CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 78-734

Name: Oxcarbazepine Oral Suspension

Sponsor: Ranbaxy, Inc.

Approval Date: June 26, 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 00-000/S-000

CONTENTS

Reviews / Information Included in this Review

Approval Letter	**X**
Tentative Approval Letter	
Labeling	
Labeling Reviews	**X**
Medical Reviews	
Chemistry Reviews	**X**
Bioequivalence Reviews	**X**
Statistical Reviews	
Microbiology Reviews	
Administrative & Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-734

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-734

Ranbaxy Inc.
Attention: Usha Sankaran
U.S Agent for: Ranbaxy Laboratories Limited
600 College Road East
Princeton, NJ 08540

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 22, 2006, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Oxcarbazepine Oral Suspension, 300 mg/5 mL.

Reference is also made to your amendments dated August 3, August 17, September 11, and September 17, 2007; December 1, 2008; and May 21, and June 25, 2009.

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 Oxcarbazepine Oral Suspension, 300 mg/5 mL, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Trileptal Oral Suspension, 300 mg/5 mL, of Novartis Pharmaceuticals Corp. (Novartis). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

The RLD upon which you have based your ANDA, Novartis' Trileptal Oral Suspension, is subject to a period of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent No. 7,037,525 (the '525 patent) is scheduled to expire on August 12, 2018 (with pediatric exclusivity added).

Your ANDA contains a paragraph IV certification under section 505(j)(2)(A)(vii)(IV) of the Act stating that the ‘525 patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Oxcarbazepine Oral Suspension, 300 mg/5 mL, under this ANDA. You have notified the agency that Ranbaxy Laboratories Limited (Ranbaxy) complied with the requirements of section 505(j)(2)(B) of the Act, and that no action for infringement of the ‘525 patent was brought against Ranbaxy within the statutory 45-day period, which action would have resulted in a 30-month stay of approval under section 505(j)(5)(B)(iii).

With respect to 180-day generic drug exclusivity, we note that Ranbaxy was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification to the ‘525 patent. Therefore, with this approval, Ranbaxy is eligible for 180-days of generic drug exclusivity for Oxcarbazepine Oral Suspension, 300 mg/5 mL. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, will begin to run from the commercial marketing date 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.

We 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
Division of Drug Marketing, Advertising, and Communications
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 Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Within 14 days of the date of this letter, submit updated content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the approved labeling. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission as ***"Miscellaneous Correspondence – SPL for Approved ANDA 78-734".***

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Robert L. West
6/26/2009 11:40:33 AM
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-734

LABELING REVIEWS

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

ANDA Number:	78-734
Date of Submission:	May 21, 2009
Applicant's Name:	Ranbaxy Laboratories Limited
Established Name:	Oxcarbazepine Oral Suspension, 300 mg/5 mL.
Proposed Proprietary Name:	None

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

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

CONTAINER: 250 mL

- Satisfactory in final print as of August 17, 2007 submission.

CARTON: 250 mL.

- Satisfactory in final print as of August 17, 2007 submission.

PROFESSIONAL PACKAGE INSERT

- Satisfactory in final print as of May 21, 2009 submission.

REVISIONS NEEDED POST-APPROVAL: None

NOTE TO CHEMIST: None

FOR THE RECORD:

1. MODEL LABELING

   This review was based on the labeling for Trileptal® by Novartis [NDA 21-285/S-021; approved April 23, 2009].

2. USP ITEM

   No

3. PROPRIETARY NAME

   None

4. PATENTS/EXCLUSIVITIES

Patent Data

Appl No	Patent No	Patent Expiration	Patent Use Code	How Certified	Labeling Impact
021014	7037525	FEB 12,2018	U-724 METHOD OF TREATING SEIZURES	IV	none
021014	7037525*PED	AUG 12,2018			

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration	Labeling Impact
021014	001	PED	APR 28,2009	
021014	001	I-478	OCT 28,2008	None, expired

I-478: FOR USE AS ADJUNCTIVE THERAPY IN THE TREATMENT OF PARTIAL SEIZURES IN CHILDREN WITH EPILEPSY AGED 2-4 YEARS

5. INACTIVE INGREDIENTS

The list of inactive ingredients is accurate.

6. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Manufactured by: Ohm Laboratories Inc, Gloversville, NY, USA facility.
Manufactured for: Ranbaxy Pharmaceuticals Inc. Jacksonville, FL 32257.

7. CONTAINER/CLOSURE

Strength	Fill Size	Bottle	Cap	Press in Bottle	10 mL dosing syringe
300 mg/5 mL	250 mL	USP Type III Amber Glass	(b) (4)	(b) (4)	(b) (4)

8. PACKAGING/SCORING CONFIGURATIONS

RLD: Bottle of 250 mL.

ANDA: Bottle of 250 mL.

9. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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

ANDA: Store at 20°-25° (68° – 77°F) [see USP Controlled Room Temperature]

Date of Review: May 29, 2009 Date of Submission: May 21, 2009

Primary Reviewer: _____ _____
Melaine Shin Date:

Team Leader: _____ _____
Lillie Golson Date:

cc: ANDA 78-734
DUP/DIVISION FILE
HFD-613/MShin/LGolson (no cc)
APPROVAL SUMMARY
M:\LABELING REVIEWS\ANDA 78-734 Oxcarbazepine Oral Sus (ranbaxy)\78734 Ap2.Labeling review.doc
FINAL: May 29, 2009

OXCARBAZEPINE ORAL SUSPENSION
Rx only

Prescribing Information

DESCRIPTION

Oxcarbazepine is an antiepileptic drug available as a 300 mg/5 mL (60 mg/mL) oral suspension. Oxcarbazepine is 10, 11-Dihydro-10-oxo-5*H*-dibenz[b,f]azepine-5-carboxamide, and its molecular structure is

Oxcarbazepine is an off-white to yellow crystalline powder. It is practically insoluble in water, ethanol and ether. It is slightly soluble in chloroform, dichloromethane, acetone and methanol. Its molecular weight is 252.27.

Oxcarbazepine oral suspension contains the following inactive ingredients: artificial cherry flavor, ascorbic acid, carboxymethylcellulose sodium, colloidal silicon dioxide, copovidone, hydroxyethylcellulose, methylparaben, microcrystalline cellulose, noncrystallizing sorbital solution, propylene glycol, polyoxyl 8 stearate, povidone, propylparaben, purified water, and saccharin sodium, and sorbic acid.

CLINICAL PHARMACOLOGY

Mechanism of Action

The pharmacological activity of oxcarbazepine is primarily exerted through the 10-monohydroxy metabolite (MHD) of oxcarbazepine (see **Metabolism and Excretion** subsection). The precise mechanism by which oxcarbazepine and MHD exert their antiseizure effect is unknown; however, *in vitro* electrophysiological studies indicate that they produce blockade of voltage-sensitive sodium channels, resulting in stabilization of hyperexcited neural membranes, inhibition of repetitive neuronal firing, and diminution of propagation of synaptic impulses. These actions are thought to be important in the prevention of seizure spread in the intact brain. In addition, increased potassium conductance and modulation of high-voltage activated calcium channels may contribute to the anticonvulsant effects of the drug. No significant interactions of oxcarbazepine or MHD with brain neurotransmitter or modulator receptor sites have been demonstrated.

Pharmacodynamics

Oxcarbazepine and its active metabolite (MHD) exhibit anticonvulsant properties in animal seizure models. They protected rodents against electrically induced tonic extension seizures and, to a lesser degree, chemically induced clonic seizures, and abolished or reduced the frequency of chronically recurring focal seizures in Rhesus monkeys with aluminum implants. No development of tolerance (i.e., attenuation of anticonvulsive activity) was observed in the maximal electroshock test when mice and rats were treated daily for five days and four weeks, respectively, with oxcarbazepine or MHD.

Pharmacokinetics

Following oral administration of oxcarbazepine tablets, oxcarbazepine is completely absorbed and extensively metabolized to its pharmacologically active 10-monohydroxy metabolite (MHD). The half-life of the parent is about two hours, while the half-life of MHD is about nine hours, so that MHD is responsible for most antiepileptic activity.

Based on MHD concentrations, oxcarbazepine tablets and suspension were shown to have similar bioavailability.

After single-dose administration of oxcarbazepine oral suspension to healthy male volunteers under fasted conditions, the median t_{max} was six hours.

In a mass balance study in people, only 2% of total radioactivity in plasma was due to unchanged oxcarbazepine, with approximately 70% present as MHD, and the remainder attributable to minor metabolites.

Effect of Food: Although not directly studied, the oral bioavailability of the oxcarbazepine suspension is unlikely to be affected under fed conditions. Therefore, oxcarbazepine suspension can be taken with or without food.

Steady-state plasma concentrations of MHD are reached within 2 to 3 days in patients when oxcarbazepine is given twice a day. At steady state the pharmacokinetics of MHD are linear and show dose proportionality over the dose range of 300 to 2400 mg/day.

Distribution

The apparent volume of distribution of MHD is 49L.

Approximately 40% of MHD is bound to serum proteins, predominantly to albumin. Binding is independent of the serum concentration within the therapeutically relevant range. Oxcarbazepine and MHD do not bind to alpha-1-acid glycoprotein.

Metabolism and Excretion

Oxcarbazepine is rapidly reduced by cytosolic enzymes in the liver to its 10-monohydroxy metabolite, MHD, which is primarily responsible for the pharmacological effect of oxcarbazepine. MHD is metabolized further by conjugation with glucuronic acid. Minor amounts (4% of the dose) are oxidized to the pharmacologically inactive 10,11-dihydroxy metabolite (DHD).

Oxcarbazepine is cleared from the body mostly in the form of metabolites which are predominantly excreted by the kidneys. More than 95% of the dose appears in the urine, with less than 1% as unchanged oxcarbazepine. Fecal excretion accounts for less than 4% of the administered dose. Approximately 80% of the dose is excreted in the urine either as glucuronides of MHD (49%) or as unchanged MHD (27%); the inactive DHD accounts for approximately 3% and conjugates of MHD and oxcarbazepine account for 13% of the dose.

Special Populations

Hepatic Impairment

The pharmacokinetics and metabolism of oxcarbazepine and MHD were evaluated in healthy volunteers and hepatically-impaired subjects after a single 900 mg oral dose. Mild-to-moderate hepatic impairment did not affect the pharmacokinetics of oxcarbazepine and MHD. No dose adjustment for oxcarbazepine is recommended in patients with mild-to-moderate hepatic impairment. The pharmacokinetics of oxcarbazepine and MHD have not been evaluated in severe hepatic impairment and, therefore, caution should be exercised when dosing severely impaired patients.

Renal Impairment

There is a linear correlation between creatinine clearance and the renal clearance of MHD. When oxcarbazepine is administered as a single 300 mg dose in renally-impaired patients (creatinine clearance < 30 mL/min), the elimination half-life of MHD is prolonged to 19 hours, with a two-fold increase in AUC. Dose adjustment for oxcarbazepine is recommended in these patients (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION** sections).

Pediatric Use

Weight-adjusted MHD clearance decreases as age and weight increases, approaching that of adults. The mean weight-adjusted clearance in children 2 years to < 4 years of age is approximately 80% higher on average than that of adults. Therefore, MHD exposure in these children is expected to be about one-half that of adults when treated with a similar weight-adjusted dose. The mean weight-adjusted clearance in children 4 to 12 years of age is approximately 40% higher on average than that of adults. Therefore, MHD exposure in these children is expected to be about three-quarters that of adults when treated with a similar weight-adjusted dose. As weight increases, for patients 13 years of age and above, the weight adjusted MHD clearance is expected to reach that of adults.

Geriatric Use

Following administration of single (300 mg) and multiple (600 mg/day) doses of oxcarbazepine to elderly volunteers (60 to 82 years of age), the maximum plasma concentrations and AUC values of MHD were 30% to 60% higher than in younger volunteers (18 to 32 years of age). Comparisons of creatinine clearance in young and elderly volunteers indicate that the difference was due to age-related reductions in creatinine clearance.

Gender

No gender-related pharmacokinetic differences have been observed in children, adults, or the elderly.

Race

No specific studies have been conducted to assess what effect, if any, race may have on the disposition of oxcarbazepine.

CLINICAL STUDIES

The effectiveness of oxcarbazepine as adjunctive and monotherapy for partial seizures in adults, and as adjunctive therapy in children aged 2 to 16 years was established in seven multicenter, randomized, controlled trials.

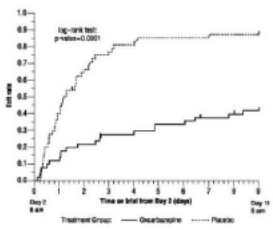
The effectiveness of oxcarbazepine as monotherapy for partial seizures in children aged 4 to 16 years was determined from data obtained in the studies described, as well as by pharmacokinetic/pharmacodynamic considerations.

Oxcarbazepine Monotherapy Trials

Four randomized, controlled, double-blind, multicenter trials, conducted in a predominately adult population, demonstrated the efficacy of oxcarbazepine as monotherapy. Two trials compared oxcarbazepine to placebo and two trials used a randomized withdrawal design to compare a high dose (2400 mg) with a low dose (300 mg) of oxcarbazepine, after substituting oxcarbazepine 2400 mg/day for one or more antiepileptic drugs (AEDs). All doses were administered on a BID schedule. A fifth randomized, controlled, rater-blind, multicenter study, conducted in a pediatric population, failed to demonstrate a statistically significant difference between low and high dose oxcarbazepine treatment groups.

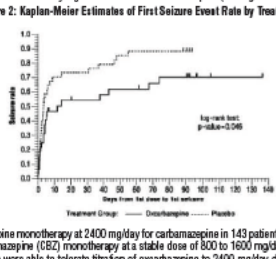
One placebo-controlled trial was conducted in 102 patients (11 to 62 years of age) with refractory partial seizures who had completed an inpatient evaluation for epilepsy surgery. Patients had been withdrawn from all AEDs and were required to have 2 to 10 partial seizures within 48 hours prior to randomization. Patients were randomized to receive either placebo or oxcarbazepine given as 1500 mg/day on Day 1 and 2400 mg/day thereafter for an additional nine days, or until one of the following three exit criteria occurred: 1) the occurrence of a fourth partial seizure, excluding Day 1, 2) two new-onset secondarily generalized seizures, where such seizures were not seen in the one-year period prior to randomization, or 3) occurrence of serial seizures or status epilepticus. The primary measure of effectiveness was a between-group comparison of the time to meet exit criteria. There was a statistically significant difference in favor of oxcarbazepine (see **Figure 1**), p = 0.0001.

Figure 1: Kaplan-Meier Estimates of Exit Rate by Treatment Group



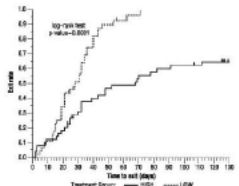
The second placebo-controlled trial was conducted in 67 untreated patients (8 to 69 years of age) with newly-diagnosed and recent-onset partial seizures. Patients were randomized to placebo or oxcarbazepine, initiated at 300 mg BID and titrated to 1200 mg/day (given as 600 mg BID) in six days, followed by maintenance treatment for 84 days. The primary measure of effectiveness was a between-group comparison of the time to first seizure. The difference between the two treatments was statistically significant in favor of oxcarbazepine (see **Figure 2**), p = 0.046.

Figure 2: Kaplan-Meier Estimates of First Seizure Event Rate by Treatment Group



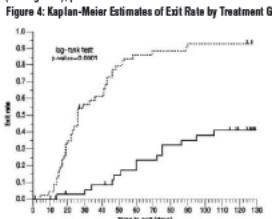
A third trial substituted oxcarbazepine monotherapy at 2400 mg/day for carbamazepine in 143 patients (12 to 65 years of age) whose partial seizures were inadequately controlled on carbamazepine (CBZ) monotherapy at a stable dose of 800 to 1600 mg/day, and maintained this oxcarbazepine dose for 56 days (baseline phase). Patients who were able to tolerate titration of oxcarbazepine to 2400 mg/day during simultaneous carbamazepine withdrawal were randomly assigned to either 300 mg/day of oxcarbazepine or 2400 mg/day oxcarbazepine. Patients were observed for 126 days or until one of the following four exit criteria occurred: 1) a doubling of the 28-day seizure frequency compared to baseline, 2) a two-fold increase in the highest consecutive two-day seizure frequency during baseline, 3) a single generalized seizure if none had occurred during baseline, or 4) a prolonged generalized seizure. The primary measure of effectiveness was a between group comparison of the time to meet exit criteria. The difference between the curves was statistically significant in favor of the oxcarbazepine 2400 mg/day group (see **Figure 3**), p = 0.0001.

Figure 3: Kaplan-Meier Estimates of Exit Rate by Treatment Group



Another monotherapy substitution trial was conducted in 87 patients (11 to 66 years of age) whose seizures were inadequately controlled on one or two AEDs. Patients were randomized to either oxcarbazepine 2400 mg/day or 300 mg/day and their standard AED regimen(s) were eliminated over the first six weeks of double-blind therapy. Double-blind treatment continued for another 84 days (total double-blind treatment of 126 days) or until one of the four exit criteria described for the previous study occurred. The primary measure of effectiveness was a between-group comparison of the percentage of patients meeting exit criteria. The results were statistically significant in favor of the oxcarbazepine 2400 mg/day group (14/34; 41.2%) compared to the oxcarbazepine 300 mg/day group (42/45; 93.3%) (p < 0.0001). The time to meeting one of the exit criteria was also statistically significant in favor of the oxcarbazepine 2400 mg/day group (see **Figure 4**), p = 0.0001.

Figure 4: Kaplan-Meier Estimates of Exit Rate by Treatment Group



A monotherapy trial was conducted in 92 pediatric patients (1 month to 16 years of age) with inadequately-controlled or new-onset partial seizures. Patients were hospitalized and randomized to either oxcarbazepine 10 mg/kg/day or were titrated up to 40 to 60 mg/kg/day within three days while withdrawing the previous AED on the second day of oxcarbazepine therapy. Seizures were recorded through continuous video-EEG monitoring from Day 3 to Day 5. Patients either completed the 5 day treatment or met one of the two exit criteria: 1) three study specific seizures (i.e. electrographic partial seizures with a behavioral correlate), 2) a prolonged study specific seizure. The primary measure of effectiveness was a between group comparison of the time to meet exit criteria in which the difference between the curves was not statistically significant (p = 0.904). The majority of patients from both dose groups completed the 5-day study without exiting.

Although this study failed to demonstrate an effect of oxcarbazepine as monotherapy in pediatric patients, several design elements, including the short treatment and assessment period, the absence of a true placebo, and the likely persistence of plasma levels of previously administered AEDs during the treatment period, make the results uninterpretable. For this reason, the results do not undermine the conclusion, based on pharmacokinetic/pharmacodynamic considerations, that oxcarbazepine is effective as monotherapy in pediatric patients 4 years old and older.

Oxcarbazepine Adjunctive Therapy Trials

The effectiveness of oxcarbazepine as an adjunctive therapy for partial seizures was established in two multicenter, randomized, double-blind, placebo-controlled trials, one in 692 patients (15 to 66 years of age) and one in 264 pediatric patients (3 to 17 years of age), and in one multicenter, rater-blind, randomized, age-stratified, parallel-group study comparing two doses of oxcarbazepine in 128 pediatric patients (1 month to < 4 years of age).

Patients in the two placebo-controlled trials were on 1 to 3 concomitant AEDs. In both of the trials, patients were stabilized on optimum dosages of their concomitant AEDs during an 8-week baseline phase. Patients who experienced at least 8 (minimum of 1 to 4 per month) partial seizures during the baseline phase were randomly assigned to placebo or to a specific dose of oxcarbazepine in addition to their other AEDs.

In these studies, the dose was increased over a two-week period until either the assigned dose was reached, or intolerance prevented increases. Patients then entered a 14- (pediatrics) or 24-week (adults) maintenance period.

In the adult trial, patients received fixed doses of 600, 1200 or 2400 mg/day. In the pediatric trial, patients received maintenance doses in the range of 30 to 46 mg/kg/day, depending on baseline weight. The primary measure of effectiveness in both trials was a between-group comparison of the percentage change in partial seizure frequency in the double-blind treatment phase relative to baseline phase. This comparison was statistically significant in favor of oxcarbazepine at all doses tested in both trials (p = 0.0001 for all doses for both trials). The number of patients randomized to each dose, the median baseline seizure rate, and the median percentage seizure rate reduction for each trial are shown in **Table 1**. It is important to note that in the high-dose group in the study in adults, over 65% of patients discontinued treatment because of adverse events; only 46 (27%) of the patients in this group completed the 28-week study (see **ADVERSE REACTIONS** section), an outcome not seen in the monotherapy studies.

Table 1: Summary of Percentage Change in Partial Seizure Frequency from Baseline for Placebo-Controlled Adjunctive Therapy Trials

Trial	Treatment Group	N	Baseline Median Seizure Rate*	Median % Reduction
1 (pediatrics)	Oxcarbazepine	136	12.5	34.8 [1]
	Placebo	128	13.1	9.4
2 (adults)	Oxcarbazepine 2400 mg/day	174	10	49.9 [1]
	Oxcarbazepine 1200 mg/day	177	9.8	40.2 [1]
	Oxcarbazepine 600 mg/day	168	9.6	26.4 [1]
	Placebo	173	8.6	7.6

[1] p = 0.0001; * = # per 28 days

Subset analyses of the antiepileptic efficacy of oxcarbazepine with regard to gender in these trials revealed no important differences in response between men and women. Because there were very few patients over the age of 65 in controlled trials, the effect of the drug in the elderly has not been adequately assessed.

The third adjunctive therapy trial enrolled 128 pediatric patients (1 month to < 4 years of age) with inadequately-controlled partial seizures on 1 to 2 concomitant AEDs. Patients who experienced at least 2 study-specific seizures (i.e., electrographic partial seizures with a behavioral correlate) during the 72-hour baseline period were randomly assigned to either oxcarbazepine 10 mg/kg/day or were titrated up to 60 mg/kg/day within 26 days. Patients were maintained on their randomized target dose for 9 days and seizures were recorded through continuous video-EEG monitoring during the last 72 hours of the maintenance period. The primary measure of effectiveness in this trial was a between-group comparison of the change in seizure frequency per 24 hours compared to the seizure frequency at baseline. For the entire group of patients enrolled, this comparison was statistically significant in favor of oxcarbazepine 60 mg/kg/day. In this study, there was no evidence that oxcarbazepine was effective in patients below the age of 2 years (N = 75).

INDICATIONS AND USAGE

Oxcarbazepine oral suspension is indicated for use as monotherapy or adjunctive therapy in the treatment of partial seizures in adults and as monotherapy in the treatment of partial seizures in children aged 4 years and above with epilepsy, and as adjunctive therapy in children aged 2 years and above with epilepsy.

CONTRAINDICATIONS

Oxcarbazepine should not be used in patients with a known hypersensitivity to oxcarbazepine or to any of its components.

WARNINGS

Hyponatremia

Clinically significant hyponatremia (sodium < 125 mmol/L) can develop during oxcarbazepine use. In the 14 controlled epilepsy studies 2.5% of oxcarbazepine-treated patients (38/1,524) had a sodium of less than 125 mmol/L at some point during treatment, compared to no such patients assigned placebo or active control (carbamazepine and phenobarbital for adjunctive and monotherapy substitution studies, and phenytoin and valproate for the monotherapy initiation studies). Clinically significant hyponatremia generally occurred during the first three months of treatment with oxcarbazepine, although there were patients who first developed a serum sodium < 125 mmol/L more than one year after initiation of therapy. Most patients who developed hyponatremia were asymptomatic but patients in the clinical trials were frequently monitored and some had their oxcarbazepine dose reduced, discontinued, or had their fluid intake restricted for hyponatremia. Whether or not these maneuvers prevented the occurrence of more severe events is unknown. Cases of symptomatic hyponatremia have been reported during postmarketing use. In clinical trials, patients whose treatment with oxcarbazepine was discontinued due to hyponatremia generally experienced normalization of serum sodium within a few days without additional treatment.

