.33	22027.47	514.38	1.00000	1.00000	1
9	5	2	1	1	2	21155.91	22701.89	600.19	B	21155.91	22701.89	600.19	1.00000	1.00000	1
10	5	2	2	1	1	22194.72	22879.63	716.96	A	22194.72	22879.63	716.96	1.00000	1.00000	1
11	6	1	1	1	1	7606.41	8304.43	409.98	A	7606.41	8304.43	409.98	1.00000	1.00000	1
12	6	1	2	1	2	18975.83	20129.42	446.17	B	18985.40	20140.79	446.17	1.00050	1.00056	1
13	7	1	1	1	1	22362.06	24845.76	567.33	A	22362.06	24845.76	567.33	1.00000	1.00000	1
14	7	1	2	1	2	11672.86	13875.81	535.64	B	11672.86	13875.81	535.64	1.00000	1.00000	1
15	8	2	1	1	2	21925.27	23033.92	635.56	B	21925.27	23033.92	635.56	1.00000	1.00000	1
16	8	2	2	1	1	28879.77	30346.37	918.82	A	28879.77	30346.37	918.82	1.00000	1.00000	1
17	9	1	1	1	1	9742.08		279.09	A	9742.08	12400.83	279.09	1.00000		1
18	9	1	2	1	2	10831.90	12695.16	343.91	B	10831.90	12695.16	343.91	1.00000	1.00000	1
19	10	2	1	1	2	19840.47	22430.34	741.92	B	19840.47	22430.34	741.92	1.00000	1.00000	1
20	10	2	2	1	1	16690.55	17827.76	498.05	A	16690.55	17827.76	498.05	1.00000	1.00000	1
21	11	2	1	1	2	4445.17		399.84	B	4445.17	6265.60	399.84	1.00000		1
22	11	2	2	1	1	4970.56		473.43	A	4970.57	8623.15	473.43	1.00000		1
23	12	1	1	1	1	4821.52		279.19	A	4821.52	8594.20	279.19	1.00000		1
24	12	1	2	1	2	4010.78		282.63	B	4010.78	6756.59	282.63	1.00000		1
25	13	2	1	1	2	46043.52	47697.09	1580.62	B	46086.50	47747.74	1580.62	1.00093	1.00106	1
26	13	2	2	1	1	59844.80	62676.81	1641.17	A	59844.80	62676.81	1641.17	1.00000	1.00000	1
27	14	1	1	1	1	10072.32	11055.46	504.95	A	10072.32	11055.46	504.95	1.00000	1.00000	1

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUICI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
28	14	1	2	1	2	6766.60	.	241.97	B	6766.60	8042.68	241.97	1.00000	.	1
29	15	2	1	1	2	13637.44	15081.54	518.26	B	13637.44	15081.54	518.26	1.00000	1.00000	1
30	15	2	2	1	1	11801.12	13770.91	407.51	A	11801.12	13770.91	407.51	1.00000	1.00000	1
31	16	1	1	1	1	16012.32	16856.89	456.88	A	16012.32	16856.90	456.88	1.00000	1.00000	1
32	16	1	2	1	2	22414.21	25657.83	875.87	B	22414.21	25657.83	875.87	1.00000	1.00000	1
33	17	1	1	1	1	26477.66	27620.86	826.89	A	26477.66	27620.86	826.89	1.00000	1.00000	1
34	17	1	2	1	2	26080.56	28302.13	626.44	B	26080.56	28302.13	626.44	1.00000	1.00000	1
35	18	2	1	1	2	12827.51	14131.81	292.98	B	12827.51	14131.81	292.98	1.00000	1.00000	1
36	18	2	2	1	1	10956.73	12722.44	261.05	A	10956.73	12722.44	261.05	1.00000	1.00000	1
37	19	1	1	1	1	26413.72	28396.58	748.52	A	26413.72	28396.58	748.52	1.00000	1.00000	1
38	19	1	2	1	2	24118.98	26672.35	649.06	B	24118.98	26672.35	649.06	1.00000	1.00000	1
39	20	2	1	1	2	23382.04	25212.95	930.94	B	23382.04	25212.95	930.94	1.00000	1.00000	1
40	20	2	2	1	1	17029.12	17684.87	494.35	A	17082.72	17748.19	494.35	1.00315	1.00358	1
41	21	1	1	1	1	7963.31	9116.73	310.36	A	7963.31	9116.73	310.36	1.00000	1.00000	1
42	21	1	2	1	2	8816.32	9741.90	288.02	B	8816.32	9741.90	288.02	1.00000	1.00000	1
43	22	2	1	1	2	7323.47	7877.69	423.83	B	7323.47	7877.69	423.83	1.00000	1.00000	1
44	22	2	2	1	1	8696.24	9389.28	406.37	A	8696.24	9389.28	406.37	1.00000	1.00000	1
45	23	1	1	1	1	9570.89	.	276.54	A	9601.60	10978.49	276.54	1.00321	.	1
46	23	1	2	1	2	6500.60	.	215.01	B	6500.60	8222.51	215.01	1.00000	.	1
47	24	2	1	1	2	12784.76	13743.50	420.23	B	12784.76	13743.50	420.23	1.00000	1.00000	1
48	24	2	2	1	1	4171.82	.	312.28	A	4171.82	7696.95	312.28	1.00000	.	1
49	25	2	1	1	2	7897.07	9331.90	260.55	B	7897.07	9331.91	260.55	1.00000	1.00000	1
50	25	2	2	1	1	11722.44	15068.93	321.50	A	11722.44	13966.24	321.50	1.00000	0.92682	1
51	27	1	1	1	1	15447.25	17496.54	586.69	A	15447.25	17496.54	586.69	1.00000	1.00000	1
52	27	1	2	1	2	29977.20	31110.16	726.23	B	29977.20	31110.16	726.23	1.00000	1.00000	1
53	28	2	1	1	2	24119.32	24708.18	687.90	B	24119.32	24708.18	687.90	1.00000	1.00000	1
54	28	2	2	1	1	28874.55	29428.25	1307.73	A	28874.55	29428.25	1307.73	1.00000	1.00000	1
55	29	1	1	1	1	12611.79	.	297.96	A	12611.79	19712.43	297.96	1.00000	.	1
56	29	1	2	1	2	9073.93	10968.34	334.93	B	9073.93	10968.34	334.93	1.00000	1.00000	1

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
57	30	2	1	1	2	4375.67	5066.10	178.37	B	4375.67	5066.10	178.37	1.00000	1.00000	1
58	30	2	2	1	1	7005.14	8386.73	232.00	A	7005.14	8386.73	232.00	1.00000	1.00000	1
59	31	2	1	1	2	7237.20	8636.55	294.94	B	7237.20	8636.55	294.94	1.00000	1.00000	1
60	31	2	2	1	1	9370.47	10686.36	320.55	A	9370.47	10686.36	320.55	1.00000	1.00000	1
61	32	1	1	1	1	12975.73	15104.50	470.99	A	12975.73	15104.50	470.99	1.00000	1.00000	1
62	32	1	2	1	2	21852.34	22779.65	643.30	B	21852.34	22779.66	643.30	1.00000	1.00000	1
63	33	2	1	1	2	12576.99	13499.09	366.43	B	12576.99	13499.09	366.43	1.00000	1.00000	1
64	33	2	2	1	1	12005.85	13939.49	297.89	A	12005.85	13071.84	297.89	1.00000	0.93776	1
65	34	1	1	1	1	18089.58	19479.05	514.69	A	18089.58	19479.05	514.69	1.00000	1.00000	1
66	34	1	2	1	2	17986.49	19563.80	428.49	B	17986.49	19563.81	428.49	1.00000	1.00000	1
67	35	2	1	1	2	18428.98	19020.11	605.70	B	18428.98	19020.11	605.70	1.00000	1.00000	1
68	35	2	2	1	1	13071.94	15546.69	439.57	A	13071.94	15546.69	439.57	1.00000	1.00000	1
69	36	1	1	1	1	19756.12	21471.04	550.28	A	19756.13	21471.04	550.28	1.00000	1.00000	1
70	36	1	2	1	2	27029.60	28012.96	611.97	B	27029.60	28012.96	611.97	1.00000	1.00000	1
71	37	2	1	1	2	17457.21	18349.14	507.96	B	17457.21	18349.14	507.96	1.00000	1.00000	1
72	37	2	2	1	1	25906.85	26884.18	636.32	A	25906.85	26832.57	636.32	1.00000	0.99808	1
73	38	1	1	1	1	7644.81	8238.39	255.04	A	7644.81	8238.39	255.04	1.00000	1.00000	1
74	38	1	2	1	2	4802.80	.	271.87	B	4802.80	12176.03	271.87	1.00000	.	1
75	39	1	1	1	1	25838.28	27084.57	579.66	A	26176.56	27441.99	579.66	1.01309	1.01320	1
76	39*	1	2	1	2	36922.17	42598.19	1026.21	B	30654.09	42197.30	1026.21	0.83024	0.99059	1
77	40	2	1	1	2	12005.03	.	358.40	B	12005.03	.	358.40	1.00000	.	1
78	40	2	2	1	1	6588.33	7165.35	317.10	A	6588.33	7165.35	317.10	1.00000	1.00000	1
79	41	1	1	1	1	14660.43	15516.69	812.86	A	14660.43	15516.69	812.86	1.00000	1.00000	1
80	41	1	2	1	2	10636.68	11501.33	509.76	B	10636.68	11501.33	509.76	1.00000	1.00000	1
81	42	2	1	1	2	50840.13	52216.06	1210.94	B	50840.13	52216.06	1210.94	1.00000	1.00000	1
82	42	2	2	1	1	75070.20	76683.88	1457.83	A	75070.20	76683.88	1457.83	1.00000	1.00000	1

* Plasma concentrations of the test product were measured until the 96-hour time point for subject 39, whereas plasma concentrations for the reference product were measured until the 48-hour time point.

Note: The above table comparing the firm to reviewer ratio of PK parameters was generated using the SAS code "CALCKE."

BIOEQUIVALENCE DEFICIENCIES

ANDA: 090842

APPLICANT: InvaGen Pharmaceuticals, Inc.

