# CENTER FOR DRUG EVALUATION AND RESEARCH

**Approval Package for:**

***APPLICATION NUMBER:***

# ANDA 203174

**Name:** Bexarotene Capsules, 75 mg

**Sponsor:** Bionpharma Inc.

**Approval Date:** August 12, 2014

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# ANDA 203174

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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# ANDA 203174

# APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 203174

Banner Pharmacaps Inc.
Attention: Vandana Garikipati
Senior Manager, Regulatory Affairs
4125 Premier Drive
High Point, NC 27265

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated June 3, 2011, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Bexarotene Capsules, 75 mg.

Reference is also made to the Complete Response letter issued by this office on July 15, 2013, and to your amendments dated October 23, December 6, December 13, and December 20, 2013; and February 14, and April 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 Bexarotene Capsules, 75 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Targretin Capsules, 75 mg, of Valeant Pharmaceuticals Luxembourg S.a.r.l. (Valeant). 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, Valeant's Targretin Capsules, 75 mg, is subject to periods of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent Nos. 5,780,676 (the '676 patent) and 5,962,731 (the '731 patent) are scheduled to expire on July 14, 2015, and October 5, 2016, respectively.

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 Bexarotene Capsules, 75 mg, under this ANDA. You have notified the agency that Banner Pharmacaps Inc. (Banner) complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation was initiated against Banner for infringement of the '676 and '731 patents within the statutory 45-day period in the United States District Court for the District of Delaware [Eisai Inc. and Valeant Pharmaceuticals Luxembourg S.a.r.l. v. Banner

Pharmacaps Inc. and Mylan Pharmaceuticals Inc., Civil Action No. 11-901]. You have also notified the agency that the case was dismissed.

With respect to 180-day generic drug exclusivity, we note that Banner was the first ANDA applicant to submit a substantially complete ANDA for Bexarotene Capsules, 75 mg, with a paragraph IV certification. Therefore, with this approval, Banner is eligible for 180 days of generic drug exclusivity for Bexarotene Capsules, 75 mg. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, will begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). Please submit correspondence to this ANDA informing the agency of the date the exclusivity begins to run.

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

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

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

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

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

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

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, MD, MPH
Acting Director
Office of Regulatory Operations
Office of Generic Drugs

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

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/s/

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ROBERT L WEST

08/12/2014

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

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# ANDA 203174

# OTHER ACTION LETTERS

**COMPLETE RESPONSE**

ANDA 203174

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

TO: Banner Pharmacaps Inc.

TEL: 336-812-8700 x 23988

ATTN: Vandana Garikipati,
Manager, Regulatory Affairs

FAX: 888-818-4197

FDA CONTACT PHONE: 240-276-8530

FROM: Esther Chuh

Dear Madam:

This facsimile is in reference to your abbreviated new drug application, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

We have completed the review and have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (____ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 203174

**COMPLETE RESPONSE**

Banner Pharmacaps Inc.
Attention: Vandana Garikipati, MS, RAC
Manager, Regulatory Affairs
4125 Premier Drive
Hibh Point, NC 27265

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated June 3, 2011, received June 6, 2011, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bexarotene Capsules,75 mg.

We acknowledge receipt of your amendments dated July 22, August 4, October 6, and December 14, 2011; and March 20, 2012.

We have completed our review of this ANDA, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

## PRODUCT QUALITY

The deficiencies presented below represent minor deficiencies.

### A. Deficiencies

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

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

(b) (4)

33.

34.

35.

36.

37.

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

1) Please provide any updated stability data that may be available.

2) Please provide side by side pictures of ANDA capsules and RLD capsules.

3) We encourage you to apply Quality by Design (QbD) principles to the pharmaceutical development of your future original ANDA product submissions. A risk-based, scientifically sound submission would be expected to include the following:

- Quality target product profile (QTPP)
- Critical quality attributes (CQAs) of the drug product
- Product design and understanding including identification of critical attributes of excipients, drug substance(s), and/or container closure systems
- Process design and understanding including identification of critical process parameters and in-process material attributes
- Control strategy and justification

An example illustrating QbD concepts can be found online at FDA's **Generic Drugs: Information for Industry** webpage:
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelope

dandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM286595.pdf

## BIOEQUIVALENCE

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

1. You did not submit the raw analytical numerical data for all the assay runs (both accepted and rejected runs). Please submit complete raw data (numerical printouts) of all sample analysis runs, including the data for the peak area/height for the drug and the internal standard (IS), the ratio of the drug peak area/height to the IS peak area/height, dilution factor (if any), and the corresponding calculated concentration for each assayed and reassayed sample, calibration standard concentration samples, and quality control samples.

2. A summary table of batch analysis was provided in your bioanalytical validation report. The report stated that, "data from reject or unused batches and/or evaluations are not included in this report but are on file at (b) (4) A batch or evaluation is listed as "Not Used" when an analytical issue is observed that could potentially affect data integrity". Please submit the data for *all* unused batches as well.

3. Please provide SOP (b) (4): Rejected and Not Used Data, Laboratory Investigations and Events.

We acknowledge that you will conduct dissolution testing for the test product using the following FDA-recommended method and specification:

Medium: Tier 1: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5
Tier 2: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5, with 0.05 g/L pancreatin enzyme (NMT 1750 USP Units of protease activity per 1000 mL)
Volume: 900 mL
Apparatus: II (Paddle)
Speed: 75 rpm
Temperature: 37ºC ± 0.5ºC
Specification: NLT (b) (4)% (Q) in 45 minutes.

## LABELING

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated (October 6, 2011).

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

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

## OTHER

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle. The resubmission to this will be considered to represent a MINOR AMENDMENT. The designation as a **RESUBMISSION/AFTER ACTION – MINOR COMPLETE RESPONSE AMENDMENT** should appear prominently in your cover letter. In addition, please designate in bold on your cover letter each review discipline (Product Quality (CMC), Labeling, Bioequivalence, Microbiology, Clinical) you are providing responses to.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.65. You may also request an extension of time in which to resubmit the ANDA. A resubmission response must fully address all the deficiencies listed.

The drug product may not be legally marketed until you have been notified in writing that this ANDA is approved.

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

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give

priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

If you have any questions, call Esther Chuh, Pharm.D., Regulatory Project Manager, at (240) 276-8530.

Sincerely yours,

*{See appended electronic signature page}*

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

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

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/s/

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ROBERT L WEST

07/15/2013

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

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# ANDA 203174

# LABELING

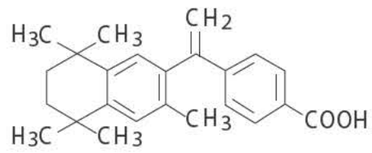
**Bexarotene capsule, liquid filled**
**Rx Only**
**Banner Pharmacaps Inc.**

**Bexarotene capsules are a member of the retinoid class of drugs that is associated with birth defects in humans. Bexarotene capsules also caused birth defects when administered orally to pregnant rats. Bexarotene capsules must not be administered to a pregnant woman. See CONTRAINDICATIONS.**

## DESCRIPTION

Bexarotene is a member of a subclass of retinoids that selectively activate retinoid X receptors (RXRs). These retinoid receptors have biologic activity distinct from that of retinoic acid receptors (RARs). Each soft gelatin capsule for oral administration contains 75 mg of bexarotene.

The chemical name is 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl) ethenyl] benzoic acid, and the structural formula is as follows:




Bexarotene is an off-white to white powder with a molecular weight of 348.48 and a molecular formula of $C_{24}H_{28}O_2$. It is insoluble in water and slightly soluble in vegetable oils and ethanol, USP.

Each Bexarotene capsule also contains the following inactive ingredients: polyethyelene glycol 400, NF, polysorbate 20, NF, povidone, USP and butylated hydroxyanisole, NF. The capsule shell contains gelatin NF, water, sorbitol sorbitan solution, NF, glycerin, USP and titanium dioxide, USP.

## CLINICAL PHARMACOLOGY

### Mechanism of Action

Bexarotene selectively binds and activates retinoid X receptor subtypes (RXRα, RXRβ, RXRγ). RXRs can form heterodimers with various receptor partners such as retinoic acid receptors (RARs), vitamin D receptor, thyroid receptor, and peroxisome proliferator activator receptors (PPARs). Once activated, these receptors function as transcription factors that regulate the expression of genes that control cellular differentiation and proliferation. Bexarotene inhibits the growth *in vitro* of some tumor cell lines of hematopoietic and squamous cell origin. It also induces tumor regression *in vivo* in some animal models. The exact mechanism of action of bexarotene in the treatment of cutaneous T-cell lymphoma (CTCL) is unknown.

### Pharmacokinetics

***Absorption***

After oral administration of Bexarotene capsules, bexarotene is absorbed with a Tmax of about two hours. Terminal half-life of bexarotene is about seven hours. Studies in patients with advanced malignancies show approximate single dose linearity within the therapeutic range and low accumulation with multiple doses. Plasma bexarotene AUC and Cmax values resulting from a 75 to 300 mg dose were 35% and 48% higher, respectively, after a fat-containing meal than after a glucose solution (see **PRECAUTIONS**: ***Drug-Food Interaction*** and **DOSAGE AND ADMINISTRATION**).

***Distribution***

Bexarotene is highly bound (>99%) to plasma proteins. The plasma proteins to which bexarotene binds have not been elucidated, and the ability of bexarotene to displace drugs bound to plasma proteins and the ability of drugs to displace bexarotene binding have not been studied (see ***PRECAUTIONS: Protein Binding***). The uptake of bexarotene by organs or tissues has not been evaluated.

***Metabolism***

Four bexarotene metabolites have been identified in plasma: 6- and 7-hydroxy-bexarotene and 6- and 7-oxo-bexarotene. *In vitro* studies suggest that cytochrome P450 3A4 is the major cytochrome P450 responsible for formation of the oxidative metabolites and that the oxidative metabolites may be glucuronidated. The oxidative metabolites are active in *in vitro* assays of retinoid receptor activation, but the relative contribution of the parent and any metabolites to the efficacy and safety of Bexarotene capsules is unknown.

***Elimination***

The renal elimination of bexarotene and its metabolites was examined in patients with Type 2 diabetes mellitus. Neither bexarotene nor its metabolites were excreted in urine in appreciable amounts. Bexarotene is thought to be eliminated primarily through the hepatobiliary system.

***Pharmacokinetics in Special Populations***

Age: Based on the population pharmacokinetic analysis of data for 232 patients aged ≥ 65 years and 343 patients aged < 65 years, age has no statistically significant effect on bexarotene pharmacokinetics.

Body Weight and Gender: Based on the population pharmacokinetics analysis of data for 614 patients with a weight range of 26 to 145 kg, the bexarotene apparent clearance increases with increasing body weight. Gender has no statistically significant effect on bexarotene pharmacokinetics.

Race: Based on the population pharmacokinetic analysis of data for 540 Caucasian and 44 Black patients, bexarotene pharmacokinetics are similar in Blacks and Caucasians. There are insufficient data to evaluate potential differences in the pharmacokinetics of bexarotene for other races.

Renal Insufficiency: No formal studies have been conducted with Bexarotene capsules in patients with renal insufficiency. Urinary elimination of bexarotene and its known metabolites is a minor excretory pathway (<1% of administered dose), but because renal insufficiency can result in significant protein binding changes, pharmacokinetics may be altered in patients with renal insufficiency (see PRECAUTIONS: Renal Insufficiency).

Hepatic Insufficiency: No specific studies have been conducted with Bexarotene capsules in patients with hepatic insufficiency.

Because less than 1% of the dose is excreted in the urine unchanged and there is *in vitro* evidence of extensive hepatic contribution to bexarotene elimination, hepatic impairment would be expected to lead to greatly decreased clearance (see WARNINGS: Hepatic insufficiency).

***Drug-Drug Interactions***

*Effect of Other Drugs on Pharmacokinetics of Bexarotene Capsules:*

*CYP3A4 Inhibitors/Inducers: In vitro* studies suggested that bexarotene is metabolized by cytochrome P450 3A4 (CYP3A4); therefore ketoconazole, itraconazole, erythromycin, gemfibrozil, grapefruit juice, and other inhibitors of CYP3A4 would be expected to lead to an increase in plasma bexarotene concentrations. However, in a clinical study, concomitant administration of Bexarotene capsules with multiple doses of ketoconazole did not alter bexarotene plasma concentrations. This suggests that bexarotene elimination is not substantially dependent on CYP3A4 metabolism. The effects of concomitant administration of inducers of CYP3A4 such as rifampin, phenytoin, and phenobarbital have not been studied.

*Gemfibrozil:* Concomitant administration of Bexarotene capsules and gemfibrozil resulted in substantial increases in plasma concentrations of bexarotene. Concomitant administration of gemfibrozil with Bexarotene capsules is not recommended (see **PRECAUTIONS:** ***Drug-Drug Interactions***).

*Paclitaxel plus Carboplatin:* The coadministration of paclitaxel (200 mg/m² IV dose over 3 hours) plus carboplatin (at a dose expected to achieve an AUC of 6 mg•min/mL) with Bexarotene Capsules (400 mg/m² orally once daily) increased the exposure to bexarotene ($AUC_{0-24}$ and $C_{max}$) by 2-fold compared to Bexarotene Capsules alone (see **PRECAUTIONS:** ***Drug-Drug Interactions***).

*Atorvastatin:* Bexarotene concentrations were not affected by concomitant atorvastatin administration.

*Effect of Bexarotene Capsules on Pharmacokinetics of Other Drugs:*

Bexarotene did not significantly inhibit the following enzymes in human liver microsomes: CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. *In vitro* data suggested a potential for bexarotene to inhibit CYP2C8 and induce CYP3A4.

*Atorvastatin:* The exposure (AUC) to atorvastatin (a substrate for CYP3A4) decreased by half when atorvastatin was coadministered with Bexarotene Capsules (400 mg/m² orally once daily).

*Tamoxifen:* Based on interim data, concomitant administration of Bexarotene Capsules and tamoxifen resulted in approximately a 35% decrease in plasma concentrations of tamoxifen, possibly through induction of CYP3A4 by bexarotene.

*Paclitaxel:* The exposure (AUC) to paclitaxel (a substrate for CYP3A4 and CYP2C8) decreased by 19% when paclitaxel (200 mg/m² IV dose over 3 hours) was coadministered with Bexarotene Capsules (400 mg/m² orally once daily).

The effect of Bexarotene Capsules on atorvastatin, tamoxifen and paclitaxel suggests that Bexarotene Capsules is an inducer for the CYP3A4 enzymes, and that it may reduce plasma concentrations of other substrates metabolized by CYP3A4, including oral or other systemic hormonal contraceptives (see **CONTRAINDICATIONS:** ***Pregnancy:*** **Category X and PRECAUTIONS:** ***Drug-Drug Interactions***).

*Carboplatin:* The coadministration of Bexarotene Capsules (400 mg/m² orally once daily) had no effect on the exposure to free or total carboplatin.

### Clinical Studies

Bexarotene capsules were evaluated in 152 patients with advanced and early stage cutaneous T-cell lymphoma (CTCL) in two multicenter, open-label, historically-controlled clinical studies conducted in the U.S., Canada, Europe, and Australia.

The advanced disease patients had disease refractory to at least one prior systemic therapy (median of two, range one to six prior systemic therapies) and had been treated with a median of five (range 1 to 11) prior systemic, irradiation, and/or topical therapies. Early disease patients were intolerant to, had disease that was refractory to, or had reached a response plateau of six months on, at least two prior therapies. The patients entered had been treated with a median of 3.5 (range 2 to 12) therapies (systemic, irradiation, and/or topical).

The two clinical studies enrolled a total of 152 patients, 102 of whom had disease refractory to at least one prior systemic therapy, 90 with advanced disease and 12 with early disease. This is the patient population for whom Bexarotene capsules are indicated.

Patients were initially treated with a starting dose of 650 mg/m²/day with a subsequent reduction of starting dose to 500 mg/m²/day. Neither of these starting doses was tolerated, and the starting dose was then reduced to 300 mg/m²/day. If, however, a patient on 300 mg/m²/day of Bexarotene capsules showed no response after eight or more weeks of therapy, the dose could be increased to 400 mg/m²/day.

Tumor response was assessed in both studies by observation of up to five baseline-defined index lesions using a Composite Assessment of Index Lesion Disease Severity (CA). This endpoint was based on a summation of the grades, for all index lesions, of erythema, scaling, plaque elevation, hypopigmentation or hyperpigmentation, and area of involvement. Also considered in response assessment was the presence or absence of cutaneous tumors and extracutaneous disease manifestations.

All tumor responses required confirmation over at least two assessments separated by at least four weeks. A partial response was defined as an improvement of at least 50% in the index lesions without worsening, or development of new cutaneous tumors or noncutaneous manifestations. A complete clinical response required complete disappearance of all manifestations of disease, but did not require confirmation by biopsy.

At the initial dose of 300 mg/m²/day, 1/62 (1.6%) of patients had a complete clinical tumor response and 19/62 (30%) of patients had a partial tumor response. The rate of relapse (25% increase in CA or worsening of other aspects of disease) in the 20 patients who had a tumor response was 6/20 (30%) over a median duration of observation of 21 weeks, and the median duration of tumor response had not been reached. Responses were seen as early as 4 weeks and new responses continued to be seen at later visits.

## INDICATIONS AND USAGE

Bexarotene capsules are indicated for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy.

## CONTRAINDICATIONS

Bexarotene capsules are contraindicated in patients with a known hypersensitivity to bexarotene or other components of the product.

### Pregnancy: Category X

Bexarotene capsules may cause fetal harm when administered to a pregnant woman. Bexarotene capsules must not be given to a pregnant woman or a woman who intends to become pregnant. If a woman becomes pregnant while taking Bexarotene capsules, Bexarotene capsules must be stopped immediately and the woman given appropriate counseling.

Bexarotene caused malformations when administered orally to pregnant rats during days 7-17 of gestation. Developmental abnormalities included incomplete ossification at 4 mg/kg/day and cleft palate, depressed eye bulge/microphthalmia, and small ears at 16 mg/kg/day. The plasma AUC of bexarotene in rats at 4 mg/kg/day is approximately one third the AUC in humans at the recommended daily dose. At doses greater than 10 mg/kg/day, bexarotene caused developmental mortality. The no effect dose for fetal effects in rats was 1 mg/kg/day (producing an AUC approximately one sixth of the AUC at the recommended human daily dose).

Women of child-bearing potential should be advised to avoid becoming pregnant when Bexarotene capsules are used. The possibility that a woman of child-bearing potential is pregnant at the time therapy is instituted should be considered. A negative pregnancy test (e.g., serum beta-human chorionic gonadotropin, beta-HCG) with a sensitivity of at least 50 mIU/L should be obtained within one week prior to Bexarotene capsules therapy, and the pregnancy test must be repeated at monthly intervals while the patient remains on Bexarotene capsules. Effective contraception must be used for one month prior to the initiation of therapy, during therapy and for at least one month following discontinuation of therapy; it is recommended that two reliable forms of contraception be used simultaneously unless abstinence is the chosen method. Bexarotene can potentially induce metabolic enzymes and thereby theoretically reduce the plasma concentrations of oral or other systemic hormonal contraceptives (see **CLINICAL PHARMACOLOGY:** ***Drug-Drug Interactions*** and **PRECAUTIONS:** ***Drug-Drug Interactions***). Thus, if treatment with Bexarotene capsules is intended in a woman with child-bearing potential, it is strongly recommended that one of the two reliable forms of contraception should be non-hormonal. Male patients with sexual partners who are pregnant, possibly pregnant, or who could become pregnant must use condoms during sexual intercourse while taking Bexarotene capsules and for at least one month after the last dose of drug. Bexarotene capsules therapy should be initiated on the second or third day of a normal menstrual period. No more than a one month supply of Bexarotene capsules should be given to the patient so that the results of pregnancy testing can be assessed and counseling regarding avoidance of pregnancy and birth defects can be reinforced.

## WARNINGS

*Lipid abnormalities:* Bexarotene capsules induce major lipid abnormalities in most patients. These must be monitored and treated during long-term therapy. About 70% of patients with CTCL who received an initial dose of ≥300 mg/m²/day of Bexarotene capsules had fasting triglyceride levels greater than 2.5 times the upper limit of normal. About 55% had values over 800 mg/dL with a median of about 1200 mg/dL in those patients. Cholesterol elevations above 300 mg/dL occurred in approximately 60% and 75% of patients with CTCL who received an initial dose of 300 mg/m²/day or greater than 300 mg/m²/day, respectively. Decreases in high density lipoprotein (HDL) cholesterol to less than 25 mg/dL were seen in about 55% and 90% of patients receiving an initial dose of 300 mg/m²/day or greater than 300 mg/m²/day, respectively, of Bexarotene capsules. The effects on triglycerides, HDL cholesterol, and total cholesterol were reversible with cessation of therapy, and could generally be mitigated by dose reduction or concomitant antilipemic therapy.

Fasting blood lipid determinations should be performed before Bexarotene capsules therapy is initiated and weekly until the lipid response to Bexarotene capsules is established, which usually occurs within two to four weeks, and at eight week intervals thereafter. Fasting triglycerides should be normal or normalized with appropriate intervention prior to initiating Bexarotene capsules therapy. Attempts should be made to maintain triglyceride levels below 400 mg/dL to reduce the risk of clinical sequelae (see **WARNINGS: Pancreatitis**). If fasting triglycerides are elevated or become elevated during treatment, antilipemic therapy should be instituted, and if necessary, the dose of Bexarotene capsules reduced or suspended. In the 300 mg/m²/day initial dose group, 60% of patients were given lipid lowering drugs. Atorvastatin was used in 48% (73/152) of patients with CTCL. Because of a potential drug-drug interaction (see **PRECAUTIONS**: ***Drug-Drug Interactions***), gemfibrozil is not recommended for use with Bexarotene capsules.

*Pancreatitis:* Acute pancreatitis has been reported in four patients with CTCL and in six patients with non-CTCL cancers treated with Bexarotene capsules; the cases were associated with marked elevations of fasting serum triglycerides, the lowest being 770 mg/dL in one patient. One patient with advanced non-CTCL cancer died of pancreatitis. Patients with CTCL who have risk factors for pancreatitis (e.g., prior pancreatitis, uncontrolled hyperlipidemia, excessive alcohol consumption, uncontrolled diabetes mellitus, biliary tract disease, and medications known to increase triglyceride levels or to be associated with pancreatic toxicity) should generally not be treated with Bexarotene capsules (see **WARNINGS**: Lipids abnormalities and **PRECAUTIONS**: ***Laboratory Tests***).

*Liver function test abnormalities:* For patients with CTCL receiving an initial dose of 300 mg/m²/day of Bexarotene capsules, elevations in liver function tests (LFTs) have been observed in 5% (SGOT/AST), 2% (SGPT/ALT), and 0% (bilirubin). In contrast, with an initial dose greater than 300 mg/m²/day of Bexarotene capsules, the incidence of LFT elevations was higher at 7% (SGOT/AST), 9% (SGPT/ALT), and 6% (bilirubin). Two patients developed cholestasis, including one patient who died of liver failure.

In clinical trials, elevation of LFTs resolved within one month in 80% of patients following a decrease in dose or discontinuation of therapy. Baseline LFTs should be obtained, and LFTs should be carefully monitored after one, two and four weeks of treatment initiation, and if stable, at least every eight weeks thereafter during treatment. Consideration should be given to a suspension or discontinuation of Bexarotene capsules if test results reach greater than three times the upper limit of normal values for SGOT/AST, SGPT/ALT, or bilirubin.

*Hepatic insufficiency:* No specific studies have been conducted with Bexarotene capsules in patients with hepatic insufficiency. Because less than 1% of the dose is excreted in the urine unchanged and there is *in vitro* evidence of extensive hepatic contribution to bexarotene elimination, hepatic impairment would be expected to lead to greatly decreased clearance. Bexarotene capsules should be used only with great caution in this population.

*Thyroid axis alterations:* Bexarotene capsules induce biochemical evidence of or clinical hypothyroidism in about half of all patients treated, causing a reversible reduction in thyroid hormone (total thyroxine [total T4]) and thyroid-stimulating hormone (TSH) levels. The incidence of decreases in TSH and total T4 were about 60% and 45%, respectively, in patients with CTCL receiving an initial dose of 300 mg/m²/day. Hypothyroidism was reported as an adverse event in 29% of patients. Treatment with thyroid hormone supplements should be considered in patients with laboratory evidence of hypothyroidism. In the 300 mg/m²/day initial dose group, 37% of patients were treated with thyroid hormone replacement. Baseline thyroid function tests should be obtained and patients monitored during treatment.

*Leukopenia:* A total of 18% of patients with CTCL receiving an initial dose of 300 mg/m²/day of Bexarotene capsules had reversible leukopenia in the range of 1000 to <3000 WBC/mm³. Patients receiving an initial dose greater than 300 mg/m²/day of Bexarotene capsules had an incidence of leukopenia of 43%. No patient with CTCL treated with Bexarotene capsules developed leukopenia of less than 1000 WBC/mm³. The time to onset of leukopenia was generally four to eight weeks. The leukopenia observed in most patients was explained by neutropenia. In the 300 mg/m²/day initial dose group, the incidence of NCI Grade 3 and Grade 4 neutropenia, respectively, was 12% and 4%. The leukopenia and neutropenia experienced during Bexarotene capsules therapy resolved after dose reduction or discontinuation of treatment, on average within 30 days in 93% of the patients with CTCL and 82% of patients with non-CTCL cancers. Leukopenia and neutropenia were rarely associated with severe sequelae or serious adverse events. Determination of WBC with differential should be obtained at baseline and periodically during treatment.

*Cataracts:* Posterior subcapsular cataracts were observed in preclinical toxicity studies in rats and dogs administered bexarotene daily for 6 months. In 15 of 79 patients who had serial slit lamp examinations, new cataracts or worsening of previous cataracts were found. Because of the high prevalence and rate of cataract formation in older patient populations, the relationship of Bexarotene capsules and cataracts cannot be determined in the absence of an appropriate control group. Patients treated with Bexarotene capsules who experience visual difficulties should have an appropriate ophthalmologic evaluation.

## PRECAUTIONS

***Pregnancy:*** **Category X.** See **CONTRAINDICATIONS**.

***General:*** Bexarotene capsules should be used with caution in patients with a known hypersensitivity to retinoids. Clinical instances of crossreactivity have not been noted.

*Vitamin A Supplementation:* In clinical studies, patients were advised to limit vitamin A intake to ≤15,000 IU/day. Because of the relationship of bexarotene to vitamin A, patients should be advised to limit vitamin A supplements to avoid potential additive toxic effects.

*Patients with Diabetes Mellitus:* Caution should be used when administering Bexarotene capsules in patients using insulin, agents enhancing insulin secretion (e.g., sulfonylureas), or insulin-sensitizers (e.g., thiazolidinedione class). Based on the mechanism of action, Bexarotene capsules could enhance the action of these agents, resulting in hypoglycemia. Hypoglycemia has not been associated with the use of Bexarotene capsules as monotherapy.

*Photosensitivity:* Retinoids as a class have been associated with photosensitivity. *In vitro* assays indicate that bexarotene is a potential photosensitizing agent. Mild phototoxicity manifested as sunburn and skin sensitivity to sunlight was observed in patients who were exposed to direct sunlight while receiving Bexarotene capsules. Patients should be advised to minimize exposure to sunlight and artificial ultraviolet light while receiving Bexarotene capsules.

***Information for Patients***

Please see accompanying "Patient's Instructions for Use"

***Laboratory Tests***

Blood lipid determinations should be performed before Bexarotene capsules are given. Fasting triglycerides should be normal or normalized with appropriate intervention prior to therapy. Hyperlipidemia usually occurs within the initial two to four weeks. Therefore, weekly lipid determinations are recommended during this interval. Subsequently, in patients not hyperlipidemic, determinations can be performed less frequently (**see WARNINGS**: ***Lipid abnormalities***).

A white blood cell count with differential should be obtained at baseline and periodically during treatment. Baseline liver function tests should be obtained and should be carefully monitored after one, two and four weeks of treatment initiation, and if stable, periodically thereafter during treatment. Baseline thyroid function tests should be obtained and then monitored during treatment as indicated (see WARNINGS: Leukopenia, Liver function test abnormalities, and Thyroid axis alterations).

***Drug-Food Interaction***

In all clinical trials, patients were instructed to take Bexarotene capsules with or immediately following a meal. In one clinical study, plasma bexarotene AUC and $C_{max}$ values were substantially higher following a fat-containing meal versus those following the administration of a glucose solution. Because safety and efficacy data are based upon administration with food, it is recommended that Bexarotene capsules be administered with food (see **CLINICAL PHARMACOLOGY: Pharmacokinetics and DOSAGE AND ADMINISTRATION**).

***Drug-Drug Interactions***

Concomitant administration of Bexarotene capsules and gemfibrozil resulted in substantial increases in plasma concentrations of bexarotene. Concomitant administration of gemfibrozil with Bexarotene capsules is not recommended (see **CLINICAL PHARMACOLOGY:** ***Drug-Drug Interactions***).

Coadministration of paclitaxel plus carboplatin with Bexarotene capsules increased bexarotene AUC by 2-fold. Caution should be excerisized when Bexarotene capsules are concomitantly administered with paclitaxel plus carboplatin (see **CLINICAL PHARMACOLOGY:** ***Drug-Drug Interactions***).

Concomitant administration of Bexarotene capsules and tamoxifen resulted in approximately a 35% decrease in plasma concentrations of tamoxifen.

The exposure (AUC) to atorvastatin decreased by half when atorvastatin was coadministered with Bexarotene Capsules. This suggest that Bexarotene Capsules is an inducer for the CYP3A4 enzymes, and that it may reduce plasma concentrations of other substrates metabolized by CYP3A4, including oral or other systemic hormonal contraceptives (see **CLINICAL PHARMACOLOGY:** ***Drug-Drug Interactions*** and **CONTRAINDICATIONS:** ***Pregnancy:*** **Category X**). Thus, if treatment with Bexarotene capsules is intended in a woman with child-bearing potential, it is strongly recommended that two reliable forms of contraception be used concurrently, one of which should be non-hormonal.

***Protein Binding***

Bexarotene is highly bound (>99%) to plasma proteins. The plasma proteins to which bexarotene binds have not been elucidated, and the ability of bexarotene to displace drugs bound to plasma proteins and the ability of drugs to displace bexarotene binding have not been studied.

***Renal Insufficiency***

No formal studies have been conducted with Bexarotene capsules in patients with renal insufficiency. Urinary elimination of bexarotene and its known metabolites is a minor excretory pathway for bexarotene (<1% of administered dose), but because renal insufficiency can result in significant protein binding changes, and bexarotene is >99% protein bound, pharmacokinetics may be altered in patients with renal insufficiency.

***Drug/Laboratory Test Interactions***

CA125 assay values in patients with ovarian cancer may be increased by Bexarotene capsule therapy.

***Carcinogenesis, Mutagenesis, Impairment of Fertility***

Long-term studies in animals to assess the carcinogenic potential of bexarotene have not been conducted. Bexarotene is not mutagenic to bacteria (Ames assay) or mammalian cells (mouse lymphoma assay). Bexarotene was not clastogenic *in vivo* (micronucleus test in mice). No formal fertility studies were conducted with bexarotene. Bexarotene caused testicular degeneration when oral doses of 1.5 mg/kg/day were given to dogs for 91 days (producing an AUC of approximately one fifth the AUC at the recommended human daily dose).

***Use in Nursing Mothers***

It is not known whether bexarotene is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from bexarotene, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

***Pediatric Use***

Safety and effectiveness in pediatric patients have not been established.

***Geriatric Use***

Of the total patients with CTCL in clinical studies of Bexarotene capsules, 64% were 60 years or older, while 33% were 70 years or older. No overall differences in safety were observed between patients 70 years or older and younger patients, but greater sensitivity of some older individuals to Bexarotene capsules cannot be ruled out. Responses to Bexarotene capsules were observed across all age group decades, without preference for any individual age group decade.

## ADVERSE REACTIONS

The safety of Bexarotene capsules has been evaluated in clinical studies of 152 patients with CTCL who received Bexarotene capsules for up to 97 weeks and in 352 patients in other studies. The mean duration of therapy for the 152 patients with CTCL was 166 days. The most common adverse events reported with an incidence of at least 10% in patients with CTCL treated at an initial dose of 300 mg/m²/day of Bexarotene capsules are shown in Table 1. The events at least possibly related to treatment are lipid abnormalities (elevated triglycerides, elevated total and LDL cholesterol and decreased HDL cholesterol), hypothyroidism, headache, asthenia, rash, leukopenia, anemia, nausea, infection, peripheral edema, abdominal pain, and dry skin. Most adverse events occurred at a higher incidence in patients treated at starting doses of greater than 300 mg/m²/day (see Table 1).

Adverse events leading to dose reduction or study drug discontinuation in at least two patients were hyperlipemia, neutropenia/leukopenia, diarrhea, fatigue/lethargy, hypothyroidism, headache, liver function test abnormalities, rash, pancreatitis, nausea, anemia, allergic reaction, muscle spasm, pneumonia, and confusion.

The moderately severe (NCI Grade 3) and severe (NCI Grade 4) adverse events reported in two or more patients with CTCL treated at an initial dose of 300 mg/m²/day of Bexarotene capsules (see Table 2) were hypertriglyceridemia, pruritus, headache, peripheral edema, leukopenia, rash, and hypercholesteremia. Most of these moderately severe or severe adverse events occurred at a higher rate in patients treated at starting doses of greater than 300 mg/m2/day than in patients treated at a starting dose of 300 mg/m²/day.

As shown in Table 3, in patients with CTCL receiving an initial dose of 300 mg/m²/day, the incidence of NCI Grade 3 or 4 elevations in triglycerides and total cholesterol was 28% and 25%, respectively. In contrast, in patients with CTCL receiving greater than 300 mg/m²/day, the incidence of NCI Grade 3 or 4 elevated triglycerides and total cholesterol was 45% and 45%, respectively. Other Grade 3 and 4 laboratory abnormalities are shown in Table 3.

In addition to the 152 patients enrolled in the two CTCL studies, 352 patients received Bexarotene capsules as monotherapy for various advanced malignancies at doses from 5 mg/m²/day to 1000 mg/m²/day. The common adverse events (incidence greater than 10%) were similar to those seen in patients with CTCL.

In the 504 patients (CTCL and non-CTCL) who received Bexarotene capsules as monotherapy, drug-related serious adverse events that were fatal, in one patient each, were acute pancreatitis, subdural hematoma, and liver failure.

In the patients with CTCL receiving an initial dose of 300 mg/m²/day of Bexarotene capsules, adverse events reported at an incidence of less than 10% and not included in Tables 1-3 or discussed in other parts of labeling and possibly related to treatment were as follows:

**Body as a Whole:** chills, cellulitis, chest pain, sepsis, and monilia.

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**Bexarotene capsule, liquid filled**
**Rx Only**

**Bexarotene capsule, liquid filled**
**Rx Only**

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**Cardiovascular:** hemorrhage, hypertension, angina pectoris, right heart failure, syncope, and tachycardia.

**Digestive:** constipation, dry mouth, flatulence, colitis, dyspepsia, cheilitis, gastroenteritis, gingivitis, liver failure, and melena.

**Hemic and Lymphatic:** eosinophilia, thrombocythemia, coagulation time increased, lymphocytosis, and thrombocytopenia.

**Metabolic and Nutritional:** LDH increased, creatinine increased, hypoproteinemia, hyperglycemia, weight decreased, weight increased, and amylase increased.

**Musculoskeletal:** arthralgia, myalgia, bone pain, myasthenia, and arthrosis.

**Nervous:** depression, agitation, ataxia, cerebrovascular accident, confusion, dizziness, hyperesthesia, hypesthesia, and neuropathy.

**Respiratory:** pharyngitis, rhinitis, dyspnea, pleural effusion, bronchitis, cough increased, lung edema, hemoptysis, and hypoxia.

**Skin and Appendages:** skin ulcer, acne, alopecia, skin nodule, macular papular rash, pustular rash, serous drainage, and vesicular bullous rash.

**Special Senses:** dry eyes, conjunctivitis, ear pain, blepharitis, corneal lesion, keratitis, otitis externa, and visual field defect.

**Urogenital:** albuminuria, hematuria, urinary incontinence, urinary tract infection, urinary urgency, dysuria, kidney function abnormal, and breast pain.

Table 1. Adverse Events with Incidence ≥10% in CTCL Trials

| | Initial Assigned Dose Group (mg/m²/day) | |
|---|---|---|
| | 300 | >300 |
| **Body System Adverse Event[1,2]** | **N=84 N (%)** | **N=53 N (%)** |
| METABOLIC AND NUTRITIONAL DISORDERS | | |
| Hyperlipemia | 66 (78.6) | 42 (79.2) |
| Hypercholesteremia | 27 (32.1) | 33 (62.3) |
| Lactic dehydrogenase increased | 6 (7.1) | 7 (13.2) |
| BODY AS A WHOLE | | |
| Headache | 25 (29.8) | 22 (41.5) |
| Asthenia | 17 (20.2) | 24 (45.3) |
| Infection | 11 (13.1) | 12 (22.6) |
| Abdominal pain | 9 (10.7) | 2 (3.8) |
| Chills | 8 (9.5) | 7 (13.2) |
| Fever | 4 (4.8) | 9 (17.0) |
| Flu syndrome | 3 (3.6) | 7 (13.2) |
| Back pain | 2 (2.4) | 6 (11.3) |
| Infection bacterial | 1 (1.2) | 7 (13.2) |
| ENDOCRINE | | |
| Hypothyroidism | 24 (28.6) | 28 (52.8) |
| SKIN AND APPENDAGES | | |
| Rash | 14 (16.7) | 12 (22.6) |
| Dry skin | 9 (10.7) | 5 (9.4) |
| Exfoliative dermatitis | 8 (9.5) | 15 (28.3) |
| Alopecia | 3 (3.6) | 6 (11.3) |
| HEMIC AND LYMPHATIC SYSTEM | | |
| Leukopenia | 14 (16.7) | 25 (47.2) |
| Anemia | 5 (6.0) | 13 (24.5) |
| Hypochromic anemia | 3 (3.6) | 7 (13.2) |
| DIGESTIVE SYSTEM | | |
| Nausea | 13 (15.5) | 4 (7.5) |
| Diarrhea | 6 (7.1) | 22 (41.5) |
| Vomiting | 3 (3.6) | 7 (13.2) |
| Anorexia | 2 (2.4) | 12 (22.6) |
| CARDIOVASCULAR SYSTEM | | |
| Peripheral edema | 11 (13.1) | 6 (11.3) |
| NERVOUS SYSTEM | | |
| Insomnia | 4 (4.8) | 6 (11.3) |

[1] Preferred English term coded according to Ligand modified COSTART 5 Dictionary.

[2] Patients are counted at most once in each AE category.

Table 2. Incidence of Moderately Severe and Severe Adverse Events Reported in at Least Two Patients (CTCL Trials)

| | Initial Assigned Dose Group (mg/m2/day) | | | |
|---|---|---|---|---|
| | 300 (N=84) | | >300 (N=53) | |
| | Mod Sev | Severe | Mod Sev | Severe |
| **Body System Adverse Event[1,2]** | **N (%)** | **N (%)** | **N (%)** | **N (%)** |
| BODY AS A WHOLE | | | | |
| Asthenia | 1 (1.2) | 0 (0.0) | 11 (20.8) | 0 (0.0) |
| Headache | 3 (3.6) | 0 (0.0) | 5 (9.4) | 1 (1.9) |
| Infection bacterial | 1 (1.2) | 0 (0.0) | 0 (0.0) | 2 (3.8) |
| CARDIOVASCULAR SYS. | | | | |
| Peripheral edema | 2 (2.4) | 1 (1.2) | 0 (0.0) | 0 (0.0) |
| DIGESTIVE SYSTEM | | | | |
| Anorexia | 0 (0.0) | 0 (0.0) | 3 (5.7) | 0 (0.0) |
| Diarrhea | 1 (1.2) | 1 (1.2) | 2 (3.8) | 1 (1.9) |
| Pancreatitis | 1 (1.2) | 0 (0.0) | 3 (5.7) | 0 (0.0) |
| Vomiting | 0 (0.0) | 0 (0.0) | 2 (3.8) | 0 (0.0) |
| ENDOCRINE | | | | |
| Hypothyroidism | 1 (1.2) | 1 (1.2) | 2 (3.8) | 0 (0.0) |
| HEM. & LYMPH. SYS. | | | | |
| Leukopenia | 3 (3.6) | 0 (0.0) | 6 (11.3) | 1 (1.9) |
| META. AND NUTR. DIS. | | | | |
| Bilirubinemia | 0 (0.0) | 1 (1.2) | 2 (3.8) | 0 (0.0) |
| Hypercholesteremia | 2 (2.4) | 0 (0.0) | 5 (9.4) | 0 (0.0) |
| Hyperlipemia | 16 (19.0) | 6 (7.1) | 17 (32.1) | 5 (9.4) |
| SGOT/AST increased | 0 (0.0) | 0 (0.0) | 2 (3.8) | 0 (0.0) |
| SGPT/ALT increased | 0 (0.0) | 0 (0.0) | 2 (3.8) | 0 (0.0) |
| RESPIRATORY SYSTEM | | | | |
| Pneumonia | 0 (0.0) | 0 (0.0) | 2 (3.8) | 2 (3.8) |
| SKIN AND APPENDAGES | | | | |
| Exfoliative dermatitis | 0 (0.0) | 1 (1.2) | 3 (5.7) | 1 (1.9) |
| Rash | 1 (1.2) | 2 (2.4) | 1 (1.9) | 0 (0.0) |

[1] Preferred English term coded according to Ligand-modified COSTART 5 Dictionary.

[2] Patients are counted at most once in each AE category. Patients are classified by the highest severity within each row.

Table 3. Treatment-Emergent Abnormal Laboratory Values in CTCL Trials

| | Initial Assigned Dose (mg/m²/day) | | | |
|---|---|---|---|---|
| | 300 | | >300 | |
| | N=83[1] | | N=53[1] | |
| **Analyte** | **Grade 3[2] (%)** | **Grade 4[2] (%)** | **Grade 3 (%)** | **Grade 4 (%)** |
| Triglycerides[3] | 21.3 | 6.7 | 31.8 | 13.6 |
| Total Cholesterol[3] | 18.7 | 6.7 | 15.9 | 29.5 |
| Alkaline Phosphatase | 1.2 | 0.0 | 0.0 | 1.9 |
| Hyperglycemia | 1.2 | 0.0 | 5.7 | 0.0 |
| Hypocalcemia | 1.2 | 0.0 | 0.0 | 0.0 |
| Hyponatremia | 1.2 | 0.0 | 9.4 | 0.0 |
| SGPT/ALT | 1.2 | 0.0 | 1.9 | 1.9 |
| Hyperkalemia | 0.0 | 0.0 | 1.9 | 0.0 |
| Hypernatremia | 0.0 | 1.2 | 0.0 | 0.0 |
| SGOT/AST | 0.0 | 0.0 | 1.9 | 1.9 |
| Total Bilirubin | 0.0 | 0.0 | 0.0 | 1.9 |
| ANC | 12.0 | 3.6 | 18.9 | 7.5 |
| ALC | 7.2 | 0.0 | 15.1 | 0.0 |
| WBC | 3.6 | 0.0 | 11.3 | 0.0 |
| Hemoglobin | 0.0 | 0.0 | 1.9 | 0.0 |

[1] Number of patients with at least one analyte value post-baseline.

[2] Adapted from NCI Common Toxicity Criteria, Grade 3 and 4, Version 2.0. Patients are considered to have had a Grade 3 or 4 value if either of the following occurred: a) Value becomes Grade 3 or 4 during the study; b) Value is abnormal at baseline and worsens to Grade 3 or 4 on study, including all values beyond study drug discontinuation, as defined in data handling conventions.

[3] The denominator used to calculate the incidence rates for fasting Total Cholesterol and Triglycerides were N=75 for the 300 mg/m²/day initial dose group and N=44 for the >300 mg/m²/day initial dose group.

**OVERDOSAGE**

Doses up to 1000 mg/m²/day of Bexarotene capsules have been administered in short-term studies in patients with advanced cancer without acute toxic effects. Single doses of 1500 mg/kg and 720 mg/kg were tolerated without significant toxicity in rats and dogs, respectively. These doses are approximately 30 and 50 times, respectively, the recommended human dose on a mg/m² basis.

No clinical experience with an overdose of Bexarotene capsules has been reported. Any overdose with Bexarotene capsules should be treated with supportive care for the signs and symptoms exhibited by the patient.

**DOSAGE AND ADMINISTRATION**

The recommended initial dose of Bexarotene capsules is 300 mg/m²/day. (See Table 4.) Bexarotene capsules should be taken as a single oral daily dose with a meal. See CONTRAINDICATIONS: Pregnancy: Category X section for precautions to prevent pregnancy and birth defects in women of childbearing potential.

Table 4. Bexarotene Capsule Initial Dose Calculation According to Body Surface Area

| Initial Dose Level (300 mg/m²/day) | | |
|---|---|---|
| **Body Surface Area (m²)** | **Total Daily Dose (mg/day)** | **Number of 75 mg Bexarotene Capsules** |
| 0.88 - 1.12 | 300 | 4 |
| 1.13 - 1.37 | 375 | 5 |
| 1.38 - 1.62 | 450 | 6 |
| 1.63 - 1.87 | 525 | 7 |
| 1.88 - 2.12 | 600 | 8 |
| 2.13 - 2.37 | 675 | 9 |
| 2.38 - 2.62 | 750 | 10 |

Dose Modification Guidelines: The 300 mg/m²/day dose level of Bexarotene capsules may be adjusted to 200 mg/m²/day then to 100 mg/m²/day, or temporarily suspended, if necessitated by toxicity. When toxicity is controlled, doses may be carefully readjusted upward. If there is no tumor response after eight weeks of treatment and if the initial dose of 300 mg/m²/day is well tolerated, the dose may be escalated to 400 mg/m²/day with careful monitoring.

Duration of Therapy: In clinical trials in CTCL, Bexarotene capsules were administered for up to 97 weeks. Bexarotene capsules should be continued as long as the patient is deriving benefit.

**HOW SUPPLIED**

Bexarotene capsules are supplied as 75 mg off-white, oblong soft gelatin capsules, imprinted with B75, in high density polyethylene bottles with child-resistant closures.

Bottles of 100 capsules, NDC 10888-5004-2

Store at 2°-25°C (36°-77°F). Avoid exposing to high temperatures and humidity after the bottle is opened.

Protect from light.

Manufactured by:
Banner Pharmacaps Inc.
4125 Premier Drive
High Point, NC 27265

Rev. 04/2014

**PATIENT'S INSTRUCTIONS FOR USE**

**BEXAROTENE** (beks-AIR-oh-teen) **CAPSULES, 75 MG**

To help you get the full benefits from this medicine, you should read this leaflet carefully and ask your doctor to explain anything you do not understand.

**What are the most important things I should know about Bexarotene** (beks-AIR-oh-teen) **capsules?**

- Bexarotene (beks-AIR-oh-teen) capsules can cause major damage to a fetus. Pregnancy must be avoided in patients receiving Bexarotene (beks-AIR-oh-teen) capsules.
- Bexarotene (beks-AIR-oh-teen) capsules can greatly increase blood levels of lipids (triglycerides and cholesterol) and these levels must be monitored and, if elevated, treated.
- Bexarotene (beks-AIR-oh-teen) capsules can cause an underactive thyroid and periodic blood tests will be needed to detect this. Medication to control the condition may be necessary.

Do not take Bexarotene (beks-AIR-oh-teen) capsules if you are pregnant or if you plan to become pregnant.

- Bexarotene (beks-AIR-oh-teen) capsules may harm your fetus (unborn baby). You should contact your doctor immediately if you believe or suspect you are pregnant while you are taking Bexarotene (beks-AIR-oh-teen) capsules and until one month after you stop taking Bexarotene (beks-AIR-oh-teen) capsules.
- If you are capable of becoming pregnant, you must have a pregnancy test, within one week before you start Bexarotene (beks-AIR-oh-teen) capsule therapy and monthly while you are taking Bexarotene (beks-AIR-oh- teen) capsules, confirming you are not pregnant.
- You must use effective contraception (birth control) continuously starting one month before beginning treatment with Bexarotene (beks-AIR-oh-teen) capsules until one month after you stop taking Bexarotene (beks-AIR-oh-teen) capsules. It is strongly recommended that two reliable forms of contraception be used together. At least one of these two forms of contraception should include condoms, diaphragms, cervical caps, IUDs, or spermicides.
- If you are male and your partner is pregnant or capable of becoming pregnant, you should discuss with your doctor the precautions you should take.

**What are Bexarotene** (beks-AIR-oh-teen) **capsules?**

Bexarotene (beks-AIR-oh-teen) capsules contain bexarotene (beks-AIR-oh-teen). Bexarotene (beks-AIR-oh-teen) capsules belong to a class of medicines known as retinoids. Each off-white, oblong soft gelatin Bexarotene capsule (beks-AIR-oh-teen) contains 75 mg of bexarotene (beks-AIR-oh-teen). Each capsule is imprinted with the name "B75" in black.

**What are the uses for Bexarotene** (beks-AIR-oh-teen) **capsules?**

This medicine is used to treat the skin problems arising from a disease called cutaneous T-cell lymphoma, or CTCL. Your doctor must supervise the use of Bexarotene (beks-AIR-oh-teen) capsules.

**Do not take Bexarotene** (beks-AIR-oh-teen) **capsules if you are allergic to this medicine.**

**If you have any of the following conditions, make sure you have discussed them with your doctor before you start to take this medicine.**

- You are pregnant or think you may be pregnant.
- You have or previously had an inflamed pancreas (pancreatitis).
- You are breastfeeding.
- You are taking gemfibrozil (Lopid®)*, a medication to reduce high triglyceride cholesterol (fats) levels in the blood.
- You are taking tamoxifen (Nolvadex®)+, paclitaxel (Taxol®)***, and atorvastatin (Lipitor®)**
- You are taking oral or systemic hormonal contraceptives.

**Medical conditions you should tell your doctor about.**

- If you are allergic to retinoid medications (for example: Accutane® [isotretinoin], Soriatane® [acitretin], Tegison® [etretinate], Vesanoid® [tretinoin])++
- If you have or ever had high triglyceride (a fatty substance) levels in your blood.
- If you have diabetes mellitus (sugar diabetes).
- If you have a history of or currently have gall bladder disease.
- If you have or have had any liver disease.
- If you regularly drink more than a small amount of alcohol.
- If you are currently taking any prescription medication especially for fungal infections, bacterial infections, or seizures.
- If you eat a lot of grapefruit or drink a lot of grapefruit juice.

**When should you be extra careful while taking Bexarotene** (beks-AIR-oh-teen) **capsules?**

- Because vitamin A in large doses may cause some side effects which are similar to those seen in patients taking Bexarotene (beks-AIR-oh-teen) capsules, do not take more than the recommended daily dietary allowance of vitamin A (4000 to 5000 International Units). If you take vitamins, check the label to see how much vitamin A they contain. If you are not sure, ask your doctor or pharmacist.
- Your skin may become more sensitive to sunlight while taking this medicine. Minimize exposure to sunlight and do not use a sunlamp.

**How should Bexarotene** (beks-AIR-oh-teen) **capsules be taken?**

- Always take Bexarotene (beks-AIR-oh-teen) capsules the way your doctor tells you.
- Your doctor will tell you how many Bexarotene (beks-AIR-oh-teen) capsules to take each day. You should take your daily dose of Bexarotene (beks-AIR-oh-teen) capsules all at once. It is best to take them once each day with or immediately following a meal. For example, you might always take your daily amount of Bexarotene (beks-AIR-oh-teen) capsules with your evening meal.
- Always swallow each capsule whole; do not chew them or dissolve them in liquid or in your mouth. Depending on your health and condition, your doctor may change your daily dose (the number of capsules you are taking) during your treatment.
- If you miss a dose, take it as soon as possible, with food. However, if it is nearly time for your next dose, skip the missed dose and continue your dose schedule as before. Do not take a double dose.
- If you take too many Bexarotene (beks-AIR-oh-teen) capsules or someone else accidentally takes your medicine, contact your doctor, emergency room or the nearest hospital immediately.

**How long before you can expect your CTCL to improve on Bexarotene** (beks-AIR-oh-teen) **capsule treatment?**

- Although some patients saw improvement within the first several weeks of Bexarotene (beks-AIR-oh-teen) capsule treatment, most patients required several months or more of treatment to improve.
- Your doctor should determine how long you should be taking Bexarotene (beks-AIR-oh-teen) capsules, and when treatment may be stopped.

**What side effects do Bexarotene** (beks-AIR-oh-teen) **capsules have?**

The most common side effect is an increase in blood lipids (fats in the blood). Periodic blood tests will be needed to determine blood levels of lipids, including triglycerides and cholesterol. Medication may be needed to control high fat levels in the blood.

Another common side effect is underactive thyroid. The symptoms of underactive thyroid may be difficult to detect because they may develop very gradually and may be very mild. For example, you may begin to feel always tired, low on energy, or feeling unusually cold all the time. A thyroid hormone medication is readily available to fully control these temporary symptoms, so contact your doctor early if you feel you are beginning to experience any of these symptoms. Periodic blood tests will be needed to detect this.

**When should you call your doctor about possible complications of Bexarotene** (beks-AIR-oh-teen) **capsule treatment?**

As an infrequent side effect of Bexarotene (beks-AIR-oh-teen) capsule treatment, pancreatitis (inflamed pancreas) may occur. Symptoms of pancreatitis include persistent nausea, vomiting, and abdominal or back pain. If you develop any of these symptoms while taking Bexarotene (beks-AIR-oh-teen) capsules, contact your doctor immediately.

**All medications have side effects. You should call your physician regarding any questions or concerns you may have when taking Bexarotene (beks-AIR-oh-teen) capsules. You can get more information by calling the toll free number 1-866-231-1749.**

**How should Bexarotene** (beks-AIR-oh-teen) **capsules be stored?**

- The capsules should be stored in a dry place in a closed container, away from light and heat. Store at 2°-25°C (36°-77°F).
- The capsules should not be used after the expiration date printed on the bottle.
- Keep this medicine out of the reach and sight of children.

If Bexarotene (beks-AIR-oh-teen) capsules are broken or leaking, do not touch the capsules or the contents and notify your pharmacist immediately. Should the contents of a broken capsule get on your skin, immediately wash the area with soap and water and notify your physician.

**Further Information**

- You can get more information on Bexarotene (beks-AIR-oh-teen) capsules from your doctor or pharmacist.

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

* Lopid® (gemfibrozil tablets, USP) is a registered trademark of Parke-Davis, Division of Warner-Lambert Co.

+ Nolvadex® (tamoxifen citrate) is a registered trademark of AstraZeneca LP.

++ Accutane® (isotretinoin) is a registered trademark of Roche Pharmaceuticals, Roche Laboratories Inc.

++ Soriatane® (acitretin) is a registered trademark of Roche Pharmaceuticals, Roche Laboratories Inc.

++ Tegison® (etretinate) is a registered trademark of Roche Pharmaceuticals, Roche Laboratories, Inc.

++ Vesanoid® (tretinoin) is a registered trademark of Roche Pharmaceuticals, Roche Laboratories Inc.

** Lipitor® (atorvastatin calcium) is a registered trademark of Pfizer Inc.

***Taxol (paclitaxel) is a registered trademark of Bristol Myers Squib Company

Manufactured by:
Banner Pharmacaps Inc.
High Point, NC 27265

Rev. 04/2014

(b) (4)



(b) (4)

BANNER

NDC # 10888-5004-2

# BEXAROTENE

## Capsules

## 75 mg

Pharmacist-Dispense attached patient leaflet

Rx only

100 Capsules

Each capsule contains: 75 mg Bexarotene

**Inactive Ingredients:** Each capsule contains polyethylene glycol 400, NF, polysorbate 20, NF, povidone, USP, and butylated hydroxyanisol, NF. The capsule shell contains gelatin, NF, water, sorbitol sorbitan solution, NF, glycerin, USP, and titanium dioxide, USP.

**Usual Dosage:** See package insert.

Store at 2°C-25°C (36°F-77°F).

AVOID EXPOSING TO HIGH TEMPERATURES AND HUMIDITY AFTER THE BOTTLE IS OPENED. PROTECT FROM LIGHT. KEEP OUT OF REACH OF CHILDREN. PATIENT: READ ACCOMPANYING PATIENT INFORMATION CAREFULLY.

Manufactured by:

**Banner Pharmacaps Inc.**
High Point, NC 27265

LOT
EXP

Rev. 10/11

(b) (4)

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# ANDA 203174

# LABELING REVIEWS

# ORIGINAL LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

| | |
|---|---|
| **Date of This Review** | May 14, 2014 |
| **ANDA Application Number** | 203174 |
| **Review Cycle Number** | Tentative Approval, 3rd Review Cycle |
| **Applicant Name** | Banner Pharmacaps, Inc. |
| **Established Name** | Bexarotene Capsules |
| **Strength(s)** | 75 mg |
| **Proposed Proprietary Name** | N/A |
| **DARRTS Received Date** | April 22, 2014 |
| **Labeling Reviewer** | Kimberly Rains |
| **Labeling Team Leader** | Malik Imam (Acting) |

## Review Conclusion

☒ No Comments – The Labels and Labeling are ready for Approval or Tentative Approval

☐ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for the Letter to Applicant

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

The Labeling Review Branch has no further questions/comments at this time based on your labeling

submission dated April 22, 2014.

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

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

## A. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 1 and 2 provide a summary of recommendations for each material analyzed in this review.

| Table 1: Review Summary of Container Label and Carton Labeling | | | |
|---|---|---|---|
| | Packaging Sizes | Submission Date | Recommendation |
| Container ☐ Draft ☒ FPL | 75 mg: 100 count bottle | 4/22/14 | ☒ Satisfactory ☐ Revise |
| Blister ☐ Draft ☐ FPL | | | ☐ Satisfactory ☐ Revise |
| Carton ☐ Draft ☐ FPL | | | ☐ Satisfactory ☐ Revise |
| Unit Dose Carton ☐ Draft ☐ FPL | | | ☐ Satisfactory ☐ Revise |
| **Table 2 Review Summary of Prescribing Information and Patient Labeling** | | | |
| | Revision Date and/or code | Submission Date | Recommendation |
| Package Insert ☐ Draft ☒ FPL | 04/2014 listed on PI | 4/22/14 | ☒ Satisfactory ☐ Revise |
| Medication Guide ☐ Draft ☐ FPL | | | ☐ Satisfactory ☐ Revise |
| Patient Information ☐ Draft ☒ FPL | 04/2014 listed on PI | 4/22/14 | ☒ Satisfactory ☐ Revise |
| PPI ☐ Draft ☐ FPL | | | ☐ Satisfactory ☐ Revise |
| SPL ☐ Draft ☒ FPL | 04/2014 listed on PI | 4/22/14 | ☒ Satisfactory ☐ Revise |

**MATERIAL ANALYSIS*****

The results for each material reviewed in this section provide the basis for the labeling comments to the Applicant and other review disciplines.