Measurement of serum sodium levels should be considered for patients during maintenance treatment with oxcarbazepine, particularly if the patient is receiving other medications known to decrease serum sodium levels (for example, drugs associated with inappropriate ADH secretion) or if symptoms possibly indicating hyponatremia develop (e.g., nausea, malaise, headache, lethargy, confusion, obtundation, or increase in seizure frequency or severity).

Anaphylactic Reactions and Angioedema

Rare cases of anaphylaxis and angioedema involving the larynx, glottis, lips and eyelids have been reported in patients after taking the first or subsequent doses of oxcarbazepine. Angioedema associated with laryngeal edema can be fatal. If a patient develops any of these reactions after treatment with oxcarbazepine, the drug should be discontinued and an alternative treatment started.

These patients should not be rechallenged with the drug (see **WARNINGS, Patients with a Past History of Hypersensitivity Reaction to Carbamazepine** subsection).

Patients with a Past History of Hypersensitivity Reaction to Carbamazepine

Patients who have had hypersensitivity reactions to carbamazepine should be informed that approximately 25% to 30% of them will experience hypersensitivity reactions with oxcarbazepine. For this reason patients should be specifically questioned about any prior experience with carbamazepine, and patients with a history of hypersensitivity reactions to carbamazepine should ordinarily be treated with oxcarbazepine only if the potential benefit justifies the potential risk. If signs or symptoms of hypersensitivity develop, oxcarbazepine should be discontinued immediately (see **WARNINGS, Anaphylactic Reactions and Angioedema** subsection; see **PRECAUTIONS, Multi-Organ Hypersensitivity** subsection).

Serious Dermatological Reactions

Serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in both children and adults in association with oxcarbazepine use. The median time of onset for reported cases was 19 days. Such serious skin reactions may be life-threatening, and some patients have required hospitalization with very rare reports of fatal outcome. Recurrence of the serious skin reactions following rechallenge with oxcarbazepine has also been reported.

The reporting rate of TEN and SJS associated with oxcarbazepine use, which is generally accepted to be an underestimate due to underreporting, exceeds the background incidence rate estimates by a factor of 3 to 10 fold. Estimates of the background incidence rate for these serious skin reactions in the general population range between 0.5 to 6 cases per million-person years. Therefore, if a patient develops a skin reaction while taking oxcarbazepine, consideration should be given to discontinuing oxcarbazepine use and prescribing another antiepileptic medication.

Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including oxcarbazepine, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed. **Table 2** shows absolute and relative risk by indication for all evaluated AEDs.

Table 2: Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events Per 1,000 Patients	Drug Patients with Events Per 1,000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1,000 Patients
Epilepsy	1	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing oxcarbazepine or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Withdrawal of AEDs

As with all antiepileptic drugs, oxcarbazepine should be withdrawn gradually to minimize the potential of increased seizure frequency.

PRECAUTIONS

Cognitive/Neuropsychiatric Adverse Events

Use of oxcarbazepine has been associated with central nervous system-related adverse events. The most significant of these can be classified into three general categories: 1) cognitive symptoms including psychomotor slowing, difficulty with concentration, and speech or language problems, 2) somnolence or fatigue, and 3) coordination abnormalities, including ataxia and gait disturbances.

Adult Patients

In one large, fixed-dose study, oxcarbazepine was added to existing AED therapy (up to three concomitant AEDs). By protocol, the dosage of the concomitant AEDs could not be reduced as oxcarbazepine was added, reduction in oxcarbazepine dosage was not allowed if intolerance developed, and patients were discontinued if unable to tolerate their highest target maintenance doses. In this trial, 65% of patients were discontinued because they could not tolerate the 2400 mg/day dose of oxcarbazepine on top of existing AEDs. The adverse events seen in this study were primarily CNS related and the risk for discontinuation was dose related.

In this trial, 7.1% of oxcarbazepine-treated patients and 4% of placebo-treated patients experienced a cognitive adverse event. The risk of discontinuation for these events was about 6.5 times greater on oxcarbazepine than on placebo. In addition, 26% of oxcarbazepine-treated patients and 12% of placebo-treated patients experienced somnolence. The risk of discontinuation for somnolence was about 10 times greater on oxcarbazepine than on placebo. Finally, 28.7% of oxcarbazepine-treated patients and 6.4% of placebo-treated patients experienced ataxia or gait disturbances. The risk for discontinuation for these events was about seven times greater on oxcarbazepine than on placebo.

In a single placebo-controlled monotherapy trial evaluating 2400 mg/day of oxcarbazepine, no patients in either treatment group discontinued double-blind treatment because of cognitive adverse events, somnolence, ataxia, or gait disturbance.

In the two dose-controlled conversion to monotherapy trials comparing 2400 mg/day and 300 mg/day oxcarbazepine, 1.1% of patients in the 2400 mg/day group discontinued double-blind treatment because of somnolence or cognitive adverse events compared to 0% in the 300 mg/day group. In these trials, no patients discontinued because of ataxia or gait disturbances in either treatment group.

Pediatric Patients

A study was conducted in pediatric patients (3 to 17 years old) with inadequately controlled partial seizures in which oxcarbazepine was added to existing AED therapy (up to two concomitant AEDs). By protocol, the dosage of concomitant AEDs could not be reduced as oxcarbazepine was added. Oxcarbazepine was titrated to reach a target dose ranging from 30 mg/kg to 46 mg/kg (based on a patient's body weight with fixed doses for pre-defined weight ranges).

Cognitive adverse events occurred in 5.8% of oxcarbazepine-treated patients (the single most common event being concentration impairment, 4 of 138 patients) and in 3.1% of patients treated with placebo. In addition, 34.8% of oxcarbazepine-treated patients and 14% of placebo-treated patients experienced somnolence. (No patient discontinued due to a cognitive adverse event or somnolence.). Finally, 23.2% of oxcarbazepine-treated patients and 7% of placebo-treated patients experienced ataxia or gait disturbances. Two (1.4%) oxcarbazepine-treated patients and 1 (0.8%) placebo-treated patient discontinued due to ataxia or gait disturbances.

Multi-Organ Hypersensitivity

Multi-organ hypersensitivity reactions have occurred in close temporal association (median time to detection 13 days: range 4 to 60) to the initiation of oxcarbazepine therapy in adult and pediatric patients. Although there have been a limited number of reports, many of these cases resulted in hospitalization and were considered life threatening. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations included lymphadenopathy, hepatitis, liver function test abnormalities, hematological abnormalities (e.g., eosinophilia, thrombocytopenia, neutropenia), pruritis, nephritis, oliguria, hepatorenal syndrome, arthralgia and asthenia. Because the disorder is variable in its expression, other organ system symptoms and signs, not noted here, may occur. If this reaction is suspected, oxcarbazepine should be discontinued and an alternative treatment started. Although there are no case reports to indicate cross sensitivity with other drugs that produce this syndrome, the experience amongst drugs associated with multi-organ hypersensitivity would indicate this to be a possibility (see **WARNINGS, Patients with a Past History of Hypersensitivity Reaction to Carbamazepine** subsection).

Information for Patients

Anaphylactic reactions and angioedema may occur during treatment with oxcarbazepine. Patients should be advised to report immediately signs and symptoms suggesting angioedema (swelling of the face, eyes, lips, tongue or difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician (see **WARNINGS, Anaphylactic Reactions and Angioedema** subsection).

Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that approximately 25% to 30% of these patients may experience hypersensitivity reactions with oxcarbazepine. Patients should be advised that if they experience a hypersensitivity reaction while taking oxcarbazepine they should consult with their physician immediately (see **WARNINGS, Patients with a Past History of Hypersensitivity Reaction to Carbamazepine** subsection).

Patients should be advised that serious skin reactions have been reported in association with oxcarbazepine. In the event a skin reaction should occur while taking oxcarbazepine patients should consult with their physician immediately (see **WARNINGS, Serious Dermatological Reactions** subsection).

Patients should be instructed that a fever associated with other organ system involvement (rash, lymphadenopathy, etc.) may be drug related and should be reported to the physician immediately (see **PRECAUTIONS, Multi-Organ Hypersensitivity** subsection).

Female patients of childbearing age should be warned that the concurrent use of oxcarbazepine with hormonal contraceptives may render this method of contraception less effective (see **Drug Interactions** subsection). Additional non-hormonal forms of contraception are recommended when using oxcarbazepine.

Patients, their caregivers, and families should be counseled that AEDs, including oxcarbazepine, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Caution should be exercised if alcohol is taken in combination with oxcarbazepine therapy, due to a possible additive sedative effect.

Patients should be advised that oxcarbazepine may cause dizziness and somnolence. Accordingly, patients should be advised not to drive or operate machinery until they have gained sufficient experience on oxcarbazepine to gauge whether it adversely affects their ability to drive or operate machinery.

Patients should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334 (see **PRECAUTIONS, Pregnancy Category C subsection**).

Laboratory Tests

Serum sodium levels below 125 mmol/L have been observed in patients treated with oxcarbazepine (see **WARNINGS** section). Experience from clinical trials indicates that serum sodium levels return toward normal when the oxcarbazepine dosage is reduced or discontinued, or when the patient was treated conservatively (e.g., fluid restriction).

Laboratory data from clinical trials suggest that oxcarbazepine use was associated with decreases in T_4, without changes in T_3 or TSH.

Drug Interactions

Oxcarbazepine can inhibit CYP2C19 and induce CYP3A4/5 with potentially important effects on plasma concentrations of other drugs. In addition, several AEDs that are cytochrome P450 inducers can decrease plasma concentrations of oxcarbazepine and MHD.

Oxcarbazepine was evaluated in human liver microsomes to determine its capacity to inhibit the major cytochrome P450 enzymes responsible for the metabolism of other drugs. Results demonstrate that oxcarbazepine and its pharmacologically active 10-monohydroxy metabolite (MHD) have little or no capacity to function as inhibitors for most of the human cytochrome P450 enzymes evaluated (CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, CYP4A9 and CYP4A11) with the exception of CYP2C19 and CYP3A4/5. Although inhibition of CYP3A4/5 by oxcarbazepine and MHD did occur at high concentrations, this is not likely to be of clinical significance. The inhibition of CYP2C19 by oxcarbazepine and MHD, however, is clinically relevant (see below).

In vitro, the UDP-glucuronyl transferase level was increased, indicating induction of this enzyme. Increases of 22% with MHD and 47% with oxcarbazepine were observed. As MHD, the predominant plasma substrate, is only a weak inducer of UDP-glucuronyl transferase, it is unlikely to have an effect on drugs that are mainly eliminated by conjugation through UDP-glucuronyl transferase (e.g., valproic acid, lamotrigine).

In addition, oxcarbazepine and MHD induce a subgroup of the cytochrome P450 3A family (CYP3A4 and CYP3A5) responsible for the metabolism of dihydropyridine calcium antagonists and oral contraceptives, resulting in a lower plasma concentration of these drugs.

As binding of MHD to plasma proteins is low (40%), clinically significant interactions with other drugs through competition for protein binding sites are unlikely.

Antiepileptic Drugs

Potential interactions between oxcarbazepine and other AEDs were assessed in clinical studies. The effect of these interactions on mean AUCs and C_{min} are summarized in **Table 3**.

Table 3: Summary of AED Interactions with Oxcarbazepine

AED Coadministered	Dose of AED (mg/day)	Oxcarbazepine Dose (mg/day)	Influence of Oxcarbazepine on AED Concentration (Mean Change, 90% Confidence Interval)	Influence of AED on MHD Concentration (Mean Change, 90% Confidence Interval)
Carbamazepine	400 to 2000	900	nc[1]	40% decrease [CI: 17% decrease, 57% decrease]
Phenobarbital	100 to 150	600 to 1800	14% increase [CI: 2% increase, 24% increase]	25% decrease [CI: 12% decrease, 51% decrease]
Phenytoin	250 to 500	600 to 1800 > 1200 to 2400	nc[1,2] up to 40% increase[3] [CI: 12% increase, 60% increase]	30% decrease [CI: 3% decrease, 48% decrease]
Valproic acid	400 to 2800	600 to 1800	nc[1]	18% decrease [CI: 13% decrease, 40% decrease]

[1] nc denotes a mean change of less than 10%

[2] Pediatrics

[3] Mean increase in adults at high oxcarbazepine doses

In vivo, the plasma levels of phenytoin increased by up to 40% when oxcarbazepine was given at doses above 1200 mg/day. Therefore, when using doses of oxcarbazepine greater than 1200 mg/day during adjunctive therapy, a decrease in the dose of phenytoin may be required. The increase of phenobarbital level, however, is small (15%) when given with oxcarbazepine.

Strong inducers of cytochrome P450 enzymes (i.e., carbamazepine, phenytoin and phenobarbital) have been shown to decrease the plasma levels of MHD (29% to 40%).

No autoinduction has been observed with oxcarbazepine.

Hormonal Contraceptives

Coadministration of oxcarbazepine with an oral contraceptive has been shown to influence the plasma concentrations of the two hormonal components, ethinylestradiol (EE) and levonorgestrel (LNG). The mean AUC values of EE were decreased by 48% [90% CI: 22 to 65] in one study and 52% [90% CI: 38 to 52] in another study. The mean AUC values of LNG were decreased by 32% [90% CI: 20 to 45] in one study and 52% [90% CI: 42 to 52] in another study. Therefore, concurrent use of oxcarbazepine with hormonal contraceptives may render these contraceptives less effective (see **Drug Interactions** sub-

OXCARBAZEPINE
ORAL SUSPENSION
Rx only

section). Studies w th other oral or implant contraceptives have not been conducted.

Calcium Antagonists

After repeated coadministration of oxcarbazepine, the AUC of felodipine was lowered by 28% [90% CI: 20 to 33].

Verapamil produced a decrease of 20% [90% CI: 18 to 27] of the plasma levels of MHD.

Other Drug Interactions

Cimetidine, erythromycin and dextropropoxyphene had no effect on the pharmacokinetics of MHD. Resu ts with warfarin show no evidence of interaction with either single or repeated doses of oxcarbazepine.

Drug/Laboratory Test Interactions

There are no known interactions of oxcarbazepine with commonly used laboratory tests.

Carcinogenesis/Mutagenesis/Impairment of Fertility

In two-year carcinogenicity studies, oxcarbazepine was administered in the diet at doses of up to 100 mg/kg/day to mice and by gavage at doses of up to 250 mg/kg to rats, and the pharmacologically active 10-hydroxy metabolite (MHD) was administered orally at doses of up to 600 mg/kg/day to rats. In mice, a dose-related increase in the incidence of hepatocellular adenomas was observed at oxcarbazepine doses ≥ 70 mg/kg/day or approximately 0.1 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. In rats, the incidence of hepatocellular carcinomas was increased in females treated with oxcarbazepine at doses ≥ 25 mg/kg/day (0.1 times the MRHD on a mg/m^2 basis), and incidences of hepatocellular adenomas and/or carcinomas were increased in males and females treated w th MHD at doses of 600 mg/kg/day (2.4 times the MRHD on a mg/m^2 basis) and ≥ 250 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis), respectively. There was an increase in the incidence of benign testicular interstitial cell tumors in rats at 250 mg oxcarbazepine/kg/day and at ≥ 250 mg MHD/kg/day, and an increase in the incidence of granular cell tumors in the cervix and vagina in rats at 600 mg MHD/kg/day.

Oxcarbazepine increased mutation frequencies in the Ames test *in vitro* in the absence of metabolic activation in one of five bacterial strains. Both oxcarbazepine and MHD produced increases in chromosomal aberrations and polyploidy in the Chinese hamster ovary assay *in vitro* in the absence of metabolic activation. MHD was negative in the Ames test and no mutagenic or clastogenic activity was found with either oxcarbazepine or MHD in V79 Chinese hamster cells *in vitro*. Oxcarbazepine and MHD were both negative for clastogenic or aneugenic effects (micronucleus formation) in an *in vivo* rat bone marrow assay.

In a fertility study in which rats were administered MHD (50, 150, or 450 mg/kg) orally prior to and during mating and early gestation, estrous cyc icity was disrupted and numbers of corpora lutea, implantations, and live embryos were reduced in females receiving the highest dose (approximately two times the MRHD on a mg/m^2 basis).

Pregnancy Category C

Increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity (embryolethality, growth retardation) were observed in the offspring of animals treated with either oxcarbazepine or its active 10-hydroxy metabolite (MHD) during pregnancy at doses similar to the maximum recommended human dose.

When pregnant rats were given oxcarbazepine (30, 300, or 1000 mg/kg) orally throughout the period of organogenesis, increased incidences of fetal malformations (craniofacial, cardiovascular, and skeletal) and variations were observed at the intermediate and high doses (approximately 1.2 and 4 times, respectively, the maximum recommended human dose [MRHD] on a mg/m^2 basis). Increased embryofetal death and decreased fetal body weights were seen at the high dose. Doses ≥ 300 mg/kg were also maternally toxic (decreased body weight gain, clinical signs), but there is no evidence to suggest that teratogenicity was secondary to the maternal effects.

In a study in which pregnant rabbits were orally administered MHD (20, 100, or 200 mg/kg) during organogenesis, embryofetal mortality was increased at the highest dose (1.5 times the MRHD on a mg/m^2 basis). This dose produced only minimal maternal toxicity.

In a study in which female rats were dosed orally with oxcarbazepine (25, 50, or 150 mg/kg) during the latter part of gestation and throughout the lactation period, a persistent reduction in body weights and altered behavior (decreased activity) were observed in offspring exposed to the highest dose (0.6 times the MRHD on a mg/m^2 basis). Oral administration of MHD (25, 75, or 250 mg/kg) to rats during gestation and lactation resulted in a persistent reduction in offspring weights at the highest dose (equivalent to the MRHD on a mg/m^2 basis).

There are no adequate and well-controlled c inical studies of oxcarbazepine in pregnant women; however, oxcarbazepine is closely related structurally to carbamazepine, which is considered to be teratogenic in humans. Given this fact, and the resu ts of the animal studies described, it is ikely that oxcarbazepine is a human teratogen. Oxcarbazepine should be used during pregnancy only if the potential benef t justifies the potential risk to the fetus.

To provide information regarding the effects of in utero exposure to oxcarbazepine, physicians are advised to recommend that pregnant patients taking oxcarbazepine enroll in the NAAED Pregnancy Registry. This can be done by cal ing the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

Labor and Delivery

The effect of oxcarbazepine on labor and delivery in humans has not been evaluated.

Nursing Mothers

Oxcarbazepine and its active metabolite (MHD) are excreted in human breast m lk. A milk-to-plasma concentration ratio of 0.5 was found for both. Because of the potential for serious adverse reactions to oxcarbazepine in nursing infants, a decision should be made about whether to discontinue nursing or to discontinue the drug in nursing women, taking into account the importance of the drug to the mother.

Patients with Renal Impairment

In rena ly-impaired patients (creatinine clearance < 30 mL/min), the elimination half-life of MHD is prolonged with a corresponding two-fold increase in AUC (see **CLINICAL PHARMACOLOGY**, **Pharmacokinetics** subsection). Oxcarbazepine therapy should be initiated at one-half the usual starting dose and increased, f necessary, at a slower than usual rate until the desired c inical response is achieved.

Pediatric Use

Oxcarbazepine is indicated for use as adjunctive therapy for partial seizures in patients aged 2 to 16 years. Oxcarbazepine is also indicated as monotherapy for partial seizures in patients aged 4 to 16 years. Oxcarbazepine has been given to 898 patients between the ages of 1 month to 17 years in controlled clinical trials (332 treated as monotherapy) and about 677 patients between the ages of 1 month to 17 years in other trials (See **ADVERSE REACTIONS** section for a description of the adverse events associated with oxcarbazepine use in this population).

Geriatric Use

There were 52 patients over age 65 in controlled clinical trials and 565 patients over the age of 65 in other trials. Following administration of single (300 mg) and multiple (600 mg/day) doses of oxcarbazepine in elderly volunteers (60 to 82 years of age), the maximum plasma concentrations and AUC values of MHD were 30% to 60% higher than in younger volunteers (18 to 32 years of age). Comparisons of creatinine clearance in young and elderly volunteers indicate that the difference was due to age-related reductions in creatinine clearance.

ADVERSE REACTIONS

Most Common Adverse Events in All Clinical Studies

Adjunctive Therapy/Monotherapy in Adults Previously Treated with other AEDs: The most commonly observed (≥ 5%) adverse experiences seen in association with oxcarbazepine and substantially more frequent than in placebo-treated patients were: Dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, abdominal pain, tremor, dyspepsia, abnormal gait.

Approximately 23% of these 1537 adu t patients discontinued treatment because of an adverse experience. The adverse experiences most commonly associated with discontinuation were: Dizziness (6.4%), diplopia (5.9%), ataxia (5.2%), vomiting (5.1%), nausea (4.9%), somnolence (3.8%), headache (2.9%), fatigue (2.1%), abnormal vision (2.1%), tremor (1.8%), abnormal gait (1.7%), rash (1.4%), hyponatremia (1%).

Monotherapy in Adults Not Previously Treated with other AEDs: The most commonly observed (≥ 5%) adverse experiences seen in association with oxcarbazepine in these patients were similar to those in previously treated patients.

Approximately 9% of these 295 adult patients discontinued treatment because of an adverse experience. The adverse experiences most commonly associated with discontinuation were: Dizziness (1.7%), nausea (1.7%), rash (1.7%), headache (1.4%).

Adjunctive Therapy/Monotherapy in Pediatric Patients 4 Years Old and Above Previously Treated with other AEDs: The most commonly observed (≥ 5%) adverse experiences seen in association w th oxcarbazepine in these patients were similar to those seen in adu ts.

Approximately 11% of these 456 pediatric patients discontinued treatment because of an adverse experience. The adverse experiences most commonly associated with discontinuation were: Somnolence (2.4%), vomiting (2%), ataxia (1.8%), diplopia (1.3%), dizziness (1.3%), fatigue (1.1%), nystagmus (1.1%).

Monotherapy in Pediatric Patients 4 Years Old and Above Not Previously Treated with other AEDs: The most commonly observed (≥ 5%) adverse experiences seen in association with oxcarbazepine in these patients were sim lar to those in adults.

Approximately 9.2% of 152 pediatric patients discontinued treatment because of an adverse experience. The adverse experiences most commonly associated (≥ 1%) with discontinuation were rash (5.3%) and maculopapular rash (1.3%).

Adjunctive Therapy/Monotherapy in Pediatric Patients 1 month to < 4 years Old Previously Treated or Not Previously Treated with other AEDs: The most commonly observed (≥ 5%) adverse experiences seen in association with oxcarbazepine in these patients were similar to those seen in older children and adults except for infections and infestations which were more frequently seen in these younger children.
Approximately 11% of these 241 pediatric patients discontinued treatment because of an adverse experience. The adverse experiences most commonly associated with discontinuation were: Convulsions (3.7%), status epilepticus (1.2%), and ataxia (1.2%).

Incidence in Controlled Clinical Studies: The prescr ber should be aware that the figures in **Tables 4, 5, 6** and **7** cannot be used to predict the frequency of adverse experiences in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis to estimate the relative contr bution of drug and nondrug factors to the adverse event incidences in the population studied.

Controlled Clinical Studies of Adjunctive Therapy/Monotherapy in Adults Previously Treated with other AEDs: **Table 4** lists treatment-emergent signs and symptoms that occurred in at least 2% of adu t patients with epilepsy treated with oxcarbazepine or placebo as adjunctive treatment and were numerically more common in the patients treated with any dose of oxcarbazepine. **Table 5** lists treatment-emergent signs and symptoms in patients converted from other AEDs to either high dose oxcarbazepine or low dose (300 mg) oxcarbazepine. Note that in some of these monotherapy studies patients who dropped out during a preliminary tolerability phase are not included in the tables.