DRUG PRODUCT: Raloxifene Hydrochloride Tablets USP, 60 mg

The Division of Bioequivalence (DBE) has completed its review of the submission acknowledged on the cover page and has identified the following deficiencies:

1. Please explain the term "No Intercept" used to assign to the original values of the raloxifene-4'-glucuronide samples which were reanalyzed for the reason "Concentration Over the Calibration Curve (OCC)" in fasting study no. BA0818122-01. The same term was also used for the raloxifene-4'-glucuronide QC samples in fasting study no. BA0818122-01.
2. Please provide objective justifications for manually integrating the peaks for samples S3P2 96.0 HR SUB3&4_61 (raloxifene), S3P2 96.0 HR SUB3&4_61 (raloxifene-4'-glucuronide), S3P2 96.0 HR SUB3&4_61 (raloxifene-6-glucuronide), and S5P2 96.0 HR SUB5&6_60 (raloxifene-4'-glucuronide) in fasting study no. BA0818122-01. Please also provide the standard operating procedure (SOP) detailing the reintegration method.
3. Please explain why subject 11 had no measurable raloxifene concentrations at all time points after receiving the test product treatment in the fasting study no. BA0818122-01, considering that this subject had measurable concentrations for both glucuronide metabolites under the same treatment. This subject also had measurable concentrations of raloxifene and raloxifene glucuronide metabolites after receiving the reference product.
4. You repeated the sample S27P1 9.0 Hour in your fasting study using the following reason: "S27P1 9.0 Hour had a concentration of 7218.021pg/mL and the analyte peak area also was very high (~100 times) when compared to the preceding and succeeding time points. No such abnormality was found in RA4G and RA6G for this particular time point. Hence S27P1 9.0 Hour was repeated under AI, suspected analytical interference from the analyst during processing." However, per your SOP No. (b) (4) "Analytical Interference (AI)" is defined as "Predose sample having interference more than LOQ standard (Std A)." Therefore, your repeat of the above-mentioned was a violation of your SOP, and is not valid. Rather, the DBE considers such repeat as "PK repeat" and biased. In such case, only the original value for this sample (S27P1 9.0 Hour) of your fasting study should be used in the data analysis of the study. The DBE reanalyzed the data using the original value of the above sample and the 90% C.I. for lnCmax of raloxifene, [65.27;101.56], failed to meet the acceptable bioequivalence limits of [80.00;125.00]. In addition, the point estimate for lnCmax of raloxifene-4'-glucuronide

was outside the limits of [80.00;125.00] and did not support the bioequivalence of test product. Therefore, your fasting bioequivalence study no. BA0818122-01 is unacceptable.

5. Please indicate what medical interventions were used to resolve the adverse events experienced by subject 13 (headache) and subject 26 (fever) in the fed study no. BA0818123-01.
6. Please submit chromatograms from at least 20% of the total number of subjects that completed fed study no. BA0818123-01 (i.e. 20% of 41 subjects, or at least 8 subjects).
7. In 2009, following the inspection by the FDA Division of Scientific Investigations (DSI) of the analytical site (b) (4) (b) (4) Form FDA-483 was issued. One of the DSI's objectable findings was (b) (4) (b) (4) (b) (4) The analytical site's response to this DSI Finding was that the SOP was revised to require (b) (4) (b) (4) for preparation of calibrators and QCs.

The sample analysis of the bioequivalence studies of your current application was conducted at (b) (4) prior to the above DSI inspection and (b) (4) response stating its commitment to revise the SOP for the preparation of calibration curve standards and quality control samples. Please indicate (b) (4) (b) (4) in the current ANDA. Also, please submit (b) (4) revised and current SOP for the preparation of calibration curve standards and quality control samples.

Sincerely yours,

{See appended electronic signature page}

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

4.5 Outcome Page

COMPLETED ASSIGNMENT FOR 90842 ID: 12889

Reviewer: Kitchens, Kelly

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Raloxifene Hydrochloride Tablets, 60 mg

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
12889	10/2/2008	Bioequivalence Study	Fasting Study	1	1
12889	10/2/2008	Bioequivalence Study	Fed Study	1	1
12889	12/6/2010	Other	Study Amendment Without Credit (WC)	0	0
				Bean Total:	2

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

/s/

KELLY M KITCHENS

01/28/2011

YIH CHAIN HUANG

01/28/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER

01/28/2011

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	90-842	
Drug Product Name	Raloxifene Hydrochloride Tablets	
Strength (s)	60 mg	
Applicant Name	InvaGen Pharmaceuticals Inc.	
Address	7 Oser Ave, Hauppauge, NY 11788	
Applicant's Point of Contact	Sudhakar r. Vidiyala, President	
Contact's Phone Number	631-231-3233	
Contact's Fax Number	631-231-4248	
Submission Date(s)	October 2, 2008	
First Generic	No.	
Reviewer	Christina Lee, Pharm.D.	
Study Number (s)	BA0818122	BA0818123
Study Type (s)	Fasting	Fed
Strength(s)	1 x 60 mg	1 x 60 mg
Clinical Site	BA Research India Ltd	
Clinical Site Address	Opposite Pushparaj Towers, Nr. Judges Bungalows, Bodakdev, Ahmedabad-380054, Gujarat, India	
Analytical Site	(b) (4)	
Analytical Address		
OUTCOME DECISION	ACCEPTABLE	

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP method for this product but there is an FDA-recommended method. The firm's dissolution testing data with the FDA-recommended method are acceptable (at the S1 level). The firm also meets the FDA-recommended specification. The DBE acknowledges that the firm will conduct dissolution testing and specification as follows:

Medium:	0.1% Polysorbate 80 in water
Apparatus:	II (Paddle)
Volume:	1000 mL
Speed/RPMs:	50 rpm
Sampling Times:	10, 20, 30 and 45 minutes
Specification:	NLT 80% (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes

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

DSI status: BA Research India Ltd (Clinical site) was inspected as routine inspection and the inspection outcome was reported by the FDA inspector on December 18, 2007 as VAI. The final conclusion of the inspection report was that “*the data for study BA0559019 are acceptable for Agency review*” (DFS: Review of Biopharmaceutics, N076847 N 000 19-Sep-2003). [REDACTED] (b) (4) (Analytical site) is a new site that is not in the current DBE DSI database. Therefore, a request for site inspection is initiated.

Table 1: SUBMISSION CONTENT CHECKLIST

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

* Both fasting and fed study SAS data included PK parameters and plasma concentrations for Raloxifene, Raloxifene-4-Glucuronide and Raloxifene-6-flucuronide.

**The long-term storage stability was reported as 64 days @ -80°C under both fasting and fed studies. The study periods for both fasting and fed studies took 38 days until the last sample analyzed.

FDA method:

Medium: 0.1% Polysorbate 80 in water
Apparatus: II (Paddle)
Volume: 1000 mL
Speed/RPMs: 50 rpm
Sampling Times: 10, 20, 30 and 45 minutes
Specification: NLT 80%, 30 min

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Dissolution Conditions		Apparatus:		USP Apparatus (II) Paddle							
		Speed of Rotation:		50 rpm							
		Medium:		0.1% Polysorbate 80 in water							
		Volume:		1000 ml							
		Temperature:		37.0 ± 0.5 C							
Firm's Proposed Specifications		NLT 80% (Q) in 30 minutes									
Dissolution Testing Site (Name, Address)		InvaGen Pharmaceuticals, Inc., Hauppauge, NY 11788									
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)					Study Report Location
						10 Min	20 Min	30 Min	45 Min	60 Min	
Study Report #: N/A	06/03/08	Test Product Raloxifene Hydrochloride Tablets, 60 mg Batch # ID080510 Mfg. Date: 05/28/2008	60 mg Tablet	12	Mean	86.4	95.2	96.0	95.4	94.4	N/A
					Range Min : Max:	(b) (4)					N/A
					%CV	4.2	2.1	1.7	1.6	1.7	N/A
Study Report #: N/A	06/03/08	Reference Product Evista® Tablets, 60 mg Batch # A489455 Exp. Date: 02/2010	60 mg Tablet	12	Mean	67.5	95.1	96.2	96.6	96.7	N/A
					Range Min : Max :	(b) (4)					N/A
					%CV	13.9	1.9	2.1	1.4	1.9	N/A

II. COMMENTS:

The firm conducted dissolution testing using the dissolution method described on the FDA website. The dissolution data meet the DBE-recommended specification of NLT 80% in 30 minutes at the S1 level. The firm proposed a specification of NLT 80% (Q) in 30 minutes, which is the same as that recommended by the DBE. The DBE acknowledges that the firm will conduct dissolution testing and specification as follows:

Medium:	0.1% Polysorbate 80 in water
Apparatus:	II (Paddle)
Volume:	1000 mL
Speed/RPMs:	50 rpm
Sampling Times:	10, 20, 30 and 45 minutes
Specification:	NLT 80% (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes

III. DEFICIENCY COMMENTS:

None.

IV. RECOMMENDATIONS:

The dissolution testing conducted by InvaGen Pharmaceuticals, Inc. for the test product Raloxifene HCl Tablets, 60 mg (Lot # ID080510) comparing it to the RLD, Evista[®] Tablets (Raloxifene HCl) manufactured by Eli Lilly using the FDA-recommended method is **acceptable**. The DBE acknowledges that the firm will conduct its dissolution testing with the FDA-recommended dissolution method and the test product should meet the specification of NLT 80%(Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-842

APPLICANT: InvaGen Pharmaceuticals, Inc.

DRUG PRODUCT: Raloxifene HCl Tablets, 60 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the bioequivalence studies will be done at a later date.

Your dissolution testing with the FDA-recommended dissolution method, and the proposed dissolution specification are acceptable. The DBE acknowledges that you will conduct the dissolution testing using the following method and specification for your test product:

The dissolution testing should be conducted in 1000 mL of 0.1% Polysorbate 80 in water, at $37^{\circ} \pm 5^{\circ}\text{C}$, using USP Apparatus 2 (paddle) at 50 rpm. The test product should meet the following specification:

Not less than 80%(Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Sincerely yours,

{See appended electronic signature page}

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

V. OUTCOME

Completed Assignment for 90842 ID: 7179

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
7179	10/2/2008	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

In Vitro Study Review

Analysis of In Vitro Study Data	1
<i>In Vitro Study Review Total</i>	1

**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
1/9/2009 09:29:32 AM
BIOPHARMACEUTICS

Chandra S. Chaurasia
1/9/2009 01:00:47 PM
BIOPHARMACEUTICS

Hoainhon T. Nguyen
1/9/2009 04:54:54 PM
BIOPHARMACEUTICS
For Dale P. Conner, Pharm. D., Director, Division of
Bioequivalence I

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 90842

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 #: **90842**

Firm Name: **InvaGen Pharmaceuticals, Inc.**

ANDA Name: **Raloxifene Hydrochloride Tablets, USP 60 mg**

RLD Name: **Evista / Eli Lilly**

Electronic AP Routing Summary Located:

V:\Chemistry Division I\Team 14\AP ROUTING SUMMARY\90842 APRV ROUT SUMRY.doc

AP/TA Letter Located:

V:\Chemistry Division I\Team 14\Final Version For DARRTS (Original)\90842.AP LTR.doc

Project Manager Evaluation:

Date: **7/23/14** Initials: **BN**

- ☒ Previously reviewed and tentatively approved --- Date 10/21/13
☐ Previously reviewed and CGMP Complete Response issued -- Date _____