### 1. Model Labeling

The review model labels and labeling used for comparison to the submitted ANDA labeling are described in Tables 3 and 4.

| Table 3: Review Model Labeling for Prescribing Information and Patient Labeling(Check all that apply) | | |
|---|---|---|
| ☒ MOST RECENTLY APPROVED REFERENCE LISTED DRUG | | |
| NDA 021055 | Bexarotene Capsules, 75 mg | Approved 1/06/2012 |
| S-008 | This "Changes Being Effected" supplemental new drug application provides for updates to the Clinical Pharmacology section of the label as requested in our Supplement Request letter issued October 3, 2011. | |
| ☐ BPCA TEMPLATE | | |
| ☐ OTHER (Describe) | | |

| Table 4: Review Model Labeling for Container Label and Carton Labeling (Check all sources that apply) | | |
|---|---|---|
| | | Approval Date |
| ☐ drugs@fda | | |
| ☐ DARRTS | | |
| ☒ DailyMed | NDA 021055 | 2011 Eisai Inc. (Rev. 11/11) |
| ☒ Annual Report | NDA 021055 ARPT-10 dated 11/25/2009 | Verified against labels shown on DailyMed 5/15/2014 |

***Reviewer Assessment:***
Are the labels and labeling contained in the submission the same as the review model labeling?
☒**Yes** ☐**No** ☐**NA**

**Reviewer Comment:**

***Reviewer Assessment:***
Does the Model Labeling have combined insert labeling for multiple dosage forms?
☐**Yes** ☒**No**

**Reviewer Comment**:

## 2. Established Name Assessment

We compared the established names of this ANDA, the Model Labeling and the USP to determine if the established name presented on the labeling is acceptable.

**Table 5: Comparison of Established Names**

**Model Labeling:** Bexarotene capsules
**ANDA:** Bexarotene capsules
**USP:** N/A

***Reviewer Assessment:***
Is the established name for ANDA acceptable?

☒Yes ☐No

**Reviewer Comment**:

### 3. Previous Labeling Reviews for ANDA and/or Related Correspondence

Table 6 contains a listing of previously completed OGD labeling reviews and other correspondence relating to this application from DARRTS. We reviewed this information to determine if previous labeling comments were addressed by the applicant or if there is new information that may impact the labeling.

Table 6: Completed Labeling Reviews or Other Correspondence for Application Under Review

| Search Date | Finalized Date of DARRTS Document | Were Previous Comments Addressed? (Yes/No/Explain) |
|---|---|---|
| 5/15/14 | 9/27/2011 | 1st review-deficiencies identified |
| 5/15/14 | 10/27/2011 | 2nd review deficiencies mitigated and acceptable |

### 4. United States Pharmacopeia (USP) & Pharmacopeia Forum (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph and determined how the monograph impacts the ANDA labeling with respect to packaging and storage. The results of this search are provided in Table 7.

Table 7: USP and PF Search Results

| | Date Searched (m/dd/yy) | Monograph or Proposed Monograph (Yes/No or N/A) | Date USP Monograph Official | Copy of Information from USP or PF |
|---|---|---|---|---|
| USP | 5/1514 | N/A | | |
| Date Searched PF | 5/15/14 | N/A | | |

N/A – The drug product is not the subject of a USP monograph and/or proposed monograph.

***Reviewer Assessment:***

Does the ANDA labeling require revision or is clarification needed from other review disciplines based on the comparison of USP or PF label/labeling requirements to the ANDA?

☐Yes ☐No ☒NA

**Reviewer Comment**:

***Reviewer Assessment:***

Do required labeling statements appear on/in the ANDA labeling?

☐Yes ☐No ☒NA

**Reviewer Comment**:

***Reviewer Assessment:***
Are the USP packaging and storage recommendations reflected in the labels and labeling?
☐**Yes** ☐**No** ☒**NA**

**Reviewer Comment**:

## 5. Patents and Exclusivities

Table 8 describes how the applicant certified to the Orange Book patent(s) for the Model Labeling and how this certification impacts the ANDA labels and labeling. For applications that have no patents N/A is entered in the patent number column.

**Table 8: Impact of Model Labeling Patents on ANDA Labeling**

| Patent Number | Patent Expiration | Patent Use Code | Patent Use Code Definition | How Applicant Filed | Labeling Impact |
|---|---|---|---|---|---|
| 5780676 | Jul 14, 2015 | 509 | TREATMENT OF CUTANEOUS MANIFESTATIONS OF CUTANEOUS T-CELL LYMPHOMA IN PATIENTS WHO ARE REFRACTORY TO AT LEAST ONE PRIOR SYSTEMIC THERAPY | PIV | None |
| 5962731 | Oct 5, 2016 | 475 | TREATMENT OF CUTANEOUS MANIFESTATIONS OF CUTANEOUS T-CELL LYMPHOMA IN PATIENTS WHO ARE REFRACTORY TO AT LEAST ONE PRIOR SYSTEMIC THERAPY | PIV | None |

***Reviewer Assessment:***
Is the Applicant's Patent Carve Out Acceptable?
☐**Yes** ☐**No** ☒**NA**

**Reviewer Comment**:

Table 9 describes how the expiration of the Orange Book exclusivities for the Model Labeling impacts the ANDA labels and labeling. For applications that have no exclusivities N/A is entered in the exclusivity code column.

**Table 9: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling**

| Exclusivity Code | Exclusivity Code Definition | Exclusivity Expiration | Labeling Impact |
|---|---|---|---|
| N/A | | | None |

***Reviewer Assessment:***
Is the Applicant's Exclusivity Carve Out Acceptable?

☐**Yes** ☐**No** ☒**NA**

**Reviewer Comment**:

## 6. Comparison of ANDA Inactive Ingredients to Model Labeling

We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling. Specific inactive ingredients that require special warnings, precautions, or label/labeling statements are highlighted in Table 10.

**Table 10: Inactive Ingredients contained in Model Product and ANDA**

| Model Labeling Inactive Ingredients | ANDA Inactive Ingredients |
|---|---|
| Each Targretin (bexarotene) capsule also contains the following inactive ingredients: polyethylene glycol 400, NF, polysorbate 20, NF, povidone, USP, and butylated hydroxyanisole, NF. The capsule shell contains gelatin, NF, sorbitol special-glycerin blend, and titanium dioxide, USP. | Each Bexarotene capsule also contains the following inactive ingredients: polyethylene glycol 400, NF, polysorbate 20, NF, povidone, USP and butylated hydroxyanisole, NF. The capsule shell contains gelatin NF, water, sorbitol sorbitan solution, NF, glycerin, USP and titanium dioxide, |

***Reviewer Assessment:***
Is the DESCRIPTION section of the labeling consistent with the component and composition statement contained in the Application?

☒**Yes** ☐**No** ☐**NA**

**Reviewer Comment**:

***Reviewer Assessment:***
Are the required labeling statements present in the ANDA labeling?

☐**Yes** ☐**No** ☒**NA**

**Reviewer Comment**:

***Reviewer Assessment***
If the labeling includes "Does not contain …"statements – Has this statement been verified by chemistry?

☐**Yes** ☐**No** ☒**NA**

**Reviewer Comment**:

## 7. Presentation of Manufacturer/Distributor/Packer on Labeling

We compared the name and address of the manufacturer of this product to the name and address listed on the labels and labeling to determine if the labeling statements are consistent with the regulations. Table 11 provides a description of this comparison.

**Table 11: Comparison of Manufacturer/Distributor/Packer Labeling Statements**

| | |
|---|---|
| **Name and Address of Facility ANDA Manufactured** | Banner Pharmacaps Inc., High Point, NC 27265 |
| **Name and Address on ANDA Labels** | Manufactured by:<br>Banner Pharmacaps Inc.<br>High Point, NC 27265 |
| **Name and Address on ANDA Labeling** | Manufactured by: Banner Pharmacaps Inc., High Point, NC 27265 |

***Reviewer Assessment:***
Does the labeling have the required qualifiers per 21 CFR 201.1?
☒**Yes** ☐**No** ☐**NA**

**Reviewer Comment**:

***Reviewer Assessment:***
For Foreign manufacturers, does the labeling have the country of origin?
☐**Yes** ☐**No** ☒**NA**

**Reviewer Comment**:

***Reviewer Assessment:***
For Foreign manufacturers, does the labeling have a US contact/distributor?
☐**Yes** ☐**No** ☒**NA**

**Reviewer Comment**:

## 8. Description of the Container/Closure

We evaluated the container/closure system of this product to determine if special child-resistant packaging is required based on packaging configuration. Additionally, we evaluated other aspects of the container closure that relate to the dosage form, product formulation, and product class. Below is a description of the container/closure for the ANDA product.

***Reviewer Assessment:***
Does the container require a child-resistant closure (CRC)?
☒**Yes** ☐**No** ☐**NA**

**Reviewer Comment**:

***Reviewer Assessment:***
If the closure is not child-resistant, does the container or carton require a labeling statement warning the product is not child-resistant?
☐**Yes** ☐**No** ☒**NA**

**Reviewer Comment**:

***Reviewer Assessment:***
Are the tamper evident requirements met for OTC and Control Substances?
☐**Yes** ☐**No** ☒**NA**

**Reviewer Comment**:

***Reviewer Assessment:***
Is there text on the cap/ferrule overseal of this injectable product?
☐**Yes** ☐**No** ☒**NA**

**Reviewer Comment**:

If yes, does this text meet the requirements of USP pertaining to text on the cap/ferrule overseal?
☐**Yes** ☐**No** ☐**NA**

**Reviewer Comment**:

***Reviewer Assessment:***
Is the cap color for this injectable product ***not*** black?
☐**Yes** ☐**No** ☒**NA**

**Reviewer Comment**:

***Reviewer Assessment:***
Does this ophthalmic products cap color match the American Academy of Ophthalmology (AAO) packaging color-coding scheme?
☐**Yes** ☐**No** ☒**NA**

**Reviewer Comment**:

***Reviewer Assessment:***
Does this light sensitive product contain necessary labeling statements?
☒**Yes** ☐**No** ☐**NA**

**Reviewer Comment**:

***Reviewer Assessment:***
Does this hygroscopic product contain necessary labeling statements?
☐**Yes** ☐**No** ☒**NA**

**Reviewer Comment**: Product is not hydroscopic.

## 9. How Supplied Section

We compared the descriptions of the model product to the ANDA finished product to determine if the scoring, film coating and imprinting are the same. Product differences are highlighted in Table 12 and

will be referred to the appropriate review discipline for evaluation. Additionally, we evaluated if the text contained in the HOW SUPPLIED section is accurate based on the ANDA finished product description.

| Table 12: Comparison of Model Labeling to ANDA finished product | |
|---|---|
| **Model Labeling** | 75 mg off-white, oblong soft gelatin capsules, imprinted with "Targretin", in high density polyethylene bottles with child-resistant closures. Bottles of 100 capsules |
| **ANDA** | 75 mg off-white, oblong soft gelatin capsules, imprinted with "B75", in high density polyethylene bottles with child-resistant closures. Bottles of 100 capsules |

***Reviewer Assessment:***
Is the description of the finished product accurate in the HOW SUPPLIED section of the insert?
☒**Yes** ☐**No** ☐**NA**

**Reviewer Comment**:

***Reviewer Assessment:***
Are the packaging sizes acceptable as compared to the Model Labeling?
☒**Yes** ☐**No** ☐**NA**

**Reviewer Comment**:

***Reviewer Assessment:***
Does the packaging configuration require the addition or deletion of labeling statements based on the comparison to Model Labeling and/or stability data?
☐**Yes** ☒**No** ☐**NA**

**Reviewer Comment**:

***Reviewer Assessment:***
Is the packaging configuration included in the net quantity statement?
☒**Yes** ☐**No** ☐**NA**

**Reviewer Comment**:

## 10. Storage and Dispensing Recommendations

We compared the storage and dispensing statements that appear on the ANDA labels to the model labeling and USP to confirm the statements do not conflict and the format is consistent with USP and OGD standards (see Table 13).

| Table 13: Model Labeling and ANDA Storage/Dispensing Recommendations |
|---|
| **Model Labeling** |
| **Insert** –Store at 2°-25°C (36°-77°F). Avoid exposing to high temperatures and humidity after the bottle is |

| |
|---|
| opened. Protect from light. |
| Container –Store at 2°-25°C (36°-77°F). Avoid exposing to high temperatures and humidity after the bottle is opened. Protect from light. Keep out of the reach of children. Patient: Read Accompanying Patient information carefully.<br>Carton – Store at 2°-25°C (36°-77°F). Avoid exposing to high temperatures and humidity after the bottle is opened. Protect from light. Keep out of the reach of children. Patient: Read Accompanying Patient information carefully. |
| **ANDA** |
| Insert- Store at 2°-25°C (36°-77°F). Avoid exposing to high temperatures and humidity after the bottle is opened. Protect from light. |
| Container: Store at 2°-25°C (36°-77°F). Avoid exposing to high temperatures and humidity after the bottle is opened. Protect from light. Keep out of the reach of children. Patient: Read Accompanying Patient information carefully. |
| **USP** |
| N/A |

***Reviewer Assessment:***
Is the storage or dispensing statements acceptable as compared to the Model Labeling?
☒**Yes** ☐**No** ☐**NA**

**Reviewer Comment**: The RLD is supplied in a carton and the ANDA is not. Per the Chemistry Review finalized on 12/23/2013, stability data for all conditions are acceptable.

***Reviewer Assessment:***
Is the storage or dispensing statement acceptable as compared to the USP?
☐**Yes** ☐**No** ☒**NA**

**Reviewer Comment**:

***Reviewer Assessment:***
Are the storage temperature recommendations acceptable?
☒**Yes** ☐**No** ☐**NA**

**Reviewer Comment**:

***Reviewer Assessment:***
Does the temperature statement conform to the format used in OGD for controlled room temperature?
☒**Yes** ☐**No** ☐**NA**

**Reviewer Comment**:

## 11. Medication Guide

We evaluated the medication guide to ensure the text is the same as the model labeling. We also ensured the directive appears on the container and carton labeling.

***Reviewer Assessment:***
The Applicant has committed to provide a sufficient number of medication guides.
☐**Yes** ☐**No** ☒**NA**

**Reviewer Comment**:

***Reviewer Assessment:***
Is the phonetic spelling of the proprietary name or established name present?
☐**Yes** ☐**No** ☒**NA**

**Reviewer Comment**:

***Reviewer Assessment:***
Is the dispensing directive present on the container and carton labeling?
☐**Yes** ☐**No** ☒**NA**

**Reviewer Comment**:

## 12. Structured Product Labeling (SPL) Data Elements

We evaluated the SPL data elements to ensure they are consistent with the information submitted in the ANDA. Additionally, we compared the size of the model and ANDA tablet/capsule size to determine if the size of the ANDA tablet/capsule poses a safety risk or require a labeling statement (see Table 14).

**Table 14: Comparison of Model and ANDA Product Size**

| | |
|---|---|
| **Model Labeling** | 75 mg: (b) (4) |
| **ANDA Labeling** | 75mg : (b) (4) |

***Reviewer Assessment:***
Are the data elements consistent with the information submitted in the ANDA?
☒**Yes** ☐**No** ☐**NA**

**Reviewer Comment**:

***Reviewer Assessment:***
Is the tablet/capsule size similar to the model labeling?
☒**Yes** ☐**No** ☐**NA**

**Reviewer Comment**:

## 13. Related Applications Containing the Same Active Ingredient

We evaluated the following applications that contain the same active ingredient from the same applicant to determine if the labels and labeling are adequately differentiated from one another.

***Reviewer Assessment:***
Are the labels and labeling of these products adequately differentiated to avoid selection errors?
☐**Yes** ☐**No** ☒**NA**

**Reviewer Comment**:

## B. QUESTIONS AND COMMENTS FOR THE CHEMIST OR BIO REVIEWER OR MICRO REVIEWER

During the course of this review, we sought clarification on the following issues to determine if a label or labeling revision is necessary.

***Comment 1 for Chemist noted in 2nd cycle review: The applicant submitted bulk packaging for repacking.***

***Reviewer Assessment:***
Do the response(s) received require a label and/or labeling revision?
☐**Yes** ☐**No** ☒**NA**

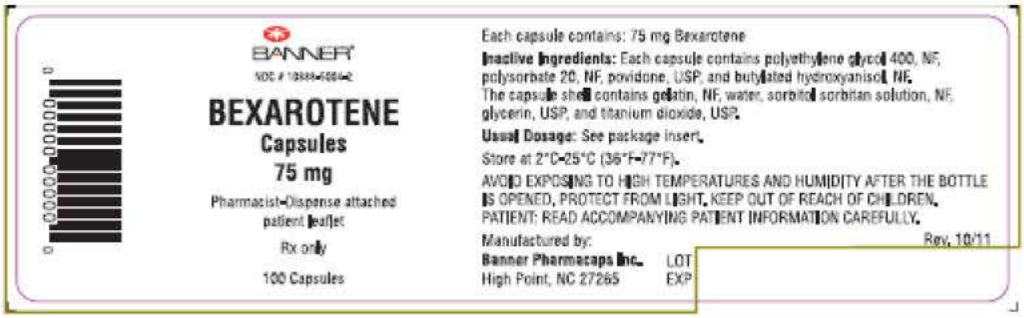
**Reviewer Comment**:

## C. SPECIAL CONSIDERATIONS: N/A

## D. POST APPROVAL REVISIONS:

Revise the presentation of the established name, "BEXAROTENE Capsules" to use title case (i.e. Bexarotene Capsules). Words set in upper and lower case letters form recognizable shapes making them easier to read than the rectangular shape that is formed by words set in all capital letters.

**Proposed Container Label:**



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/s/

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KIMBERLY M RAINS
05/30/2014

MALIK M IMAM
05/30/2014

TENTATIVE APPROVAL #1
DIVISION OF LABELING AND PROGRAM SUPPORT

REMS required? NO

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

ANDA REMS acceptable?
☐ Yes ☐ No XNA

1. APPLICANT INFORMATION:

| | |
|---|---|
| ANDA Number | 203174 |
| Date of Submission | 06 OCT 2011 |
| Applicant | Banner |
| Drug Name | Bexarotene Capsule |
| Strength(s) | 75 mg |

| Labels and Labeling Summary | |
|---|---|
| Container Labels- 100s | DRAFT Satisfactory in the October 6, 20011 |
| Package Insert | DRAFT Satisfactory in the October 6, 20011 |
| Patient leaflet* | DRAFT Satisfactory in the October 6, 20011 |

2. NOTES/QUESTIONS TO THE CHEMIST: The applicant submitted bulk packaging for repacking.

3. REFERENCE LISTED DRUG

**Reference Listed Drug**

| | |
|---|---|
| RLD on the 356(h) form | Targretin |
| NDA Number | 021055 |
| RLD established name | Bexarotene Capsules, 75 mg |
| Firm | Eisai Inc. |
| Currently approved PI | S-006 |
| AP Date | 5/16/2011 Revised 4/11 |

*Note: Phonetic spelling should only be in the Title section.

4. PATENT/ EXCLUSIVITIES- PI

Patent Data For NDA 21055

| Patent No | Patent Expiration | Use Code | Description | How Filed | Labeling Impact |
|---|---|---|---|---|---|
| 5780676 | Jul 14, 2015 | 509 | TREATMENT OF CUTANEOUS MANIFESTATIONS OF CUTANEOUS T-CELL LYMPHOMA IN PATIENTS WHO ARE REFRACTORY TO AT LEAST ONE PRIOR SYSTEMIC THERAPY | | PIV |
| 5962731 | Oct 5, 2016 | 475 | TREATMENT OF CUTANEOUS MANIFESTATIONS OF CUTANEOUS T-CELL LYMPHOMA IN PATIENTS WHO ARE REFRACTORY TO AT LEAST ONE PRIOR SYSTEMIC THERAPY | | PIV |
| 6043279 | Apr 22, 2012 | 509 | | | PIII |

| | | | | | |
|---|---|---|---|---|---|
| 6320074 | Apr 22, 2012 | 509 | | | PIII |
| 7655699 | Apr 22, 2012 | 509 | | | PIII |
| | | | | | |

Exclusivity Data For NDA 21055

| Code/sup | Expiration | Description | Labeling impact |
|---|---|---|---|
| None | | | |

5. MANUFACTURING FACILITY: by: Banner Pharmacaps Inc., High Point, NC 27265

6. STORAGE CONDITIONS:

NDA: Store at 2°-25°C (36°-77°F). Avoid exposing to high temperatures and humidity after the bottle is opened. Protect from light.

ANDA: Same as RLD.

7. DESCRIPTION

**ANDA:**

Bexarotene is a member of a subclass of retinoids that selectively activate retinoid X receptors (RXRs). These retinoid receptors have biologic activity distinct from that of retinoic acid receptors (RARs). Each soft gelatin capsule for oral administration contains 75 mg of bexarotene.

The chemical name is 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl) ethenyl] benzoic acid, and the structural formula is as follows:

Each Bexarotene capsule also contains the following inactive ingredients: polyethylene glycol 400, NF, polysorbate 20, NF, povidone, USP and butylated hydroxyanisole, NF. The capsule shell contains gelatin NF, water, sorbitol sorbitan solution, NF, glycerin, USP and titanium dioxide, USP.

**RLD**

Targretin (bexarotene) is a member of a subclass of retinoids that selectively activate retinoid X receptors (RXRs). These retinoid receptors have biologic activity distinct from that of retinoic acid receptors (RARs). Each soft gelatin capsule for oral administration contains 75 mg of bexarotene. The chemical name is 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl) ethenyl] benzoic acid, and the structural formula is as follows:

Bexarotene is an off-white to white powder with a molecular weight of 348.48 and a molecular formula of C24H28O2. It is insoluble in water and slightly soluble in vegetable oils and ethanol, USP.
Each Targretin (bexarotene) capsule also contains the following inactive ingredients: polyethylene glycol 400, NF, polysorbate 20, NF, povidone, USP, and butylated hydroxyanisole, NF. The capsule shell contains gelatin, NF, sorbitol special-glycerin blend, and titanium dioxide,USP.

8. INACTIVE INGREDIENTS: The listing of inactive ingredients in the DESCRIPTION section is consistent with the listing found in the components section.

**Components/Composition**
**Innovator:**
Each Targretin (bexarotene) capsule also contains the following inactive ingredients: polyethylene glycol 400, NF, polysorbate 20, NF, povidone, USP, and butylated hydroxyanisole, NF. The capsule shell contains gelatin, NF, sorbitol special-glycerin blend, and titanium dioxide, USP.

**ANDA 203174:**

Each Bexarotene capsule also contains the following inactive ingredients: polyethylene glycol 400, NF, polysorbate 20, NF, povidone, USP and butylated hydroxyanisole, NF. The capsule shell contains gelatin NF, water, sorbitol sorbitan solution, NF, glycerin, USP and titanium dioxide, USP.

9. PACKAGING CONFIGURATIONS: HOW SUPPLIED

NDA-

Targretin capsules are supplied as 75 mg off-white, oblong soft gelatin capsules, imprinted with "Targretin", in high density polyethylene bottles with child-resistant closures.
Bottles of 100 capsules..... (b) (4)
Store at 2°-25°C (36°-77°F). Avoid exposing to high temperatures and humidity after the bottle is opened. Protect from light. Manufactured for: Eisai Inc. Woodcliff Lake, NJ 07677

**ANDA- Product Line**:

Bexarotene capsules are supplied as 75 mg off-white, oblong soft gelatin capsules, imprinted with **B75,** in high density polyethylene bottles with child-resistant closures.

Bottles of 100 capsules, NDC 10888-5004-2
Store at 2°-25°C (36°-77°F). Avoid exposing to high temperatures and humidity after the bottle is opened. Protect from light.

10. This drug product is not the subject of a USP monograph.

| | | | |
|---|---|---|---|
| Date of Review: | 10/27/11 | Date of Submission: | 06 OCT 2011 |
| Primary Reviewer: | Angela Payne | Date: | |
| Team Leader: | John Grace | Date: | |

cc: ANDA: 203174
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
E:\FIRMSAM\banner\LTRS&REV\203174tap1labdfsreview.doc
Review

---

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

---

/s/

---

ANGELA M PAYNE
10/27/2011
Draft labels and labeling

JOHN F GRACE
10/27/2011

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# ANDA 203174

# CHEMISTRY REVIEWS

**FINAL Version for DARRTS – 12/18/13**
**CMC is adequate. Bio is pending. Labeling is acceptable. EES is pending.**

Chemist Name/ Ping Tong/11/18/2013, 11/20/2013, 12/9/2013
Chemistry Team Leader /Bhagwant Rege/11/21/13, 12/10/2013
Division Director/Andre Raw/12/16/13
Project Manager / Jasmeet Kalsi /11/22/13, 12/18/13

# ANDA 203174

## Bexarotene Capsules, 75mg

## Banner Pharmacaps Inc.

**Ping Tong, Ph.D.**
**Chemistry Division I**

# Table of Contents

# Chemistry Review Data Sheet

## 1. ANDA 203174

## 2. REVIEW #2

## 3. REVIEW DATE: 11/12/2013

## 4. REVIEWER: Ping Tong

## 5. PREVIOUS DOCUMENTS:

| Submission(s) Reviewed | Document Date |
|---|---|
| New/ANDA (SD #1) | 06/03/2011 |
| Patent & Exclusivity/Patent Certification Quality/Response To Information Request (SD #2) | 07/22/2011 |
| Quality/Response To Information Request (SD #3) | 08/04/2011 |
| Patent & Exclusivity/Patent Certification (SD #4) | 09/06/2011 |
| Patent & Exclusivity/Patent Certification (SD #6) | 10/18/2011 |
| Patent & Exclusivity/Patent Certification (SD #7) | 11/17/2011 |
| Bioequivalence/Other (SD #8) | 12/14/2011 |
| Bioequivalence/Response to Information Request (SD #9) | 03/20/2012 |

## 6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Bioequivalence/Response to Information Request; Resubmission/After Action-Complete; Quality/Response to Information Requested (SD #10) | 10/23/2013 |
| Electronic Submission/Gateway (Quality/Response to ECDs, SD #11) | 12/06/2013 |
| Facility Withdrawal (SD#12) | 12/13/2013 |

## 7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | Banner Pharmacaps Inc. |
| Address: | 4125 Premier Drive<br>High Point, NC 27265 |
| Representative: | Vandana Garikipati, Manager, Regulatory Affairs |
| Telephone: | 336-812-8700 ext. 23988 |

## 8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: N/A
Non-Proprietary Name (USAN): Bexarotene Capsules

## 9. LEGAL BASIS FOR SUBMISSION:

The basis for Banner Pharmacaps Inc.'s (BPI) proposed ANDA for Bexarotene Capsules, 75 mg is the approved, reference listed drug (RLD), Targretin® Capsules, the subject of NDA 021055 held by Eisai and approved December, 29, 1999.

According to the information published in the Electronic Orange Book, there is no unexpired exclusivity for the RLD, Targretin®.

BPI's proposed drug product, Bexarotene Capsules, 75 mg, described in this application, is the same with regard to active ingredients (bexarotene), strength (75 mg), dosage form (capsule), route of administration (oral) and conditions of use (see section 1.14 for labeling) as that approved for the RLD, Targretin® Capsules.

## 10. PHARMACOL. CATEGORY:

Anticancer

## 11. DOSAGE FORM:

Soft Gel Capsules

## 12. STRENGTH/POTENCY:

75mg

## 13. ROUTE OF ADMINISTRATION:

Oral

## 14. Rx/OTC DISPENSED: _xx_ Rx __ OTC

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

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

## 15b. NANOTECHNOLOGY PRODUCT TRACKING:

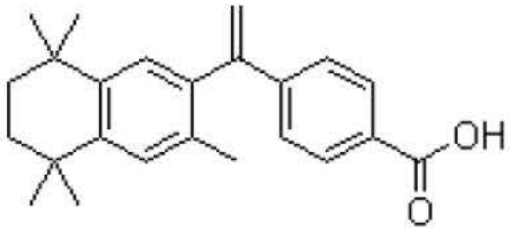
☐ NANO product – Form Completed (See Appendix A.4)

☒ Not a NANO product

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

*Chemical Name:* 4-[1-(3,5,5,8,8-pentamethyl-6,7-dihydronaphthalen-2-yl)ethenyl] benzoic acid

Molecular Structure:




Molecular Formula: $C_{24}H_{28}O_2$

Molecular Weight: 348.478

## 17. RELATED/SUPPORTING DOCUMENTS:

### A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| (b) (4) | II | | (b) (4) | 1 | Adequate | 12/6/2013 | P. Tong |
| | IV | | | 4 | | | |
| | III | | | 4 | | | |
| | IV | | | 1 | Adequate | | |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | III | | | 4 | | | |

[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: N/A**

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| | | |
| | | |
| | | |
| | | |

## 18. STATUS

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Microbiology | N/A | | |
| Methods Validation | N/A | | |
| Labeling | Adequate | 10/27/2011 | A. Payne |
| Bioequivalence | Inadequate | 9/27/2012 | H. Mandula |
| Dissolution | Adquate | 9/27/2012 | H. Mandula |
| Toxicology/Clinical | N/A | | |
| EA | N/A | | |
| Radiopharmaceutical | N/A | | |
| Samples Requested | 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:

## 20. EES INFORMATION

| Drug Substance | | | |
|---|---|---|---|
| **Function** | **Site Information** | **FEI/CFN#** | **Status** |
| Drug Substance Manufacturing | (b) (4) | | OC Recommendation (4-3-2013) |
| Drug Substance Manufacturing | | | OC Recommendation (10-10-2013 |
| **Drug Product** | | | |
| **Function** | **Site Information** | **FEI/CFN#** | **Status** |
| Drug product manufacturing; Raw material testing; Finished | Banner Pharmacaps Inc. 4125 Premier Drive | FEI 3001451366 | OC Recommendat |

| | | | |
|---|---|---|---|
| product testing; Stability testing; Bulk packaging and warehousing | High Point, NC 27265 | CFN 106352 | ion (11-22-2013) |
| (b) (4) | | | |
| | | | |
| | | | Pending |
| | | | |
| | | | OC Recommendation (7-24-2012) |

(b) (4)

# Chemistry Review for ANDA 203174

## Executive Summary

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

CMC is adequate. Bio is pending. Labeling is acceptable. EES is pending.

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

N/A

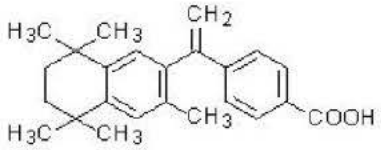
## II. Summary of Chemistry Assessments

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

**DESCRIPTION**

Bexarotene is a member of a subclass of retinoids that selectively activate retinoid X receptors (RXRs). These retinoid receptors have biologic activity distinct from that of retinoic acid receptors (RARs). Each soft gelatin capsule for oral administration contains 75 mg of bexarotene.

The chemical name is 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl) ethenyl] benzoic acid, and the structural formula is as follows:




Bexarotene is an off-white to white powder with a molecular weight of 348.48 and a molecular formula of $C_{24}H_{28}O_2$. It is insoluble in water and slightly soluble in vegetable oils and ethanol, USP.

Each Bexarotene capsule also contains the following inactive ingredients: polyethyelene glycol 400, NF, polysorbate 20, NF, povidone, USP and butylated hydroxyanisole, NF. The capsule shell contains gelatin NF, water, sorbitol sorbitan solution, NF, glycerin, USP and titanium dioxide, USP.

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

**INDICATIONS AND USAGE**

Bexarotene capsules are indicated for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy.

**DOSAGE AND ADMINISTRATION**

The recommended initial dose of Bexarotene capsules is 300 mg/m$^2$/day. (See Table 4.) Bexarotene capsules should be taken as a single oral daily dose with a meal. See CONTRAINDICATIONS: Pregnancy: Category X section for precautions to prevent pregnancy and birth defects in women of child-bearing potential.

Table 4. Bexarotene Capsule Initial Dose Calculation According to Body Surface Area

| Initial Dose Level (300 mg/m$^2$/day) | | |
|---|---|---|
| **Body Surface Area (m$^2$)** | **Total Daily Dose (mg/day)** | **Number of 75 mg Bexarotene Capsules** |
| 0.88 - 1.12 | 300 | 4 |
| 1.13 - 1.37 | 375 | 5 |
| 1.38 - 1.62 | 450 | 6 |
| 1.63 - 1.87 | 525 | 7 |
| 1.88 - 2.12 | 600 | 8 |
| 2.13 - 2.37 | 675 | 9 |
| 2.38 - 2.62 | 750 | 10 |

Dose Modification Guidelines: The 300 mg/m$^2$/day dose level of Bexarotene capsules may be adjusted to 200 mg/m$^2$/day then to 100 mg/m$^2$/day, or temporarily suspended, if necessitated by toxicity. When toxicity is controlled, doses may be carefully readjusted upward. If there is no tumor response after eight weeks of treatment and if the initial dose of 300 mg/m$^2$/day is well tolerated, the dose may be escalated to 400 mg/m$^2$/day with careful monitoring.

Duration of Therapy: In clinical trials in CTCL, Bexarotene capsules were administered for up to 97 weeks.

Bexarotene capsules should be continued as long as the patient is deriving benefit.

**HOW SUPPLIED**

Bexarotene capsules are supplied as 75 mg off-white, oblong soft gelatin capsules, imprinted with B75, in high density polyethylene bottles with child-resistant closures.

Bottles of 100 capsules, NDC 10888-5004-2
Store at 2°-25°C (36°-77°F). Avoid exposing to high temperatures and humidity after the bottle is opened. Protect from light.

Manufactured by:
Banner Pharmacaps Inc.
4125 Premier Drive
High Point, NC 27265

## Basis for Approvability or Not-Approval Recommendation

Not approvable due to minor deficiencies.

# 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

## *A.4 Nanotechnology Product Information*

N/A

Office of Pharmaceutical Science MAPP 5015.9, Attachement A:

**1) This review contains new information added to the table below:**
**Yes** ☐ **No** ☐ Review date: _____

2) Are any nanoscale materials included in this application?
(If yes, please proceed to the next questions.) Yes ☐; No ☐ ;
Maybe (please specify):_____

3 a) What nanomaterial is included in the product?
(Examples of this are listed as search terms in Attachment B.)

_____

3 b) What is the source of the nanomaterial?_____

4) Is the nanomaterial a reformulation of a previously approved product?

Yes ☐ No ☐

5) What is the nanomaterial functionality?
Carrier_____; Excipient_____; Packaging_____
API_____; Other_____

6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble (e.g., gold nanoparticle) in an aqueous environment?
Soluble _____; Insoluble_____

7) Was particle size or size range of the nanomaterial included in the application?
Yes ☐ (Complete 8); No ☐ (go to 9).

| |
|---|
| 8) What is the reported particle size?<br>Mean particle size_____ ; Size range distribution_____;<br>Other_____ |
| 9) Please indicate the reason(s) why the particle size or size range was not provided:<br>_____ |
| 10) What other properties of the nanoparticle were reported in the application (See Attachment E)?<br>_____ |
| 11) List all methods used to characterize the nanomaterial?<br>_____ |

## R REGIONAL INFORMATION

### *R.1 Executed Batch Records*

Provided

### *R.2 Comparability Protocols*

N/A

### *R.3 Methods Validation Package*

N/A

## II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

***Documents***

| | |
|---|---|
| Patent Certification: | Provided in section 1.3.5.2 |
| Exclusivity: | Provided in section 1.3.5 |
| GDEA Certification: | Provided in section 1.3.3 |
| Debarment Certification: | Provided in section 1.3.3 |
| cGMP Statement: | Provided in section 3.2.P.3.1 |
| Reprocessing Statement: | Provided in section 3.2.P.3.3 |
| Letters of Authorization: | Provided in section 1.4.1 |
| Request for Bio-waiver: | N/A |

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

Environnemental Impact Considerations/Categorical Exclusions:
N/A

## III. List of Deficiencies To Be Communicated

### CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 203174

APPLICANT: Banner Pharmacaps Inc.

DRUG PRODUCT: Bexarotene Capsules 75mg

The following deficiencies listed below may be delivered via the easily correctable deficiency method (10 day firm response expected) if the situation allows ☐ YES ☐ NO

N/A

Administrative

**A. Reviewer's Signature**

**B. Endorsement Block**

Chemist Name/ Ping Tong/11/18/2013, 11/20/2013, 12/9/2013
Chemistry Team Leader /Bhagwant Rege/11/21/13, 12/10/2013
Division Director/Andre Raw/12/16/13
Project Manager / Jasmeet Kalsi /11/22/13, 12/18/13

**TYPE OF LETTER:**
CMC is adequate. Labeling is acceptable. EES and Bio are pending.

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

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/s/

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PING TONG
12/20/2013

JASMEET K KALSI
12/20/2013

BHAGWANT D REGE
12/20/2013

ANDRE S RAW
12/23/2013

Final version for DARRTS 7/9/2013
CMC and Bio are deficient. Labeling is acceptable. EES is pending

Chemist Name/Date: Xihao Li/06/12/2013
Chemistry Team Leader Name Bhagwant Rege/06/13/2013
Deputy Division Director Name: Bing Cai/7/7/2013
Project Manager Name/Date: Tania Mazza/7/9/2013

# ANDA 203174

## Bexarotene Capsules, 75mg

## Banner Pharmacaps Inc.

**Xihao Li, Ph.D.**
**Chemistry Division I**

# Table of Contents

# Chemistry Review Data Sheet

## 1. ANDA 203174

## 2. REVIEW #1

## 3. REVIEW DATE: 03/12/2013

## 4. REVIEWER: Xihao Li

## 5. PREVIOUS DOCUMENTS:

| Previous Document(s) | Document Date |
|---|---|
| N/A | |

## 6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| New/ANDA (SD #1) | 06/03/2011 |
| Patent & Exclusivity/Patent Certification Quality/Response To Information Request (SD #2) | 07/22/2011 |
| Quality/Response To Information Request (SD #3) | 08/04/2011 |
| Patent & Exclusivity/Patent Certification (SD #4) | 09/06/2011 |
| Patent & Exclusivity/Patent Certification (SD #6) | 10/18/2011 |
| Patent & Exclusivity/Patent Certification (SD #7) | 11/17/2011 |
| Bioequivalence/Other (SD #8) | 12/14/2011 |
| Bioequivalence/Response to Information Request (SD #9) | 03/20/2012 |

## 7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | Banner Pharmacaps Inc. |
| Address: | 4125 Premier Drive<br>High Point, NC 27265 |

| | |
|---|---|
| Representative: | Vandana Garikipati, Manager, Regulatory Affairs |
| Telephone: | 336-812-8700 ext. 23988 |

## 8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: N/A
Non-Proprietary Name (USAN): Bexarotene Capsules

## 9. LEGAL BASIS FOR SUBMISSION:

The basis for Banner Pharmacaps Inc.'s (BPI) proposed ANDA for Bexarotene Capsules, 75 mg is the approved, reference listed drug (RLD), Targretin® Capsules, the subject of NDA 021055 held by Eisai and approved December, 29, 1999.

According to the information published in the Electronic Orange Book, there is no unexpired exclusivity for the RLD, Targretin®.

BPI's proposed drug product, Bexarotene Capsules, 75 mg, described in this application, is the same with regard to active ingredients (bexarotene), strength (75 mg), dosage form (capsule), route of administration (oral) and conditions of use (see section 1.14 for labeling) as that approved for the RLD, Targretin® Capsules.

## 10. PHARMACOL. CATEGORY:

Anticancer

## 11. DOSAGE FORM:

Soft Gel Capsules

## 12. STRENGTH/POTENCY:

75mg

## 13. ROUTE OF ADMINISTRATION:

Oral

## 14. Rx/OTC DISPENSED: _xx_ Rx __ OTC

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

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

## 15b. NANOTECHNOLOGY PRODUCT TRACKING:

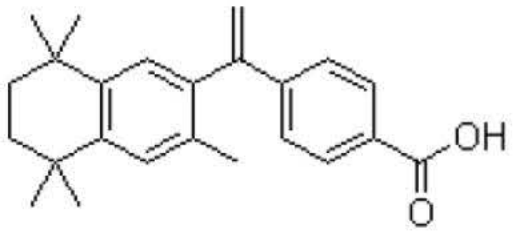
☐ NANO product – Form Completed (See Appendix A.4)

☒ Not a NANO product

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

*Chemical Name:* 4-[1-(3,5,5,8,8-pentamethyl-6,7-dihydronaphthalen-2-yl)ethenyl] benzoic acid

Molecular Structure:




Molecular Formula: $C_{24}H_{28}O_2$

Molecular Weight: 348.478

## 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 | | |
| | IV | | | 4 | | | |
| | III | | | 4 | | | |
| | IV | | | 1 | Adequate | | |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | III | | | 4 | | | |

[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: N/A**

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| | | |
| | | |
| | | |
| | | |

## 18. STATUS

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Microbiology | N/A | | |
| Methods Validation | N/A | | |
| Labeling | Adequate | 10/27/2011 | A. Payne |
| Bioequivalence | Inadequate | 09/27/2012 | H. Mandula |
| Toxicology/Clinical | N/A | | |
| EA | N/A | | |
| Radiopharmaceutical | N/A | | |
| Samples Requested | 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:

## 20. EES INFORMATION

| Drug Substance | | | |
|---|---|---|---|
| **Function** | **Site Information** | **FEI/CFN#** | **Status** |
| Drug Substance Manufacturing | (b) (4) | | OC Recommendation (Apr. 03, 2013) |
| Drug Substance Manufacturing | | | OC recommendation withhold |
| **Drug Product** | | | |
| **Function** | **Site Information** | **FEI/CFN#** | **Status** |
| Drug product manufacturing; Raw material testing; Finished product testing; Stability testing; Bulk packaging and | Banner Pharmacaps Inc. 4125 Premier Drive High Point, NC 27265 | FEI 3001451366 DUNS 002193829 | Pending |

| | | | |
|---|---|---|---|
| warehousing | | | |
| | | | (b) (4) Address is not in EES |
| | | | OC Recommendation (July 24, 2012) |
| | | | OC Recommendation (July 24, 2012) |

# Chemistry Review for ANDA 203174

## Executive Summary

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

Not approvable due to CMC minor deficiencies. Bio is inadequate. Labeling is acceptable. EES is pending.

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

N/A

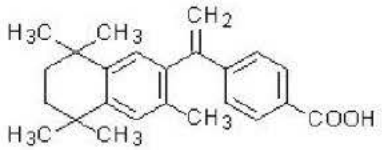
## II. Summary of Chemistry Assessments

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

**DESCRIPTION**

Bexarotene is a member of a subclass of retinoids that selectively activate retinoid X receptors (RXRs). These retinoid receptors have biologic activity distinct from that of retinoic acid receptors (RARs). Each soft gelatin capsule for oral administration contains 75 mg of bexarotene.

The chemical name is 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl) ethenyl] benzoic acid, and the structural formula is as follows:




Bexarotene is an off-white to white powder with a molecular weight of 348.48 and a molecular formula of $C_{24}H_{28}O_2$. It is insoluble in water and slightly soluble in vegetable oils and ethanol, USP.

Each Bexarotene capsule also contains the following inactive ingredients: polyethyelene glycol 400, NF, polysorbate 20, NF, povidone, USP and butylated hydroxyanisole, NF. The capsule shell contains gelatin NF, water, sorbitol sorbitan solution, NF, glycerin, USP and titanium dioxide, USP.

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

**INDICATIONS AND USAGE**

Bexarotene capsules are indicated for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy.

**DOSAGE AND ADMINISTRATION**

The recommended initial dose of Bexarotene capsules is 300 mg/m$^2$/day. (See Table 4.) Bexarotene capsules should be taken as a single oral daily dose with a meal. See CONTRAINDICATIONS: Pregnancy: Category X section for precautions to prevent pregnancy and birth defects in women of child-bearing potential.

Table 4. Bexarotene Capsule Initial Dose Calculation According to Body Surface Area

| Initial Dose Level (300 mg/m$^2$/day) | | |
|---|---|---|
| **Body Surface Area (m$^2$)** | **Total Daily Dose (mg/day)** | **Number of 75 mg Bexarotene Capsules** |
| 0.88 - 1.12 | 300 | 4 |
| 1.13 - 1.37 | 375 | 5 |
| 1.38 - 1.62 | 450 | 6 |
| 1.63 - 1.87 | 525 | 7 |
| 1.88 - 2.12 | 600 | 8 |
| 2.13 - 2.37 | 675 | 9 |
| 2.38 - 2.62 | 750 | 10 |

Dose Modification Guidelines: The 300 mg/m$^2$/day dose level of Bexarotene capsules may be adjusted to 200 mg/m$^2$/day then to 100 mg/m$^2$/day, or temporarily suspended, if necessitated by toxicity. When toxicity is controlled, doses may be carefully readjusted upward. If there is no tumor response after eight weeks of treatment and if the initial dose of 300 mg/m$^2$/day is well tolerated, the dose may be escalated to 400 mg/m$^2$/day with careful monitoring.

Duration of Therapy: In clinical trials in CTCL, Bexarotene capsules were administered for up to 97 weeks.

Bexarotene capsules should be continued as long as the patient is deriving benefit.

**HOW SUPPLIED**

Bexarotene capsules are supplied as 75 mg off-white, oblong soft gelatin capsules, imprinted with B75, in high density polyethylene bottles with child-resistant closures.

Bottles of 100 capsules, NDC 10888-5004-2
Store at 2°-25°C (36°-77°F). Avoid exposing to high temperatures and humidity after the bottle is opened. Protect from light.

Manufactured by:
Banner Pharmacaps Inc.
4125 Premier Drive
High Point, NC 27265

## Basis for Approvability or Not-Approval Recommendation

Not approvable due to minor deficiencies.





Following this page, 65 pages Withheld in Full as (b)(4)

# 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

## *A.4 Nanotechnology Product Information*

N/A

Office of Pharmaceutical Science MAPP 5015.9, Attachement A:

**1) This review contains new information added to the table below:**
**Yes** ☐ **No** ☐ Review date: _____

2) Are any nanoscale materials included in this application?
(If yes, please proceed to the next questions.) Yes ☐; No ☐ ;
Maybe (please specify):_____

3 a) What nanomaterial is included in the product?
(Examples of this are listed as search terms in Attachment B.)

_____

3 b) What is the source of the nanomaterial?_____

4) Is the nanomaterial a reformulation of a previously approved product?

Yes ☐ No ☐

5) What is the nanomaterial functionality?
Carrier_____; Excipient_____; Packaging_____
API_____; Other_____

6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble (e.g., gold nanoparticle) in an aqueous environment?
Soluble _____; Insoluble_____

7) Was particle size or size range of the nanomaterial included in the application?
Yes ☐ (Complete 8); No ☐ (go to 9).

| |
|---|
| 8) What is the reported particle size?<br>Mean particle size_____ ; Size range distribution_____;<br>Other_____ |
| 9) Please indicate the reason(s) why the particle size or size range was not provided:<br>_____ |
| 10) What other properties of the nanoparticle were reported in the application (See Attachment E)?<br>_____ |
| 11) List all methods used to characterize the nanomaterial?<br>_____ |

## R REGIONAL INFORMATION

### *R.1 Executed Batch Records*

Provided

### *R.2 Comparability Protocols*

N/A

### *R.3 Methods Validation Package*

N/A

## II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

***Documents***

| | |
|---|---|
| Patent Certification: | Provided in section 1.3.5.2 |
| Exclusivity: | Provided in section 1.3.5 |
| GDEA Certification: | Provided in section 1.3.3 |
| Debarment Certification: | Provided in section 1.3.3 |
| cGMP Statement: | Provided in section 3.2.P.3.1 |
| Reprocessing Statement: | Provided in section 3.2.P.3.3 |
| Letters of Authorization: | Provided in section 1.4.1 |
| Request for Bio-waiver: | N/A |

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

Environnemental Impact Considerations/Categorical Exclusions:
N/A

## III. List of Deficiencies To Be Communicated

### CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 203174

APPLICANT: Banner Pharmacaps Inc.

DRUG PRODUCT: Bexarotene Capsules 75mg

The following deficiencies listed below may be delivered via the easily correctable deficiency method (10 day firm response expected) if the situation allows ☐ YES ☒ NO

The deficiencies presented below represent minor deficiencies.

**A. Deficiencies**

(b) (4)

1.

2.

3.

4.

5.

6.

7.

8.

9.

10.



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

35 (b) (4)

36

37

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

1) Please provide any updated stability data that may be available.

2) Please provide side by side pictures of ANDA capsules and RLD capsules.

3) We encourage you to apply Quality by Design (QbD) principles to the pharmaceutical development of your future original ANDA product submissions. A risk-based, scientifically sound submission would be expected to include the following:

- Quality target product profile (QTPP)
- Critical quality attributes (CQAs) of the drug product
- Product design and understanding including identification of critical attributes of excipients, drug substance(s), and/or container closure systems
- Process design and understanding including identification of critical process parameters and in-process material attributes
- Control strategy and justification

An example illustrating QbD concepts can be found online at FDA's **Generic Drugs: Information for Industry** webpage:
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM286595.pdf

Sincerely yours,

*{See appended electronic signature page}*

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

APPEARS THIS WAY ON ORIGINAL

## ADMINISTRATIVE

### A. Reviewer's Signature

### B. Endorsement Block

Chemist Name/Date: Xihao Li/06/12/2013
Chemistry Team Leader Name Bhagwant Rege/06/13/2013
Deputy Division Director Name: Bing Cai/7/7/2013
Project Manager Name/Date: Tania Mazza/7/9/2013

**TYPE OF LETTER:**
CMC and Bio are deficient. Labeling is acceptable. EES is pending

---

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

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/s/

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XIHAO LI
07/09/2013

TANIA B MAZZA
07/09/2013

BHAGWANT D REGE
07/09/2013

BING CAI
07/09/2013

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# ANDA 203174

# BIOEQUIVALENCE REVIEWS

# DIVISION OF BIOEQUIVALENCE REVIEW

| | | | |
|---|---|---|---|
| **ANDA No.** | 203174 | | |
| **Drug Product Name** | Bexarotene Capsules | | |
| **Strength(s)** | 75 mg | | |
| **Applicant Name** | Banner Pharmacaps Inc. | | |
| **Applicant Address** | 4125 Premier Drive<br>High Point, NC 27264 | | |
| **US Agent Name and the mailing address** | Vandana Garikipati,<br>Manager, Regulatory Affairs | | |
| **US agent's Telephone Number** | 888-818-4197 | | |
| **US Agent's Fax Number** | 336-812-8700 | | |
| **Original Submission Date(s)** | October 6, 2011 | | |
| **Submission Date(s) of Amendment(s) Under Review** | October 23, 2013 | | |
| **First Generic (Yes or No)** | Yes[1] | | |
| **Reviewer** | Deanah L. Mitchell, Ph.D. | | |
| | | | |
| **Study Number (s)** | BXN-PO-541 | | |
| **Study Type (s)** | Fed | | |
| **Strength (s)** | 75 mg | | |
| **Clinical Site** | Algorithme Pharma Inc. | | |
| **Clinical Site Address** | 1200 Beaumont Ave.<br>Mount-Royal, Quebec, Canada<br>H3P 3P1 | | |
| **Analytical Site** | (b) (4) | | |
| **Analytical Site Address** | | | |
| | | | |
| **OSI Status** | **ADEQUATE** | | |
| **OVERALL REVIEW RESULT** | **ADEQUATE** | | |
| **REVISED/NEW DRAFT GUIDANCE INCLUDED** | **NO** | | |
| **BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #** | **STUDY/TEST TYPE** | **STRENGTH** | **REVIEW RESULT** |
| **#1, #10** | **FED STUDY** | **75 MG** | **ADEQUATE** |
| **#1, #10** | **DISSOLUTION** | **75 MG** | **ADEQUATE** |

[1] DARRTS Search: ANDA 203174; REV-RPM-03 (Filing Review): Final Date 08/24/2011.

# 1 EXECUTIVE SUMMARY

This is a review of an amendment.

On October 6, 2011, Banner Pharmacaps Inc. submitted a fed bioequivalence (BE) study comparing its test product, Bexarotene Capsules, 75 mg, to the corresponding reference product, Eisai Pharmaceutical's Targretin® (Bexarotene) Capsules, 75 mg.[2] The fed BE study was designed as a single dose, 3 period, partial replicate (TRR, RRT and RTR), crossover study of the Bexarotene 75 mg Capsule in healthy male volunteers. The firm conducted this 3-ay crossover design for reference scale approach.

A deficiency letter was sent to the firm on July 15, 2013[3] requesting the firm to (1) submit complete raw data (numerical printouts) of all sample analysis runs, (2) submit data for all unused batches from the bioanalytical validation report and (3) provide SOP (b) (4) Rejected and Not Used Data, Laboratory Investigations and Events.

On October 24, 2013, the firm responded satisfactorily to the deficiencies.

The dissolution testing was previously found acceptable.[2]

No Office of Scientific Investigation (OSI) inspection is pending or necessary.[2]

The application is **adequate** with no deficiencies.

---

[2] DARRTS. Search: ANDA 203174. Mandula, Haritha/09-27-2012/REV-BIOEQ-01(General Review).
[3] DARRTS. Search: ANDA 203174. Chuh, Eunjung E/07-15-2013/COR-ANDAACTION-09(Complete Response).

# 2 TABLE OF CONTENTS

## 3 RESPONSE TO DEFICIENCY

*(Letter Date: 07/15/2013)*

### 3.1 DBI Deficiency Comment #1:

*You did not submit the raw analytical numerical data for all the assay runs (both accepted and rejected runs). Please submit complete raw data (numerical printouts) of all sample analysis runs, including the data for the peak area/height for the drug and the internal standard (IS), the ratio of the drug peak area/height to the IS peak area/height, dilution factor (if any), and the corresponding calculated concentration for each assayed and reassayed sample, calibration standard concentration samples, and quality control samples.*

**Firm's Response to Deficiency Comment #1:**

**As requested, you will find attached the raw analytical numerical data for all batches of the sample analysis study, including accepted, rejected and not used batches. Please refer to the regression tables presented in the file named "Regression tables of all batches in study BXNP0- 541", which contain all the requested information. Batches containing subject samples correspond to batches BXN541.04, BXN541.05, BXN541.07 to BXN541.16, and BXN541 .18 to BXN541.46. Batches BXN541.01 to BXN541.03, BXN541.06 and BXN541.17 correspond to Test Curves. We would like to mention that the regression tables of all accepted subject batches are presented in appendix 3 of the analytical report. In addition, it is to note that the dilution factor is obtained in the regression tables via the column "Volume (mL)", where the undiluted sample volume is 0.200 mL as per analytical method. In the regression tables starting from batch BXN541.15, all samples with a volume of 0.040 mL inscribed in this column were therefore diluted with a factor of 5. This is the only dilution factor that was used during the study.**

**Reviewer's Comment #1:**

The firm provided the raw analytical numerical data for all batches (BXN541.1- BXN541.46), including accepted, rejected and not used batches of the sample analysis study. The firm's response to Deficiency Comment #1 is **acceptable**.

### 3.2 DBI Deficiency Comment #2

*A summary table of batch analysis was provided in your bioanalytical validation report.*
*The report stated that, "data from reject or unused batches and/or evaluations are not included in this report but are on file at* (b) (4) *A batch or evaluation is listed as "Not Used" when an analytical issue is observed that could potentially affect data integrity". Please submit the data for all unused batches as well.*

**Firm's Response to Deficiency Comment #2:**

**As requested, you will find attached the relevant documentation for the unused validation evaluations in the validation (either rejected or not used). The numerical data of these unused evaluations is included when available (i.e. when generated). Please refer to the file named "Rejected and Not Used validation data BXN-V1-466".**

**Reviewer's Comment #2**

The firm provided the rejected and unused analytical numerical data for all batches. Three batches were "rejected" batches (BXN466.07, BXN466.09 and BXN466.17). Two batches were "not used" batches (BXN466.14 and BXN466.15). The table below shows the batch numbers that were rejected, the description and reason for either rejection or unused batch.

**Rejected Batches**

| Batch No. | Description | Reason |
|---|---|---|
| BXN466.07 | Short-term, long-term and freeze-thaw stabilities in human | The calibration curve did not meet acceptance criteria since both zero-calibrants were not analytically acceptable (coded UIS: Unacceptable Internal Standard Response) |
| BXN466.09 | Stock check evaluation | No stock solution has a percentage difference of ≤ 5.0% with at least, one of the 2 other stock solutions |
| BXN466.17 | Dilution integrity 1000.00 ng/mL | The accuracy (%Nominal) of Diluted QC samples did not fall between 85.00 – 115.00%. |

**Not Used Batches**

| Batch No. | Description | Reason |
|---|---|---|
| BXN466.14 | Stock check, stock interference check and long term stability in solution for drug and IS | It was observed after injection, of a few samples an unexpected chromatography.<br><br>The firm's Supplementary Information stated, "*Since all samples showed a high response for the drug, but the IS response in the LOQ is low and both the SC and SIC IS samples did not show IS, the batch was not injected*." |
| BXN466.15 | SC and SIC for BXN and IS | Unexpected results were observed for BXN and IS in some samples. Hypothesis: an inversion between BXN and IS is suspected during the preparation of the BXN stock solution lot.<br><br>The firm's Supplementary Information |

| | | |
|---|---|---|
| | | stated, "*The SIC IS showed no ISTD response but a high response for BXN. Same response for BXN was also observed in the LOQ samples. For this reason the batch was not injected.*" |

**SC**- Stock Check
**SIC**-Stock Interference Check

The firm defined the reasons for Stock Check (SC) and Stock Interference Check (SIC) in the SOP and the reviewer agrees with the firm's decision for the rejected and unused batches based on the SOP. The firm's response to Deficiency Comment #2 is **acceptable**.