Table 4: Treatment-Emergent Adverse Event Incidence in a Controlled Clinical Study of Adjunctive Therapy in Adults (Events in at Least 2% of Patients Treated with 2400 mg/day of Oxcarbazepine and Numerically More Frequent Than in the Placebo Group)

	Oxcarbazepine Dosage (mg/day)			
Body System/ Adverse Event	**OXC 600 N = 163 %**	**OXC 1200 N = 171 %**	**OXC 2400 N = 126 %**	**Placebo N = 166 %**
Body as a Whole				
Fatigue	15	12	15	7
Asthenia	6	3	6	5
Edema Legs	2	1	2	1
Weight Increase	1	2	2	1
Feeling Abnormal	0	1	2	0
Cardiovascular System				
Hypotension	0	1	2	0
Digestive System				
Nausea	15	25	29	10
Vomiting	13	25	36	5
Pain Abdominal	10	13	11	5
Diarrhea	5	6	7	6
Dyspepsia	5	5	6	2
Constipation	2	2	6	4
Gastritis	2	1	2	1
Metabolic and Nutritional Disorders				
Hyponatremia	3	1	2	1
Musculoskeletal System				
Muscle Weakness	1	2	2	0
Sprains and Strains	0	2	2	1
Nervous System				
Headache	32	28	26	23
Dizziness	26	32	49	13
Somnolence	20	28	36	12
Ataxia	9	17	31	5
Nystagmus	7	20	26	5
Gait Abnormal	5	10	17	1
Insomnia	4	2	3	1
Tremor	3	8	16	5
Nervousness	2	4	2	1
Agitation	1	1	2	1
Coordination Abnormal	1	3	2	1
EEG Abnormal	0	0	2	0
Speech Disorder	1	1	3	0
Confusion	1	1	2	1
Cranial Injury NOS	1	0	2	1
Dysmetria	1	2	3	0
Thinking Abnormal	0	2	4	0
Respiratory System				
Rhinitis	2	4	5	4
Skin and Appendages				
Acne	1	2	2	0
Special Senses				
Diplopia	14	30	40	5
Vertigo	6	12	15	2
Vision Abnormal	6	14	13	4
Accommodation Abnormal	0	0	2	0

Table 5: Treatment-Emergent Adverse Event Incidence in Controlled Clinical Studies of Monotherapy in Adults Previously Treated with Other AEDs (Events in at Least 2% of Patients Treated with 2400 mg/day of Oxcarbazepine and Numerically More Frequent Than in the Low Dose Control Group)

	Oxcarbazepine Dosage (mg/day)	
Body System/ Adverse Event	**2400 N = 86 %**	**300 N = 86 %**
Body as a Whole		
Fatigue	21	5
Fever	3	0
A lergy	2	0
Edema Generalized	2	1
Pain Chest	2	0
Digestive System		
Nausea	22	7
Vom ting	15	5
Diarrhea	7	5
Dyspepsia	6	1
Anorexia	5	3
Pain Abdominal	5	3
Mouth Dry	3	0
Hemorrhage Rectum	2	0
Toothache	2	1
Hemic and Lymphatic System		
Lymphadenopathy	2	0
Infections and Infestations		
Infection Viral	7	5
Infection	2	0
Metabolic and Nutritional Disorders		
Hyponatremia	5	0
Thirst	2	0
Nervous System		
Headache	31	15
Dizziness	28	8
Somnolence	19	5
Anxiety	7	5
Ataxia	7	1
Confusion	7	0
Nervousness	7	0
Insomnia	6	3
Tremor	6	3
Amnesia	5	1
Convulsions Aggravated	5	2
Emotional Labil ty	3	2
Hypoesthesia	3	1
Coordination Abnormal	2	1
Nystagmus	2	0
Speech Disorder	2	0
Respiratory System		
Upper Respiratory Tract Infection	10	5
Coughing	5	0
Bronch tis	3	0
Pharyngitis	3	0
Skin and Appendages		
Hot Flushes	2	1
Purpura	2	0
Special Senses		
Vision Abnormal	14	2
Diplopia	12	1
Taste Perversion	5	0
Vertigo	3	0
Earache	2	1
Ear Infection NOS	2	0
Urogenital and Reproductive System		
Urinary Tract Infection	5	1
Micturition Frequency	2	1
Vaginitis	2	0

Controlled Clinical Study of Monotherapy in Adults Not Previously Treated with other AEDs: **Table 6** lists treatment-emergent signs and symptoms in a controlled clinical study of monotherapy in adults not previously treated w th other AEDs that occurred in at least 2% of adult patients w th epilepsy treated with oxcarbazepine or placebo and were numerically more common in the patients treated w th oxcarbazepine.

Table 6: Treatment-Emergent Adverse Event Incidence in a Controlled Clinical Study of Monotherapy in Adults Not Previously Treated with Other AEDs (Events in at Least 2% of Patients Treated with Oxcarbazepine and Numerically More Frequent Than in the Placebo Group)

Body System/ Adverse Event	**Oxcarbazepine N = 55 %**	**Placebo N = 49 %**
Body as a Whole		
Falling Down NOS	4	0
Digestive System		
Nausea	16	12
Diarrhea	7	2
Vomiting	7	6
Constipation	5	0
Dyspepsia	5	4
Musculoskeletal System		
Pain Back	4	2
Nervous System		
Dizziness	22	6
Headache	13	10
Ataxia	5	0
Nervousness	5	2
Amnesia	4	2
Coordination Abnormal	4	2
Tremor	4	0
Respiratory System		
Upper Respiratory Tract Infection	7	0
Epistaxis	4	0
Infection Chest	4	0
Sinusitis	4	2
Skin and Appendages		
Rash	4	2
Special Senses		
Vision Abnormal	4	0

Controlled Clinical Studies of Adjunctive Therapy/Monotherapy in Pediatric Patients Previously Treated with other AEDs: **Table 7** lists treatment-emergent signs and symptoms that occurred in at least 2% of pediatric patients with epilepsy treated with oxcarbazepine or placebo as adjunctive treatment and were numerica ly more common in the patients treated with oxcarbazepine.

Table 7: Treatment-Emergent Adverse Event Incidence in Controlled Clinical Studies of Adjunctive Therapy/Monotherapy in Pediatric Patients Previously Treated with Other AEDs (Events in at Least 2% of Patients Treated with Oxcarbazepine and Numerically More Frequent Than in the Placebo Group)

Body System/ Adverse Event	**Oxcarbazepine N = 171 %**	**Placebo N = 139 %**
Body as a Whole		
Fatigue	13	9
Allergy	2	0
Asthenia	2	1
Digestive System		
Vomiting	33	14
Nausea	19	5
Constipation	4	1
Dyspepsia	2	0
Nervous System		
Headache	31	19
Somnolence	31	13
Dizziness	28	8
Ataxia	13	4
Nystagmus	9	1
Emotional Labi ity	8	4
Gait Abnormal	8	3
Tremor	6	4
Speech Disorder	3	1
Concentration Impaired	2	1
Convulsions	2	1
Muscle Contractions Involuntary	2	1
Respiratory System		
Rhinitis	10	9
Pneumonia	2	1
Skin and Appendages		
Bruising	4	2
Sweating Increased	3	0
Special Senses		
Diplopia	17	1
Vision Abnormal	13	1
Vertigo	2	0

Other Events Observed in Association with the Administration of Oxcarbazepine

In the paragraphs that fo low, the adverse events other than those in the preceding tables or text, that occurred in a total of 565 ch ldren and 1574 adults exposed to oxcarbazepine and that are reasonably likely to be related to drug use are presented. Events common in the population, events reflecting chronic lness and events ikely to reflect concomitant illness are omitted particularly f minor. They are listed in order of decreasing frequency. Because the reports cite events observed in open label and uncontrolled trials, the role of oxcarbazepine in their causation cannot be reliably determined.

Body as a Whole: Fever, malaise, pain chest precordial, rigors, weight decrease.

Cardiovascular System: Bradycardia, cardiac failure, cerebral hemorrhage, hypertension, hypotension postural, palpitation, syncope, tachycardia.

Digestive System: Appet te increased, blood in stool, cholel thiasis, colitis, duodenal ulcer, dysphagia, enteritis, eructation, esophagitis, flatulence, gastric ulcer, gingival bleeding, gum hyperplasia, hematemesis, hemorrhage rectum, hemorrhoids, hiccup, mouth dry, pain biliary, pain right hypochondrium, retching, sialoadenitis, stomatitis, stomat tis ulcerative.

Hemic and Lymphatic System: Leukopenia, thrombocytopenia.

Laboratory Abnormality: Gamma-GT increased, hyperglycemia, hypocalcemia, hypoglycemia, hypokalemia, liver enzymes elevated, serum transaminase increased.

Musculoskeletal System: Hypertonia muscle.

Nervous System: Aggressive reaction, amnesia, anguish, anxiety, apathy, aphasia, aura, convulsions aggravated, delirium, delusion, depressed level of consciousness, dysphonia, dystonia, emotional lability, euphoria, extrapyramidal disorder, feeling drunk, hemiplegia, hyperkinesia, hyperreflexia, hypoesthesia, hypokinesia, hyporeflexia, hypotonia, hysteria, libido decreased, ibido increased, manic reaction, migraine, muscle contractions involuntary, nervousness, neuralgia, oculogyric crisis, panic disorder, paralysis, paroniria, personality disorder, psychosis, ptosis, stupor, tetany.

Respiratory System: Asthma, dyspnea, epistaxis, laryngismus, pleurisy.

Skin and Appendages: Acne, alopecia, angioedema, bruising, dermatitis contact, eczema, facial rash, flushing, follicu itis, heat rash, hot flushes, photosensitivity reaction, pruritus genital, psoriasis, purpura, rash erythematous, rash maculopapular, viti igo, urticaria.

Special Senses: Accommodation abnormal, cataract, conjunctival hemorrhage, edema eye, hemianopia, mydriasis, otitis externa, photophobia, scotoma, taste perversion, tinnitus, xerophthalmia.

Surgical and Medical Procedures: Procedure dental oral, procedure female reproductive, procedure musculoskeletal, procedure skin.

Urogenital and Reproductive System: Dysuria, hematuria, intermenstrual bleeding, leukorrhea, menorrhagia, micturition frequency, pain renal, pain urinary tract, polyuria, priapism, renal calculus.

Other: Systemic lupus erythematosus.

Postmarketing and Other Experience

The following adverse events not seen in controlled clinical trials have been observed in named patient programs or postmarketing experience:

Body as a Whole: Multi-organ hypersensitivity disorders characterized by features such as rash, fever, lymphadenopathy, abnormal iver function tests, eosinophilia and arthralgia (see **PRECAUTIONS**, **Multi-Organ Hypersensitivity** subsection).

Anaphylaxis (see **WARNINGS**, **Anaphylactic Reactions and Angioedema** subsection).

Skin and Appendages: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (see **WARNINGS**, **Serious Dermatological Reactions** subsection).

DRUG ABUSE AND DEPENDENCE

Abuse

The abuse potential of oxcarbazepine has not been evaluated in human studies.

Dependence

Intragastric injections of oxcarbazepine to four cynomolgus monkeys demonstrated no signs of physical dependence as measured by the desire to self-administer oxcarbazepine by lever pressing activity.

OVERDOSAGE

Human Overdose Experience

Isolated cases of overdose with oxcarbazepine have been reported. The maximum dose taken was approximately 24,000 mg. All patients recovered with symptomatic treatment.

Treatment and Management

There is no specific antidote. Symptomatic and supportive treatment should be administered as appropriate. Removal of the drug by gastric lavage and/or inactivation by administering activated charcoal should be considered.

DOSAGE AND ADMINISTRATION

Oxcarbazepine oral suspension is recommended as adjunctive treatment in the treatment of partial seizures in adults and children aged 2 to 16 years. Oxcarbazepine oral suspension is also recommended as monotherapy in the treatment of partial seizures in adults and children aged 4 to 16 years. All dosing should be given in a twice-a-day (BID) regimen. Oxcarbazepine oral suspension and oxcarbazepine film-coated tablets may be interchanged at equal doses.

Oxcarbazepine oral suspension should be kept out of the reach and sight of children.

Before using oxcarbazepine oral suspension, shake the bottle well and prepare the dose immediately afterwards. The prescr bed amount of oral suspension should be withdrawn from the bottle using the oral dosing syringe supplied. Oxcarbazepine oral suspension can be mixed in a sma l glass of water just prior to administration or, a ternatively, may be swallowed directly from the syringe. After each use, close the bottle and rinse the syringe with warm water and allow it to dry thoroughly.

Oxcarbazepine oral suspension can be taken with or without food (see **CLINICAL PHARMACOLOGY**, **Pharmacokinetics** subsection).

Adults

Adjunctive Therapy

Treatment with oxcarbazepine oral suspension should be initiated with a dose of 600 mg/day, given in a BID regimen. If clinically indicated, the dose may be increased by a maximum of 600 mg/day at approximately weekly intervals; the recommended daily dose is 1200 mg/day. Daily doses above 1200 mg/day show somewhat greater effectiveness in controlled trials, but most patients were not able to tolerate the 2400 mg/day dose, primarily because of CNS effects. It is recommended that the patient be observed closely and plasma levels of the concomitant AEDs be monitored during the period of oxcarbazepine oral suspension titration, as these plasma levels may be a tered, especially at oxcarbazepine oral suspension doses greater than 1200 mg/day (see **PRECAUTIONS**, **Drug Interactions** subsection).

Conversion to Monotherapy

Patients receiving concom tant AEDs may be converted to monotherapy by initiating treatment with oxcarbazepine oral suspension at 600 mg/day (given in a BID regimen) while simultaneously in tiating the reduction of the dose of the concomitant AEDs. The concomitant AEDs should be completely withdrawn over 3 to 6 weeks, while the maximum dose of oxcarbazepine oral suspension should be reached in about 2 to 4 weeks. Oxcarbazepine oral suspension may be increased as clinically indicated by a maximum increment of 600 mg/day at approximately weekly intervals to achieve the recommended daily dose of 2400 mg/day. A daily dose of 1200 mg/day has been shown in one study to be effective in patients in whom monotherapy has been in tiated with oxcarbazepine oral suspension. Patients should be observed closely during this transition phase.

Initiation of Monotherapy

Patients not currently being treated with AEDs may have monotherapy initiated with oxcarbazepine oral suspension. In these patients, oxcarbazepine oral suspension should be initiated at a dose of 600 mg/day (given in a BID regimen); the dose should be increased by 300 mg/day every third day to a dose of 1200 mg/day. Controlled trials in these patients examined the effectiveness of a 1200 mg/day dose; a dose of 2400 mg/day has been shown to be effective in patients converted from other AEDs to oxcarbazepine oral suspension monotherapy (see above).

Pediatric Patients

Adjunctive Therapy (Aged 2 to 16 years)

In pediatric patients aged 4 to 16 years, treatment should be initiated at a daily dose of 8 to 10 mg/kg generally not to exceed 600 mg/day, given in a BID regimen. The target maintenance dose of oxcarbazepine oral suspension should be achieved over two weeks, and is dependent upon patient weight, according to the following chart:

20 to 29 kg - 900 mg/day
29.1 to 39 kg - 1200 mg/day
> 39 kg to 1800 mg/day

In the clinical trial, in which the intention was to reach these target doses, the median daily dose was 31 mg/kg with a range of 6 to 51 mg/kg.

In pediatric patients aged 2 to < 4 years, treatment should also be initiated at a daily dose of 8 to 10 mg/kg generally not to exceed 600 mg/day, given in a BID regimen. For patients under 20 kg, a starting dose of 16 to 20 mg/kg may be considered (see **CLINICAL PHARMACOLOGY**). The maximum maintenance dose of oxcarbazepine oral suspension should be achieved over 2 to 4 weeks and should not exceed 60 mg/kg/day in a BID regimen.

In the clinical trial in pediatric patients (2 to 4 years of age) in which the intention was to reach the target dose of 60 mg/kg/day, 50% of patients reached a final dose of at least 55 mg/kg/day.

Under adjunctive therapy (with and without enzyme-inducing AEDs), when normalized by body weight, apparent clearance (L/hr/kg) decreased when age increased such that children 2 to < 4 years of age may require up to twice the oxcarbazepine dose per body weight compared to adults; and children 4 to ≤ 12 years of age may require a 50% higher oxcarbazepine oral suspension dose per body weight compared to adults.

Conversion to Monotherapy (Aged 4 to 16 years)

Patients receiving concom tant antiepileptic drugs may be converted to monotherapy by initiating treatment with oxcarbazepine oral suspension at approximately 8 to 10 mg/kg/day given in a BID regimen, wh le simultaneously initiating the reduction of the dose of the concom tant antiepileptic drugs. The concomitant antiepileptic drugs can be completely withdrawn over 3 to 6 weeks while oxcarbazepine oral suspension may be increased as clinically indicated by a maximum increment of 10 mg/kg/day at approximately weekly intervals to achieve the recommended da ly dose. Patients should be observed closely during this trans tion phase.

The recommended total daily dose of oxcarbazepine oral suspension is shown in the table below.

Initiation of Monotherapy (Aged 4 to 16 years)

Patients not currently being treated with antiepileptic drugs may have monotherapy initiated with oxcarbazepine oral suspension. In these patients, oxcarbazepine oral suspension should be initiated at a dose of 8 to 10 mg/kg/day given in a BID regimen. The dose should be increased by 5 mg/kg/day every third day to the recommended daily dose shown in the table below.

Table 8: Range of Maintenance Doses of Oxcarbazepine Oral Suspension for Children by Weight During Monotherapy

	From	To
Weight in kg	**Dose (mg/day)**	**Dose (mg/day)**
20	600	900
25	900	1200
30	900	1200
35	900	1500
40	900	1500
45	1200	1500
50	1200	1800
55	1200	1800
60	1200	2100
65	1200	2100
70	1500	2100

Patients with Hepatic Impairment

In general, dose adjustments are not required in patients with mild-to-moderate hepatic impairment (see **CLINICAL PHARMACOLOGY**, **Pharmacokinetics**, **Special Populations** subsection).

Patients with Renal Impairment

In patients w th impaired renal function (creatinine clearance < 30 mL/min) oxcarbazepine oral suspension therapy should be initiated at one-half the usual starting dose (300 mg/day) and increased slowly to achieve the desired clinical response (see **CLINICAL PHARMACOLOGY**, **Pharmacokinetics**, **Special Populations** subsection).

HOW SUPPLIED

300 mg/5mL (60 mg/mL)

Oxcarbazepine oral suspension is an off-white to slightly yellow liquid which contains 300 mg of oxcarbazepine per 5 mL and is filled in 250 mL amber glass bottle with child resistant closure and is supplied with a 10 mL dosing syringe and press in bottle adapter.

NDC 63304-653-25 Bottle of 250 mL

Use within 7 weeks of first opening the bottle.

Store oxcarbazepine oral suspension in the original container. Shake well before using.

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

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

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32257 USA
by: Ohm Laboratories Inc.
Gloversv lle, NY 12078 USA

May 2009 FDA-04

00000000

LITRATURE SIZE : 273 x 314 MM
FONT SIZE : 4.44 PT.
COLOR : BLACK
TRACK (b) (4)

RANBAXY

NDC 63304-653-25

OXCARBAZEPINE

Oral Suspension

300 mg/5 mL

IMPORTANT: Shake well before using.

Use within 7 weeks of first opening the bottle.

Rx only **250 mL**

Each 5 mL contains 300 mg oxcarbazepine.

Usual Dosage: See package insert.

Store in original container.

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

Keep this and all drugs out of the reach of children.

0807

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32257 USA
by: Ohm Laboratories Inc.
Gloversville, NY 12078

LOT:

EXP:

non-varnish area for Lot & Exp

(b) (4)

(b) (4)

RANBAXY

NDC 63304-653-25

OXCARBAZEPINE

Oral Suspension

300 mg/5 mL

Shake well before using.

Rx only

250 mL

Each 5 mL contains 300 mg oxcarbazepine.

IMPORTANT: Shake well before using.

For oral use only.

Usual Dosage: See package insert.

See enclosed Oxcarbazepine Oral Suspension Instruction Sheet.

Store in original container.

Use within 7 weeks of first opening the bottle.

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

Keep this and all drugs out of the reach of children.

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32257 USA
by: Ohm Laboratories Inc.
Gloversville, NY 12078 0807

RANBAXY

NDC 63304-653-25

OXCARBAZEPINE

Oral Suspension

300 mg/5 mL

Shake well before using.

Rx only

250 mL

FPO
0000000

NON VARNISH

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

/s/

Melaine Shin
6/9/2009 08:53:44 PM
LABELING REVIEWER

Lillie Golson
6/10/2009 10:55:47 AM
LABELING REVIEWER

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

ANDA Number:	78-734
Date of Submission:	August 17, 2007 & September 17, 2007
Applicant's Name:	Ranbaxy Laboratories Limited
Established Name:	Oxcarbazepine Oral Suspension, 300 mg/5 mL.
Proposed Proprietary Name:	None

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

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

CONTAINER: 250 mL

- Satisfactory in final print as of August 17, 2007 submission.

CARTON: 250 mL.

- Satisfactory in final print as of August 17, 2007 submission.

PROFESSIONAL PACKAGE INSERT

- Satisfactory in final print as of September 17, 2007 submission.

REVISIONS NEEDED POST-APPROVAL: None

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Trileptal®

NDA Number: 21-285

NDA Drug Name: Oxcarbazepine

NDA Firm: Novartis

Date of Approval of NDA Insert and supplement #: S-014; approved June 19, 2007

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

Was this approval based upon an OGD labeling guidance? No

NOTE TO CHEMIST: None

FOR THE RECORD:

****September 17, 2007 submission was made in response to our request to revise their labeling based on the revised oxcarbazepine tablet-only generic template incorporating OCC's additional comments on September 12, 2007. See email below.**

1. MODEL LABELING

   This review was based on the labeling for Trileptal® by Novartis [NDA 21-285/S-014; approved June 19, 2007]. A generic labeling template was created and includes the carve out due to exclusivity I-478 FOR USE AS ADJUNCTIVE THERAPY IN THE TREATMENT OF PARTIAL SEIZURES IN CHILDREN WITH EPILEPSY AGED 2-4 YEARS.

2. USP ITEM

   No

3. PROPRIETARY NAME

   None

4. PATENTS/EXCLUSIVITIES

Patent Data

Appl No	Patent No	Patent Expiration	Patent Use Code	How Certified	Labeling Impact
021014	7037525	FEB 12,2018	U-724	IV	none
021014	7037525*PED	AUG 12,2018			

U-724 METHOD OF TREATING SEIZURES

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration	Labeling Impact
021014	001	PED	APR 28,2009	
021014	001	I-478	OCT 28,2008	None, the generic labeling template includes the carve out with BPCA disclaimer due to I-478

I-478: FOR USE AS ADJUNCTIVE THERAPY IN THE TREATMENT OF PARTIAL SEIZURES IN CHILDREN WITH EPILEPSY AGED 2-4 YEARS

5. INACTIVE INGREDIENTS

   The list of inactive ingredients is accurate.

6. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

   Manufactured by: Ohm Laboratories Inc, Gloversville, NY, USA facility.
   Manufactured for: Ranbaxy Pharmaceuticals Inc. Jacksonville, FL 32257.

7. CONTAINER/CLOSURE

Strength	Fill Size	Bottle	Cap	Press in Bottle (b) (4)	10 mL dosing syringe
300 mg/5 mL	250 mL	USP Type III Amber Glass	(b) (4)	(b) (4)	(b) (4)

8. PACKAGING/SCORING CONFIGURATIONS

RLD: Bottle of 250 mL.

ANDA: Bottle of 250 mL.

9. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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

ANDA: Store at 20°-25° (68° – 77°F) [see USP Controlled Room Temperature]

Date of Review: September 22, 2007Date of Submission: August 17, 2007 & September 17, 2007

Primary Reviewer: _____ _____
Melaine Shin Date:

Team Leader: _____ _____
Lillie Golson Date:

cc: ANDA 78-734
DUP/DIVISION FILE
HFD-613/MShin/LGolson (no cc)
APPROVAL SUMMARY
File Path: V:\FIRMSNZ\RANBAXY\LTRS&REV\78734 Ap1.Labeling review.doc
FINAL: September 22, 2007

OXCARBAZEPINE ORAL SUSPENSION
Rx only

Prescribing Information

DESCRIPTION

Oxcarbazepine is an antiepileptic drug available as a 300 mg/5 mL (60 mg/mL) oral suspension. Oxcarbazepine is 10, 11-Dihydro-10-oxo-5*H*-dibenz[b, *f*]azepine-5-carboxamide, and its structural formula is

Oxcarbazepine is an off-white to yellow crystalline powder. It is sparingly soluble in chloroform. Its molecular weight is 252.27.

Oxcarbazepine oral suspension contains the following inactive ingredients: artificial cherry flavor, ascorbic acid, carboxymethylcellulose sodium, colloidal silicon dioxide, copovidone, hydroxyethylcellulose, methylparaben, microcrystalline cellulose, noncrystallizing sorbital solution, propylene glycol, polyoxyl 8 stearate, povidone, propylparaben, purified water, saccharin sodium, sorbic acid.

CLINICAL PHARMACOLOGY

Mechanism of Action

The pharmacological activity of oxcarbazepine is primarily exerted through the 10- monohydroxy metabolite (MHD) of oxcarbazepine (see **Metabolism and Excretion** subsection). The precise mechanism by which oxcarbazepine and MHD exert their antiseizure effect is unknown; however, *in vitro* electrophysiological studies indicate that they produce blockade of voltage-sensitive sodium channels, resulting in stabilization of hyperexcited neural membranes, inhibition of repetitive neuronal firing, and diminution of propagation of synaptic impulses. These actions are thought to be important in the prevention of seizure spread in the intact brain. In addition, increased potassium conductance and modulation of high-voltage activated calcium channels may contribute to the anticonvulsant effects of the drug. No significant interactions of oxcarbazepine or MHD with brain neurotransmitter or modulator receptor sites have been demonstrated.

Pharmacodynamics

Oxcarbazepine and its active metabolite (MHD) exhibit anticonvulsant properties in animal seizure models. They protected rodents against electrically induced tonic extension seizures and, to a lesser degree, chemically induced clonic seizures, and abolished or reduced the frequency of chronically recurring focal seizures in Rhesus monkeys with aluminum implants. No development of tolerance (i.e., attenuation of anticonvulsive activity) was observed in the maximal electroshock test when mice and rats were treated daily for five days and four weeks, respectively, with oxcarbazepine or MHD.

Pharmacokinetics

Following oral administration of oxcarbazepine tablets, oxcarbazepine is completely absorbed and extensively metabolized to its pharmacologically active 10-monohydroxy metabolite (MHD). The half-life of the parent is about two hours, while the half-life of MHD is about nine hours, so that MHD is responsible for most antiepileptic activity.

Based on MHD concentrations, oxcarbazepine tablets and suspension were shown to have similar bioavailability.

After single-dose administration of oxcarbazepine oral suspension to healthy male volunteers under fasted conditions, the median t_{max} was six hours.

In a mass balance study in people, only 2% of total radioactivity in plasma was due to unchanged oxcarbazepine, with approximately 70% present as MHD, and the remainder attributable to minor metabolites.

Effect of Food: Although not directly studied, the oral bioavailability of the oxcarbazepine suspension is unlikely to be affected under fed conditions. Therefore, oxcarbazepine suspension can be taken with or without food.

Steady-state plasma concentrations of MHD are reached within 2 to 3 days in patients when oxcarbazepine is given twice a day. At steady state the pharmacokinetics of MHD are linear and show dose proportionality over the dose range of 300 to 2400 mg/day.

Distribution

The apparent volume of distribution of MHD is 49L.

Approximately 40% of MHD is bound to serum proteins, predominantly to albumin. Binding is independent of the serum concentration within the therapeutically relevant range. Oxcarbazepine and MHD do not bind to alpha-1-acid glycoprotein.

Metabolism and Excretion

Oxcarbazepine is rapidly reduced by cytosolic enzymes in the liver to its 10-monohydroxy metabolite, MHD, which is primarily responsible for the pharmacological effect of oxcarbazepine. MHD is metabolized further by conjugation with glucuronic acid. Minor amounts (4% of the dose) are oxidized to the pharmacologically inactive 10,11-dihydroxy metabolite (DHD).

Oxcarbazepine is cleared from the body mostly in the form of metabolites which are predominantly excreted by the kidneys. More than 95% of the dose appears in the urine, with less than 1% as unchanged oxcarbazepine. Fecal excretion accounts for less than 4% of the administered dose. Approximately 80% of the dose is excreted in the urine either as glucuronides of MHD (49%) or as unchanged MHD (27%); the inactive DHD accounts for approximately 3% and conjugates of MHD and oxcarbazepine account for 13% of the dose.

Special Populations

Hepatic Impairment

The pharmacokinetics and metabolism of oxcarbazepine and MHD were evaluated in healthy volunteers and hepatically-impaired subjects after a single 900 mg oral dose. Mild-to-moderate hepatic impairment did not affect the pharmacokinetics of oxcarbazepine and MHD. No dose adjustment for oxcarbazepine is recommended in patients with mild-to-moderate hepatic impairment. The pharmacokinetics of oxcarbazepine and MHD have not been evaluated in severe hepatic impairment and, therefore, caution should be exercised when dosing severely impaired patients.

Renal Impairment

There is a linear correlation between creatinine clearance and the renal clearance of MHD. When oxcarbazepine is administered as a single 300 mg dose in renally-impaired patients (creatinine clearance < 30 mL/min), the elimination half-life of MHD is prolonged to 19 hours, with a two-fold increase in AUC. Dose adjustment for oxcarbazepine is recommended in these patients (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION** sections).

Pediatric Use

Weight-adjusted MHD clearance decreases as age and weight increases, approaching that of adults. The mean weight-adjusted clearance in children 4 to 12 years of age is approximately 40% higher on average than that of adults. Therefore, MHD exposure in these children is expected to be about three-quarters that of adults when treated with a similar weight-adjusted dose. As weight increases, for patients 13 years of age and above, the weight adjusted MHD clearance is expected to reach that of adults.

Additional pharmacokinetic information for pediatric patients ages 2 to 4 years of age is approved for Novartis Pharmaceuticals corporation's oxcarbazepine tablets and oral suspension. However due to Novartis' marketing exclusivity rights, this drug product is not labeled for this pediatric age group.

Geriatric Use

Following administration of single (300 mg) and multiple (600 mg/day) doses of oxcarbazepine to elderly volunteers (60 to 82 years of age), the maximum plasma concentrations and AUC values of MHD were 30% to 60% higher than in younger volunteers (18 to 32 years of age). Comparisons of creatinine clearance in young and elderly volunteers indicate that the difference was due to age-related reductions in creatinine clearance.

Gender

No gender-related pharmacokinetic differences have been observed in children, adults, or the elderly.

Race

No specific studies have been conducted to assess what effect, if any, race may have on the disposition of oxcarbazepine.

CLINICAL STUDIES

The effectiveness of oxcarbazepine as adjunctive and monotherapy for partial seizures in adults, and as adjunctive therapy in children aged 2 to 16 was established in seven multicenter, randomized, controlled trials.

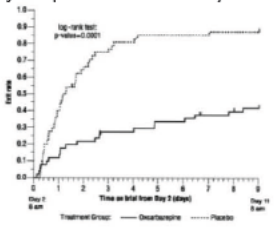
The effectiveness of oxcarbazepine as monotherapy for partial seizures in children aged 4 to 16 was determined from data obtained in the studies described, as well as by pharmacokinetic/pharmacodynamic considerations.

Oxcarbazepine Monotherapy Trials

Four randomized, controlled, double-blind, multicenter trials, conducted in a predominately adult population, demonstrated the efficacy of oxcarbazepine as monotherapy. Two trials compared oxcarbazepine to placebo and two trials used a randomized withdrawal design to compare a high dose (2400 mg) with a low dose (300 mg) of oxcarbazepine, after substituting oxcarbazepine 2400 mg/day for one or more antiepileptic drugs (AEDs). All doses were administered on a BID schedule. A fifth randomized, controlled, rater-blind, multicenter study, conducted in a pediatric population, failed to demonstrate a statistically significant difference between low and high dose oxcarbazepine treatment groups.

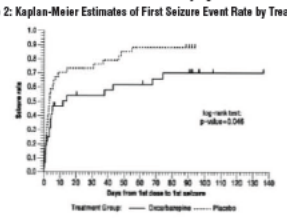
One placebo-controlled trial was conducted in 102 patients (11 to 62 years of age) with refractory partial seizures who had completed an inpatient evaluation for epilepsy surgery. Patients had been withdrawn from all AEDs and were required to have 2 to 10 partial seizures within 48 hours prior to randomization. Patients were randomized to receive either placebo or oxcarbazepine given as 1500 mg/day on Day 1 and 2400 mg/day thereafter for an additional nine days, or until one of the following three exit criteria occurred: 1) the occurrence of a fourth partial seizure, excluding Day 1, 2) two new-onset secondarily generalized seizures, where such seizures were not seen in the one-year period prior to randomization, or 3) occurrence of serial seizures or status epilepticus. The primary measure of effectiveness was a between-group comparison of the time to meet exit criteria. There was a statistically significant difference in favor of oxcarbazepine (see **Figure 1**), p = 0.0001.

Figure 1: Kaplan-Meier Estimates of Exit Rate by Treatment Group



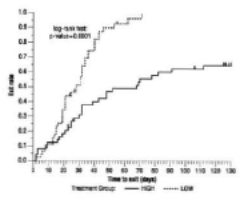
The second placebo-controlled trial was conducted in 67 untreated patients (8 to 69 years of age) with newly-diagnosed and recent-onset partial seizures. Patients were randomized to placebo or oxcarbazepine, initiated at 300 mg BID and titrated to 1200 mg/day (given as 600 mg BID) in six days, followed by maintenance treatment for 84 days. The primary measure of effectiveness was a between-group comparison of the time to first seizure. The difference between the two treatments was statistically significant in favor of oxcarbazepine (see **Figure 2**), p = 0.046.

Figure 2: Kaplan-Meier Estimates of First Seizure Event Rate by Treatment Group



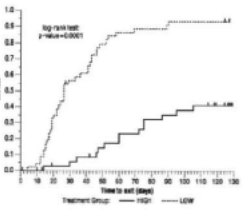
A third trial substituted oxcarbazepine monotherapy at 2400 mg/day for carbamazepine in 143 patients (12 to 65 years of age) whose partial seizures were inadequately controlled on carbamazepine (CBZ) monotherapy at a stable dose of 800 to 1600 mg/day, and maintained this oxcarbazepine dose for 56 days (baseline phase). Patients who were able to tolerate titration of oxcarbazepine to 2400 mg/day during simultaneous carbamazepine withdrawal were randomly assigned to either 300 mg/day of oxcarbazepine or 2400 mg/day oxcarbazepine. Patients were observed for 126 days or until one of the following four exit criteria occurred: 1) a doubling of the 28-day seizure frequency compared to baseline, 2) a two-fold increase in the highest consecutive two-day seizure frequency during baseline, 3) a single generalized seizure if none had occurred during baseline, or 4) a prolonged generalized seizure. The primary measure of effectiveness was a between group comparison of the time to meet exit criteria. The difference between the curves was statistically significant in favor of the oxcarbazepine 2400 mg/day group (see **Figure 3**), p = 0.0001.

Figure 3: Kaplan-Meier Estimates of Exit Rate by Treatment Group



Another monotherapy substitution trial was conducted in 87 patients (11 to 66 years of age) whose seizures were inadequately controlled on one or two AEDs. Patients were randomized to either oxcarbazepine 2400 mg/day or 300 mg/day and their standard AED regimen(s) were eliminated over the first six weeks of double-blind therapy. Double-blind treatment continued for another 84 days (total double-blind treatment of 126 days) or until one of the four exit criteria described for the previous study occurred. The primary measure of effectiveness was a between-group comparison of the percentage of patients meeting exit criteria. The results were statistically significant in favor of the oxcarbazepine 2400 mg/day group (14/34; 41.2%) compared to the oxcarbazepine 300 mg/day group (42/45; 93.3%) (p < 0.0001). The time to meeting one of the exit criteria was also statistically significant in favor of the oxcarbazepine 2400 mg/day group (see **Figure 4**), p = 0.0001.

Figure 4: Kaplan-Meier Estimates of Exit Rate by Treatment Group



A monotherapy trial was conducted in 92 pediatric patients (1 month to 16 years of age) with inadequately-controlled or new-onset partial seizures. Patients were hospitalized and randomized to either oxcarbazepine 10 mg/kg/day or were titrated up to 40 to 60 mg/kg/day within three days while withdrawing the previous AED on the second day of oxcarbazepine therapy. Seizures were recorded through continuous video-EEG monitoring from day 3 to day 5. Patients either completed the 5 day treatment or met one of the two exit criteria: 1) three study specific seizures (i.e. electrographic partial seizures with a behavioral correlate), 2) a prolonged study specific seizure. The primary measure of effectiveness was a between group comparison of the time to meet exit criteria in which the difference between the curves was not statistically significant (p = 0.904). The majority of patients from both dose groups completed the 5-day study without exiting.

Although this study failed to demonstrate an effect of oxcarbazepine as monotherapy in pediatric patients, several design elements, including the short treatment and assessment period, the absence of a true placebo, and the likely persistence of plasma levels of previously administered AEDs during the treatment period, make the results uninterpretable. For this reason, the results do not undermine the conclusion, based on pharmacokinetic/pharmacodynamic considerations, that oxcarbazepine is effective as monotherapy in pediatric patients 4 years old and older.

Oxcarbazepine Adjunctive Therapy Trials

The effectiveness of oxcarbazepine as an adjunctive therapy for partial seizures was established in two multicenter, randomized, double-blind, placebo-controlled trials, one in 692 patients (15 to 66 years of age) and one in 264 pediatric patients (3 to 17 years of age).

Patients in these trials were on 1 to 3 concomitant AEDs. In both of the trials, patients were stabilized on optimum dosages of their concomitant AEDs during an 8-week baseline phase. Patients who experienced at least 8 (minimum of 1 to 4 per month) partial seizures during the baseline phase were randomly assigned to placebo or to a specific dose of oxcarbazepine in addition to their other AEDs.

In these studies, the dose was increased over a two-week period until either the assigned dose was reached, or intolerance prevented increases. Patients then entered a 14- (pediatrics) or 24 week (adults) maintenance period.

In the adult trial, patients received fixed doses of 600, 1200 or 2400 mg/day. In the pediatric trial, patients received maintenance doses in the range of 30 to 46 mg/kg/day, depending on baseline weight. The primary measure of effectiveness in both trials was a between-group comparison of the percentage change in partial seizure frequency in the double-blind treatment phase relative to baseline phase. This comparison was statistically significant in favor of oxcarbazepine at all doses tested in both trials (p = 0.0001 for all doses for both trials). The number of patients randomized to each dose, the median baseline seizure rate, and the median percentage seizure rate reduction for each trial are shown in **Table 1**. It is important to note that in the high-dose group in the study in adults, over 65% of patients discontinued treatment because of adverse events; only 46 (27%) of the patients in this group completed the 28-week study (see **ADVERSE REACTIONS** section), an outcome not seen in the monotherapy studies.

Table 1: Summary of Percentage Change in Partial Seizure Frequency from Baseline for Placebo-Controlled Adjunctive Therapy Trials

Trial	Treatment Group	N	Baseline Median Seizure Rate*	Median % Reduction
1 (pediatrics)	Oxcarbazepine	136	12.5	34.8 [1]
	Placebo	128	13.1	9.4
2 (adults)	Oxcarbazepine 2400 mg/day	174	10	49.9 [1]
	Oxcarbazepine 1200 mg/day	177	9.8	40.2 [1]
	Oxcarbazepine 600 mg/day	168	9.6	26.4 [1]
	Placebo	173	8.6	7.6

[1] p = 0.0001; * = # per 28 days

Subset analyses of the antiepileptic efficacy of oxcarbazepine with regard to gender in these trials revealed no important differences in response between men and women. Because there were very few patients over the age of 65 in controlled trials, the effect of the drug in the elderly has not been adequately assessed.

Additional clinical trial information in pediatric patients ages 2 to 4 years is approved for Novartis Pharmaceuticals corporation's oxcarbazepine tablets and oral suspension. However due to Novartis' marketing exclusivity rights, this drug product is not labeled for this pediatric age group.

INDICATIONS AND USAGE

Oxcarbazepine is indicated for use as monotherapy or adjunctive therapy in the treatment of partial seizures in adults and as monotherapy in the treatment of partial seizures in children aged 4 years and above with epilepsy, and as adjunctive therapy in children aged 4 years and above with epilepsy.

Additional pediatric use information in patients ages 2 to 4 years is approved for Novartis Pharmaceuticals corporation's oxcarbazepine tablets and oral suspension. However due to Novartis' marketing exclusivity rights, this drug product is not labeled for this pediatric age group.

CONTRAINDICATIONS

Oxcarbazepine should not be used in patients with a known hypersensitivity to oxcarbazepine or to any of its components.

WARNINGS

Hyponatremia

Clinically significant hyponatremia (sodium < 125 mmol/L) can develop during oxcarbazepine use. In the 14 controlled epilepsy studies 2.5% of oxcarbazepine-treated patients (38/1,524) had a sodium of less than 125 mmol/L at some point during treatment, compared to no such patients assigned placebo or active control (carbamazepine and phenobarbital for adjunctive and monotherapy substitution studies, and phenytoin and valproate for the monotherapy initiation studies). Clinically significant hyponatremia generally occurred during the first three months of treatment with oxcarbazepine, although there were patients who first developed a serum sodium < 125 mmol/L more than one year after initiation of therapy. Most patients who developed hyponatremia were asymptomatic but patients in the clinical trials were frequently monitored and some had their oxcarbazepine dose reduced, discontinued, or had their fluid intake restricted for hyponatremia. Whether or not these maneuvers prevented the occurrence of more severe events is unknown. Cases of symptomatic hyponatremia have been reported during postmarketing use. In clinical trials, patients whose treatment with oxcarbazepine was discontinued due to hyponatremia generally experienced normalization of serum sodium within a few days without additional treatment.

Measurement of serum sodium levels should be considered for patients during maintenance treatment with oxcarbazepine, particularly if the patient is receiving other medications known to decrease serum sodium levels (for example, drugs associated with inappropriate ADH secretion) or if symptoms possibly indicating hyponatremia develop (e.g., nausea, malaise, headache, lethargy, confusion, obtundation, or increase in seizure frequency or severity).

Anaphylactic Reactions and Angioedema

Rare cases of anaphylaxis and angioedema involving the larynx, glottis, lips and eyelids have been reported in patients after taking the first or subsequent doses of oxcarbazepine. Angioedema associated with laryngeal edema can be fatal. If a patient develops any of these reactions after treatment with oxcarbazepine, the drug should be discontinued and an alternative treatment started.

These patients should not be rechallenged with the drug (see **WARNINGS, Patients with a Past History of Hypersensitivity Reaction to Carbamazepine subsection**).

Patients with a Past History of Hypersensitivity Reaction to Carbamazepine

Patients who have had hypersensitivity reactions to carbamazepine should be informed that approximately 25% to 30% of them will experience hypersensitivity reactions with oxcarbazepine. For this reason patients should be specifically questioned about any prior experience with carbamazepine, and patients with a history of hypersensitivity reactions to carbamazepine should ordinarily be treated with oxcarbazepine only if the potential benefit justifies the potential risk. If signs or symptoms of hypersensitivity develop, oxcarbazepine should be discontinued immediately (see **WARNINGS, Anaphylactic Reactions and Angioedema** subsection; see **PRECAUTIONS, Multi-Organ Hypersensitivity** subsection).

Serious Dermatological Reactions

Serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in both children and adults in association with oxcarbazepine use. The median time of onset for reported cases was 19 days. Such serious skin reactions may be life-threatening, and some patients have required hospitalization with very rare reports of fatal outcome. Recurrence of the serious skin reactions following rechallenge with oxcarbazepine has also been reported.

The reporting rate of TEN and SJS associated with oxcarbazepine use, which is generally accepted to be an underestimate due to underreporting, exceeds the background incidence rate estimates by a factor of 3 to 10 fold. Estimates of the background incidence rate for these serious skin reactions in the general population range between 0.5 to 6 cases per million-person years. Therefore, if a patient develops a skin reaction while taking oxcarbazepine, consideration should be given to discontinuing oxcarbazepine use and prescribing another antiepileptic medication.

Withdrawal of AEDs

As with all antiepileptic drugs, oxcarbazepine should be withdrawn gradually to minimize the potential of increased seizure frequency.

PRECAUTIONS

Cognitive/Neuropsychiatric Adverse Events

Use of oxcarbazepine has been associated with central nervous system-related adverse events. The most significant of these can be classified into three general categories: 1) cognitive symptoms including psychomotor slowing, difficulty with concentration, and speech or language problems, 2) somnolence or fatigue, and 3) coordination abnormalities, including ataxia and gait disturbances.

Adult Patients

In one large, fixed dose study, oxcarbazepine was added to existing AED therapy (up to three concomitant AEDs). By protocol, the dosage of the concomitant AEDs could not be reduced as oxcarbazepine was added, reduction in oxcarbazepine dosage was not allowed if intolerance developed, and patients were discontinued if unable to tolerate their highest target maintenance doses. In this trial, 65% of patients were discontinued because they could not tolerate the 2400 mg/day dose of oxcarbazepine on top of existing AEDs. The adverse events seen in this study were primarily CNS related and the risk for discontinuation was dose related.

In this trial, 7.1% of oxcarbazepine-treated patients and 4% of placebo-treated patients experienced a cognitive adverse event. The risk of discontinuation for these events was about 6.5 times greater on oxcarbazepine than on placebo. In addition, 26% of oxcarbazepine-treated patients and 12% of placebo-treated patients experienced somnolence. The risk of discontinuation for somnolence was about 10 times greater on oxcarbazepine than on placebo. Finally, 28.7% of oxcarbazepine-treated patients and 5.4% of placebo-treated patients experienced ataxia or gait disturbances. The risk for discontinuation for these events was about seven times greater on oxcarbazepine than on placebo.

In a single placebo-controlled monotherapy trial evaluating 2400 mg/day of oxcarbazepine, no patients in either treatment group discontinued double-blind treatment because of cognitive adverse events, somnolence, ataxia, or gait disturbance.

In the two dose-controlled conversion to monotherapy trials comparing 2400 mg/day and 300 mg/day oxcarbazepine, 1.1% of patients in the 2400 mg/day group discontinued double-blind treatment because of somnolence or cognitive adverse events compared to 0% in the 300 mg/day group. In these trials, no patients discontinued because of ataxia or gait disturbances in either treatment group.

Pediatric Patients

A study was conducted in pediatric patients (3 to 17 years old) with inadequately controlled partial seizures in which oxcarbazepine was added to existing AED therapy (up to two concomitant AEDs). By protocol, the dosage of concomitant AEDs could not be reduced as oxcarbazepine was added. Oxcarbazepine was titrated to reach a target dose ranging from 30 mg/kg to 46 mg/kg (based on a patients body weight with fixed doses for pre-defined weight ranges).

Cognitive adverse events occurred in 5.8% of oxcarbazepine-treated patients (the single most common event being concentration impairment, 4 of 138 patients) and in 3.1% of patients treated with placebo. In addition, 34.8% of oxcarbazepine-treated patients and 14% of placebo-treated patients experienced somnolence. (No patient discontinued due to a cognitive adverse event or somnolence.). Finally, 23.2% of oxcarbazepine-treated patients and 7% of placebo-treated patients experienced ataxia or gait disturbances. Two (1.4%) oxcarbazepine-treated patients and 1 (0.8%) placebo-treated patient discontinued due to ataxia or gait disturbances.