Original Rec'd date <u>10/2/08</u>	Date of Application <u>10/2/08</u>	Date Acceptable for Filing <u>10/6/08</u>
Patent Certification (type) <u>PIV</u>	Date Patent/Excl. expires <u>3/10/17</u>	Citizens' Petition/Legal Case? Yes ☐ No ☐ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☐ DMF#: <u>(b) (4)</u> (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: 12/9/14* ☐ Warning Letter Issued; Date:

Has there been an amendment providing for a Major change in formulation since filing? Yes ☐ No ☐ Comment:

Date of Acceptable Quality (Chemistry) 9/15/14 Addendum Needed: Yes ☐ No ☐ Comment:

Date of Acceptable Bio 8/19/11 Bio reviews in DARRTS: Yes ☐ No ☐ (Volume location: _____)

Date of Acceptable Labeling 11/16/10 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: 9/23/14 REMS Required: Yes ☐ No ☐ REMS Acceptable: Yes ☐ No ☐

☒ Regulatory Support

☒ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: 9/16/14

☒ Division

☒ Bob West / Peter Rickman

☐ Kathleen Uhl

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

Reference ID: 3645455

Revised, Jun 2013

OGD APPROVAL ROUTING SUMMARY

1. **Regulatory Support Branch Evaluation**

Martin Shimer

Date: 9/16/2014

Chief, Reg. Support Branch

Initials: MHS

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)	Determ. of Involvement? Yes ☐ No ☐
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☒ No ☐ Was applicant sued w/in 45 days: Yes ☒ No ☐ Has case been settled: Yes ☒ No ☐ Date settled: Is applicant eligible for 180 day NO Is a forfeiture memo needed: Yes ☐ No ☒ If yes, has it been completed	Pediatric Exclusivity System RLD = <u>Evista Tablets</u> NDA# <u>20-815</u> Date Checked <u>9/23/14</u> Nothing Submitted ☒ Written request issued ☐ Study Submitted ☐
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 March 4, 2014. At the time the TA was issued the reason cited for TA was another sponsor's blocking 180 day exclusivity. Currently the only unexpired patents are the '811, '719, '064 and '330 patents. Invagen provided PIV certifications to each of these patents. Invagen was not sued on the '330. Invagen was sued on the '811, '719 and '064 patents but this suit was voluntarily WD by Lilly. The only remaining barrier to the approval of this ANDA is 180 day exclusivity granted to TEVA ANDA 78193 which is set to expire on 9/24/2014. ANDA is eligible for Full Approval on or after 9/24/2014.	

2. **Labeling Endorsement**

Reviewer, CH:

Labeling Team Leader, JG:

Date 9/23/14

Date 9/23/14

REMS required?

☐ Yes ☒ No

REMS acceptable?

☐ Yes ☒ No ☐ n/a

Comments:

From: Grace, John F

Sent: Tuesday, September 23, 2014 9:29 AM

To: Hoppes, Charles V; Nguyen, Bic (CDER); Golson, Lillie D

Subject: RE: 90842

concur.

From: Hoppes, Charles V

Sent: Tuesday, September 23, 2014 9:29 AM

To: Nguyen, Bic (CDER); Golson, Lillie D

Cc: Grace, John F

Subject: RE: 90842

Thanks Bic,

Yes, labeling should still be OK as there have been no updates to RLD labeling. Also, I have copied John who has resumed TL duties for present.

Reference ID: 3645455

Revised, Jun 2013

Thanks,

Charlie.

3. **Paragraph IV Evaluation**

PIV's Only

David Read

Date 9/23/14

Initials rlw/for

OGD Regulatory Counsel

Pre-MMA Language included ☐

Post-MMA Language Included ☒

Comments: Acceptable for approval. E-mail confirmation from D.Read to R.West 9/23/14.

4. **Quality Division Director /Deputy Director Evaluation**

Date 9/23/14

Initials rlw/for

Chemistry Div. I (Raw)

Comments: Chemistry Review #4, concluding that the CMC section of this ANDA is acceptable for final approval was endorsed by B. Cai, Ph.D., Deputy Director, Division of Chemistry I, on 9/15/14. The pending DMF (b) (4) noted in the review has been NAI'ed by the CMC Team.

OGD Office Management Evaluation

5. **Peter Rickman**

Date 9/23/14

Initials rlw/for

Director, DLPS

Para.IV Patent Cert: Yes ☐ ☐ ☐ No ☐

Pending Legal Action: Yes ☐ ☐ No ☐

Petition: Yes ☐ No ☐

Entered to APTrack database ☐

GDUFA User Fee Obligation Status Met ☐ Unmet ☐

Press Release Acceptable ☐

Date PETS checked for first generic drug _____

Comments: This ANDA was granted tentative approval on 3/4/14. Final approval was blocked at that time by Teva's 180-day generic drug exclusivity under ANDA 78-193 for Raloxifene HCl Tablets USP, 60 mg that will expire on 9/24/14. Refer to the administrative summary completed at the time of the tentative approval. With the expiration of Teva's 180-day generic drug exclusivity, InvaGen's ANDA is eligible for final approval.

Final-printed labeling (FPL) remains acceptable for final approval as evidenced by labeling endorsement dated 9/23/14 above.

CMC found acceptable for final approval (Chemistry Review #4) 9/15/14.

OR

6. **Robert L. West**

Date 9/23/14

Initials RLWest

Deputy Director, OGD

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 7/1/14 (Verified 9/23/14). No "OAI" Alerts noted.

InvaGen provided paragraph IV certifications to the '811, '719, '064 and '330 patents and was sued within the 45-day period on the '811, '719 and '064 patents. The litigation was voluntarily withdrawn by the NDA holder, Eli Lilly.

There are no additional unexpired patents or exclusivity currently listed in the "Orange Book" for this drug patent.

7. ***OGD Director Evaluation***

Kathleen Uhl

Comments: RL West for Jason Woo, M.D., M.P.H., Acting Director, Office of Regulatory Operations, 9/23/14.

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

Application Oracle

Application Establishments Status Milestones Comments Contacts ProductProcess

Application: A 90842/000 Subtype: N/A Sponsor: INVAGEN PHARMS

Drug Name: BALOXIFENE HYDROCHLORIDE

FEI / CFN	Establishment Name	Profile Code	Last Milestone Name	Last Milestone Date	Last Compliance Status	Last Compliance Date	OAI Alert	EER Re-eval Date
(b) (4)								
3003950641	INVAGEN PHARMACEUTICAL	TCM OC RECOMMENDATION		08-APR-2014	AC	08-APR-2014		08-MAR-2015

Current Overall OC Recmnd: Date: (b) (4)

Recommendation: ACCEPTABLE

Overall Re-eval Date: (b) (4)

Overall OC Recommendation History:

Date	Recommendation	Overall Re-eval Date
(b) (4)	PENDING	
08-APR-2014	ACCEPTABLE	(b) (4)

OAI Alert Comments

Save

Close

Forms Services

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	
N020815	001	6797719	Mar 10, 2017		Y		

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
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.

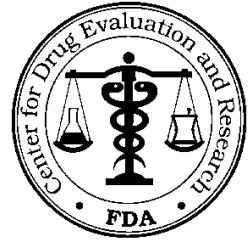
/s/

BIC N NGUYEN
10/20/2014

EASILY CORRECTABLE DEFICIENCY EMAIL

ANDA 090842

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



APPLICANT: InvaGen Pharmaceuticals, Inc.

TEL: 631-231-3233

ATTN: Ram Mohan Kathuroju

FAX: 631-231-4248

FROM: Bic Nguyen

FDA CONTACT PHONE: 240-402-9188

Dear Sir:

This communication is in reference to your abbreviated new drug application (ANDA) dated October 2, 2008, 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 240-402-9188.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

We have completed our review, and have the following comments:

PRODUCT QUALITY

A. Deficiencies

(b) (4)



Sincerely yours,

{See appended electronic signature page}

Andre S. Raw, Ph.D.
Director
Division of Chemistry I
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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

/s/

GURURAJ BYKADI
08/14/2014

ROUTING SHEET

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

Division: **I** Team: **14** PM: **Bic Nguyen**

Electronic ANDA:

Yes ☒ No ☒

ANDA #: **090842**

Firm Name: **InvaGen Pharmaceuticals, Inc**

ANDA Name: **Raloxifene Hydrochloride Tablets, 60 mg**

RLD Name: **Evista / Eli Lilly**

Electronic AP Routing Summary Located:

V:\Chemistry Division I\Team 14\AP ROUTING SUMMARY\90842 2ndTAAPRV ROUT SUMRY.doc

AP/TA Letter Located:

V:\Chemistry Division I\Team 14\Final Version For DARRTS (Original)\90842.2ndTA LTR.doc

Project Manager Evaluation:

Date: **12/31/12** Initials: **BN**

- ☒ Previously reviewed and tentatively approved --- Date 6/21/12
☐ Previously reviewed and CGMP Complete Response issued -- Date _____

Original Rec'd date <u>10/6/2008</u>	Date of Application <u>10/2/2008</u>	Date Acceptable for Filing <u>10/6/2008</u>
Patent Certification (type) <u>MOU, PIII, PIV</u>	Date Patent/Excl. expires <u>3/2/14</u>	Citizens' Petition/Legal Case? Yes ☐ No ☐ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☐ DMF#: <u>(b) (4)</u> (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: 3/2/14* ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filing? Yes ☐ No ☐ Comment:
Date of Acceptable Quality (Chemistry) 6/14/12 Addendum Needed: Yes ☐ No ☐ Comment:
Date of Acceptable Bio 8/19/11 Bio reviews in DARRTS: Yes ☐ No ☐ (Volume location: _____)
Date of Acceptable Labeling 11/16/10 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

Reference ID: 3464371

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 ☐ (required if sub after 6/1/92)	Determ. of Involvement? Yes ☐ No ☐
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	Pediatric Exclusivity System RLD = _____ NDA# _____ Date Checked _____ Nothing Submitted ☐ Written request issued ☐ Study Submitted ☐
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 6/21/2012. At the time the TA was issued the reason cited for TA was the sponsor's PIII certs to the unexpired '847 and '050 patents both of which expire on 3/2/2014, firm proposes a carve-out of ODE exclusivity. Invagen had been sued by Lilly with respect to the '811, '719 and '064 patents with Lilly voluntarily dismissing this litigation. Invagen was not sued wrt the '120, '383 and '330 patents. Request for final approval submitted by InvaGen on 12/24/2013-InvaGen provided a synopsis of this litigation history in this cover letter and also submitted a copy of the dismissal order for CA 09 CV 0087 in the SD of IN dated 12/8/2010. Even after the expiration of 4 patents which expire on 3/2/2014, this ANDA will remain eligible for TA only. (b) (4) (b) (4) holds the 180 day exclusivity seat for this product. (b) (4) exclusivity seat is associated with multiple patents which expire after 3/2/2014. Therefore, (b) (4) 180 day exclusivity will be a barrier to the approval of all subsequent applicants. For the record: at this point (b) (4) is the sole applicant to hold the patent-by-patent 180 day exclusivity seats for the '811, '719, and '064 patents with each of these patents expiring on 3/10/2017. (b) (4) also shares a 180 day exclusivity seat for the later-listed '330 patent with TEVA(ANDA 78193) as each of these applicants submitted a valid patent certification to the '330 patent on 10/28/2011. However, in the end since (b) (4) is the sole applicant eligible for 180 day exclusivity wrt the '811, '719 and '064 patents and shares seat wrt the '330 patent we do not have an exclusivity stand-off in which Applicant A blocks Applicant B with respect to patents 1, 2 and 3 while Applicant B blocks Applicant A with respect to patent 4. This scenario is Applicant A blocks Applicant B wrt patents 1, 2 and 3 and Applicant A and Applicant B share the exclusivity seat for patent 4. Under this non-mutually blocking scenario Applicant A is considered the sole applicant eligible for 180 day exclusivity with exclusivity awarded solely to Applicant A-in this case (b) (4) (b) (4) This ANDA is eligible for TA only due to blocking pre-MMA 180 day exclusivity.	