### 3.3 DBI Deficiency Comment #3

*Please provide SOP* (b) (4)*: Rejected and Not Used Data, Laboratory Investigations and Events.*

**Firm's Response to Deficiency Comment #3:**

**As requested, you will find attached a copy of the above-mentioned SOP for your perusal.**

**Reviewer's Comment #3:**

The reviewer asked the firm to provide the Standard Operating Procedure (SOP) for *SOP* (b) (4) (b) (4) *Rejected and Not Used Data, Laboratory Investigations and Events: Effective Date* (b) (4) In the fed study (Study No. BXN-P0-541), five samples were reanalyzed as part of a laboratory investigation of aberrant subject sample values or subject samples where an inversion was suspected. The samples were coded as "Laboratory Investigation (LI)" and repeated in duplicate. The original and repeat values for these four samples were within 20% except for one sample. That one sample was S36-P3-11. In original run, no numerical drug level was reported for this sample, instead, it was reported as > ULQ (greater than Upper Limit of Quantitation). The firm reassayed this sample by dilution and obtained a drug level of 934.53 ng/mL. The same sample, S36-P3-11 was reassayed again in duplicate by dilution due to the reason of "Laboratory Investigation (LI)". The duplicate values obtained were 208.76 ng/mL and 214.25 ng/mL. These two duplicate values did not confirm the value of 934.53 ng/mL but confirmed each other. Therefore, the mean concentration of the duplicate re-assays was reported. Therefore, the reviewer requested the SOP that outlined "Laboratory Investigation".

In the current amendment, the firm provided SOP (b) (4). The firm's SOP states for "Study Specific Laboratory Investigations: As part of the review of data, rejected data, not used data, occasional unexpected results or trends may arise. Such phenomena which may be identified either within one single study or across studies, can potentially require the initiation of a preliminary investigation and/or an event in order to determine a cause. If a preliminary investigation fails to determine a cause, an event may be required. Note: In some cases where no cause is suspected at first, an event can also be initiated without having done a preliminary

investigation." The firm did not provide documentation or the investigation form for this particular reanalysis.

The firm's criterion for "Study Specific Laboratory Investigations" is not objective. Therefore, the reviewer reanalyzed the data using the original sample value of 934.53 ng/mL. The study data still passed the BE criteria. The results are summarized below:

**SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA**

| Parameter | T/R Ratio | Lower 90% CI | Upper 90% CI | s2wr | sWR | Criteria Bound | Method Used | OUTCOME |
|---|---|---|---|---|---|---|---|---|
| LAUCT | 1.06 | 100.53 | 111.16 | 0.0464141 | 0.2154393 | -0.020767 | Unscaled | PASS |
| LAUCI | 1.04 | 99.81 | 110.10 | 0.0338657 | 0.1840262 | -0.016076 | Unscaled | PASS |
| LCMAX | 1.14 | 103.79 | 126.06 | 0.1081612 | 0.3288787 | -0.02744 | Scaled/PE | PASS |

Since the firm provided the SOP that DB requested and the study still passed the BE criteria after reanalyzing with the original value of the suspect sample, the firm's response is **adequate**. The firm will be asked in the future to please provide the Standard Operating Procedures (SOPs) for all types of reassays including those that describe criteria for identifying "Study Specific Laboratory Investigations". The SOP(s) should clearly state objective criteria for defining these assays, the method of reassay, and acceptance criteria for selecting which value to report for the reassayed sample. The SOP should be in place prior to the start of the study; otherwise, the Division of Bioequivalence may not accept reassayed values of samples.

## 4 DEFICIENCY COMMENT

In the future, the firm will be asked to provide the Standard Operating Procedures (SOPs) for all types of reassays including those that describe criteria for identifying "Study Specific Laboratory Investigations". The SOP(s) should clearly state objective criteria for defining these assays, the method of reassay, and acceptance criteria for selecting which value to report for the reassayed sample. The SOP should be in place prior to the start of the study; otherwise, the Division of Bioequivalence may not accept reassayed values of samples.

## 5 RECOMMENDATIONS

1. The Division of Bioequivalence accepts the fed BE study (No. BXN-PO-541) conducted by Banner Pharmacaps Inc. on its Bexarotene Capsules, 75 mg, lot # 1400001 comparing it to Eisai Pharmaceutical's Targretin® (Bexarotene) Capsules, 75 mg, lot # 004681.

2. The dissolution review was previously found acceptable.[2]

3. The Division of Bioequivalence deems the test product, Bexarotene Capsules, 75 mg, manufactured by Banner Pharmacaps Inc., to be bioequivalent to the reference product, Eisai Pharmaceutical's Targretin® (Bexarotene) Capsules, 75 mg.

## 5.1 Additional Attachments

None.

APPEARS THIS WAY ON ORIGINAL

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 203174

APPLICANT: Banner Pharmacaps Inc.

DRUG PRODUCT: Bexarotene Capsules, 75 mg

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

In the future, please provide the Standard Operating Procedures (SOPs) for all types of reassays including those that describe criteria for identifying "Study Specific Laboratory Investigations". The SOP(s) should clearly state objective criteria for defining these assays, the method of reassay, and acceptance criteria for selecting which value to report for the reassayed sample. The SOP should be in place prior to the start of the study; otherwise, the Division of Bioequivalence may not accept reassay values of samples.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns 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

## 5.2 Outcome Page

ANDA: 203174

*Productivity:*

| *ID* | *Letter Date* | *Productivity Category* | *Sub Category* | *Productivity* | *Subtotal* |
|---|---|---|---|---|---|
| 21592 | 10/23/2013 | Other (REGULAR) | Study Amendment | 1 | 1 |
| | | | | Total: | 1 |

---

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

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/s/

---

DEANAH L MITCHELL
02/11/2014

APRIL C BRADDY
02/18/2014

BING V LI on behalf of HOAINHON N CARAMENICO
02/19/2014

HOAINHON N CARAMENICO on behalf of DALE P CONNER
02/20/2014

# DIVISION OF BIOEQUIVALENCE REVIEW

| | |
|---|---|
| **ANDA No.** | 203174 |
| **Drug Product Name** | Bexarotene Capsules |
| **Strength(s)** | 75 mg |
| **Applicant Name** | Banner Pharmacaps Inc |
| **Applicant Address** | 4125 Premier Dr,<br>High Point, NC 27265 |
| **US Agent Name and the mailing address** | Vandana Garikipati, Manager, Regulatory Affairs or Madhu Hariharn, Ph.D. |
| **US agent's Telephone Number** | 336-812-8700 ext 23300 |
| **US Agent's Fax Number** | 888-818-4197/336-812-9091 |
| **Original Submission Date(s)** | 10/06/2011 |
| **Submission Date(s) of Amendment(s) Under Review** | 12/14/2011 (Dissolution amendment-previously reviewed)<br>03/20/2012 (Dissolution amendment-current review) |
| **First Generic (Yes or No)** | Yes[1] |
| **Reviewer** | Haritha Mandula, Ph.D. |
| | |
| **Study Number (s)** | BXN-P0-541 |
| **Study Type (s)** | fed |
| **Strength (s)** | 75 mg |
| **Clinical Site** | Algorithme Pharma Inc. |
| **Clinical Site Address** | 1200 Beaumont Ave.<br>Mount-Royal, Quebec, Canada<br>H3P 3P1 |
| **Analytical Site** | (b) (4) |
| **Analytical Site Address** | |
| | |
| **DSI Status** | **ADEQUATE** |
| **REVIEW RESULT** | **INADEQUATE** |

| **BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #** | **STUDY/TEST TYPE** | **STRENGTH** | **REVIEW RESULT** |
|---|---|---|---|
| **1** | **FED STUDY** | **75 MG** | **INADEQUATE** |
| **1** | **DISSOLUTION** | **75 MG** | **ADEQUATE** |

[1] DARRTS Search: ANDA 203174; REV-RPM-03 (Filing Review): Final Date 08/24/2011.

# 1 EXECUTIVE SUMMARY

This is a First Generic application.

**Bioequivalence (BE) STUDY:**

As per the recommendation in the guidance on the public web site, this application contains a fed bioequivalence (BE) study comparing the test product, Bexarotene Capsules, 75 mg, to the corresponding reference product, Eisai Pharmaceutical's Targretin® Capsules, 75 mg. The fed BE study was designed as a single dose, 3 period, partial replicate (TRR, RRT and RTR), crossover study of the Bexarotene 75 mg Capsule in healthy male volunteers. The firm conducted this 3 way crossover design for reference scaling if applicable. The following are the steps to statistically analyze the PK data obtained by this design.

1. To find out the reference-scaling eligibility of a PK parameter, determine the $S_{WR}$ (the estimated within-subject standard deviation on the log scale for the RLD) of each PK parameter (Cmax, AUCt and AUCi). If the $S_{WR}$ of a PK parameter is $\geq$ 0.294, then only that PK parameter is eligible for reference scaling. (Note the value $\geq$0.294 means that PK parameter is highly variable with RMSE of $\geq$0.3).

2. On reference scaling if the Criteria Bound value for that PK parameter is $\leq$ 0.00 (Note: no rounding to 0), then that parameter meets/passes one of the two bioequivalence criteria.

3. Additionally, the reference scaled PK parameter should also have the ratio of geometric means (T/R) within 0.80 to 1.25 to be deemed bioequivalent (the second criterion).

4. Those PK parameters that are not eligible for reference scaling should be statistically analyzed using the standard average bioequivalence approach.

Using the above mentioned steps, statistically analyzed data are shown in the tables below with yellow highlighting of relevant values that meet BE criteria:

**Bexarotene Capsules**
**Dose 1 x 75 mg**
**SUMMARY OF STATISTICAL ANALYSIS- Bexarotene**
**Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals**

**Fasting Bioequivalence Study, Study No. BXN-P0-541 (N=47 for average bioequivalence and 46 for reference scaled bioequivalence)**

| | Geometric Means | | | 90% CI | |
|---|---|---|---|---|---|
| Parameter | Test | Reference | T/R Ratio | Lower CI | Upper CI |
| LAUCT | 985.96 | 930.79 | 1.06 | 100.75 | 111.37 |
| LAUCI | 999.18 | 955.92 | 1.05 | 99.60 | 109.70 |
| LCMAX | 355.09 | 309.43 | 1.15 | 104.07 | 126.54 |

| Parameter | T/R Ratio | Lower 90% CI | Upper 90% CI | s2wr | sWR | Criteria Bound | Method Used | OUTCOME |
|---|---|---|---|---|---|---|---|---|
| LAUCT | 1.06 | 100.75 | 111.37 | 0.0440675 | 0.2099227 | -0.018908 | Unscaled | PASS |
| LAUCI | 1.04 | 99.60 | 109.70 | 0.0356269 | 0.1887509 | -0.017248 | Unscaled | PASS |
| LCMAX | 1.14 | 104.07 | 126.54 | 0.0970164 | 0.3114746 | -0.018125 | Scaled/PE | PASS |

Based on the statistical analysis results shown above, the PK parameters meet the BE acceptance criteria. However, the fed study is **incomplete** due to deficiencies related to analytical parts of the studies.

## DISSOLUTION TESTING:

As per the last "dissolution only" review [See DARRTS for ANDA 203174 at YE, YUMEI 02/21/2012 N/A 02/21/2012 REV-BIOEQ-02(Dissolution Review) Original-1 (Unknown) Archive], there were 2 deficiencies. The firm has satisfactorily responded to the 2 deficiencies. Therefore, the **dissolution testing is complete**. The dissolution testing data show that the firm's method is appropriate for the Test Product than the FDA method. The following table summarizes the dissolution data on the Test Product (biolot 140000127A manufactured on 1/17/2011) to elucidates the selection of the firm's dissolution testing method

| | FDA Method | FDA method | Firm's Method | Firm's method |
|---|---|---|---|---|
| | Tier 1 | Tier 2 | Tier 1 | Tier 2 |
| Date of testing | 2/18/2012 | 3/5/2012 | 5/25/2011 | Not Submitted |
| % Diss at 45" | 19 (b) (4) | 22 (b) (4) | 92 (b) (4) | Not Submitted |

The firm proposed a specification of NLT (b) (4)% (Q) in 45 minutes which is the same as the FDA-recommended specification. Based on the data, the reviewer agrees with the firm's proposed specification.

**OSI Inspections:**

The clinical site was inspected for NDA (b) (4) on (b) (4) and the outcome was VAI [DARRTS Search: NDA (b) (4) CONSULT REV-OSI-05 (Bioequivalence Establishment Inspection Report Review); Final Date: 01/20/2010]. These findings were verified as not applicable to the current study as the site had already implemented corrective actions at the time the current study was conducted.

The analytical site was inspected for NDA (b) (4) on (b) (4) and the outcome was VAI [DARRTS Search: NDA (b) (4); CONSULT REV-OSI-05 (Bioequivalence Establishment Inspection Report Review); Final Date: 01/20/2010]. These findings were verified as not applicable to the current study as the site had already implemented corrective actions at the time the current study was conducted.

The application is **Inadequate**.

# 2 TABLE OF CONTENTS

# 3 SUBMISSION SUMMARY

## 3.1 Drug Product Information[2]

| | |
|---|---|
| **Test Product** | Bexarotene Capsules, 75 mg |
| **Reference Product** | Targretin (Bexarotene) Capsules, 75 mg |
| **RLD Manufacturer** | Eisai Inc. |
| **NDA No.** | N021055 |
| **RLD Approval Date** | December 29, 1999 |
| **Indication** | Targretin (bexarotene) capsules are indicated for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy. |

## 3.2 PK/PD Information[3]

| | |
|---|---|
| **Bioavailability** | After oral administration of Targretin capsules, bexarotene is absorbed with a Tmax of about two hours. Following oral administration, single dose linearity is seen within the therapeutic range and low accumulation with multiple doses. |
| **Food Effect** | Plasma bexarotene AUC and Cmax values resulting from a 75 to 300 mg dose were 35% and 48% higher, respectively, after a fat-containing meal than after a glucose solution. RLD label indicates that Targretin capsules should be taken as a single oral daily dose with a meal. |
| **Tmax** | About 2 hours |
| **Metabolism** | Four bexarotene metabolites have been identified in plasma: 6- and 7-hydroxy-bexarotene and 6- and 7-oxo-bexarotne. In vitro studies suggest that cytochrome P450 3A4 is the major cytochrome P450 responsible for formation of the oxidative metabolites and that the oxidative metabolites may be glucuronidated. The oxidative metabolites are active in *in vitro* assays of retinoid receptor activation, but the relative contribution of the parent and any metabolites to the efficacy and safety of Targretin capsules in unknown. |
| **Excretion** | The renal elimination of bexarotene and its metabolites was examined in patients with Type 2 diabetes mellitus. Neither bexarotene nor its metabolites were excreted in urine in appreciable amounts. Bexarotene is thought to be eliminated primarily through the hepatobiliary system. |
| **Half-life** | Terminal half-life of bexarotene is about seven hours. |
| **Dosage and Administration** | The recommended initial dose of Targretin capsules is 300 mg/m2/day. Targretin capsules should be taken as a single dose with a meal. Dose modification guidelines: The 300 mg/m2/day dose level of Targretin capsules may be adjusted to 200 mg/m2/day then to 100 mg/m2/day, or temporarily suspended, if necessitated by toxicity. When toxicity is controlled, doses may be carefully readjusted upward. If there is no tumor response after eight weeks of treatment and if the initial dose of 300 mg/m2/day is well tolerated, the dose may be escalated to 400 |

[2] Electronic Orange Book; Last accessed: 04/17/2012.
[3] DARRTS Search: NDA 021055; REV-RPM-04 (Labeling Review); Final Date: 01/04/2012.

| | |
|---|---|
| | mg/m2/day with careful monitoring. Duration of Therapy: In clinical trials in CTCL, Targretin capsules were administered for up to 97 weeks. Targretin capsules should be continued as long as the patient is deriving benefit. |
| **Maximum Daily Dose** | 400 mg/m2/day. |
| **Drug Specific Issues (if any)** | Black Box Warning: Targretin capsules are a member of the retinoid class of drugs that is associated with birth defects in humans. Targretin capsules also caused birth defects when administered orally to pregnant rats. Targretin capsules must not be administered to a pregnant woman. |

## 3.3 OGD Recommendations for Drug Product[4]

| | |
|---|---|
| **Number of studies recommended:** | 1, Fed |

| | | |
|---|---|---|
| **1.** | **Type of study:** | Fed |
| | **Design:** | Single-dose, two-treatment, two-period crossover in-vivo |
| | **Strength:** | 75 mg |
| | **Subjects:** | Healthy males, general population. |
| | **Additional Comments:** | 1. Females should be excluded from study given the potential for embryo-fetal toxicity.<br>2. The protocol should specify and require both formal pregnancy counseling for male subjects regarding the risk to their female partner and a section regarding the counseling in the Informed Consent document.<br>3. Adequate contraception must be continued for at least 1 month following the last dose of bexarotene.<br>4. The protocol should include following specific exclusion criteria in addition to other exclusion criteria:<br>• Subjects demonstrating abnormalities in lipid profile or thyroid-function on screening laboratory evaluations.<br>• Subjects receiving systemic therapy with Vitamin A in doses of greater than 15000 IU (5000 mcg) per day.<br>• Subjects who are taking gemfibrozil or tamoxifen.<br>• Use of any other retinoid class drug (e.g. Isotretinoin) within 30 days of entry into the study.<br>• Use of topical medications such as corticosteroids or tar baths.<br>5. In addition to the exclusion of drugs that are also known to cause photosensitivity, subjects should be advised to avoid prolonged exposure to the sun or UV light during the study. Similarly, it would be prudent to exclude subjects with a known history of skin cancer.<br>6. The protocol should include an appropriate plan for continued follow-up, standard care for subsequent follow up, and treatment of subjects who continue to demonstrate |

[4] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227413.pdf; Last accessed: 04/17/2012.

| | | |
|---|---|---|
| | | thyroid and/or lipid abnormalities at the end of study laboratory evaluations. |

| | |
|---|---|
| **Analytes to measure (in plasma/serum/blood):** | Bexarotene in plasma |
| **Bioequivalence based on:** | 90% CI of Bexarotene. |
| **Waiver request of in-vivo testing:** | (appropriate strengths) |
| **Source of most recent recommendations:** | http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227413.pdf |
| **Summary of OGD or DBE History** | Office of Generic Drugs (OGD) has not approved any ANDAs for this drug product.<br><br>The following control correspondences have been received for this drug product:<br><br>Control # / Firm / Letter Date<br>10-0486<br>11-0708<br>08-0390<br>11-0109<br>(b) (4)<br><br>The following protocols have been submitted for this drug product:<br><br>Protocol # / Firm / Comments / Letter Date<br>09-027<br>10-006<br>(b) (4) |

## 3.4 Contents of Submission

| Study Types | Yes/No? | How many? |
|---|---|---|
| **Single-dose fasting** | No | -- |
| **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** | No | -- |

## 3.5 Pre-Study Bioanalytical Method Validation

| Information Requested | Data |
|---|---|
| **Bioanalytical method validation report location** | 0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\fed-study-bxn-p0-541 |
| **Analyte** | Bexarotene |
| **Internal standard (IS)** | Bexarotene-D4 |
| **Method description** | Liquid-liquid extraction<br>Reversed-phase HPLC with MS/MS detection |
| **Limit of quantitation** | 1.00 ng/mL |
| **Average recovery of drug (%)** | 100.8% (6.68%) |
| **Average recovery of IS (%)** | 109.9% (4.19%) |
| **Standard curve concentrations (ng/mL)** | 1.00 ng/mL, 2.00 ng/mL, 5.00 ng/mL, 15.00 ng/mL, 45.00 ng/mL, 80.00 ng/mL, 140.00 ng/mL, 170.00 ng/mL, 200.00 ng/mL |
| **QC concentrations (ng/mL)** | 1.00 ng/mL, 3.00 ng/mL, 20.00 ng/mL, 150.00 ng/mL |
| **QC Intraday precision range (%)** | 1.5% to 4.0% |
| **QC Intraday accuracy range (%)** | 96.8% to 104.9% |
| **QC Interday precision range (%)** | 2.0% to 7.7% |
| **QC Interday accuracy range (%)** | 97.0% to 106.7% |
| **Bench-top stability (hrs)** | 29.7 hours at 4°C nominal for Bexarotene<br>29.7 hours at -20°C nominal for Bexarotene<br><br>29.7 hours at 4°C nominal for Bexarotene in the presence of Bexarotene Acyl Glucuronide<br>29.7 hours at -20°C nominal for Bexarotene in the presence of Bexarotene Acyl Glucuronide |
| **Stock stability (days)** | 119 days in EtOH:$H_2O$ 99:1% v/v at a concentration of 100.00 µg/mL at 4°C nominal for Bexarotene<br><br>118 days in EtOH:$H_2O$ 99:1% v/v at a concentration of 100.00 ng/mL at 4°C nominal for Bexarotene<br><br>119 days in EtOH:$H_2O$ 99:1% v/v at a concentration of 100.00 µg/mL at 4°C nominal for Bexarotene-D4<br><br>119 days in MeOH:$H_2O$ 50:50% v/v at a concentration of 240.00 ng/mL at 4°C nominal for Bexarotene-D4 |
| **Processed stability (hrs)** | 142.8 hours at 4°C nominal for Bexarotene<br>142.8 hours at 4°C nominal for Bexarotene in the presence of Bexarotene Acyl Glucuronide |
| **Freeze-thaw stability (cycles)** | 3 cycles for Bexarotene<br>3 cycles for Bexarotene in the presence of Bexarotene Acyl Glucuronide |
| **Long-term storage stability (days)** | 124 days at -80°C nominal for Bexarotene<br><br>123 days at -80°C nominal for Bexarotene in the presence of Bexarotene Acyl Glucuronide |
| **Dilution integrity** | 1000.00 ng/mL, diluted 10-fold |
| **Selectivity** | No significant interference was observed in the 10 blank |

| | |
|---|---|
| | matrix lots screened |

| | |
|---|---|
| **SOPs submitted** | Yes |
| **Was the % recovery consistent across QC concentrations?** | Yes |
| **Is the same anticoagulant used in the pre-method validation study used in the sample assay?** | Yes, K2EDTA |
| **If not, was cross validation study conducted?** | |
| **Was the dilution factor adequate for the current study sample analysis?** | Yes |
| **Was the same dilution medium (plasma/solvent) used during validation and sample analysis?** | Yes |
| **Does the duration of the each of the stability parameters support the sample preparation and assay dates** | Yes |
| **Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?** | Yes |

**Comments on the Pre-Study Method Validation:**

- The anticoagulant used during pre-study method validation is K2 EDTA. The same anticoagulant was used during the study sample analysis.

- Sample pre-treatment involved the liquid-liquid extraction of Bexarotene from 0.200 mL of human plasma. Bexarotene-D4 was used as the internal standard (IS). The compounds were identified and quantified using reversed-phase HPLC with MS/MS detection over a theoretical concentration range of 1.00 ng/mL to 200.00 ng/mL.

- A summary table of batch analysis was provided in the validation report. The report stated that, data from reject or unused batches and/or evaluations are not included in this report but are on file at [redacted] (b) (4) A batch or evaluation is listed as " Not Used" when an analytical issue is observed that could potentially affect data integrity. The firm will be asked to submit the data for unused batches as well.

- The validation for the stability parameters (including bench top stability, processed stability, freeze-thaw stability and long-term stability) were performed in the presence of bexarotene acyl glucuronide to mimic the plasma samples during the study.

- The pre-study method validation is incomplete.

## 3.6 In Vivo Studies

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

| Study Ref. No. | Study Objective | Study Design | Treatments (Dose, Dosage Form, Route) [Product ID] | Subjects No. (M/F) Type Age (years): Mean (Range) | Mean Parameters (±SD) | | | | | | Study Report Location |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | $C_{max}$ (ng/mL) | $T_{max}$ * (hr) | $AUC_T$ (ng·h/mL) | $AUC_\infty$ (ng·h/mL) | $T_{½}$ * (hr) | $K_{el}$ * (hr-1) | |
| Study # BXN-P0-541 | Single Dose, Partial Replicate, Crossover Comparative Bioavailability Study of Bexarotene 75 mg Capsules in Healthy Male Volunteers / Fed State | Randomized single-dose crossover | Bexarotene 75 mg Capsules p.o. [Batch # 140000127A]<br>Targretin® 75 mg Capsules p.o. [Batch # 004681] | 47 completing (47M) Healthy subjects 40 (22-64) | 398.18 ± 176.87<br>348.26 ± 176.66 | 1.75 (1.00 - 6.00)<br>1.75 (1.00 - 4.00) | 1059.93 ± 436.46<br>1021.78 ± 496.24 | 1073.84 ± 437.81**<br>1050.02 ± 499.85** | 2.22**<br>2.96** | 0.3513**<br>0.3324** | 5.3.1.2 |

* Median (range) is presented for $T_{max}$, and only the mean is presented for $T½_{el}$ and $K_{el}$.
**n=46 observations for the Test and 88 observations for the Reference.

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

**Bexarotene Capsules**
**75 mg**
**Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals**
**Fed Bioequivalence Study, Study No. BXN-P0-541**

| | Geometric Means | | | 90% CI | |
|---|---|---|---|---|---|
| Parameter | Test | Reference | T/R Ratio | Lower CI | Upper CI |
| LAUCT | 985.96 | 930.79 | 1.06 | 100.75 | 111.37 |
| LAUCI | 999.18 | 955.92 | 1.05 | 99.60 | 109.70 |
| LCMAX | 355.09 | 309.43 | 1.15 | 104.07 | 126.54 |

| Parameter | T/R Ratio | Lower 90% CI | Upper 90% CI | s2wr | sWR | Criteria Bound | Method Used | OUTCOME |
|---|---|---|---|---|---|---|---|---|
| LAUCT | 1.06 | 100.75 | 111.37 | 0.0440675 | 0.2099227 | -0.018908 | Unscaled | PASS |
| LAUCI | 1.04 | 99.60 | 109.70 | 0.0356269 | 0.1887509 | -0.017248 | Unscaled | PASS |
| LCMAX | 1.14 | 104.07 | 126.54 | 0.0970164 | 0.3114746 | -0.018125 | Scaled/PE | PASS |

**Are the PK parameters within the acceptance limits for the 90% CI and meeting BE?** Yes

**Table 3. Reanalysis of Study Samples**

| Study No. BXN-P0-541<br>0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\fed-study-bxn-p0-541 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Reason why assay was repeated** | **Number of samples reanalyzed** | | | | **Number of recalculated values used after** | | | |
| | **Actual number** | | **% of total assays** | | **Actual number** | | **% of total assays** | |
| | **T** | **R** | **T** | **R** | **T** | **R** | **T** | **R** |
| Pharmacokinetic | 0 | 0 | 0.0 | 0.0 | 0 | 0 | 0.0 | 0.0 |
| SLP (Sample Lost in | 6 | 2 | 0.2 | 0.1 | N/AP | N/AP | N/AP | N/AP |
| >ULQ (Above Upper Limit of Quantitation) | 96 | 184 | 3.6 | 6.9 | N/AP | N/AP | N/AP | N/AP |
| UIS (Unacceptable Internal Standard | 37 | 62 | 1.4 | 2.3 | N/AP | N/AP | N/AP | N/AP |
| ID (Inadequate Dilution) | 1 | 7 | 0.0 | 0.3 | N/AP | N/AP | N/AP | N/AP |
| LI (Laboratory Investigation) | 0 | 5* | 0.0 | 0.2 | N/AP | N/AP | N/AP | N/AP |
| Total | 140 | 260 | 5.3 | 9.7 | 0 | 0 | 0.0 | 0.0 |

*The table as provided by the firm indicates 4 samples, however as per the firm's analytical report, 5 samples have been reported for this reason. Based on the firm's analytical report, the reviewer corrected the above table.

**Please provide detailed explanation for all repeats not related to analytical reasons.**

Five samples from reference treatment were repeated as part of a laboratory investigation of aberrant subject sample values or subject samples where an inversion is suspected. Samples coded LI are repeated in duplicate, if sufficient sample volume permits. The original and repeat values for these four samples are within 20% except for one sample. That one sample was S36-p3-11. In original run, no numerical drug level was reported for this sample, instead, it was reported as > ULQ (greater than Upper Limit of Quantitation). The firm reassayed this sample by dilution and obtained a drug level of 934.53 ng/mL. The same sample, S36-P3-11 was reassayed again in duplicate by dilution due to the reason of "Laboratory Investigation (LI)". The duplicate values obtained were 208.76 ng/mL and 214.25 ng/mL. These two duplicate values did not confirm the value of 934.53 ng/mL but confirmed each other. Therefore, the mean concentration of the duplicate re-assays was reported. The "Laboratory Investigation (LI)" is covered under the SOP (b) (4) However, the firm did not provide this SOP. The firm will be asked to provide this SOP.

**Table 4. SOP's Dealing with Bioanalytical Repeats of Study Samples**

| SOP No. | Effective Date of SOP | SOP Title |
|---|---|---|
| (b) (4) | | Sample Coding and Re-assay |

| **Reanalysis SOPs submitted?** | |
|---|---|
| Do you agree that the reassay criteria: **analytical and pharmacokinetic** | Yes |
| If not, list the criteria that you don't agree and provide additional comment below | |
| Are the data in the summary table consistent with the data in the full analytical report? | Yes |
| If not, provide comment below | |
| Did reviewer reanalyze study results? | No |
| Was the study outcome changed based on reviewer reanalysis? | Not applicable |
| Did the firm provide a comprehensive table of repeat samples in the format recommended by the DBE? | Yes |
| Did the firm provide numerical raw data (e.g. peak height, peak area, response count of IS and analyte) in run sequence order (i.e. Run log)? | No |

**Comments from the Reviewer:**

1. The firm did not provide the raw analytical numerical data for all the assay runs of the study subject samples. The firm will be asked to provide this information.

2. 37 samples from the test treatment and 62 samples from the reference treatment were repeated for the reason "Unacceptable Internal Standard Response". The reviewer obtained the internals standard mean for each run and spot checked the samples. The firm selected the samples in an objective manner. The reviewer agrees with the firm's analysis.

3. Starting at the batch BXN541.15, the sample numbers 04 to 08, inclusively, of all periods, of all subjects, were pre-diluted by a factor of 5 for their original analysis. This was done in order to minimize the repeat assays of samples with an expected concentration greater than the upper limit of quantitation (> 200.00 ng/mL).

4. For the repeat reason code >ULQ (above upper limit of quantitation), the reviewer examined the original and repeat measurement of all 280 samples (96 test and 184 reference) samples in the fed BE study and found the repeat assays were justified. The reviewer has identified the samples that are for Cmax values and also have noted that those samples that are not the Cmax values are from the same subjects with the time points around the identified Cmax value. The reviewer has also examined the reassay samples and determined that these samples were at least 85% of the highest standard concentration. As a result, the study repeat analysis for the fed study is acceptable.

5. Five samples from reference treatment were repeated as part of a laboratory investigation of aberrant subject sample values or subject samples where an

inversion is suspected. Samples coded LI are repeated in duplicate, if sufficient sample volume permits. The original and repeat values for these four samples are within 20% except for one sample. That one sample was S36-p3-11. In original run, no numerical drug level was reported for this sample, instead, it was reported as > ULQ (greater than Upper Limit of Quantitation). The firm reassayed this sample by dilution and obtained a drug level of 934.53 ng/mL. The same sample, S36-P3-11 was reassayed again in duplicate by dilution due to the reason of "Laboratory Investigation (LI)". The duplicate values obtained were 208.76 ng/mL and 214.25 ng/mL. These two duplicate values did not confirm the value of 934.53 ng/mL but confirmed each other. Therefore, the mean concentration of the duplicate re-assays was reported. The "Laboratory Investigation (LI)" is covered under the SOP (b) (4). However, the firm did not provide this SOP. The firm will be asked to provide this SOP.

## 3.7 Formulation

| | |
|---|---|
| **Location in appendix** | Section 4.2, Page 38 |
| **If a tablet, is the RLD scored?** | Not applicable |
| **If a tablet, is the test product biobatch scored** | Not applicable |
| **Is the formulation acceptable?** | **FORMULATION ACCEPTABLE** |
| **If not acceptable, why?** | |

## 3.8 In Vitro Dissolution

| | |
|---|---|
| **Location of DBE Dissolution Review** | DARRTS[5, 6, 7] and current review |
| **Submitted Method (USP, FDA, or Firm)** | Both |
| **Recommended Method (details below)** | Firm's method |
| **Medium** | Tier 1 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5<br><br>Tier 2 Medium: 0.5%* HDTMA in 0.05 M phosphate buffer, pH 7.5 with pancreatin enzyme |
| **Volume (mL)** | 900 mL |
| **USP Apparatus type** | II (Paddle) |
| **Rotation (rpm)** | 75 rpm |
| **Specifications** | NLT (b) (4)% (Q) in 45 minutes. |

[5] DARRTS Search: ANDA 203174; REV-BIOEQ-02 (Dissolution Review): Final Date; 12/19/2011.
[6] DARRTS Search: ANDA 203174; REV-BIOEQ-02 (Dissolution Review): Final Date: 02/21/2012.
[7] DARRTS Search: ANDA 203174; REV-BIOEQ-02 (Dissolution Review); Final Date: 02/21/2012.

| | |
|---|---|
| **Do the data meet the recommended specifications at S1, L1, A1, or B1 acceptance criteria?** | Yes at L1 level |
| **If a modified-release tablet, was testing done on ½ tablets?** | Not applicable |
| **F2 metric calculated?** | If yes, see Dissolution Section 4.3 |
| **If no, reason why F2 not calculated** | |
| **Is method acceptable?** | **Acceptable** |
| **If not then why?** | |

## 3.9 Waiver Request(s) For Immediate Release Dosage Forms

| | |
|---|---|
| **Strengths for which waivers are requested, if applicable** | Not applicable |
| **Waiver regulation cited?** | Not applicable |
| **Strengths considered for 21 CFR 320.24 (b)(6)** | Not applicable |
| **Proportional to strength tested in vivo?** | Not applicable |
| **Is dissolution acceptable?** | Yes. |
| **Waivers granted?** | **Not applicable** |
| **If not then why?** | |

**Dissolution amendment:**

The following deficiency has been identified:

1. ***Your dissolution testing is incomplete. You submitted dissolution testing data using your own proposed dissolution method. Your method differs from the current FDA-recommended method. In order for DBI to properly evaluate your proposed dissolution method and compare it with the FDA-recommended method, please conduct additional dissolution testing on the test and reference products (12 units each) using the following FDA method:***

Medium:
Tier I-0.5% Hexadecyltrimethylammonium bromide (HDTMA) in 0.05 M phosphate buffer, pH 7.5
Tier 2-0.5% HDTMA in 0.05M phosphate buffer, pH 7.5 with 0.05 g/L pancreatin enzyme
Apparatus: II (Paddle)
Speed: 50 rpm
Volume: 900 mL
Temperature: 37°C ± 0.5°C
Sampling Time Points: 15, 30, 45 and 60 minutes and until at least 80% of the labeled amount of the drug in the dosage form is dissolved.

For the requested dissolution testing, please submit the complete dissolution method information which should include the following:

- A completed dissolution study report with each method used
- Individual dissolution testing data for 12 dosage units of each strength of the test and reference products.
- Mean, range and coefficient of variation (%CV) data of the dissolution results.
- Comparative mean dissolution graphs for each strength.
- Analytical method validation report.

The DBI will determine the most suitable method and specification for your test product following the evaluation of the dissolution testing data from both methods.

**Firm's response:**

The dissolution method (document PD10-017) and individual testing data for 12 dosage units (document PD11-191) report run by BPI's proposed method were provided in the original submission. Per this deficiency request, BPI conducted dissolution testing using the above FDA recommended method and a comparative dissolution study report (document # PD12-074) is being provided in section 5.3.1.3 of this amendment. For ease of review eCTD summary table 5 is provided in section 2.7 of this amendment.

Additionally, the method development report which addresses the studies conducted with 50, 75, (b) (4) rpm speeds (document # PD12-075) is also provided in section 3.2.P.5.6.

The method validation report, document # PD11-086 effective March 31, 2011 was performed and provided in section 3.2.P.5.3 of the original application. During the method validation the following parameters were considered. Linearity, Precision (Repeatability and Intermediate Precision), Accuracy, Range, Specificity, and Robustness. No further validation is deemed to be necessary since the method was not modified or changed.

**Reviewer's Comment:** The firm's response to **Deficiency Comment # 1 is acceptable**. As requested, the firm submitted dissolution data using the FDA-recommended method.

2. ***The DBI notes that your*** (b) (4) ***dissolution method (75 rpm),*** (b) (4) ***Finally, please also state if you plan to use*** (b) (4) ***for the testing using the FDA recommended dissolution method).***

**Firm's response:**

(b) (4)

(b) (4)

It is noted that the firm has submitted an analytical method validation report for its method, which will be reviewed in its entirety when the firm submit data using the FDA-recommended method.

**Reviewer's comment**: The firm's response to Deficiency Comment # 2 is acceptable (b) (4)
(b) (4)

**Validation of Analytical Method used in Dissolution Testing for Bexarotene Capsules:**

(b) (4)

(b) (4)

Reviewer's Comments:

1. There is no USP method for this product, but there is an FDA-recommended method. However, the firm proposed a different method. The FDA-recommended method and the firm's proposed method are listed below[5]:

| | FDA-recommended Method | Firm's Proposed Method |
|---|---|---|
| **Medium** | Tier 1 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5<br><br>Tier 2 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 with 0.05 g/L pancreatin enzyme | Tier 1 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5<br><br>Tier 2 Medium: 0.5%* HDTMA in 0.05 M phosphate buffer, pH 7.5 with pancreatin enzyme |
| **Volume** | 900 mL | 900 mL |
| **Apparatus** | II (Paddle) | II (Paddle) |
| **Speed** | 50 rpm | 75 rpm |
| **Sampling Times** | 15, 30, 45 and 60 minutes | 15, 30, 45, 60 and 75 minutes |
| **Temperature** | 37ºC ± 0.5ºC | 37ºC ± 0.5ºC |
| **Specification** | NLT (b) (4) % (Q), 45minutes | |

*In the current version of firm's dissolution method (PD10-017), Tier 2 medium was typed as (b) (4) HDTMA in 0.05 M phosphate buffer pH 7.5 with pancreatin enzyme in Section 4.1 Dissolution Apparatus. According to the Section 5.9.2 Tier 2 Dissolution Sample Preparation mentioned above, the final concentration of HDTMA in Tier 2 dissolution medium should be 0.5%.

2. The firm was asked to repeat the dissolution testing using the FDA-recommended method (900 mL of Tier 1 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5, 900 mL of Tier 2 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 with 0.05 g/L pancreatin enzyme at 37ºC ± 0.5ºC using USP Apparatus II (Paddle) at 50 rpm. The sampling times should be 15, 30, 45 and 60 minutes).
3. In addition, as indicated in the Sample Preparation for Tier 2 Media provided in the amendment above. (b) (4)

(b) (4)

the firm was asked to justify said approach. (b) (4) Finally, the firm was asked to state if it (b) (4) using the above FDA-recommended method if said method ultimately becomes the quality control method for the proposed product.

4. Under the firm's dissolution testing conditions, both of the test and referenced products showed higher variability at the first 2 sampling time points of 15 and 30 minutes [CV% 46%-17% (test) and 91%-12% (reference), respectively]. However, the variability of the test and reference products decreased as the time increased. Overall, the release of the drug from the test and reference products was quite comparable. The firm's dissolution data for both the test and reference products show that more than (b) (4)% of the labeled amount of Bexarotene for any unit tested dissolved in 45 minutes. The median Tmax in current application is 1.75 hours [1.00-6.00 hours (test) and 1.00-4.00 hours (reference)] for the fed BE study per the firm's study report.
5. Based on the data submitted, firm's dissolution method appeared to be more appropriate for the test product since the test product was dissolved almost completely at about 60 min using the firm's method. The dissolution of the test product using the FDA-method was not complete (Tier 1: mean of 28 (range (b) (4) (b) (4)%) in 60 minutes, Tier 2: mean of 32 ((b) (4)%) in 60 minutes).
6. The firm did not submit Tier 2 dissolution data using the firm's method[8].
7. The firm proposed a dissolution specification of Q= (b) (4)% in 45 minutes. This is the same as the FDA-recommended specification of NLT (b) (4)% (Q) in 45 minutes. Based on the data, the reviewer agrees with the firm's proposed specification of NLT (b) (4)% (Q) in 45 minutes.
8. The firm's dissolution testing is complete.

### 3.10 Deficiency Comments

- A summary table of batch analysis was provided in the validation report. The report stated that, data from reject or unused batches and/or evaluations are not included in this report but are on file at (b) (4) A batch or evaluation is listed as "Not Used" when an analytical issue is observed that could potentially affect data integrity. The firm will be asked to submit the data for unused batches as well.

[8] Tier 2 data for gelatin capsules is not required, because the cross linking may or may not occur in that particular lot but Tier 2 is an option allowed for gelatin capsules in general. The specification is usually set based on data from fresh production lot. Tier 2 with enzyme is used to correct for the cross linking and expected to bring the dissolution back to the original rate. If not, then the product is considered having stability problem other than cross linking.

- The firm did not submit the raw analytical numerical data for all the assay runs (both accepted and rejected) of the study subject samples. The firm should submit complete raw data (numerical printouts) of all sample analysis runs, including the data for the peak area for the drug, peak area for the internal standard, the ratio of the peak area for the drug to the peak area for the internal standard, dilution factor (if any), and the corresponding calculated concentration for each assayed sample for all subject samples, calibration standard concentration samples, and quality control samples.
- The firm did not provide SOP [redacted] (b) (4) "Rejected and Not Used Data, Laboratory Investigations and Events". The firm will be asked to provide this information.

## 3.11 Recommendations

1. The Division of Bioequivalence finds the fed BE study (BXN-P0-541) conducted by Banner Pharmacaps Inc. on its Bexarotene Capsules, 75 mg, lot # 140000127, comparing it to Eisai Pharmaceutical's Targretin® Capsules, 75 mg, lot # 004681, incomplete due to deficiencies mentioned above.

2. The firm's *in vitro* dissolution testing is incomplete due to the deficiency mentioned above.

## 3.12 Comments for Other OGD Disciplines

| Discipline | Comment |
|---|---|
| | |

# 4 APPENDIX

## 4.1 Individual Study Reviews

### 4.1.1 Single-dose Fed Bioequivalence Study

#### 4.1.1.1 Study Design

**Table 5 Study Information**

| | |
|---|---|
| **Study Number** | BXN-P0-541 |
| **Study Title** | Single Dose, Partial Replicate, Crossover Comparative Bioavailability Study of Bexarotene 75 mg Capsules in Healthy Male Volunteers / Fed State |
| **Clinical Site (Name & Address)** | Algorithme Pharma Inc.<br>1200 Beaumont Ave.<br>Mount-Royal,<br>Quebec, Canada<br>H3P 3P1<br>(514) 858-6077 |
| **Principal Investigator** | Eric Sicard, M.D., Clinical Investigator |
| **Dosing Dates** | Period 1: 2011/03/26<br>Period 2: 2011/04/02<br>Period 3: 2011/04/09 |
| **Analytical Site (Name & Address)** | (b) (4) |
| **Analysis Dates** | Between 2011/04/13 and 2011/05/10 |
| **Analytical Director** | (b) (4) |
| **Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)** | 45 days |

**Table 6. Product information**

| Product | Test | Reference |
|---|---|---|
| **Treatment ID** | A | B |
| **Product Name** | Bexarotene | Targretin® |
| **Manufacturer** | Banner Pharmacaps Inc., NC, USA | Eisai Inc., NJ, USA |
| **Batch/Lot No.** | 140000127A | 004681 |
| **Manufacture Date** | 1/17/2011 | N/A |

| | | |
|---|---|---|
| **Expiration Date** | 03/11 (Retest Date) | 07/12 |
| **Strength** | 75 mg | 75 mg |
| **Dosage Form** | Capsules | Capsules |
| **Bio-Batch Size** | N/A | N/A |
| **Production Batch Size** | (b) (4) | N/A |
| **Potency (Assay)** | 99.6% | 100.4% |
| **Content Uniformity (expressed as mean, %CV or per USP)** | Meets USP<905>, AV=1.4 | N/A |
| **Dose Administered** | 75 mg | 75 mg |
| **Route of Administration** | p.o. | p.o. |

| | |
|---|---|
| **Was the drug product administered per labeling (for specialized dosage forms e.g. ODT)?** | Yes |
| **Is the bio-batch size at least the recommended minimum of 100K for oral solid dosage form?** | Yes |

## Table 7. Study Design, Single-Dose Fed Bioequivalence Study

| | |
|---|---|
| **Number of Subjects** | **Enrolled: 48**<br>**Dosed: 48**<br>**Completed: 46**[9]<br>**Samples Analyzed: 47**<br>**Data Analyzed: 47 subjects for average-bioequivalence statistical analysis and 46 subjects for reference-scaled-bioequivalence statistical analysis.** |
| **No. of Sequences** | 3 |
| **No. of Periods** | 3 |
| **No. of Treatments** | 2 |
| **No. of Groups** | 1 |
| **Washout Period** | 7 days |
| **Randomization Scheme (Sequence of T and R)** | **TRR: 002, 005, 007, 012, 015, 018, 020, 022, 026, 030, 031, 036, 038, 041, 045 and 048.**<br>**RRT: 001, 006, 009,010, 014, 017, 019, 023, 027, 029, 032, 035, 039, 040, 044 and 047.**<br>**RTR: 003, 004, 008, 011, 013, 016, 021, 024, 025, 028, 033, 034, 037, 042, 043 and 046.** |
| **Blood Sampling Times** | Pre-dose, 0.5, 1, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 6, 8, 10, 12, 16, 24 and 36 hours after drug administration. |
| **Blood Volume Collected/Sample** | The total volume of blood collected per subject is 359 mL. |
| **Anticoagulant Used** | K2EDTA |

[9] Of the forty-eight (48) healthy male subjects who were included in the study, forty-six (46) subjects completed all three study periods and forty-seven (47) subjects completed at least two clinical study periods with a crossover (Test vs Reference).

| | |
|---|---|
| **Blood Sample Processing & Storage (include storage temperature)** | Blood samples were collected in pre-cooled K2 EDTA vacutainers. As soon as possible following blood collection, samples were centrifuged at a temperature of 4°C nominal and at approximately 1500 g for 10 minutes. The plasma obtained was separated into duplicate polypropylene culture tubes, when feasible. The tubes were labeled with a code number that did not reveal formulation identity. The samples were frozen in an upright position and retained in the clinic's freezers at a temperature of -80°C nominal or on dry ice until shipment to the analytical facility. The samples were stored frozen at a temperature of -80°C nominal until assayed. The sample processing process (from sample collection to sample storage) must have been performed within 45 minutes. |
| **IRB Approval** | Yes, the protocol was approved by institutional review board (b) (4) on 02/18/2011 and the amendment 01 of the protocol was approved on 02/25/2011. |
| **Informed Consent** | Yes, the informed consent form was approved by institutional review board (b) (4) on 02/18/2011 and the amendment 01 of the informed consent form was approved on 02/25/2011. |
| **Length of Fasting** | Following an overnight fast of at least 10 hours, subjects received a high-fat, high-calorie breakfast 30 minutes prior to drug administration. Fasting continued for at least 4 hours following drug administration, after which a standardized lunch was served. |
| **Length of Confinement** | In each period, subjects were to arrive at the clinical site at least 10.5 hours before dosing. Subjects were allowed to leave the clinical site after the 24-hour post-dose blood draw and were asked to return to the clinical site before the remaining blood sample. |
| **Safety Monitoring** | The safety parameters assessed included the occurrence of AEs and the measurement of clinical laboratory parameters.<br><br>Clinical laboratory parameters (hematology, biochemistry, and urinalysis) were carried out in accordance with Standard Operating Procedures (SOPs) of the licenses laboratory of (b) (4) (b) (4) A list of the laboratory variables evaluated at screening and post-study is given in the protocol. Post-study tests were performed after the collection of the last blood sample of the study at the 48-hour post-dose return visit. Subjects with clinically significant lipid profile values (total cholesterol, HDL, LDL, triglycerides) and/or thyroid values (TSH/T4/T3) were requested to come back for a follow-up test about 4-weeks after the end of study return visit, in case of any persistent abnormal results, the physician in charge may have requested another follow-up visit or referred the subject to this own physician for further evaluation.<br><br>Vital signs were to be monitored and ECGs were to be recorded when judged necessary by the physician in charge. |

| | |
|---|---|
| **Was the study design used for the fed BE study acceptable?** | YES/NO |

| | |
|---|---|
| **Standard FDA Meal Used?** | Yes, the meal was comprised of approximately 240 mL of whole milk, 2 large eggs, 4 ounces of hash brown potatoes (2 potato patties), 1 english muffin with approximately 4.5 g of butter and 2 strips of bacon. |

| If No, then meal components and composition is listed in the tables below | | |
|---|---|---|
| **Composition of Non-standard FDA Meal Used in Fed Bioequivalence Study** | | |
| **Composition** | **Percent** | **Kcal** |
| **Fat** | 55 | 518 |
| **Carbohydrate** | 30 | 284 |
| **Protein** | 15 | 136 |
| **Total** | | 938 |

**Comments on Study Design:**

The study design is acceptable.

#### 4.1.1.2 Clinical Results

**Table 8. Demographics Profile of Subjects Completing the Bioequivalence Study**

| Study No. BXN-P0-541 | | | |
|---|---|---|---|
| | | Treatment Groups | |
| | | Test Product N = 47 | Reference Product N = 47 |
| Age (years) | Mean ± SD | 40 ± 10 | 40 ± 10 |
| | Range | 22 - 64 | 22 - 64 |
| Age Groups | < 18 | 0 | 0 |
| | 18 – 39 | 21 (44.7%) | 21 (44.7%) |
| | 40 – 64 | 26 (55.3%) | 26 (55.3%) |
| | 65 – 75 | 0 | 0 |
| | > 75 | 0 | 0 |
| Sex | Male | 47 (100.0%) | 47 (100.0%) |
| | Female | 0 | 0 |
| Race | White | 42 (89.4%) | 42 (89.4%) |
| | Black | 4 (8.5%) | 4 (8.5%) |
| | Asian | 0 | 0 |
| | American Native or Alaska Native | 0 | 0 |
| | Pacific Islander | 0 | 0 |
| | Others | 1 (2.1%) | 1 (2.1%) |
| BMI ($kg/m^2$) | Mean ± SD | 25.00 ± 2.43 | 25.00 ± 2.43 |
| | Range | 19.75 – 29.21 | 19.75 – 29.21 |
| Other Factors | | NA | NA |

NA: Not Applicable

## Table 9. Dropout Information, Fasting Bioequivalence Study

| Study No. BXN-P0-541 | | | | |
|---|---|---|---|---|
| **Subject No** | **Reason for dropout/replacement** | **Period** | **Replaced?** | **Replaced with** |
| (b) (6) | Withdrew consent for period 2 only due to adverse events experienced in period 1 (headache of mild intensity and upper respiratory tract infection of mild intensity). | 2* | No | NA |
| | Withdrawn before dosing of period 3 for reasons other than safety (positive cannabinoids test). | 3** | No | NA |

NA: Not Applicable
* Subject completed periods 1 and 3 and was included in the average bioequivalence (unscaled) analysis only.
** This subject did not receive the Test formulation and was not included in the pharmacokinetic and statistical analyses.

## Table 10. Study Adverse Events, Fasting Bioequivalence Study

| Study No. BXN-P0-541 | | |
|---|---|---|
| **System Organ Class<br>MedDRA Term** | **Test (N=47)** | **Reference (N=95)** |
| Subjects with at least one AE [n(%)] | 5 ( 10.6) | 16 ( 16.8) |
| NERVOUS SYSTEM DISORDERS [n(%)] | 2 ( 4.3) | 7 ( 7.4) |
| Headache [n(%)] | 2 ( 4.3) | 7 ( 7.4) |
| Somnolence [n(%)] | 0 | 1 ( 1.1) |
| GASTROINTESTINAL DISORDERS [n(%)] | 1 ( 2.1) | 3 ( 3.2) |
| Diarrhoea [n(%)] | 1 ( 2.1) | 1 ( 1.1) |
| Abdominal Pain [n(%)] | 1 ( 2.1) | 0 |
| Gastroenteritis [n(%)] | 0 | 1 ( 1.1) |
| Lip Dry [n(%)] | 0 | 1 ( 1.1) |
| Nausea [n(%)] | 0 | 1 ( 1.1) |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS [n(%)] | 1 ( 2.1) | 3 ( 3.2) |
| Upper Respiratory Tract Infection [n(%)] | 0 | 2 ( 2.1) |
| Nasal Dryness [n(%)] | 0 | 1 ( 1.1) |
| Rhinorrhoea [n(%)] | 1 ( 2.1) | 0 |
| INVESTIGATIONS [n(%)] | 0 | 2 ( 2.1) |
| Blood Thyroid Stimulating Hormone Increased [n(%)] | 0 | 1 ( 1.1) |
| Thyroxine Free Decreased [n(%)] | 0 | 1 ( 1.1) |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS [n(%)] | 0 | 2 ( 2.1) |
| Pruritus [n(%)] | 0 | 1 ( 1.1) |
| Rash [n(%)] | 0 | 1 ( 1.1) |
| EYE DISORDERS [n(%)] | 0 | 1 ( 1.1) |
| Eye Pruritus [n(%)] | 0 | 1 ( 1.1) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS [n(%)] | 1 ( 2.1) | 0 |

| Study No. BXN-P0-541 | | |
|---|---|---|
| **System Organ Class**<br>**MedDRA Term** | **Test**<br>**(N=47)** | **Reference**<br>**(N=95)** |
| Fatigue [n(%)] | 1 ( 2.1) | 0 |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS [n(%)] | 0 | 1 ( 1.1) |
| Vessel Puncture Site Reaction [n(%)] | 0 | 1 ( 1.1) |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS [n(%)] | 0 | 1 ( 1.1) |
| Myalgia [n(%)] | 0 | 1 ( 1.1) |

Note: Population is the sum of all drug administrations.
Each adverse event is counted only once for each subject per drug administration within each System Organ Class and Preferred Term.

**Do any of the adverse events require statistical analysis consideration (e.g. emesis)?**
No

**If yes, does the time exceed two times the median Tmax value (immediate release products) or the labeled dosing interval (modified release products) according to the *Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products*?**
Not applicable.

**Was the adverse event profile observed during the fasting bioequivalence study comparable for the test and reference product? Please comment.**
Yes, the adverse event profile was comparable between the test and reference products.

**Are there any safety concerns based on the adverse event profile?**
No. All the reported adverse events resolved completely upon follow-up.

**Table 11. Protocol Deviations, Fasting Bioequivalence Study**

| Study No. BXN-P0-541 | | |
|---|---|---|
| **Type** | **Subjects # (Test)** | **Subjects # (Ref.)** |
| Blood sampling time deviations | (b) (6) | |
| Blood collection time unknown | | |
| Urine microscopic examination was performed in error during screening evaluation based on the hazy appearance of urine.** | NA | NA |
| Subject declared drinking a glass of orange juice prior to his 48 hour return visit. | (b) (6) | NA |
| The maximum time to freezer was 48 minutes for sample 18. | | (b) (6) |
| The maximum time to freezer was 47 minutes for sample 18. | NA | |

NA: Not Applicable

* Subject had deviation for both administrations of the same treatment. ** This deviation was reported at screening for subject # (b) (6)

**Did dropouts/adverse events/protocol deviations affect the study outcome?**

**Comments on Dropouts/Adverse Events/Protocol Deviations:**

1. Of the forty-eight (48) healthy male subjects who were included in the study, forty-six (46) subjects completed all three study periods and forty-seven (47) subjects completed at least two clinical study periods with a crossover (Test vs Reference).
2. Subject # (b) (6) withdrew consent for period 2 only due to adverse events experienced in period I (headache of mild intensity and upper respiratory tract infection of mild intensity) and received one single oral dose of the Targretin 75 mg capsule in period I and one single oral dose of the Bexarotene 75 gm capsule in period 3. Since this subject completed at least two clinical study periods with a crossover (Test vs. Reference), this subject was included in the pharmacokinetic population and in the average-bioequivalence statistical analysis. However, this subject was excluded from the reference-scaled statistical analysis since subject # (b) (6) did not have evaluable data in all 3 periods.
3. Subject # (b) (6) was withdrawn before dosing of period 3 for reasons other than safety (positive cannabinoids test) and received on single oral dose of the Targretin 75 mg capsule in period 1 and in period 2. Since this subject did not receive the test formulation, samples taken in periods 1 and 2 were not assayed and this subject was not included in the pharmacokinetic and statistical analyses.
4. Per the firm's report, "Sixteen (16) (33.3%) of the forty-eight (48) subjects included in this study experienced a total of twenty-eight (28) AEs. Six (6) AEs were reported after the administration of the test product and 22 AEs were reported after the administration of the reference product. The severity of AEs ranged from mild to severe. Three (3) severe AEs (Test: diarrhoea; Reference; headache and gastroenteritis) were observed during the study. All the reported AEs were expected and possibly related to the Investigations product".
    - Subject (b) (6), period 3 (test treatment) reported severe diarrhoea at 5:00 hours on (b) (6) (time since last dose 21:00) and resolved completely at 6:00 hrs on (b) (6) (time since last dose 5 days 1:00 hrs).
    - Subject (b) (6), period 2 (reference treatment) reported severe headache on (b) (6) at 16:00 hrs (time since last dose 07:52) and resolved completely at (b) (6) at 00:07 hours (time since last dose: 08:07 hrs).
    - Subject (b) (6) period 1 (reference treatment) reported severe gastroenteritis on (b) (6) (time of last dose: 2 days 15:26 hrs) and resolved completed on (b) (6) (23:59 hrs).
5. Protocol deviations included blood sampling time deviations (~10% for all the reported deviations) which were insignificant.
6. Protocol deviations also included maximum time to freeze the samples as >45 minutes in some subjects, however, the stability of Bexarotene in human whole blood in an Ice/water bath was demonstrated for about 2.1 hours in the presence

of Bexarotene acyl glucuronide. Hence this deviation may not have any impact on the outcome of the study.