Multi-Organ Hypersensitivity

Multi-organ hypersensitivity reactions have occurred in close temporal association (median time to detection 13 days: range 4 to 60) to the initiation of oxcarbazepine therapy in adult and pediatric patients. Although there have been a limited number of reports, many of these cases resulted in hospitalization and some were considered life threatening. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations included lymphadenopathy, hepatitis, liver function test abnormalities, hematological abnormalities (e.g., eosinophilia, thrombocytopenia, neutropenia), pruritis, nephritis, oliguria, hepatorenal syndrome, arthralgia and asthenia. Because the disorder is variable in its expression, other organ system symptoms and signs, not noted here, may occur. If this reaction is suspected, oxcarbazepine should be discontinued and an alternative treatment started. Although there are no case reports to indicate cross sensitivity with other drugs that produce this syndrome, the experience amongst drugs associated with multi-organ hypersensitivity would indicate this to be a possibility (see **WARNINGS**, Patients with a Past History of Hypersensitivity Reaction to Carbamazepine subsection).

Information for Patients

Anaphylactic reactions and angioedema may occur during treatment with oxcarbazepine. Patients should be advised to report immediately signs and symptoms suggesting angioedema (swelling of the face, eyes, lips, tongue or difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician (see **WARNINGS, Anaphylactic Reactions and Angioedema subsection**).

Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that approximately 25% to 30% of these patients may experience hypersensitivity reactions with oxcarbazepine. Patients should be advised that if they experience a hypersensitivity reaction while taking oxcarbazepine they should consult with their physician immediately (see **WARNINGS, Patients with a Past History of Hypersensitivity Reaction to Carbamazepine** subsection).

Patients should be advised that serious skin reactions have been reported in association with oxcarbazepine. In the event a skin reaction should occur while taking oxcarbazepine, patients should consult with their physician immediately (see **WARNINGS, Serious Dermatological Reactions** subsection).

Patients should be instructed that a fever associated with other organ system involvement (rash, lymphadenopathy, etc.) may be drug related and should be reported to the physician immediately (see **PRECAUTIONS, Multi-Organ Hypersensitivity** subsection).

Female patients of childbearing age should be warned that the concurrent use of oxcarbazepine with hormonal contraceptives may render this method of contraception less effective (see **Drug Interactions** subsection). Additional non-hormonal forms of contraception are recommended when using oxcarbazepine.

Caution should be exercised if alcohol is taken in combination with oxcarbazepine therapy, due to a possible additive sedative effect.

Patients should be advised that oxcarbazepine may cause dizziness and somnolence. Accordingly, patients should be advised not to drive or operate machinery until they have gained sufficient experience on oxcarbazepine to gauge whether it adversely affects their ability to drive or operate machinery.

Laboratory Tests

Serum sodium levels below 125 mmol/L have been observed in patients treated with oxcarbazepine (see **WARNINGS** section). Experience from clinical trials indicates that serum sodium levels return toward normal when the oxcarbazepine dosage is reduced or discontinued, or when the patient was treated conservatively (e.g., fluid restriction).

Laboratory data from clinical trials suggest that oxcarbazepine use was associated with decreases in T_4, without changes in T_3 or TSH.

Drug Interactions

Oxcarbazepine can inhibit CYP2C19 and induce CYP3A4/5 with potentially important effects on plasma concentrations of other drugs. In addition, several AEDs that are cytochrome P450 inducers can decrease plasma concentrations of oxcarbazepine and MHD.

Oxcarbazepine was evaluated in human liver microsomes to determine its capacity to inhibit the major cytochrome P450 enzymes responsible for the metabolism of other drugs. Results demonstrate that oxcarbazepine and its pharmacologically active 10-monohydroxy metabolite (MHD) have little or no capacity to function as inhibitors for most of the human cytochrome P450 enzymes evaluated (CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, CYP4A9 and CYP4A11) with the exception of CYP2C19 and CYP3A4/5. Although inhibition of CYP3A4/5 by oxcarbazepine and MHD did occur at high concentrations, it is not likely to be of clinical significance. The inhibition of CYP2C19 by oxcarbazepine and MHD, however, is clinically relevant (see below).

In vitro, the UDP-glucuronyl transferase level was increased, indicating induction of this enzyme. Increases of 22% with MHD and 47% with oxcarbazepine were observed. As MHD, the predominant plasma substrate, is only a weak inducer of UDP-glucuronyl transferase, it is unlikely to have an effect on drugs that are mainly eliminated by conjugation through UDP-glucuronyl transferase (e.g., valproic acid, lamotrigine).

In addition, oxcarbazepine and MHD induce a subgroup of the cytochrome P450 3A family (CYP3A4 and CYP3A5) responsible for the metabolism of dihydropyridine calcium antagonists and oral contraceptives, resulting in a lower plasma concentration of these drugs.

As binding of MHD to plasma proteins is low (40%), clinically significant interactions with other drugs through competition for protein binding sites are unlikely.

Antiepileptic Drugs

Potential interactions between oxcarbazepine and other AEDs were assessed in clinical studies. The effect of these interactions on mean AUCs and C_{min} are summarized in **Table 2.**

Table 2: Summary of AED interactions with Oxcarbazepine

AED Coadministered	Dose of AED (mg/day)	Oxcarbazepine Dose (mg/day)	Influence of Oxcarbazepine on AED Concentration (Mean Change, 90% Confidence Interval)	Influence of AED on MHD Concentration (Mean Change, 90% Confidence Interval)
Carbamazepine	400 to 2000	900	nc[1]	40% decrease [CI: 17% decrease, 57% decrease]
Phenobarbital	100 to 150	600 to 1800	14% increase [CI: 2% increase, 24% increase]	25% decrease [CI: 12% decrease, 51% decrease]
Phenytoin	250 to 500	600 to 1800 > 1200 to 2400	nc[1,2] up to 40% increase[3] [CI: 12% increase, 60% increase]	30% decrease [CI: 3% decrease, 48% decrease]
Valproic acid	400 to 2800	600 to 1800	nc[1]	18% decrease [CI: 13% decrease, 40% decrease]

[1] nc denotes a mean change of less than 10%

[2] Pediatrics

[3] Mean increase in adults at high oxcarbazepine doses

In vivo, the plasma levels of phenytoin increased by up to 40% when oxcarbazepine was given at doses above 1200 mg/day. Therefore, when using doses of oxcarbazepine greater than 1200 mg/day during adjunctive therapy, a decrease in the dose of phenytoin may be required. The increase of phenobarbital level, however, is small (15%) when given with oxcarbazepine.

Strong inducers of cytochrome P450 enzymes (i.e., carbamazepine, phenytoin and phenobarbital) have been shown to decrease the plasma levels of MHD (29% to 40%).

No autoinduction has been observed with oxcarbazepine.

Hormonal Contraceptives

Coadministration of oxcarbazepine with an oral contraceptive has been shown to influence the plasma concentrations of the two hormonal components, ethinylestradiol (EE) and levonorgestrel (LNG). The mean AUC values of EE were decreased by 48% [90% CI: 22 to 65] in one study and 52% [90% CI: 38 to 52] in another study. The mean AUC values of LNG were decreased by 32% [90% CI: 20 to 45] in one study and 52% [90% CI: 42 to 52] in another study. Therefore, concurrent use of oxcarbazepine with hormonal contraceptives may render these contraceptives less effective (see **Drug Interactions** subsection). Studies with other oral or implant contraceptives have not been conducted.

Calcium Antagonists

After repeated coadministration of oxcarbazepine, the AUC of felodipine was lowered by 28% [90% CI: 20 to 33].

Verapamil produced a decrease of 20% [90% CI: 18 to 27] of the plasma levels of MHD.

Other Drug Interactions

Cimetidine, erythromycin and dextropropoxyphene had no effect on the pharmacokinetics of MHD. Results with warfarin show no evidence of interaction with either single or repeated doses of oxcarbazepine.

Drug/Laboratory Test Interactions

There are no known interactions of oxcarbazepine with commonly used laboratory tests.

Carcinogenesis/Mutagenesis/Impairment of Fertility

In two-year carcinogenicity studies, oxcarbazepine was administered in the diet at doses of up to 100 mg/kg/day to mice and by gavage at doses of up to 250 mg/kg to rats, and the pharmacologically active 10-hydroxy metabolite (MHD) was administered orally at doses of up to 600 mg/kg/day to rats. In mice, a dose-related increase in the incidence of hepatocellular adenomas was observed at oxcarbazepine doses ≥ 70 mg/kg/day or approximately 0.1 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. In rats, the incidence of hepatocellular carcinomas was increased in females treated with oxcarbazepine at doses ≥ 25 mg/kg/day (0.1 times the MRHD on a mg/m^2 basis), and incidences of hepatocellular adenomas and/or carcinomas were increased in males and females treated with MHD at doses of 600 mg/kg/day (2.4 times the MRHD on a mg/m^2 basis) and ≥ 250 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis), respectively. There was an increase in the incidence of benign testicular interstitial cell tumors in rats at 250 mg oxcarbazepine/kg/day and at ≥ 250 mg MHD/kg/day, and an increase in the incidence of granular cell tumors in the cervix and vagina in rats at 600 mg MHD/kg/day.

Oxcarbazepine increased mutation frequencies in the Ames test *in vitro* in the absence of metabolic activation in one of five bacterial strains. Both oxcarbazepine and MHD produced increases in chromosomal aberrations and polyploidy in the Chinese hamster ovary assay *in vitro* in the absence of metabolic activation. MHD was negative in the Ames test, and no mutagenic or clastogenic activity was found with either oxcarbazepine or MHD in V79 Chinese hamster cells *in vitro*. Oxcarbazepine and MHD were both negative for clastogenic or aneugenic effects (micronucleus formation) in an *in vivo* rat bone marrow assay.

OXCARBAZEPINE
ORAL SUSPENSION
Rx only

FPO

In a fertility study in which rats were administered MHD (50, 150, or 450 mg/kg) orally prior to and during mating and early gestation, estrous cyclicity was disrupted and numbers of corpora lutea, implantations, and live embryos were reduced in females receiving the highest dose (approximately two times the MRHD on a mg/m^2 basis).

Pregnancy Category C

Increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity (embryolethality, growth retardation) were observed in the offspring of animals treated with either oxcarbazepine or its active 10-hydroxy metabolite (MHD) during pregnancy at doses similar to the maximum recommended human dose.

When pregnant rats were given oxcarbazepine (30, 300, or 1000 mg/kg) orally throughout the period of organogenesis, increased incidences of fetal malformations (craniofacial, cardiovascular, and skeletal) and variations were observed at the intermediate and high doses (approximately 1.2 and 4 times, respectively, the maximum recommended human dose [MRHD] on a mg/m^2 basis). Increased embryofetal death and decreased fetal body weights were seen at the high dose. Doses ≥ 300 mg/kg were also maternally toxic (decreased body weight gain, clinical signs), but there is no evidence to suggest that teratogenicity was secondary to the maternal effects.

In a study in which pregnant rabbits were orally administered MHD (20, 100, or 200 mg/kg) during organogenesis, embryofetal mortality was increased at the highest dose (1.5 times the MRHD on a mg/m^2 basis). This dose produced only minimal maternal toxicity.

In a study in which female rats were dosed orally with oxcarbazepine (25, 50, or 150 mg/kg) during the latter part of gestation and throughout the lactation period, a persistent reduction in body weights and altered behavior (decreased activity) were observed in offspring exposed to the highest dose (0.6 times the MRHD on a mg/m^2 basis). Oral administration of MHD (25, 75, or 250 mg/kg) to rats during gestation and lactation resulted in a persistent reduction in offspring weights at the highest dose (equivalent to the MRHD on a mg/m^2 basis).

There are no adequate and well-controlled clinical studies of oxcarbazepine in pregnant women; however, oxcarbazepine is closely related structurally to carbamazepine, which is considered to be teratogenic in humans. Given this fact, and the results of the animal studies described, it is likely that oxcarbazepine is a human teratogen. Oxcarbazepine should be used during pregnancy only f the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of oxcarbazepine on labor and delivery in humans has not been evaluated.

Nursing Mothers

Oxcarbazepine and ts active metabolite (MHD) are excreted in human breast milk. A milk-to-plasma concentration ratio of 0.5 was found for both. Because of the potential for serious adverse reactions to oxcarbazepine in nursing infants, a decision should be made about whether to discontinue nursing or to discontinue the drug in nursing women, taking into account the importance of the drug to the mother.

Patients with Renal Impairment

In renally-impaired patients (creatinine clearance < 30 mL/min), the elimination half- ife of MHD is prolonged with a corresponding two-fold increase in AUC (see **CLINICAL PHARMACOLOGY**, **Pharmacokinetics** subsection). Oxcarbazepine therapy should be initiated at one-half the usual starting dose and increased, if necessary, at a slower than usual rate until the desired clinical response is achieved.

Pediatric Use

Oxcarbazepine is indicated for use as adjunctive therapy for partial seizures in patients aged 4 to 16 years. Oxcarbazepine is also indicated as monotherapy for partial seizures in patients aged 4 to 16 years. Oxcarbazepine has been given to 770 patients between the ages of 3 to 17 years in controlled clinical trials (332 treated as monotherapy) and about 615 patients between the ages of 3 to 17 years in other trials. (See **ADVERSE REACTIONS** section for a description of the adverse events associated with oxcarbazepine use in this population.)

Additional pediatric use information in patients ages 2 to 4 years is approved for Novartis Pharmaceuticals corporation's oxcarbazepine tablets and oral suspension. However due to Novartis' marketing exclusivity rights, this drug product is not labeled for this pediatric age group.

Geriatric Use

There were 52 patients over age 65 in contro led clinical trials and 565 patients over the age of 65 in other trials. Following administration of single (300 mg) and multiple (600 mg/day) doses of oxcarbazepine in elderly volunteers (60 to 82 years of age), the maximum plasma concentrations and AUC values of MHD were 30% to 60% higher than in younger volunteers (18 to 32 years of age). Comparisons of creatinine clearance in young and elderly volunteers indicate that the difference was due to age-related reductions in creatinine clearance.

ADVERSE REACTIONS

Most Common Adverse Events in All Clinical Studies

Adjunctive Therapy/Monotherapy in Adults Previously Treated with other AEDs: The most commonly observed (≥ 5%) adverse experiences seen in association with oxcarbazepine and substantially more frequent than in placebo-treated patients were: Dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, abdominal pain, tremor, dyspepsia, abnormal gait.

Approximately 23% of these 1,537 adult patients discontinued treatment because of an adverse experience. The adverse experiences most commonly associated with discontinuation were: Dizziness (6.4%), diplopia (5.9%), ataxia (5.2%), vomiting (5.1%), nausea (4.9%), somnolence (3.8%), headache (2.9%), fatigue (2.1%), abnormal vision (2.1%), tremor (1.8%), abnormal gait (1.7%), rash (1.4%), hyponatremia (1%).

Monotherapy in Adults not Previously Treated with other AEDs: The most commonly observed (≥ 5%) adverse experiences seen in association with oxcarbazepine in these patients were similar to those in previously treated patients.

Approximately 9% of these 295 adult patients discontinued treatment because of an adverse experience. The adverse experiences most commonly associated with discontinuation were: Dizziness (1.7%), nausea (1.7%), rash (1.7%), headache (1.4%).

Adjunctive Therapy/Monotherapy in Pediatric Patients 4 Years Old and Above Previously Treated with other AEDs: The most commonly observed (≥ 5%) adverse experiences seen in association with oxcarbazepine in these patients were similar to those seen in adults.

Approximately 11% of these 456 pediatric patients discontinued treatment because of an adverse experience. The adverse experiences most commonly associated with discontinuation were: Somnolence (2.4%), vomiting (2%), ataxia (1.8%), diplopia (1.3%), dizziness (1.3%), fatigue (1.1%), nystagmus (1.1%).

Monotherapy in Pediatric Patients 4 Years Old and Above not Previously Treated with other AEDs: The most commonly observed (≥ 5%) adverse experiences seen in association w th oxcarbazepine in these patients were similar to those in adults.

Approximately 9.2% of 152 pediatric patients discontinued treatment because of an adverse experience. The adverse experiences most commonly associated (≥ 1%) with discontinuation were rash (5.3%) and maculopapular rash (1.3%).

Adjunctive Therapy/Monotherapy in Pediatric Patients 1 month to < 4 Old Previously Treated or not Previously Treated with other AEDs: The most commonly observed (≥ 5%) adverse experiences seen in association with oxcarbazepine in these patients were similar to those seen in older children and adults except for infections and infestations which were more frequently seen in these younger children.
Approximately 11% of these 241 pediatric patients discontinued treatment because of an adverse experience. The adverse experiences most commonly associated with discontinuation were: Convulsions (3.7%), status epilepticus (1.2%), and ataxia (1.2%).

Incidence in Controlled Clinical Studies: The prescriber should be aware that the figures in **Tables 3**, **4**, **5** and **6** cannot be used to predict the frequency of adverse experiences in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis to estimate the relative contribution of drug and nondrug factors to the adverse event incidences in the population studied.

Controlled Clinical Studies of Adjunctive Therapy/Monotherapy in Adults Previously Treated with other AEDs: **Table 3** lists treatment-emergent signs and symptoms that occurred in at least 2% of adult patients with epilepsy treated with oxcarbazepine or placebo as adjunctive treatment and were numerically more common in the patients treated with any dose of oxcarbazepine. **Table 4** lists treatment-emergent signs and symptoms in patients converted from other AEDs to either high dose oxcarbazepine or low dose (300 mg) oxcarbazepine. Note that in some of these monotherapy studies patients who dropped out during a preliminary tolerability phase are not included in the tables.

Table 3: Treatment-Emergent Adverse Event Incidence in a Controlled Clinical Study of Adjunctive Therapy in Adults (Events in at Least 2% of Patients Treated with 2400 mg/day of Oxcarbazepine and Numerically More Frequent Than in the Placebo Group)

	Oxcarbazepine Dosage (mg/day)			
Body System/ Adverse Event	OXC 600 N = 163 %	OXC 1200 N = 171 %	OXC 2400 N = 126 %	Placebo N = 166 %
Body as a Whole				
Fatigue	15	12	15	7
Asthenia	6	3	6	5
Edema Legs	2	1	2	1
Weight Increase	1	2	2	1
Feeling Abnormal	0	1	2	0
Cardiovascular System				
Hypotension	0	1	2	0
Digestive System				
Nausea	15	25	29	10
Vom ting	13	25	36	5
Pain Abdominal	10	13	11	5
Diarrhea	5	6	7	6
Dyspepsia	5	5	6	2
Constipation	2	2	6	4
Gastritis	2	1	2	1
Metabolic and Nutritional Disorders				
Hyponatremia	3	1	2	1
Musculoskeletal System				
Muscle Weakness	1	2	2	0
Sprains and Strains	0	2	2	1
Nervous System				
Headache	32	28	26	23
Dizziness	26	32	49	13
Somnolence	20	28	36	12
Ataxia	9	17	31	5
Nystagmus	7	20	26	5
Gait Abnormal	5	10	17	1
Insomnia	4	2	3	1
Tremor	3	8	16	5
Nervousness	2	4	2	1
Agitation	1	1	2	1
Coordination Abnormal	1	3	2	1
EEG Abnormal	0	0	2	0
Speech Disorder	1	1	3	0
Confusion	1	1	2	1
Cranial Injury NOS	1	0	2	1
Dysmetria	1	2	3	0
Thinking Abnormal	0	2	4	0
Respiratory System				
Rhinitis	2	4	5	4
Skin and Appendages				
Acne	1	2	2	0
Special Senses				
Diplopia	14	30	40	5
Vertigo	6	12	15	2
Vision Abnormal	6	14	13	4
Accommodation Abnormal	0	0	2	0

Table 4: Treatment-Emergent Adverse Event Incidence in Controlled Clinical Studies of Monotherapy in Adults Previously Treated with Other AEDs (Events in at Least 2% of Patients Treated with 2400 mg/day of Oxcarbazepine and Numerically More Frequent Than in the Low Dose Control Group)

	Oxcarbazepine Dosage (mg/day)	
Body System/ Adverse Event	2400 N = 86 %	300 N = 86 %
Body as a Whole		
Fatigue	21	5
Fever	3	0
Allergy	2	0
Edema Generalized	2	1
Pain Chest	2	0
Digestive System		
Nausea	22	7
Vomiting	15	5
Diarrhea	7	5
Dyspepsia	6	1
Anorexia	5	3
Pain Abdominal	5	3
Mouth Dry	3	0
Hemorrhage Rectum	2	0
Toothache	2	1
Hemic and Lymphatic System		
Lymphadenopathy	2	0
Infections and Infestations		
Infection Viral	7	5
Infection	2	0
Metabolic and Nutritional Disorders		
Hyponatremia	5	0
Thirst	2	0
Nervous System		
Headache	31	15
Dizziness	28	8
Somnolence	19	5
Anxiety	7	5
Ataxia	7	1
Confusion	7	0
Nervousness	7	0
Insomnia	6	3
Tremor	6	3
Amnesia	5	1
Convulsions Aggravated	5	2
Emotional Lability	3	2
Hypoesthesia	3	1
Coordination Abnormal	2	1
Nystagmus	2	0
Speech Disorder	2	0
Respiratory System		
Upper Respiratory Tract Infection	10	5
Coughing	5	0
Bronchitis	3	0
Pharyngitis	3	0
Skin and Appendages		
Hot Flushes	2	1
Purpura	2	0
Special Senses		
Vision Abnormal	14	2
Diplopia	12	1
Taste Perversion	5	0
Vertigo	3	0
Earache	2	1
Ear Infection NOS	2	0
Urogenital and Reproductive System		
Urinary Tract Infection	5	1
Micturition Frequency	2	1
Vaginitis	2	0

Controlled Clinical Study of Monotherapy in Adults not Previously Treated with other AEDs: **Table 5** lists treatment-emergent signs and symptoms in a controlled clinical study of monotherapy in adults not previously treated with other AEDs that occurred in at least 2% of adult patients with epilepsy treated with oxcarbazepine or placebo and were numerically more common in the patients treated with oxcarbazepine.

Table 5: Treatment-Emergent Adverse Event Incidence in a Controlled Clinical Study of Monotherapy in Adults not Previously Treated with Other AEDs (Events in at Least 2% of Patients Treated with Oxcarbazepine and Numerically More Frequent Than in the Placebo Group)

Body System/ Adverse Event	Oxcarbazepine N = 55 %	Placebo N = 49 %
Body as a Whole		
Falling Down NOS	4	0
Digestive System		
Nausea	16	12
Diarrhea	7	2
Vomiting	7	6
Constipation	5	0
Dyspepsia	5	4
Musculoskeletal System		
Pain Back	4	2
Nervous System		
Dizziness	22	6
Headache	13	10
Ataxia	5	0
Nervousness	5	2
Amnesia	4	2
Coordination Abnormal	4	2
Tremor	4	0
Respiratory System		
Upper Respiratory Tract Infection	7	0
Epistaxis	4	0
Infection Chest	4	0
Sinusitis	4	2
Skin and Appendages		
Rash	4	2
Special Senses		
Vision Abnormal	4	0

Controlled Clinical Studies of Adjunctive Therapy/Monotherapy in Pediatric Patients Previously Treated with other AEDs: **Table 6** lists treatment-emergent signs and symptoms that occurred in at least 2% of pediatric patients with ep lepsy treated with oxcarbazepine or placebo as adjunctive treatment and were numerically more common in the patients treated with oxcarbazepine.