2. **Labeling Endorsement**

Reviewer, RW:

Labeling Team Leader, KL:

Date 2/12/14

Date 2/12/14

REMS required?

REMS acceptable?

☐ Yes ☒ No

☐ Yes ☒ No ☐ n/a

Comments:

From: Lee, Koung U

Sent: Wednesday, February 12, 2014 3:12 PM

To: Wu, Ruby (Chi-Ann); Nguyen, Bic (CDER)

Subject: RE: 90842 Raloxifene

Thanks Ruby, I concur.
Reference ID: 3464371

Koung

From: Wu, Ruby (Chi-Ann)
Sent: Wednesday, February 12, 2014 2:48 PM
To: Nguyen, Bic (CDER); Lee, Koung U
Subject: RE: 90842 Raloxifene

Hi Koung,

The labeling ap summary signed off 11/16/10 remains acceptable.

Patent '330 was added to the orange book after the labeling review was signed off. Firm filed PIV, which does not affect the labeling.

Hi Bic,

I believe the firm provided split certification for patent '811 and patent '064. Does the split certification need to be described in the letter?

Thanks,

Ruby

3. ***Paragraph IV Evaluation***

PIV's Only

David Read

Date 26Feb2014

InitialsDTR

OGD Regulatory Counsel

Pre-MMA Language included ☐

Post-MMA Language Included ☒

Comments: Changes to 2ndTA letter saved to the V drive.

4. ***Quality Division Director /Deputy Director Evaluation***

Date 2/24/2014

Chemistry Div. I (Raw)

InitialsBC

Comments: CMC remains adequate

OGD Office Management Evaluation

5. **Peter Rickman**

Date 3/2/2014

Initials wpr

Director, DLPS

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 previously TA'd on 6/21/2012 because the applicant's made PIII patent certs to the unexpired '847 and '050 patents both of which expire on 3/2/2014. The applicant proposes a carve-out of ODE exclusivity. Invagen had been sued by Lilly with respect to the '811, '719 and '064 patents with Lilly voluntarily dismissing this litigation. Invagen was not sued on the '120, '383 and '330 patents. Even after the expiration of the 4 patents which expire on 3/2/2014, this ANDA will remain eligible for TA only. (b) (4) holds the 180 day exclusivity seat for this product. Chemistry acceptable 6/14/2012. Bio acceptable 8/19/2011 (fasting and fed studies 60 mg), no OSI issues that are specific to this ANDA. Labeling acceptable 11/16/2010, TL sign-off 2/12/2014. EER acceptable 3/2/2014. This ANDA is eligible for TA only due to blocking 180 day exclusivity.

OR

Reference ID: 3464371

Revised, Jun 2013

6. **Robert L. West**

Date _____
Initials _____

Deputy Director, OGD

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:

7. ***OGD Director Evaluation***

Kathleen Uhl

Comments:

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

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/s/

BIC N NGUYEN
03/04/2014

ROUTING SHEET

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

Division: **I** Team: **14** PM: **Benjamin Danso**

Electronic ANDA:
Yes ☒ No ☒

ANDA #: **090842**

Firm Name: **InvaGen Pharmaceuticals, Inc.**

ANDA Name: **Raloxifene Hydrochloride Tablets, 60 mg**

RLD Name: **Evista / Eli Lilly**

Electronic AP Routing Summary Located:

V:\Chemistry Division I\Team 14\AP ROUTING SUMMARY

AP/TA Letter Located:

V:\Chemistry Division I\Team 14\Final Version For DARRTS (Original)

Project Manager Evaluation:

Date: **01/17/12** Initials: **bd**

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

Original Rec'd date <u>10/06/2008</u>	Date of Application <u>10/02/2008</u>	Date Acceptable for Filing <u>10/06/2008</u>
Patent Certification (type) <u>MOU, PIII & PIV</u>	Date Patent/Excl. expires <u>03/12/2014</u>	Citizens' Petition/Legal Case? Yes ☐ No ☒ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒ DMF#: <u>(b) (4)</u> (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☒ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☐ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

EER Status: ☐ Pending ☒ Acceptable ☐ OAI EES Date Acceptable: 05/21/2012 ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filing? Yes ☐ No ☐ Comment:
Date of Acceptable Quality (Chemistry) 06/14/2012 Addendum Needed: Yes ☐ No ☐ Comment:
Date of Acceptable Bio 08/19/2011 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location:)
Date of Acceptable Labeling 11/16/2010 Attached labeling to Letter: Yes ☐ No ☒ Comment:
Date of Acceptable Sterility Assurance (Micro) N/A

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

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

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

Routing:

☒ Labeling Endorsement, Date emailed: 05/22/2012 REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☐

☒ Regulatory Support

☒ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: 06/05/2012

☒ Division

☐ 1st Generic Review

☒ Bob West / Peter Rickman

☐ Keith Webber

☐ Filed AP Routing Summary in DARRTS

☐ Notified Firm and Faxed Copy of Approval Letter

☐ Sent Email to "CDER-OGDAPPROVALS" distribution list

OGD APPROVAL ROUTING SUMMARY1. **Regulatory Support Branch Evaluation****Martin Shimer****Date: 1/29/2012**

Chief, Reg. Support Branch

Initials: MHS

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)	Determ. of Involvement? Yes ☐ No ☐
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	Pediatric Exclusivity System RLD = _____ NDA# _____ Date Checked _____ Nothing Submitted ☐ Written request issued ☐ Study Submitted ☐
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: Application submitted on 10/6/2008, BOS=Evista NDA 20815, PIII to '763, '117, '086, '968, '049, '847, and '050 patents, PIV to '120, '383, '811, '719 and '064 patents, carving out ODE. ANDA ack for filing with a PIV on 10/6/2008(LO dated 12/5/2008). Patent Amendment rec'd on 1/2/2009-RR from Eli Lilly in Indianapolis IN signed and dated 12/22/2008. Patent Amendment rec'd on 2/26/2009-CA 09 CV 0087 filed in the Southern D of IN, Indianapolis Division on 1/28/2009 for infringement of the '811, '719, and '064 patents, since suit was filed within 45 days there is an automatic 30 month stay of approval which expired on 6/22/2011. Patent Amendment rec'd on 4/3/2009-Letter from Finnegan indicating that CA 09 CV 0087 was brought in the Southern D of IN, Indianapolis Division. Patent Amendment rec'd on 11/21/2011-3 exhibits related to the court rulings in the TEVA CA, exhibit #1 is a District Court decision in which the validity and enforceability of the asserted claims of the '086, '968 and '050 were confirmed while the asserted claims of the '811 and '064 patents were invalid, with respect to the '719 patent no claims were asserted due to stipulation by Eli Lilly that if the claims of the '811 and '064 were held to be invalid Eli Lilly would not assert any claims of the '719 against TEVA, exhibit #2 is a copy of a CAFC decision affirming the DC judgement, exhibit #3 is a copy of a dismissal order for CA 09 CV 0087 entered by the Court on 12/8/2010. Patent Amendment rec'd on 11/22/2011-PIV to the '330 patent. Patent Amendment rec'd on 11/28/2011-notice sent via ^{(b) (4)} to Eli Lilly in Indianapolis IN with notice delivered on 11/28/2011. Patent Amendment rec'd on 1/17/12-applicant states that they were not sued within 45 days on the '330 patent. Patent Summary: '763-PIII orig exp. 7/28/12 '117-PIII orig exp. 7/28/12 '086-PIII orig exp. 7/28/12 '968-PIII orig exp. 7/28/12 '049-PIII orig exp 7/28/12 '847-PIII orig exp 3/2/14 '050-PIII orig exp 3/2/14 '120-PIV orig-not sued '383-PIV orig-not sued '811-PIV orig-Sued-case dismissed '719-PIV orig-Sued-case dismissed '064-PIV orig-Sued-case dismissed '330-PIV amendment 11/28/22-not sued ANDA is eligible for TA only due to PIII certs to multiple unexpired patents, the last of which will expire on 3/2/14.	

2. **Labeling Endorsement**

Reviewer, Ruby Wu:

Date 05/22/2012Initials RW

Reference ID: 3149006

Labeling Team Leader, Koung Lee:

Date 05/22/2012Initials KL

REMS required?
☐ Yes ☒ No

REMS acceptable?
☐ Yes ☐ No ☒ n/a

Comments:

From: Lee, Koung U
Sent: Tuesday, May 22, 2012 3:34 PM
To: Wu, Ruby (Chi-Ann); Kirby, Christina
Subject: RE: Please Endorse ANDA 090842, Raloxifene Tablets - Tentative Approval

I concur. Thanks.

Koung

From: Wu, Ruby (Chi-Ann)
Sent: Tuesday, May 22, 2012 9:44 AM
To: Kirby, Christina
Cc: Lee, Koung U
Subject: RE: Please Endorse ANDA 090842, Raloxifene Tablets - Tentative Approval

Koung,

The labeling review signed off 11/16/10 remains acceptable. The products are not subject of a REMS. Firm filed PIV to patent '330 on January 16, 2012.

Ruby

3. **Paragraph IV Evaluation**

PIV's Only

David Read

Date **5Jun2012**

OGD Regulatory Counsel

Initials **DTR**

Pre-MMA Language included ☐

Post-MMA Language Included ☐

Comments:TA letter okay.