#### 4.1.1.3 Bioanalytical Results

**Table 12. Sample Analysis Calibration and Quality Control – Within the Fasting Bioequivalence Study**

| Bioequivalence Study No. BXN-P0-541<br>Bexarotene | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Standard Curve Samples** | | | | | | | | |
| Concentration (ng/mL) | 1.00 | 2.00 | 5.00 | 15.00 | 45.00 | 80.00 | 140.00 | 170.00 | 200.00 |
| Inter day Precision (%CV) | 2.5 | 5.1 | 3.4 | 2.8 | 2.9 | 2.3 | 1.8 | 2.1 | 2.6 |
| Inter day Accuracy (%Actual) | 99.5 | 99.9 | 103.4 | 99.6 | 98.9 | 98.8 | 101.1 | 98.9 | 99.9 |
| Linearity | 0.9954 to 0.9998 | | | | | | | | |
| Linearity Range (ng/mL) | 1.00 to 200.00 | | | | | | | | |
| Sensitivity/LOQ (ng/mL) | 1.00 | | | | | | | | |

| Bioequivalence Study No. BXN-P0-541<br>Bexarotene | | | | |
|---|---|---|---|---|
| **Parameter** | **Quality Control Samples** | | | |
| Concentration (ng/mL) | 3.00 | 20.00 | 70.00 | 150.00 |
| Inter day Precision (%CV) | 5.5 | 2.9 | 3.5 | 2.7 |
| Inter day Accuracy (%Actual) | 99.9 | 101.4 | 97.9 | 98.9 |

| | |
|---|---|
| **Number of Rejected Runs (Run ID, volume/page location)** | There were no rejected runs. The firm did not provide the raw data. The firm will be asked to provide this information. |
| **If sample and QC diluted during study, specify all dilution factors** | The firm did not provide the raw data. The reviewer could not verify this information. |
| **Was 100% of raw numerical data submitted?** | No |

| | |
|---|---|
| **Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?** | Yes |
| **Do you agree with the firm's accepted and rejected runs?** | Yes |

| | |
|---|---|
| **Any interfering peaks in chromatograms?** | No |
| **Were 20% of chromatograms included?** | Yes |
| **Were chromatograms serially or randomly selected?** | Serially |
| **Were the chromatograms submitted by the firm acceptable?** | Yes |

#### 4.1.1.4 Pharmacokinetic Results

**Table 13. Arithmetic Mean Pharmacokinetic Parameters**

Mean plasma concentrations are presented in Table 17 and Figure 1

| Fasting Bioequivalence Study, Study No. BXN-PO-541 | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Parameter (units) | Test | | | | Reference | | | | T/R |
| | Mean | %CV | Min | Max | Mean | % CV | Min | Max | |
| AUC0-t (hr *ng/ml) | 1059.9 | 41.18 | 422.9 | 2786 | 1021.8 | 48.6 | 411.1 | 2954.78 | 1.04 |
| AUC∞ (hr *ng/ml) | 1073.8 | 40.7 | 429.2 | 2797.8 | 1050.1 | 47.6 | 416.8 | 2962 | 1.02 |
| Cmax (ng/ml) | 398.2 | 44.4 | 81.23 | 939.2 | 348.3 | 50.7 | 75.86 | 933.51 | 1.14 |
| Tmax* (hr) | 1.75 | . | 1 | 6 | 1.75 | . | 1 | 4 | 1 |
| Kel ($hr^{-1}$) | 0.35 | 28.8 | 0.08 | 0.59 | 0.3323 | 37.2 | 0.03 | 0.6 | 1.06 |
| T1/2 (hr) | 2.21 | 49.9 | 1.16 | 8.62 | 2.96 | 113.7 | 1.15 | 22.7 | 0.75 |

* Tmax values are presented as median, range

**Table 14. Geometric Means and 90% Confidence Intervals - Firm Calculated**

| Bexarotene<br>Dose (1 x 75 mg)<br>Least Squares Geometric Means*, Ratio of Means (%), and 90% Confidence Intervals (%), and Reference Intra-Subject CV (ISCV) (%) and "η" Upper 95% Confidence Limit when Applicable | | | | | | |
|---|---|---|---|---|---|---|
| Fed Bioequivalence Study (Study No. BXN-P0-541) | | | | | | |
| Parameter (units) | Test | RLD | Ratio | 90% C.I. | ISCV | η |
| AUC0-t (hr *ng/ml) | 985.66 | 931.07 | 105.86 | 100.09-111.97 | 21.2 | N/AP |
| AUC∞ (hr *ng/ml) | 999.23 | 955.26 | 104.60 | 99.23-110.27 | 19.0 | N/AP |
| Cmax (ng/ml) | 355.10 | 309.91 | 114.58 | 104.28-125.90 | 31.9 | -0.0181 |

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

**Bexarotene Capsules**
**75 mg**
**Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals**

**Fed Bioequivalence Study, Study No. BXN-P0-541**

| | Geometric Means | | | 90% CI | |
|---|---|---|---|---|---|
| Parameter | Test | Reference | T/R Ratio | Lower CI | Upper CI |
| LAUCT | 985.96 | 930.79 | 1.06 | 100.75 | 111.37 |
| LAUCI | 999.18 | 955.92 | 1.05 | 99.60 | 109.70 |
| LCMAX | 355.09 | 309.43 | 1.15 | 104.07 | 126.54 |

| Parameter | T/R Ratio | Lower 90% CI | Upper 90% CI | s2wr | sWR | Criteria Bound | Method Used | OUTCOME |
|---|---|---|---|---|---|---|---|---|
| LAUCT | 1.06 | 100.75 | 111.37 | 0.0440675 | 0.2099227 | -0.018908 | Unscaled | PASS |
| LAUCI | 1.04 | 99.60 | 109.70 | 0.0356269 | 0.1887509 | -0.017248 | Unscaled | PASS |
| LCMAX | 1.14 | 104.07 | 126.54 | 0.0970164 | 0.3114746 | -0.018125 | Scaled/PE | PASS |

**Table 16. Additional Study Information, Fasting Study No. BXN-P0-541**

| | | |
|---|---|---|
| **DBE SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)** | CONTINU2 | |
| **Reason(s) for Selecting Above SAS Program Macro** | Reviewer agrees with the firm's selection of Kel and thalf. | |
| **Root mean square error, AUC0-t** | 0.2099 | |
| **Root mean square error, AUC∞** | 0.1887 | |
| **Root mean square error, Cmax** | 0.3115 | |
| | **Test** | **Reference** |
| **If CALCKE program is used, please state how many subjects used by you for determining Kel and AUC∞** | n/a | n/a |
| **If CALCKE program is used, please state if you agree or disagree with firm's determination of Kel and AUC∞** | n/a | n/a |
| **Indicate the number of subjects with the following:** | | |
| **measurable drug concentrations at 0 hr** | none | none |
| **first measurable drug concentration as Cmax** | none | none |
| **Cmax at the first time point** | none | none |
| **Were the subjects dosed as more than one group?** | No | |

| **Ratio of AUC0-t/AUC∞[10]** | | | | |
|---|---|---|---|---|
| **Treatment** | **n** | **Mean** | **Minimum** | **Maximum** |
| **Test** | 46 | 0.99 | 0.97 | 0.99 |
| **Reference** | 88 | 0.99 | 0.87 | 0.99 |
| **If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.** | Not applicable | | | |

## Comments on Pharmacokinetic and Statistical Analysis:

The 90% CI's for the least squares geometric means of Ln AUC0-t, Ln AUC∞ and LnCmax calculated by the reviewer agree with the firm's calculations and meet the criteria for BE.

[10] See individual test to reference ratios of PK Parameters in SAS Output.

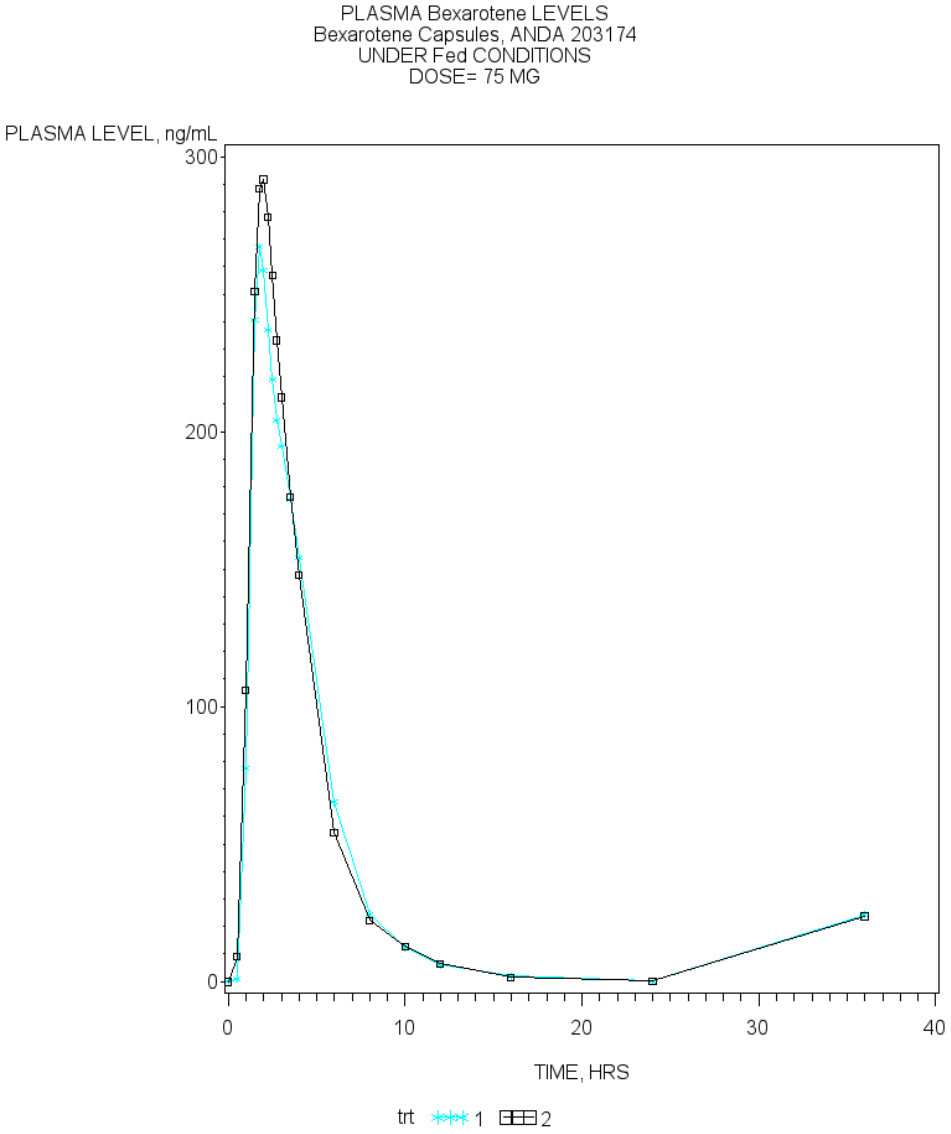
**Summary and Conclusions, Single-Dose Fed Bioequivalence Study:**

Incomplete due to the deficiencies stated in the Deficiency Section.

**Table 17. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study**

| | Test (n=47) | | Reference (n=93) | | RatioTR |
|---|---|---|---|---|---|
| Time (hr) | Mean (ng/mL) | CV% | Mean (ng/mL) | CV% | (T/R) |
| 0.00 | 0.00 | . | 0.00 | . | . |
| 0.50 | 7.32 | 365.87 | 11.99 | 451.50 | 0.61 |
| 1.00 | 96.31 | 107.52 | 132.11 | 133.64 | 0.73 |
| 1.50 | 280.38 | 72.62 | 272.25 | 74.79 | 1.03 |
| 1.75 | 314.35 | 64.54 | 290.67 | 65.34 | 1.08 |
| 2.00 | 311.59 | 59.23 | 281.48 | 60.06 | 1.11 |
| 2.25 | 295.92 | 55.30 | 262.42 | 55.95 | 1.13 |
| 2.50 | 271.77 | 53.23 | 237.70 | 55.40 | 1.14 |
| 2.75 | 244.43 | 52.77 | 216.90 | 54.33 | 1.13 |
| 3.00 | 214.04 | 53.71 | 200.72 | 52.33 | 1.01 |
| 3.50 | 171.41 | 53.80 | 166.35 | 52.31 | 1.03 |
| 4.00 | 143.00 | 58.62 | 141.22 | 54.93 | 1.01 |
| 6.00 | 56.08 | 93.61 | 51.59 | 64.98 | 1.09 |
| 8.00 | 21.59 | 82.55 | 20.85 | 70.57 | 1.04 |
| 10.00 | 11.36 | 98.19 | 11.32 | 91.25 | 1.00 |
| 12.00 | 6.09 | 162.71 | 5.29 | 83.27 | 1.15 |
| 16.00 | 1.42 | 123.26 | 1.71 | 85.26 | 0.83 |
| 24.00 | 0.09 | 392.72 | 0.36 | 230.50 | 0.25 |
| 36.00 | 0.00 | . | 0.05 | 732.30 | . |

**Figure 1. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study[11]**




[11] For individual subjects' concentration vs time profile, please see SAS Output





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

## 4.2 Formulation Data

| Ingredient | Amount (mg) / Capsule | Amount (%) / Capsule |
|---|---|---|
| | Strength 75 mg | Strength 75 mg |
| (b) (4) | | |
| Bexarotene, (b) (4) | 75.00 mg | (b) (4) |
| Polysorbate 20 NF | (b) (4) | |
| Povidone (b) (4) USP | | |
| Polyethylene Glycol 400 NF | | |
| Butylated Hydroxyanisole (b) (4) NF | | |
| (b) (4) | | |
| Gelatin NF | I | |
| Glycerin USP | | |
| Sorbitol (b) (4) | | |
| (b) (4) Water (b) (4) | | |
| $TiO_2$ (b) (4) | | |
| (b) (4 | | (b) (4) |

**NDA 021055 Formulation: NOT TO BE RELEASED UNDER FOIA**[12]

[12] Enterprise Search: NDA 021055: http://fdaesearch.fda.gov:81/SecureES/loadNativeDocument.do?theId=16807439&theLib=bph_lib#xml=http://fdaesearch.fda.gov:81/SecureES/loadPdfDocument.do?theId=16807439&theLib=bph_lib; Last accessed: -6/22/2012/

| | |
|---|---|
| **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 |
| **Are the amounts of all inactive ingredients based on Maximum Daily Dose (MDD) within IIG (per unit) limits?** | YES |
| **If no, are they all above/within IIG (per day) limits?** | The recommended initial dose of Targretin capsules is 300 mg/m2/day. Maximum is 400 mg/m2/day. The maximum daily dose based on initial dose level of 300 mg/m2/day for a body surface area of 2.38-2.62 m2 is 750 mg which equals 10 tablets/day[13]. The use of all the inactive ingredients are equal to or less than that present in the RLD except for polyethylene glycol. However the amount of polyethylene glycol based on MDD is within the IIG limits based on MDD[14]. |
| **If no, are additional data or Pharm/Tox consult necessary?** | NO |
| **Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)?** | YES |
| **Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?** | There is only one strength submitted for this drug product. |
| **Are all strengths of the RLD product dose-proportional?** | There is only one strength of the RLD. |
| **Are all strengths of the test formulation acceptable** | YES |
| **Additional Attachment for Formulation Calculations** | There are no additional calculations. |

[13] http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021055s006lbl.pdf; Last accessed: 08/13/2012.

[14] (b) (4)

## 4.3 Dissolution Data

| Dissolution Review Path | |
|---|---|

### Table 33. Dissolution Data

### A. FDA-method (Tier 1 and Tier 2)

| | | |
|---|---|---|
| **Dissolution Conditions** | **Apparatus:** | USP Apparatus 2 (paddles) |
| | **Speed of Rotation:** | 50 rpm |
| | **Medium:** | 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 (FDA-method, Tier 1) |
| | **Volume:** | 900 mL |
| | **Temperature:** | 37.0 ± 0.5°C |
| **Firm's Proposed Specifications** | Q= (b)(4)%, T=45 minutes | |
| **Dissolution Testing Site (Name, Address)** | Banner Pharmacaps<br>4125 Premier Drive High Point, NC 27265 | |

| 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) | | | | Study Report Location |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 15 | 30 | 45 | 60 | |
| A12-125 | 2/28/12 | Banner Pharmacaps<br>Lot no. 140000127<br>Manufacture Date: 01/17/11 | 75 mg Soft Gelatin Capsule | 12 | Mean | 2 | 10 | 19 | 28 | 5.3.1.3 |
| | | | | | Range | (b) (4) | | | | |
| | | | | | %CV | 53 | 47 | 54 | 58 | |
| N/A | 2/28/12 | Eisai Pharmaceutical (Targretin)<br>Lot 004681<br>Expiration Date: 07/12 | 75 mg Soft Gelatin Capsule | 12 | Mean | 2 | 41 | 80 | 93 | 5.3.1.3 |
| | | | | | Range | (b) (4) | | | | |
| | | | | | %CV | 118 | 38 | 14 | 6 | |

| | | |
|---|---|---|
| **Dissolution Conditions** | **Apparatus:** | USP Apparatus 2 (paddles) |
| | **Speed of Rotation:** | 50 rpm |
| | **Medium:** | 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 with 0.05 g/L pancreatin enzyme (FDA-method, Tier 2) |
| | **Volume:** | 900 mL |
| | **Temperature:** | 37.0 ± 0.5°C |
| **Firm's Proposed Specifications** | Q= (b) (4)%, T=45 minutes | |
| **Dissolution Testing Site (Name, Address)** | Banner Pharmacaps<br>4125 Premier Drive High Point, NC 27265 | |

| 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) | | | | Study Report Location |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 15 | 30 | 45 | 60 | |
| A12-125 | 3/1/12 and 3/5/12 | Banner Pharmacaps<br>Lot no. 140000127<br>Manufacture Date: 01/17/11 | 75 mg Soft Gelatin Capsule | 12 | Mean | 2 | 12 | 22 | 32 | 5.3.1.3 |
| | | | | | Range | (b) (4) | | | | |
| | | | | | %CV | 56 | 40 | 42 | 37 | |

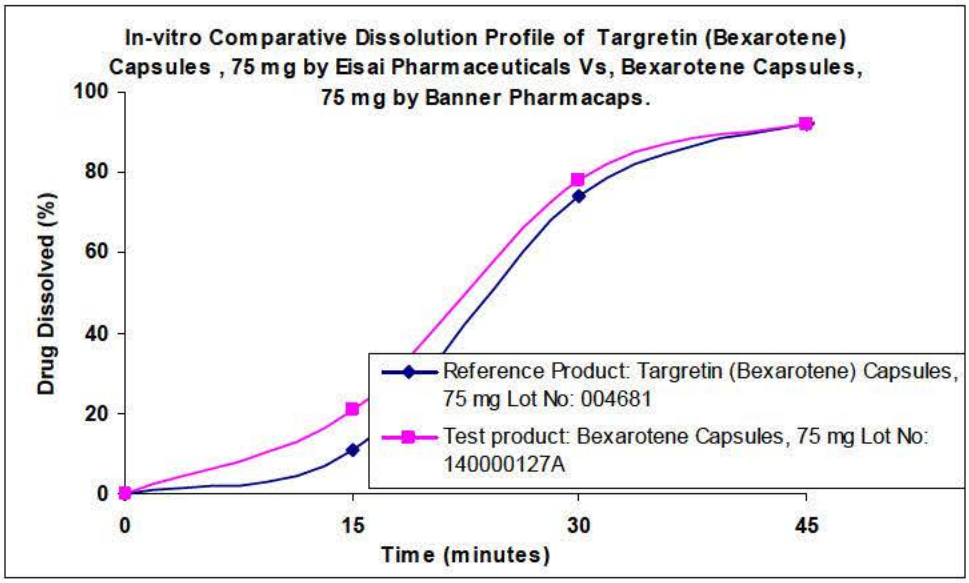
**B. Firm's Method* (Tier 1).**

| | | |
|---|---|---|
| **Dissolution Conditions** | **Apparatus:** | USP Apparatus 2 (paddles) |
| | **Speed of Rotation:** | 75 rpm |
| | **Medium:** | 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 |
| | **Volume:** | 900 mL |
| | **Temperature:** | 37.0 ± 0.5°C |
| **Firm's Proposed Specifications** | Q=(b)(4)%, T=45 minutes | |
| **Dissolution Testing Site (Name, Address)** | Banner Pharmacaps<br>4125 Premier Drive High Point, NC 27265 | |

| 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) | | | | | Study Report Location |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 15 | 30 | 45 | 60 | 75 | |
| A11-111 | 5/25/11 | Banner Pharmacaps<br>Lot no. 140000127A<br>Manufacture Date: 01/17/11 | 75 mg Soft Gelatin Capsule | 12 | Mean | 21 | 78 | 92 | 96 | 97 | 5.3.1.3 |
| | | | | | Range | (b) (4) | | | | | |
| | | | | | %CV | 46 | 17 | 4 | 3 | 2 | |
| A11-107 | 5/25/11 | Eisai Pharmaceutical (Targretin)<br>Lot 004681<br>Expiration Date: 07/12 | 75 mg Soft Gelatin Capsule | 12 | Mean | 11 | 74 | 92 | 96 | 97 | 5.3.1.3 |
| | | | | | Range | (b) (4) | | | | | |
| | | | | | %CV | 91 | 12 | 2 | 1 | 1 | |

*** The firm did not provide Tier 2 data using its own method.**

**Figure 5. Dissolution Profiles**



## 4.4 Office of Scientific Investigation (OSI) Inspection Report Review

### 4.4.1 Summarization of the OSI Inspection of Clinical Site

The following is the history of the inspections held for the clinical site: Algorithme Pharma Inc., 1200 Beaumont Ave. Mount-Royal, Quebec, Canada, H3P 3P1.

BE inspections at Algorithme:

1. NDA 22416, 12/11/2009, VAI[15]

**Following the inspection at Algorithme Pharma, Mount-Royal (November 30 – December 4, 2009, and December 14-18, 2009), Form FDA-483 was issued.**

**ANDA 22416**

**OSI Finding -1**: **The firm failed to assure complete drug accountability following drug dispensation and prior to subject dosing**.

**OSI's Evaluation:**

The firm's pharmacist dispensed test and reference tablets into vials 2 to 3 days prior to subject dosing at the Mount-Royal site. These vials were then transferred to and stored in a Temporary Drug Room (TDR) at the Montreal clinical site. However, the shipping slip did not list how many vials were received at the TDR and whether they were sealed. Additionally, when vials were removed from the TDR on dosing days, the identities of the individual tablets inside the vials were not confirmed.

Although the firm should improve their drug accountability practices, this finding should not affect study outcome. The firm's response notes that products used for dosing were confirmed by visual check at dosing as documented on case report forms. DSI accepts this as confirmation that subjects received the correct drug product.

The firm's response also indicated that they have since implemented corrective actions in their drug accountability documentation practices.

**Impact on current ANDA:**

The finding may not have any impact on the current ANDA, since the firm has taken corrective actions as stated in their response to the form 483 letter provided on January 8, 2010. The current study (ANDA 203174) took place in March, 2011, after the firm's corrective action.

[15] DARRTS Search: ANDA 79179; CONSULT REV-OSI-05 (Bioequivalence Establishment Inspection Report Review); Final Date: 12/30/2008.

### 4.4.2 Summarization of the OSI Inspection of Analytical Site

The following is the history of the inspections held for the analytical site: (b) (4) (b) (4)

BE inspections at (b) (4)

1. NDA 22416, (b) (4), VAI[16]

**Following the inspection at (b) (4) Form FDA-483 was issued. (b) (4) responded to the Form FDA-483 observations in a letter dated January 8, 2010**.

**ANDA 22416**

(b) (4)

**Impact on current ANDA:**

The finding may not have any impact on the current ANDA, since the firm has taken corrective actions as stated in their response to the form 483 letter provided on January 8, 2010. The current study (ANDA 203174) took place in March, 2011, after the firm's corrective action.

## 4.5 Consult Reviews

[16] DARRTS Search: ANDA 79179; CONSULT REV-OSI-05 (Bioequivalence Establishment Inspection Report Review); Final Date: 12/30/2008.

## 4.6 SAS Output

### 4.6.1 Fed Study Data

**Fed CONCENTRATION DATASET**

| Obs | sub | sequ | per | GRP | treat | c1 | c2 | c3 | c4 | c5 | c6 | c7 | c8 | c9 | c10 | c11 | c12 | c13 | c14 | c15 | c16 | c17 | c18 | c19 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | (b) (6) | BBA | 3 | 1 | A | 0 | 0 | 8.77 | 95.13 | 218.39 | 278.2 | 329.47 | 358.81 | 325.22 | 285.12 | 220.74 | 143.05 | 37.17 | 13.98 | 6.12 | 3.61 | 1.38 | 0 | 0 |
| 2 | | BBA | 1 | 1 | B | 0 | 0 | 12.4 | 134.79 | 228.38 | 273.74 | 270.45 | 234.37 | 218.74 | 193.13 | 159.44 | 123.11 | 33.28 | 14.94 | 6.08 | 4.25 | 1.28 | 0 | 0 |
| 3 | | BBA | 2 | 1 | B | 0 | 0 | 2.27 | 21.57 | 91.26 | 207.06 | 230.7 | 252.39 | 241.64 | 211.82 | 156.63 | 123.91 | 59.63 | 19.09 | 7.48 | 4.93 | 1.44 | 0 | 0 |
| 4 | | ABB | 1 | 1 | A | 0 | 23.28 | 221.94 | 315.89 | 242.29 | 210.88 | 165.8 | 111.69 | 106.87 | 89.54 | 63.45 | 47.59 | 17.42 | 7.91 | 3.86 | 2.79 | 1.57 | 1.2 | 0 |
| 5 | | ABB | 2 | 1 | B | 0 | 10.81 | 158.75 | 189.99 | 174.6 | 131.67 | 109.5 | 86.07 | 63.83 | 50.12 | 56.68 | 43.79 | 16.15 | 5.62 | 3.59 | 3.27 | 2.73 | 2.08 | 0 |
| 6 | | ABB | 3 | 1 | B | 0 | 0 | 39.48 | 210.77 | 258.28 | 306.72 | 332.05 | 195.36 | 148.4 | 225.72 | 132.77 | 88.68 | 27.15 | 8.52 | 3.35 | 2.39 | 1.19 | 0 | 0 |
| 7 | | BAB | 2 | 1 | A | 0 | 1.09 | 38.75 | 265.89 | 268.9 | 249.91 | 181.11 | 171.06 | 132.91 | 108.71 | 94.69 | 62.28 | 16.34 | 9.4 | 7.18 | 3.2 | 0 | 0 | 0 |
| 8 | | BAB | 1 | 1 | B | 0 | 0 | 116.46 | 274.58 | 257.67 | 208.99 | 185.24 | 136.7 | 101.11 | 89.18 | 66.44 | 54.95 | 15.01 | 5.33 | 2.97 | 1.44 | 0 | 0 | 0 |
| 9 | | BAB | 3 | 1 | B | 0 | 0 | 128.85 | 251.48 | 264.59 | 214.87 | 187.24 | 144.18 | 119.47 | 90.4 | 78.69 | 59.09 | 17.97 | 14.58 | 9.97 | 4.29 | 1.18 | 0 | 0 |
| 10 | | BAB | 2 | 1 | A | 0 | 6.85 | 187.1 | 466.94 | 444.15 | 430.94 | 385.91 | 307.69 | 249.92 | 182.3 | 135.44 | 119 | 36.1 | 14.59 | 6.04 | 3.08 | 0 | 0 | 0 |
| 11 | | BAB | 1 | 1 | B | 0 | 0 | 3.31 | 32.49 | 54.8 | 59.37 | 80.99 | 109.15 | 146.34 | 192.12 | 275.26 | 255.4 | 100.37 | 30.62 | 16.47 | 4.67 | 1.22 | 0 | 0 |
| 12 | | BAB | 3 | 1 | B | 0 | 0 | 16.06 | 105.97 | 279.15 | 359.31 | 419 | 399.31 | 371.51 | 316.02 | 251.36 | 185.79 | 48.86 | 18.91 | 5.36 | 2.62 | 0 | 0 | 0 |
| 13 | | ABB | 1 | 1 | A | 0 | 5.45 | 159.37 | 322.89 | 306.15 | 260.03 | 232.07 | 176.93 | 155.35 | 126.74 | 95.49 | 78.4 | 26.88 | 11.46 | 5.73 | 2.76 | 0 | 0 | 0 |
| 14 | | ABB | 2 | 1 | B | 0 | 9.1 | 141.51 | 130.81 | 123.99 | 110.73 | 103.18 | 94.58 | 77.65 | 69.28 | 45.45 | 34.21 | 13.28 | 7.15 | 4.36 | 2.54 | 1.18 | 1.9 | 1.43 |
| 15 | | ABB | 3 | 1 | B | 0 | 0 | 43.58 | 221.09 | 266.23 | 258.48 | 245.89 | 224.58 | 176.12 | 164.31 | 132.16 | 96.63 | 35.69 | 15.29 | 7.57 | 3.64 | 1.7 | 0 | 0 |
| 16 | | BBA | 3 | 1 | A | 0 | 170.01 | 330.5 | 258.65 | 221.03 | 182.31 | 157.26 | 140.13 | 129.19 | 95.39 | 72.9 | 57.8 | 18.44 | 8.39 | 3.84 | 2.6 | 1.15 | 0 | 0 |
| 17 | | BBA | 1 | 1 | B | 0 | 219.78 | 246.29 | 181.65 | 153.56 | 141.8 | 117.22 | 109.52 | 97.41 | 86.87 | 61.13 | 44.27 | 16.74 | 6.78 | 3.87 | 1.98 | 1.48 | 1.8 | 0 |
| 18 | | BBA | 2 | 1 | B | 0 | 0 | 14.79 | 259.59 | 316.03 | 283.01 | 244.72 | 196.12 | 159.87 | 156.61 | 110.05 | 81.62 | 23.22 | 8.98 | 5.05 | 2.28 | 0 | 0 | 0 |
| 19 | | ABB | 1 | 1 | A | 0 | 0 | 46.27 | 187.86 | 295.49 | 318.77 | 334.46 | 296.22 | 226.1 | 202.68 | 135.24 | 102.42 | 29.15 | 11.54 | 5.44 | 3.5 | 1.16 | 0 | 0 |
| 20 | | ABB | 2 | 1 | B | 0 | 1.94 | 94.62 | 292.19 | 299.38 | 291.87 | 313.51 | 272.7 | 289.71 | 253.42 | 189.82 | 130.39 | 38.79 | 12.71 | 8.45 | 3.93 | 1.54 | 0 | 0 |
| 21 | | ABB | 3 | 1 | B | 0 | 0 | 2.07 | 20.19 | 55.56 | 73.65 | 96.2 | 120.88 | 161.42 | 232.05 | 244.08 | 203.18 | 73.3 | 24.04 | 9.74 | 4.87 | 1.33 | 0 | 0 |
| 22 | | BAB | 2 | 1 | A | 0 | 0 | 42.3 | 326.65 | 441.12 | 488.17 | 524.26 | 428.81 | 432.42 | 347.17 | 233.67 | 195.32 | 45.09 | 20.74 | 11.3 | 6.42 | 2.09 | 0 | 0 |

| Obs | sub | sequ | per | GRP | treat | c1 | c2 | c3 | c4 | c5 | c6 | c7 | c8 | c9 | c10 | c11 | c12 | c13 | c14 | c15 | c16 | c17 | c18 | c19 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 23 | (b) (6) | BAB | 1 | 1 | B | 0 | 0 | 1.01 | 51.81 | 111.16 | 128.53 | 139.87 | 140.99 | 202.21 | 236.29 | 280.58 | 307.23 | 110.28 | 43.54 | 33.63 | 13.6 | 3.81 | 0 | 0 |
| 24 | | BAB | 3 | 1 | B | 0 | 74.14 | 838.18 | 721.5 | 626.45 | 553.51 | 492.93 | 412.12 | 345.99 | 307.23 | 221.79 | 162.21 | 57.47 | 24.57 | 13.78 | 7.56 | 3.68 | 0 | 0 |
| 25 | | BBA | 3 | 1 | A | 0 | 0 | 23.12 | 58.99 | 70.03 | 76.18 | 104.75 | 105.14 | 90.96 | 75.82 | 121.97 | 89.57 | 119.83 | 44.37 | 15.84 | 6.38 | 1.86 | 0 | 0 |
| 26 | | BBA | 1 | 1 | B | 0 | 0 | 8.81 | 111.72 | 220.64 | 252.99 | 277.05 | 236.58 | 205.4 | 202.41 | 144.36 | 112.86 | 58.14 | 23.7 | 9.3 | 4.01 | 1.55 | 0 | 0 |
| 27 | | BBA | 2 | 1 | B | 0 | 1.43 | 350.23 | 465.91 | 376.39 | 358.48 | 251.8 | 218.9 | 191.64 | 162.37 | 115.43 | 80.3 | 24.55 | 11.56 | 5.31 | 2.41 | 1.01 | 0 | 0 |
| 28 | | BBA | 3 | 1 | A | 0 | 0 | 31.25 | 536.26 | 538.11 | 443.4 | 385.16 | 323.36 | 290.19 | 250.49 | 179.23 | 106.46 | 39.75 | 17.43 | 8.1 | 3.69 | 1.27 | 0 | 0 |
| 29 | | BBA | 1 | 1 | B | 0 | 1.17 | 59.21 | 296.76 | 354.25 | 332.22 | 299.56 | 244.16 | 264.94 | 201.16 | 210.59 | 138.15 | 32.66 | 16.62 | 6.58 | 3.22 | 1.11 | 0 | 0 |
| 30 | | BBA | 2 | 1 | B | 0 | 0 | 16.61 | 185.13 | 265.13 | 261.41 | 221.61 | 186.3 | 193.94 | 177.09 | 122.52 | 124.57 | 68.84 | 29.58 | 10.54 | 5.29 | 1.84 | 0 | 0 |
| 31 | | BAB | 2 | 1 | A | 0 | 3.3 | 60.56 | 175.3 | 286.05 | 390.03 | 449.65 | 406.57 | 369.05 | 344.68 | 246.38 | 182.33 | 58.04 | 22.42 | 10.98 | 5.52 | 1.97 | 0 | 0 |
| 32 | | BAB | 1 | 1 | B | 0 | 0 | 39.59 | 439.51 | 556.24 | 557 | 482.07 | 405.28 | 348.12 | 266.69 | 186.73 | 138.81 | 34.32 | 17.58 | 8.29 | 5.06 | 2.63 | 2.14 | 0 |
| 33 | | BAB | 3 | 1 | B | 0 | 0 | 138.29 | 349.36 | 400.34 | 383.26 | 335.45 | 304.85 | 254.51 | 245.25 | 158.39 | 115.57 | 31.03 | 12.97 | 7.01 | 4.5 | 2.58 | 1.87 | 0 |
| 34 | | ABB | 1 | 1 | A | 0 | 0 | 157.71 | 400.58 | 349.21 | 322.98 | 293.9 | 260.52 | 195.8 | 165.26 | 115.33 | 76.79 | 25.97 | 11.41 | 3.95 | 1.52 | 0 | 0 | 0 |
| 35 | | ABB | 2 | 1 | B | 0 | 1.6 | 176.77 | 316.96 | 390.58 | 351.94 | 321.86 | 281.88 | 217.35 | 164.51 | 136.99 | 96.36 | 25.67 | 10.69 | 3.83 | 1.98 | 0 | 0 | 0 |
| 36 | | ABB | 3 | 1 | B | 0 | 0 | 93.35 | 471.02 | 440.45 | 389.46 | 313.17 | 269.72 | 235.55 | 177.57 | 138.54 | 106.32 | 32.54 | 13.03 | 4.7 | 1.86 | 0 | 0 | 0 |
| 37 | | BAB | 2 | 1 | A | 0 | 2.67 | 41.54 | 316.98 | 336.41 | 328.95 | 273.87 | 244.91 | 179.82 | 146.72 | 120.12 | 114.48 | 29.61 | 13.25 | 5.36 | 2.51 | 0 | 0 | 0 |
| 38 | | BAB | 1 | 1 | B | 0 | 1.38 | 175.03 | 290.94 | 242.03 | 183.39 | 160.75 | 138.95 | 108.56 | 103.35 | 107.03 | 72.8 | 29.79 | 10.99 | 4.46 | 1.82 | 0 | 0 | 0 |
| 39 | | BAB | 3 | 1 | B | 0 | 0 | 9.25 | 110.34 | 204.02 | 191.42 | 198.11 | 186.51 | 194.61 | 161.98 | 120.74 | 141.02 | 40.41 | 12.99 | 5.54 | 2.57 | 1.13 | 0 | 0 |
| 40 | | BBA | 3 | 1 | A | 0 | 74.9 | 368.35 | 453.59 | 402.41 | 342.01 | 311.5 | 259.48 | 251.03 | 225.28 | 184.3 | 131.14 | 37.31 | 12.63 | 5.45 | 2.88 | 0 | 0 | 0 |
| 41 | | BBA | 1 | 1 | B | 0 | 1.17 | 145.11 | 419.35 | 481.43 | 501.73 | 442.7 | 382.16 | 291.05 | 298.97 | 205.27 | 129.78 | 33.07 | 12.04 | 5.77 | 2.54 | 1.17 | 0 | 0 |
| 42 | | BBA | 2 | 1 | B | 0 | 4.96 | 175.54 | 362.22 | 362.63 | 379.96 | 325.59 | 288.61 | 208.56 | 209.36 | 150.56 | 97.99 | 27.42 | 9.42 | 5.53 | 2.97 | 1.26 | 0 | 0 |
| 43 | | ABB | 1 | 1 | A | 0 | 1.15 | 257.98 | 576.26 | 479.2 | 370.51 | 271.83 | 213.29 | 161.38 | 149.01 | 126.42 | 100.12 | 22.71 | 9.33 | 4.27 | 1.2 | 0 | 0 | 0 |
| 44 | | ABB | 2 | 1 | B | 0 | 51.1 | 816.95 | 933.51 | 844.22 | 712.49 | 600.04 | 572.17 | 522.11 | 511.59 | 441.19 | 392.13 | 123 | 54.38 | 30.33 | 10.81 | 3.74 | 0 | 0 |
| 45 | | ABB | 3 | 1 | B | 0 | 1.04 | 220.66 | 518 | 424.31 | 339.21 | 254.71 | 209.13 | 178.61 | 170.86 | 144.82 | 112.78 | 27.64 | 11.11 | 4.72 | 1.46 | 0 | 0 | 0 |
| 46 | | BAB | 2 | 1 | A | 0 | 2.87 | 226.85 | 566.07 | 451.57 | 363.65 | 291.76 | 222.29 | 194.13 | 148.17 | 130.18 | 90.02 | 21.75 | 9.64 | 6.67 | 2.48 | 1.27 | 0 | 0 |
| 47 | | BAB | 1 | 1 | B | 0 | 1.74 | 260.95 | 443.32 | 391.43 | 328.97 | 278.36 | 229.27 | 220.37 | 178.05 | 148.1 | 120.96 | 35.98 | 16.91 | 9.61 | 3.32 | 2.01 | 0 | 0 |
| 48 | | BAB | 3 | 1 | B | 0 | 4.8 | 171.82 | 412.41 | 367.31 | 303.87 | 287.9 | 265.65 | 256.8 | 222.57 | 164.33 | 128.21 | 47.41 | 20.49 | 10.84 | 4.2 | 1.99 | 0 | 0 |
| 49 | | BBA | 3 | 1 | A | 0 | 0 | 12.94 | 34.79 | 40.9 | 74.51 | 85.81 | 90.23 | 94.82 | 105.51 | 94.98 | 114.42 | 47.66 | 13.29 | 6.2 | 3.38 | 0 | 0 | 0 |
| 50 | | BBA | 1 | 1 | B | 0 | 1.36 | 162.03 | 297.29 | 244.95 | 180.31 | 156.11 | 138.85 | 126.2 | 107.79 | 92.23 | 73.97 | 16.73 | 7.59 | 3.84 | 1.64 | 0 | 0 | 0 |
| 51 | | BBA | 2 | 1 | B | 0 | 6.89 | 184.72 | 309.42 | 286.87 | 248.53 | 204.24 | 182.05 | 164.25 | 140.86 | 94.75 | 82.48 | 24.21 | 7.62 | 4.04 | 2.03 | 0 | 0 | 0 |

| Obs | sub | sequ | per | GRP | treat | c1 | c2 | c3 | c4 | c5 | c6 | c7 | c8 | c9 | c10 | c11 | c12 | c13 | c14 | c15 | c16 | c17 | c18 | c19 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 52 | (b) (6) | ABB | 1 | 1 | A | 0 | 11.9 | 155.2 | 337.78 | 306.31 | 229.43 | 165.25 | 119.29 | 86.63 | 76.14 | 52.36 | 36.79 | 9.92 | 5.05 | 2.34 | 1.43 | 0 | 0 | 0 |
| 53 | | ABB | 2 | 1 | B | 0 | 1.39 | 105.96 | 241.51 | 224.69 | 142.04 | 99.83 | 77.93 | 55.67 | 45.68 | 34.02 | 25.66 | 9.29 | 4.43 | 1.98 | 1.67 | 1.54 | 1.24 | 0 |
| 54 | | ABB | 3 | 1 | B | 0 | 0 | 1.5 | 77.02 | 133.04 | 161.72 | 168.09 | 143.43 | 115.82 | 136.61 | 114.28 | 112.94 | 28.36 | 9.63 | 3.72 | 1.93 | 0 | 0 | 0 |
| 55 | | BBA | 3 | 1 | A | 0 | 0 | 3.36 | 14.5 | 20.81 | 40.05 | 140.68 | 274.6 | 354.02 | 331.3 | 301.85 | 214.25 | 52.8 | 18.63 | 9.38 | 3.43 | 1.36 | 0 | 0 |
| 56 | | BBA | 1 | 1 | B | 0 | 0 | 39.39 | 177.72 | 166.79 | 188.61 | 209.6 | 238.78 | 241.9 | 264.11 | 177.21 | 139.67 | 35.1 | 12.4 | 6.05 | 3.79 | 1.13 | 0 | 0 |
| 57 | | BBA | 2 | 1 | B | 0 | 0 | 3.33 | 31.93 | 61.12 | 170.81 | 316.04 | 341.06 | 321.51 | 281.1 | 199.09 | 157.09 | 48.45 | 18.56 | 13.57 | 4.39 | 1.48 | 0 | 0 |
| 58 | | ABB | 1 | 1 | A | 0 | 1.2 | 28.32 | 121.48 | 148.86 | 199.85 | 238.65 | 284.51 | 266.01 | 238.69 | 182.1 | 223.37 | 98.53 | 30.66 | 12.69 | 5.71 | 1.52 | 0 | 0 |
| 59 | | ABB | 2 | 1 | B | 0 | 0 | 1.17 | 51.16 | 107.53 | 138.89 | 168.87 | 190.57 | 185.71 | 196.6 | 197.4 | 181.24 | 74.14 | 35.06 | 19.18 | 9.52 | 1.63 | 0 | 0 |
| 60 | | ABB | 3 | 1 | B | 0 | 1.6 | 24.64 | 183.08 | 249.16 | 268.84 | 275.3 | 255.91 | 263.16 | 263.98 | 198.83 | 163.29 | 67.52 | 29.25 | 19.3 | 12.34 | 1.62 | 0 | 0 |
| 61 | | BAB | 2 | 1 | A | 0 | 4.67 | 139.44 | 498.23 | 553.68 | 490.86 | 413.93 | 362.86 | 297.33 | 242.95 | 176.16 | 123.54 | 43.21 | 21.18 | 10.22 | 4.68 | 2.04 | 0 | 0 |
| 62 | | BAB | 1 | 1 | B | 0 | 1.88 | 254.96 | 469.31 | 448.73 | 407.03 | 332.76 | 295.6 | 293.31 | 245.94 | 175.78 | 141.99 | 53.07 | 22.52 | 10.88 | 5.76 | 1.95 | 0 | 0 |
| 63 | | BAB | 3 | 1 | B | 0 | 0 | 73.88 | 575.41 | 590.53 | 545.37 | 480.63 | 428.14 | 379.25 | 298.08 | 226.72 | 176.13 | 50.76 | 17.33 | 9.52 | 5.35 | 1.5 | 0 | 0 |
| 64 | | ABB | 1 | 1 | A | 0 | 5.47 | 201.33 | 546.6 | 658.85 | 528.3 | 456.61 | 425.83 | 340.36 | 268.94 | 166.3 | 104.74 | 23.07 | 6.39 | 2.76 | 1.05 | 0 | 0 | 0 |
| 65 | | ABB | 2 | 1 | B | 0 | 0 | 57.24 | 494.52 | 543.69 | 490.03 | 413.44 | 367.23 | 311.11 | 321.7 | 261.66 | 192.62 | 44.98 | 14.28 | 5.34 | 2.09 | 0 | 0 | 0 |
| 66 | | ABB | 3 | 1 | B | 0 | 2.28 | 152.36 | 366.45 | 393.57 | 390.68 | 349.66 | 325.42 | 283.82 | 229.36 | 239.41 | 159.2 | 45.11 | 17.79 | 6.15 | 2.19 | 0 | 0 | 0 |
| 67 | | BBA | 3 | 1 | A | 0 | 0 | 8.6 | 227.06 | 383.93 | 549.34 | 556.11 | 514.14 | 427.81 | 401.76 | 364.33 | 323.08 | 130.46 | 63.59 | 27.89 | 15.32 | 3.96 | 1.69 | 0 |
| 68 | | BBA | 1 | 1 | B | 0 | 1.65 | 197.37 | 558.99 | 489.88 | 491.44 | 464.1 | 425.01 | 416.67 | 360.92 | 253.7 | 200.75 | 80.66 | 38.77 | 20.15 | 9.24 | 3.3 | 1.22 | 0 |
| 69 | | BBA | 2 | 1 | B | 0 | 0 | 24.95 | 200.61 | 319.34 | 388.02 | 397.73 | 360.65 | 359.94 | 348.44 | 329.69 | 268.93 | 91.65 | 43.85 | 17.23 | 13.21 | 4.26 | 1.94 | 0 |
| 70 | | BAB | 2 | 1 | A | 0 | 0 | 28.62 | 131.86 | 206.24 | 239.28 | 243.03 | 204.72 | 186.76 | 122.43 | 135.63 | 137.59 | 71.47 | 16.83 | 10.54 | 4.11 | 1.75 | 0 | 0 |
| 71 | | BAB | 1 | 1 | B | 0 | 0 | 0 | 5.56 | 17.37 | 45.66 | 67.86 | 111.3 | 137.16 | 158.23 | 161.04 | 152.22 | 151.58 | 52.09 | 24.47 | 7.55 | 2.71 | 0 | 0 |
| 72 | | BAB | 3 | 1 | B | 0 | 0 | 1.43 | 56.06 | 118.57 | 171.81 | 187.6 | 190.79 | 173.85 | 154.43 | 139.53 | 180.85 | 108.3 | 25.86 | 11.76 | 7.08 | 1.75 | 0 | 0 |
| 73 | | BAB | 2 | 1 | A | 0 | 0 | 0 | 1.4 | 8.16 | 15.52 | 24.87 | 26.16 | 33.7 | 42.18 | 44.59 | 57.8 | 81.23 | 52.5 | 39.2 | 66.57 | 8.52 | 0 | 0 |
| 74 | | BAB | 1 | 1 | B | 0 | 0 | 0 | 0 | 2.2 | 7.72 | 20.8 | 38.25 | 74.91 | 88.74 | 153.34 | 233.06 | 91.43 | 64.97 | 28.67 | 15.2 | 3.49 | 0 | 0 |
| 75 | | BAB | 3 | 1 | B | 0 | 0 | 0 | 0 | 2.42 | 10.74 | 18.85 | 28.14 | 54.82 | 94.34 | 144.27 | 220.7 | 117.46 | 42.24 | 18.68 | 8.09 | 4.26 | 0 | 0 |
| 76 | | ABB | 1 | 1 | A | 0 | 0 | 40.49 | 496.28 | 484.09 | 427.39 | 357.43 | 275.77 | 254.64 | 219.89 | 141.75 | 119.56 | 40.72 | 17.68 | 12.31 | 5.36 | 1.87 | 0 | 0 |
| 77 | | ABB | 2 | 1 | B | 0 | 0 | 83.13 | 335.46 | 326.41 | 240.43 | 208.92 | 166.14 | 154.45 | 143.62 | 128.11 | 88.43 | 31.65 | 13.76 | 6.99 | 4.25 | 1.87 | 0 | 0 |
| 78 | | ABB | 3 | 1 | B | 0 | 0 | 125.47 | 408.86 | 395.61 | 354.89 | 270.33 | 235.1 | 193 | 172.28 | 132.48 | 101.71 | 32.36 | 15.57 | 8.05 | 3.66 | 1.56 | 0 | 0 |
| 79 | | BBA | 3 | 1 | A | 0 | 0 | 3.74 | 99.82 | 244.47 | 328.36 | 344.71 | 292.26 | 299.4 | 281.33 | 203.19 | 156.1 | 41.89 | 13.94 | 6.15 | 2.48 | 0 | 0 | 0 |
| 80 | | BBA | 1 | 1 | B | 0 | 0 | 16.67 | 98.26 | 139.97 | 169.27 | 203.83 | 199.79 | 159.89 | 143.25 | 112.37 | 123.22 | 26.29 | 10.41 | 4.47 | 1.92 | 0 | 0 | 0 |

| Obs | sub | sequ | per | GRP | treat | c1 | c2 | c3 | c4 | c5 | c6 | c7 | c8 | c9 | c10 | c11 | c12 | c13 | c14 | c15 | c16 | c17 | c18 | c19 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 81 | (b) (6) | BBA | 2 | 1 | B | 0 | 32.15 | 277.35 | 227.54 | 187.56 | 185.4 | 162.5 | 146.38 | 111.47 | 103.48 | 72.35 | 48.17 | 13.32 | 6.97 | 3.29 | 1.86 | 0 | 0 | 0 |
| 82 | | BAB | 2 | 1 | A | 0 | 0 | 5.28 | 67.74 | 127.9 | 167.41 | 157.43 | 192.5 | 160.97 | 134.34 | 100.08 | 92.1 | 88.53 | 35.84 | 18.09 | 10.37 | 4.07 | 0 | 0 |
| 83 | | BAB | 1 | 1 | B | 0 | 0 | 111.27 | 316.07 | 361.66 | 295.48 | 303.58 | 277.9 | 267.7 | 242.18 | 196.05 | 160.89 | 60.96 | 30.19 | 15.36 | 14.91 | 6.05 | 0 | 0 |
| 84 | | BAB | 3 | 1 | B | 0 | 0 | 7.28 | 110.89 | 169.8 | 201.91 | 183.04 | 190.93 | 191.39 | 168.29 | 138.05 | 107.35 | 88.87 | 29.78 | 23.66 | 13.07 | 4.77 | 0 | 0 |
| 85 | | BBA | 3 | 1 | A | 0 | 0 | 2.96 | 13.76 | 36.37 | 94.85 | 162.15 | 253.1 | 258.54 | 271.96 | 260.29 | 239.05 | 93.58 | 39.58 | 52.06 | 19.15 | 3.44 | 0 | 0 |
| 86 | | BBA | 1 | 1 | B | 0 | 0 | 1.71 | 21.43 | 49.76 | 135.49 | 180.97 | 211.21 | 238.71 | 245.23 | 242.2 | 191.82 | 90.5 | 41.15 | 57.82 | 23.63 | 5.35 | 1.26 | 0 |
| 87 | | BBA | 2 | 1 | B | 0 | 0 | 36.97 | 78.78 | 148.24 | 178.85 | 186.17 | 223.53 | 213.33 | 212.28 | 212.14 | 252.79 | 112.65 | 49.14 | 37.32 | 14.13 | 3.8 | 0 | 0 |
| 88 | | ABB | 1 | 1 | A | 0 | 0 | 15.36 | 71.83 | 132.27 | 198.27 | 213.11 | 215.91 | 225.26 | 223.37 | 218.44 | 230.27 | 81.84 | 35.11 | 11.21 | 4.66 | 1.15 | 0 | 0 |
| 89 | | ABB | 2 | 1 | B | 0 | 14.87 | 152.56 | 204.09 | 180.18 | 169.21 | 140.45 | 116.91 | 117.3 | 90.23 | 71.32 | 58.52 | 19.8 | 9.44 | 6.59 | 4.93 | 3.16 | 4.58 | 3.36 |
| 90 | | ABB | 3 | 1 | B | 0 | 21.6 | 132.89 | 159.85 | 131.86 | 111.19 | 86.95 | 71.67 | 65.45 | 57.39 | 40.42 | 31.23 | 16.1 | 7.71 | 4.66 | 5.87 | 5.52 | 3.34 | 0 |
| 91 | | ABB | 1 | 1 | A | 0 | 0 | 138.23 | 531.39 | 531.07 | 458.88 | 372.78 | 335.8 | 277.7 | 263.39 | 185.72 | 135.97 | 26.62 | 8.37 | 3.99 | 1.41 | 0 | 0 | 0 |
| 92 | | ABB | 2 | 1 | B | 0 | 0 | 64.65 | 400.06 | 431.24 | 424.73 | 403.47 | 371.59 | 319.51 | 301.15 | 201.01 | 159.12 | 33.26 | 9.48 | 4.6 | 1.93 | 0 | 0 | 0 |
| 93 | | ABB | 3 | 1 | B | 0 | 0 | 56.9 | 299.74 | 345.35 | 326.6 | 324.88 | 282.22 | 263.98 | 252.6 | 226.91 | 177.89 | 22.6 | 10.82 | 4.9 | 2.4 | 0 | 0 | 0 |
| 94 | | BBA | 3 | 1 | A | 0 | 0 | 0 | 37.98 | 99.04 | 209.96 | 384.35 | 419.87 | 394.23 | 358.85 | 232.51 | 180.44 | 47.26 | 17.04 | 6.52 | 2.41 | 0 | 0 | 0 |
| 95 | | BBA | 1 | 1 | B | 0 | 0 | 8.32 | 106.7 | 172 | 217.05 | 221.02 | 194.6 | 155.18 | 128.56 | 78.94 | 59.98 | 19.99 | 6.85 | 4.03 | 2.06 | 1.61 | 1.52 | 0 |
| 96 | | BBA | 2 | 1 | B | 0 | 0 | 233.32 | 365.52 | 361.77 | 325.96 | 288.49 | 242.38 | 158.05 | 169.5 | 132.12 | 102.92 | 24.69 | 10.87 | 5.77 | 2.46 | 1.02 | 0 | 0 |
| 97 | | BAB | 2 | 1 | A | 0 | 3.45 | 32.45 | 159.81 | 229.02 | 358.29 | 354.33 | 322.1 | 297.16 | 259.03 | 233.2 | 179.5 | 35.39 | 12.41 | 6.7 | 3.17 | 0 | 0 | 0 |
| 98 | | BAB | 1 | 1 | B | 0 | 466.07 | 541.06 | 454.4 | 379.3 | 305.95 | 292.49 | 263.05 | 202.86 | 165.26 | 126.35 | 91.28 | 23.95 | 9.31 | 4.4 | 2.27 | 1.38 | 0 | 0 |
| 99 | | BAB | 3 | 1 | B | 0 | 4.64 | 73.62 | 335.38 | 508.76 | 534.84 | 452.09 | 355.81 | 304.06 | 270.03 | 222.3 | 179.97 | 38.83 | 14.46 | 5.39 | 2.72 | 0 | 0 | 0 |
| 100 | | BAB | 2 | 1 | A | 0 | 0 | 5.8 | 29.69 | 36.28 | 48.47 | 68.02 | 65.49 | 74.01 | 74.11 | 123.42 | 141.58 | 95.34 | 27.26 | 8.81 | 5.42 | 1.56 | 0 | 0 |
| 101 | | BAB | 1 | 1 | B | 0 | 0 | 0 | 3.25 | 5.71 | 11.52 | 23.55 | 31.53 | 54.45 | 72.66 | 118.63 | 149.45 | 117.97 | 35.22 | 10.25 | 6.54 | 2.17 | 0 | 0 |
| 102 | | BAB | 3 | 1 | B | 0 | 0 | 2.99 | 24.84 | 33.82 | 35.88 | 44.21 | 57.04 | 69.68 | 99.44 | 128.09 | 133.46 | 81.96 | 30.37 | 10.3 | 4.83 | 1.58 | 0 | 0 |
| 103 | | BBA | 3 | 1 | A | 0 | 1.12 | 227.26 | 499.27 | 457.46 | 357.48 | 293.59 | 262.68 | 232.07 | 193.86 | 164.35 | 137.76 | 33.11 | 13.68 | 4.91 | 2.41 | 0 | 0 | 0 |
| 104 | | BBA | 1 | 1 | B | 0 | 10.45 | 365.06 | 322.56 | 303.1 | 287.94 | 267.31 | 221.01 | 191.3 | 167.62 | 130.08 | 94.21 | 24.89 | 8.61 | 4.66 | 1.87 | 1.21 | 0 | 0 |
| 105 | | BBA | 2 | 1 | B | 0 | 0 | 10.2 | 112.73 | 185.44 | 221.82 | 206.66 | 182 | 164.81 | 136.07 | 101.34 | 76.48 | 22.63 | 8.56 | 3.88 | 2.25 | 1.17 | 0 | 0 |
| 106 | | ABB | 1 | 1 | A | 0 | 9.28 | 272.22 | 567.23 | 590.98 | 505.56 | 440.26 | 335.69 | 328.99 | 274.69 | 178.82 | 137.7 | 41.58 | 15.29 | 13.09 | 5.11 | 1.52 | 0 | 0 |
| 107 | | ABB | 2 | 1 | B | 0 | 0 | 8.81 | 80.8 | 116.84 | 136.17 | 154.98 | 169.51 | 165.86 | 168.9 | 169.89 | 150.69 | 121.75 | 44.96 | 49.92 | 21.6 | 4.14 | 1.53 | 0 |
| 108 | | ABB | 3 | 1 | B | 0 | 2.46 | 524.75 | 674.24 | 581.48 | 480.77 | 422.39 | 341.26 | 305.9 | 262.71 | 211.5 | 172.17 | 49.69 | 15.98 | 8.33 | 4.5 | 1.03 | 0 | 0 |
| 109 | | BAB | 2 | 1 | A | 0 | 0 | 17.24 | 71.97 | 92.25 | 96.41 | 114.52 | 111.13 | 106.92 | 83.56 | 64.75 | 63 | 31.52 | 11.8 | 6.85 | 3.64 | 1.65 | 0 | 0 |