Table 6: Treatment-Emergent Adverse Event Incidence in Controlled Clinical Studies of Adjunctive Therapy/Monotherapy in Pediatric Patients Previously Treated with Other AEDs (Events in at Least 2% of Patients Treated with Oxcarbazepine and Numerically More Frequent Than in the Placebo Group)

Body System/ Adverse Event	Oxcarbazepine N = 171 %	Placebo N = 139 %
Body as a Whole		
Fatigue	13	9
A lergy	2	0
Asthenia	2	1
Digestive System		
Vomiting	33	14
Nausea	19	5
Constipation	4	1
Dyspepsia	2	0
Nervous System		
Headache	31	19
Somnolence	31	13
Dizziness	28	8
Ataxia	13	4
Nystagmus	9	1
Emotional Lability	8	4
Gait Abnormal	8	3
Tremor	6	4
Speech Disorder	3	1
Concentration Impaired	2	1
Convulsions	2	1
Muscle Contractions Involuntary	2	1
Respiratory System		
Rhinitis	10	9
Pneumonia	2	1
Skin and Appendages		
Bruising	4	2
Sweating Increased	3	0
Special Senses		
Diplopia	17	1
Vision Abnormal	13	1
Vertigo	2	0

Other Events Observed in Association with the Administration of Oxcarbazepine

In the paragraphs that follow, the adverse events other than those in the preceding tables or text, that occurred in a total of 565 children and 1,574 adults exposed to oxcarbazepine and that are reasonably likely to be related to drug use are presented. Events common in the population, events reflecting chronic illness and events likely to reflect concomitant illness are omitted particularly if minor. They are listed in order of decreasing frequency. Because the reports cite events observed in open label and uncontrolled trials, the role of oxcarbazepine in their causation cannot be re iably determined.

Body as a Whole: Fever, malaise, pain chest precordial, rigors, weight decrease.

Cardiovascular System: Bradycardia, cardiac failure, cerebral hemorrhage, hypertension, hypotension postural, palpitation, syncope, tachycardia.

Digestive System: Appetite increased, blood in stool, cholelithiasis, colitis, duodenal ulcer, dysphagia, enteritis, eructation, esophagitis, flatulence, gastric ulcer, gingival bleeding, gum hyperplasia, hematemesis, hemorrhage rectum, hemorrhoids, hiccup, mouth dry, pain biliary, pain right hypochondrium, retching, sialoadenitis, stomatitis, stomatitis ulcerative.

Hemic and Lymphatic System: Leukopenia, thrombocytopenia.

Laboratory Abnormality: Gamma-GT increased, hyperglycemia, hypocalcemia, hypoglycemia, hypokalemia, liver enzymes elevated, serum transaminase increased.

Musculoskeletal System: Hypertonia muscle.

Nervous System: Aggressive reaction, amnesia, anguish, anxiety, apathy, aphasia, aura, convulsions aggravated, delirium, delusion, depressed level of consciousness, dysphonia, dystonia, emotional lability, euphoria, extrapyramidal disorder, feeling drunk, hemiplegia, hyperkinesia, hyperreflexia, hypoesthesia, hypokinesia, hyporeflexia, hypotonia, hysteria, libido decreased, libido increased, manic reaction, migraine, muscle contractions involuntary, nervousness, neuralgia, oculogyric crisis, panic disorder, paralysis, paroniria, personality disorder, psychosis, ptosis, stupor, tetany.

Respiratory System: Asthma, dyspnea, epistaxis, laryngismus, pleurisy.

Skin and Appendages: Acne, alopecia, angioedema, bruising, dermatitis contact, eczema, facial rash, flushing, folliculitis, heat rash, hot flushes, photosensitivity reaction, pruritus genital, psoriasis, purpura, rash erythematous, rash maculopapular, vitiligo, urticaria.

Special Senses: Accommodation abnormal, cataract, conjunctival hemorrhage, edema eye, hemianopia, mydriasis, otitis externa, photophobia, scotoma, taste perversion, tinnitus, xerophthalmia.

Surgical and Medical Procedures: Procedure dental oral, procedure female reproductive, procedure musculoskeletal, procedure skin.

Urogenital and Reproductive System: Dysuria, hematuria, intermenstrual bleeding, leukorrhea, menorrhagia, micturition frequency, pain renal, pain urinary tract, polyuria, priapism, renal calculus.

Other: Systemic lupus erythematosus.

Postmarketing and Other Experience

The following adverse events not seen in controlled clinical trials have been observed in named patient programs or postmarketing experience:

Body as a Whole: Multi-organ hypersensitivity disorders characterized by features such as rash, fever, lymphadenopathy, abnormal liver function tests, eosinophilia and arthralgia (see **PRECAUTIONS**, **Multi-Organ Hypersensitivity** subsection).

Anaphylaxis (see **WARNINGS, Anaphylactic Reactions and Angioedema** subsection).

Digestive system: Pancreatitis and/or lipase and/or amylase increase.

Skin and Appendages: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (see **WARNINGS**, **Serious Dermatological Reactions** subsection).

DRUG ABUSE AND DEPENDENCE

Abuse

The abuse potential of oxcarbazepine has not been evaluated in human studies.

Dependence

Intragastric injections of oxcarbazepine to four cynomolgus monkeys demonstrated no signs of physical dependence as measured by the desire to self-administer oxcarbazepine by lever pressing activity.

OVERDOSAGE

Human Overdose Experience

Isolated cases of overdose with oxcarbazepine have been reported. The maximum dose taken was approximately 24,000 mg. All patients recovered with symptomatic treatment.

Treatment and Management

There is no specific antidote. Symptomatic and supportive treatment should be administered as appropriate. Removal of the drug by gastric lavage and/or inactivation by administering activated charcoal should be considered.

DOSAGE AND ADMINISTRATION

Oxcarbazepine is recommended as adjunctive treatment in the treatment of partial seizures in adults and children aged 4 to 16 years. Oxcarbazepine is also recommended as monotherapy in the treatment of partial seizures in adults and children aged 4 to 16 years. All dosing should be given in a twice-a-day (BID) regimen. Oxcarbazepine oral suspension and oxcarbazepine film-coated tablets may be interchanged at equal doses.

Oxcarbazepine should be kept out of the reach and sight of children.

Before using oxcarbazepine oral suspension, shake the bottle well and prepare the dose immediately afterwards. The prescribed amount of oral suspension should be withdrawn from the bottle using the oral dosing syringe supplied. Oxcarbazepine oral suspension can be mixed in a small glass of water just prior to administration or, alternatively, may be swallowed directly from the syringe. After each use, close the bottle and rinse the syringe with warm water and allow it to dry thoroughly.

Oxcarbazepine can be taken with or without food (see **CLINICAL PHARMACOLOGY**, **Pharmacokinetics** subsection).

Adults

Adjunctive Therapy

Treatment with oxcarbazepine should be initiated with a dose of 600 mg/day, given in a BID regimen. If clinically indicated, the dose may be increased by a maximum of 600 mg/day at approximately weekly intervals; the recommended da ly dose is 1200 mg/day. Da ly doses above 1200 mg/day show somewhat greater effectiveness in controlled trials, but most patients were not able to tolerate the 2400 mg/day dose, primarily because of CNS effects. It is recommended that the patient be observed closely and plasma levels of the concomitant AEDs be monitored during the period of oxcarbazepine titration, as these plasma levels may be altered, especially at oxcarbazepine doses greater than 1200 mg/day (see **PRECAUTIONS**, **Drug Interactions** subsection).

Conversion to Monotherapy

Patients receiving concomitant AEDs may be converted to monotherapy by initiating treatment with oxcarbazepine at 600 mg/day (given in a BID regimen) while simultaneously initiating the reduction of the dose of the concomitant AEDs. The concomitant AEDs should be completely withdrawn over 3 to 6 weeks, while the maximum dose of oxcarbazepine should be reached in about 2 to 4 weeks. Oxcarbazepine may be increased as clinically indicated by a maximum increment of 600 mg/day at approximately weekly intervals to achieve the recommended daily dose of 2400 mg/day. A daily dose of 1200 mg/day has been shown in one study to be effective in patients in whom monotherapy has been initiated with oxcarbazepine. Patients should be observed closely during this transition phase.

Initiation of Monotherapy

Patients not currently being treated with AEDs may have monotherapy initiated with oxcarbazepine. In these patients, oxcarbazepine should be initiated at a dose of 600 mg/day (given in a BID regimen); the dose should be increased by 300 mg/day every third day to a dose of 1200 mg/day. Controlled trials in these patients examined the effectiveness of a 1200 mg/day dose; a dose of 2400 mg/day has been shown to be effective in patients converted from other AEDs to oxcarbazepine monotherapy (see above).

Pediatric Patients

Adjunctive Therapy (Aged 4 to 16 years)

In pediatric patients aged 4 to 16 years, treatment should be initiated at a daily dose of 8 to 10 mg/kg generally not to exceed 600 mg/day, given in a BID regimen. The target maintenance dose of oxcarbazepine should be achieved over two weeks, and is dependent upon patient weight, according to the following chart:

20 to 29 kg - 900 mg/day
29.1 to 39 kg - 1200 mg/day
> 39 kg to 1800 mg/day

In the clinical trial, in which the intention was to reach these target doses, the median daily dose was 31 mg/kg with a range of 6 to 51 mg/kg.

Under adjunctive therapy (with and without enzyme-inducing AEDs), when norma ized by body weight, apparent clearance (L/hr/kg) decreased when age increased such that children 4 to ≤ 12 years of age may require a 50% higher oxcarbazepine dose per body weight compared to adults.

Pediatric dosing and drug clearance information for pediatric patients ages 2 to < 4 years is approved for Novartis Pharmaceuticals corporation's oxcarbazepine tablets and oral suspension. However due to Novartis' marketing exclusivity rights, this drug product is not labeled for this age group.

Conversion to Monotherapy (Aged 4 to 16 years)

Patients receiving concomitant antiepileptic drugs may be converted to monotherapy by initiating treatment with oxcarbazepine at approximately 8 to 10 mg/kg/day given in a BID regimen, while simultaneously initiating the reduction of the dose of the concomitant antiepileptic drugs. The concomitant antiepileptic drugs can be completely withdrawn over 3 to 6 weeks while oxcarbazepine may be increased as clinically indicated by a maximum increment of 10 mg/kg/day at approximately weekly intervals to achieve the recommended daily dose. Patients should be observed closely during this transition phase.

The recommended total daily dose of oxcarbazepine is shown in the table below.

Initiation of Monotherapy (Aged 4 to 16 years)

Patients not currently being treated w th antiepileptic drugs may have monotherapy initiated with oxcarbazepine. In these patients, oxcarbazepine should be initiated at a dose of 8 to 10 mg/kg/day given in a BID regimen. The dose should be increased by 5 mg/kg/day every third day to the recommended daily dose shown in the table below.

Table 7: Range of Maintenance Doses of oxcarbazepine for Children by Weight During Monotherapy

	From	To
Weight in kg	Dose (mg/day)	Dose (mg/day)
20	600	900
25	900	1200
30	900	1200
35	900	1500
40	900	1500
45	1200	1500
50	1200	1800
55	1200	1800
60	1200	2100
65	1200	2100
70	1500	2100

Patients with Hepatic Impairment

In general, dose adjustments are not required in patients with mild-to-moderate hepatic impairment (see **CLINICAL PHARMACOLOGY**, **Pharmacokinetics**, **Special Populations** subsection).

Patients with Renal Impairment

In patients with impaired renal function (creatine clearance < 30 mL/min) oxcarbazepine therapy should be initiated at one-half the usual starting dose (300 mg/day) and increased slowly to achieve the desired clinical response (see **CLINICAL PHARMACOLOGY**, **Pharmacokinetics**, **Special Populations** subsection).

HOW SUPPLIED:

300 mg/5mL (60 mg/mL)

Oxcarbazepine oral suspension are off-wh te to slightly yellow liquid suspension with characteristic fruity flavor filled in 250 mL amber glass bottle with child resistant closure.

Supp ied with a 10 mL dosing syringe and press in bottle adapter.

Use within 7 weeks of first opening the bottle.

Store oxcarbazepine oral suspension in original container. Shake well before using

NDC 63304-653-25 Bottles of 250 mL

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

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32257 USA
by: Ohm Laboratories Inc.
Gloversville, NY 12078
September 2007

FDA-03

(b) (4)

RANBAXY

NDC 63304-653-25

OXCARBAZEPINE

Oral Suspension

300 mg/5 mL

IMPORTANT: Shake well before using.

Use within 7 weeks of first opening the bottle.

Rx only **250 mL**

Each 5 mL contains 300 mg oxcarbazepine.

Usual Dosage: See package insert.

Store in original container.

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

Keep this and all drugs out of the reach of children.

0807

N 3 63304 65325 0

EPIC 0000000

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32257 USA
by: Ohm Laboratories Inc.
Gloversville, NY 12078

LOT:

EXP:

non-varnish area for Lot & Exp

(b) (4)

(b) (4)

RANBAXY

NDC 63304-653-25

OXCARBAZEPINE

Oral Suspension

300 mg/5 mL

Shake well before using.

Rx only

250 mL

Each 5 mL contains 300 mg oxcarbazepine.

IMPORTANT: Shake well before using.

For oral use only.

Usual Dosage: See package insert.

See enclosed Oxcarbazepine Oral Suspension Instruction Sheet.

Store in original container.

Use within 7 weeks of first opening the bottle.

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

Keep this and all drugs out of the reach of children.

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32257 USA
by: Ohm Laboratories Inc.
Gloversville, NY 12078 0807

RANBAXY

NDC 63304-653-25

OXCARBAZEPINE

Oral Suspension

300 mg/5 mL

Shake well before using.

Rx only

250 mL

FPO
0000000

NON VARNISH

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

/s/

Melaine Shin
9/24/2007 09:33:59 AM
LABELING REVIEWER

Lillie Golson
9/25/2007 01:11:58 PM
LABELING REVIEWER

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

ANDA Number:	78-734
Date of Submission:	December 22, 2006
Applicant's Name:	Ranbaxy Laboratories Limited
Established Name:	Oxcarbazepine Oral Suspension, 300 mg/5 mL.
Proposed Proprietary Name:	None

Labeling Deficiencies:

CONTAINER: 250 mL

- Delete "Each 5 mL contains…" statement from the principal display panel.

CARTON: 250 mL.

- Relocate "Each 5 mL contains…." statement to the side display panel.

PROFESSIONAL PACKAGE INSERT

- Please note that the reference listed drug Trileptal®, has a marketing exclusivity, I-478: FOR USE AS ADJUNCTIVE THERAPY IN THE TREATMENT OF PARTIAL SEIZURES IN CHILDREN WITH EPILEPSY AGED 2-4 YEARS which expires on April 28, 2009. We consulted the New Drug Division and the Pediatric and Maternal Health Staff and the Division of Neurology Products, and now have a generic labeling template reflecting the carve outs of the information protected by exclusivity I-478 and applicable disclaimers. Please revise your insert labeling according to the attached generic labeling template.

- In the DESCRIPTION section, revise "Oxcarbazepine oral suspension contain…." To read "Oxcarbazepine oral suspension cotains…" and "hydroxy ethylcellulose" to read "hydroxyethyl cellulose"

Please revise your labeling, as instructed above, and submit the revised labeling in final print.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please

provide a side-by-side comparison of your proposed labeling with attached generic labeling template 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

Attachment: Generic oxcarbazepine model labeling

FOR THE RECORD:

1. MODEL LABELING

   This review was based on the labeling for Trileptal® by Novartis [NDA 21-285/S-014; approved June 19, 2007]. A generic labeling template was created and includes the carve out due to exclusivity I-478 FOR USE AS ADJUNCTIVE THERAPY IN THE TREATMENT OF PARTIAL SEIZURES IN CHILDREN WITH EPILEPSY AGED 2-4 YEARS.

2. USP ITEM

   No

3. PROPRIETARY NAME

   None

4. PATENTS/EXCLUSIVITIES

Patent Data

Appl No	Patent No	Patent Expiration	Patent Use Code	How Certified	Labeling Impact
021014	7037525	FEB 12,2018	U-724	IV	none
021014	7037525*PED	AUG 12,2018			

U-724 METHOD OF TREATING SEIZURES

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration	Labeling Impact
021014	001	PED	APR 28,2009	
021014	001	I-478	OCT 28,2008	None, the generic labeling template includes the carve out with BPCA disclaimer due to I-478

I-478: FOR USE AS ADJUNCTIVE THERAPY IN THE TREATMENT OF PARTIAL SEIZURES IN CHILDREN WITH EPILEPSY AGED 2-4 YEARS

5. INACTIVE INGREDIENTS

   The list of inactive ingredients is accurate.

6. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

   Manufactured by: Ohm Laboratories Inc, Gloversville, NY, USA facility.
   Manufactured for: Ranbaxy Pharmaceuticals Inc. Jacksonville, FL 32257.

7. CONTAINER/CLOSURE

Strength	Fill Size	Bottle	Cap	Press in Bottle (b) (4)	10 mL dosing syringe (b) (4)
300 mg/5 mL	250 mL	USP Type III Amber Glass	(b) (4)	(b) (4)	

8. PACKAGING/SCORING CONFIGURATIONS

RLD: Bottle of 250 mL.

ANDA: Bottle of 250 mL.

9. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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

ANDA: Store at 20°-25° (68° – 77°F) [see USP Controlled Room Temperature]

Date of Review: July 23, 2007 **Date of Submission: December 22, 2006**

Primary Reviewer: _____ _____
Melaine Shin Date:

Team Leader: _____ _____
Lillie Golson Date:

cc: ANDA 78-734
DUP/DIVISION FILE
HFD-613/MShin/LGolson (no cc)
Review
File Path: V:\FIRMSNZ\RANBAXY\LTRS&REV\78734 NA1.Labeling review.doc
FINAL: July 30, 2007

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

/s/

Melaine Shin
7/30/2007 02:10:37 PM
LABELING REVIEWER

Lillie Golson
7/30/2007 07:07:47 PM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-734

CHEMISTRY REVIEWS

ANDA 78-734

Oxcarbazepine Oral Suspension
300 mg/5 mL

Ranbaxy Laboratories Limited, India

Mujahid L. Shaikh
Team 11

Division of Chemistry III
Office of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. ANDA 78-734

2. REVIEW #: 3

3. REVIEW DATE: May 18, 2009 (Revised on June 25, 2009)

4. REVIEWER: Mujahid L. Shaikh

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original submission	December 22, 2007
Accepted for filing	December 26, 2007
Acknowledgement letter for acceptance of the ANDA	-
Minor Amendment	July 30, 2007
Bio Amendment (Dissolution)	August 3, 2007
Labeling Amendment	August 17, 2007
Bio amendment (Response to September 7, 2007 bio deficiency letter)	September 11, 2007
Labeling amendment	September 17, 2007
CMC Telephone Amendment	June 16, 2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	December 1, 2008
Telephone amendment	June 25, 2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Ranbaxy Laboratories Limited
Address:	Sector 18, Udyog Vihar, Gurgaon 122001, India
Representative:	U.S. Agent: Usha Sankaran, Ranbaxy Inc., 600 College Road East, Princeton, NJ 08540
Telephone:	U.S. Agent Telephone # 609-720-8061 Fax# 609-514-9797

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None used
b) Non-Proprietary Name (USAN): Oxcarbazepine Oral Suspension

9. LEGAL BASIS FOR SUBMISSION:
The Reference Listed Drug (RLD) is Trileptal® Oral Suspension containing 300 mg of Oxycarbazepine manufactured by Novartis Pharmaceutical Corporation and approved in NDA 21-285 and approved on January 14, 2000.

10. PHARMACOL. CATEGORY: Indicated as adjunctive therapy for partial seizure in adult with epilepsy.

11. DOSAGE FORM: Oral Suspension

12. STRENGTH/POTENCY: 300 mg/5 mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): Not a SPOTS product

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

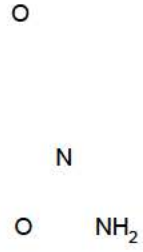
Oxcarbazepine

Chemical Name: 10,11-Dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide

Molecular Formula: $C_{15}H_{12}N_2O_2$

Molecular Weight: 252.27

CAS Registry No.: [28721-07-5]



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]			(b) (4)	1	Adequate	May 18, 2009	CR # 7 completed by M. Shaikh
				4			
				4			
				4			
				4			
				4			
				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: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not applicable		
EES	Acceptable	3-17-08	S. Ferguson
Methods Validation	Waived	6-11-07	M. Shaikh
Labeling	Acceptable	6/10/09	M. Shin/L. Golson
Bioequivalence	Acceptable	9-27-07	K.Bough/M. Makary/Barbara Davit
EA	Adequate	6-11-07	M. Shaikh
Radiopharmaceutical	Not applicable		

19. ORDER OF REVIEW

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

The Chemistry Review for A/NDA 78-734

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: None

II. Summary of Chemistry Assessments

Drug Product: The proposed drug product is Oxcarbazepine Oral Suspension 300 mg/5 mL. The Reference listed Drug is (RLD) is Trileptal ® (Oxcarbazepine) Oral Suspension containing 300 mg of Oxcarbazepine is approved in May 25, 2001 and manufactured by Novartis.

Drug Substance: The active ingredient in proposed drug product is Oxcarbazepine and it is a non-USP material and its acceptance specifications are based on its manufacturer and other information available to this chemist for Oxcarbazepine.

B. Description of How the Drug Product is intended to be Used: Oral
Oxcarbazepine Oral Suspension is used as Monotherapy or adjunctive therapy for partial seizure in adults and children ages 4 to 16 with epilepsy.

The MDD of the drug product is 2400 mg based on the FPL for the RLD.

	IT	QT
Drug Substance (ICH Q3A)	(b) (4) %	(b) (4) %
Drug Product (ICH Q3B)	%	%

C. Basis for Approvability or Not-Approval Recommendation

Based on this CMC, a not approvable letter is being issued to Ranbaxy with deficiencies identified with respect to release and stability specifications for the drug product.

DMF (b) (4) Adequate.
EER Status: Acceptable
Labeling: Approvable
Bio status: Acceptable
Ranbaxy has accepted DBE recommended dissolution specification/method.

40 Pages have been Withheld as b4 (CCI/TS) immediately following this page

Endorsements:

HFD-630 /M. Shaikh /Chemistry Reviewer/5/18/09/6/25/09
HFD-630 / Aloka Srinivasan, Ph.D./Team Leader/5/21/09
HFD-617 /Lisa Kwok, Pharm. D. /Project Manager/6/9/09

V:\Chemistry Division III\Team 11\Final Version For DFS Folder\Mujahid\78734.R03.QBR..doc

APPROVAL

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

/s/

Mujahid Shaikh
6/26/2009 08:15:16 AM
CHEMIST
Latiff Husain is acting team leader.

Latiff Hussain
6/26/2009 08:25:28 AM
CHEMIST
For Aloka Srinivasan as acting TL

Lisa Kwok
6/26/2009 11:31:43 AM
CSO

ANDA 78-734

Oxcarbazepine Oral Suspension
300 mg/5 mL

Ranbaxy Laboratories Limited, India

Mujahid L. Shaikh
Team 11

Division of Chemistry III
Office of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. ANDA 78-734

2. REVIEW #: 2

3. REVIEW DATE: November 5, 2007 (Revised on August 26, 2008)

4. REVIEWER: Mujahid L. Shaikh

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original submission	December 22, 2007

6. SUBMISSION(S) BEING REVIEWED*:

Submission(s) Reviewed	Document Date
*Minor Amendment	July 30, 2007
Bio Amendment (Dissolution)	August 3, 2007
Labeling Amendment	August 17, 2007
Bio amendment (Response to September 7, 2007 bio deficiency letter)	September 11, 2007
Labeling amendment	September 17, 2007
*CMC Telephone Amendment	June 16, 2008

Note: This ANDA was accepted for filing on December 26, 2006 and an acknowledgment letter was send to the firm.

7. NAME & ADDRESS OF APPLICANT:

Name:	Ranbaxy Laboratories Limited
Address:	Sector 18, Udyog Vihar, Gurgaon 122001, India
Representative:	U.S. Agent: Usha Sankaran, Ranbaxy Inc., 600 College Road East, Princeton, NJ 08540
Telephone:	U.S. Agent Telephone # 609-720-8061 Fax# 609-514-9797

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None used
b) Non-Proprietary Name (USAN): Oxcarbazepine Oral Suspension

9. LEGAL BASIS FOR SUBMISSION:
The Reference Listed Drug (RLD) is Trileptal® Oral Suspension containing 300 mg of Oxycarbazepine manufactured by Novartis Pharmaceutical Corporation and approved in NDA 21-285 and approved on January 14, 2000.