4. **Quality Division Director /Deputy Director Evaluation**

Date **6/14/12**

Chemistry Div. **I (Raw)**

Initials **ASR**

Comments:CMC Acceptable

5. **First Generic Evaluation**

First Generics Only

Frank Holcombe

Date _____

Assoc. Dir. For Chemistry

Initials _____

Comments: (First generic drug review)

OGD Office Management Evaluation

6. **Peter Rickman**

Date **6/21/2012**

Director, DLPS

Initials **wpr**

Para.IV Patent Cert: Yes ☒ No ☐

Pending Legal Action: Yes ☐ No ☒

Petition: Yes ☐ No ☒

Comments: BOS=Evista NDA 20815, Applicant provided PIII certs to the '763, '117, '086, '968, '049, '847, and '050 patents. Applicant also provided PIVcerts to the '120, '383, '811, '719, '064 and '330 patents. The applicant is carving out ODE. The applicant was sued for infringement of the '811, '719, and '064 patents. The applicant notified the agency that Lilly (PO) voluntary dismissed it's litigation against InvaGen without prejudice. Chemistry acceptable 6/14/2012. Bio acceptable 8/19/2011 (fasting and fed studies 60 mg). Labeling acceptable 11/16/2010, TL sign off 5/22/2012. EER acceptable 5/21/2012. ANDA is eligible for TA only due to PIII patent certs which will expire on 3/2/14.

Reference ID: 3149086

AND/OR

7. **Robert L. West**

Date _____

Initials _____

Deputy Director, OGD

Para.IV Patent Cert: Yes ☐ No ☐

Pending Legal Action: Yes ☐ No ☐

Petition: Yes ☐ No ☐

Press Release Acceptable ☐

Date PETS checked for first generic drug _____

Comments:

8. ***OGD Director Evaluation***

Keith Webber

Deputy Director, OPS

Comments:

First Generic Approval ☐

PD or Clinical for BE ☐

Special Scientific or Reg.Issue ☐

Press Release Acceptable ☐

Comments:

9. Project Manager

Date 06/21/2012

Initials CK

Check Communication and Routing Summary into DARRTS

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/s/

CHRISTINA L KIRBY
06/21/2012

BIOEQUIVALENCE AMENDMENT

ANDA 090842

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



APPLICANT: InvaGen Pharmaceuticals, Inc.

TEL: 631-231-3233

ATTN: Sudhakar R. Vidiyala

FAX: 631-231-4248

FROM: Teresa Ramson

FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on October 2, 2008, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Raloxifene Hydrochloride Tablets, USP, 60 mg.

Reference is also made to amendments submitted on December 6, 2010 and on May 16, 2011.

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 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.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**

Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

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

**Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810**

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

Please submit your response in electronic format. This will improve document availability to review staff.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

ANDA: 090842
APPLICANT: InvaGen Pharmaceuticals, Inc.
DRUG PRODUCT: Raloxifene Hydrochloride Tablets USP, 60 mg

The Division of Bioequivalence (DBE) has completed its review of the submission acknowledged on the cover page and has identified the following deficiencies:

1. SOP (b) (4) (Criteria for sample reanalysis and reporting) does not include objective criteria for repeating the analysis of sample S27P1 9.0 Hour, of which the original analysis was found to be analytically valid. Therefore, the original value (7218.021 pg/mL) should be used in the statistical analysis. When using the original assay value for said sample, the 90% confidence interval (C.I.) for lnCmax of raloxifene was [65.27;101.56] and did not meet bioequivalence acceptance criteria. As a result, fasting study no. BA0818122-01 is **unacceptable**.
2. Please revise your SOP (b) (4) for future studies to include objective criteria for reanalysis of samples with anomalous values, otherwise known as pharmacokinetic (PK) repeats.
3. Please revise your SOP (b) (4) (Chromatographic integration) to include objective criteria for performing manual integration of chromatogram peaks. Please be advised to implement **pre-established** SOPs for your analytical procedures in future studies.

Sincerely yours,

{See appended electronic signature page}

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

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/s/

DALE P CONNER
07/06/2011

BIOEQUIVALENCE AMENDMENT

ANDA 090842

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



APPLICANT: InvaGen Pharmaceuticals, Inc.

TEL: 631-231-3233

ATTN: Sudhakar Vidiyala

FAX: 631-231-4248

FROM: Teresa Ramson

FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on October 2, 2008, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Raloxifene Hydrochloride Tablets, USP, 60 mg.

Reference is also made to your amendment dated, December 6, 2010.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response**.

Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

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

*Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855*

After the effective date, 01-Aug-2010, ANDAs will only be accepted at the new mailing address listed above. **DO NOT submit your ANDA Regulatory documents to this address prior to 01-Aug-2010.** For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): <http://www.fda.gov/cder/ogd> or Federal Register: <http://www.gpoaccess.gov/fr/>

Please submit your response in electronic format. This will improve document availability to review staff.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

Reference ID: 2898540

ANDA: 090842

APPLICANT: InvaGen Pharmaceuticals, Inc.

DRUG PRODUCT: Raloxifene Hydrochloride Tablets USP, 60 mg

The Division of Bioequivalence (DBE) has completed its review of the submission acknowledged on the cover page and has identified the following deficiencies:

1. Please explain the term "No Intercept" used to assign to the original values of the raloxifene-4'-glucuronide samples which were reanalyzed for the reason "Concentration Over the Calibration Curve (OCC)" in fasting study no. BA0818122-01. The same term was also used for the raloxifene-4'-glucuronide QC samples in fasting study no. BA0818122-01.
2. Please provide objective justifications for manually integrating the peaks for samples S3P2 96.0 HR SUB3&4_61 (raloxifene), S3P2 96.0 HR SUB3&4_61 (raloxifene-4'-glucuronide), S3P2 96.0 HR SUB3&4_61 (raloxifene-6-glucuronide), and S5P2 96.0 HR SUB5&6_60 (raloxifene-4'-glucuronide) in fasting study no. BA0818122-01. Please also provide the standard operating procedure (SOP) detailing the reintegration method.
3. Please explain why subject 11 had no measurable raloxifene concentrations at all time points after receiving the test product treatment in the fasting study no. BA0818122-01, considering that this subject had measurable concentrations for both glucuronide metabolites under the same treatment. This subject also had measurable concentrations of raloxifene and raloxifene glucuronide metabolites after receiving the reference product.
4. You repeated the sample S27P1 9.0 Hour in your fasting study using the following reason: "S27P1 9.0 Hour had a concentration of 7218.021pg/mL and the analyte peak area also was very high (≈ 100 times) when compared to the preceding and succeeding time points. No such abnormality was found in RA4G and RA6G for this particular time point. Hence S27P1 9.0 Hour was repeated under AI, suspected analytical interference from the analyst during processing." However, per your SOP No. (b) (4) "Analytical Interference (AI)" is defined as "Predose sample having interference more than LOQ standard (Std A)." Therefore, your repeat of the above-mentioned was a violation of your SOP, and is not valid. Rather, the DBE considers such repeat as "PK repeat" and biased. In such case, only the original value for this sample (S27P1 9.0 Hour) of your fasting study should be used in the data analysis of

the study. The DBE reanalyzed the data using the original value of the above sample and the 90% C.I. for lnCmax of raloxifene, [65.27;101.56], failed to meet the acceptable bioequivalence limits of [80.00;125.00]. In addition, the point estimate for lnCmax of raloxifene-4'-glucuronide was outside the limits of [80.00;125.00] and did not support the bioequivalence of test product. Therefore, your fasting bioequivalence study no. BA0818122-01 is unacceptable.

5. Please indicate what medical interventions were used to resolve the adverse events experienced by subject 13 (headache) and subject 26 (fever) in the fed study no. BA0818123-01.
6. Please submit chromatograms from at least 20% of the total number of subjects that completed fed study no. BA0818123-01 (i.e. 20% of 41 subjects, or at least 8 subjects).
7. In 2009, following the inspection by the FDA Division of Scientific Investigations (DSI) of the analytical site (b) (4) (b) (4) Form FDA-483 was issued. One of the DSI's objectable findings was (b) (4) (b) (4) (b) (4) The analytical site's response to this DSI Finding was that the SOP was revised to require (b) (4) (b) (4) for preparation of calibrators and QCs.

The sample analysis of the bioequivalence studies of your current application was conducted at (b) (4) prior to the above DSI inspection and (b) (4) response stating its commitment to revise the SOP for the preparation of calibration curve standards and quality control samples. Please indicate if (b) (4) in the current ANDA. Also, please submit (b) (4) revised and current SOP for the preparation of calibration curve standards and quality control samples.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence 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/

DALE P CONNER
02/02/2011

Electronic Log Book

Electronic Log Book ID 179
Contact: Invagen Pharmaceuticals Inc.
Contact Person: Sudhakar R Vidiyala

Reason: Outgoing, FDA Request for
Information
Contact Type: Phone

Category: ANDA
ANDA/Control/Protocol #: 090842

FDA Contact: Alpita Popat

Contact Time and Date 12/3/2010 at 3:10:08 PM

Subject: Bioequivalence

Query

The reviewer would requested the following information from the firm as a telephone amendment.

Please submit DBE summary tables 10 (Study Information), 12 (Dropout Information), and 13 (Protocol Deviations) for the fasting and fed bioequivalence studies, and DBE summary table 16 (Composition of Meal Used in Fed Bioequivalence Study) using the table formats below. Please use the following criteria when preparing the summary tables:

- Please provide the Bioequivalence Summary Tables as pdf files and in MSWord. Place the MSWord format of all the tables in Module 2.7 and the pdf files in the appropriate eCTD/CTD locations.
- Margins for the paper should be 1 for the top and bottom and 1.25 for the left and right sides.
- All text should be Times New Roman 10.
- Please use the Default Table Style when creating the tables when they are created in Microsoft Word. (Select Menu Table-Table Auto Format-Table Normal)
- Tables 10-16 should be in PORTRAIT orientation.

In addition, please submit a table that summarizes the repeats for analytical reasons and reassay for Raloxifene, Raloxifene-4-Glucuronide, and Raloxifene-6-Glucuronide in Human Plasma for the fasting and fed bioequivalence studies. Your DBE Summary Table 9 indicated that this information is located in the Bioanalytical Report; however, the Bioanalytical Report was not located. Please submit the Bioanalytical Report. Also, please submit SOPs repeat analysis and report of final values, and analytical run

acceptance criteria.

Response

Spoke to Somaraju Indukuri and the firm will gather data and submit as a telephone amendment within 10 business days.

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

/s/

ALPITA POPAT
12/13/2010

****Please send an email to the labeling reviewer (chi-ann.wu@fda.hhs.gov) to confirm that you received the labeling comments****

Labeling Comments

ANDA 090842

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (240-276-8952)



TO: InvaGen Pharmaceuticals, Inc.

TEL: 631-231-3233

ATTN: Sudhakar R. Vidiyala

FAX: 631-231-4248

FROM: Ruby Wu

Dear Sir:

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

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

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

**Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20857**

After the effective date, **01-Aug-2010**, ANDAs will only be accepted at the new mailing address listed above. **DO NOT** submit your **ANDA Regulatory documents to this address prior to 01-Aug-2010**. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): <http://www.fda.gov/cder/ogd> or Federal Register: <http://www.gpoaccess.gov/fr/>

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

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

ANDA Number: 090842
Dates of Submission: July 7, 2009 (amendment)
Applicant's Name: Invagen Pharmaceuticals, Inc.
Established Name: Raloxifene Hydrochloride Tablets USP, 60 mg

Labeling Deficiencies:

1. GENERAL COMMENT:

Please respond to the following question on your cover letter: please comment on how many Medication Guides will be provided for each packaging configuration.