| Obs | sub | sequ | per | GRP | treat | c1 | c2 | c3 | c4 | c5 | c6 | c7 | c8 | c9 | c10 | c11 | c12 | c13 | c14 | c15 | c16 | c17 | c18 | c19 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 110 | (b) (6) | BAB | 1 | 1 | B | 0 | 0 | 6.34 | 36.14 | 51.03 | 55.55 | 62.51 | 62 | 60.28 | 69.65 | 73.56 | 75.86 | 47.66 | 21.03 | 12.68 | 5.06 | 1.99 | 0 | 0 |
| 111 | | BAB | 3 | 1 | B | 0 | 0 | 52.79 | 116.81 | 117.26 | 106.67 | 97.84 | 92.57 | 76.28 | 71.81 | 63.88 | 105.57 | 40.03 | 17.54 | 7.01 | 4.72 | 1.77 | 0 | 0 |
| 112 | | ABB | 1 | 1 | A | 0 | 0 | 42.39 | 241.92 | 335.48 | 275.41 | 196.43 | 162.76 | 131.32 | 107.49 | 68.63 | 48.45 | 14.23 | 3.84 | 1.52 | 0 | 0 | 0 | 0 |
| 113 | | ABB | 2 | 1 | B | 0 | 2.25 | 40.2 | 128.7 | 135.89 | 147.31 | 132.28 | 102.45 | 85.19 | 75.55 | 61.27 | 48.53 | 36.66 | 12.98 | 4.33 | 1.16 | 0 | 0 | 0 |
| 114 | | ABB | 3 | 1 | B | 0 | 0 | 24.65 | 158.84 | 173.1 | 178.08 | 167.37 | 148.86 | 141.43 | 117.67 | 90.31 | 62.35 | 32.23 | 9.35 | 2.94 | 0 | 0 | 0 | 0 |
| 115 | | BBA | 3 | 1 | A | 0 | 4.97 | 222.67 | 515.45 | 446.72 | 394.04 | 338.42 | 289.13 | 270.95 | 241.37 | 194.84 | 154.51 | 47.69 | 21.24 | 8.71 | 5.41 | 2.12 | 0 | 0 |
| 116 | | BBA | 1 | 1 | B | 0 | 1.55 | 155.09 | 356.9 | 299.74 | 274.85 | 236.66 | 213.4 | 212.33 | 198.83 | 161.93 | 133.01 | 38.48 | 15.62 | 9.11 | 3.84 | 1.14 | 0 | 0 |
| 117 | | BBA | 2 | 1 | B | 0 | 0 | 100.94 | 347.04 | 405.84 | 369.25 | 334.79 | 283.69 | 268.11 | 249.81 | 194.43 | 182.8 | 54.75 | 19.75 | 10.02 | 6.6 | 1.92 | 0 | 0 |
| 118 | | BBA | 3 | 1 | A | 0 | 0 | 82.24 | 683.59 | 695.65 | 562.28 | 442.23 | 349.87 | 275.48 | 224.91 | 150.77 | 141.74 | 36.33 | 22.31 | 14.72 | 4.99 | 2 | 0 | 0 |
| 119 | | BBA | 1 | 1 | B | 0 | 59.37 | 551.83 | 540.5 | 448.92 | 378.69 | 329.48 | 294.22 | 239.61 | 217.16 | 132.52 | 121.52 | 34.92 | 16.5 | 10.7 | 4.92 | 1.59 | 0 | 0 |
| 120 | | BBA | 2 | 1 | B | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| 121 | | ABB | 1 | 1 | A | 0 | 0 | 5.19 | 322.35 | 772.5 | 939.18 | 905.98 | 830.96 | 740.91 | 649.91 | 508.46 | 465.53 | 149.09 | 60.29 | 33.19 | 13.97 | 4.13 | 0 | 0 |
| 122 | | ABB | 2 | 1 | B | 0 | 5.46 | 66.91 | 733.57 | 854.25 | 848.49 | 764.55 | 745.51 | 630.57 | 571.99 | 469.71 | 419.82 | 122.24 | 50.91 | 27.73 | 12.16 | 3.81 | 0 | 0 |
| 123 | | ABB | 3 | 1 | B | 0 | 1.08 | 34.48 | 533.17 | 679.55 | 722.03 | 651.62 | 609.64 | 611.24 | 559.12 | 458.94 | 380.74 | 120.23 | 46.51 | 28.02 | 10.94 | 3.42 | 0 | 0 |
| 124 | | BAB | 2 | 1 | A | 0 | 0 | 19.26 | 82.31 | 149.01 | 199.94 | 300.27 | 412.47 | 401.77 | 309.5 | 242.29 | 238.74 | 79.07 | 22.36 | 8.88 | 3.06 | 0 | 0 | 0 |
| 125 | | BAB | 1 | 1 | B | 0 | 0 | 11.5 | 60.69 | 104.66 | 131.89 | 139.94 | 142.33 | 129.71 | 145.41 | 142.41 | 190.01 | 106.54 | 76.67 | 31.06 | 6.37 | 1.22 | 0 | 0 |
| 126 | | BAB | 3 | 1 | B | 0 | 1.14 | 25.52 | 160.84 | 275.55 | 350.26 | 378.73 | 375.22 | 332.77 | 307.18 | 246.53 | 156.35 | 38.56 | 13.71 | 4.67 | 1.38 | 0 | 0 | 0 |
| 127 | | BAB | 2 | 1 | A | 0 | 0 | 3.33 | 42.41 | 69.4 | 91.65 | 138.96 | 181.52 | 246.04 | 323.32 | 380.12 | 346.3 | 335.99 | 98.74 | 49.3 | 18.34 | 6.11 | 1.22 | 0 |
| 128 | | BAB | 1 | 1 | B | 0 | 14.3 | 716.12 | 780.18 | 781.32 | 693.12 | 636.71 | 574.06 | 522.5 | 461.17 | 372.97 | 321.63 | 107.19 | 49.06 | 31 | 10.81 | 3.93 | 1.04 | 0 |
| 129 | | BAB | 3 | 1 | B | 0 | 53.78 | 581.16 | 719.36 | 654.26 | 575.93 | 506.75 | 450.01 | 416.14 | 373.56 | 343.74 | 294.77 | 97.92 | 35.84 | 25.55 | 11.74 | 3.63 | 0 | 0 |
| 130 | | BBA | 3 | 1 | A | 0 | 3.95 | 262.55 | 204.26 | 179.81 | 145.35 | 124.03 | 99.88 | 78.41 | 67.99 | 60.58 | 45.41 | 24.1 | 7.74 | 3.37 | 1.75 | 0 | 0 | 0 |
| 131 | | BBA | 1 | 1 | B | 0 | 0 | 95.58 | 183.74 | 178.57 | 168.59 | 152.31 | 129.32 | 100.98 | 83.51 | 104.42 | 120.3 | 21.37 | 8.22 | 4.07 | 1.51 | 0 | 0 | 0 |
| 132 | | BBA | 2 | 1 | B | 0 | 0 | 1.2 | 3.89 | 24.94 | 42.29 | 54.72 | 63.55 | 67.26 | 65.74 | 51.12 | 77.57 | 62.43 | 16.15 | 15.51 | 3.39 | 1.19 | 0 | 0 |
| 133 | | ABB | 1 | 1 | A | 0 | 0 | 180.47 | 631.86 | 743.39 | 732.94 | 666.38 | 580.35 | 467.1 | 389.07 | 276.42 | 204.98 | 55.69 | 22.6 | 10.6 | 4.33 | 1.37 | 0 | 0 |
| 134 | | ABB | 2 | 1 | B | 0 | 0 | 241.38 | 516.81 | 533.12 | 468.85 | 428.29 | 386.02 | 351.67 | 320.22 | 256.18 | 224.83 | 78.25 | 29.94 | 8.89 | 4.41 | 2.13 | 1.17 | 0 |
| 135 | | ABB | 3 | 1 | B | 0 | 0 | 138.56 | 414.85 | 483.21 | 425.6 | 412.64 | 378.36 | 337.89 | 292.03 | 221.05 | 161.76 | 64.08 | 18.69 | 11.93 | 6.17 | 2.02 | 1.54 | 0 |
| 136 | | BAB | 2 | 1 | A | 0 | 0 | 8.86 | 136.18 | 203.15 | 249.82 | 233.14 | 220.02 | 188.5 | 181.18 | 165.72 | 149.59 | 68.83 | 25.98 | 10.08 | 3.49 | 0 | 0 | 0 |
| 137 | | BAB | 1 | 1 | B | 0 | 1.09 | 155.76 | 287.78 | 272.77 | 264.29 | 253.63 | 217.05 | 183.82 | 171.31 | 110.04 | 85.28 | 25.14 | 9.61 | 4.61 | 2.08 | 0 | 0 | 0 |
| 138 | | BAB | 3 | 1 | B | 0 | 0 | 18.96 | 136.8 | 156.15 | 180.24 | 178.25 | 178.95 | 167.11 | 158.55 | 125.63 | 119.93 | 42.51 | 16.19 | 6.29 | 3.1 | 0 | 0 | 0 |

| Obs | sub | sequ | per | GRP | treat | c1 | c2 | c3 | c4 | c5 | c6 | c7 | c8 | c9 | c10 | c11 | c12 | c13 | c14 | c15 | c16 | c17 | c18 | c19 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 139 | (b) (6) | ABB | 1 | 1 | A | 0 | 6.59 | 158.53 | 432.9 | 439.87 | 379.12 | 282.22 | 234.92 | 199.87 | 153.96 | 108.06 | 80.38 | 27.4 | 15.39 | 11.52 | 5.6 | 2.67 | 0 | 0 |
| 140 | | ABB | 2 | 1 | B | 0 | 0 | 121.39 | 377.74 | 355.74 | 329.28 | 298.95 | 248.64 | 247.16 | 197.02 | 149.05 | 104.18 | 30.34 | 14.63 | 7.74 | 4.63 | 2.65 | 1.12 | 0 |
| 141 | | ABB | 3 | 1 | B | 0 | 19.36 | 308.56 | 260.22 | 247.72 | 236.11 | 207.94 | 170.84 | 148.93 | 122.36 | 97.78 | 68.72 | 23.08 | 11.63 | 5.51 | 4.19 | 2.94 | 1.9 | 0 |

**Fed PHARMACOKINETIC DATASET**

| Obs | sub | sequ | per | group | treat | AUCT | AUCI | CMAX | TMAX | KE | THALF | trt | seq |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | (b) (6) | BBA | 1 | 1 | B | 792.90 | 797.89 | 273.74 | 2.00 | 0.26545 | 2.6112 | 2 | 3 |
| 2 | | BBA | 2 | 1 | B | 767.69 | 772.99 | 252.39 | 2.50 | 0.27932 | 2.4815 | 2 | 3 |
| 3 | | BBA | 3 | 1 | A | 941.81 | 947.36 | 358.81 | 2.50 | 0.24713 | 2.8048 | 1 | 3 |
| 4 | | ABB | 1 | 1 | A | 656.21 | 669.54 | 315.89 | 1.50 | 0.08039 | 8.6226 | 1 | 1 |
| 5 | | ABB | 2 | 1 | B | 484.55 | 540.15 | 189.99 | 1.50 | 0.03717 | 18.6471 | 2 | 1 |
| 6 | | ABB | 3 | 1 | B | 758.45 | 765.35 | 332.05 | 2.25 | 0.17276 | 4.0121 | 2 | 1 |
| 7 | | BAB | 1 | 1 | B | 567.04 | 571.54 | 274.58 | 1.50 | 0.32718 | 2.1186 | 2 | 2 |
| 8 | | BAB | 2 | 1 | A | 605.60 | 619.38 | 268.90 | 1.75 | 0.25804 | 2.6862 | 1 | 2 |
| 9 | | BAB | 3 | 1 | B | 638.70 | 641.96 | 264.59 | 1.75 | 0.35097 | 1.9750 | 2 | 2 |
| 10 | | BAB | 1 | 1 | B | 966.80 | 969.02 | 275.26 | 3.50 | 0.45197 | 1.5336 | 2 | 2 |
| 11 | | BAB | 2 | 1 | A | 1128.10 | 1135.07 | 466.94 | 1.50 | 0.41330 | 1.6771 | 1 | 2 |
| 12 | | BAB | 3 | 1 | B | 1130.14 | 1133.99 | 419.00 | 2.25 | 0.55266 | 1.2542 | 2 | 2 |
| 13 | | ABB | 1 | 1 | A | 770.30 | 778.10 | 322.89 | 1.50 | 0.35591 | 1.9476 | 1 | 1 |
| 14 | | ABB | 2 | 1 | B | 435.22 | . | 141.51 | 1.00 | . | . | 2 | 1 |
| 15 | | ABB | 3 | 1 | B | 777.43 | 779.94 | 266.23 | 1.75 | 0.38867 | 1.7834 | 2 | 1 |
| 16 | | BBA | 1 | 1 | B | 651.31 | 652.63 | 246.29 | 1.00 | 0.25251 | 2.7450 | 2 | 3 |
| 17 | | BBA | 2 | 1 | B | 697.24 | 703.23 | 316.03 | 1.75 | 0.37691 | 1.8390 | 2 | 3 |
| 18 | | BBA | 3 | 1 | A | 770.64 | 776.37 | 330.50 | 1.00 | 0.20138 | 3.4420 | 1 | 3 |
| 19 | | ABB | 1 | 1 | A | 838.07 | 842.60 | 334.46 | 2.25 | 0.26021 | 2.6638 | 1 | 1 |
| 20 | | ABB | 2 | 1 | B | 1012.34 | 1017.86 | 313.51 | 2.25 | 0.27064 | 2.5612 | 2 | 1 |
| 21 | | ABB | 3 | 1 | B | 830.00 | 833.99 | 244.08 | 3.50 | 0.33079 | 2.0954 | 2 | 1 |
| 22 | | BAB | 1 | 1 | B | 1236.88 | 1247.16 | 307.23 | 4.00 | 0.35656 | 1.9440 | 2 | 2 |

| Obs | sub | sequ | per | group | treat | AUCT | AUCI | CMAX | TMAX | KE | THALF | trt | seq |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 23 | (b) (6) | BAB | 2 | 1 | A | 1391.21 | 1398.64 | 524.26 | 2.25 | 0.28117 | 2.4652 | 1 | 2 |
| 24 | | BAB | 3 | 1 | B | 1985.02 | 1999.43 | 838.18 | 1.00 | 0.23616 | 2.9351 | 2 | 2 |
| 25 | | BBA | 1 | 1 | B | 831.03 | 833.88 | 277.05 | 2.25 | 0.39065 | 1.7743 | 2 | 3 |
| 26 | | BBA | 2 | 1 | B | 1010.92 | 1013.52 | 465.91 | 1.50 | 0.32368 | 2.1415 | 2 | 3 |
| 27 | | BBA | 3 | 1 | A | 729.77 | 734.86 | 121.97 | 3.50 | 0.35002 | 1.9803 | 1 | 3 |
| 28 | | BBA | 1 | 1 | B | 992.28 | 995.98 | 354.25 | 1.75 | 0.29228 | 2.3716 | 2 | 3 |
| 29 | | BBA | 2 | 1 | B | 880.68 | 886.94 | 265.13 | 1.75 | 0.28706 | 2.4146 | 2 | 3 |
| 30 | | BBA | 3 | 1 | A | 1172.57 | 1175.76 | 538.11 | 1.75 | 0.34582 | 2.0044 | 1 | 3 |
| 31 | | BAB | 1 | 1 | B | 1300.43 | 1302.13 | 557.00 | 2.00 | 0.28109 | 2.4660 | 2 | 2 |
| 32 | | BAB | 2 | 1 | A | 1255.23 | 1262.04 | 449.65 | 2.25 | 0.28223 | 2.4559 | 1 | 2 |
| 33 | | BAB | 3 | 1 | B | 1073.86 | 1099.67 | 400.34 | 1.75 | 0.06847 | 10.1231 | 2 | 2 |
| 34 | | ABB | 1 | 1 | A | 884.48 | 887.44 | 400.58 | 1.50 | 0.50394 | 1.3754 | 1 | 1 |
| 35 | | ABB | 2 | 1 | B | 931.94 | 936.14 | 390.58 | 1.75 | 0.43566 | 1.5910 | 2 | 1 |
| 36 | | ABB | 3 | 1 | B | 1006.55 | 1010.40 | 471.02 | 1.50 | 0.48027 | 1.4433 | 2 | 1 |
| 37 | | BAB | 1 | 1 | B | 681.30 | 685.34 | 290.94 | 1.50 | 0.44954 | 1.5419 | 2 | 2 |
| 38 | | BAB | 2 | 1 | A | 839.09 | 844.99 | 336.41 | 1.75 | 0.41543 | 1.6685 | 1 | 2 |
| 39 | | BAB | 3 | 1 | B | 714.91 | 716.52 | 204.02 | 1.75 | 0.41453 | 1.6721 | 2 | 2 |
| 40 | | BBA | 1 | 1 | B | 1243.86 | 1247.39 | 501.73 | 2.00 | 0.29044 | 2.3866 | 2 | 3 |
| 41 | | BBA | 2 | 1 | B | 989.87 | 994.63 | 379.96 | 2.00 | 0.25231 | 2.7472 | 2 | 3 |
| 42 | | BBA | 3 | 1 | A | 1237.54 | 1245.08 | 453.59 | 1.50 | 0.36957 | 1.8755 | 1 | 3 |
| 43 | | ABB | 1 | 1 | A | 1037.77 | 1040.03 | 576.26 | 1.50 | 0.53617 | 1.2928 | 1 | 1 |
| 44 | | ABB | 2 | 1 | B | 2954.78 | 2962.02 | 933.51 | 1.50 | 0.39411 | 1.7588 | 2 | 1 |
| 45 | | ABB | 3 | 1 | B | 1022.45 | 1025.22 | 518.00 | 1.50 | 0.52712 | 1.3150 | 2 | 1 |
| 46 | | BAB | 1 | 1 | B | 1090.69 | 1093.27 | 443.32 | 1.50 | 0.39782 | 1.7424 | 2 | 2 |
| 47 | | BAB | 2 | 1 | A | 1029.07 | 1032.83 | 566.07 | 1.50 | 0.28642 | 2.4201 | 1 | 2 |
| 48 | | BAB | 3 | 1 | B | 1113.30 | 1116.33 | 412.41 | 1.50 | 0.39360 | 1.7611 | 2 | 2 |
| 49 | | BBA | 1 | 1 | B | 641.74 | 646.16 | 297.29 | 1.50 | 0.38244 | 1.8124 | 2 | 3 |
| 50 | | BBA | 2 | 1 | B | 760.39 | 766.58 | 309.42 | 1.50 | 0.33069 | 2.0961 | 2 | 3 |
| 51 | | BBA | 3 | 1 | A | 484.09 | 493.76 | 114.42 | 4.00 | 0.34254 | 2.0236 | 1 | 3 |

| Obs | sub | sequ | per | group | treat | AUCT | AUCI | CMAX | TMAX | KE | THALF | trt | seq |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 52 | (b) (6) | ABB | 1 | 1 | A | 573.72 | 577.79 | 337.78 | 1.50 | 0.32899 | 2.1069 | 1 | 1 |
| 53 | | ABB | 2 | 1 | B | 411.11 | 451.21 | 241.51 | 1.50 | 0.03050 | 22.7256 | 2 | 1 |
| 54 | | ABB | 3 | 1 | B | 545.05 | 548.13 | 168.09 | 2.25 | 0.50363 | 1.3763 | 2 | 1 |
| 55 | | BBA | 1 | 1 | B | 830.72 | 834.55 | 264.11 | 3.00 | 0.29417 | 2.3563 | 2 | 3 |
| 56 | | BBA | 2 | 1 | B | 894.88 | 897.39 | 341.06 | 2.50 | 0.41491 | 1.6706 | 2 | 3 |
| 57 | | BBA | 3 | 1 | A | 932.26 | 935.23 | 354.02 | 2.75 | 0.36611 | 1.8933 | 1 | 3 |
| 58 | | ABB | 1 | 1 | A | 1108.49 | 1112.74 | 284.51 | 2.50 | 0.35043 | 1.9780 | 1 | 1 |
| 59 | | ABB | 2 | 1 | B | 905.22 | 909.25 | 197.40 | 3.50 | 0.41521 | 1.6694 | 2 | 1 |
| 60 | | ABB | 3 | 1 | B | 1084.79 | 1090.09 | 275.30 | 2.25 | 0.36791 | 1.8840 | 2 | 1 |
| 61 | | BAB | 1 | 1 | B | 1300.49 | 1307.26 | 469.31 | 1.50 | 0.28427 | 2.4384 | 2 | 2 |
| 62 | | BAB | 2 | 1 | A | 1289.51 | 1295.05 | 553.68 | 1.75 | 0.31024 | 2.2343 | 1 | 2 |
| 63 | | BAB | 3 | 1 | B | 1478.27 | 1483.26 | 590.53 | 1.75 | 0.30573 | 2.2672 | 2 | 2 |
| 64 | | ABB | 1 | 1 | A | 1291.28 | 1293.66 | 658.85 | 1.75 | 0.45149 | 1.5353 | 1 | 1 |
| 65 | | ABB | 2 | 1 | B | 1368.97 | 1373.29 | 543.69 | 1.75 | 0.48042 | 1.4428 | 2 | 1 |
| 66 | | ABB | 3 | 1 | B | 1195.53 | 1199.69 | 393.57 | 1.75 | 0.52368 | 1.3236 | 2 | 1 |
| 67 | | BBA | 1 | 1 | B | 1725.60 | 1732.56 | 558.99 | 1.50 | 0.16239 | 4.2684 | 2 | 3 |
| 68 | | BBA | 2 | 1 | B | 1554.21 | 1564.86 | 397.73 | 2.25 | 0.15941 | 4.3481 | 2 | 3 |
| 69 | | BBA | 3 | 1 | A | 1954.32 | 1956.87 | 556.11 | 2.25 | 0.29136 | 2.3790 | 1 | 3 |
| 70 | | BAB | 1 | 1 | B | 911.40 | 916.69 | 161.04 | 3.50 | 0.40611 | 1.7068 | 2 | 2 |
| 71 | | BAB | 2 | 1 | A | 832.99 | 836.38 | 243.03 | 2.25 | 0.37177 | 1.8645 | 1 | 2 |
| 72 | | BAB | 3 | 1 | B | 902.71 | 908.05 | 190.79 | 2.50 | 0.33099 | 2.0942 | 2 | 2 |
| 73 | | BAB | 1 | 1 | B | 859.96 | . | 233.06 | 4.00 | . | . | 2 | 2 |
| 74 | | BAB | 2 | 1 | A | 700.60 | . | 81.23 | 6.00 | . | . | 1 | 2 |
| 75 | | BAB | 3 | 1 | B | 801.68 | . | 220.70 | 4.00 | . | . | 2 | 2 |
| 76 | | ABB | 1 | 1 | A | 1122.75 | 1128.55 | 496.28 | 1.50 | 0.30538 | 2.2698 | 1 | 1 |
| 77 | | ABB | 2 | 1 | B | 791.19 | 799.67 | 335.46 | 1.50 | 0.21768 | 3.1842 | 2 | 1 |
| 78 | | ABB | 3 | 1 | B | 962.66 | 967.07 | 408.86 | 1.50 | 0.30619 | 2.2638 | 2 | 1 |
| 79 | | BBA | 1 | 1 | B | 611.56 | 616.10 | 203.83 | 2.25 | 0.42261 | 1.6402 | 2 | 3 |
| 80 | | BBA | 2 | 1 | B | 622.62 | 628.02 | 277.35 | 1.00 | 0.33284 | 2.0825 | 2 | 3 |

| Obs | sub | sequ | per | group | treat | AUCT | AUCI | CMAX | TMAX | KE | THALF | trt | seq |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 81 | (b) (6) | BBA | 3 | 1 | A | 945.26 | 951.09 | 344.71 | 2.25 | 0.43163 | 1.6059 | 1 | 3 |
| 82 | | BAB | 1 | 1 | B | 1210.55 | 1223.39 | 361.66 | 1.75 | 0.30651 | 2.2614 | 2 | 2 |
| 83 | | BAB | 2 | 1 | A | 769.79 | 786.27 | 192.50 | 2.50 | 0.24356 | 2.8459 | 1 | 2 |
| 84 | | BAB | 3 | 1 | B | 879.41 | 896.99 | 201.91 | 2.05 | 0.26721 | 2.5940 | 2 | 2 |
| 85 | | BBA | 1 | 1 | B | 1167.92 | 1171.94 | 245.23 | 3.00 | 0.25470 | 2.7215 | 2 | 3 |
| 86 | | BBA | 2 | 1 | B | 1221.61 | 1231.35 | 252.79 | 4.00 | 0.37326 | 1.8570 | 2 | 3 |
| 87 | | BBA | 3 | 1 | A | 1170.87 | 1178.37 | 271.96 | 3.00 | 0.44945 | 1.5422 | 1 | 3 |
| 88 | | ABB | 1 | 1 | A | 1034.24 | 1037.23 | 230.27 | 4.00 | 0.37527 | 1.8471 | 1 | 1 |
| 89 | | ABB | 2 | 1 | B | 655.28 | . | 204.09 | 1.50 | . | . | 2 | 1 |
| 90 | | ABB | 3 | 1 | B | 455.77 | 525.45 | 159.85 | 1.50 | 0.04925 | 14.0744 | 2 | 1 |
| 91 | | ABB | 1 | 1 | A | 1203.41 | 1206.38 | 531.39 | 1.50 | 0.47775 | 1.4509 | 1 | 1 |
| 92 | | ABB | 2 | 1 | B | 1178.93 | 1183.90 | 431.24 | 1.75 | 0.39792 | 1.7419 | 2 | 1 |
| 93 | | ABB | 3 | 1 | B | 1036.19 | 1042.50 | 345.35 | 1.75 | 0.37598 | 1.8436 | 2 | 1 |
| 94 | | BBA | 1 | 1 | B | 530.49 | . | 221.02 | 2.25 | . | . | 2 | 3 |
| 95 | | BBA | 2 | 1 | B | 948.25 | 950.95 | 365.52 | 1.50 | 0.32068 | 2.1615 | 2 | 3 |
| 96 | | BBA | 3 | 1 | A | 1011.53 | 1016.49 | 419.87 | 2.50 | 0.48898 | 1.4175 | 1 | 3 |
| 97 | | BAB | 1 | 1 | B | 1361.06 | 1362.22 | 541.06 | 1.00 | 0.44505 | 1.5575 | 2 | 2 |
| 98 | | BAB | 2 | 1 | A | 1018.39 | 1027.88 | 358.29 | 2.00 | 0.34119 | 2.0315 | 1 | 2 |
| 99 | | BAB | 3 | 1 | B | 1261.24 | 1266.78 | 534.84 | 2.00 | 0.44813 | 1.5468 | 2 | 2 |
| 100 | | BAB | 1 | 1 | B | 657.12 | 665.55 | 149.45 | 4.00 | 0.26119 | 2.6538 | 2 | 2 |
| 101 | | BAB | 2 | 1 | A | 635.78 | 641.23 | 141.58 | 4.00 | 0.29179 | 2.3755 | 1 | 2 |
| 102 | | BAB | 3 | 1 | B | 602.04 | 607.03 | 133.46 | 4.00 | 0.30772 | 2.2525 | 2 | 2 |
| 103 | | BBA | 1 | 1 | B | 956.39 | 957.48 | 365.06 | 1.00 | 0.44287 | 1.5651 | 2 | 3 |
| 104 | | BBA | 2 | 1 | B | 564.08 | 569.91 | 221.82 | 2.00 | 0.19462 | 3.5616 | 2 | 3 |
| 105 | | BBA | 3 | 1 | A | 1135.12 | 1140.20 | 499.27 | 1.50 | 0.44426 | 1.5602 | 1 | 3 |
| 106 | | ABB | 1 | 1 | A | 1426.67 | 1430.79 | 590.98 | 1.75 | 0.35089 | 1.9754 | 1 | 1 |
| 107 | | ABB | 2 | 1 | B | 1086.21 | 1090.76 | 169.89 | 3.50 | 0.24616 | 2.8159 | 2 | 1 |
| 108 | | ABB | 3 | 1 | B | 1632.43 | 1635.54 | 674.24 | 1.50 | 0.34270 | 2.0226 | 2 | 1 |
| 109 | | BAB | 1 | 1 | B | 429.19 | 434.71 | 75.86 | 4.00 | 0.31893 | 2.1734 | 2 | 2 |

| Obs | sub | sequ | per | group | treat | AUCT | AUCI | CMAX | TMAX | KE | THALF | trt | seq |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 110 | (b) (6) | BAB | 2 | 1 | A | 422.94 | 429.22 | 114.52 | 2.25 | 0.24644 | 2.8127 | 1 | 2 |
| 111 | | BAB | 3 | 1 | B | 530.55 | 538.29 | 117.26 | 1.75 | 0.23165 | 2.9922 | 2 | 2 |
| 112 | | ABB | 1 | 1 | A | 560.11 | 562.39 | 335.48 | 1.75 | 0.59482 | 1.1653 | 1 | 1 |
| 113 | | ABB | 2 | 1 | B | 449.00 | 450.99 | 147.31 | 2.00 | 0.60375 | 1.1481 | 2 | 1 |
| 114 | | ABB | 3 | 1 | B | 527.42 | 532.26 | 178.08 | 2.00 | 0.59862 | 1.1579 | 2 | 1 |
| 115 | | BBA | 1 | 1 | B | 983.41 | 986.75 | 356.90 | 1.50 | 0.33348 | 2.0786 | 2 | 3 |
| 116 | | BBA | 2 | 1 | B | 1208.31 | 1215.17 | 405.84 | 1.75 | 0.28593 | 2.4242 | 2 | 3 |
| 117 | | BBA | 3 | 1 | A | 1301.50 | 1310.52 | 515.45 | 1.50 | 0.23610 | 2.9358 | 1 | 3 |
| 118 | | BBA | 1 | 1 | B | 1372.79 | 1377.85 | 551.83 | 1.00 | 0.30681 | 2.2592 | 2 | 3 |
| 119 | | BBA | 2 | 1 | B | . | . | . | . | . | . | 2 | 3 |
| 120 | | BBA | 3 | 1 | A | 1381.44 | 1387.75 | 695.65 | 1.75 | 0.30206 | 2.2947 | 1 | 3 |
| 121 | | ABB | 1 | 1 | A | 2786.03 | 2797.77 | 939.18 | 2.00 | 0.33999 | 2.0387 | 1 | 1 |
| 122 | | ABB | 2 | 1 | B | 2692.10 | 2703.27 | 854.25 | 1.75 | 0.32773 | 2.1150 | 2 | 1 |
| 123 | | ABB | 3 | 1 | B | 2380.48 | 2389.33 | 722.03 | 2.00 | 0.35317 | 1.9626 | 2 | 1 |
| 124 | | BAB | 1 | 1 | B | 1003.98 | 1006.01 | 190.01 | 4.00 | 0.52919 | 1.3098 | 2 | 2 |
| 125 | | BAB | 2 | 1 | A | 1165.67 | 1171.98 | 412.47 | 2.50 | 0.49721 | 1.3941 | 1 | 2 |
| 126 | | BAB | 3 | 1 | B | 1050.93 | 1053.39 | 378.73 | 2.25 | 0.57401 | 1.2076 | 2 | 2 |
| 127 | | BAB | 1 | 1 | B | 2655.84 | 2661.02 | 781.32 | 1.75 | 0.19097 | 3.6296 | 2 | 2 |
| 128 | | BAB | 2 | 1 | A | 2008.26 | 2013.52 | 380.12 | 3.50 | 0.22236 | 3.1173 | 1 | 2 |
| 129 | | BAB | 3 | 1 | B | 2279.52 | 2290.53 | 719.36 | 1.50 | 0.32069 | 2.1614 | 2 | 2 |
| 130 | | BBA | 1 | 1 | B | 601.87 | 605.48 | 183.74 | 1.50 | 0.43263 | 1.6022 | 2 | 3 |
| 131 | | BBA | 2 | 1 | B | 414.18 | 416.82 | 77.57 | 4.00 | 0.38996 | 1.7775 | 2 | 3 |
| 132 | | BBA | 3 | 1 | A | 551.44 | 555.25 | 262.55 | 1.00 | 0.42151 | 1.6445 | 1 | 3 |
| 133 | | ABB | 1 | 1 | A | 1858.57 | 1861.77 | 743.39 | 1.75 | 0.37173 | 1.8646 | 1 | 1 |
| 134 | | ABB | 2 | 1 | B | 1650.54 | 1660.98 | 533.12 | 1.75 | 0.10548 | 6.5717 | 2 | 1 |
| 135 | | ABB | 3 | 1 | B | 1382.70 | 1383.98 | 483.21 | 1.75 | 0.30049 | 2.3067 | 2 | 1 |
| 136 | | BAB | 1 | 1 | B | 790.89 | 796.39 | 287.78 | 1.50 | 0.38261 | 1.8116 | 2 | 2 |
| 137 | | BAB | 2 | 1 | A | 880.22 | 887.48 | 249.82 | 2.00 | 0.49460 | 1.4014 | 1 | 2 |
| 138 | | BAB | 3 | 1 | B | 681.22 | 687.57 | 180.24 | 2.00 | 0.44801 | 1.5472 | 2 | 2 |

| Obs | sub | sequ | per | group | treat | AUCT | AUCI | CMAX | TMAX | KE | THALF | trt | seq |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 139 | (b) (6) | ABB | 1 | 1 | A | 971.90 | 982.72 | 439.87 | 1.75 | 0.23393 | 2.9630 | 1 | 1 |
| 140 | | ABB | 2 | 1 | B | 990.61 | 1000.03 | 377.74 | 1.50 | 0.11675 | 5.9369 | 2 | 1 |
| 141 | | ABB | 3 | 1 | B | 813.35 | 842.34 | 308.56 | 1.00 | 0.06428 | 10.7825 | 2 | 1 |

### 4.6.2 Fed Study Output

The SAS System 1

| Obs | SUBJ | SEQU | PER | GROUP | TRT | AUCT | AUCI | CMAX | TMAX | KEL | THALF | SEQ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | (b) (6) BBA | 3 | 1 | A | | 941.81 | 947.36 | 358.81 | 2.50 | 0.24713 | 2.8048 | 2 |
| 2 | ABB | 1 | 1 | A | | 656.21 | 669.54 | 315.89 | 1.50 | 0.08039 | 8.6226 | 1 |
| 3 | BAB | 2 | 1 | A | | 605.60 | 619.38 | 268.90 | 1.75 | 0.25804 | 2.6862 | 3 |
| 4 | BAB | 2 | 1 | A | | 1128.10 | 1135.07 | 466.94 | 1.50 | 0.41330 | 1.6771 | 3 |
| 5 | ABB | 1 | 1 | A | | 770.30 | 778.10 | 322.89 | 1.50 | 0.35591 | 1.9476 | 1 |
| 6 | BBA | 3 | 1 | A | | 770.64 | 776.37 | 330.50 | 1.00 | 0.20138 | 3.4420 | 2 |
| 7 | ABB | 1 | 1 | A | | 838.07 | 842.60 | 334.46 | 2.25 | 0.26021 | 2.6638 | 1 |
| 8 | BAB | 2 | 1 | A | | 1391.21 | 1398.64 | 524.26 | 2.25 | 0.28117 | 2.4652 | 3 |
| 9 | BBA | 3 | 1 | A | | 729.77 | 734.86 | 121.97 | 3.50 | 0.35002 | 1.9803 | 2 |
| 10 | BBA | 3 | 1 | A | | 1172.57 | 1175.76 | 538.11 | 1.75 | 0.34582 | 2.0044 | 2 |
| 11 | BAB | 2 | 1 | A | | 1255.23 | 1262.04 | 449.65 | 2.25 | 0.28223 | 2.4559 | 3 |
| 12 | ABB | 1 | 1 | A | | 884.48 | 887.44 | 400.58 | 1.50 | 0.50394 | 1.3754 | 1 |
| 13 | BAB | 2 | 1 | A | | 839.09 | 844.99 | 336.41 | 1.75 | 0.41543 | 1.6685 | 3 |
| 14 | BBA | 3 | 1 | A | | 1237.54 | 1245.08 | 453.59 | 1.50 | 0.36957 | 1.8755 | 2 |
| 15 | ABB | 1 | 1 | A | | 1037.77 | 1040.03 | 576.26 | 1.50 | 0.53617 | 1.2928 | 1 |
| 16 | BAB | 2 | 1 | A | | 1029.07 | 1032.83 | 566.07 | 1.50 | 0.28642 | 2.4201 | 3 |
| 17 | BBA | 3 | 1 | A | | 484.09 | 493.76 | 114.42 | 4.00 | 0.34254 | 2.0236 | 2 |
| 18 | ABB | 1 | 1 | A | | 573.72 | 577.79 | 337.78 | 1.50 | 0.32899 | 2.1069 | 1 |
| 19 | BBA | 3 | 1 | A | | 932.26 | 935.23 | 354.02 | 2.75 | 0.36611 | 1.8933 | 2 |
| 20 | ABB | 1 | 1 | A | | 1108.49 | 1112.74 | 284.51 | 2.50 | 0.35043 | 1.9780 | 1 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 21 | (b) (6) | BAB | 2 | 1 | A | 1289.51 | 1295.05 | 553.68 | 1.75 | 0.31024 | 2.2343 | 3 |
| 22 | | ABB | 1 | 1 | A | 1291.28 | 1293.66 | 658.85 | 1.75 | 0.45149 | 1.5353 | 1 |
| 23 | | BBA | 3 | 1 | A | 1954.32 | 1956.87 | 556.11 | 2.25 | 0.29136 | 2.3790 | 2 |
| 24 | | BAB | 2 | 1 | A | 832.99 | 836.38 | 243.03 | 2.25 | 0.37177 | 1.8645 | 3 |
| 25 | | BAB | 2 | 1 | A | 700.60 | . | 81.23 | 6.00 | . | . | 3 |
| 26 | | ABB | 1 | 1 | A | 1122.75 | 1128.55 | 496.28 | 1.50 | 0.30538 | 2.2698 | 1 |
| 27 | | BBA | 3 | 1 | A | 945.26 | 951.09 | 344.71 | 2.25 | 0.43163 | 1.6059 | 2 |
| 28 | | BAB | 2 | 1 | A | 769.79 | 786.27 | 192.50 | 2.50 | 0.24356 | 2.8459 | 3 |
| 29 | | BBA | 3 | 1 | A | 1170.87 | 1178.37 | 271.96 | 3.00 | 0.44945 | 1.5422 | 2 |
| 30 | | ABB | 1 | 1 | A | 1034.24 | 1037.23 | 230.27 | 4.00 | 0.37527 | 1.8471 | 1 |
| 31 | | ABB | 1 | 1 | A | 1203.41 | 1206.38 | 531.39 | 1.50 | 0.47775 | 1.4509 | 1 |
| 32 | | BBA | 3 | 1 | A | 1011.53 | 1016.49 | 419.87 | 2.50 | 0.48898 | 1.4175 | 2 |
| 33 | | BAB | 2 | 1 | A | 1018.39 | 1027.88 | 358.29 | 2.00 | 0.34119 | 2.0315 | 3 |
| 34 | | BAB | 2 | 1 | A | 635.78 | 641.23 | 141.58 | 4.00 | 0.29179 | 2.3755 | 3 |
| 35 | | BBA | 3 | 1 | A | 1135.12 | 1140.20 | 499.27 | 1.50 | 0.44426 | 1.5602 | 2 |
| 36 | | ABB | 1 | 1 | A | 1426.67 | 1430.79 | 590.98 | 1.75 | 0.35089 | 1.9754 | 1 |
| 37 | | BAB | 2 | 1 | A | 422.94 | 429.22 | 114.52 | 2.25 | 0.24644 | 2.8127 | 3 |
| 38 | | ABB | 1 | 1 | A | 560.11 | 562.39 | 335.48 | 1.75 | 0.59482 | 1.1653 | 1 |
| 39 | | BBA | 3 | 1 | A | 1301.50 | 1310.52 | 515.45 | 1.50 | 0.23610 | 2.9358 | 2 |
| 40 | | BBA | 3 | 1 | A | 1381.44 | 1387.75 | 695.65 | 1.75 | 0.30206 | 2.2947 | 2 |
| 41 | | ABB | 1 | 1 | A | 2786.03 | 2797.77 | 939.18 | 2.00 | 0.33999 | 2.0387 | 1 |
| 42 | | BAB | 2 | 1 | A | 1165.67 | 1171.98 | 412.47 | 2.50 | 0.49721 | 1.3941 | 3 |
| 43 | | BAB | 2 | 1 | A | 2008.26 | 2013.52 | 380.12 | 3.50 | 0.22236 | 3.1173 | 3 |
| 44 | | BBA | 3 | 1 | A | 551.44 | 555.25 | 262.55 | 1.00 | 0.42151 | 1.6445 | 2 |
| 45 | | ABB | 1 | 1 | A | 1858.57 | 1861.77 | 743.39 | 1.75 | 0.37173 | 1.8646 | 1 |
| 46 | | BAB | 2 | 1 | A | 880.22 | 887.48 | 249.82 | 2.00 | 0.49460 | 1.4014 | 3 |
| 47 | | ABB | 1 | 1 | A | 971.90 | 982.72 | 439.87 | 1.75 | 0.23393 | 2.9630 | 1 |
| 48 | | BBA | 1 | 1 | B | 792.90 | 797.89 | 273.74 | 2.00 | 0.26545 | 2.6112 | 2 |
| 49 | | ABB | 2 | 1 | B | 484.55 | 540.15 | 189.99 | 1.50 | 0.03717 | 18.6471 | 1 |
| 50 | | BAB | 1 | 1 | B | 567.04 | 571.54 | 274.58 | 1.50 | 0.32718 | 2.1186 | 3 |
| 51 | | BAB | 1 | 1 | B | 966.80 | 969.02 | 275.26 | 3.50 | 0.45197 | 1.5336 | 3 |
| 52 | | ABB | 2 | 1 | B | 435.22 | . | 141.51 | 1.00 | . | . | 1 |
| 53 | | BBA | 1 | 1 | B | 651.31 | 652.63 | 246.29 | 1.00 | 0.25251 | 2.7450 | 2 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 54 | (b) (6) | ABB | 2 | 1 | B | 1012.34 | 1017.86 | 313.51 | 2.25 | 0.27064 | 2.5612 | 1 |
| 55 | | BAB | 1 | 1 | B | 1236.88 | 1247.16 | 307.23 | 4.00 | 0.35656 | 1.9440 | 3 |
| 56 | | BBA | 1 | 1 | B | 831.03 | 833.88 | 277.05 | 2.25 | 0.39065 | 1.7743 | 2 |
| 57 | | BBA | 1 | 1 | B | 992.28 | 995.98 | 354.25 | 1.75 | 0.29228 | 2.3716 | 2 |
| 58 | | BAB | 1 | 1 | B | 1300.43 | 1302.13 | 557.00 | 2.00 | 0.28109 | 2.4660 | 3 |
| 59 | | ABB | 2 | 1 | B | 931.94 | 936.14 | 390.58 | 1.75 | 0.43566 | 1.5910 | 1 |
| 60 | | BAB | 1 | 1 | B | 681.30 | 685.34 | 290.94 | 1.50 | 0.44954 | 1.5419 | 3 |
| 61 | | BBA | 1 | 1 | B | 1243.86 | 1247.39 | 501.73 | 2.00 | 0.29044 | 2.3866 | 2 |

| Obs | SUBJ | SEQU | PER | GROUP | TRT | AUCT | AUCI | CMAX | TMAX | KEL | THALF | SEQ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 62 | (b) (6) | ABB | 2 | 1 | B | 2954.78 | 2962.02 | 933.51 | 1.50 | 0.39411 | 1.7588 | 1 |
| 63 | | BAB | 1 | 1 | B | 1090.69 | 1093.27 | 443.32 | 1.50 | 0.39782 | 1.7424 | 3 |
| 64 | | BBA | 1 | 1 | B | 641.74 | 646.16 | 297.29 | 1.50 | 0.38244 | 1.8124 | 2 |
| 65 | | ABB | 2 | 1 | B | 411.11 | 451.21 | 241.51 | 1.50 | 0.03050 | 22.7256 | 1 |
| 66 | | BBA | 1 | 1 | B | 830.72 | 834.55 | 264.11 | 3.00 | 0.29417 | 2.3563 | 2 |
| 67 | | ABB | 2 | 1 | B | 905.22 | 909.25 | 197.40 | 3.50 | 0.41521 | 1.6694 | 1 |
| 68 | | BAB | 1 | 1 | B | 1300.49 | 1307.26 | 469.31 | 1.50 | 0.28427 | 2.4384 | 3 |
| 69 | | ABB | 2 | 1 | B | 1368.97 | 1373.29 | 543.69 | 1.75 | 0.48042 | 1.4428 | 1 |
| 70 | | BBA | 1 | 1 | B | 1725.60 | 1732.56 | 558.99 | 1.50 | 0.16239 | 4.2684 | 2 |
| 71 | | BAB | 1 | 1 | B | 911.40 | 916.69 | 161.04 | 3.50 | 0.40611 | 1.7068 | 3 |
| 72 | | BAB | 1 | 21 | B | 859.96 | . | 233.06 | 4.00 | . | . | 3 |
| 73 | | ABB | 2 | 1 | B | 791.19 | 799.67 | 335.46 | 1.50 | 0.21768 | 3.1842 | 1 |
| 74 | | BBA | 1 | 1 | B | 611.56 | 616.10 | 203.83 | 2.25 | 0.42261 | 1.6402 | 2 |
| 75 | | BAB | 1 | 1 | B | 1210.55 | 1223.39 | 361.66 | 1.75 | 0.30651 | 2.2614 | 3 |
| 76 | | BBA | 1 | 1 | B | 1167.92 | 1171.94 | 245.23 | 3.00 | 0.25470 | 2.7215 | 2 |
| 77 | | ABB | 2 | 1 | B | 655.28 | . | 204.09 | 1.50 | . | . | 1 |
| 78 | | ABB | 2 | 1 | B | 1178.93 | 1183.90 | 431.24 | 1.75 | 0.39792 | 1.7419 | 1 |
| 79 | | BBA | 1 | 1 | B | 530.49 | . | 221.02 | 2.25 | . | . | 2 |
| 80 | | BAB | 1 | 1 | B | 1361.06 | 1362.22 | 541.06 | 1.00 | 0.44505 | 1.5575 | 3 |
| 81 | | BAB | 1 | 1 | B | 657.12 | 665.55 | 149.45 | 4.00 | 0.26119 | 2.6538 | 3 |
| 82 | | BBA | 1 | 1 | B | 956.39 | 957.48 | 365.06 | 1.00 | 0.44287 | 1.5651 | 2 |
| 83 | | ABB | 2 | 1 | B | 1086.21 | 1090.76 | 169.89 | 3.50 | 0.24616 | 2.8159 | 1 |
| 84 | | BAB | 1 | 1 | B | 429.19 | 434.71 | 75.86 | 4.00 | 0.31893 | 2.1734 | 3 |
| 85 | | ABB | 2 | 1 | B | 449.00 | 450.99 | 147.31 | 2.00 | 0.60375 | 1.1481 | 1 |
| 86 | | BBA | 1 | 1 | B | 983.41 | 986.75 | 356.90 | 1.50 | 0.33348 | 2.0786 | 2 |
| 87 | | BBA | 1 | 1 | B | 1372.79 | 1377.85 | 551.83 | 1.00 | 0.30681 | 2.2592 | 2 |
| 88 | | ABB | 2 | 1 | B | 2692.10 | 2703.27 | 854.25 | 1.75 | 0.32773 | 2.1150 | 1 |
| 89 | | BAB | 1 | 1 | B | 1003.98 | 1006.01 | 190.01 | 4.00 | 0.52919 | 1.3098 | 3 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 90 | (b) (6) | BAB | 1 | 1 | B | 2655.84 | 2661.02 | 781.32 | 1.75 | 0.19097 | 3.6296 | 3 |
| 91 | | BBA | 1 | 1 | B | 601.87 | 605.48 | 183.74 | 1.50 | 0.43263 | 1.6022 | 2 |
| 92 | | ABB | 2 | 1 | B | 1650.54 | 1660.98 | 533.12 | 1.75 | 0.10548 | 6.5717 | 1 |
| 93 | | BAB | 1 | 1 | B | 790.89 | 796.39 | 287.78 | 1.50 | 0.38261 | 1.8116 | 3 |
| 94 | | ABB | 2 | 1 | B | 990.61 | 1000.03 | 377.74 | 1.50 | 0.11675 | 5.9369 | 1 |
| 95 | | BBA | 2 | 1 | B | 767.69 | 772.99 | 252.39 | 2.50 | 0.27932 | 2.4815 | 2 |
| 96 | | ABB | 3 | 1 | B | 758.45 | 765.35 | 332.05 | 2.25 | 0.17276 | 4.0121 | 1 |
| 97 | | BAB | 3 | 1 | B | 638.70 | 641.96 | 264.59 | 1.75 | 0.35097 | 1.9750 | 3 |
| 98 | | BAB | 3 | 1 | B | 1130.14 | 1133.99 | 419.00 | 2.25 | 0.55266 | 1.2542 | 3 |
| 99 | | ABB | 3 | 1 | B | 777.43 | 779.94 | 266.23 | 1.75 | 0.38867 | 1.7834 | 1 |
| 100 | | BBA | 2 | 1 | B | 697.24 | 703.23 | 316.03 | 1.75 | 0.37691 | 1.8390 | 2 |
| 101 | | ABB | 3 | 1 | B | 830.00 | 833.99 | 244.08 | 3.50 | 0.33079 | 2.0954 | 1 |
| 102 | | BAB | 3 | 1 | B | 1985.02 | 1999.43 | 838.18 | 1.00 | 0.23616 | 2.9351 | 3 |
| 103 | | BBA | 2 | 1 | B | 1010.92 | 1013.52 | 465.91 | 1.50 | 0.32368 | 2.1415 | 2 |
| 104 | | BBA | 2 | 1 | B | 880.68 | 886.94 | 265.13 | 1.75 | 0.28706 | 2.4146 | 2 |
| 105 | | BAB | 3 | 1 | B | 1073.86 | 1099.67 | 400.34 | 1.75 | 0.06847 | 10.1231 | 3 |
| 106 | | ABB | 3 | 1 | B | 1006.55 | 1010.40 | 471.02 | 1.50 | 0.48027 | 1.4433 | 1 |
| 107 | | BAB | 3 | 1 | B | 714.91 | 716.52 | 204.02 | 1.75 | 0.41453 | 1.6721 | 3 |
| 108 | | BBA | 2 | 1 | B | 989.87 | 994.63 | 379.96 | 2.00 | 0.25231 | 2.7472 | 2 |
| 109 | | ABB | 3 | 1 | B | 1022.45 | 1025.22 | 518.00 | 1.50 | 0.52712 | 1.3150 | 1 |
| 110 | | BAB | 3 | 1 | B | 1113.30 | 1116.33 | 412.41 | 1.50 | 0.39360 | 1.7611 | 3 |
| 111 | | BBA | 2 | 1 | B | 760.39 | 766.58 | 309.42 | 1.50 | 0.33069 | 2.0961 | 2 |
| 112 | | ABB | 3 | 1 | B | 545.05 | 548.13 | 168.09 | 2.25 | 0.50363 | 1.3763 | 1 |
| 113 | | BBA | 2 | 1 | B | 894.88 | 897.39 | 341.06 | 2.50 | 0.41491 | 1.6706 | 2 |
| 114 | | ABB | 3 | 1 | B | 1084.79 | 1090.09 | 275.30 | 2.25 | 0.36791 | 1.8840 | 1 |
| 115 | | BAB | 3 | 1 | B | 1478.27 | 1483.26 | 590.53 | 1.75 | 0.30573 | 2.2672 | 3 |
| 116 | | ABB | 3 | 1 | B | 1195.53 | 1199.69 | 393.57 | 1.75 | 0.52368 | 1.3236 | 1 |
| 117 | | BBA | 2 | 1 | B | 1554.21 | 1564.86 | 397.73 | 2.25 | 0.15941 | 4.3481 | 2 |
| 118 | | BAB | 3 | 1 | B | 902.71 | 908.05 | 190.79 | 2.50 | 0.33099 | 2.0942 | 3 |
| 119 | | BAB | 3 | 1 | B | 801.68 | . | 220.70 | 4.00 | . | . | 3 |
| 120 | | ABB | 3 | 1 | B | 962.66 | 967.07 | 408.86 | 1.50 | 0.30619 | 2.2638 | 1 |
| 121 | | BBA | 2 | 1 | B | 622.62 | 628.02 | 277.35 | 1.00 | 0.33284 | 2.0825 | 2 |
| 122 | | BAB | 3 | 1 | B | 879.41 | 896.99 | 201.91 | 2.05 | 0.26721 | 2.5940 | 3 |

The SAS System

| Obs | SUBJ | SEQU | PER | GROUP | TRT | AUCT | AUCI | CMAX | TMAX | KEL | THALF | SEQ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 123 | (b) (6) | BBA | 2 | 1 | B | 1221.61 | 1231.35 | 252.79 | 4.00 | 0.37326 | 1.8570 | 2 |
| 124 | | ABB | 3 | 1 | B | 455.77 | 525.45 | 159.85 | 1.50 | 0.04925 | 14.0744 | 1 |
| 125 | | ABB | 3 | 1 | B | 1036.19 | 1042.50 | 345.35 | 1.75 | 0.37598 | 1.8436 | 1 |
| 126 | | BBA | 2 | 1 | B | 948.25 | 950.95 | 365.52 | 1.50 | 0.32068 | 2.1615 | 2 |
| 127 | | BAB | 3 | 1 | B | 1261.24 | 1266.78 | 534.84 | 2.00 | 0.44813 | 1.5468 | 3 |
| 128 | | BAB | 3 | 1 | B | 602.04 | 607.03 | 133.46 | 4.00 | 0.30772 | 2.2525 | 3 |
| 129 | | BBA | 2 | 1 | B | 564.08 | 569.91 | 221.82 | 2.00 | 0.19462 | 3.5616 | 2 |
| 130 | | ABB | 3 | 1 | B | 1632.43 | 1635.54 | 674.24 | 1.50 | 0.34270 | 2.0226 | 1 |
| 131 | | BAB | 3 | 1 | B | 530.55 | 538.29 | 117.26 | 1.75 | 0.23165 | 2.9922 | 3 |
| 132 | | ABB | 3 | 1 | B | 527.42 | 532.26 | 178.08 | 2.00 | 0.59862 | 1.1579 | 1 |
| 133 | | BBA | 2 | 3 1 | B | 1208.31 | 1215.17 | 405.84 | 1.75 | 0.28593 | 2.4242 | 2 |
| 134 | | BBA | 2 | 1 | B | . | . | . | . | . | 2 | |
| 135 | | ABB | 3 | 1 | B | 2380.48 | 2389.33 | 722.03 | 2.00 | 0.35317 | 1.9626 | 1 |
| 136 | | BAB | 3 | 1 | B | 1050.93 | 1053.39 | 378.73 | 2.25 | 0.57401 | 1.2076 | 3 |
| 137 | | BAB | 3 | 1 | B | 2279.52 | 2290.53 | 719.36 | 1.50 | 0.32069 | 2.1614 | 3 |
| 138 | | BBA | 2 | 1 | B | 414.18 | 416.82 | 77.57 | 4.00 | 0.38996 | 1.7775 | 2 |
| 139 | | ABB | 3 | 1 | B | 1382.70 | 1383.98 | 483.21 | 1.75 | 0.30049 | 2.3067 | 1 |
| 140 | | BAB | 3 | 1 | B | 681.22 | 687.57 | 180.24 | 2.00 | 0.44801 | 1.5472 | 3 |
| 141 | | ABB | 3 | 1 | B | 813.35 | 842.34 | 308.56 | 1.00 | 0.06428 | 10.7825 | 1 |

| Obs | SUBJ | SEQU | PER | GROUP | TRT | AUCT | AUCI | CMAX | TMAX | KEL |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | (b) (6) ABB | 2 | 1 | B | 484.55 | 540.15 | 189.99 | 1.50 | 0.03717 | |
| 2 | ABB | 2 | 1 | B | 435.22 | . | 141.51 | 1.00 | . | |
| 3 | ABB | 2 | 1 | B | 1012.34 | 1017.86 | 313.51 | 2.25 | 0.27064 | |
| 4 | ABB | 2 | 1 | B | 931.94 | 936.14 | 390.58 | 1.75 | 0.43566 | |
| 5 | ABB | 2 | 1 | B | 2954.78 | 2962.02 | 933.51 | 1.50 | 0.39411 | |
| 6 | ABB | 2 | 1 | B | 411.11 | 451.21 | 241.51 | 1.50 | 0.03050 | |
| 7 | ABB | 2 | 1 | B | 905.22 | 909.25 | 197.40 | 3.50 | 0.41521 | |
| 8 | ABB | 2 | 1 | B | 1368.97 | 1373.29 | 543.69 | 1.75 | 0.48042 | |
| 9 | ABB | 2 | 1 | B | 791.19 | 799.67 | 335.46 | 1.50 | 0.21768 | |
| 10 | ABB | 2 | 1 | B | 655.28 | . | 204.09 | 1.50 | . | |
| 11 | ABB | 2 | 1 | B | 1178.93 | 1183.90 | 431.24 | 1.75 | 0.39792 | |
| 12 | ABB | 2 | 1 | B | 1086.21 | 1090.76 | 169.89 | 3.50 | 0.24616 | |
| 13 | ABB | 2 | 1 | B | 449.00 | 450.99 | 147.31 | 2.00 | 0.60375 | |
| 14 | ABB | 2 | 1 | B | 2692.10 | 2703.27 | 854.25 | 1.75 | 0.32773 | |
| 15 | ABB | 2 | 1 | B | 1650.54 | 1660.98 | 533.12 | 1.75 | 0.10548 | |
| 16 | ABB | 2 | 1 | B | 990.61 | 1000.03 | 377.74 | 1.50 | 0.11675 | |
| 17 | BBA | 1 | 1 | B | 792.90 | 797.89 | 273.74 | 2.00 | 0.26545 | |
| 18 | BBA | 1 | 1 | B | 651.31 | 652.63 | 246.29 | 1.00 | 0.25251 | |
| 19 | BBA | 1 | 1 | B | 831.03 | 833.88 | 277.05 | 2.25 | 0.39065 | |
| 20 | BBA | 1 | 1 | B | 992.28 | 995.98 | 354.25 | 1.75 | 0.29228 | |
| 21 | BBA | 1 | 1 | B | 1243.86 | 1247.39 | 501.73 | 2.00 | 0.29044 | |
| 22 | BBA | 1 | 1 | B | 641.74 | 646.16 | 297.29 | 1.50 | 0.38244 | |
| 23 | BBA | 1 | 1 | B | 830.72 | 834.55 | 264.11 | 3.00 | 0.29417 | |
| 24 | BBA | 1 | 1 | B | 1725.60 | 1732.56 | 558.99 | 1.50 | 0.16239 | |
| 25 | BBA | 1 | 1 | B | 611.56 | 616.10 | 203.83 | 2.25 | 0.42261 | |
| 26 | BBA | 1 | 1 | B | 1167.92 | 1171.94 | 245.23 | 3.00 | 0.25470 | |
| 27 | BBA | 1 | 1 | B | 530.49 | . | 221.02 | 2.25 | . | |
| 28 | BBA | 1 | 1 | B | 956.39 | 957.48 | 365.06 | 1.00 | 0.44287 | |