10. PHARMACOL. CATEGORY: Indicated as adjunctive therapy for partial seizure in adult with epilepsy.

11. DOSAGE FORM: Oral Suspension

12. STRENGTH/POTENCY: 300 mg/5 mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): Not a SPOTS product

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

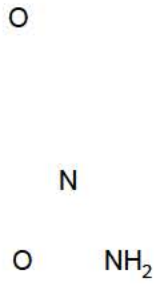
Oxcarbazepine

Chemical Name: 10,11-Dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide

Molecular Formula: $C_{15}H_{12}N_2O_2$

Molecular Weight: 252.27

CAS Registry No.: [28721-07-5]



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]			(b) (4)	3	Adequate	January 4, 2008 As listed in DARRTS	CR # 6 completed by Mike Darj
				4			
				4			
				4			
				4			
				4			
				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:

(b) (4)

[redacted]

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not applicable		
EES	Acceptable	3-17-08	S. Ferguson
Methods Validation	Waived	6-11-07	M. Shaikh
Labeling	Acceptable	9-24-07	M. Shin/L. Golson
Bioequivalence	Acceptable	9-27-07	K.Bough/M. Makary/Barbara Davit
EA	Adequate	6-11-07	M. Shaikh
Radiopharmaceutical	Not applicable		

19. ORDER OF REVIEW

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

The Chemistry Review for A/NDA 78-734

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NA (Minor)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: None

II. Summary of Chemistry Assessments

Drug Product: The proposed drug product is Oxcarbazepine Oral Suspension 300 mg/5 mL. The Reference listed Drug is (RLD) is Trileptal ® (Oxcarbazepine) Oral Suspension containing 300 mg of Oxcarbazepine is approved in May 25, 2001 and manufactured by Novartis.

Drug Substance: The active ingredient in proposed drug product is Oxcarbazepine and it is a non-USP material and its acceptance specifications are based on its manufacturer and other information available to this chemist for Oxcarbazepine.

B. Description of How the Drug Product is intended to be Used: Oral
Oxcarbazeine Oral Suspension is used as Monotherapy or adjunctive therapy for partial seizure in adults and children ages 4 to 16 with epilepsy.

The MDD of the drug product is 2400 mg based on the FPL for the RLD.

C. Basis for Approvability or Not-Approval Recommendation

Based on this CMC, a not approvable letter is being issued to Ranbaxy with deficiencies identified with respect to release and stability specifications for the drug product.

Referenced DMF (b) (4) is adequate.
EER Status: Acceptable
Labeling information: Approvable
Bio status: Acceptable and Ranbaxy has accepted DBE recommended dissolution specification/method.

Review of July 30, 2007 CMC Minor Amendment and August 3, 2207 Bio amendment for ANDA 78-734

Ranbaxy submitted Minor amendment on July 30, 2007 to submit response to June 20, 2007 deficiency letter which included following deficiencies. Review of the response is also discussed below:

(b) (4)

24 Pages have been Withheld as b4 (CCI/TS) immediately following this page

cc: ANDA 78-734
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-630 /M. Shaikh /Chemistry Reviewer/8/26/2008
HFD-630 / Aloka Srinivasan, Ph.D./Team Leader/8/26/2008
HFD-617 /Lisa Kwok, Pharm. D. /Project Manager/8/27/2008

F/T by: LK

V:\Chemistry Division III\Team 11\Final Version For DFS\Mujahid\78734.R02.QBR.DOC

NOT APPROVABLE - MINOR

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

/s/

Benjamin Lim
8/27/2008 04:37:51 PM
CHEMIST
Sign for Mujahid

Lisa Kwok
8/27/2008 04:42:03 PM
CSO

Aloka Srinivasan
8/28/2008 10:27:07 AM
CHEMIST

ANDA 78-734

Oxcarbazepine Oral Suspension
300 mg/5 mL

Ranbaxy Laboratories Limited, India

Mujahid L. Shaikh
Team 11

Division of Chemistry III
Office of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. NDA or ANDA 78-734

2. REVIEW #: 1

3. REVIEW DATE: June 11, 2007

4. REVIEWER: Mujahid L. Shaikh

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	December 22, 2007

Note: This ANDA was accepted for filing on December 26, 2006 and an acknowledgment letter was send to the firm.

7. NAME & ADDRESS OF APPLICANT:

Name:	Ranbaxy Laboratories Limited
Address:	Sector 18, Udyog Vihar, Gurgaon 122001, India
Representative:	U.S. Agent: Abha Pant, Ranbaxy Inc., 600 College Road East, Princeton, NJ 08540
Telephone:	U.S. Agent Telephone # 609-720-5666 Fax# 609-514-9797

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None used
b) Non-Proprietary Name (USAN): Oxcarbazepine Oral Suspension

9. LEGAL BASIS FOR SUBMISSION:
The Reference Listed Drug (RLD) is Trileptal® Oral Suspension containing 300 mg of Oxycarbazepine manufactured by Novartis Pharmaceutical Corporation and approved in NDA 21-285 and approved on January 14, 2000.

10. PHARMACOL. CATEGORY: Indicated as adjunctive therapy for partial seizure in adult with epilepsy.

11. DOSAGE FORM: Oral Suspension

12. STRENGTH/POTENCY: 300 mg/5 mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

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

SPOTS product – Form Completed

x Not a SPOTS product

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

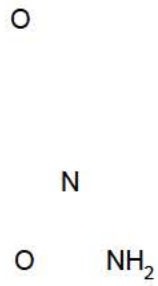
Oxcarbazepine

Chemical Name: 10,11-Dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide

Molecular Formula: $C_{15}H_{12}N_2O_2$

Molecular Weight: 252.27

CAS Registry No.: [28721-07-5]



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]			(b) (4)	3	Adequate	March 12, 2007	CR # 4 completed by M. Shaikh
				4			
				4			
				4			
				4			
				4			
				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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
		(b) (4)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES	Pending		
Methods Validation	Waived	6-11-07	M. Shaikh
Labeling	Pending Review		
Bioequivalence	Pending review		
EA	Adequate	6-11-07	M. Shaikh
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

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

The Chemistry Review for A/NDA 78-734

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NA (Minor)

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

II. Summary of Chemistry Assessments

Drug Product: The proposed drug product is Oxcarbazepine Oral Suspension 300 mg/5 mL. The Reference listed Drug is (RLD) is Trileptal ® (Oxcarbazepine) Oral Suspension containing 300 mg of Oxcarbazepine is approved in May 25, 2001 and manufactured by Novartis.

Drug Substance: The active ingredient in proposed drug product is Oxcarbazepine and it is a non-USP material and its acceptance specifications are based on its manufacturer and other information available to this chemist for Oxcarbazepine.

B. Description of How the Drug Product is intended to be Used: Oral
Oxcarbazeine Oral Suspension is used as Monotherapy or adjunctive therapy for partial seizure in adults and children ages 4 to 16 with epilepsy.

The MDD of the drug product is 2400 mg based on the FPL for the RLD.

C. Basis for Approvability or Not-Approval Recommendation

Based on this CMC, a not approvable letter is being issued to Ranbaxy with deficiencies identified with respect to acceptance specifications for Oxcarbazepine drug substance and release and stability specifications for the drug product.

Referenced DMF (b) (4) is adequate.
EER Status: Pending
Labeling information is pending review.
Bio information is pending review.

47 Pages have been Withheld as b4 (CCI/TS) immediately following this page

cc: ANDA 78-734
ANDA DUP
DIV FILE
Field Copy
Endorsements:

HFD-630 /M. Shaikh /Chemistry Reviewer/6/11/07
HFD-630 / Shing Liu, Ph.D./Team Leader/6/19/07
HFD-617 /Lisa Kwok, Pharm. D. /Project Manager/6/20/07

F/T by: LK

V:\FIRMSNZ\RANBAXY\LTRS&REV\78734.R01.QBR.DOC

NOT APPROVABLE - MINOR

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

/s/

Mujahid Shaikh
6/20/2007 12:11:29 PM
CHEMIST

Lisa Kwok
6/20/2007 03:25:23 PM
CSO

Shing Hou Liu
6/20/2007 03:39:48 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-734

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

REVIEW OF A STUDY AMENDMENT

ANDA No.	78-734
Drug Product Name	Oxcarbazepine Oral Suspension
Strength(s)	300 mg/ 5 mL
Applicant Name	Ranbaxy Laboratories Ltd.
Address	600 College Road East, Princeton, NJ 08540
Applicant's Point of Contact	Abha Pant – US Contact for Ranbaxy
Contact's Telephone Number	609-720-5666
Contact's Fax Number	609-720-1155
Original Submission Date(s)	22 December 2006
Submission Date(s) of Amendment(s) Under Review	11 September 2007
Reviewer	Kristopher J. Bough, PhD
Study Number (s)	**228_OXCAR_06**
Study Type (s)	**Fasting**
Strength (s)	**2 x 300 mg/ 5 mL (600 mg) per period**
Clinical Site	Ranbaxy – Clinical Pharmacology Unit
Clinical Site Address	Majeedia Hospital (2nd Floor), Jamia Hamdard (Hamdard University) Hamdard Nagar, New Delhi 110 062 India
Analytical Site	Ranbaxy – Clinical Pharmacology & Pharmacokinetics
Analytical Site Address	Plot No. 20, Sector 18, Udyog Vihar Industrial Area Gurgaon 122 015, Haryana India
Study Number (s)	**233_OXCAR_06**
Study Type (s)	**Fed**
Strength (s)	**2 x 300 mg/ 5 mL (600 mg) per period**
Clinical Site	Ranbaxy – Clinical Pharmacology Unit
Clinical Site Address	Same as fasted above
Analytical Site	Ranbaxy – Clinical Pharmacology & Pharmacokinetics
Analytical Site Address	Same as fasted above

1 EXECUTIVE SUMMARY

The firm previously submitted two single-dose, two-way, crossover bioequivalence (BE) studies under fasting and fed conditions comparing its test product, Oxcarbazepine Oral Suspension, 300 mg/5 mL, with the reference listed drug (RLD), Trileptal® (Oxcarbazepine) Oral Suspension, 300 mg/5 mL, manufactured by Novartis. However, the original application was incomplete due to apparent inconsistencies in bioanalytical methodologies and lack of potency data for the products tested.

In the current submission, the firm responds to listed deficiencies. The firm's responses are acceptable. As per the original review, the fasting study was performed in 35 healthy male subjects at a dose of 2 x 300 mg per 5 mL. The study results are: (point-estimate, 90% CI for lnAUCt 0.93, 88.09-97.21; lnAUC∞ 0.96, 91.89-100.31; lnCmax 1.09, 99.22-120.17). The fed study was performed in 33 healthy male subjects at a dose of 2 x 300 mg per 5 mL. The study results are: (point-estimate, 90% CI for lnAUCt 0.92, 87.53-97.39; lnAUC∞ 0.89, 83.20-95.04; lnCmax 0.89, 80.26-98.13). Although not required for the determination of BE, metabolic data support the claim of product equality; 10-monohydroxyoxcarbazepine (MHC) data from both fasting and fed BE studies meet the 90% CI criteria for BE.

The product formulation and dissolution testing are both acceptable.[1]

However, the application remains **incomplete** pending acceptable DSI inspection of both the clinical and analytical study sites.

[1] The firm acknowledged that dissolution testing would be performed according to the DBE-recommended method and specification in the study amendment dated 03 Aug 2007.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Oxcarbazepine Oral Suspension, 300 mg/5 mL
Reference Product	Trileptal® (oxcarbazepine) Oral Suspension, 300 mg/5 mL
RLD Manufacturer	Novartis
NDA No.	21-285
RLD Approval Date	25 May 2001
Indication	Anticonvulsant

3.2 PK/PD Information

Bioavailability	Rapidly absorbed
Food Effect	None
Tmax	6 hours for oxcarbazepine 4.5-8 hours for 10-monohydroxy-carbazepine (MHC, active metabolite)
Metabolism	• Rapid & extensive first-pass metabolism • MHC is primarily responsible for therapeutic effects of oxcarbazepine
Excretion	Renal = 95-96% (>99% as metabolites)
Half-life	• 1-2.5 hours for oxcarbazepine • 8-11 hours for MHC
Drug Specific Issues (if any)	May lose efficacy with use of hormonal contraceptives; Hyponatremia

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2, fasting and fed

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	2 x 300 mg/5 mL (600 mg dose)
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	None

2.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	2 x 300 mg/5 mL (600 mg dose)
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	None

Analytes to measure (in plasma/serum/blood):	oxcarbazepine and MHC in plasma (using an achiral assay)
Bioequivalence based on:	90% CI based on oxcarbazepine
Waiver request of in-vivo testing:	N/A
Source of most recent recommendations:	OGD Control #04-697
Summary of OGD or DBE History (for details, see Appendix 4.4):	**First generic** for oral suspension

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting		
Single-dose fed		
Steady-state		
In vitro dissolution		
Waiver requests		
BCS Waivers		
Clinical Endpoints		
Failed Studies		
Amendment(s)	YES	1

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Data	
Bioanalytical method validation report location		
Analyte	Oxcarbazepine	10-hydroxy carbazepine
Internal standard (IS)	(b) (4)	
Method description	LCMS/Solid phase extraction	LCMS/Solid phase extraction
Limit of quantitation	57.8 ng/mL	0.154 µg/mL
Average recovery of drug (%)	67.56	78.07
Average recovery of IS (%)	88.9	88.9
Standard curve concentrations	57.8, 111.2, 222.4, 370.7, 926.8, 2206.8, 4597.5, 6049.3 (ng/mL)	0.154, 0.296, 0.593, 0.988, 2.470, 5.882, 12.254, 16.123 (µg/mL)
QC concentrations	58.3, 170.5, 2185.9, 4553.9 (ng/mL)	0.155, 0.454, 5.820, 12.124 (µg/mL)
QC within batch precision range	0.9-5.0	1.6-5.5
QC within batch accuracy range	97.7-111.9	94.5-108.1
QC between batch precision range	2.5-3.4	2.8-5.4
QC between batch accuracy range	99.0-108.5	97.2-105.9
Bench top stability (hrs)	6.00 hrs at room temperature	6.00 hrs at room temperature
Stock stability of drug (days)	20 days at 1-10°C	20 days at 1-10°C
In injector stability (hrs)	52.98 hrs at 10°C±1°C	52.98 hrs at 10°C±1°C
Freeze thaw stability (cycle)	3 cycles	3 cycles
Long term storage stability (days)	139 days below –15°C & below -50°C (using anticoagulant EDTA) 139 days below –15°C & below -50°C (using anticoagulant ACPD)	139 days below –15°C & below -50°C (using anticoagulant EDTA) 139 days below –15°C & below -50°C (using anticoagulant ACPD)
Dilution integrity	Concentration diluted 2 times and 4 times	Concentration diluted 2 times and 4 times
Selectivity	No interfering peaks noted in eight lots of blank plasma samples with ACPD as anticoagulant and 6 lots of blank plasma samples with EDTA as anticoagulant	No interfering peaks noted in eight lots of blank plasma samples with ACPD as anticoagulant and 6 lots of blank plasma samples with EDTA as anticoagulant.

SOPs submitted	Yes
Bioanalytical method is acceptable	Yes

Comments on the Pre-Study Method Validation: (From the original review) The nominal concentration was reported as the LLOQ for both oxcarbazepine and MHC; the firm should report the mean back-calculated values (see also bioanalytical comments below). All other values were cross-checked with the method validation data provided in the original submission. Acceptable.

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

FASTING Study:

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, route) [Product ID]	Subjects (No. (M/F) type Age: mean (range)	Mean Parameters (± SD)						Study Report Location
					Oxcarbazepine						
					C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$T½$ (h)	K_{el} (h^{-1})	
228_OXCAR_06	To compare the single-dose oral bioavailability of oxcarbazepine 300 mg/5mL oral suspension of OHM Laboratories (a subsidiary of Ranbaxy Pharmaceuticals Inc) with Trileptal® 300 mg/5mL oral suspension (containing oxcarbazepine 300 mg/5mL) of Novartis Pharmaceutical Corporation, USA in healthy, adult, male, human subjects under fasting condition	An open label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, crossover bioavailability study	T: Oxcarbazepine oral suspension 300 mg/5mL (Batch No.-6530601, Expiry - July 2008), oral R: Trileptal® (oxcarbazepine) oral suspension 300 mg/5mL (Batch No.-H5144; Expiry - August 2007), oral	40 healthy subjects (all Male) were enrolled and 35 subjects completed both the periods of the study. Mean age: 25.93 years Range: 18 – 44 years	**Test** 1787.11 (±736.048) **Ref.** 1637.02 (±693.820)	**Test** 0.9872 **Ref.** 1.4395	**Test** 5529.2367 (±1928.66838) **Ref.** 5963.7210 (±2195.46087)	**Test** 6750.3313 (±2025.46948) **Ref.** 6822.3909 (±2278.31056)	**Test** 8.1240 **Ref.** 6.1490	**Test** 0.1172 **Ref.** 0.1368	Module 5 Vol. 1-9 page no. 0125 -3348
					10-Hydroxy Carbazepine						
					C_{max} (µg/mL)	T_{max} (h)	AUC_{0-t} (µg.h/mL)	$AUC_{0-\infty}$ (µg.h/mL)	$T½$ (h)	K_{el} (h^{-1})	
					Test 5.4683 (±1.37451) **Ref.** 6.0025 (±1.78706)	**Test** 5.5429 **Ref.** 7.0000	**Test** 136.1892 (±36.56374) **Ref.** 148.0392 (±36.09909)	**Test** 145.1123 (±37.62314) **Ref.** 159.2426 (±37.62886)	**Test** 11.9931 **Ref.** 12.1763	**Test** 0.0593 **Ref.** 0.0589	

FED Study:

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, route) [Product ID]	Subjects (No. (M/F) type Age: mean (range)	Mean Parameters (± SD)						Study Report Location
					Oxcarbazepine						
					C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	T½ (h)	K_{el} (h^{-1})	
233_OXCAR_06	To compare the single-dose oral bioavailability of oxcarbazepine 300 mg/5mL oral suspension of OHM Laboratories, USA (a subsidiary of Ranbaxy Pharmaceuticals Inc.) with Trileptal® 300 mg/5mL oral suspension (containing oxcarbazepine 300 mg/5mL) of Novartis Pharmaceutical Corporation, USA in healthy, adult, male, human subjects under fed condition.	An open label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, crossover bioavailability study	T: Oxcarbazepine oral suspension 300 mg/5mL (Batch No.- 6530601, Expiry - July 2008), oral R: Trileptal® (oxcarbazepine) oral suspension 300 mg/5mL (Lot No.- H5144; Expiry - August 2007), oral	40 healthy subjects (all Male) were enrolled and 33 subjects completed both the periods of the study. Mean age: 24.85 years Range: 18 – 40 years	**Test** 2324.39 (±866.676) **Ref.** 2621.77 (±1033.962)	**Test** 1.8283 **Ref.** 2.5706	**Test** 10072.4740 (±3102.75734) **Ref.** 11074.5624 (±3920.10234)	**Test** 10809.9908 (±3252.46264) **Ref.** 12326.3859 (±4309.40018)	**Test** 6.2907 **Ref.** 9.5189	**Test** 0.1584 **Ref.** 0.1383	Module 5 Vol. 10-19 page no. 3349-6461
					10-Hydroxy Carbazepine						
					C_{max} (µg/mL)	T_{max} (h)	AUC_{0-t} (µg.h/mL)	$AUC_{0-\infty}$ (µg.h/mL)	T½ (h)	K_{el} (h^{-1})	
					Test 9.5773 (±1.74271) **Ref.** 10.1450 (±1.99909)	**Test** 5.9217 **Ref.** 7.0283	**Test** 226.7499 (±42.87751) **Ref.** 241.7189 (±51.74696)	**Test** 237.6201 (±44.80455) **Ref.** 251.3782 (±52.50002)	**Test** 11.6473 **Ref.** 11.5720	**Test** 0.0620 **Ref.** 0.0618	

Oxcarbazepine (228_OXCAR_06) Dose (300 mg/5mL Oral Suspension) Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting bioequivalence study				
Oxcarbazepine				
Parameter	**Test**	**Reference**	**Ratio**	**90% CI**
AUC_{0-t} (µg.h/mL)	5190.4368	5598.0363	92.54	88.09 – 97.21
$AUC_{0-\infty}$ (ng.h/mL)	6446.2251	6462.6121	96.01	91.88 – 100.32
C_{max} (ng/mL)	1646.78	1501.46	109.19	99.22 – 120.17
10-hydroxy carbazepine				
Parameter	**Test**	**Reference**	**Ratio**	**90% CI**
AUC_{0-t} (µg.h/mL)	131.0597	143.3401	91.54	N/AP
$AUC_{0-\infty}$ (µg.h/mL)	139.9556	154.2913	90.81	N/AP
C_{max} (µg/mL)	5.2947	5.7710	91.79	N/AP

Oxcarbazepine (233_OXCAR_06) Dose (300 mg/5mL Oral Suspension) Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed bioequivalence study				
Oxcarbazepine				
Parameter	**Test**	**Reference**	**Ratio**	**90% CI**
AUC_{0-t} (ng.h/mL)	9599.0274	10413.5336	92.33	87.53 – 97.39
$AUC_{0-\infty}$ (ng.h/mL)	10315.5987	11557.6395	88.93	83.37 – 94.85
C_{max} (ng/mL)	2159.94	2437.94	88.75	80.26 – 98.13
10-hydroxy carbazepine				
Parameter	**Test**	**Reference**	**Ratio**	**90% CI**
AUC_{0-t} (µg.h/mL)	222.4559	235.6732	94.41	N/AP
$AUC_{0-\infty}$ (µg.h/mL)	233.1824	245.3980	94.99	N/AP
C_{max} (µg/mL)	9.4110	9.9544	94.52	N/AP

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

Calculations from the original review:

FASTING Study:

Oxcarbazepine (parent), 300 mg/5 mL Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	5186.30	5604.49	0.93	88.09	97.21
AUC∞ (hr *ng/ml)	6163.38	6419.41	0.96	91.89	100.31
Cmax (ng/ml)	1646.13	1507.53	1.09	99.22	120.17

10-Monohydroxyoxcarbazepine (metabolite), 300 mg/5 mL Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (µg*hr/ml)	131.10	143.21	0.92	87.87	95.38
AUC∞ (µg*hr/ml)	139.99	154.15	0.91	87.08	94.70
Cmax (µg/ml)	5.30	5.77	0.92	86.47	97.44

FED Study:

Oxcarbazepine (parent), 300 mg/5 mL Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	9596.81	10394.30	0.92	87.53	97.39
AUC∞ (hr *ng/ml)	10209.02	11480.12	0.89	83.20	95.04
Cmax (ng/ml)	2159.57	2433.29	0.89	**80.26**	98.13

10-Monohydroxyoxcarbazepine (metabolite), 300 mg/5 mL Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (µg*hr/ml)	222.67	235.85	0.94	91.11	97.84
AUC∞ (µg*hr/ml)	233.46	245.76	0.95	91.40	98.72
Cmax (µg/ml)	9.42	9.96	0.95	91.71	97.41

Table 3. Reanalysis of Study Samples

See also original review DFS N078734 Bioequivalence Review

Did use of recalculated plasma concentration data change study outcome? No.

Comments: The in vivo BE studies under fasting and fed conditions are **incomplete** pending the firm's response to the deficiencies listed below.

3.7 Formulation

Location in appendix	Section **Error! Reference source not found.**
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	N/A
Is the formulation acceptable?	**ACCEPTABLE**
If not acceptable, why?	N/A

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DFS
Source of Method (USP, FDA or Firm)	FDA[2]
Medium	Water with 1% SDS
Volume (mL)	900 mL
USP Apparatus type	USP 2 (paddle)
Rotation (rpm)	75 rpm
DBE-recommended specifications	NLT (b)(4)% (Q) in 30 min
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	Rapidly dissolving oral suspension
Is method acceptable?	**ACCEPTABLE** [3]
If not then why?	N/A

3.9 Waiver Request(s)

Not applicable.