2. CONTAINER (Bottles of 30s and 1000s):

- a. "Each film-coated tablet..."
- b. Please revise the "PHARMACIST" statement to read:
 "PHARMACIST: Dispense the enclosed Medication Guide to each patient." or
 "PHARMACIST: Dispense the accompanying Medication Guide to each patient." Or
 "PHARMACIST: Dispense the Medication Guide provided separately to each patient."

Please note that if the medication guides are not physically attached to the bottle of 1000s, please use the last statement.

3. PHYSICIAN INSERT

- a. "CONTENTS" and "FULL PRESCRIBING INFORMATION" should be separated by a horizontal line [refer to 21 CFR 201.57(d)(2)].
- b. The Agency recommends two-column format for the "HIGHLIGHTS" and "CONTENTS" sections.
- c. HIGHLIGHTS, "To report SUSPECTED ADVERSE REACTIONS" subsection: To be in accord with 21 CFR 201.57(a)(11)(ii), please include the name and phone number of the manufacturer.
- d. FULL PRESCRIBING INFORMATION
 - i. Throughout the insert, revise "in the" to read "in a" whenever you are referring to a study or trial conducted by the RLD.
 - ii. 6.1, third paragraph, subtitle: delete "(MORE)"
 - iii. Table 1, Title: "Table 1: Adverse Reactions Occurring in Placebo–Controlled Osteoporosis Clinical Trials at a Frequency $\geq 2.0\%$ and in more Raloxifene Hydrochloride Tablets -Treated (60 mg Once Daily) Women than Placebo–Treated Women"
 - iv. 12.3, third sentence: "...in systemic..." [add a space]
 - v. 14.1, first paragraph, first sentence: delete "(MORE)"

3. Stand-alone MEDICATION GUIDE

Revise to be consistent with the Medication Guide attached to the insert labeling.

Revise your labeling, as instructed above, and submit final printed labeling electronically.

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

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the previously submitted labeling with all differences annotated and explained.

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
-----	-----	-----	-----
ANDA-90842	ORIG-1	INVAGEN PHARMACEUTICA LS INC	RALOXIFENE HYDROCHLORIDE

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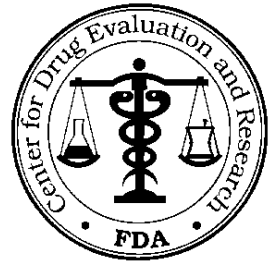
/s/

CHI-ANN Y WU
05/10/2010
for Wm Peter Rickman

QUALITY DEFICIENCY - MINOR

ANDA 90-842

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



APPLICANT: Invagen Pharmaceuticals Inc.

TEL: 631-231-3233

ATTN: Sudhakar R. Vidiyala

FAX: 631-231-4248

FROM: Benjamin Danso

FDA CONTACT PHONE: (240) 276-8527

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated October 2, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Raloxifene Hydrochloride Tablets, 60 mg.

Reference is also made to your amendment dated July 22, 2009.

The Division of Chemistry 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.

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

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

SPECIAL INSTRUCTIONS: Chemistry comments provided. Please include in response.

Please submit your response in electronic format.
This will improve document availability to review staff.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-842

APPLICANT: Invagen Inc.

DRUG PRODUCT: Raloxifene Hydrochloride Tablets, 60 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. The Drug Master File (b) (4) which describes the manufacture of the drug substance, has been found deficient. The DMF holder has been notified by a separate letter. Please respond to these deficiencies only after you have learned that the DMF holder has responded.

2.

(b) (4)

3.

4. Please provide any additional long term stability data that may be available.

Sincerely yours,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
-----	-----	-----	-----
ANDA-90842	ORIG-1	INVAGEN PHARMACEUTICA LS INC	RALOXIFENE HYDROCHLORIDE

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
10/19/2009

Telephone Fax

ANDA 90-842

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (240-276-8952)



TO: InvaGen Pharmaceuticals, Inc.

TEL: 631-231-3233

ATTN: Sudhakar R. Vidiyala

FAX: 631-231-4248

FROM: Ruby Wu

Dear Sir:

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

Pages (including cover): 4

SPECIAL INSTRUCTIONS:

Labeling comments

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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

ANDA Number: 90-842

Dates of Submission: October 2, 2008 (original)

Applicant's Name: Invagen Pharmaceuticals, Inc.

Established Name: Raloxifene Hydrochloride Tablets USP, 60 mg

Labeling Deficiencies:

1. GENERAL COMMENT:

The drug product is now subject of a USP monograph titled "Raloxifene Hydrochloride Tablets". We encourage you to use "USP" in the established name of your drug product.

2. CONTAINER (Bottles of 30s and 1000s):

- a. Correct the spelling of the established name.
- b. Add "Each tablet contains 60 mg raloxifene hydrochloride, USP."
- c. Include a statement instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed, and state how the Medication Guide is provided. These statements shall appear on the label in a prominent and conspicuous manner. 21 CFR 208.24 (d)
For example:
- "PHARMACIST: PLEASE DISPENSE WITH ATTACHED MEDICATION GUIDE"
or
- "PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY"

3. PHYSICIAN INSERT

- a. GENERAL COMMENT: revise "Raloxifene hydrochloride Tablets" to read "raloxifene hydrochloride tablets" unless "Raloxifene" appears at the beginning of a sentence.
- b. HIGHLIGHTS
 - i. Title: "Initial" should appear on the next line and it should read "Initial U.S. Approval: 1997"
 - ii. Recent Major Changes: please delete "Indications and Usage, Invasive Breast Cancer Risk Reduction (1) 9/2007"
 - iii. Indications and usage: "Raloxifene hydrochloride tablet is..."
 - iv. "To report SUSPECTED ADVERSE REACTIONS" subsection: To be in accord with 21 CFR 201.57(a)(11)(ii), please include the name and phone number of the manufacturer.
- c. CONTENTS: Renumber (b) (4) to read "14.5". You should keep the same number system as the RLD.
- d. FULL PRESCRIBING INFORMATION
 - i. 1.1: Delete (b) (4)
 - ii. 2.2: "For osteoporosis treatment..."
 - iii. 5.11: Delete (b) (4)
 - iv. 5.12: Delete "Raloxifene hydrochloride tablets do not eliminate the risk of breast cancer [see Clinical Studies (14.4)]."
 - v. 6.1, sixth paragraph, first sentence: "Table 1 lists adverse reactions occurring in osteoporosis treatment and placebo-controlled clinical trials at a frequency $\geq$ 2.0% in the raloxifene hydrochloride-treated women than in placebo-treated women."
 - vi. Table 1, Title: "Table 1: Adverse Reactions Occurring in Placebo–Controlled Osteoporosis Clinical Trials at a Frequency $\geq$ 2.0%"
 - vii. Table 1: "† Includes only patients with an intact uterus: raloxifene hydrochloride tablets treatment trial: Treatment Trial: n=1948, Placebo, n=1999."
 - viii. 6.1: add at the end of this section
Breast Pain — Across all placebo-controlled trials, raloxifene was indistinguishable from placebo with regard to frequency and severity of breast pain and tenderness. Raloxifene was associated with less breast pain and tenderness than reported by women receiving estrogens with or without added progestin.

Gynecologic Cancers — Raloxifene-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 —

The safety of raloxifene (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. Therapy was discontinued due to an adverse reaction in 25% of 5044 raloxifene-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-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)].

- ix. 11: revise "HPMC" to read "hypromellose"
- x. 12.2, second paragraph, first sentence: "In the osteoporosis treatment trial, raloxifene..."
- xi. 12.3, first paragraph, first sentence: "...osteoporosis treatment trial using..."
- xii. 12.3, Special Populations, Renal Impairment, first sentence: "...In the osteoporosis treatment trial, raloxifene..."
- xiii. Renumber (b) (4) to read "14.5". You should keep the same number system as the RLD.
- xiv. (b) (4) delete (b) (4)
- xv. 16.1: use lower case "w" for "white" and replace the colon with a period.
- xvi. 16.2: to be consistent with the RLD, please add "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."
- e. Medication Guide
 - i. What is raloxifene hydrochloride, bullet: "...tablets treat osteoporosis..."
 - ii. What is raloxifene hydrochloride: Delete "You and your doctor should talk about whether the possible benefit of raloxifene hydrochloride tablets in lowering your chance of getting invasive breast cancer is greater than its possible risks."
 - iii. How should I take raloxifene hydrochloride tablets: Delete "It is not known how long you should keep taking raloxifene hydrochloride tablets to lower your chance of getting invasive breast cancers."
 - iv. What else should I know about raloxifene hydrochloride tablets, fourth bullet: Delete "Because raloxifene hydrochloride tablets do not eliminate the chance of developing breast cancers"
 - v. Inactive Ingredients: revise "HPMC" to read "hypromellose"
 - vi. Replace "The brands listed are trademarks of their respective owners and are not trademarks of Eli Lilly and Company. The makers of these brands are not affiliated with and do not endorse Eli Lilly and Company or its products." with registered trademark statements for Coumadin and Jantoven."
 - vii. To facilitate reporting adverse events, add the following text and toll free number to the end of the "What are the possible or reasonably likely side effects" subsection of the Medication Guide: "Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088." (refer to 21 CFR 208.20(b)(7)(iii))

3. Stand-alone MEDICATION GUIDE

Please comment on how many medication guide will be provided for each packaging configuration.

Revise your labeling, as instructed above, and submit final printed labeling electronically.

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

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the previously submitted labeling with all differences annotated and explained.

{See appended electronic signature page}

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

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

/s/

Ruby Wu
5/19/2009 03:55:49 PM
for Wm Peter Rickman

COMPLETE RESPONSE -- MINOR

ANDA 90-842

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



APPLICANT: Invagen Pharmaceuticals Inc.

TEL: 631-231-3233

ATTN: Sudhakar R. Vidiyala

FAX: 631-231-4248

FROM: Benjamin Danso

FDA CONTACT PHONE: (240) 276-8527

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated October 2, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Raloxifene Hydrochloride Tablets, 60 mg.

SPECIAL INSTRUCTIONS: Chemistry comments provided. Please include in response.

Please submit your response in electronic format.

This will improve document availability to review staff.

We have completed the review of your ANDA and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (3 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. Upon OGD's acceptance for filing of your ANDA, it was determined that an adequate amount of information was submitted to allow for review of your Bioequivalence and Microbiology data. You will be notified in a separate communication of any further deficiencies identified during our review of your Bioequivalence and Microbiology data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-842

APPLICANT: InvaGen Pharmaceuticals, Inc.