29 (b) (6) BBA 1 1 B 983.41 986.75 356.90 1.50 0.33348

| Obs | THALF | SEQ | LAUCT | LAUCINF | LCMAX | lat1r | lai1r | lc1r |
|---|---|---|---|---|---|---|---|---|
| 1 | 18.6471 | 1 | 6.18321 | 6.29184 | 5.24697 | 6.18321 | 6.29184 | 5.24697 |
| 2 | . | 1 | 6.07585 | . | 4.95237 | 6.07585 | . | 4.95237 |
| 3 | 2.5612 | 1 | 6.92002 | 6.92546 | 5.74783 | 6.92002 | 6.92546 | 5.74783 |
| 4 | 1.5910 | 1 | 6.83727 | 6.84176 | 5.96763 | 6.83727 | 6.84176 | 5.96763 |
| 5 | 1.7588 | 1 | 7.99118 | 7.99363 | 6.83895 | 7.99118 | 7.99363 | 6.83895 |
| 6 | 22.7256 | 1 | 6.01885 | 6.11193 | 5.48691 | 6.01885 | 6.11193 | 5.48691 |
| 7 | 1.6694 | 1 | 6.80818 | 6.81262 | 5.28523 | 6.80818 | 6.81262 | 5.28523 |
| 8 | 1.4428 | 1 | 7.22182 | 7.22496 | 6.29838 | 7.22182 | 7.22496 | 6.29838 |
| 9 | 3.1842 | 1 | 6.67354 | 6.68420 | 5.81550 | 6.67354 | 6.68420 | 5.81550 |
| 10 | . | 1 | 6.48506 | . | 5.31856 | 6.48506 | . | 5.31856 |
| 11 | 1.7419 | 1 | 7.07236 | 7.07657 | 6.06666 | 7.07236 | 7.07657 | 6.06666 |
| 12 | 2.8159 | 1 | 6.99045 | 6.99463 | 5.13515 | 6.99045 | 6.99463 | 5.13515 |
| 13 | 1.1481 | 1 | 6.10701 | 6.11144 | 4.99254 | 6.10701 | 6.11144 | 4.99254 |
| 14 | 2.1150 | 1 | 7.89808 | 7.90222 | 6.75022 | 7.89808 | 7.90222 | 6.75022 |
| 15 | 6.5717 | 1 | 7.40886 | 7.41516 | 6.27875 | 7.40886 | 7.41516 | 6.27875 |
| 16 | 5.9369 | 1 | 6.89832 | 6.90779 | 5.93421 | 6.89832 | 6.90779 | 5.93421 |
| 17 | 2.6112 | 2 | 6.67570 | 6.68197 | 5.61218 | 6.67570 | 6.68197 | 5.61218 |
| 18 | 2.7450 | 2 | 6.47899 | 6.48101 | 5.50651 | 6.47899 | 6.48101 | 5.50651 |
| 19 | 1.7743 | 2 | 6.72267 | 6.72609 | 5.62420 | 6.72267 | 6.72609 | 5.62420 |
| 20 | 2.3716 | 2 | 6.90000 | 6.90372 | 5.87000 | 6.90000 | 6.90372 | 5.87000 |
| 21 | 2.3866 | 2 | 7.12597 | 7.12881 | 6.21806 | 7.12597 | 7.12881 | 6.21806 |
| 22 | 1.8124 | 2 | 6.46419 | 6.47104 | 5.69471 | 6.46419 | 6.47104 | 5.69471 |
| 23 | 2.3563 | 2 | 6.72230 | 6.72690 | 5.57637 | 6.72230 | 6.72690 | 5.57637 |
| 24 | 4.2684 | 2 | 7.45333 | 7.45736 | 6.32613 | 7.45333 | 7.45736 | 6.32613 |
| 25 | 1.6402 | 2 | 6.41601 | 6.42341 | 5.31729 | 6.41601 | 6.42341 | 5.31729 |
| 26 | 2.7215 | 2 | 7.06298 | 7.06642 | 5.50220 | 7.06298 | 7.06642 | 5.50220 |
| 27 | . | 2 | 6.27380 | . | 5.39825 | 6.27380 | . | 5.39825 |
| 28 | 1.5651 | 2 | 6.86317 | 6.86430 | 5.90006 | 6.86317 | 6.86430 | 5.90006 |
| 29 | 2.0786 | 2 | 6.89103 | 6.89442 | 5.87746 | 6.89103 | 6.89442 | 5.87746 |

| Obs | SUBJ | SEQU | PER | GROUP | TRT | AUCT | AUCI | CMAX | TMAX | KEL |
|---|---|---|---|---|---|---|---|---|---|---|
| 30 | (b) (6) BBA | 1 | 1 | B | 1372.79 | 1377.85 | 551.83 | 1.00 | 0.30681 | |
| 31 | BBA | 1 | 1 | B | 601.87 | 605.48 | 183.74 | 1.50 | 0.43263 | |
| 32 | BAB | 1 | 1 | B | 567.04 | 571.54 | 274.58 | 1.50 | 0.32718 | |
| 33 | BAB | 1 | 1 | B | 966.80 | 969.02 | 275.26 | 3.50 | 0.45197 | |
| 34 | BAB | 1 | 1 | B | 1236.88 | 1247.16 | 307.23 | 4.00 | 0.35656 | |
| 35 | BAB | 1 | 1 | B | 1300.43 | 1302.13 | 557.00 | 2.00 | 0.28109 | |
| 36 | BAB | 1 | 1 | B | 681.30 | 685.34 | 290.94 | 1.50 | 0.44954 | |
| 37 | BAB | 1 | 1 | B | 1090.69 | 1093.27 | 443.32 | 1.50 | 0.39782 | |
| 38 | BAB | 1 | 1 | B | 1300.49 | 1307.26 | 469.31 | 1.50 | 0.28427 | |
| 39 | BAB | 1 | 1 | B | 911.40 | 916.69 | 161.04 | 3.50 | 0.40611 | |
| 40 | BAB | 1 | 1 | B | 859.96 | . | 233.06 | 4.00 | . | |
| 41 | BAB | 1 | 1 | B | 1210.55 | 1223.39 | 361.66 | 1.75 | 0.30651 | |
| 42 | BAB | 1 | 1 | B | 1361.06 | 1362.22 | 541.06 | 1.00 | 0.44505 | |
| 43 | BAB | 1 | 1 | B | 657.12 | 665.55 | 149.45 | 4.00 | 0.26119 | |
| 44 | BAB | 1 | 1 | B | 429.19 | 434.71 | 75.86 | 4.00 | 0.31893 | |
| 45 | BAB | 1 | 1 | B | 1003.98 | 1006.01 | 190.01 | 4.00 | 0.52919 | |
| 46 | BAB | 1 | 1 | B | 2655.84 | 2661.02 | 781.32 | 1.75 | 0.19097 | |
| 47 | BAB | 1 | 1 | B | 790.89 | 796.39 | 287.78 | 1.50 | 0.38261 | |

| Obs | THALF | SEQ | LAUCT | LAUCINF | LCMAX | lat1r | lai1r | lc1r |
|---|---|---|---|---|---|---|---|---|
| 30 | 2.2592 | 2 | 7.22460 | 7.22828 | 6.31324 | 7.22460 | 7.22828 | 6.31324 |
| 31 | 1.6022 | 2 | 6.40004 | 6.40603 | 5.21352 | 6.40004 | 6.40603 | 5.21352 |
| 32 | 2.1186 | 3 | 6.34042 | 6.34833 | 5.61524 | 6.34042 | 6.34833 | 5.61524 |
| 33 | 1.5336 | 3 | 6.87399 | 6.87629 | 5.61772 | 6.87399 | 6.87629 | 5.61772 |
| 34 | 1.9440 | 3 | 7.12035 | 7.12863 | 5.72760 | 7.12035 | 7.12863 | 5.72760 |
| 35 | 2.4660 | 3 | 7.17045 | 7.17175 | 6.32257 | 7.17045 | 7.17175 | 6.32257 |
| 36 | 1.5419 | 3 | 6.52400 | 6.52992 | 5.67312 | 6.52400 | 6.52992 | 5.67312 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 37 | 1.7424 | 3 | 6.99456 | 6.99693 | 6.09429 | 6.99456 | 6.99693 | 6.09429 |
| 38 | 2.4384 | 3 | 7.17050 | 7.17569 | 6.15126 | 7.17050 | 7.17569 | 6.15126 |
| 39 | 1.7068 | 3 | 6.81499 | 6.82077 | 5.08165 | 6.81499 | 6.82077 | 5.08165 |
| 40 | . | 3 | 6.75689 | . | 5.45130 | 6.75689 | . | 5.45130 |
| 41 | 2.2614 | 3 | 7.09883 | 7.10938 | 5.89070 | 7.09883 | 7.10938 | 5.89070 |
| 42 | 1.5575 | 3 | 7.21602 | 7.21687 | 6.29353 | 7.21602 | 7.21687 | 6.29353 |
| 43 | 2.6538 | 3 | 6.48787 | 6.50062 | 5.00696 | 6.48787 | 6.50062 | 5.00696 |
| 44 | 2.1734 | 3 | 6.06190 | 6.07468 | 4.32889 | 6.06190 | 6.07468 | 4.32889 |
| 45 | 1.3098 | 3 | 6.91172 | 6.91375 | 5.24708 | 6.91172 | 6.91375 | 5.24708 |
| 46 | 3.6296 | 3 | 7.88451 | 7.88646 | 6.66098 | 7.88451 | 7.88646 | 6.66098 |
| 47 | 1.8116 | 3 | 6.67316 | 6.68008 | 5.66220 | 6.67316 | 6.68008 | 5.66220 |

ref2 6

| Obs | SUBJ | SEQU | PER | GROUP | TRT | AUCT | AUCI | CMAX | TMAX | KEL |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | (b) (6) ABB | 3 | 1 | B | 758.45 | 765.35 | 332.05 | 2.25 | 0.17276 | |
| 2 | ABB | 3 | 1 | B | 777.43 | 779.94 | 266.23 | 1.75 | 0.38867 | |
| 3 | ABB | 3 | 1 | B | 830.00 | 833.99 | 244.08 | 3.50 | 0.33079 | |
| 4 | ABB | 3 | 1 | B | 1006.55 | 1010.40 | 471.02 | 1.50 | 0.48027 | |
| 5 | ABB | 3 | 1 | B | 1022.45 | 1025.22 | 518.00 | 1.50 | 0.52712 | |
| 6 | ABB | 3 | 1 | B | 545.05 | 548.13 | 168.09 | 2.25 | 0.50363 | |
| 7 | ABB | 3 | 1 | B | 1084.79 | 1090.09 | 275.30 | 2.25 | 0.36791 | |
| 8 | ABB | 3 | 1 | B | 1195.53 | 1199.69 | 393.57 | 1.75 | 0.52368 | |
| 9 | ABB | 3 | 1 | B | 962.66 | 967.07 | 408.86 | 1.50 | 0.30619 | |
| 10 | ABB | 3 | 1 | B | 455.77 | 525.45 | 159.85 | 1.50 | 0.04925 | |
| 11 | ABB | 3 | 1 | B | 1036.19 | 1042.50 | 345.35 | 1.75 | 0.37598 | |
| 12 | ABB | 3 | 1 | B | 1632.43 | 1635.54 | 674.24 | 1.50 | 0.34270 | |
| 13 | ABB | 3 | 1 | B | 527.42 | 532.26 | 178.08 | 2.00 | 0.59862 | |
| 14 | ABB | 3 | 1 | B | 2380.48 | 2389.33 | 722.03 | 2.00 | 0.35317 | |
| 15 | ABB | 3 | 1 | B | 1382.70 | 1383.98 | 483.21 | 1.75 | 0.30049 | |
| 16 | ABB | 3 | 1 | B | 813.35 | 842.34 | 308.56 | 1.00 | 0.06428 | |
| 17 | BBA | 2 | 1 | B | 767.69 | 772.99 | 252.39 | 2.50 | 0.27932 | |
| 18 | BBA | 2 | 1 | B | 697.24 | 703.23 | 316.03 | 1.75 | 0.37691 | |
| 19 | BBA | 2 | 1 | B | 1010.92 | 1013.52 | 465.91 | 1.50 | 0.32368 | |
| 20 | BBA | 2 | 1 | B | 880.68 | 886.94 | 265.13 | 1.75 | 0.28706 | |
| 21 | BBA | 2 | 1 | B | 989.87 | 994.63 | 379.96 | 2.00 | 0.25231 | |
| 22 | BBA | 2 | 1 | B | 760.39 | 766.58 | 309.42 | 1.50 | 0.33069 | |
| 23 | BBA | 2 | 1 | B | 894.88 | 897.39 | 341.06 | 2.50 | 0.41491 | |
| 24 | BBA | 2 | 1 | B | 1554.21 | 1564.86 | 397.73 | 2.25 | 0.15941 | |
| 25 | BBA | 2 | 1 | B | 622.62 | 628.02 | 277.35 | 1.00 | 0.33284 | |
| 26 | BBA | 2 | 1 | B | 1221.61 | 1231.35 | 252.79 | 4.00 | 0.37326 | |
| 27 | BBA | 2 | 1 | B | 948.25 | 950.95 | 365.52 | 1.50 | 0.32068 | |
| 28 | BBA | 2 | 1 | B | 564.08 | 569.91 | 221.82 | 2.00 | 0.19462 | |

29 (b) (6) BBA 2 1 B 1208.31 1215.17 405.84 1.75 0.28593

| Obs | THALF | SEQ | LAUCT | LAUCINF | LCMAX | lat2r | lai2r | lc2r |
|---|---|---|---|---|---|---|---|---|
| 1 | 4.0121 | 1 | 6.63128 | 6.64033 | 5.80529 | 6.63128 | 6.64033 | 5.80529 |
| 2 | 1.7834 | 1 | 6.65599 | 6.65922 | 5.58436 | 6.65599 | 6.65922 | 5.58436 |
| 3 | 2.0954 | 1 | 6.72142 | 6.72622 | 5.49750 | 6.72142 | 6.72622 | 5.49750 |
| 4 | 1.4433 | 1 | 6.91429 | 6.91810 | 6.15490 | 6.91429 | 6.91810 | 6.15490 |
| 5 | 1.3150 | 1 | 6.92996 | 6.93266 | 6.24998 | 6.92996 | 6.93266 | 6.24998 |
| 6 | 1.3763 | 1 | 6.30088 | 6.30652 | 5.12450 | 6.30088 | 6.30652 | 5.12450 |
| 7 | 1.8840 | 1 | 6.98914 | 6.99402 | 5.61786 | 6.98914 | 6.99402 | 5.61786 |
| 8 | 1.3236 | 1 | 7.08635 | 7.08982 | 5.97526 | 7.08635 | 7.08982 | 5.97526 |
| 9 | 2.2638 | 1 | 6.86970 | 6.87427 | 6.01337 | 6.86970 | 6.87427 | 6.01337 |
| 10 | 14.0744 | 1 | 6.12198 | 6.26425 | 5.07424 | 6.12198 | 6.26425 | 5.07424 |
| 11 | 1.8436 | 1 | 6.94331 | 6.94937 | 5.84456 | 6.94331 | 6.94937 | 5.84456 |
| 12 | 2.0226 | 1 | 7.39783 | 7.39973 | 6.51359 | 7.39783 | 7.39973 | 6.51359 |
| 13 | 1.1579 | 1 | 6.26799 | 6.27714 | 5.18223 | 6.26799 | 6.27714 | 5.18223 |
| 14 | 1.9626 | 1 | 7.77506 | 7.77877 | 6.58207 | 7.77506 | 7.77877 | 6.58207 |
| 15 | 2.3067 | 1 | 7.23179 | 7.23272 | 6.18045 | 7.23179 | 7.23272 | 6.18045 |
| 16 | 10.7825 | 1 | 6.70116 | 6.73618 | 5.73192 | 6.70116 | 6.73618 | 5.73192 |
| 17 | 2.4815 | 2 | 6.64339 | 6.65027 | 5.53098 | 6.64339 | 6.65027 | 5.53098 |
| 18 | 1.8390 | 2 | 6.54713 | 6.55569 | 5.75584 | 6.54713 | 6.55569 | 5.75584 |
| 19 | 2.1415 | 2 | 6.91861 | 6.92119 | 6.14399 | 6.91861 | 6.92119 | 6.14399 |
| 20 | 2.4146 | 2 | 6.78069 | 6.78778 | 5.58022 | 6.78069 | 6.78778 | 5.58022 |
| 21 | 2.7472 | 2 | 6.89757 | 6.90237 | 5.94007 | 6.89757 | 6.90237 | 5.94007 |
| 22 | 2.0961 | 2 | 6.63383 | 6.64194 | 5.73470 | 6.63383 | 6.64194 | 5.73470 |
| 23 | 1.6706 | 2 | 6.79669 | 6.79950 | 5.83206 | 6.79669 | 6.79950 | 5.83206 |
| 24 | 4.3481 | 2 | 7.34872 | 7.35555 | 5.98577 | 7.34872 | 7.35555 | 5.98577 |
| 25 | 2.0825 | 2 | 6.43393 | 6.44257 | 5.62528 | 6.43393 | 6.44257 | 5.62528 |
| 26 | 1.8570 | 2 | 7.10793 | 7.11586 | 5.53256 | 7.10793 | 7.11586 | 5.53256 |
| 27 | 2.1615 | 2 | 6.85461 | 6.85746 | 5.90132 | 6.85461 | 6.85746 | 5.90132 |
| 28 | 3.5616 | 2 | 6.33520 | 6.34548 | 5.40187 | 6.33520 | 6.34548 | 5.40187 |
| 29 | 2.4242 | 2 | 7.09697 | 7.10264 | 6.00596 | 7.09697 | 7.10264 | 6.00596 |

| Obs | SUBJ | SEQU | PER | GROUP | TRT | AUCT | AUCI | CMAX | TMAX | KEL |
|---|---|---|---|---|---|---|---|---|---|---|
| 30 | (b) (6) | BBA | 2 | 1 | B | . | . | . | . | . |
| 31 | | BBA | 2 | 1 | B | 414.18 | 416.82 | 77.57 | 4.00 | 0.38996 |
| 32 | | BAB | 3 | 1 | B | 638.70 | 641.96 | 264.59 | 1.75 | 0.35097 |
| 33 | | BAB | 3 | 1 | B | 1130.14 | 1133.99 | 419.00 | 2.25 | 0.55266 |
| 34 | | BAB | 3 | 1 | B | 1985.02 | 1999.43 | 838.18 | 1.00 | 0.23616 |
| 35 | | BAB | 3 | 1 | B | 1073.86 | 1099.67 | 400.34 | 1.75 | 0.06847 |
| 36 | | BAB | 3 | 1 | B | 714.91 | 716.52 | 204.02 | 1.75 | 0.41453 |
| 37 | | BAB | 3 | 1 | B | 1113.30 | 1116.33 | 412.41 | 1.50 | 0.39360 |
| 38 | | BAB | 3 | 1 | B | 1478.27 | 1483.26 | 590.53 | 1.75 | 0.30573 |
| 39 | | BAB | 3 | 1 | B | 902.71 | 908.05 | 190.79 | 2.50 | 0.33099 |
| 40 | | BAB | 3 | 1 | B | 801.68 | . | 220.70 | 4.00 | . |
| 41 | | BAB | 3 | 1 | B | 879.41 | 896.99 | 201.91 | 2.05 | 0.26721 |
| 42 | | BAB | 3 | 1 | B | 1261.24 | 1266.78 | 534.84 | 2.00 | 0.44813 |
| 43 | | BAB | 3 | 1 | B | 602.04 | 607.03 | 133.46 | 4.00 | 0.30772 |
| 44 | | BAB | 3 | 1 | B | 530.55 | 538.29 | 117.26 | 1.75 | 0.23165 |
| 45 | | BAB | 3 | 1 | B | 1050.93 | 1053.39 | 378.73 | 2.25 | 0.57401 |
| 46 | | BAB | 3 | 1 | B | 2279.52 | 2290.53 | 719.36 | 1.50 | 0.32069 |
| 47 | | BAB | 3 | 1 | B | 681.22 | 687.57 | 180.24 | 2.00 | 0.44801 |

| Obs | THALF | SEQ | LAUCT | LAUCINF | LCMAX | lat2r | lai2r | lc2r |
|---|---|---|---|---|---|---|---|---|
| 30 | . | 2 | . | . | . | . | . | . |
| 31 | 1.7775 | 2 | 6.02629 | 6.03265 | 4.35118 | 6.02629 | 6.03265 | 4.35118 |
| 32 | 1.9750 | 3 | 6.45943 | 6.46453 | 5.57818 | 6.45943 | 6.46453 | 5.57818 |
| 33 | 1.2542 | 3 | 7.03010 | 7.03350 | 6.03787 | 7.03010 | 7.03350 | 6.03787 |
| 34 | 2.9351 | 3 | 7.59338 | 7.60062 | 6.73123 | 7.59338 | 7.60062 | 6.73123 |
| 35 | 10.1231 | 3 | 6.97902 | 7.00277 | 5.99231 | 6.97902 | 7.00277 | 5.99231 |
| 36 | 1.6721 | 3 | 6.57215 | 6.57441 | 5.31822 | 6.57215 | 6.57441 | 5.31822 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 37 | 1.7611 | 3 | 7.01508 | 7.01781 | 6.02202 | 7.01508 | 7.01781 | 6.02202 |
| 38 | 2.2672 | 3 | 7.29863 | 7.30199 | 6.38102 | 7.29863 | 7.30199 | 6.38102 |
| 39 | 2.0942 | 3 | 6.80540 | 6.81130 | 5.25117 | 6.80540 | 6.81130 | 5.25117 |
| 40 | . | 3 | 6.68671 | . | 5.39680 | 6.68671 | . | 5.39680 |
| 41 | 2.5940 | 3 | 6.77925 | 6.79905 | 5.30782 | 6.77925 | 6.79905 | 5.30782 |
| 42 | 1.5468 | 3 | 7.13985 | 7.14424 | 6.28197 | 7.13985 | 7.14424 | 6.28197 |
| 43 | 2.2525 | 3 | 6.40032 | 6.40858 | 4.89380 | 6.40032 | 6.40858 | 4.89380 |
| 44 | 2.9922 | 3 | 6.27390 | 6.28840 | 4.76439 | 6.27390 | 6.28840 | 4.76439 |
| 45 | 1.2076 | 3 | 6.95743 | 6.95977 | 5.93682 | 6.95743 | 6.95977 | 5.93682 |
| 46 | 2.1614 | 3 | 7.73172 | 7.73654 | 6.57836 | 7.73172 | 7.73654 | 6.57836 |
| 47 | 1.5472 | 3 | 6.52388 | 6.53316 | 5.19429 | 6.52388 | 6.53316 | 5.19429 |

| Obs | SUBJ | PER | TRT | SEQ | ilat | ilai | ilc | dlat | dlai | dlc |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | (b) (6) 3 | B | 1 | 0.07924 | 0.04051 | 0.22927 | -0.44807 | -0.34849 | -0.55831 | |
| 2 | 3 | B | 1 | 0.28086 | . | 0.50895 | -0.58014 | . | -0.63199 | |
| 3 | 3 | B | 1 | -0.08962 | -0.08935 | 0.18985 | 0.19860 | 0.19924 | 0.25034 | |
| 4 | 3 | B | 1 | -0.09078 | -0.09159 | -0.06835 | -0.07702 | -0.07634 | -0.18727 | |
| 5 | 3 | B | 1 | -0.51574 | -0.51614 | -0.18790 | 1.06122 | 1.06097 | 0.58898 | |
| 6 | 3 | B | 1 | 0.19227 | 0.14999 | 0.51669 | -0.28203 | -0.19459 | 0.36241 | |
| 7 | 3 | B | 1 | 0.11209 | 0.11126 | 0.19922 | -0.18096 | -0.18140 | -0.33263 | |
| 8 | 3 | B | 1 | 0.00931 | 0.00783 | 0.35368 | 0.13547 | 0.13514 | 0.32312 | |
| 9 | 3 | B | 1 | 0.25192 | 0.24945 | 0.29270 | -0.19616 | -0.19007 | -0.19787 | |
| 10 | 3 | B | 1 | 0.63790 | . | 0.24285 | 0.36308 | . | 0.24433 | |
| 11 | 3 | B | 1 | 0.08508 | 0.08241 | 0.31988 | 0.12905 | 0.12719 | 0.22211 | |
| 12 | 3 | B | 1 | 0.06896 | 0.06881 | 0.55741 | -0.40738 | -0.40510 | -1.37843 | |
| 13 | 3 | B | 1 | 0.14063 | 0.13791 | 0.72818 | -0.16098 | -0.16570 | -0.18969 | |
| 14 | 3 | B | 1 | 0.09580 | 0.09608 | 0.17886 | 0.12302 | 0.12345 | 0.16816 | |
| 15 | 3 | B | 1 | 0.20724 | 0.20534 | 0.38162 | 0.17707 | 0.18244 | 0.09830 | |
| 16 | 3 | B | 1 | 0.07951 | 0.06834 | 0.25342 | 0.19716 | 0.17160 | 0.20229 | |
| 17 | 2 | B | 2 | 0.18826 | 0.18756 | 0.31122 | 0.03231 | 0.03170 | 0.08120 | |
| 18 | 2 | B | 2 | 0.13417 | 0.13628 | 0.16943 | -0.06814 | -0.07468 | -0.24933 | |
| 19 | 2 | B | 2 | -0.22792 | -0.22395 | -1.08032 | -0.19594 | -0.19510 | -0.51979 | |
| 20 | 2 | B | 2 | 0.22661 | 0.22392 | 0.56295 | 0.11931 | 0.11594 | 0.28978 | |
| 21 | 2 | B | 2 | 0.10911 | 0.11137 | 0.03813 | 0.22840 | 0.22644 | 0.27800 | |
| 22 | 2 | B | 2 | -0.36673 | -0.35445 | -0.97483 | -0.16964 | -0.17090 | -0.03999 | |
| 23 | 2 | B | 2 | 0.07812 | 0.07760 | 0.16514 | -0.07440 | -0.07260 | -0.25569 | |
| 24 | 2 | B | 2 | 0.17677 | 0.17265 | 0.16501 | 0.10461 | 0.10180 | 0.34036 | |
| 25 | 2 | B | 2 | 0.42649 | 0.42462 | 0.37142 | -0.01792 | -0.01916 | -0.30799 | |
| 26 | 2 | B | 2 | -0.01995 | -0.01925 | 0.08828 | -0.04495 | -0.04945 | -0.03036 | |
| 27 | 2 | B | 2 | 0.35501 | . | 0.39016 | -0.58081 | . | -0.50307 | |
| 28 | 2 | B | 2 | 0.43531 | 0.43407 | 0.56218 | 0.52797 | 0.51882 | 0.49820 | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 29 | (b) (6) | 2 | B | 2 | 0.17727 | 0.17965 | 0.30333 | -0.20595 | -0.20822 | -0.12850 |
| 30 | | 2 | B | 2 | . | . | . | . | . | . |
| 31 | | 2 | B | 2 | 0.09936 | 0.10008 | 0.78809 | 0.37374 | 0.37338 | 0.86234 |
| 32 | | 3 | B | 3 | 0.00630 | 0.02228 | -0.00237 | -0.11901 | -0.11620 | 0.03706 |
| 33 | | 3 | B | 3 | 0.07625 | 0.07955 | 0.31841 | -0.15611 | -0.15721 | -0.42015 |
| 34 | | 3 | B | 3 | -0.11894 | -0.12137 | 0.03257 | -0.47304 | -0.47199 | -1.00364 |
| 35 | | 3 | B | 3 | 0.06034 | 0.05322 | -0.04897 | 0.19143 | 0.16898 | 0.33025 |
| 36 | | 3 | B | 3 | 0.18424 | 0.18716 | 0.32266 | -0.04815 | -0.04449 | 0.35490 |
| 37 | | 3 | B | 3 | -0.06841 | -0.06731 | 0.28056 | -0.02052 | -0.02087 | 0.07227 |
| 38 | | 3 | B | 3 | -0.07255 | -0.07254 | 0.05044 | -0.12813 | -0.12631 | -0.22976 |
| 39 | | 3 | B | 3 | -0.08517 | -0.08695 | 0.32677 | 0.00958 | 0.00947 | -0.16952 |
| 40 | | 3 | B | 3 | -0.16986 | . | -1.02677 | 0.07018 | . | 0.05449 |
| 41 | | 3 | B | 3 | -0.29292 | -0.28691 | -0.33917 | 0.31958 | 0.31033 | 0.58288 |
| 42 | | 3 | B | 3 | -0.25196 | -0.24530 | -0.40641 | 0.07617 | 0.07263 | 0.01156 |
| 43 | | 3 | B | 3 | 0.01075 | 0.00879 | 0.00248 | 0.08755 | 0.09204 | 0.11316 |
| 44 | | 3 | B | 3 | -0.12068 | -0.11957 | 0.19411 | -0.21201 | -0.21372 | -0.43550 |
| 45 | | 3 | B | 3 | 0.12648 | 0.12968 | 0.43021 | -0.04571 | -0.04602 | -0.68975 |
| 46 | | 3 | B | 3 | -0.20309 | -0.20386 | -0.67919 | 0.15279 | 0.14992 | 0.08262 |
| 47 | | 3 | B | 3 | 0.18164 | 0.18176 | 0.09250 | 0.14928 | 0.14692 | 0.46791 |

The Mixed Procedure

Model Information

| | |
|---|---|
| Data Set | WORK.PKN |
| Dependent Variable | LCMAX |
| Covariance Structures | Factor Analytic, Variance Components |
| Subject Effects | SUBJ, SUBJ |
| Group Effect | |
| Estimation Method | REML |
| Residual Variance Method | None |
| Fixed Effects SE Method | Model-Based |
| Degrees of Freedom Method | Satterthwaite |

Class Level Information

| Class | Levels | Values |
|---|---|---|
| SEQ | 3 | 1 2 3 |
| SUBJ | 47 | 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 48 |
| PER | 3 | 1 2 3 |
| TRT | 2 | A B |

Dimensions

| | |
|---|---|
| Covariance Parameters | 5 |
| Columns in X | 9 |
| Columns in Z Per Subject | 2 |
| Subjects | 47 |
| Max Obs Per Subject | 3 |

Number of Observations

| | |
|---|---|
| Number of Observations Read | 141 |
| Number of Observations Used | 140 |
| Number of Observations Not Used | 1 |

Iteration History

| Iteration | Evaluations | -2 Res Log Like | Criterion |
|---|---|---|---|
| 0 | 1 | 219.67621501 | |
| 1 | 2 | 176.31571570 | 0.77558598 |
| 2 | 1 | 171.86054189 | 0.05600066 |
| 3 | 1 | 170.59655945 | 0.00257918 |
| 4 | 1 | 170.50910342 | 0.17336653 |
| 5 | 1 | 170.50719410 | 0.00006933 |
| 6 | 1 | 170.50719329 | 0.00000000 |

Convergence criteria met but final hessian is not positive definite.

The Mixed Procedure

Estimated G Matrix

| Row | Effect | TRT | SUBJ | Col1 | Col2 |
|---|---|---|---|---|---|
| 1 | TRT | A | 1 | 0.2313 | 0.1564 |
| 2 | TRT | B | 1 | 0.1564 | 0.1703 |

Covariance Parameter Estimates

| Cov Parm | Subject | Group | Estimate |
|---|---|---|---|
| FA(1,1) | SUBJ | | 0.4809 |
| FA(2,1) | SUBJ | | 0.3253 |
| FA(2,2) | SUBJ | | 0.2539 |
| Residual | SUBJ | TRT A | 0.02225 |
| Residual | SUBJ | TRT B | 0.09488 |

Fit Statistics

| | |
|---|---|
| -2 Res Log Likelihood | 170.5 |
| AIC (smaller is better) | 180.5 |
| AICC (smaller is better) | 181.0 |
| BIC (smaller is better) | 189.8 |

Null Model Likelihood Ratio Test

| DF | Chi-Square | Pr > ChiSq |
|---|---|---|
| 4 | 49.17 | <.0001 |

Type 3 Tests of Fixed Effects

| Effect | Num DF | Den DF | F Value | Pr > F |
|---|---|---|---|---|
| SEQ | 2 | 43.9 | 0.86 | 0.4308 |
| PER | 2 | 89.7 | 1.77 | 0.1758 |
| TRT | 1 | 44.7 | 5.59 | 0.0224 |

Estimates

| Label | Estimate | Standard Error | DF | t Value | Pr > \|t\| | Alpha | Lower | Upper |
|---|---|---|---|---|---|---|---|---|
| T vs. R | 0.1376 | 0.05820 | 44.7 | 2.36 | 0.0224 | 0.1 | 0.03988 | 0.2354 |

Least Squares Means

| Effect | TRT | Estimate | Standard Error | DF | t Value | Pr > \|t\| |
|---|---|---|---|---|---|---|
| TRT | A | 5.8724 | 0.07348 | 44 | 79.92 | <.0001 |
| TRT | B | 5.7347 | 0.06822 | 43.8 | 84.07 | <.0001 |

The Mixed Procedure

Model Information

| | |
|---|---|
| Data Set | WORK.PKN |
| Dependent Variable | LAUCT |
| Covariance Structures | Factor Analytic, Variance Components |
| Subject Effects | SUBJ, SUBJ |
| Group Effect | TRT |
| Estimation Method | REML |
| Residual Variance Method | None |
| Fixed Effects SE Method | Model-Based |
| Degrees of Freedom Method | Satterthwaite |

Class Level Information

| Class | Levels | Values |
|---|---|---|
| SEQ | 3 | 1 2 3 |
| SUBJ | 47 | 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 48 |
| PER | 3 | 1 2 3 |
| TRT | 2 | AoB |

Dimensions

| | |
|---|---|
| Covariance Parameters | 5 |
| Columns in X | 9 |
| Columns in Z Per Subject | 2 |
| Subjects | 47 |
| Max Obs Per Subject | 3 |

Number of Observations

| | |
|---|---|
| Number of Observations Read | 141 |
| Number of Observations Used | 140 |
| Number of Observations Not Used | 1 |

Iteration History

| Iteration | Evaluations | -2 Res Log Like | Criterion |
|---|---|---|---|
| 0 | 1 | 166.53419548 | |
| 1 | 2 | 83.44570316 | 469.63136300 |
| 2 | 1 | 70.25744195 | 1.51814248 |
| 3 | 1 | 64.11413509 | 0.03286862 |
| 4 | 1 | 62.36953737 | 0.00122461 |
| 5 | 1 | 62.25878481 | 0.53026205 |
| 6 | 1 | 62.25767239 | 0.00000007 |
| 7 | 1 | 62.25766603 | 0.00000000 |

Convergence criteria met.

The Mixed Procedure

Estimated G Matrix

| Row | Effect | TRT | SUBJ | Col1 | Col2 |
|---|---|---|---|---|---|
| 1 | TRT | A | 1 | 0.1407 | 0.1376 |
| 2 | TRT | B | 1 | 0.1376 | 0.1464 |

Covariance Parameter Estimates

| Cov Parm | Subject | Group | Estimate |
|---|---|---|---|
| FA(1,1) | SUBJ | | 0.3750 |
| FA(2,1) | SUBJ | | 0.3669 |
| FA(2,2) | SUBJ | | 0.1085 |
| Residual | SUBJ | TRT A | 0.008081 |
| Residual | SUBJ | TRT B | 0.04310 |

Fit Statistics

| | |
|---|---|
| -2 Res Log Likelihood | 62.3 |
| AIC (smaller is better) | 72.3 |
| AICC (smaller is better) | 72.7 |
| BIC (smaller is better) | 81.5 |

Null Model Likelihood Ratio Test

| DF | Chi-Square | Pr > ChiSq |
|---|---|---|
| 4 | 104.28 | <.0001 |

Type 3 Tests of Fixed Effects

| Effect | Num DF | Den DF | F Value | Pr > F |
|---|---|---|---|---|
| SEQ | 2 | 44.9 | 0.10 | 0.9090 |
| PER | 2 | 85.2 | 1.97 | 0.1457 |
| TRT | 1 | 44.4 | 3.73 | 0.0600 |

Estimates

| Label | Estimate | Standard Error | DF | t Value | Pr > \|t\| | Alpha | Lower | Upper |
|---|---|---|---|---|---|---|---|---|
| T vs. R | 0.05757 | 0.02983 | 44.4 | 1.93 | 0.0600 | 0.1 | 0.007466 | 0.1077 |

Least Squares Means

| Effect | TRT | Estimate | Standard Error | DF | t Value | Pr > \|t\| |
|---|---|---|---|---|---|---|
| TRT | A | 6.8936 | 0.05628 | 44 | 122.49 | <.0001 |
| TRT | B | 6.8360 | 0.05985 | 44 | 114.21 | <.0001 |

The Mixed Procedure

Model Information

| | |
|---|---|
| Data Set | WORK.PKN |
| Dependent Variable | LAUCINF |
| Covariance Structures | Factor Analytic, Variance Components |
| Subject Effects | SUBJ, SUBJ |
| Group Effect | TRT |
| Estimation Method | REML |
| Residual Variance Method | None |
| Fixed Effects SE Method | Model-Based |
| Degrees of Freedom Method | Satterthwaite |

Class Level Information

| Class | Levels | Values |
|---|---|---|
| SEQ | 3 | 1 2 3 |
| SUBJ | 47 | 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 48 |
| PER | 3 | 1 2 3 |
| TRT | 2 | AoB |

Dimensions

| | |
|---|---|
| Covariance Parameters | 5 |
| Columns in X | 9 |
| Columns in Z Per Subject | 2 |
| Subjects | 47 |
| Max Obs Per Subject | 3 |

Number of Observations

| | |
|---|---|
| Number of Observations Read | 141 |
| Number of Observations Used | 134 |
| Number of Observations Not Used | 7 |

Iteration History

| Iteration | Evaluations | -2 Res Log Like | Criterion |
|---|---|---|---|
| 0 | 1 | 155.12654716 | |
| 1 | 2 | 68.95983429 | 475.70669170 |
| 2 | 1 | 55.64367336 | 1.17891480 |
| 3 | 1 | 49.47902588 | 0.02628071 |
| 4 | 1 | 47.89758528 | 0.00092387 |
| 5 | 1 | 47.80586767 | 0.33077303 |
| 6 | 1 | 47.80488442 | 0.00000017 |
| 7 | 1 | 47.80486811 | 0.00000001 |

Convergence criteria met.

The Mixed Procedure

Estimated G Matrix

| Row | Effect | TRT | SUBJ | Col1 | Col2 |
|---|---|---|---|---|---|
| 1 | TRT | A | 1 | 0.1388 | 0.1355 |
| 2 | TRT | B | 1 | 0.1355 | 0.1420 |

Covariance Parameter Estimates

| Cov Parm | Subject | Group | Estimate |
|---|---|---|---|
| FA(1,1) | SUBJ | | 0.3725 |
| FA(2,1) | SUBJ | | 0.3638 |
| FA(2,2) | SUBJ | | 0.09827 |
| Residual | SUBJ | TRT A | 0.009031 |
| Residual | SUBJ | TRT B | 0.03598 |

Fit Statistics

| | |
|---|---|
| -2 Res Log Likelihood | 47.8 |
| AIC (smaller is better) | 57.8 |
| AICC (smaller is better) | 58.3 |
| BIC (smaller is better) | 67.1 |

Null Model Likelihood Ratio Test

| DF | Chi-Square | Pr > ChiSq |
|---|---|---|
| 4 | 107.32 | <.0001 |

Type 3 Tests of Fixed Effects

| Effect | Num DF | Den DF | F Value | Pr > F |
|---|---|---|---|---|
| SEQ | 2 | 43.7 | 0.10 | 0.9019 |
| PER | 2 | 81.4 | 1.07 | 0.3477 |
| TRT | 1 | 41.3 | 2.38 | 0.1305 |

Estimates

| Label | Estimate | Standard Error | DF | t Value | Pr > \|t\| | Alpha | Lower | Upper |
|---|---|---|---|---|---|---|---|---|
| T vs. R | 0.04427 | 0.02869 | 41.3 | 1.54 | 0.1305 | 0.1 | -0.00401 | 0.09255 |

Least Squares Means

| Effect | TRT | Estimate | Standard Error | DF | t Value | Pr > \|t\| |
|---|---|---|---|---|---|---|
| TRT | A | 6.9069 | 0.05671 | 43 | 121.80 | <.0001 |
| TRT | B | 6.8627 | 0.05921 | 43.1 | 115.90 | <.0001 |

The GLM Procedure

Class Level Information

| Class | Levels | Values |
|---|---|---|
| SEQ | 3 | 1 2 3 |

| | |
|---|---|
| Number of Observations Read | 47 |
| Number of Observations Used | 46 |

The GLM Procedure

Dependent Variable: ilat

| Source | DF | Sum of Squares | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| Model | 2 | 0.26563279 | 0.13281640 | 3.17 | 0.0521 |
| Error | 43 | 1.80261224 | 0.04192121 | | |
| Corrected Total | 45 | 2.06824504 | | | |

| R-Square | Coeff Var | Root MSE | ilat Mean |
|---|---|---|---|
| 0.128434 | 362.3892 | 0.204747 | 0.056499 |

| Source | DF | Type I SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 2 | 0.26563279 | 0.13281640 | 3.17 | 0.0521 |

| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 2 | 0.26563279 | 0.13281640 | 3.17 | 0.0521 |

| Parameter | Estimate | Error | t Value | Pr > \|t\| |
|---|---|---|---|---|
| average | 0.05947797 | 0.03024809 | 1.97 | 0.0557 |

| Parameter | 90% Confidence Limits | |
|---|---|---|
| average | 0.00862879 | 0.11032716 |

Standard

| Obs | Dependent | Source | DF | SS | MS | FValue | ProbF |
|---|---|---|---|---|---|---|---|
| 1 | ilat | Model | 2 | 0.26563279 | 0.13281640 | 3.17 | 0.0521 |
| 2 | ilat | Error | 43 | 1.80261224 | 0.04192121 | _ | _ |
| 3 | ilat | Corrected Total | 45 | 2.06824504 | _ | _ | _ |

The GLM Procedure

Class Level Information

| Class | Levels | Values |
|---|---|---|
| SEQ | 3 | 1 2 3 |

| | |
|---|---|
| Number of Observations Read | 47 |
| Number of Observations Used | 46 |

The GLM Procedure

Dependent Variable: dlat

| Source | DF | Sum of Squares | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| Model | 2 | 0.00146757 | 0.00073378 | 0.01 | 0.9917 |
| Error | 43 | 3.78980840 | 0.08813508 | | |
| Corrected Total | 45 | 3.79127597 | | | |

| R-Square | Coeff Var | Root MSE | dlat Mean |
|---|---|---|---|
| 0.000387 | -20822.83 | 0.296876 | -0.001426 |

| Source | DF | Type I SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 2 | 0.00146757 | 0.00073378 | 0.01 | 0.9917 |

| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 2 | 0.00146757 | 0.00073378 | 0.01 | 0.9917 |

| Obs | method_ used | unscabe_ lower | unscabe_ upper | dfi | s2i | param | StdErr |
|---|---|---|---|---|---|---|---|
| 1 | Unscaled | 1.00749 | 1.11370 | 43 | 0.041921 | LAUCT | 0.03024809 |

| Obs | pointest | x | boundx | ni | dfd | s2wr | nd | theta |
|---|---|---|---|---|---|---|---|---|
| 1 | 1.06128 | .002622682 | 0.012172 | 46 | 43 | 0.044068 | 46 | 0.79669 |

| Obs | y | boundy | sWR | critbound | outcome |
|---|---|---|---|---|---|
| 1 | -0.035108 | -0.025456 | 0.20992 | -0.018908 | PASS |

| Obs | method_ used | unscabe_ lower | unscabe_ upper | param | pointest | s2wr | sWR | critbound | outcome |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Unscaled | 1.00749 | 1.11370 | LAUCT | 1.06128 | 0.044068 | 0.20992 | -0.018908 | PASS |

The GLM Procedure

Class Level Information

| Class | Levels | Values |
|---|---|---|
| SEQ | 3 | 1 2 3 |

| | |
|---|---|
| Number of Observations Read | 47 |
| Number of Observations Used | 42 |

The GLM Procedure

Dependent Variable: ilai

| Source | DF | Sum of Squares | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| Model | 2 | 0.15201140 | 0.07600570 | 2.23 | 0.1215 |
| Error | 39 | 1.33183915 | 0.03414972 | | |
| Corrected Total | 41 | 1.48385055 | | | |

| R-Square | Coeff Var | Root MSE | ilai Mean |
|---|---|---|---|
| 0.102444 | 542.8955 | 0.184796 | 0.034039 |

| Source | DF | Type I SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 2 | 0.15201140 | 0.07600570 | 2.23 | 0.1215 |

| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 2 | 0.15201140 | 0.07600570 | 2.23 | 0.1215 |

| Parameter | Estimate | Error | t Value | Pr > \|t\| |
|---|---|---|---|---|
| average | 0.03755424 | 0.02856341 | 1.31 | 0.1963 |

| Parameter | 90% Confidence Limits | |
|---|---|---|
| average | -0.01057154 | 0.08568002 |

Standard

dev iglmilai1 24

| Obs | Dependent | Source | DF | SS | MS | FValue | ProbF |
|---|---|---|---|---|---|---|---|
| 1 | ilai | Model | 2 | 0.15201140 | 0.07600570 | 2.23 | 0.1215 |
| 2 | ilai | Error | 39 | 1.33183915 | 0.03414972 | _ | _ |
| 3 | ilai | Corrected Total | 41 | 1.48385055 | _ | _ | _ |

The GLM Procedure

Class Level Information

| Class | Levels | Values |
|---|---|---|
| SEQ | 3 | 1 2 3 |

| | |
|---|---|
| Number of Observations Read | 47 |
| Number of Observations Used | 42 |

The GLM Procedure

Dependent Variable: dlai

| Source | DF | Sum of Squares | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| Model | 2 | 0.02936303 | 0.01468152 | 0.21 | 0.8147 |
| Error | 39 | 2.77889744 | 0.07125378 | | |
| Corrected Total | 41 | 2.80826047 | | | |

| R-Square | Coeff Var | Root MSE | dlai Mean |
|---|---|---|---|
| 0.010456 | 1456.326 | 0.266934 | 0.018329 |

| Source | DF | Type I SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 2 | 0.02936303 | 0.01468152 | 0.21 | 0.8147 |

| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 2 | 0.02936303 | 0.01468152 | 0.21 | 0.8147 |

| Obs | method_ used | unscabe_ lower | unscabe_ upper | dfi | s2i | param | StdErr |
|---|---|---|---|---|---|---|---|
| 1 | Unscaled | 0.99600 | 1.09697 | 39 | 0.034150 | LAUCINF | 0.02856341 |

| Obs | pointest | x | boundx | ni | dfd | s2wr | nd | theta |
|---|---|---|---|---|---|---|---|---|
| 1 | 1.03827 | .000594453 | .007341066 | 42 | 39 | 0.035627 | 42 | 0.79669 |

| Obs | y | boundy | sWR | critbound | outcome |
|---|---|---|---|---|---|
| 1 | -0.028384 | -0.020284 | 0.18875 | -0.017248 | PASS |

| method_obs | seed | scale_lower | scale_upper | parameters | points | 2 | sweep | Wrt | Rcrit | unscaled | cutoff |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 Unscaled | 0.99600 | 1.09697 | LAUCINF | 1.03827 | 0.035627 | 0.18875 | -0.017248 | PASS | | | |

The GLM Procedure

Class Level Information

| Class | Levels | Values |
|---|---|---|
| SEQ | 3 | 1 2 3 |

| | |
|---|---|
| Number of Observations Read | 47 |
| Number of Observations Used | 46 |

intermediate analysis - &ipar glm

The GLM Procedure

Dependent Variable: ilc

| Source | DF | Sum of Squares | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| Model | 2 | 0.82833672 | 0.41416836 | 2.59 | 0.0867 |
| Error | 43 | 6.87771648 | 0.15994689 | | |
| Corrected Total | 45 | 7.70605320 | | | |

| R-Square | Coeff Var | Root MSE | ilc Mean |
|---|---|---|---|
| 0.107492 | 301.3727 | 0.399934 | 0.132704 |

| Source | DF | Type I SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 2 | 0.82833672 | 0.41416836 | 2.59 | 0.0867 |

| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 2 | 0.82833672 | 0.41416836 | 2.59 | 0.0867 |

| Parameter | Estimate | Error | t Value | Pr > \|t\| |
|---|---|---|---|---|
| average | 0.13271098 | 0.05908388 | 2.25 | 0.0299 |

| Parameter | 90% Confidence Limits | |
|---|---|---|
| average | 0.03338681 | 0.23203516 |

Standard

dev iglmilc1

| Obs | Dependent | Source | DF | SS | MS | FValue | ProbF |
|---|---|---|---|---|---|---|---|
| 1 | ilc | Model | 2 | 0.82833672 | 0.41416836 | 2.59 | 0.0867 |
| 2 | ilc | Error | 43 | 6.87771648 | 0.15994689 | _ | _ |
| 3 | ilc | Corrected Total | 45 | 7.70605320 | _ | _ | _ |

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The GLM Procedure

Class Level Information

| Class | Levels | Values |
|---|---|---|
| SEQ | 3 | 1 2 3 |

| | |
|---|---|
| Number of Observations Read | 47 |
| Number of Observations Used | 46 |

The GLM Procedure

Dependent Variable: dlc

| Source | DF | Sum of Squares | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| Model | 2 | 0.06415293 | 0.03207647 | 0.17 | 0.8482 |
| Error | 43 | 8.34341335 | 0.19403287 | | |
| Corrected Total | 45 | 8.40756629 | | | |

| R-Square | Coeff Var | Root MSE | dlc Mean |
|---|---|---|---|
| 0.007630 | -1313.836 | 0.440492 | -0.033527 |

| Source | DF | Type I SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 2 | 0.06415293 | 0.03207647 | 0.17 | 0.8482 |

| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| SEQ | 2 | 0.06415293 | 0.03207647 | 0.17 | 0.8482 |

| Obs | method_ used | unscabe_ lower | unscabe_ upper | dfi | s2i | param | StdErr |
|---|---|---|---|---|---|---|---|
| 1 | Scaled/PE | 1.04069 | 1.26541 | 43 | 0.15995 | LCMAX | 0.05908388 |

| Obs | pointest | x | boundx | ni | dfd | s2wr | nd | theta |
|---|---|---|---|---|---|---|---|---|
| 1 | 1.14192 | 0.014121 | 0.053840 | 46 | 43 | 0.097016 | 46 | 0.79669 |

| Obs | y | boundy | sWR | critbound | outcome |
|---|---|---|---|---|---|
| 1 | -0.077292 | -0.056043 | 0.31147 | -0.018125 | PASS |

| Obs | Method | _Weight_ | _Scale_ | _Points_ | _Criterion_ | _Subcomponent_ |
|---|---|---|---|---|---|---|
| 1 | Scaled/PE | 1.04069 | 1.26541 | LCMAX | 1.14192 | 0.097016 | 0.31147 | -0.018125 | PASS |

SUMMARY OF STATISTICAL ANALYSIS - UNSCALED DATA

| Parameter | Geometric Means Test | Reference | T/R Ratio |
|---|---|---|---|
| LAUCT | 985.96 | 930.79 | 1.06 |
| LAUCI | 999.18 | 955.92 | 1.05 |
| LCMAX | 355.09 | 309.43 | 1.15 |

SUMMARY OF STATISTICAL ANALYSIS - UNSCALED DATA

| 90% CI | |
|---|---|
| Lower CI | Upper CI |
| 100.75 | 111.37 |
| 99.60 | 109.70 |
| 104.07 | 126.54 |

,  Lower  ,
'  Parameter  T/R Ratio  90% CI  ,
'  LAUCT  ,  1.06  ,  100.75  ,
' '  LAUCI  ,  1.04  ,  99.60  ,
'  LCMAX  ,  1.14  ,  104.07  ,
'

| Upper 90% CI | s2wr | sWR | Criteria Bound |
|---|---|---|---|
| 111.37 | 0.0440675 | 0.2099227 | -0.018908 |
| 109.70 | 0.0356269 | 0.1887509 | -0.017248 |
| 126.54 | 0.0970164 | 0.3114746 | -0.018125 |

,
, Method Used OUTCOME ,
' Unscaled , PASS ,
' Unscaled , PASS ,
' Scaled/PE , PASS ,
'

BIOEQUIVALENCE DEFICIENCIES

ANDA: 203174

APPLICANT: Banner Pharmacaps Inc.

DRUG PRODUCT: Bexarotene Capsules, 75 mg

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

1. You did not submit the raw analytical numerical data for all the assay runs (both accepted and rejected runs). Please submit complete raw data (numerical printouts) of all sample analysis runs, including the data for the peak area/height for the drug and the internal standard (IS), the ratio of the drug peak area/height to the IS peak area/height, dilution factor (if any), and the corresponding calculated concentration for each assayed and reassayed sample, calibration standard concentration samples, and quality control samples.

2. A summary table of batch analysis was provided in your bioanalytical validation report. The report stated that, "data from reject or unused batches and/or evaluations are not included in this report but are on file at (b) (4) A batch or evaluation is listed as "Not Used" when an analytical issue is observed that could potentially affect data integrity". Please submit the data for *all* unused batches as well.

3. Please provide SOP (b) (4): Rejected and Not Used Data, Laboratory Investigations and Events.

We acknowledge that you will conduct dissolution testing for the test product using the following FDA-recommended method and specification:

Medium: Tier 1: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5
Tier 2: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5, with 0.05 g/L pancreatin enzyme (NMT 1750 USP Units of protease activity per 1000 mL)
Volume: 900 mL
Apparatus: II (Paddle)
Speed: 75 rpm
Temperature: 37°C ± 0.5°C
Specification: NLT (b)(4)% (Q) in 45 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

## 4.7 Outcome Page

ANDA: 203174

| *ID* | *Letter Date* | *Productivity Category* | *Sub Category* | *Productivity* | *Subtotal* |
|---|---|---|---|---|---|
| 17217 | 10/6/2011 | Bioequivalence Study (REGULAR) | Fed Study | 1 | 1 |
| 17217 | 3/20/2012 | Dissolution Data (REGULAR) | Dissolution Amendment | 1 | 1 |
| | | | | Total: | 2 |

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

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/s/

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HARITHA MANDULA
09/21/2012

SHRINIWAS G NERURKAR
09/21/2012

HOAINHON N CARAMENICO on behalf of DALE P CONNER
09/27/2012

# DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

| | |
|---|---|
| **ANDA No.** | 203174 |
| **Drug Product Name** | Bexarotene Capsules |
| **Strength (s)** | 75 mg |
| **Applicant Name** | Banner Pharmacaps Inc. |
| **Address** | 4125 Premier Drive<br>High Point, NC 27265 |
| **Applicant's Point of Contact** | Vandana Garikipati<br>Manager, Regulatory Affairs |
| **Contact's Phone Number** | (336) 812-8700, extension 23988 |
| **Contact's Fax Number** | (888) 818-4197 |
| **Original Submission Date(s)** | 06/03/2011 |
| **Submission Date(s) of Amendment(s) Under Review** | 12/14/2011 |
| **First Generic** | Yes |
| **Reviewer** | Yumei Ye, Ph.D. |
| | |
| **Study Number (s)** | BXN-P0-541 |
| **Study Type (s)** | Fed |
| **Strength(s)** | 75 mg |
| **Clinical Site** | Algorithme Pharma Inc. |
| **Clinical Site Address** | 1200 Beaumont Ave.<br>Mount-Royal, Quebec, Canada, H3P 3P1 |
| **Analytical Site** | (b) (4) |
| **Analytical Address** | |
| **Dissolution Method** | Incorrect |
| | |
| **OUTCOME DECISION** | **INADEQUATE** |

## 1. EXECUTIVE SUMMARY

This is a "dissolution only" amendment review.

The original "dissolution only" review [DARRTS: ANDA # 203174 REVBIOQ-02 (Dissolution Review) Submit Date: 12/19/2011] was entered in DARRTS. However, the (b) (5) the firm submitted a gratuitous amendment dated 12/14/2011 that was not addressed in the review dated 12/19/2011 mentioned above.[1] As per the original "dissolution only" review, the following two deficiencies were identified:[2]

1. The firm should conduct the additional dissolution testing using the FDA-recommended method in 900 mL of Tier 1 Medium: 0.5% Hexadecyltrimethylammonium bromide (HDTMA) in 0.05 M phosphate buffer, pH 7.5, 900 mL of Tier 2 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 with 0.05 g/L pancreatin enzyme at 37ºC ± 0.5ºC using USP Apparatus II (Paddle) at 50 rpm. The sampling times should be 15, 30, 45 and 60 minutes.

2. The firm's Long-Term Storage Stability (LTSS) data of 24 days for Bexarotene in human plasma at -80˚C is not sufficient to cover the maximum storage period of 45 days of the samples in the fed bioequivalence (BE) study. Therefore, the firm will be asked to provide the LTSS data for Bexarotene in human plasma, using the same anticoagulant and storage condition used in the *in vivo* BE study, to cover the maximum storage period (45 days) of study samples for the fed (BXN-P0-541) BE study.

In the current amendment dated 12/14/2011, the firm provided the update to the study report (clinical study report and analytical report) for the fed BE study and a minor update to the dissolution method for its test product. The update to the clinical study report is associated with the result of a subject's extended post-study follow-up due to an abnormal clinically significant laboratory value the subject had at the post-study visit.[3] The amendment to the analytical report includes the updated stabilities evaluations, such as the LTSS data for Bexarotene in human plasma.[3] The amendment to the dissolution method is evaluated in this review. The other updates to the study report (clinical study report and analytical report) for the fed BE study including the LTSS data for Bexarotene in human plasma will be reviewed later by the Division of Bioequivalence I (DB I).

In the current amendment, the firm updated the Tier 2 testing procedure in the current version of firm's dissolution method (PD10-017) for Bexarotene Capsules. However, the firm's dissolution method still differs from the FDA-recommended method for this

[1] Please see the detail in the Section 7 Additional Attachment of this review.
[2] DARRTS: ANDA # 203174 REVBIOQ-02 (Dissolution Review) Submit Date: 12/19/2011 (Last accessed: 01/05/2011)
[3] DARRTS: ANDA # 203174 Bioequivalence/Other Submit Date: 12/14/2011 EDR: Module 1.2. Cover Letter (Last accessed: 01/05/2011)

product. Therefore, the firm's dissolution testing remains **inadequate**. The firm should conduct the additional dissolution testing using the FDA-recommended method in 900 mL of Tier 1 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5, 900 mL of Tier 2 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 with 0.05 g/L pancreatin enzyme at 37ºC ± 0.5ºC using USP Apparatus II (Paddle) at 50 rpm. The sampling times should be 15, 30, 45 and 60 minutes.

The DB will review the fed BE study at a later date.

(b) (5)

An addendum to the 12/19/2011 review has also be entered into DARRTS to clarify this issue.

## 2. TABLE of CONTENTS

## 3. BACKGROUND

On June 03, 2011, Banner Pharmacaps Inc., submitted its application on its test product, Bexarotene Capsules, 75 mg. Although there is an FDA-recommended method for this product, the firm conducted its dissolution testing using its own method. The FDA-recommended method and the firm's proposed method are listed below:[2]

| | FDA-recommended Method | Firm's Proposed Method |
|---|---|---|
| **Medium** | Tier 1 Medium: 0.5% HDTMA* in 0.05 M phosphate buffer, pH 7.5<br><br>Tier 2 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 with 0.05 g/L pancreatin enzyme | (b) (4) |
| **Volume** | 900 mL | |
| **Apparatus** | II (Paddle) | |
| **Speed** | 50 rpm | |
| **Sampling Times** | 15, 30, 45 and 60 minutes | |
| **Temperature** | 37ºC ± 0.5ºC | |
| **Specification** | NLT (b) (4)% (Q), 45minutes | |

* Hexadecyltrimethylammonium bromide (HDTMA)

The DB has performed a "dissolution only" review on the firm's original dissolution testing [DARRTS: ANDA # 203174 REVBIOQ-02 (Dissolution Review) Submit Date: 12/19/2011]. At that time, the firm's dissolution testing was found **incomplete**. (b) (5) the firm submitted a gratuitous amendment dated 12/14/2011 that was not addressed in the review dated 12/19/2011. As per the original "dissolution only" review, the following two deficiencies were identified:

1. The firm should conduct the additional dissolution testing using the FDA-recommended method in 900 mL of Tier 1 Medium: 0.5% Hexadecyltrimethylammonium bromide (HDTMA) in 0.05 M phosphate buffer, pH 7.5, Tier 2 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 with 0.05 g/L pancreatin enzyme at 37ºC ± 0.5ºC using USP Apparatus II (Paddle) at 50 rpm. The sampling times should be 15, 30, 45 and 60 minutes.

2. The firm's Long-Term Storage Stability (LTSS) data of 24 days for Bexarotene in human plasma at -80˚C is not sufficient to cover the maximum storage period of 45 days of the samples in the fed bioequivalence (BE) study. Therefore, the firm will be asked to provide the LTSS data for Bexarotene in human plasma, using the same anticoagulant and storage condition used in the *in vivo* BE study, to cover the maximum storage period (45 days) of study samples for the fed (BXN-P0-541) BE study.

## 4. REVIEW of CURRENT AMENDMENT

**Deficiency #1**

The firm should conduct the additional dissolution testing using the FDA-recommended method in 900 mL of Tier 1 Medium: 0.5% Hexadecyltrimethylammonium bromide (HDTMA) in 0.05 M phosphate buffer, pH 7.5 Tier 2 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 with 0.05 g/L pancreatin enzyme at 37ºC ± 0.5ºC using USP Apparatus II (Paddle) at 50 rpm. The sampling times should be 15, 30, 45 and 60 minutes.

**Firm's updates on the dissolution method:**

*The firm has updated its dissolution method (PD10-017). The current version of the method has updated the Tier 2 dissolution procedure to perform stepwise addition of the surfactant as this its dissolution as this will ensure complete reaction of the pancreatin media to the capsule before addition of the surfactant. The updates associated with the Tier 2 dissolution procedure are listed below:*

***5. PREPARATION OF REAGENTS AND SOLUTIONS***

(b) (4)

[redacted]

**Reviewer's Comments:**

The updated dissolution method for Bexarotene Capsules in the current version of firm's method (PD10-017) still differs from the FDA-recommended method for this product. The FDA-recommended method and the firm's proposed method are listed below:

| | **FDA-recommended Method** | **Firm's Proposed Method** |
|---|---|---|
| **Medium** | Tier 1 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5<br><br>Tier 2 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 with 0.05 g/L pancreatin enzyme | Tier 1 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5<br><br>Tier 2 Medium: 0.5%* HDTMA in 0.05 M phosphate buffer, pH 7.5 with pancreatin enzyme |
| **Volume** | 900 mL | 900 mL |
| **Apparatus** | II (Paddle) | II (Paddle) |
| **Speed** | 50 rpm | 75 rpm |
| **Sampling Times** | 15, 30, 45 and 60 minutes | 15, 30, 45, 60 and 75 minutes |
| **Temperature** | 37ºC ± 0.5ºC | 37ºC ± 0.5ºC |
| **Specification** | NLT (b)(4)% (Q), 45minutes | |

*In the current version of firm's dissolution method (PD10-017), Tier 2 medium was typed as (b)(4)% HDTMA in 0.05 M phosphate buffer pH 7.5 with pancreatin enzyme in Section 4.1 Dissolution Apparatus. According to the Section 5.9.2 Tier 2 Dissolution Sample Preparation mentioned above, the final concentration of HDTMA in Tier 2 dissolution medium should be 0.5%.

Therefore, the firm's dissolution testing remains **inadequate**. The firm should conduct the additional dissolution testing using the FDA-recommended method in 900 mL of Tier 1 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5, 900 mL of Tier 2 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 with 0.05 g/L pancreatin enzyme at 37ºC ± 0.5ºC using USP Apparatus II (Paddle) at 50 rpm. The sampling times should be 15, 30, 45 and 60 minutes.

In addition, as indicated in the Sample Preparation for Tier 2 Media provided in the amendment above (b) (4) the firm should justify said approach (b) (4) Finally, the firm should also state if (b) (4) for its additional dissolution testing using the above FDA-recommended method if said method ultimately becomes the quality control method for the proposed product.

It is noted that the firm has submitted an analytical method validation report for its method, which will be reviewed in its entirety when the firm submit data using the FDA-recommended method.

## 5. DEFICIENCY COMMENTS

1. The firm should conduct additional dissolution testing using the FDA-recommended method in 900 mL of Tier 1 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5, 900 mL of Tier 2 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 with 0.05 g/L pancreatin enzyme at 37ºC ± 0.5ºC using USP Apparatus II (Paddle) at 50 rpm. The sampling times should be 15, 30, 45 and 60 minutes.

2. The reviewer notes that in the firm's proposed dissolution method (b) (4) [redacted] Since no information about the reference product was found by this reviewer to support this approach (b) (4) [redacted] the firm should justify said approach. (b) (4) [redacted] Furthermore, the firm should also state if (b) (4) [redacted] for its additional dissolution testing using the above FDA-recommended method (see Deficiency Comment # 1) if said method ultimately becomes the quality control method for the proposed product.

## 6. RECOMMENDATIONS

1. The *in vitro* dissolution testing conducted by Banner Pharmacaps Inc. on its test product, Bexarotene Capsules, 75 mg (Lot No. 140000127A), comparing to Eisai Inc.'s Targretin® (bexarotene) Capsules, 75 mg (Lot No. 004681) is **inadequate**.

2. The firm should conduct dissolution testing using the following FDA-recommended method:

   Medium: Tier 1 - 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5
   Tier 2 - 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 with 0.05 g/L pancreatin enzyme
   Apparatus: II (Paddle)
   Speed: 50 rpm
   Volume: 900 mL
   Temperature: 37°C ± 0.5°C
   Sampling Time Points: 15, 30, 45, and 60 minutes

## 7. ADDITIONAL ATTACHMENT

**From:** Chun, Nam
**Sent:** Wednesday, December 28, 2011 8:48 AM
**To:** Ye, Yumei; Braddy, April
**Cc:** Solana-Sodeinde, Diana A
**Subject:** RE: Finalized - ANDA 203174 Dissolution Review (REV-BIOEQ-02)

Good morning Yumei,

Thank you for your reply.
[redacted] (b) (5) and assign you the amendment piece.

Thanks,

***Nam (Esther) Chun, Pharm.D.***
LCDR, U.S. Public Health Service
Regulatory Project Manager, Branch VI
Division of Bioequivalence I
Office of Generic Drugs
FDA

---

**From:** Ye, Yumei
**Sent:** Tuesday, December 27, 2011 3:28 PM
**To:** Chun, Nam; Braddy, April
**Cc:** Solana-Sodeinde, Diana A
**Subject:** RE: Finalized - ANDA 203174 Dissolution Review (REV-BIOEQ-02)

Good afternoon, Esther:

Thank you very much for your message! I looked at the amendment dated December 14, 2011.

In the amendment, the firm only made the modification in the Section 5 (Preparation of Reagents and Solutions) of the dissolution method (#PD10-017C), [redacted] (b) (5) . However, the firm provided the Long-Term Storage Stability (LTSS) data of 124 days for Bexarotene in human plasma at -80°C, which is sufficient to cover the maximum study sample storage period of 45 days for the firm's fed BE study. [redacted] (b) (5)

Per my discussion with April, please go ahead and [redacted] (b) (5) assign this amendment piece to me as an amendment review.

Thanks!

Yumei

---

**From:** Chun, Nam
**Sent:** Tuesday, December 27, 2011 2:00 PM
**To:** Ye, Yumei; Braddy, April
**Cc:** Solana-Sodeinde, Diana A
**Subject:** FW: Finalized - ANDA 203174 Dissolution Review (REV-BIOEQ-02)

Hi Yumei,

I processed below dissolution review completed by you on December 19, 2011 and (b) (5) .
However, I notice the firm has submitted an amendment on December 14, 2011 and according to the cover letter, the firm is amending the dissolution method.
Can you please take a look at the amendment dated December 14, 2011 and determine if this affects your dissolution review?
(b) (5) and assign this amendment piece to you to include in your review.

Thanks,

***Nam (Esther) Chun, Pharm.D.***
LCDR, U.S. Public Health Service
Regulatory Project Manager, Branch VI
Division of Bioequivalence I
Office of Generic Drugs
FDA

BIOEQUIVALENCE DEFICIENCIES

(b) (5)

| | |
|---|---|
| ANDA: | 203174 |
| APPLICANT: | Banner Pharmacaps Inc. |
| DRUG PRODUCT: | Bexarotene Capsules, 75 mg |

The Division of Bioequivalence I (DB I) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence (BE) study will be conducted later. The following deficiencies have been identified:

1. Your dissolution testing data are incomplete. You have submitted dissolution testing data using your own proposed dissolution method. Your method differs from the current FDA-recommended method. In order for the DB I to properly evaluate your proposed dissolution method and compare it with the FDA-recommended method, please conduct additional dissolution testing on the test and reference products (12 units each) using the following FDA method:

   Medium:

   Tier 1 - 0.5% Hexadecyltrimethylammonium bromide (HDTMA) in 0.05 M phosphate buffer, pH 7.5

   Tier 2 - 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 with 0.05 g/L pancreatin enzyme

   Apparatus: II (Paddle)
   Speed: 50 rpm
   Volume: 900 mL
   Temperature: 37°C ± 0.5°C
   Sampling Time Points: 15, 30, 45, and 60 minutes and until at least 80% of the labeled amount of the drug in the dosage form is dissolved.

For the requested dissolution testing, please submit the complete dissolution method information which should include the following:

- A complete dissolution study report with each method used.
- Individual dissolution testing data for 12 dosage units of each strength of the test and reference products.
- Mean, range and coefficient of variation (%CV) data of the dissolution results.
- Comparative mean dissolution graphs for each strength.
- Analytical Method Validation Report

The DB I will determine the most suitable method and specification for your test product following the evaluation of the dissolution testing data from both methods.

2. The DB I notes that in your proposed dissolution method (75 rpm), (b) (4) (b) (4) Finally, please also state if you plan to (b) (4) (b) (4) (b) (4) for the testing using the FDA-recommended dissolution method.

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

## 8. OUTCOME

ANDA: 203174

### 9. *Completed Assignment for 203174 ID: 15754*

**Reviewer:** Ye, Yumei **Date Completed:**
**Verifier:** , **Date Verified:**
**Division:** Division of Bioequivalence
**Description:** Bexarotene Capsules, 75 mg

---

*Productivity:*

| *ID* | *Letter Date* | *Productivity Category* | *Sub Category* | *Productivity* | *Subtotal* |
|---|---|---|---|---|---|
| 15754 | 12/14/2011 | Other | Dissolution Amendment | 0 | 0 |
| | | | | Bean Total: | 0 |

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/s/

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YUMEI YE
02/16/2012

UTPAL M MUNSHI
02/17/2012

HOAINHON N CARAMENICO on behalf of DALE P CONNER
02/21/2012

# DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

| | |
|---|---|
| **ANDA No.** | 203174 |
| **Drug Product Name** | Bexarotene Capsules |
| **Strength (s)** | 75 mg |
| **Applicant Name** | Banner Pharmacaps Inc. |
| **Address** | 4125 Premier Drive<br>High Point, NC 27265 |
| **Applicant's Point of Contact** | Vandana Garikipati<br>Manager, Regulatory Affairs |
| **Contact's Phone Number** | (336) 812-8700, extension 23988 |
| **Contact's Fax Number** | (888) 818-4197 |
| **Submission Date(s)** | 06/03/2011 |
| **First Generic** | Yes |
| **Reviewer** | Yumei Ye, Ph.D. |
| | |
| **Study Number (s)** | BXN-P0-541 |
| **Study Type (s)** | Fed |
| **Strength(s)** | 75 mg |
| **Clinical Site** | Algorithme Pharma Inc. |
| **Clinical Site Address** | 1200 Beaumont Ave.<br>Mount-Royal, Quebec, Canada, H3P 3P1 |
| **Analytical Site** | (b) (4) |
| **Analytical Address** | |
| **Dissolution Method** | |
| | |
| **OUTCOME DECISION** | **INADEQUATE** |

# I. EXECUTIVE SUMMARY

This is an **addendum** to the review of the dissolution testing data for above submission [DARRTS: ANDA # 203174 REVBIOQ-02 (Dissolution Review) Submit Date: 12/19/2011]. (b) (5) Specifically, the firm submitted a gratuitous amendment dated 12/14/2011 that was not addressed in the original "dissolution only" review dated 12/19/2011. (b) (5)

Documentation regarding the above issue is provided in Section II of this addendum below.

ANDA 203174 remains inadequate.

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(b) (5)

[2] DARRTS: ANDA # 203174 Bioequivalence/Other Submit Date: 12/14/2011 EDR: Module 1.2. Cover Letter (Last accessed: 01/05/2011)

(b) (5)

## II. ADDITIONAL ATTACHMENT

**From:** Chun, Nam
**Sent:** Wednesday, December 28, 2011 8:48 AM
**To:** Ye, Yumei; Braddy, April
**Cc:** Solana-Sodeinde, Diana A
**Subject:** RE: Finalized - ANDA 203174 Dissolution Review (REV-BIOEQ-02)

Good morning Yumei,

Thank you for your reply
(b) (5) and assign you the amendment piece.

Thanks,

***Nam (Esther) Chun, Pharm.D.***
LCDR, U.S. Public Health Service
Regulatory Project Manager, Branch VI
Division of Bioequivalence I
Office of Generic Drugs
FDA

---

**From:** Ye, Yumei
**Sent:** Tuesday, December 27, 2011 3:28 PM
**To:** Chun, Nam; Braddy, April
**Cc:** Solana-Sodeinde, Diana A
**Subject:** RE: Finalized - ANDA 203174 Dissolution Review (REV-BIOEQ-02)

Good afternoon, Esther:

Thank you very much for your message! I looked at the amendment dated December 14, 2011.

In the amendment, the firm only made the modification in the Section 5 (Preparation of Reagents and Solutions) of the dissolution method (#PD10-017C), (b) (5) . However, the firm provided the Long-Term Storage Stability (LTSS) data of 124 days for Bexarotene in human plasma at -80°C, which is sufficient to cover the maximum study sample storage period of 45 days for the firm's fed BE study. (b) (5) .

Per my discussion with April, please go ahead and (b) (5) assign this amendment piece to me as an amendment review.

Thanks!

Yumei

---

**From:** Chun, Nam
**Sent:** Tuesday, December 27, 2011 2:00 PM

**To:** Ye, Yumei; Braddy, April
**Cc:** Solana-Sodeinde, Diana A
**Subject:** FW: Finalized - ANDA 203174 Dissolution Review (REV-BIOEQ-02)

Hi Yumei,

I processed below dissolution review completed by you on December 19, 2011 and (b) (5)

However, I notice the firm has submitted an amendment on December 14, 2011 and according to the cover letter, the firm is amending the dissolution method.
Can you please take a look at the amendment dated December 14, 2011 and determine if this affects your dissolution review?
(b) (5) and assign this amendment piece to you to include in your review.

Thanks,

***Nam (Esther) Chun, Pharm.D.***
LCDR, U.S. Public Health Service
Regulatory Project Manager, Branch VI
Division of Bioequivalence I
Office of Generic Drugs
FDA

BIOEQUIVALENCE DEFICIENCY

| | |
|---|---|
| ANDA: | 203174 |
| APPLICANT: | Banner Pharmacaps Inc. |
| DRUG PRODUCT: | Bexarotene Capsules, 75 mg |

**NOTE TO THE BIO PROJECT MANAGER:**

(b) (5)

## III. OUTCOME

ANDA: 203174

***Completed Assignment for 203174 ID: 15784***

**Reviewer:** Ye, Yumei **Date Completed:**
**Verifier:** , **Date Verified:**
**Division:** Division of Bioequivalence
**Description:**

---

*Productivity:*

| *ID* | *Letter Date* | *Productivity Category* | *Sub Category* | *Productivity* | *Subtotal* |
|---|---|---|---|---|---|
| 15784 | 12/28/2011 | Other | Addendum | 0 | 0 |
| | | | | Bean Total: | 0 |

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/s/

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YUMEI YE
02/15/2012

UTPAL M MUNSHI
02/17/2012

HOAINHON N CARAMENICO on behalf of DALE P CONNER
02/21/2012

# DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

| | |
|---|---|
| **ANDA No.** | 203174 |
| **Drug Product Name** | Bexarotene Capsules |
| **Strength (s)** | 75 mg |
| **Applicant Name** | Banner Pharmacaps Inc. |
| **Address** | 4125 Premier Drive<br>High Point, NC 27265 |
| **Applicant's Point of Contact** | Vandana Garikipati<br>Manager, Regulatory Affairs |
| **Contact's Phone Number** | (336) 812-8700, extension 23988 |
| **Contact's Fax Number** | (888) 818-4197 |
| **Submission Date(s)** | 06/03/2011 |
| **First Generic** | Yes |
| **Reviewer** | Yumei Ye, Ph.D. |
| | |
| **Study Number (s)** | BXN-P0-541 |
| **Study Type (s)** | Fed |
| **Strength(s)** | 75 mg |
| **Clinical Site** | Algorithme Pharma Inc. |
| **Clinical Site Address** | 1200 Beaumont Ave.<br>Mount-Royal, Quebec, Canada, H3P 3P1 |
| **Analytical Site** | (b) (4) |
| **Analytical Address** | |
| **Dissolution Method** | |
| | |
| **OUTCOME DECISION** | **INADEQUATE** |

# I. EXECUTIVE SUMMARY

**** First-Generic****

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. However, the firm proposed a different dissolution method. The FDA-recommended method and the firm's proposed method are listed below:

| | FDA-recommended Method | Firm's Proposed Method |
|---|---|---|
| **Medium** | Tier 1 Medium: 0.5% HDTMA* in 0.05 M phosphate buffer, pH 7.5<br><br>Tier 2 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 with 0.05 g/L pancreatin enzyme | (b) (4) |
| **Volume** | 900 mL | |
| **Apparatus** | II (Paddle) | |
| **Speed** | 50 rpm | |
| **Sampling Times** | 15, 30, 45 and 60 minutes | |
| **Temperature** | 37ºC ± 0.5ºC | |
| **Specification** | NLT (b) (4)% (Q), 45minutes | |

* Hexadecyltrimethylammonium bromide (HDTMA)

The firm's dissolution testing on its test product is **inadequate**. The firm should conduct its dissolution testing using the above FDA-recommended method.

***Non—Dissolution Testing Issues:*** The firm's Long-Term Storage Stability (LTSS) data of 24 days for Bexarotene in human plasma at -80˚C is not sufficient to cover the maximum storage period of 45 days of the samples in the fed bioequivalence (BE) study. Therefore, the firm will be asked to provide the LTSS data for Bexarotene in human plasma, using the same anticoagulant and storage condition used in the *in vivo* BE study, to cover the maximum storage period (45 days) of the study samples for the fed (BXN-P0-541) BE study.

The Division of Bioequivalence (DB) will review the fed BE study at a later date.

**Table 1: SUBMISSION CONTENT CHECKLIST**

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

**Reviewer's Notes:**

The firm submitted the Long-Term Storage Stability (LTSS) data of 24 days for Bexarotene in human plasma at -80˚C. However, the study samples storage period was 45 days (03/26/2011 - 05/10/2011) for the fed BE study. Therefore, the firm's LTSS data of 24 days for Bexarotene in human plasma at -80˚C is not sufficient to cover the maximum storage period of 45 days of the samples in the fed BE study. The firm will be asked to provide the LTSS data for Bexarotene in human plasma, using the same anticoagulant and storage condition used in the *in vivo* BE study, to cover the maximum storage period (45 days) of the study samples for the fed (BXN-P0-541) BE study.

**FDA Recommended Dissolution Method for Bexarotene Capsules**

**Dissolution Reference from FDA External Dissolution Database**[1]

| Drug Name | Dosage Form | USP Apparatus | Speed (RPMs) | Medium | Volume (mL) | Recommended Sampling Times (minutes) | Date Updated |
|---|---|---|---|---|---|---|---|
| Bexarotene | Capsule | II (Paddle) | 50 | Tier 1 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 Tier 2 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 with 0.05 g/L pancreatin enzyme | 900 | 15, 30, 45 and 60 | 08/17/2006 |

**Dissolution Reference from FDA Internal Dissolution Database**[2]

**(NOT TO BE RELEASED UNDER FOIA)**
**Bexarotene**

Dosage Form: Capsule

Medium: Tier 1 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 Tier 2 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 with 0.05 g/L pancreatin enzyme

Apparatus: II (Paddle)

Speed/RPMs: 50

Modify Date: 8/17/2006

Sampling Times: 15, 30, 45 and 60

Volume: 900

Notes: Revised: 9/5/2005 by dh per Tran e-mail 9/5/2006 Tier 2:NLT (b)(4)% (Q), 45 minutes 900 mL 0.5% HDTMA in 0.05 M pH 7.5 phosphate buffer with 0.005% pancreatin USP paddle, 50 rpm

Specification: NLT (b)(4)% (Q), 45minutes

[1] DB External Dissolution Database, last accessed: 12/08/2011 http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm
[2] DB Internal Dissolution Database, last accessed: 12/08/2011, http://cdsogd1/bio/DissGrid.ASP



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## II. COMMENTS:

1. There is no USP method for this product, but there is an FDA-recommended method. However, the firm proposed a different dissolution method. The FDA-recommended method and the firm's proposed method are listed below:

| | FDA-recommended Method | Firm's Proposed Method |
|---|---|---|
| **Medium** | Tier 1 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5<br><br>Tier 2 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 with 0.05 g/L pancreatin enzyme | (b) (4) |
| **Volume** | 900 mL | |
| **Apparatus** | II (Paddle) | |
| **Speed** | 50 rpm | |
| **Sampling Times** | 15, 30, 45 and 60 minutes | |
| **Temperature** | 37°C ± 0.5°C | |
| **Specification** | NLT (b) (4)% (Q), 45minutes | |

2. The firm's specification is the same as the FDA-recommended specification.

3. The firm's dissolution testing on its test product is **inadequate**. The firm should conduct its dissolution testing using the above FDA-recommended method.

4. Under the firm's dissolution testing conditions, both of the test and reference products showed higher variability at the first 2 sampling time points of 15 and 30 minutes [CV%: 46% - 17% (test) and 91% - 12% (reference), respectively]. However, the variability of the test and reference products decreased as the time increased. Overall, the release of the drug from the test and reference products was quite comparable. The firm's dissolution data for both the test and reference products show that more than (b) (4)% of the labeled amount of Bexarotene for any unit tested dissolved in 45 minutes. The median Tmax in current application is 1.75 hours [1.00 – 6.00 hours (test) and 1.00 – 4.00 hours (reference)] for the fed BE study per the firm's study report.

(b) (4)

5. The firm's LTSS data of 24 days for Bexarotene in human plasma at -80˚C is not sufficient to cover the maximum storage period of 45 days of the samples in the fed BE study. Therefore, the firm will be asked to provide the LTSS data for Bexarotene in human plasma, using the same anticoagulant and storage condition

[3] DARRTS: ANDA #s. (b) (4) (Last accessed: 12/09/2011)

used in the *in vivo* BE study, to cover the maximum storage period (45 days) of study samples for the fed (BXN-P0-541) BE study.

## III. DEFICIENCY COMMENTS:

1. The firm's dissolution testing on its test product is **inadequate**. The firm should conduct its dissolution testing using the FDA-recommended method in 900 mL of Tier 1 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 Tier 2 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 with 0.05 g/L pancreatin enzyme at 37ºC ± 0.5ºC using USP Apparatus II (Paddle) at 50 rpm. The sampling times should be 15, 30, 45 and 60 minutes.

2. The firm's LTSS data of 24 days for Bexarotene in human plasma at -80˚C is not sufficient to cover the maximum storage period of 45 days of the samples in the fed BE study. Therefore, the firm will be asked to provide the LTSS data for Bexarotene in human plasma, using the same anticoagulant and storage condition used in the *in vivo* BE study, to cover the maximum storage period (45 days) of study samples for the fed (BXN-P0-541) BE study.

## IV. RECOMMENDATIONS:

1. The *in vitro* dissolution testing conducted by Banner Pharmacaps Inc. on its test product, Bexarotene Capsules, 75 mg (Lot No. 140000127A), comparing to Eisai Inc.'s Targretin® (bexarotene) Capsules, 75 mg (Lot No. 004681) is inadequate.

2. The firm should conduct dissolution testing using the following FDA-recommended method:

   Medium: Tier 1 - 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5
   Tier 2 - 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 with 0.05 g/L pancreatin enzyme
   Apparatus: II (Paddle)
   Speed: 50 rpm
   Volume: 900 mL
   Temperature: 37°C ± 0.5°C
   Sampling Time Points: 15, 30, 45, and 60 minutes

3. The firm will be asked to provide sufficient LTSS data for Bexarotene in human plasma, using the same anticoagulant and storage condition used in the *in vivo* BE study, to cover the maximum storage period (45 days) of study samples for the fed (BXN-P0-541) BE study.

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



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## V. OUTCOME

ANDA: 203174

***Completed Assignment for 203145 ID: 15568***

**Reviewer:** Ye, Yumei **Date Completed:**
**Verifier:** , **Date Verified:**
**Division:** Division of Bioequivalence
**Description:** Bexarotene Capsules, 75 mg

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*Productivity:*

| *ID* | *Letter Date* | *Productivity Category* | *Sub Category* | *Productivity* | *Subtotal* |
|---|---|---|---|---|---|
| 15568 | 5/7/2011 | Dissolution Data | Dissolution Review | 1 | 1 |
| | | | | Bean Total: | 1 |

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

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/s/

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YUMEI YE
12/16/2011

APRIL C BRADDY
12/16/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
12/19/2011

**BIOEQUIVALENCE CHECKLIST for First Generic ANDA**
FOR APPLICATION COMPLETENESS

**ANDA#** 203174 **FIRM NAME** **Banner Pharmacaps Inc.**

**DRUG NAME** Bexarotene Capsules, 75 mg

**DOSAGE FORM** Capsules
SUBJ: Request for examination of: Bioequivalence Study

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

| | **Summary of Findings by Division of Bioequivalence** |
|---|---|
| ☒ | **Study meets statutory requirements** |
| ☐ | **Study does NOT meet statutory requirements** |
| | **Reason:** |
| | |
| ☐ | **Waiver meets statutory requirements** |
| ☐ | **Waiver does NOT meet statutory requirements** |
| | **Reason:** |

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

Reviewed by:

_____ Date: _____
Glendolynn S. Johnson, Pharm.D.
Reviewer

_____ Date: _____
Nilufer M. Tampal, Ph.D.
Acting Team Leader

_____ Date: _____
Hoainhon N. Caramenico
Acting Deputy Director

| Item Verified: | YES | NO | Required Amount | Amount Sent | Comments |
|---|---|---|---|---|---|
| Protocol | ☒ | ☐ | | | EDR: 5.3.1.2.4 |
| Assay Methodology | ☒ | ☐ | | | **EDR**: 5.3.1.4 |
| Procedure SOP | ☒ | ☐ | | | **EDR**: 5.3.1.4 (Appendix 4) |
| Methods Validation | ☒ | ☐ | | | **EDR**: 5.3.1.4 |
| Study Results Ln/Lin | ☒ | ☐ | | | **EDR**: 5.3.1.2.3 |
| Adverse Events | ☒ | ☐ | | | **EDR**: 5.3.1.2.22 |
| IRB Approval | ☒ | ☐ | | | **EDR**: 5.3.1.2.6 |
| Dissolution Data | ☒ | ☐ | | | **EDR**: 5.3.1.3 |
| Pre-screening of Patients | ☒ | ☐ | | | **EDR**: 5.3.1.2.24 |
| Chromatograms | ☒ | ☐ | | | **EDR**: 5.3.1.4 (Appendix 5) |
| Consent Forms | ☒ | ☐ | | | **EDR**: 5.3.1.2.6 |
| Composition | ☒ | ☐ | | | **EDR**: 2.7.1 |
| Summary of Study | ☒ | ☐ | | | **EDR**: 5.3.1.2.3 |
| Individual Data & Graphs, Linear & Ln | ☒ | ☐ | | | **EDR**: 5.3.1.2.21 |
| PK/PD Data Disk Submitted) | ☒ | ☐ | | | **EDR**: 5.3.1.2.25.3 |

| | | | | | |
|---|---|---|---|---|---|
| Randomization Schedule | ☒ | ☐ | | | **EDR**: 5.3.1.2.10 |
| Protocol Deviations | ☒ | ☐ | | | **EDR**: 5.3.1.2.17 |
| Clinical Site | ☒ | ☐ | | | **EDR**: 5.3.1.2.3 |
| Analytical Site | ☒ | ☐ | | | **EDR**: 5.3.1.2.3 |
| Study Investigators | ☒ | ☐ | | | **EDR**: 5.3.1.2.7 |
| Medical Records | ☒ | ☐ | | | **EDR**: 5.3.1.2.24 |
| Clinical Raw Data | ☒ | ☐ | | | **EDR**: 5.3.1.2.3 |
| Test Article Inventory | ☒ | ☐ | | | **EDR**: 5.3.1.2 |
| BIO Batch Size | ☒ | ☐ | | | (b) (4) Capsules |
| Assay of Active Content Drug | ☒ | ☐ | | | 99.6% (Test Product)<br>100.4% (Reference Product) |
| Content Uniformity | ☒ | ☐ | | | Range: 90.0-110.0%<br>Mean: 99.6 % |
| Date of Manufacture | ☒ | ☐ | | | 01/17/2011 (Test Product) |
| Exp. Date of RLD | ☒ | ☐ | | | 07/12 (Reference Product) |
| BioStudy Lot Numbers | ☒ | ☐ | | | 140000127A (Test Product)<br>004681 (Reference Product) |
| Statistics | ☒ | ☐ | | | **EDR**: 5.3.1.2.12 |

| | | | | | |
|---|---|---|---|---|---|
| Summary results provided by the firm indicate studies pass BE criteria | ☒ | ☐ | | | **EDR**: 5.3.1.2.3* |
| Waiver requests for other strengths / supporting data | ☐ | ☒ | | | None (only 1 strength) |

*Note: The firm used a mixed scaled approach to assess the bioequivalence for this study.

- Average bioequivalence. The ratio of geometric LSmeans with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and Reference product for the ln-transformed parameters $C_{max}$, $AUC_T$ and $AUC_\infty$ were all to be within the 80 to 125% bioequivalence range.

- Reference-scaled bioequivalence. In the event that the Reference-to-Reference intra-subject CV was equal to or greater than 30%, the Test-to-Reference ratio of geometric LSmeans was within the bioequivalence range of 80-125% and the average BE criteria was not met for one of the PK parameters, a scaling approach to the bioequivalence assessment was to be used for the specific parameters not meeting the BE criteria. The Test product was considered to be bioequivalent to the Reference product if the upper bound of the 95% confidence interval of the criteria $(\overline{Y}_T - \overline{Y}_R)^2 - \theta \cdot s^2_{WR}$ was below or equal to zero (where $\theta = \left(\frac{\ln(1.25)}{\sigma_{W0}}\right)^2$, $\sigma_{W0}$=0.25, and $\mu_T$, $\mu_R$ and $s^2_{WR}$ were based on ln-transformed data).

# Additional Comments regarding the ANDA:

This is a **first generic** application for Bexarotene Capsules for the 75 mg strength.

This application is an electronic submission. All of the requested information is located in the electronic document room (EDR). The firm has submitted a fed BE study for Bexarotene Capsules, 75 mg. There is one strength for this test product, hence no waiver request was submitted. The reference product used by the firm for this application is Targretin® (bexarotene) Capsules, 75 mg by Eisai Inc. (NDA # 021055, approved December 29, 1999). Targretin® is also the reference listed drug product in the Orange Book.

**Fed Study (BXN-PO-541)**

The fed study (BXN-PO-541) is a 2-treatment, 3-period, 3 sequence partial replicate crossover study and the study results for Bexarotene (90% confidence intervals) are listed below.

| PARAMETER* | REFERENCE INTRA-SUBJECT CV (%) | AVERAGE BIOEQUIVALENCE | | | | | SCALED BIOEQUIVALENCE** |
|---|---|---|---|---|---|---|---|
| | | GEOMETRIC LS MEANS | | RATIO | 90% CONFIDENCE LIMITS | | "η" UPPER 95% CONFIDENCE LIMIT |
| | | TEST | REFERENCE | | LOWER | UPPER | |
| $C_{max}$ | 31.9 | 355.10 | 309.91 | 114.58 | 104.28 | 125.90 | -0.0181 |
| $AUC_T$ | 21.2 | 985.66 | 931.07 | 105.86 | 100.09 | 111.97 | N/AP |
| $AUC_\infty$ | 19.0 | 999.23 | 955.26 | 104.60 | 99.23 | 110.27 | N/AP |

* units are ng/mL for $C_{max}$ and ng·h/mL for $AUC_T$ and $AUC_\infty$
** Scaled-BE criteria is met when 95% CI upper bound is lower or equal to 0.

The firm conducted dissolution testing with the FDA-recommended method listed below.

| Drug Name | Dosage Form | USP Apparatus | Speed (RPMs) | Medium | Volume (mL) | Recommended Sampling Times (minutes) | Date Updated |
|---|---|---|---|---|---|---|---|
| Bexarotene | Capsule | II (Paddle) | 50 | Tier 1 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 Tier 2 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 with 0.05 g/L pancreatin enzyme | 900 | 15, 30, 45 and 60 | 08/17/2006 |

Note: Method Listed in External OGD Database. Last accessed 07/07/2011.

Several control documents have been submitted to the OGD for this drug product[1] including CC #10-0486 (b) (4) #08-0390 (b) (4) and #11-0109 (b) (4).

The following are recommended to establish bioequivalence of bexarotene capsules[2]:

**Active ingredient:** Bexarotene
**Form/Route:** Capsule/Oral
**Recommended studies:** 1 study
Type of study: Fed Design: Single-dose, two-treatment, two-period crossover in vivo Strength: 75 mg
Subjects: Healthy males, general population. Additional comments:

1. Females should be excluded from study given the potential for embryo-fetal toxicity.

1 OGD Control Database. Last accessed 07/07/11.
2 http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227413.pdf . Last accessed 07/07/11.

2. The protocol should specify and require both formal pregnancy counseling for male subjects regarding the risk to their female partner and a section regarding the counseling in the Informed Consent document.

3. Adequate contraception must be continued for at least 1 month following the last dose of bexarotene.

4. The protocol should include following specific exclusion criteria in addition to other exclusion criteria:

- Subjects demonstrating abnormalities in lipid profile or thyroid-function on screening laboratory evaluations.
- Subjects receiving systemic therapy with Vitamin A in doses of greater than 15000 IU (5000 mcg) per day.
- Subjects who are taking gemfibrozil or tamoxifen.
- Use of any other retinoid class drug (e.g. Isotretinoin) within 30 days of entry into the study.
- Use of topical medications such as corticosteroids or tar baths.
-

5. In addition to the exclusion of drugs that are also know to cause photosensitivity, subjects should be advised to avoid prolonged exposure to the sun or UV light during the study. Similarly, it would be prudent to exclude subjects with a known history of skin cancer.

6. The protocol should include an appropriate plan for continued follow-up, standard care for subsequent follow up, and treatment of subjects who continue to demonstrate thyroid and/or lipid abnormalities at the end of study laboratory evaluations.

**Analytes to measure (in appropriate biological fluid):** Bexarotene in plasma
**Bioequivalence based on (90% CI)**: Bexarotene
**Waiver request of in vivo testing:** Not Applicable

**Dissolution test method and sampling times:**
Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units of the test and reference products. Specifications will be determined upon review of the application.
*Recommended Sep 2010*

From the Division of Bioequivalence standpoint, this submission is **acceptable for filing**.

## Additional Information Requested from the Firm:

None

**Enter Review Productivity and Generate Report**

http://cdsogd1/bioprod

*Productivity:*

| *ID* | *Letter Date* | *Productivity Category* | *Sub Category* | *Productivity* | *Subtotal* |
|---|---|---|---|---|---|
| 14475 | 6/3/2011 | Paragraph 4 | Paragraph 4 Checklist | 1 | 1 |
| | | | | Bean Total: | 1 |

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

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/s/

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GLENDOLYNN S JOHNSON
07/11/2011

NILUFER M TAMPAL
07/12/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
07/13/2011

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# ANDA 203174

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

# ROUTING SHEET

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

| Division: I | Team: 12 | PM: Select |
|---|---|---|

**Electronic ANDA:** Yes ☒ No ☐

**ANDA #:203174**
**Firm Name:Banner Pharmacaps Inc.**
**ANDA Name:Bexarotene Capsules, 75 mg**
**RLD Name:Targretin/Valeant/NDA 21055**

## Electronic AP Routing Summary Located:
**V:\Chemistry Division I\Team 12\Electronic AP Summary**

## AP/TA Letter Located:
**V:\Chemistry Division I\Team 12\Approval Letters**

***Project Manager Evaluation:*** **Date: 2/12/14 Initials:** SKB

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

| | | |
|---|---|---|
| Original Rec'd date 6/6/11 | Date of Application 6/3/11 | Date Acceptable for Filing 6/6/11 |
| Patent Certification (type) PIII/PIV | Date Patent/Excl. expires PIII: '279, '074, '699 (4/22/12); PIV: '676, '761 | Citizens' Petition/Legal Case? Yes☐ No ☒ (If YES, attach email from PM to CP coord) |
| First Generic Yes ☒ No ☐ **DMF#:** (b) (4) (provide MF Jackets) | Priority Approval (Top 100, PEPFAR, etc.)? Yes ☒ No ☐ Comment: FIRST GENERIC Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☐ Date: EMAILED OGDREQUEST | |
| ☐ 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: 3/4/14 (until 9/12/14)* ☐ Warning Letter Issued; Date:

Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☒ Comment:
Date of Acceptable Quality (Chemistry) 12/23/13 Addendum Needed: Yes ☐ No ☒ Comment:
Date of Acceptable Bio 2/20/14 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location: )
Date of Acceptable Labeling 5/30/14 Attached labeling to Letter: Yes ☐ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) _____

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

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

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

***Routing:***

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

☒ Regulatory Support

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

☒ Division

☒ Bob West / Peter Rickman

☐ Kathleen Uhl

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

**OGD APPROVAL ROUTING SUMMARY**

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

**Martin Shimer** **Date: 2/18/2014**
Chief, Reg. Support Branch **Initials:** MHS

| | |
|---|---|
| Contains GDEA certification: Yes ☒ No ☐ | Determ. of Involvement? Yes ☐ No ☒ |
| (required if sub after 6/1/92) | Pediatric Exclusivity System |
| | RLD =Targretin Caps NDA# 21-055<br>Date Checked 8/12/14<br>Nothing Submitted ☒<br>Written request issued ☐<br>Study Submitted ☐ |
| Patent/Exclusivity Certification: Yes ☒ No ☐<br>If Para. IV Certification- did applicant:<br>Notify patent holder/NDA holder Yes ☒ No ☐<br>Was applicant sued w/in 45 days:Yes ☒ No ☐<br>Has case been settled: Yes ☒ No ☐<br>Date settled:12/17/2013<br>Is applicant eligible for 180 day Yes<br>Is a forfeiture memo needed: Yes ☐ No ☒<br>If yes, has it been completed | |
| Generic Drugs Exclusivity for each strength: Yes ☒ No ☐ | |
| Date of latest Labeling Review/Approval Summary _____ | |
| Any filing status changes requiring addition Labeling Review Yes ☐ No ☒ | |

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

Comments:ANDA submitted on 6/6/2011, BOS=Targretin NDA 21-055, PIII certs to '279, '074, and '699 patents, PIV to '676 and '731 patents. Patent Amendment rec'd on 7/25/2011-no change in certs. ANDA ack for filing with a PIV on 6/6/2011 (LO dated 8/24/2011).
Patent Amendment rec'd on 9/6/2011-RR from Eisai in Woodcliff Lake NJ signed and dated 8/30/2011, cover letter of amendment indicates that Eisai is owner of the patent and the NDA.
Patent Amendment rec'd on 10/18/2011-CA 11 CV 901 filed in the D of DE on 10/5/2011 for infringement of the '676 and '731 patents.
Patent Amendment rec'd on 12/20/2013-copy of settlement and license agreement indicating that the license effective date is 7/9/2015.
Patent Amendment rec'd on 2/14/2014-Stipulation and Order of Dismissal for CA 11-901 in which all claims, counterclaims and defenses are dismissed without prejudice on December 17, 2013.
This ANDA is currently the only application pending before OGD for Bexarotene Capsules. As the first applicant which also contained a PIV certification this ANDA is eligible for Full Approval with an award of 180 day exclusivity. In order to retain this eligibility for 180 day exclusivity the Full Approval must be issued by NLT 10/6/2014.

2. ***Labeling Endorsement***

Reviewer, Kimberly Rains: Labeling Team Leader, Malik Imam:
Date8/5/14 Date8/5/14

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

Comments:
From: Imam, Malik
Sent: Tuesday, August 05, 2014 11:19 AM
To: Rains, Kimberly E; Basi, Surjit
Cc: Grace, John F
Subject: RE: AP Package 203174/Bexarotene/Banner

Hello Surjit,

Please endorse the AP routing form on behalf of Kim and myself.

Thanks
Malik

From: Rains, Kimberly E
Sent: Tuesday, August 05, 2014 10:58 AM
To: Basi, Surjit; Imam, Malik
Cc: Grace, John F
Subject: RE: AP Package 203174/Bexarotene/Banner

Hello Surjit,
I concur with approval.
Thank you,

Kim
From: Basi, Surjit
Sent: Monday, August 04, 2014 4:32 PM
To: Rains, Kimberly E; Imam, Malik
Cc: Grace, John F
Subject: AP Package 203174/Bexarotene/Banner

Hello Kim and Malik,

AP package for ANDA 203174 is ready. Please provide concurrence. A draft of the AP letter and latest labeling review are attached.

V:\Chemistry Division I\Team 12\Approval Letters

V:\Chemistry Division I\Team 12\Electronic AP Summary

Thank you,
Surjit

3. ***Paragraph IV Evaluation*** **PIV's Only**
David Read **Date 8/4/14**
OGD Regulatory Counsel **InitialsDTR**
Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:From: Read, David T
Sent: Monday, August 04, 2014 3:01 PM
To: Basi, Surjit; Levine, Susan
Subject: RE: AP Package: ANDA 203174/Bexarotene/Banner

Done. Surjit – you have the App Summ open. Can you sign for me? Thanks.

Dave

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 7/29/14**
Chemistry Div. **I (Raw)** **InitialsASR**
Comments:CMC Adequate.

***OGD Office Management Evaluation***

5. Peter Rickman **Date 8/12/14**
Director, DLPS **Initials rlw/for**

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

Comments: Bioequivalence studies (fasting study only as per current posted Guidance) found acceptable. In-vitro dissolution testing also found acceptable. Bio study sites have accedptable OSI inspection histories. Office-level bio endorsed 9/27/12, 2/20/14.

Final-printed labeling (FPL) found acceptable for approval 5/30/14, as endorsed 8/5/14. No REMS is required - Patient information leaflet only.

CMC found acceptable (Chemistry Review #2) 12/23/13.

OR

6. Robert L. West **Date 8/12/14**
Deputy Director, OGD **Initials RLWest**

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

Comments: Acceptable EES dated 3/4/14 (Verified 8/12/14). No "OAI" Alerts noted.

Banner provided paragraph IV certifications to the '676 and '731 patents and was sued within the 45-day period. The patent litigation was subsequently dismissed with the parties entering into a settlement and license agreement. This agreement becomes effective 7/9/15. There are no additional patents or exclusivity currently listed in the "Orange Book" for this drug product.

As noted above, Banner is eligible for 180-day generic drug exclusivity for this drug product.

Based upon the settlement and license agreement, this first-generic ANDA is recommended for approval.

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

Comments: RLWest for Jason Woo, M.D., M.P.H., Acting Director, Office of Regulatory Operations 8/12/14.
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg. Issue ☐
Press Release Acceptable ☐

Comments:

8. Project Manager **Date 08/12/14**
**Initials SKB**

Comments:

EES DATA:

Establishment Evaluation System

File Edit Search Navigate Options Help Window ORACLE

blishments | Status | Milestones | Comments | Contacts | Product/Process

3174/000 Subtype: N/A Sponsor: BANNER PHARMACAPS

ROTENE

| Establishment Name | Profile Code | Last Milestone Name | Last Milestone Date | Last Compliance Status | Last Compliance Date | OAI Alert | EER Re-eval Date |
|---|---|---|---|---|---|---|---|
| IER PHARMACAPS INC | CSG | OC RECOMMENDATION | 22-NOV-2013 | AC | 22-NOV-2013 | | 18-SEP-2015 (b) (4) (b) (4) (b) (4) |
| IER PHARMACAPS | CHG | OC RECOMMENDATION | 04-MAR-2014 | AC | 04-MAR-2014 | | 22-FEB-2015 (b) (4) |

ecmnd: Date: 04-MAR-2014 Recommendation: ACCEPTABLE Overall Re-eval Date: 12-SEP-2014

ndation History:

| ommendation | Overall Re-eval Date |
|---|---|
| CEPTABLE | 22-FEB-2014 |
| NDING | |

OAI Alert Comments

9:35 AM 8/12/2014

# Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

**Patent and Exclusivity Search Results from query on Appl No 021055 Product 001 in the OB_Rx list.**

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## Patent Data

| Appl No | Prod No | Patent No | Patent Expiration | Drug Substance Claim | Drug Product Claim | Patent Use Code | Delist Requested |
|---|---|---|---|---|---|---|---|
| N021055 | 001 | 5780676 | Jul 14, 2015 | | | U - 509 | |
| N021055 | 001 | 5962731 | Oct 5, 2016 | | | U - 475 | |

## Exclusivity Data

**There is no unexpired exclusivity for this product.**

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

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/s/

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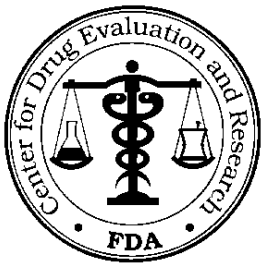
SURJIT K BASI
08/12/2014

# FDA FAX




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

TO: BANNER PHARMACAPS INC TEL: 336-812-2292

ATTN: Vandana Garikipati FAX: 888-818-4197

This facsimile is in reference to your abbreviated new drug application(s), submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

**Pages (including cover): 3**

**SPECIAL INSTRUCTIONS:**

DATE: 2/6/2014

TO: BANNER PHARMACAPS INC

ATTN: Vandana Garikipati

E-Mail: vandana.garikipati@bannerls.com

FAX: 888-818-4197

**RE:** Update summary of filed and pending original ANDA(s)

Dear Sir or Madam:

The Office of Generic Drugs (OGD) in the Center for Drug Evaluation and Research, Food and Drug Administration (FDA), is providing you with this one-time communication on the status of your filed and pending original abbreviated new drug application(s) (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act. OGD is providing these updates as an interim measure to help applicants assess the status of their current submissions as we transition towards predictable goal times pursuant to the Generic Drug User Fee Amendments of 2012 (GDUFA).

Your status update is limited to available review information as of January 29, 2014. Any additional information regarding your ANDA collected after this date is neither considered nor provided. Furthermore, your ANDA status is subsequently subject to revision pending additional information or concerns raised by any of the discipline reviews (bioequivalence, clinical, chemistry, microbiology, labeling, facility), other unforeseen legal, scientific or regulatory issues, or inspectional results, which can also impact the status or ability to issue a complete response. Any applicable fees can also affect the status of your ANDA.

OGD is providing your ANDA status update in the attached chart with a list of applicable acronyms. The chart only contains current information regarding discipline review and does not forecast if and when OGD will issue a complete response, tentative approval, or final approval letter.

Please do not respond to this communication by asking FDA or your Regulatory Project Manager for additional or more detailed information. This is a one-time communication intended to assist you to ascertain the current status of submissions. It is not feasible for us to respond to a high volume of follow up inquiries.

Sincerely yours,

CAPT Aaron W. Sigler, USPHS
Chief, Review Support Branch

| ANDA | DRUG NAME | CHEM | BIO | MICRO | LABEL | CLINICAL | FACILITY |
|---|---|---|---|---|---|---|---|
| 202539 | PARICALCITOL | IQ | IQ | NA | AQ | NA | AC |
| 203174 | BEXAROTENE | AQ | IQ | NA | AQ | NA | AC |
| 204648 | DICLOFENAC POTASSIUM | IQ | IQ | NA | IQ | NA | AC |

(b) (4)

## CHART ACRONYMS

### Column Headings

ANDA - The application number for your Abbreviated New Drug Application
DRUG NAME - The official filed name of the drug associated with the ANDA number
CHEM - Product Quality Chemistry Review
BIO - Bioequivalence Review, typically including OSI, if applicable
MICRO - Microbiology Review
LABEL - Labeling Review
CLINICAL - Clinical Review
FACILITY - Overall Facility inspections summary. All facilities must be acceptable at the time of 29 JAN 14 in order to warrant an adequate notation. If one of more facility is not acceptable then the FACILITY column will be marked as such. OSI information is not considered.

### Discipline Notations

IQ - Inadequate. This particular discipline is currently found to be inadequate.

AQ - Adequate. This particular discipline was found to be adequate when the information was gathered for this communication.

UR - Under Review. This particular discipline is currently assigned OR under review with the discipline team.

NR -Not Reviewed. This particular discipline is either currently not under review or assigned.

NA - Not applicable. This particular discipline is not required for the approval of this ANDA.

### Facility Notations

PN - Pending, i.e., one or more facilities have been inspected and are pending an outcome.

AC - All facilities are acceptable at the time of this publication.

*Please note that you may receive your updates in multiple communications over time, based on the number of ANDAs pending in OGD.

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

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/s/

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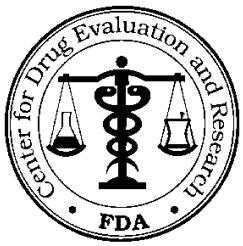
AARON W SIGLER
02/07/2014

# EASILY CORRECTABLE DEFICIENCY FAX

ANDA 203174

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




APPLICANT: Banner Pharmacaps Inc. TEL: 336-812-2292

ATTN: Vandana Garikipati, Manager, RA FAX: 888-818-4197

FROM: Esther Chuh FDA CONTACT PHONE: (240) 276-9663

Dear Sir or Madam:

This communication is in reference to your abbreviated new drug application (ANDA) dated June 3, 2011, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bexarotene Capsules, 75 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, Esther Chuh at (240) 276-9663.

We have completed our review, as amended, and have the following comments:

**PRODUCT QUALITY**

1. (b) (4)

2.

3.

4.

Sincerely yours,

*{See appended electronic signature page}*

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

---

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

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/s/

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BHAGWANT D REGE
11/22/2013

OFFICE OF GENERIC DRUGS EXPEDITED REVIEW REQUESTED

ANDA#/SUPPLEMENT#: MULTIPLE ANDAs
DRUG: See list below of pre-MMA Exepedite Candidates

APPLICANT: MULTIPLE APPLICANTS
DATE OF SUBMISSION:VARIOUS

The Office of Generic Drugs may grant expedited review status to either an Original or Supplemental abbreviated new drug application for the following reasons (MaPP 5240.1,& MaPP 5240.3). At least one of the criteria must be met to receive Expedited Review Status:

1. PUBLIC HEALTH NEED. Events that affect the availability of a drug for which there is no alternative

2. EXTRAORDINARY HARDSHIP ON THE APPLICANT.

   a) Catastrophic events such as explosion, fire storms damage.

   b) Events that could not have been reasonably foreseen and for which the applicant could not plan. Examples include:

      - Abrupt discontinuation of supply of active ingredient, packaging material, or container closure; and
      - Relocation of a facility or change in an existing facility because of a catastrophic event(see item 2.a)

3. AGENCY NEED.
   a) Matters regarding the government's drug purchase program, upon request from the appropriate FDA office.
   b) Federal or state legal/regulatory actions, including mandated formation changes or labeling changes if it is in the Agency's best interest.
   c) Expiration-date extension or packaging change when the drug product is the subject of a government contract award.
   d) Request for approval of a strength that was previously tentatively approved (To be used in those cases where l8O-day generic drug exclusivity prevented full approval of all strengths).
   e) MaPP 5240.3 conditions.