DRUG PRODUCT: Raloxifene Hydrochloride Tablets, 60 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. The Drug master file (b) (4), which describes the manufacture of the drug substance, has been found deficient. The DMF holder has been notified by a separate letter. Please respond to this deficiency only after you have learned that the DMF holder has responded.

2.

3.

4.

5.

6.

7.

8.

9.

(b) (4)

10.

11.

12.

13.

14.

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

1. All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval. We have requested an evaluation from the Office of Compliance.

2. Your labeling information is pending review.
Deficiencies, if any, will be communicated separately.
3. Your bioequivalence information is pending review.
Deficiencies, if any, will be communicated separately.
4. Please provide any additional long term stability data
that may be available.

Sincerely yours,

{See appended electronic signature page}

Rashmikanth 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
5/4/2009 12:25:12 PM

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR
FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD)

Format please go to: <http://www.fda.gov/cder/regulatory/ersr/ectd.htm>

*For a Comprehensive Table of Contents Headings and Hierarchy please go to:

<http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf>

** For more CTD and eCTD informational links see the final page of the ANDA Checklist

*** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage <http://www.fda.gov/cder/ogd/> ***

ANDA #: 90-842

FIRM NAME: INVAGEN PHARMACEUTICALS, INC.

PIV: YES

Electronic or Paper Submission: ELECTRONIC (ECTD FORMAT)

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: RALOXIFENE HYDROCHLORIDE

Bio Assignments:

☒ BPH

☐ BCE

☐ BST

☒ BDI

☐ Micro Review
(No)

DOSAGE FORM: TABLETS, 60 MG

Random Queue: 5

Chem Team Leader: Bykadi, Raj

Chem PM: Ben Danso

Labeling Reviewer: Ruby Wu

Bio PM: Nam J. Chun (Esther)

Letter Date: OCTOBER 2, 2008

Received Date: OCTOBER 6, 2008

Comments: EC -1 YES

On Cards: YES

Therapeutic Code: 3020400 BONE/CALCIUM-PHOSPHOROUS

Archival copy: ELECTRONIC (ECTD FORMAT)

Sections I

Review copy: NA

E-Media Disposition: YES SENT TO EDR

Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product

(Must be completed for ALL Original Applications)

Refer to the Part 3 Combination Algorithm

Reviewing

CSO/CST Ted Palat

Date 12/04/2008

Recommendation:

☒ FILE

☐ REFUSE to RECEIVE

Supervisory Concurrence/Date: _____

Date: _____

ADDITIONAL COMMENTS REGARDING THE ANDA:

2. Please revise the reprocessing statement to cite 21 CFR 211.115.

Comment included in ACK letter.

Establishment Evaluation System

File Edit Search Navigate Options Window Help

Application Drawer

Application Establishments Status Milestones Comments Contacts Product

Application: N 90842/000 Sponsor: INVAGEN PHARMS

Drug Name: RALOXIFENE HYDROCHLORIDE

Establishment CFN / FEI	Name	Profile Code	Name	Last Milestone Date	Last Compliance Status	Date	OAI Alert
	INVAGEN PHARMACEUTICALS	TCN	SUBMITTED TO OC	04-DEC-2008	PN	04-DEC-2008	(b) (4)

Overall Compliance:

Date Recommendation

Save Close

Record: 2/2 <OSC> <DBG>

MODULE 1

ADMINISTRATIVE

ACCEPTABLE

1.1	1.1.2 Signed and Completed Application Form (356h) (original signature) (Check Rx/OTC Status) RX YES	☒
1.2	Cover Letter Dated: OCTOBER 2, 2008	☒
1.2.1	Form FDA 3674 (PDF) YES	☒
*	Table of Contents (paper submission only) YES	☒
1.3.2	Field Copy Certification (original signature) NA (N/A for E-Submissions)	☒
1.3.3	Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other: 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) YES	☒
1.3.4	Financial Certifications Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES, form 3454 Disclosure Statement (Form FDA 3455, submit copy to Regulatory Branch Chief) NA	☒

1.3.5	1.3.5.1 Patent Information Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations 1.3.5.2 Patent Certification 1. Patent number(s) below 2. Paragraph: (Check all certifications that apply) MOU ☒ PI ☐ PII ☐ PIII ☒ PIV ☒ (Statement of Notification) ☒ 3. Expiration of Patent(s): 3/10/2017 a. Pediatric exclusivity submitted? NO b. Expiration of Pediatric Exclusivity? NA 4. Exclusivity Statement: YES	☒
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Summary of Sponsor Patent Certifications

PIII – ‘763, ‘117, ‘086, ‘968, ‘049, ‘847, ‘050

PIV – ‘120, ‘383, ‘811, ‘719, ‘064

MOU – ‘811 (U-825), ‘064 (U-657)

Invagen intends to market before the exclusivities expire. They state the ODE doesn't apply because their labeling doesn't contain the indication under I-539.

Orange Book Patent Listing:

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
020815	001	5393763	Jul 28, 2012			U-114	Y
020815	001	5457117	Jul 28, 2012			U-114	Y
020815	001	5478847	Mar 2, 2014			U-114	Y
020815	001	5811120	Mar 2, 2014				
020815	001	5972383	Mar 2, 2014			U-287	
020815	001	6458811	Mar 10, 2017	Y	Y	U-825	
020815	001	6797719	Mar 10, 2017		Y		
020815	001	6894064	Mar 10, 2017		Y	U-657	
020815	001	6906086	Jul 28, 2012			U-657	

020815	001	6906086	Jul 28, 2012		U-662	
020815	001	RE38968	Jul 28, 2012		U-657	
020815	001	RE38968	Jul 28, 2012		U-662	
020815	001	RE39049	Jul 28, 2012		U-657	
020815	001	RE39049	Jul 28, 2012		U-662	
020815	001	RE39050	Mar 2, 2014		U-657	
020815	001	RE39050	Mar 2, 2014		U-662	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
020815	001	I-539	Sep 13, 2010
020815	001	ODE	Sep 13, 2014
U-114	USE FOR INHIBITING BONE RESORPTION		
U-287	TREATMENT OR PREVENTION OF OSTEOPOROSIS		
U-825	USE FOR PREVENTION OF BREAST CANCER		
U-657	PREVENTION OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN		
U-662	TREATMENT OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN		
I-539	REDUCTION IN RISK OF INVASIVE BREAST CANCER IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS OR AT HIGH RISK FOR INVASIVE BREAST CANCER		
ODE	ORPHAN DRUG EXCLUSIVITY		

1.4.1	References Letters of Authorization - DMF letters of authorization - Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient YES, DMF (b) (4) - Type III DMF authorization letter(s) for container closure YES - US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) NA	☒
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(b) (4)

1.12.11	Basis for Submission NDA# : 20-815 Ref Listed Drug: EVISTA Firm: ELI LILLY AND COMPANY ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒
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MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	Comparison between Generic Drug and RLD-505(j)(2)(A) 1. Conditions of use SAME, treatment of osteoporosis 2. Active ingredients SAME 3. Inactive ingredients JUSTIFIED 4. Route of administration SAME 5. Dosage Form SAME 6. Strength SAME	☒
1.12.14	Environmental Impact Analysis Statement YES	☒
1.12.15	Request for Waiver Request for Waiver of In-Vivo BA/BE Study(ies): NA	☒
1.14.1	Draft Labeling (Mult Copies N/A for E-Submissions) 1.14.1.1 4 copies of draft (each strength and container) 1 copy, e-submission 1.14.1.2 1 side by side labeling comparison of containers and carton with all differences annotated and explained YES 1.14.1.3 1 package insert (content of labeling) submitted electronically YES ***Was a proprietary name request submitted? NO (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	Listed Drug Labeling 1.14.3.1 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained YES 1.14.3.3 1 RLD label and 1 RLD container label YES	☒

2.3	Quality Overall Summary (QOS) E-Submission: PDF YES Word Processed e.g., MS Word YES A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ Question based Review (QbR) YES 2.3.S Drug Substance (Active Pharmaceutical Ingredient) YES 2.3.S.1 General Information 2.3.S.2 Manufacture 2.3.S.3 Characterization 2.3.S.4 Control of Drug Substance 2.3.S.5 Reference Standards or Materials 2.3.S.6 Container Closure System 2.3.S.7 Stability 2.3.P Drug Product YES 2.3.P.1 Description and Composition of the Drug Product 2.3.P.2 Pharmaceutical Development 2.3.P.2.1 Components of the Drug Product 2.3.P.2.1.1 Drug Substance 2.3.P.2.1.2 Excipients 2.3.P.2.2 Drug Product 2.3.P.2.3 Manufacturing Process Development 2.3.P.2.4 Container Closure System 2.3.P.3 Manufacture 2.3.P.4 Control of Excipients 2.3.P.5 Control of Drug Product 2.3.P.6 Reference Standards or Materials 2.3.P.7 Container Closure System 2.3.P.8 Stability	☒
2.7	Clinical Summary (Bioequivalence) Model Bioequivalence Data Summary Tables E-Submission: PDF YES Word Processed e.g., MS Word YES 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods 2.7.1.1 Background and Overview Table 1. Submission Summary YES Table 4. Bioanalytical Method Validation YES Table 6. Formulation Data YES 2.7.1.2 Summary of Results of Individual Studies Table 5. Summary of In Vitro Dissolution YES 2.7.1.3 Comparison and Analyses of Results Across Studies Table 2. Summary of Bioavailability (BA) Studies YES Table 3. Statistical Summary of the Comparative BA Data YES 2.7.1.4 Appendix YES 2.7.4.1.3 Demographic and Other Characteristics of Study Population Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study YES 2.7.4.2.1.1 Common Adverse Events Table 8. Incidence of Adverse Events in Individual Studies YES	☒

MODULE 3
3.2.S DRUG SUBSTANCE

ACCEPTABLE

3.2.S.1	General Information 3.2.S.1.1 Nomenclature 3.2.S.1.2 Structure 3.2.S.1.3 General Properties	☒
3.2.S.2	Manufacturer 3.2.S.2.1 Manufacturer(s) (This section includes contract manufacturers and testing labs) Drug Substance (Active Pharmaceutical Ingredient) 1. Name and Full Address(es) of the Facility(ies) 2.3.S.2 Manufacture Who manufactures the drug substance? <i>Drug Substance:</i> Raloxifene Hydrochloride. <i>Manufacturer:</i> (b) (4) <i>DMF #:</i> <i>Address:</i> 2. Function or Responsibility YES 3. Type II DMF number for API - (b) (4) 4. CFN or FEI numbers NO	☒
3.2.S.3	Characterization	☒
3.2.S.4	Control of Drug Substance (Active Pharmaceutical Ingredient) 3.2.S.4.1 Specification Testing specifications and data from drug substance manufacturer(s) YES 3.2.S.4.2 Analytical Procedures YES 3.2.S.4.3 Validation of Analytical Procedures 1. Spectra and chromatograms for reference standards and test samples YES 2. Samples-Statement of Availability and Identification of: a. Drug Substance YES b. Same lot number(s) R08069 3.2.S.4.4 Batch Analysis 1. COA(s) specifications and test results from drug substance mfgr(s) YES 2. Applicant certificate of analysis YES 3.2.S.4.5 Justification of Specification	☒
3.2.S.5	Reference Standards or Materials	☒
3.2.S.6	Container Closure Systems	☒
3.2.S.7	Stability	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE



3.2.P.1

Description and Composition of the Drug Product

1. Unit composition

Composition of Drug Product

Table #1

Item #	Ingredient	60 mg (mg/tablet)
1	Raloxifene Hydrochloride	60.0
2	Mannitol, USP (b) (4)	(b) (4)
3	Croscopovidone, NF (b) (4)	
4	Hydroxy Propyl Cellulose, NF (b) (4)	
5	Polaxomer 407, NF (b) (4)	
6		
7		
8	Magnesium stearate, NF (b) (4)	
9	Opadry White (b) (4)	
10	(b) (4)	
Total Tablet Weight (b) (4)		288.0

2. Inactive ingredients and amounts are appropriate per IIG YES

(b) (4)

3.2.P.2	Pharmaceutical Development Pharmaceutical Development Report YES	☒
3.2.P.3	Manufacture 3.2.P.3.1 Manufacture(s) (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es) of the Facility(ies) 2.3.P.3 Manufacture Who manufactures the drug product? InvaGen Pharmaceuticals Inc, 7 Oser Avenue, Hauppauge, New York 11788 USA 2. CGMP Certification: YES 3. Function or Responsibility YES 4. CFN or FEI numbers NO 3.2.P.3.2 Batch Formula YES 3.2.P.3.3 Description of Manufacturing Process and Process Controls 1. Description of the Manufacturing Process YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES (b) (4) 3. If sterile product: Aseptic fill / Terminal sterilization NA 4. Reprocessing Statement YES, please revise . (comment in ACK letter.) 3.2.P.3.4 Controls of Critical Steps and Intermediates 3.2.P.3.5 Process Validation and/or Evaluation 1. Microbiological sterilization validation NA 2. Filter validation (if aseptic fill) NA	☐

3.2.P.4	Controls of Excipients (Inactive Ingredients) Source of inactive ingredients identified YES 3.2.P.4.1 Specifications 1. Testing specifications (including identification and characterization) YES 2. Suppliers' COA (specifications and test results) YES 3.2.P.4.2 Analytical Procedures 3.2.P.4.3 Validation of Analytical Procedures 3.2.P.4.4 Justification of Specifications Applicant COA YES	☒
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MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	Controls of Drug Product 3.2.P.5.1 Specification(s) YES 3.2.P.5.2 Analytical Procedures YES 3.2.P.5.3 Validation of Analytical Procedures Samples - Statement of Availability and Identification of: 1. Finished Dosage Form YES 2. Same lot numbers ID080510 3.2.P.5.4 Batch Analysis Certificate of Analysis for Finished Dosage Form YES 3.2.P.5.5 Characterization of Impurities 3.2.P.5.6 Justification of Specifications	☒
3.2.P.7	Container Closure System 1. Summary of Container/Closure System (if new resin, provide data) YES 2. Components Specification and Test Data YES 3. Packaging Configuration and Sizes 16.1 How Supplied Raloxifene hydrochloride 60 mg tablets are White film coated round biconvex, de-bossed with IG on one side and 256 on the other, supplied in bottles of 30 (NDC 67787-256-30) and 1000 (NDC 67787-256-10): 4. Container/Closure Testing YES 5. Source of supply and suppliers address YES	☒
3.2.P.8	3.2.P.8.1 Stability (Finished Dosage Form) 1. Stability Protocol submitted YES 2. Expiration Dating Period (b)(4) months 3.2.P.8.2 Post-approval Stability and Conclusion Post Approval Stability Protocol and Commitments YES 3.2.P.8.3 Stability Data 1. 3 month accelerated stability data YES 2. Batch numbers on stability records the same as the test batch YES	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	3.2.R.1.S Executed Batch Records for drug substance (if available) NO 3.2.R.2.S Comparability Protocols NO 3.2.R.3.S Methods Validation Package YES, 3.2.S.4.3 Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒
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3.2.R (Drug Product)	3.2.R.1.P.1 Executed Batch Records Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation YES (b) (4) 3.2.R.1.P.2 Information on Components YES 3.2.R.2.P Comparability Protocols NO 3.2.R.3.P Methods Validation Package YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒
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MODULE 5

CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	Tabular Listing of Clinical Studies	☒
5.3.1 (complete study data)	Bioavailability/Bioequivalence 1. Formulation data same? a. Comparison of all Strengths (check proportionality of multiple strengths) NA b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) NA 2. Lot Numbers of Products used in BE Study(ies): A: ID080510, R: A489455 3. Study Type: IN-VIVO PK STUDY(IES) (Continue with the appropriate study type box below)	☒

5.3.1.2 Comparative BA/BE Study Reports

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



Table 3 Statistical Summary of the Comparative Bioavailability Data (Raloxifene)

Raloxifene Hydrochloride Tablets 1x60 mg Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study (BA0818122-01)				
Parameter	Test	Reference	Ratio	90%CI
AUCt	11429.994	11296.142	101.18%	(91.98%; 111.32%)
AUCi	13444.650	13817.596	97.30%	(90.53%; 104.58%)
Cmax	366.023	392.507	93.25%	(84.42%; 103.00%)
Fed Bioequivalence Study (BA0818123-01)				
Parameter	Test	Reference	Ratio	90%CI
AUCt	14512.346	14938.412	97.15%	(86.01%; 109.73%)
AUCi	16591.929	16905.619	98.14%	(87.96%; 109.51%)
Cmax	491.736	493.522	99.64%	(91.02%; 109.08%)

2. Summary Bioequivalence tables:

Table 10. Study Information YES

Table 12. Dropout Information YES

Table 13. Protocol Deviations YES

5.3.1.3**In Vitro-In-Vivo Correlation Study Reports**

1. Summary Bioequivalence tables:

Table 11. Product Information YES

Table 16. Composition of Meal Used in Fed Bioequivalence Study YES

5.3.1.4**Reports of Bioanalytical and Analytical Methods for Human Studies**

1. Summary Bioequivalence table:

Table 9. Reanalysis of Study Samples YES

Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses YES

Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples YES

5.3.7**Case Report Forms and Individual Patient Listing YES**

5.4

Literature References**Possible Study Types:**

Study Type

IN-VIVO BE STUDY(IES) with PK ENDPOINTS (i.e., fasting/fed/sprinkle) FASTING AND FED ON 60 MG

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

2. EDR Email: Data Files Submitted: YES SENT TO EDR

3. In-Vitro Dissolution: YES



Study Type	IN-VIVO BE STUDY with CLINICAL ENDPOINTS NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p < 0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	IN-VITRO BE STUDY(IES) (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐
Study Type	NASALLY ADMINISTERED DRUG PRODUCTS 1. <u>Solutions</u> (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. <u>Suspensions</u> (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p < 0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	IN-VIVO BE STUDY(IES) with PD ENDPOINTS (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐

Study Type	TRANSDERMAL DELIVERY SYSTEMS 1. <u>In-Vivo PK Study</u> 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. <u>Adhesion Study</u> 3. <u>Skin Irritation/Sensitization Study</u>	☐
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Updated 8/11/2008

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Active Ingredient Search - Microsoft Internet Explorer

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Address http://www.accessdata.fda.gov/scripts/cder/job/docs/tempai.cfm

Active Ingredient Search Results from "OB_Rx" table for query on "RALOXIFENE."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Strength	Proprietary	Applicant Name
020815			Yes RALOXIFENE HYDROCHLORIDE	TABLET; ORAL 60MG	EVISTA	LILLY

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FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through September, 2008
Patent and Generic Drug Product Data Last Updated: November 17, 2008

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Orange Book Detail Record Search - Microsoft Internet Explorer

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Address http://www.accessdata.fda.gov/scripts/cder/job/docs/jobdetail.cfm?Appl_No=020815&TABLE1=OB_Rx Go Links

Search results from the "OB_Rx" table for query on "020815."

Active Ingredient:	RALOXIFENE HYDROCHLORIDE
Dosage Form/Route:	TABLET; ORAL
Proprietary Name:	EVISTA
Applicant:	LILLY
Strength:	60MG
Application Number:	020815
Product Number:	001
Approval Date:	Dec 9, 1997
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	

Patent and Exclusivity Info for this product: [View](#)

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 Generic Drug Product Information & Patent Information - **Daily**
 Orange Book Data Updated Through September, 2008
 Patent and Generic Drug Product Data Last Updated: November 17, 2008

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Patent and Exclusivity Search Results - Microsoft Internet Explorer							
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
020815	001	5393763	Jul 28, 2012			U-114	Y
020815	001	5457117	Jul 28, 2012			U-114	Y
020815	001	5478847	Mar 2, 2014			U-114	Y
020815	001	5811120	Mar 2, 2014				
020815	001	5972383	Mar 2, 2014			U-287	
020815	001	6458811	Mar 10, 2017	Y	Y	U-825	
020815	001	6797719	Mar 10, 2017		Y		
020815	001	6894064	Mar 10, 2017		Y	U-657	
020815	001	6906086	Jul 28, 2012			U-657	
020815	001	6906086	Jul 28, 2012			U-662	
020815	001	RE38968	Jul 28, 2012			U-657	
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020815	001	RE39050	Mar 2, 2014			U-657	
020815	001	RE39050	Mar 2, 2014			U-662	
Exclusivity Data							
Appl No	Prod No	Exclusivity Code	Exclusivity Expiration				
020815	001	ODE	Sep 13, 2014				
020815	001	I-539	Sep 13, 2010				

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

/s/

Martin Shimer
12/5/2008 10:06:43 AM



ANDA 90-842

Invagen Pharmaceuticals, Inc.
Attention: Sudhakar R. Vidiyala
7 Oser Avenue
Hauppauge, NY 11788

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.

NAME OF DRUG: Raloxifene Hydrochloride Tablets, 60 mg

DATE OF APPLICATION: October 2, 2008

DATE (RECEIVED) ACCEPTABLE FOR FILING: October 6, 2008

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 copy of a court order or judgment 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 (240) 276-8419.

We will correspond with you further after we have had the opportunity to review the application.

In the interim, please revise your reprocessing statement to reference 21 CFR 211.115.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Benjamin Danso
Project Manager
240-276-8527

Sincerely yours,

{See appended electronic signature page}

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

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this page is the manifestation of the electronic signature.**

/s/

Martin Shimer
12/5/2008 10:06:24 AM
Signing for Wm Peter Rickman