RECOMMENDATIONS:

| DISCIPLINE | STATUS | SIGNATURE/DATE |
|---|---|---|
| Team Project Manager (PM must Endorse) | Grant☒ Deny☐ | |
| Chemistry Team Leader (sign as needed) | Grant☒ Deny☐ | |
| Micro Team Leader (sign as needed) | Grant☒ Deny☐ | |
| Labeling Team Leader (sign as needed) | Grant☒ Deny☐ | |
| Chem. Div./Deputy Director (DO must Endorse) | Grant☒ Deny☐ | |
| Office Director/Deputy Director (email concurrence) (Original ANDAs) | Grant☒ Deny☐ | |

RETURN TO PROJECT MANAGER CHEMISTRY TEAM: SELECT TEAM #
a) When expedited review is denied, notify the applicant by telephone

ENTER FORM INTO DFS DATE 10/18/13
Paste Email Copy Below:

On 10/8/13 OGD Leadership decided to grant expedite review status to the following listed pre-GDUFA (Submitted prior to 10/1/12) Paragraph IV applications that were submitted on the first day that any valid Paragraph IV application for the drug in question may be submitted. This action is being taken to ensure consistency in review priority in order to for timely review and FDA action on these ANDAs. These are ANDA if submitted in the year 1 and 2 cohorts, FDA would expedite review under the GDUFA Commitment provided in the Generic Drug User Fee Act Program Performance Goals and Procedures (http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf)

(b) (4)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 201963 | Actavis | Pramipexole Dihydrochloride | Extended-release Tablets | 0.375 mg, 0.75 mg, 1.5 mg, 3 mg and 4.5 mg | Mirapex ER | 6/1/2010 | 10/1/2013 |

(b) (4)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 202118 | Teva | Darunavir Ethanolate | Tablets | 75 mg, 150 mg, 300 mg, 400 mg and 600 mg | Prezista | 6/23/2010 | 10/23/2013 |
| 202136 | Mylan | Darunavir Ethanolate | Tablets | 75 mg, 150 mg, 300 mg, 400 mg and 600 mg | Prezista | 6/23/2010 | 10/23/2013 |
| 202103 | Apotex | Dasatinib | Tablets | 20 mg, 50 mg, 70 mg and 100 mg | Sprycel | 6/28/2010 | 10/28/2013 |
| 202090 | Roxance | Sodium Oxybate | Oral Solution | 500 mg/mL | Xyrem | 7/8/2010 | 11/8/2013 |
| 202144 | Watson | Hydromorphone Hydrochloride | Extended-release Tablets | 16 mg | Exlago | 8/2/2010 | 12/2/2013 |
| 202294 | Handa | Dexlansoprazole | Delayed-release Capsules | 60 mg | Dexilant | 8/25/2010 | 12/25/2013 |
| 201676 | Zydus | Sirolimus | Tablets | 0.5 mg | Rapamune | 8/25/2010 | 12/25/2013 |
| 200744 | Nycomed | Tacrolimus | Ointment | 0.10% | Protopic | 9/9/2010 | 1/9/2014 |
| 202337 | Mylan | Doxepin Hydrochloride | Tablets | 3 mg and 6 mg | Silenor | 9/16/2010 | 1/16/2014 |

(b) (4)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 91182 | Statson | Glycopyrrolate | Tablets | 2 mg | Robinul Forte | 10/12/2010 | 2/12/2014 |
| (b) (4) | | | | | | | |
| 202487 | Teva | Sitagliptin Phosphate | Tablets | 25 mg, 50 mg and 100 mg | Januvia | 10/18/2010 | 2/18/2014 |
| 202425 | Apotex | Sitagliptin Phosphate | Tablets | 25 mg, 50 mg and 100 mg | Januvia | 10/18/2010 | 2/18/2014 |
| (b) (4) | | | | | | | |
| 202426 | Apotex | Sitagliptin Phosphate and Metformin Hydrochloride | Tablets | 50 mg/500 mg and 50 mg/1000 mg | Janumet | 10/18/2010 | 2/18/2014 |
| (b) (4) | | | | | | | |
| 202349 | Watson | Estradiol Valerate and Dienogest | Tablets | 3 mg;2 mg/2 mg;2 mg/3 mg and 1 mg | Natazia | 10/22/2010 | 2/22/2014 |
| 202509 | Anchen | Dutasteride and Tamsulosin Hydrochloride | Capsules | 0.5 mg/0.4 mg | Jalyn | 10/26/2010 | 2/26/2014 |
| 91118 | Ranbaxy | Minocycline Hydrochloride | Extended-release Tablet | 80 mg | Solodyn | 10/27/2010 | 2/27/2014 |
| (b) (4) | | | | | | | |
| 202511 | Novel Labs | Sodium Sulfate, Potassium Sulfate and Magnesium Sulfate | Oral Solution | 17.5 g/3.13 g/1.6 g | Suprep Bowel Prep Kit | 11/8/2010 | 3/8/2014 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 200744 | Fougera | Tacrolimus | Ointment | 0.03% | Protopic | 11/22/2010 | 3/22/2014 |
| 200652 | Roxane | Alosetron Hydrochloride | Tablets | 0.5 mg and 1 mg | Lotronex | 12/2/2010 | 4/2/2014 |
| 202731 | Teva | Dexmethylphenidate Hydrochloride | Extended-release Capsules | 40 mg | Focalin XR | 12/20/2010 | 4/20/2014 |
| 202573 | Roxane | Ritonavir | Tablets | 100 mg | Norvir | 12/21/2010 | 4/21/2014 |
| (b) (4) | | | | | | | |
| (b) (4) | | | | | | | |
| 202827 | Roxane | Lisdexamfetamine Dimesylate | Capsules | 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg | Vyvanse | 2/23/2011 | 6/23/2014 |
| 202830 | Amneal | Lisdexamfetamine Dimesylate | Capsules | 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg | Vyvanse | 2/23/2011 | 6/23/2014 |
| 202835 | Mylan | Lisdexamfetamine Dimesylate | Capsules | 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg | Vyvanse | 2/23/2011 | 6/23/2014 |
| 202836 | Sandoz | Lisdexamfetamine Dimesylate | Capsules | 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg | Vyvanse | 2/23/2011 | 6/23/2014 |
| (b) (4) | | | | | | | |
| 202308 | Sandoz | Azithromycin | Ophthalmic Solution | 1% | Azasite | 3/3/2011 | 7/3/2014 |
| 202993 | Par | Dextromethorphan Hydrobromide and Quinidine Sulfate | Capsules | 20 mg/10 mg | Nuedexta | 3/7/2011 | 7/7/2014 |
| 202931 | Mylan | Frovatriptan | Tablets | 2.5 mg | Frova | 3/9/2011 | 7/9/2014 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Succinate | | | | | |
| 203007 | Natco | Lapatinib Ditosylate | Tablets | 250 mg | Tykerb | 3/14/2011 | 7/14/2014 |
| (b) (4) | | | | | | | |
| 202912 | Lupin | Abacavir Sulfate, Lamivudine and Zidovudine | Tablets | 300 mg/150 mg/300 mg | Trizivir | 3/22/2011 | 7/22/2014 |
| 203005 | Alkem | Mycophenolic Mofetil | For Oral Suspension | 200 mg/mL | Cellcept | 3/25/2011 | 7/25/2014 |
| (b) (4) | | | | | | | |
| 203039 | Teva | Clozapine | Orally Disintegrating Tablets | 150 mg and 200 mg | Fazaclo | 4/8/2011 | 8/8/2014 |
| 203139 | TWI | Megestrol Acetate | Oral Suspension | 125 mg/mL | Megace ES | 4/27/2011 | 8/27/2014 |
| (b) (4) | | | | | | | |
| (b) (4) | | | | | | | |
| 202521 | Sandoz | Palonosetron Hydrochloride | Injection | 0.05 mg/mL, 1.5 mL and 5 mL vials | Aloxi | 5/27/2011 | 9/27/2014 |
| (b) (4) | | | | | | | |
| 203286 | Zydus | Mesalamine | Delayed-release Tablets | 800 mg | Asacol HD | 7/13/2011 | 11/13/2014 |
| (b) (4) | | | | | | | |
| 202206 | Anchen | Pramipexole Dihydrochloride | Extended-release Tablets | 2.25 mg and 3.75 mg | Mirapex ER | 7/26/2011 | 11/26/2014 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 203371 | Famy Care | Norethindrone and Ethinyl Estradiol and Ferrous Fumarate | Chewable Tablets | 0.8 mg/0.025 mg and 75 mg | Generess Fe | 8/5/2011 | 12/5/2014 |
| 203347 | Hetero | Maraviroc | Tablets | 150 mg and 300 mg | Selzentry | 8/8/2011 | 12/8/2014 |
| 203560 | Actavis | Deferasirox | Tablets | 125 mg, 250 mg, and 500 mg | Exjade | 10/28/2011 | 2/28/2015 |
| 203611 | Actavis | Gabapentin | Tablets | 300 mg and 600 mg | Gralise | 10/31/2011 | 3/3/2015 |
| 203564 | Silarx | Lamivudine | Oral Solution | 10 mg/mL | Epivir | 11/22/2011 | 3/22/2015 |
| 203649 | Sandoz | Treprostinil Sodium | Injection | 10 mg/mL, 20 mL vial | Remodulin | 12/2/2011 | 4/2/2015 |
| (b) (4) | | | | | | | |
| (b) (4) | | | | | | | |
| 203741 | Alkem | Nebivolol Hydrochloride | Tablets | 2.5 mg, 5 mg, 10 mg, and 20 mg | Bystolic | 12/19/2011 | 4/19/2015 |
| 203683 | Watson | Nebivolol Hydrochloride | Tablets | 2.5 mg, 5 mg, 10 mg, and 20 mg | Bystolic | 12/19/2011 | 4/19/2015 |
| 203821 | Glenmark | Nebivolol Hydrochloride | Tablets | 2.5 mg, 5 mg, 10 mg, and 20 mg | Bystolic | 12/19/2011 | 4/19/2015 |
| 203966 | Torrent | Nebivolol Hydrochloride | Tablets | 2.5 mg, 5 mg, 10 mg, and 20 mg | Bystolic | 12/19/2011 | 4/19/2015 |
| 203828 | Indchemie | Nebivolol Hydrochloride | Tablets | 2.5 mg, 5 mg, 10 mg, and 20 mg | Bystolic | 12/19/2011 | 4/19/2015 |
| (b) (4) | | | | | | | |
| 203689 | Watson | Vardenafil | Orally Disintegrating | 10 mg | Staxyn | 12/22/2011 | 4/22/2015 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Hydrochloride | Tablets | | | | |
| (b) (4) | | | | | | | |
| 203790 | Actavis | Adapalene and Benzoyl Peroxide | Gel | 0.1%/2.5% | Epiduo | 12/30/2011 | 4/30/2015 |
| (b) (4) | | | | | | | |
| (b) (4) | | | | | | | |
| 204025 | Accord | Fosaprepitant Dimeglumine | Injection | 150 mg/vial | Emend | 1/25/2012 | 5/25/2015 |
| (b) (4) | | | | | | | |
| (b) (4) | | | | | | | |
| (b) (4) | | | | | | | |
| 204029 | Abon | Clofarabine | Injection | 1 mg/mL, 20 mL vial | Clolar | 2/23/2012 | 6/23/2015 |
| (b) (4) | | | | | | | |
| 204082 | Roxane | Desvenlafaxine Succinate | Extended-release Tablets | 50 mg and 100 mg | Pristiq | 2/29/2012 | 6/29/2015 |
| (b) (4) | | | | | | | |
| 204065 | Watson | Desvenlafaxine Succinate | Extended-release Tablets | 50 mg and 100 mg | Pristiq | 2/29/2012 | 6/29/2015 |
| (b) (4) | | | | | | | |
| 204083 | Roxane | Desvenlafaxine Succinate | Extended-release Tablets | 50 mg and 100 mg | Pristiq | 2/29/2012 | 6/29/2015 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 204095 | Mylan | Desvenlafaxine Succinate | Extended-release Tablets | 50 mg and 100 mg | Pristiq | 2/29/2012 | 6/29/2015 |
| 204003 | Alembic | Desvenlafaxine Succinate | Extended-release Tablets | 50 mg and 100 mg | Pristiq | 2/29/2012 | 6/29/2015 |
| 204020 | Zydus | Desvenlafaxine Succinate | Extended-release Tablets | 50 mg and 100 mg | Pristiq | 2/29/2012 | 6/29/2015 |
| 204009 | Anchen | Desvenlafaxine Succinate | Extended-release Tablets | 50 mg and 100 mg | Pristiq | 2/29/2012 | 6/29/2015 |

(b) (4)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 204028 | Sandoz | Desvenlafaxine Succinate | Extended-release Tablets | 50 mg and 100 mg | Pristiq | 2/29/2012 | 6/29/2015 |
| 204079 | Lupin | Moxifloxacin Hydrochloride | Ophthalmic Solution | 0.5% | Moxeza | 2/29/2012 | 6/29/2015 |

(b) (4)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 204403 | Alvogen | Rivastigmine | Transdermal System Extended-release | 4.6 mg/24 hr and 9.4 mg/24 hr | Exelon Patch | 6/12/2012 | 7/22/2015 |

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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|---|---|---|---|---|---|---|---|
| (b) (4) | | | | | | | |
| 204268 | Perrigo | Testosterone | Gel | 1.62% | Androgel | 4/6/2012 | 8/6/2015 |
| (b) (4) | | | | | | | |
| 204299 | Novel Labs | Zolpidem Tartrate | Sublingual Tablets | 1.75 mg and 3.5 mg | Intermezzo | 4/10/2012 | 8/10/2015 |
| (b) (4) | | | | | | | |
| 90694 | Lupin | Duloxetine Hydrochloride | Delayed-release Capsules | 40 mg | Cymbalta | 5/10/2012 | 9/10/2015 |
| (b) (4) | | | | | | | |
| (b) (4) | | | | | | | |
| (b) (4) | | | | | | | |
| 204438 | Par | Glycopyrrolate | Oral Solution | 1 mg/5 mL | Cuvposa | 6/20/2012 | *9/30/2015* |
| (b) (4) | | | | | | | |
| 203485 | Accord | Pemetrexed Disodium | For Injection | 1000 mg/vial | Alimta | 6/27/2012 | *9/30/2015* |
| 202027 | Apotex | Diclofenac Sodium | Topical Solution | 1.5% | Pennsaid | 7/11/2012 | 1/11/2015 |
| (b) (4) | | | | | | | |
| 204571 | Watson | Testosterone | Gel | 10 mg/actuation | Fortesta | 8/14/2012 | 2/14/2015 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| (b) (4) | | | | | | | | |
| (b) (4) | | | | | | | | |
| 202191 | Novel Labs | Metoclopramide Hydrochloride | Orally Disintegrating Tablets | 5 mg and 10 mg | Metozolv ODT | 8/24/2010 | 12/24/2013 | CR |
| (b) (4) | | | | | | | | |
| 202362 | Mylan | Atovaquone and Proguanil Hydrochloride | Tablets | 62.5 mg/25 mg | Malarone | 9/14/2010 | 1/14/2014 | CR |
| 202327 | Watson | Sitagliptin Phosphate | Tablets | 25 mg, 50 mg and 100 mg | Januvia | 10/18/2010 | 2/18/2014 | CR |
| 202365 | Watson | Sitagliptin Phosphate and Metformin Hydrochloride | Tablets | 50 mg/500 mg and 50 mg/1000 mg | Janumet | 10/18/2010 | 2/18/2014 | CR |
| (b) (4) | | | | | | | | |
| (b) (4) | | | | | | | | |
| 202595 | Natco | Oseltamivir Phosphate | Capsules | 75 mg | Tamiflu | 11/15/2010 | 3/15/2014 | CR |
| (b) (4) | | | | | | | | |
| 202470 | River's Edge | Desonide | Gel | 0.05% | Desonate | 12/1/2010 | 4/1/2014 | CR |
| 202564 | Actavis | Clindamycin Phosphate and Tretinoin | Gel | 1.2%/0.025% | Ziana | 12/17/2010 | 4/17/2014 | CR |
| (b) (4) | | | | | | | | |
| 202802 | Actavis | Lisdexamfetamine Dimesylate | Capsules | 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg | Vyvanse | 2/23/2011 | 6/23/2014 | CR |
| (b) (4) | | | | | | | | |
| 203056 | Sandoz | Bimatoprost | Ophthalmic Solution | 0.01% | Lumigan | 4/5/2011 | 8/5/2014 | CR |
| 203113 | Lupin | Norethindrone Acetate and Ethinyl Estradiol / Ethinyl Estradiol and Ferrous Fumarate | Tablets | 1 mg/0.01 mg, 0.01 mg and 75 mg | Lo Loestrin Fe | 4/29/2011 | 8/29/2014 | CR |
| 203174 | Banner | Bexarotene | Capsules | 75 mg | Targretin | 6/6/2011 | 10/6/2014 | CR |
| 203217 | Teva | Risedronate Sodium | Delayed-release Tablets | 35 mg | Atelvia | 6/9/2011 | 10/9/2014 | CR |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 203294 | Aurobindo | Azithromycin | for Injection | 500 mg/vial | Zithromax | 6/17/2011 | 10/17/2014 | CR |
| 202159 | Hikma | Hydromorphone Hydrochloride | Injection | 2 mg/mL | Dilaudid | 6/22/2011 | 10/22/2014 | CR |
| 202595 | Natco | Oseltamivir Phosphate | Capsules | 30 mg and 45 mg | Tamiflu | 8/2/2011 | 12/2/2014 | CR |
| 203382 | Sandoz | Maraviroc | Tablets | 150 mg and 300 mg | Selzentry | 8/8/2011 | 12/8/2014 | CR |
| (b) (4) | | | | | | | | |
| 202842 | Par | Dexmethylphenidate | Extended-release Capsules | 35 mg | Focalin XR | 9/29/2011 | 1/29/2015 | CR |
| (b) (4) | | | | | | | | |
| (b) (4) | | | | | | | | |
| 203563 | Sandoz | Levoleucovorin Calcium | Injection | 10 mg/mL, 17.5 mL vial and 25 mL vial | Fusilev | 10/26/2011 | 2/26/2015 | CR |
| 203557 | Sandoz | Piperacillin Sodium and Tazobactam Sodium | For Injection | 12 g/1.5 g per vial (pharmacy bulk) | Zosyn | 12/6/2011 | 4/6/2015 | CR |
| 202743 | Perrigo | Azelastine Hydrochloride | Nasal Spray | 205.5 mcg/spray | Astepro | 12/15/2011 | 4/15/2015 | CR |
| 203659 | Amerigen | Nebivolol Hydrochloride | Tablets | 2.5 mg, 5 mg, 10 mg, and 20 mg | Bystolic | 12/19/2011 | 4/19/2015 | CR |
| 204172 | Lupin | Desvenlafaxine Succinate | Extended-release Tablets | 50 mg and 100 mg | Pristiq | 2/29/2012 | 6/29/2015 | CR |
| 204144 | Anchen | Sitagliptin Phosphate and Metformin Hydrochloride | Extended-release Tablets | 50 mg/500 mg and 50 mg/1000 mg | Janumet XR | 3/16/2012 | 7/16/2015 | CR |

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/s/

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ROBERT T GAINES
10/24/2013

ROBERT L WEST
10/24/2013
Deputy Director, Office of Generic Drugs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA See Attached

Date: 8/20/2012

Attention:
Department of Regulatory Affairs
BANNER PHARMACAPS
4125 PREMIER DR
HIGH POINT, NC 27265

RE: Request to Withdraw Applications from the Generic Drug Backlog to Avoid Incurring Backlog Fee

Dear Sir or Madam:

This letter is in reference to your Abbreviated New Drug Applications (ANDAs), included in the attached list, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III), enacted on July 9, 2012, establish a one-time backlog fee for any ANDA that is pending at the US Food and Drug Administration (FDA) on October 1, 2012 and has not received a tentative approval.

FDA is issuing this letter to encourage applicants who have pending ANDAs for which the applicants no longer wish to seek approval to notify FDA of the request to withdraw those ANDAs (see Federal Register Notice Docket Number FDA-2012-N-0879). **Requests for withdrawal should be submitted in writing individually for each ANDA as a "Request for Withdrawal" to the affected ANDA**. A decision to withdraw the ANDA is without prejudice to refiling.

Any ANDA that is not withdrawn by September 28, 2012 will incur the obligation to pay the backlog fee. Payment of backlog fees will be due no later than 30 calendar days after publication in the Federal Register of a notice (to be issued by October 31, 2012) announcing the amount of the backlog fee. Applicants with original ANDAs that fail to pay the backlog fee by the due date will be placed on a publicly available arrears list, and FDA will not receive new ANDAs or supplements submitted by those applicants, or any affiliates of those applicants, until the outstanding fee is paid.

To avoid incurring the backlog fee for an application, you, the applicant, must submit a request to withdraw the application and that request must be received by the FDA on or before **September 28, 2012**. However, to expedite this process, you are encouraged to submit the request by **September 15, 2012**.

You should submit the request to withdraw your applications by standard application submission methods. If an application was submitted via the FDA electronic gateway, a request for withdrawal should be submitted to the application via the gateway. Alternatively, you should send written notification to the ANDA archival file at the following address: Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Document Control Room, Metro Park North VII, 7620 Standish Pl., Rockville, MD 20855.

In addition, please provide electronic confirmation of all ANDAs you wish to withdraw by sending an email to OGDGDUFA@fda.hhs.gov within the timeframe specified above**.**

For your convenience, a list of pending ANDAs for which we have identified you as the applicant is attached. **However, this list may be incomplete. Therefore, it is important to note that the absence of an ANDA from this list does not exempt that ANDA from incurring a backlog fee. Please verify the list for completeness of all ANDAs you have submitted. Discrepancies should be reported to the email address noted above.**

The GDUFA statute exempts only generic Positron Emission Tomography (PET) products from the user fees. There are no additional exemptions or waivers for GDUFA fees beyond those in the statute.

If you have questions regarding this communication, contact Thomas Hinchliffe at OGDGDUFA@fda.hhs.gov.

Please direct general GDUFA questions to ASKGDUFA@fda.hhs.gov.

Sincerely,

*{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

CC: Attached List of ANDAs

**PENDING ANDAs**
**(List produced as of 8/20/2012)**

| ANDA # | Drug Name |
|---|---|
| 203174 | BEXAROTENE |

APPEARS THIS WAY ON ORIGINAL

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/s/

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ROBERT L WEST
08/22/2012
Deputy Director, Office of Generic Drugs, for

# BIOEQUIVALENCE AMENDMENT

ANDA 203174

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

APPLICANT: Banner Pharmacaps Inc.

TEL: (336) 812-8700 Ext. 23988

ATTN: Vandana Garikipati

FAX: 1(888) 818-4197

FROM: Teresa Ramson

FDA CONTACT PHONE: (240) 276-8782

Dear Sir or Madam:

This facsimile is in reference to the bioequivalence data submitted on June 03, 2011, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bexarotene Capsules, 75 mg.

Reference is also made to amendment submitted on December 14, 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 ____ page(s). 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.*

| | |
|---|---|
| ANDA: | 203174 |
| APPLICANT: | Banner Pharmacaps Inc. |
| DRUG PRODUCT: | Bexarotene Capsules, 75 mg |

The Division of Bioequivalence I (DB I) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence (BE) study will be conducted later. The following deficiencies have been identified:

1. Your dissolution testing data are incomplete. You have submitted dissolution testing data using your own proposed dissolution method. Your method differs from the current FDA-recommended method. In order for the DB I to properly evaluate your proposed dissolution method and compare it with the FDA-recommended method, please conduct additional dissolution testing on the test and reference products (12 units each) using the following FDA method:

   Medium:

   Tier 1 - 0.5% Hexadecyltrimethylammonium bromide (HDTMA) in 0.05 M phosphate buffer, pH 7.5

   Tier 2 - 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 with 0.05 g/L pancreatin enzyme

   Apparatus: II (Paddle)
   Speed: 50 rpm
   Volume: 900 mL
   Temperature: 37°C ± 0.5°C
   Sampling Time Points: 15, 30, 45, and 60 minutes and until at least 80% of the labeled amount of the drug in the dosage form is dissolved.

   For the requested dissolution testing, please submit the complete dissolution method information which should include the following:

   - A complete dissolution study report with each method used.
   - Individual dissolution testing data for 12 dosage units of each strength of the test and reference products.

- Mean, range and coefficient of variation (%CV) data of the dissolution results.
- Comparative mean dissolution graphs for each strength.
- Analytical Method Validation Report

The DB I will determine the most suitable method and specification for your test product following the evaluation of the dissolution testing data from both methods.

2. The DB I notes that in your proposed dissolution method (75 rpm), [redacted] (b) (4) (b) (4) (b) (4) Finally, please also state if you [redacted] (b) (4) (b) (4) for the testing using the FDA-recommended dissolution method.

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/

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DALE P CONNER
02/23/2012

# Telephone Fax

ANDA 203174

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
***Angela.payne@fda.hhs.gov***

TO: Banner Pharmacaps Inc. TEL: 336-812-2-8700

ATTN: Vandana Garikipati FAX: 888-818-4197

FROM: Mrs. Angela Payne

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 Bexarotene Capsules.

**Pages (including cover):** 3

***SPECIAL INSTRUCTIONS:***

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

***Office of Generic Drugs***
***Document Control Room***
***7620 Standish Place***
***Rockville, Maryland 20855***

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

*See attached labeling comments.*

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

---

ANDA Number: 203174 Date of Submission: 03 JUN 2011

Applicant's Name: Banner Pharmacaps Inc

Established Name: Bexarotene Capsule 75 mg, soft gelatin capsule

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Labeling Comments:

1. CONTAINER - 100s

   a. Decrease the prominence of the company logo to be less then the established name and strength.

   b. Net quantity statement should not be in bold font.

   c. Add "Pharmacist- Dispense attached patient leaflet" on to the main panel.

2. PACKAGE INSERT-

   TITLE section- Add "Rx Only" after the title section. In addition, it is not necessary to cite bexarotene twice in the title section, delete one. Delete or relocate manufacturer name so that it is not in close proximity to the established name information.

3. PATIENT LEAFLET-

   a. Place the title "Patient's Instructions For Use" before the established name in the title section.

   b. We encourage you to add the phonetic spelling for the product to follow the established name.

   c. We encourage you to add the "1-800 FDA 1088- Report Adverse Reaction statement.

Revise your labels and labeling, as instructed above, and submit final print (or draft) electronically.

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

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling and your previous labeling, and the latest approved labeling for the reference listed drug 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

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/s/

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JOHN F GRACE
09/27/2011
for Wm Peter Rickman

# ANDA FILING CHECKLIST
## (CTD or eCTD FORMAT)
## FOR COMPLETENESS AND ACCEPTABILITY of an APPLICATION

ANDA: 203174
APPLICANT: BANNER PHARMACAPS INC.
RELATED APPLICATION(S): NA

DRUG NAME: BEXAROTENE
DOSAGE FORM: CAPSULES, 75 MG

LETTER DATE: **JUNE 3, 2011**
RECEIVED DATE: JUNE 6, 2011

☒ P-IV
☒ FIRST GENERIC
☐ EXPEDITED REVIEW REQUEST (Approved/Denied)
☐ PEPFAR

Electronic or Paper Submission: Gateway  Type II DMF# BEXAROTENE - (b) (4)

**BASIS OF SUBMISSION:**
**NDA/ANDA: 21-055**
**FIRM: EISAI**
**RLD: TARGRETIN**

****Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s).**

**Review Team:**

| | |
|---|---|
| CHEM Team: **DC1 TM 12**<br>☒ **Activity** | Bio Team: **DBE 1 TM4: Nilufer Tampal**<br>☐ **Activity** |
| CHEM Team Leader: Bing Cai<br>☒ **No Assignment Needed in DARRTS** | Bio PM: Diana Solana **Sodeinde**<br>☐ **FYI** |
| CHEM RPM: **Eunjung (Esther) Chuh**<br>☒ **FYI** | Clinical Endpoint Team: **(No)**<br>☐ **Activity** |
| DMF Review Team Leader: **Aloka Srinivasan**<br>☒ **FYI** | |
| Labeling Reviewer: **Payne, Angela**<br>☒ **Activity** | Micro Review: **(No)**<br>☐ **Activity** |

| | |
|---|---|
| Regulatory Reviewer: Iain Margand<br><br>Date: **8/9/2011** | Recommendation:<br><br>☒ **FILE** ☐ **REFUSE to RECEIVE** |

Comments: EC - 1 YES
Therapeutic Code: 5010208 TREATMENT-NOT SPECIFIC OR BOTH
On Cards: YES
Archival copy: **ELECTRONIC (GATEWAY)**
Sections: I

- **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/**

1. Edit Application Property Type in DARRTS where applicable for

a. First Generic Received
☒ Yes ☐ No
b. Market Availability
☒ Rx ☐ OTC
c. Pepfar
☐ Yes ☒ No
d. Product Type
☐ Small Molecule Drug
e. USP Drug Product (at time of filing review)
☐ Yes ☒ No

2. Edit Submission Patent Records
   ☒ Yes
3. Edit Contacts Database with Bioequivalence Recordation where applicable
   ☐ Yes
4. EER (in Draft)
   ☐ Yes

**ADDITIONAL COMMENTS REGARDING THE ANDA:**

7/21/2011 – Requested the following via e-mail:

(b) (4)

[redacted]

Contact: Vandana Garikipati 336-812-8700 X 23988

Establishment Evaluation System

File Edit Search Navigate Options Help Window

ORACLE

Application Drawer

STOP SAVE

Application | Establishments | Status | Milestones | Comments | Contacts | Product

Application: A 203174/000 Subtype: N/A Sponsor: BARRER PHARMACAPS

Drug Name: BEXAROTENE

| CFN / FEI | Establishments Name | Profile Code | Last Milestone Name | Last Compliance Date | Status | Date | OAI Alert |
|---|---|---|---|---|---|---|---|
| | | | | (b) (4) | | | |
| | | | | (b) (4) | | | |
| | | | | (b) (4) | | | |
| 1063522 | BARRER PHARMACAPS INC | CS6 | DRAFT | 21-JUL-2011 | | | |

Overall Compliance:

| Date | Recommendation | Re-evaluation Date |
|---|---|---|
| | | |
| | | |

OAI Alert Comments

Save Close

OracleAS Forms Services

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ANDA 203174 - Message (Rich Text)

File Edit View Insert Format Tools Actions Help Toolbars Adobe PDF

Reply | Reply to All | Forward

From: Margand, Iain

To: \vgankipati@banpharm.com]

Cc:

Subject: ANDA 203174

Sent: Fri 7/29/2011 9:31 AM

Hello Vandana,

(b) (4)

Regards,

Iain

*Iain Margand, R.Ph.*
*CDR, USPHS*
*Senior Regulatory Management Officer*
*FDA/CDER/OGD/DLPS*
*7500 Standish Place, MPN I*
*Rockville, MD 20855*
*240-276-8676*

ANDA 203174 - Message (Rich Text)

File Edit View Insert Format Tools Actions Help Toolbars Adobe PDF

Reply | Reply to All | Forward

From: Margand, Iain
To: 'vgankipati@barpharm.com'
Cc:
Subject: ANDA 203174

Sent: Thu 7/21/2011 11:12 AM

Hello Vandana,

The filing review for ANDA 203174, Bexarotene Capsules, 75 mg, has been completed. The following information is requested in order to file the application with the Office:

1) A revised PII certification statement to state the product will not be marketed until after the expiration of patents.

(b) (4)

Please provide the requested information to the Office within 10 business days. If you have questions or require clarification of any material, please contact me directly.

Regards,

Iain

*Iain Margand, R.Ph.*
*CDR, USPHS*
*Senior Regulatory Management Officer*
*FDA/CDER/OGD/DLPS*
*7520 Standish Place, MPN I*
*Rockville, MD 20855*
*240-276-8676*

**BIOEQUIVALENCE CHECKLIST for First Generic ANDA**
FOR APPLICATION COMPLETENESS

**ANDA#** 203174 **FIRM NAME** **Banner Pharmacaps Inc.**

**DRUG NAME** Bexarotene Capsules, 75 mg

**DOSAGE FORM** Capsules
SUBJ: Request for examination of: Bioequivalence Study

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

| | **Summary of Findings by Division of Bioequivalence** |
|---|---|
| ☒ | **Study meets statutory requirements** |
| ☐ | **Study does NOT meet statutory requirements** |
| | **Reason:** |
| ☐ | **Waiver meets statutory requirements** |
| ☐ | **Waiver does NOT meet statutory requirements** |
| | **Reason:** |

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

Reviewed by:

_____ Date: _____
Glendolynn S. Johnson, Pharm.D.
Reviewer

_____ Date: _____
Nilufer M. Tampal, Ph.D.
Acting Team Leader

_____ Date: _____
Hoainhon N. Caramenico
Acting Deputy Director

BIO_1G_CHKLST.dot v.4/4/2003

| | | | | | |
|---|---|---|---|---|---|
| Summary results provided by the firm indicate studies pass BE criteria | ☒ | ☐ | | | **EDR**: 5.3.1.2.3* |
| Waiver requests for other strengths / supporting data | ☐ | ☒ | | | None (only 1 strength) |

*Note: The firm used a mixed scaled approach to assess the bioequivalence for this study.

- Average bioequivalence. The ratio of geometric LSmeans with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and Reference product for the ln-transformed parameters $C_{max}$, $AUC_T$ and $AUC_\infty$ were all to be within the 80 to 125% bioequivalence range.

- Reference-scaled bioequivalence. In the event that the Reference-to-Reference intra-subject CV was equal to or greater than 30%, the Test-to-Reference ratio of geometric LSmeans was within the bioequivalence range of 80-125% and the average BE criteria was not met for one of the PK parameters, a scaling approach to the bioequivalence assessment was to be used for the specific parameters not meeting the BE criteria. The Test product was considered to be bioequivalent to the Reference product if the upper bound of the 95% confidence interval of the criteria $\left(\overline{Y}_T - \overline{Y}_R\right)^2 - \theta \cdot s^2_{WR}$ was below or equal to zero (where $\theta = \left(\frac{\ln(1.25)}{\sigma_{W0}}\right)^2$, $\sigma_{W0}$=0.25, and $\mu_T$, $\mu_R$ and $s^2_{WR}$ were based on ln-transformed data).

# Additional Comments regarding the ANDA:

This is a **first generic** application for Bexarotene Capsules for the 75 mg strength.

This application is an electronic submission. All of the requested information is located in the electronic document room (EDR). The firm has submitted a fed BE study for Bexarotene Capsules, 75 mg. There is one strength for this test product, hence no waiver request was submitted. The reference product used by the firm for this application is Targretin® (bexarotene) Capsules, 75 mg by Eisai Inc. (NDA # 021055, approved December 29, 1999). Targretin® is also the reference listed drug product in the Orange Book.

**Fed Study (BXN-PO-541)**

The fed study (BXN-PO-541) is a 2-treatment, 3-period, 3 sequence partial replicate crossover study and the study results for Bexarotene (90% confidence intervals) are listed below.

| PARAMETER* | REFERENCE INTRA-SUBJECT CV (%) | AVERAGE BIOEQUIVALENCE | | | | | SCALED BIOEQUIVALENCE** |
|---|---|---|---|---|---|---|---|
| | | GEOMETRIC LS MEANS | | RATIO | 90% CONFIDENCE LIMITS | | "η" UPPER 95% CONFIDENCE LIMIT |
| | | TEST | REFERENCE | | LOWER | UPPER | |
| $C_{max}$ | 31.9 | 355.10 | 309.91 | 114.58 | 104.28 | 125.90 | -0.0181 |
| $AUC_T$ | 21.2 | 985.66 | 931.07 | 105.86 | 100.09 | 111.97 | N/AP |
| $AUC_\infty$ | 19.0 | 999.23 | 955.26 | 104.60 | 99.23 | 110.27 | N/AP |

* units are ng/mL for $C_{max}$ and ng·h/mL for $AUC_T$ and $AUC_\infty$

** Scaled-BE criteria is met when 95% CI upper bound is lower or equal to 0.

The firm conducted dissolution testing with the FDA-recommended method listed below.

| Drug Name | Dosage Form | USP Apparatus | Speed (RPMs) | Medium | Volume (mL) | Recommended Sampling Times (minutes) | Date Updated |
|---|---|---|---|---|---|---|---|
| Bexarotene | Capsule | II (Paddle) | 50 | Tier 1 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 Tier 2 Medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 with 0.05 g/L pancreatin enzyme | 900 | 15, 30, 45 and 60 | 08/17/2006 |

Note: Method Listed in External OGD Database. Last accessed 07/07/2011.

Several control documents have been submitted to the OGD for this drug product[1] including CC #10-0486 (b) (4), #08-0390 (b) (4) and #11-0109 (b) (4).

The following are recommended to establish bioequivalence of bexarotene capsules[2]:

**Active ingredient:** Bexarotene
**Form/Route:** Capsule/Oral
**Recommended studies:** 1 study
Type of study: Fed Design: Single-dose, two-treatment, two-period crossover in vivo Strength: 75 mg
Subjects: Healthy males, general population. Additional comments:

1. Females should be excluded from study given the potential for embryo-fetal toxicity.

1 OGD Control Database. Last accessed 07/07/11.
2 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227413.pdf. Last accessed 07/07/11.

2. The protocol should specify and require both formal pregnancy counseling for male subjects regarding the risk to their female partner and a section regarding the counseling in the Informed Consent document.

3. Adequate contraception must be continued for at least 1 month following the last dose of bexarotene.

4. The protocol should include following specific exclusion criteria in addition to other exclusion criteria:
- Subjects demonstrating abnormalities in lipid profile or thyroid-function on screening laboratory evaluations.
- Subjects receiving systemic therapy with Vitamin A in doses of greater than 15000 IU (5000 mcg) per day.
- Subjects who are taking gemfibrozil or tamoxifen.
- Use of any other retinoid class drug (e.g. Isotretinoin) within 30 days of entry into the study.
- Use of topical medications such as corticosteroids or tar baths.
-

5. In addition to the exclusion of drugs that are also know to cause photosensitivity, subjects should be advised to avoid prolonged exposure to the sun or UV light during the study. Similarly, it would be prudent to exclude subjects with a known history of skin cancer.

6. The protocol should include an appropriate plan for continued follow-up, standard care for subsequent follow up, and treatment of subjects who continue to demonstrate thyroid and/or lipid abnormalities at the end of study laboratory evaluations.

**Analytes to measure (in appropriate biological fluid):** Bexarotene in plasma
**Bioequivalence based on (90% CI)**: Bexarotene
**Waiver request of in vivo testing:** Not Applicable

**Dissolution test method and sampling times:**
Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units of the test and reference products. Specifications will be determined upon review of the application.
*Recommended Sep 2010*

From the Division of Bioequivalence standpoint, this submission is **acceptable for filing**.

## Additional Information Requested from the Firm:

None

**Active ingredient:** Bexarotene

**Form/Route:** Capsule/Oral

**Recommended studies:** 1 study

Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 75 mg
Subjects: Healthy males, general population.
Additional comments:

1. Females should be excluded from study given the potential for embryo-fetal toxicity.
2. The protocol should specify and require both formal pregnancy counseling for male subjects regarding the risk to their female partner and a section regarding the counseling in the Informed Consent document.
3. Adequate contraception must be continued for at least 1 month following the last dose of bexarotene.
4. The protocol should include following specific exclusion criteria in addition to other exclusion criteria:
    - Subjects demonstrating abnormalities in lipid profile or thyroid-function on screening laboratory evaluations.
    - Subjects receiving systemic therapy with Vitamin A in doses of greater than 15000 IU (5000 mcg) per day.
    - Subjects who are taking gemfibrozil or tamoxifen.
    - Use of any other retinoid class drug (e.g. Isotretinoin) within 30 days of entry into the study.
    - Use of topical medications such as corticosteroids or tar baths.
5. In addition to the exclusion of drugs that are also know to cause photosensitivity, subjects should be advised to avoid prolonged exposure to the sun or UV light during the study. Similarly, it would be prudent to exclude subjects with a known history of skin cancer.
6. The protocol should include an appropriate plan for continued follow-up, standard care for subsequent follow up, and treatment of subjects who continue to demonstrate thyroid and/or lipid abnormalities at the end of study laboratory evaluations.

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**Analytes to measure (in appropriate biological fluid):** Bexarotene in plasma

**Bioequivalence based on (90% CI)**: Bexarotene

**Waiver request of in vivo testing:** Not Applicable

**Dissolution test method and sampling times:**

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

*Recommended Sep 2010*

RE: ANDA 203174 - Message (Rich Text)

File Edit View Insert Format Tools Actions Help Toolbars Adobe PDF

Reply | Reply to All | Forward

You replied on 7/27/2011 8:27 AM.

From: CDER EESQUESTIONS
To: Margand, Iain
Cc:
Subject: RE: ANDA 203174

Sent: Wed 7/27/2011 8:08 AM

Hi Iain,

Thanks for checking with us about this. Since the (b)(4) site is performing intermediate steps, it does not need to be submitted in EES.

Sincerely,

**Marisa Stock**
CDER/OC/OMPQ/DOMPA
phone: (301) 796-4753

---

**From:** Margand, Iain
**Sent:** Thursday, July 21, 2011 11:32 AM
**To:** CDER EESQUESTIONS
**Subject:** ANDA 203174

Good Afternoon,

I am not sure if the first manufacturing site for the API should be entered into EES or not as it appears as though a portion of the process is performed at the (b)(4) site and is completed at the NJ site. If the (b)(4) site should be added to EES for this ANDA. I do not see it listed in the EES sites so it will need to added.

Any help or guidance would be greatly appreciated.

Thank you,

Iain

<< OLE Object: Picture (Device Independent Bitmap) >>

## MODULE 1: ADMINISTRATIVE

| | | COMMENT (S) |
|---|---|---|
| **1.1** | **Signed and Completed Application Form (356h)** (Rx/OTC Status) Yes<br>(original signature) | |
| **1.1.2** | **Establishment Information:** N/A<br>1. Drug Substance Manufacturer<br>2. Drug Product Manufacturer<br>3. Outside Testing Facility(ies) | |
| **1.2** | **Cover Letter** Yes | |
| **1.2.1** | **Form FDA 3674** (PDF) B | |
| * | **Table of Contents** (paper submission only) N/A | |
| **1.3.2** | **Field Copy Certification** (N/A for E-Submissions) N/A<br>(original signature) | |
| **1.3.3** | **Debarment Certification-GDEA** (Generic Drug Enforcement Act)/Other:<br>(no qualifying statement)<br>1. Debarment Certification (original signature) Yes<br>2. List of Convictions statement (original signature) Yes | |
| **1.3.4** | **Financial Certifications**<br>Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) Yes<br>Disclosure Statement (Form FDA 3455) N/A | |
| **1.3.5** | **Patent Information**<br>Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations<br>**Patent Certification**<br>1. Patent number(s)<br>2. Paragraph: (Check all certifications that apply)<br>MOU ☐ PI ☐ PII ☐ PIII ☒ PIV ☒ (Statement of Notification) ☐<br>3. Expiration of Patent(s): 10/5/2016<br>a. Pediatric exclusivity submitted? N/A<br>b. Expiration of Pediatric Exclusivity? YES<br>4. Exclusivity Statement: State marketing intentions? | '676 PIV<br>'731 PIV<br>'279 PIII<br>'074 PIII<br>'699 PIII |

| Appl No | Prod No | Patent No | Patent Expiration | Drug Substance Claim | Drug Product Claim | Patent Use Code | Delist Requested |
|---|---|---|---|---|---|---|---|
| N021055 | 001 | 5780676 | Jul 14, 2015 | | | U - 509 | |
| N021055 | 001 | 5962731 | Oct 5, 2016 | | | U - 475 | |
| N021055 | 001 | 6043279 | Apr 22, 2012 | | | U - 509 | |
| N021055 | 001 | 6320074 | Apr 22, 2012 | Y | | U - 509 | |
| N021055 | 001 | 7655699 | Apr 22, 2012 | Y | Y | U - 509 | |

See 7/22/2011 amendment for PIII cert stating product will not be marketed until expiration of '279, '074 and '699 patents.

<>

**There is no unexpired exclusivity for this product.**

| | | |
|---|---|---|
| **1.4.1** | **References**<br>Letters of Authorization<br>1. DMF letters of authorization<br>a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient Yes<br>b. Type II DMF# BEXAROTENE - (b) (4)<br>c. Type III DMF authorization letter(s) for container closure Yes<br>2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) N/A | |
| **1.12.4** | **Request for Comments and Advice** - Proprietary name requested No<br>If Yes, did the firm provide the request as a separate electronic amendment labeled "Proprietary Name Request" at initial time of filing<br>1. Yes Select<br>2. No - contact the firm to submit the request as a separate electronic amendment. | |
| **1.12.11** | **Basis for Submission**<br>NDA#: 21-055<br>Ref Listed Drug: TARGRETIN<br>Firm: EISAI<br>**ANDA suitability petition required?** N/A<br>If Yes, provide petition number and copy of approved petition<br>**ANDA Citizen's Petition Required?** N/A<br>If Yes, provide petition number and copy of petition | |

**MODULE 1: ADMINISTRATIVE (Continued)**

| | | COMMENT (S) |
|---|---|---|
| **1.12.12** | **Comparison between Generic Drug and RLD-505(j)(2)(A)**<br>1. Conditions of use Same<br>2. Active ingredients Bexarotene<br>3. Inactive ingredients<br>4. Route of administration Oral<br>5. Dosage Form Capsule<br>6. Strength 75 mg | |
| **1.12.14** | **Environmental Impact Analysis Statement**<br>(cite 21CFR 25.31, if applicable) Yes | |
| **1.12.15** | **Request for Waiver**<br>Request for Waiver of In-Vivo BA/BE Study(ies) N/A | |
| **1.14.1** | **Draft Labeling** (Multi Copies N/A for E-Submissions)<br>**1.14.1.1** 4 copies of draft for paper submission only (each strength and container) Yes<br>**1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences visually highlighted and annotated Yes<br>**1.14.1.3** 1 package insert (content of labeling) and SPL submitted electronically Yes | |
| **1.14.3** | **Listed Drug Labeling**<br>**1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences visually highlighted and annotated Yes<br>**1.14.3.3** RLD package insert, 1 RLD label and 1 RLD container label Yes | |

| | | COMMENT (S) |
|---|---|---|
| **2.3** | **Quality Overall Summary (QOS)**<br>**E-Submission: PDF** Yes<br>**Word Processed e.g., MS Word** Yes - see 7/22/2011 amendment<br><br>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/<br><br>**Question based Review (QbR)** Yes<br><br>**2.3.S Drug Substance (Active Pharmaceutical Ingredient)** Yes<br>2.3.S.1 General Information<br>2.3.S.2 Manufacture<br>2.3.S.3 Characterization<br>2.3.S.4 Control of Drug Substance<br>2.3.S.5 Reference Standards or Materials<br>2.3.S.6 Container Closure System<br>2.3.S.7 Stability<br><br>**2.3.P Drug Product** Yes<br>2.3.P.1 Description and Composition of the Drug Product<br>2.3.P.2 Pharmaceutical Development<br>2.3.P.2.1 Components of the Drug Product<br>2.3.P.2.1.1 Drug Substance<br>2.3.P.2.1.2 Excipients<br>2.3.P.2.2 Drug Product<br>2.3.P.2.3 Manufacturing Process Development<br>2.3.P.2.4 Container Closure System<br>2.3.P.3 Manufacture<br>2.3.P.4 Control of Excipients<br>2.3.P.5 Control of Drug Product<br>2.3.P.6 Reference Standards or Materials<br>2.3.P.7 Container Closure System<br>2.3.P.8 Stability | |
| **2.7** | **Clinical Summary (Bioequivalence)**Model BE Data Summary Tables<br>**E-Submission: PDF** Yes<br>**Word Processed: e.g., MS Word** Yes<br><br>**2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods**<br>**2.7.1.1 Background and Overview**<br>Table 1. Submission Summary Yes<br>Table 4. Bioanalytical Method Validation Yes<br>Table 6. Formulation Data Yes<br>**2.7.1.2 Summary of Results of Individual Studies**<br>Table 5. Summary of In Vitro Dissolution Yes<br>**2.7.1.3 Comparison and Analyses of Results Across Studies**<br>Table 2. Summary of Bioavailability (BA) Studies Yes<br>Table 3. Statistical Summary of the Comparative BA Data Yes<br>**2.7.1.4 Appendix** Select<br>**2.7.4.1.3 Demographic and Other Characteristics of Study Population**<br>Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study Yes<br>**2.7.4.2.1.1 Common Adverse Events**<br>Table 8. Incidence of Adverse Events in Individual Studies Yes | |

**MODULE 3: 3.2.S DRUG SUBSTANCE**

| | | COMMENT (S) |
|---|---|---|
| **3.2.S.1** | **General Information** (Do not refer to DMF) Yes<br>**3.2.S.1.1 Nomenclature**<br>**3.2.S.1.2 Structure**<br>**3.2.S.1.3 General Properties** | |
| **3.2.S.2** | **Manufacturer**<br>**Drug Substance (Active Pharmaceutical Ingredient)**<br>1. Name and Full Address(es)of the Facility(ies) Yes<br>2. Contact name, phone and fax numbers, email address Yes<br>3. Specify Function or Responsibility Yes<br>4. Type II DMF number for API DMF# (b) (4)<br>5. CFN or FEI numbers | |
| **3.2.S.3** | **Characterization** Yes<br>Provide the following in tabular format:<br>1. Name of Impurity(ies)<br>2. Structure of Impurity(ies)<br>3. Origin of Impurity(ies) | |
| **3.2.S.4** | **Control of Drug Substance (Active Pharmaceutical Ingredient)**<br>**3.2.S.4.1 Specification** Yes<br>Testing specifications and data from drug substance manufacturer(s)<br>**3.2.S.4.2 Analytical Procedures** Yes<br>**3.2.S.4.3 Validation of Analytical Procedures**<br>(API that is USP or reference made to DMF, must provide verification of USP or DMF procedures) Yes<br>1. Spectra and chromatograms for reference standards and test samples Yes<br>2. Samples-Statement of Availability and Identification of:<br>a. Drug Substance Yes<br>b. API lot number(s)<br>**3.2.S.4.4 Batch Analysis**<br>1. COA(s) specifications and test results from drug substance mfgr(s) Yes<br>2. Applicant certificate of analysis Yes<br>**3.2.S.4.5 Justification of Specification** Yes | |
| **3.2.S.5** | **Reference Standards or Materials** (Do not refer to DMF) Yes | |
| **3.2.S.6** | **Container Closure Systems** Select Refer to DMF# (b) (4) | |
| **3.2.S.7** | **Stability**<br>1. Retest date or expiration date of API Yes<br><br>Refer to (b) (4) DMF (b) (4) for applicable information. The proposed re-test period is (b) (4) according to the manufacturer's COA, provided in Section 3.2.S.4.4. | |

**MODULE 3: 3.2.P DRUG PRODUCT**

| | | COMMENT (S) |
|---|---|---|
| **3.2.P.1** | **Description and Composition of the Drug Product**<br>1. Unit composition with indication of the function of the inactive ingredient(s) Yes<br>2. Inactive ingredients and amounts are appropriate per IIG (per/dose justification) Yes - see below<br>3. Conversion from % to mg/dose values for inactive ingredients (if applicable) N/A<br>4. Elemental iron: provide daily elemental iron calculation or statement of adherence to 21CFR73.1200 (calculation of elemental iron intake based on **maximum daily dose (MDD)** of the drug product is preferred if this section is applicable) Yes<br>(b) (4)<br>5. Injections: If the reference listed drug is packaged with a drug specific diluent then the diluent must be Q1/Q2 and must be provided in the package configuration N/A | |
| **3.2.P.2** | **Pharmaceutical Development**<br>Pharmaceutical Development Report Yes | |
| **3.2.P.3** | **Manufacture**<br>**3.2.P.3.1 Drug Product**<br>(Finished Dosage Manufacturer and Outside Contract Testing Laboratories)<br>1. Name and Full Address(es)of the Facility(ies) Yes<br>2. Contact name, phone and fax numbers, email address Yes<br>3. Specify Function or Responsibility Yes<br>4. CGMP Certification (from both applicant and drug product manufacturer if different entities) Yes<br>5. CFN or FEI numbers<br>**3.2.P.3.2 Batch Formula** Yes<br>**3.2.P.3.3 Description of Manufacturing Process and Process Controls**<br>1. Description of the Manufacturing Process Yes<br>2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified Yes<br>3. Master packaging records for intended marketing container(s) Select<br>4. If sterile product N/A<br>5. Reprocessing Statement (cite 21CFR 211.115, submitted by the drug product manufacturer and the applicant, if different entities) Yes<br>**3.2.P.3.4 Controls of Critical Steps and Intermediates** Yes<br>**3.2.P.3.5 Process Validation and/or Evaluation** N/A<br>1. Microbiological sterilization validation Select<br>2. Filter validation (if aseptic fill) Select | Commercial Batch:<br>(b) (4) capsules |

| | | |
|---|---|---|
| **3.2.P.4** | **Controls of Excipients** (Inactive Ingredients)<br>Source of inactive ingredients identified Select see 3.2.R.1.P.2<br>**3.2.P.4.1 Specifications**<br>1. Testing specifications (including identification and characterization) Yes<br>2. Suppliers' COA (specifications and test results) Yes<br>**3.2.P.4.2 Analytical Procedures** No USP/NF<br>**3.2.P.4.3 Validation of Analytical Procedures** N/A<br>**3.2.P.4.4 Justification of Specifications:**<br>1. Applicant COA Yes | |

| | | COMMENT (S) |
|---|---|---|
| **3.2.P.5** | **Controls of Drug Product**<br>**3.2.P.5.1 Specification(s)** Yes<br>**3.2.P.5.2 Analytical Procedures** Yes<br>**3.2.P.5.3 Validation of Analytical Procedures**<br>(if using USP procedure, must provide verification of USP procedure) Yes<br>Samples - Statement of Availability and Identification of:<br>1. Finished Dosage Form Yes<br>2. Lot number(s) and strength of Drug Product(s)<br>**3.2.P.5.4 Batch Analysis**<br>Certificate of Analysis for Finished Dosage Form Yes<br>**3.2.P.5.5 Characterization of Impurities** Yes<br>**3.2.P.5.6 Justification of Specifications** Yes | Lot# 140000127 |
| **3.2.P.7** | **Container Closure System**<br>1. Summary of Container/Closure System (if new resin, provide data) Yes<br>2. Components Specification and Test Data Select<br>3. Packaging Configuration and Sizes<br>4. Container/Closure Testing (recommended additional testing for all plastic)Select<br>a. Solid Orals: water permeation, light transmissionSelect<br>b. Liquids: leachables, extractables, light transmissionSelect<br>5. Source of supply and suppliers address Yes | (b) (4) |
| **3.2.P.8** | **3.2.P.8.1 Stability (Finished Dosage Form)**<br>1. Stability Protocol submitted Yes<br>2. Expiration Dating Period 24 months<br>**3.2.P.8.2 Post-approval Stability and Conclusion**<br>Post Approval Stability Protocol and Commitments Yes<br>**3.2.P.8.3 Stability Data** ****Refrigerated Product****<br>1. Accelerated stability data<br>a. four (4) time points 0,1,2,3 Yes<br>**-OR-**<br>b. three (3) time points 0,3,6 (if 3 time points for accelerated stability data are submitted then provide 3 exhibit batches along with 12 months of room temperature stability data –Refer to Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products November 2003, Section B) Select<br>2. Batch numbers on stability records the same as the test batch Yes | Bottle lot#: 140000127A<br><br>Bulk lot#: 140000127 |

## MODULE 3: 3.2.R REGIONAL INFORMATION (Drug Substance)

| | | COMMENT (S) |
|---|---|---|
| **3.2.R Drug Substance** | **3.2.R.1.S Executed Batch Records for drug substance (if available)** Select<br>**3.2.R.2.S Comparability Protocols** Select<br>**3.2.R.3.S Methods Validation Package** Select<br>Methods Validation Package (3 copies for paper and N/A for E-Submissions) (Required for Non-USP drugs) | |

## MODULE 3: 3.2.R REGIONAL INFORMATION (Drug Product)

| | | COMMENT (S) |
|---|---|---|
| **3.2.R Drug Product** | **3.2.R.1.P.1**<br>**Executed Batch Records**<br>Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures)<br>Batch Reconciliation and Label Reconciliation Select<br>(b) (4) | |

| | | |
|---|---|---|
| | a. Bulk Package Label (1.14.1) Yes<br>b. Bulk Package Stability (accelerated stability data [0,1,2,3] **–OR-** room temperature [0,3,6]) (3.2.P.8) Yes<br>c. Bulk Package Container and Closure information (3.2.P.7) Select<br>**3.2.R.1.P.2 Information on Components** Yes<br>**3.2.R.2.P Comparability Protocols** N/A<br>**3.2.R.3.P Methods Validation Package** Select see 3.2.P.5<br>Methods Validation Package (3 copies for paper and N/A for E-Submissions)<br>(Required for Non-USP drugs) | |

## MODULE 5: CLINICAL STUDY REPORTS

| | | COMMENT (S) |
|---|---|---|
| **5.2** | **Tabular Listing of Clinical Studies** Yes | |
| **5.3.1** (complete study data) | **Bioavailability/Bioequivalence**<br>**1. Formulation data same?**<br>a. Comparison of all Strengths<br>(check proportionality of multiple strengths) N/A<br>b. Parenterals, Ophthalmics, Otics and Topicals<br>(21 CFR 314.94 (a)(9)(iii)-(v) N/A<br>**2. Lot Numbers and strength of Products used in BE Study(ies)**<br>140000127A<br>**3. Study Type: IN-VIVO PK STUDY(IES)**<br>(Continue with the appropriate study type box below) | |
| | **5.3.1.2 Comparative BA/BE Study Reports**<br>1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) Yes<br>2. Summary Bioequivalence tables:<br>Table 10. Study Information Yes<br>Table 12. Dropout Information Yes<br>Table 13. Protocol Deviations Yes<br>**5.3.1.3 In Vitro-In-Vivo Correlation Study Reports**<br>1. Summary Bioequivalence tables Select<br>Table 11. Product Information Yes<br>Table 16. Composition of Meal Used in Fed Bioequivalence Study Yes<br>**5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies**<br>1. Summary Bioequivalence table:<br>Table 9. Reanalysis of Study Samples Yes<br>Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses Yes<br>Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples Yes<br><br>**Case Report Forms** should be placed under the study to which they pertain, and appropriately tagged. Refer to The eCTD Backbone File Specification for Study Tagging //www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf | |
| **5.4** | **Literature References** | |
| | **Possible Study Types:** | |
| Study Type | **IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle)<br>FED ON 75 MG<br>1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) Select<br>2. EDR Email: Data Files Submitted Select<br>3. In-Vitro Dissolution Yes | |

**Table 3 Statistical Summary of the Comparative Bioavailability Data**

| Bexarotene<br>Dose (1 x 75 mg)<br>Least Squares Geometric Means*, Ratio of Means (%), and 90% Confidence Intervals (%), and Reference Intra-Subject CV (ISCV) (%) and "η" Upper 95% Confidence Limit when Applicable | | | | | | |
|---|---|---|---|---|---|---|
| Fed Bioequivalence Study (Study No. BXN-P0-541) | | | | | | |
| Parameter | Test | Reference | Ratio | 90% C.I. | ISCV | η |
| $AUC_T$ | 985.66 | 931.07 | 105.86 | 100.09-111.97 | 21.2 | N/AP |
| $AUC_\infty$ | 999.23 | 955.26 | 104.60 | 99.23-110.27 | 19.0 | N/AP |
| $C_{max}$ | 355.10 | 309.91 | 114.58 | 104.28-125.90 | 31.9 | -0.0181 |

* units are ng/mL for $C_{max}$ and ng·h/mL for $AUC_T$ and $AUC_\infty$

| | | |
|---|---|---|
| Study Type | **IN-VIVO BE STUDY with CLINICAL ENDPOINTS**<br>1. Properly defined BE endpoints (eval. by Clinical Team) Select<br>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) Select<br>3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) Select<br>4. EDR Email: Data Files Submitted Select | |
| Study Type | **IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) Select<br>1. Study(ies) meets BE criteria (90% CI of 80-125) Select<br>2. EDR Email: Data Files Submitted Select<br>3. In-Vitro Dissolution Select | |
| Study Type | **NASALLY ADMINISTERED DRUG PRODUCTS**<br>**1. <u>Solutions</u> (Q1/Q2 sameness)** Select<br>a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) Select<br>**2. <u>Suspensions</u> (Q1/Q2 sameness):**<br>a. In-Vivo PK Study Select<br>1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) Select<br>2. EDR Email: Data Files Submitted Select<br>b. In-Vivo BE Study with Clinical End Points Select<br>1. Properly defined BE endpoints (eval. by Clinical Team) Select<br>2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) Select<br>3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) Select<br>4. EDR Email: Data Files Submitted Select<br>c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) Select | |
| Study Type | **IN-VIVO BE STUDY(IES) with PD ENDPOINTS**<br>(e.g., topical corticosteroid vasoconstrictor studies)<br>1. Pilot Study (determination of ED50) Select<br>2. Pivotal Study (study meets BE criteria 90%CI of 80-125) Select | |
| Study Type | **TRANSDERMAL DELIVERY SYSTEMS**<br>1. <u>In-Vivo PK Study</u> Select<br>a. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) Select<br>b. In-Vitro Dissolution Select<br>c. EDR Email: Data Files Submitted Select<br>2. <u>Adhesion Study</u> Select<br>3. <u>Skin Irritation/Sensitization Study</u> Select | |

Updated 05/16/2011



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/s/

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IAIN MARGAND
08/24/2011

MARTIN H Shimer
08/24/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 203174

Banner Pharmacaps Inc.
Attention: Vandana Garikipati
4125 Premier Drive
High Point, NC 27265

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the electronic correspondences dated June 21 and 29, 2011 and your amendments dated June 22 and August 4, 2011.

NAME OF DRUG: Bexarotene Capsules, 75 mg

DATE OF APPLICATION: June 3, 2011

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 6, 2011

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) 276-8675.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Esther Chuh
Project Manager
240-276-8530

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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/s/

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MARTIN H Shimer
08/24/2011
Signing for Wm Peter Rickman

M E M O R A N D U M

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

DATE : June 17, 2011

TO : Director
Division of Bioequivalence (HFD-650)

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

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 203174 for Bexarotene Capsules, 75 mg to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to 21 USC 355(j)(5)(B)(iv).

Banner Pharmacaps Inc. has submitted ANDA 203174 for Bexarotene Capsules, 75 mg. The ANDA contains a certification pursuant to 21 USC 355(j)(5)(B)(iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also it is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Banner Pharmacaps Inc. on June 3, 2011 for its Bexarotene product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

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

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/s/

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EDA E HOWARD
06/22/2011