[2] DBE Dissolution Database
[3] The firm acknowledged the DBE-recommended dissolution specification in the Study Amendment submitted 03 Aug 2007.

3.10 Deficiency Comments

None.

3.11 Recommendations

1. The firm's response to deficiencies is acceptable.

2. The single-dose, crossover BE studies under fasting (study #228_OXCAR_06) and fed (study #233_OXCAR_06) conditions submitted by Ranbaxy comparing its test product, Oxcarbazepine Oral Solution, 300 mg/5 mL, lot #6530601, to the RLD, Trileptal® (oxcarbazepine) Oral Suspension, 300 mg/5 mL, lot #H5144, manufactured by Novartis, are acceptable.

3. Dissolution testing is acceptable. The firm acknowledged the DBE-recommended dissolution specification [NLT (b)(4)% (Q) in 30 min] in its study amendment (submission date: 03 August 2007).

4. The product formulation is acceptable.

5. However, the application remains **incomplete** pending DSI inspection.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
DSI	Pending Initial DSI Inspection

4 APPENDIX

4.1 DBE Deficiency #1

Please submit potency (assay) data for the reference listed product (lot # H5144). In future submissions, please be sure to include potency data for both test and reference products within the bioequivalence section of your application.

Firm's Response #1

The potency (assay) for the reference listed product (lot# H5144) is (b) (4) mg (b) (4)%) as indicated in the certificate of analysis for the RLD (lot #H5144) provided in Module 5, Section 5.3.1.3, Page 6471.

Ranbaxy commits to include potency data for both test and reference products within the bioequivalence section in all future submissions as recommended by the Agency.

DBE Comment #1

The drug content for the test product ((b) (4)%) does not differ by >5% from the RLD (b) (4)%), as recommended in our General BA/BE Guidance for Industry.

The firm's response is acceptable.

4.2 DBE Deficiency #2

The QC values reported in your original submission for the fasted oxcarbazepine (study #228_OXCAR_006) do not coincide with those you provided in your study amendment (electronic biosummary Table 14, submission date: 03 August 2007). Please explain which observations (n) were used to determine your mean concentrations and how you calculated the percent nominal values for each QC sample. In future submissions, please include the mean concentrations for both QC and standard samples instead of listing the nominal values; mean concentrations should be included in the biosummary tables for the pre- and within-study assay reports (e.g., Tables 4 and 14).

Firm's Response #2

We note and acknowledge the Agency's comments.

The difference in the QC values for the fasted study provided in the original ANDA and in the bioequivalency amendment dated August 3, 2007 is a result of an error in the statistical calculation of the mean, percent nominal, SD and CV values provided in page no. 2407 (Table 1) of the original ANDA. The biosummary table 14 provided in the bioequivalency amendment dated August 3, 2007 reflects the corrected values. We inadvertently missed to clarify this in the above referenced amendment.

The revised page 2047 (Table 1) of the original ANDA reflecting the correct values for the mean, percent nominal, SD and CV values for the fasted study is enclosed.

The percent nominal values for QC samples were calculated as follows.

$$\% \text{ Nominal} = \frac{\text{Mean concentration of QC sample}}{\text{Nominal concentration of QC sample}} \times 100$$

Ranbaxy commits to include the mean concentrations for both QC and standard samples instead of listing the nominal values in the biosummary tables (e.g., Tables 4 and 14) in all the future submissions as recommended by the Agency.

DBE Comment #2

The Biosummary Table 14 provided in the bioequivalency amendment dated August 3, 2007 reflects the corrected values.

As per the data submitted, the 'correct' values are given below:

Oxcarbazepine (parent)								
Parameter (n=30)	**Standard Curve Samples**							
Concentration (ng/mL)	58.79	114.90	226.18	381.96	966.92	2298 98	5020.46	6173.44
Inter day Precision (%CV)	2.9	4.3	5.6	5.4	4.5	4.5	4.6	6.0
Inter day Accuracy (%Actual)	100.3	100.1	98.5	99.8	101.0	100.9	97.0	102.5
Linearity	0.9954 – 0.9996							
Linearity Range (ng/mL)	58.79 – 6173.44							
Sensitivity/LOQ (ng/mL)	58.79							

Parameter (n=76)	**Quality Control Samples**			
Concentration (ng/mL)	**148.25**	**751.76**	**2301.87**	**5017.28**
Inter day Precision (%CV)	**8.0**	**7.3**	**7.6**	**8.8**
Inter day Accuracy (%Actual)	**97.8**	**99.2**	**95.6**	**99.0**

The firm's response is acceptable.

4.3 Detailed Regulatory History (If Applicable)

The DBE has reviewed the following ANDA's regarding oxcarbazepine **TABLETS**:
77-747 (Apotex, 7/14/05)
77-795 (Roxane, 7/14/05)
(b) (4)
(b) (4)
77-801 (Taro, 7/14/05)
77-802 (Glenmark, 7/15/05)
78-005 (Teva, 11/25/05)
(b) (4)
78-069 (Breckenridge, 12/22/05)

This is a first generic application for an oral suspension.

4.4 Consult Reviews

N/A

4.5 Additional Attachments

None.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-734

APPLICANT: Ranbaxy Laboratories, Ltd.

DRUG PRODUCT: Oxcarbazepine Oral Suspension, 300 mg/5 mL

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

We acknowledge that you will perform dissolution testing using the DBE-recommended method and specification as follows:

Medium	Water with 1% SDS
Temperature	37 ± 0.5°C
Volume (mL)	900 mL
USP Apparatus type	USP 2 (paddle)
Rotation (rpm)	75 rpm
DBE-recommended specifications	NLT (b)(4)% (Q) in 30 min

Please note that the DBE has recently developed new data summary tables in a format consistent with the Common Technical Document (CTD). In order to improve the efficiency of the review process, please submit these tables in electronic format (MS Word or pdf) with the rest of your bioequivalence submission. The templates for these tables are available to you under the title "Model Bioequivalence Data Summary Tables" at our website at http://www.fda.gov/cder/ogd/index.htm.

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

Sincerely yours,

{See appended electronic signature page}

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

4.6 Outcome Page

ANDA: 78-734

(NOTE: Bioequivalence is acceptable. However, the application remains incomplete because the clinical and analytical study sites are pending initial DSI inspection.)

1.	**Study Amendment**	Strength(s):	300 mg/5 mL
	(STA)	Outcome:	**IC***
	Submission Date(s)	11 Sep 2007	
	Clinical Site:	Ranbaxy – Clinical Pharmacology Unit Majeedia Hospital (2nd Floor), Jamia Hamdard (Hamdard University) Hamdard Nagar, New Delhi 110 062 India	
	Analytical Site:	Ranbaxy – Clinical Pharmacology & Pharmacokinetics Plot No. 20, Sector 18, Udyog Vihar Industrial Area Gurgaon 122 015, Haryana India	

*Bioequivalence is acceptable pending acceptable DSI inspection

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

---

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

/s/

Kristopher Bough
9/27/2007 08:14:47 AM
BIOPHARMACEUTICS

Moheb H. Makary
9/27/2007 08:20:09 AM
BIOPHARMACEUTICS

Barbara Davit
9/27/2007 12:19:46 PM
BIOPHARMACEUTICS

BIOEQUIVALENCY AMENDMENT

ANDA 78-734

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Ranbaxy Laboratories Limited
U.S. Agent: Ranbaxy Inc.

ATTN: Scott Tomsky

FROM: Aaron Sigler

TEL: 609-720-5666

FAX: 609-514-9797

PROJECT MANAGER: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on December 22, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Oxcarbazepine Oral Suspension, 300 mg/5 mL.

Reference is also made to your amendment dated August 03, 2007.

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

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-734

APPLICANT: Ranbaxy Laboratories, Ltd.

DRUG PRODUCT: Oxcarbazepine Oral Suspension, 300 mg/5 mL

The Division of Bioequivalence has completed its review and has identified the following deficiencies:

1. Please submit potency (assay) data for the reference listed product (lot # H5144). In future submissions, please be sure to include potency data for both test and reference products within the bioequivalence section of your application.

2. The QC values reported in your original submission for the fasted oxcarbazepine (study #228_OXCAR_006) do not coincide with those you provided in your study amendment (electronic biosummary Table 14, submission date: 03 August 2007). Please explain which observations (n) were used to determine your mean concentrations and how you calculated the percent nominal values for each QC sample. In future submissions, please include the mean concentrations for both QC and standard samples instead of listing the nominal values; mean concentrations should be included in the biosummary tables for the pre- and within-study assay reports (e.g., Tables 4 and 14).

Sincerely yours,

{See appended electronic signature page}

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

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

/s/

Barbara Davit
9/6/2007 06:23:38 PM
Signing for Dale P Conner

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-734
Drug Product Name	Oxcarbazepine Oral Suspension
Strength(s)	300 mg/ 5 mL
Applicant Name	Ranbaxy Laboratories Ltd.
Address	600 College Road East, Princeton, NJ 08540
Applicant's Point of Contact	Abha Pant, US Contact for Ranbaxy
Contact's Telephone Number	609-720-5666
Contact's Fax Number	609-720-1155
Original Submission Date(s)	22 December 2006
Submission Date(s) of Amendment(s) Under Review	03 August 2007
Reviewer	Kristopher J. Bough, PhD
Study Number (s)	**228_OXCAR_06**
Study Type (s)	**Fasting**
Strength (s)	**2 x 300 mg/ 5 mL (600 mg) per period**
Clinical Site	Ranbaxy – Clinical Pharmacology Unit
Clinical Site Address	Majeedia Hospital (2nd Floor), Jamia Hamdard (Hamdard University) Hamdard Nagar, New Delhi 110 062 India
Analytical Site	Ranbaxy – Clinical Pharmacology & Pharmacokinetics
Analytical Site Address	Plot No. 20, Sector 18, Udyog Vihar Industrial Area Gurgaon 122 015, Haryana India
Study Number (s)	**233_OXCAR_06**
Study Type (s)	**Fed**
Strength (s)	**2 x 300 mg/ 5 mL (600 mg) per period**
Clinical Site	Ranbaxy – Clinical Pharmacology Unit
Clinical Site Address	Same as fasted above
Analytical Site	Ranbaxy – Clinical Pharmacology & Pharmacokinetics
Analytical Site Address	Same as fasted above

1 EXECUTIVE SUMMARY

The firm submitted two single-dose, two-way, crossover bioequivalence (BE) studies under fasting and fed conditions comparing its test product, Oxcarbazepine Oral Suspension, 300 mg/5 mL, with the reference listed drug (RLD), Trileptal® (Oxcarbazepine) Oral Suspension, 300 mg/5 mL, manufactured by Novartis.

The fasting study was performed in 35 healthy male subjects at a dose of 2 x 300 mg per 5 mL. The study results are: (point-estimate, 90% CI for lnAUCt 0.93, 88.09-97.21; lnAUC∞ 0.96, 91.89-100.31; lnCmax 1.09, 99.22-120.17). The fed study was performed in 33 healthy male subjects at a dose of 2 x 300 mg per 5 mL. The study results are: (point-estimate, 90% CI for lnAUCt 0.92, 87.53-97.39; lnAUC∞ 0.89, 83.20-95.04; lnCmax 0.89, 80.26-98.13). Although not required for the determination of BE, metabolic data support the claim of product equality; 10-monohydroxyoxcarbazepine (MHC) data from both fasting and fed BE studies meet the 90% CI criteria for BE. However, the in vivo BE studies are incomplete due to deficiencies in subject sample analyses and incomplete potency (assay) data.

Dissolution testing is acceptable. As per the study amendment (submission date: 03 Aug 2007), the firm acknowledged the DBE-recommended dissolution method and specification as requested.

Product formulation is acceptable. Although three excipients exceed the maximum levels for previously-approved oral dosage forms, the quantity of components do not pose a safety risk.

However, the application is **incomplete** with deficiencies and pending DSI inspection.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Oxcarbazepine Oral Suspension, 300 mg/5 mL
Reference Product	Trileptal® (oxcarbazepine) Oral Suspension, 300 mg/5 mL
RLD Manufacturer	Novartis
NDA No.	21-285
RLD Approval Date	25 May 2001
Indication	Anticonvulsant

3.2 PK/PD Information

Bioavailability	Rapidly absorbed
Food Effect	None
Tmax	6 hours for oxcarbazepine 4.5-8 hours for 10-monohydroxy-carbazepine (MHC, active metabolite)
Metabolism	• Rapid & extensive first-pass metabolism • MHC is primarily responsible for therapeutic effects of oxcarbazepine
Excretion	Renal = 95-96% (>99% as metabolites)
Half-life	• 1-2.5 hours for oxcarbazepine • 8-11 hours for MHC
Drug Specific Issues (if any)	May lose efficacy with use of hormonal contraceptives; Hyponatremia

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2, fasting and fed

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	2 x 300 mg/5 mL (600 mg dose)
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	None

2.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	2 x 300 mg/5 mL (600 mg dose)
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	None

Analytes to measure (in plasma/serum/blood):	oxcarbazepine and MHC in plasma (using an achiral assay)
Bioequivalence based on:	90% CI based on oxcarbazepine
Waiver request of in-vivo testing:	N/A
Source of most recent recommendations:	OGD Control #04-697
Summary of OGD or DBE History (for details, see Appendix 4.4):	**First generic** for oral suspension

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	YES	1
Single-dose fed	YES	1
Steady-state		
In vitro dissolution	YES	1
Waiver requests		
BCS Waivers		
Clinical Endpoints		
Failed Studies		
Amendment(s)	YES	1

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Data	
Bioanalytical method validation report location		
Analyte	Oxcarbazepine	10-hydroxy carbazepine
Internal standard (IS)	[redacted] (b) (4)	
Method description	LCMS/Solid phase extraction	LCMS/Solid phase extraction
Limit of quantitation	57.8 ng/mL	0.154 µg/mL
Average recovery of drug (%)	67.56	78.07
Average recovery of IS (%)	88.9	88.9
Standard curve concentrations	57.8, 111.2, 222.4, 370.7, 926.8, 2206.8, 4597.5, 6049.3 (ng/mL)	0.154, 0.296, 0.593, 0.988, 2.470, 5.882, 12.254, 16.123 (µg/mL)
QC concentrations	58.3, 170.5, 2185.9, 4553.9 (ng/mL)	0.155, 0.454, 5.820, 12.124 (µg/mL)
QC within batch precision range	0.9-5.0	1.6-5.5
QC within batch accuracy range	97.7-111.9	94.5-108.1
QC between batch precision range	2.5-3.4	2.8-5.4
QC between batch accuracy range	99.0-108.5	97.2-105.9
Bench top stability (hrs)	6.00 hrs at room temperature	6.00 hrs at room temperature
Stock stability of drug (days)	20 days at 1-10°C	20 days at 1-10°C
In injector stability (hrs)	52.98 hrs at 10°C±1°C	52.98 hrs at 10°C±1°C
Freeze thaw stability (cycle)	3 cycles	3 cycles
Long term storage stability (days)	139 days below –15°C & below -50°C (using anticoagulant EDTA) 139 days below –15°C & below -50°C (using anticoagulant ACPD)	139 days below –15°C & below -50°C (using anticoagulant EDTA) 139 days below –15°C & below -50°C (using anticoagulant ACPD)
Dilution integrity	Concentration diluted 2 times and 4 times	Concentration diluted 2 times and 4 times
Selectivity	No interfering peaks noted in eight lots of blank plasma samples with ACPD as anticoagulant and 6 lots of blank plasma samples with EDTA as anticoagulant	No interfering peaks noted in eight lots of blank plasma samples with ACPD as anticoagulant and 6 lots of blank plasma samples with EDTA as anticoagulant.

SOPs submitted	Yes
Bioanalytical method is acceptable	Yes

Comments on the Pre-Study Method Validation: The nominal concentration was reported as the LLOQ for both oxcarbazepine and MHC; the firm should report the mean back-calculated values (see also bioanalytical comments below). All other values were cross-checked with the method validation data provided in the original submission.

Acceptable.

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

FASTING Study:

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, route) [Product ID]	Subjects (No. (M/F) type Age: mean (range)	Mean Parameters (± SD)						Study Report Location
					Oxcarbazepine						
					C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	T½ (h)	K_{el} (h^{-1})	
228_OXCAR_06	To compare the single-dose oral bioavailability of oxcarbazepine 300 mg/5mL oral suspension of OHM Laboratories (a subsidiary of Ranbaxy Pharmaceuticals Inc) with Trileptal® 300 mg/5mL oral suspension (containing oxcarbazepine 300 mg/5mL) of Novartis Pharmaceutical Corporation, USA in healthy, adult, male, human subjects under fasting condition	An open label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, crossover bioavailability study	T: Oxcarbazepine oral suspension 300 mg/5mL (Batch No.-6530601, Expiry - July 2008), oral R: Trileptal® (oxcarbazepine) oral suspension 300 mg/5mL (Batch No.-H5144; Expiry - August 2007), oral	40 healthy subjects (all Male) were enrolled and 35 subjects completed both the periods of the study. Mean age: 25.93 years Range: 18 – 44 years	**Test** 1787.11 (±736.048) **Ref.** 1637.02 (±693.820)	**Test** 0.9872 **Ref.** 1.4395	**Test** 5529.2367 (±1928.66838) **Ref.** 5963.7210 (±2195.46087)	**Test** 6750.3313 (±2025.46948) **Ref.** 6822.3909 (±2278.31056)	**Test** 8.1240 **Ref.** 6.1490	**Test** 0.1172 **Ref.** 0.1368	Module 5 Vol. 1-9 page no. 0125 -3348
					10-Hydroxy Carbazepine						
					C_{max} (µg/mL)	T_{max} (h)	AUC_{0-t} (µg.h/mL)	$AUC_{0-\infty}$ (µg.h/mL)	T½ (h)	K_{el} (h^{-1})	
					Test 5.4683 (±1.37451) **Ref.** 6.0025 (±1.78706)	**Test** 5.5429 **Ref.** 7.0000	**Test** 136.1892 (±36.56374) **Ref.** 148.0392 (±36.09909)	**Test** 145.1123 (±37.62314) **Ref.** 159.2426 (±37.62886)	**Test** 11.9931 **Ref.** 12.1763	**Test** 0.0593 **Ref.** 0.0589	

FED Study:

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, route) [Product ID]	Subjects (No. (M/F) type Age: mean (range)	Mean Parameters (± SD)						Study Report Location
					Oxcarbazepine						
					C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	T½ (h)	K_{el} (h^{-1})	
233_OXCAR_06	To compare the single-dose oral bioavailability of oxcarbazepine 300 mg/5mL oral suspension of OHM Laboratories, USA (a subsidiary of Ranbaxy Pharmaceuticals Inc.) with Trileptal® 300 mg/5mL oral suspension (containing oxcarbazepine 300 mg/5mL) of Novartis Pharmaceutical Corporation, USA in healthy, adult, male, human subjects under fed condition.	An open label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, crossover bioavailability study	T: Oxcarbazepine oral suspension 300 mg/5mL (Batch No.- 6530601, Expiry - July 2008), oral R: Trileptal® (oxcarbazepine) oral suspension 300 mg/5mL (Lot No.- H5144; Expiry - August 2007), oral	40 healthy subjects (all Male) were enrolled and 33 subjects completed both the periods of the study. Mean age: 24.85 years Range: 18 – 40 years	**Test** 2324.39 (±866.676) **Ref.** 2621.77 (±1033.962)	**Test** 1.8283 **Ref.** 2.5706	**Test** 10072.4740 (±3102.75734) **Ref.** 11074.5624 (±3920.10234)	**Test** 10809.9908 (±3252.46264) **Ref.** 12326.3859 (±4309.40018)	**Test** 6.2907 **Ref.** 9.5189	**Test** 0.1584 **Ref.** 0.1383	Module 5 Vol. 10-19 page no. 3349-6461
					10-Hydroxy Carbazepine						
					C_{max} (µg/mL)	T_{max} (h)	AUC_{0-t} (µg.h/mL)	$AUC_{0-\infty}$ (µg.h/mL)	T½ (h)	K_{el} (h^{-1})	
					Test 9.5773 (±1.74271) **Ref.** 10.1450 (±1.99909)	**Test** 5.9217 **Ref.** 7.0283	**Test** 226.7499 (±42.87751) **Ref.** 241.7189 (±51.74696)	**Test** 237.6201 (±44.80455) **Ref.** 251.3782 (±52.50002)	**Test** 11.6473 **Ref.** 11.5720	**Test** 0.0620 **Ref.** 0.0618	

Oxcarbazepine (228_OXCAR_06) Dose (300 mg/5mL Oral Suspension) Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting bioequivalence study				
Oxcarbazepine				
Parameter	**Test**	**Reference**	**Ratio**	**90% CI**
AUC_{0-t} (µg.h/mL)	5190.4368	5598.0363	92.54	88.09 – 97.21
$AUC_{0-\infty}$ (ng.h/mL)	6446.2251	6462.6121	96.01	91.88 – 100.32
C_{max} (ng/mL)	1646.78	1501.46	109.19	99.22 – 120.17
10-hydroxy carbazepine				
Parameter	**Test**	**Reference**	**Ratio**	**90% CI**
AUC_{0-t} (µg.h/mL)	131.0597	143.3401	91.54	N/AP
$AUC_{0-\infty}$ (µg.h/mL)	139.9556	154.2913	90.81	N/AP
C_{max} (µg/mL)	5.2947	5.7710	91.79	N/AP

Oxcarbazepine (233_OXCAR_06) Dose (300 mg/5mL Oral Suspension) Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed bioequivalence study				
Oxcarbazepine				
Parameter	**Test**	**Reference**	**Ratio**	**90% CI**
AUC_{0-t} (ng.h/mL)	9599.0274	10413.5336	92.33	87.53 – 97.39
$AUC_{0-\infty}$ (ng.h/mL)	10315.5987	11557.6395	88.93	83.37 – 94.85
C_{max} (ng/mL)	2159.94	2437.94	88.75	80.26 – 98.13
10-hydroxy carbazepine				
Parameter	**Test**	**Reference**	**Ratio**	**90% CI**
AUC_{0-t} (µg.h/mL)	222.4559	235.6732	94.41	N/AP
$AUC_{0-\infty}$ (µg.h/mL)	233.1824	245.3980	94.99	N/AP
C_{max} (µg/mL)	9.4110	9.9544	94.52	N/AP

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

FASTING Study:

Oxcarbazepine (parent), 300 mg/5 mL Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	5186.30	5604.49	0.93	88.09	97.21
AUC∞ (hr *ng/ml)	6163.38	6419.41	0.96	91.89	100.31
Cmax (ng/ml)	1646.13	1507.53	1.09	99.22	120.17

10-Monohydroxyoxcarbazepine (metabolite), 300 mg/5 mL Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (µg*hr/ml)	131.10	143.21	0.92	87.87	95.38
AUC∞ (µg*hr/ml)	139.99	154.15	0.91	87.08	94.70
Cmax (µg/ml)	5.30	5.77	0.92	86.47	97.44

FED Study:

Oxcarbazepine (parent), 300 mg/5 mL Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	9596.81	10394.30	0.92	87.53	97.39
AUC∞ (hr *ng/ml)	10209.02	11480.12	0.89	83.20	95.04
Cmax (ng/ml)	2159.57	2433.29	0.89	**80.26**	98.13

10-Monohydroxyoxcarbazepine (metabolite), 300 mg/5 mL Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (µg*hr/ml)	222.67	235.85	0.94	91.11	97.84
AUC∞ (µg*hr/ml)	233.46	245.76	0.95	91.40	98.72
Cmax (µg/ml)	9.42	9.96	0.95	91.71	97.41

Table 3. Reanalysis of Study Samples

FASTING Study:

Oxcarbazepine

Study No. 228_OXCAR_06 Additional information in Appendix 16.3 (Module 5, BE Study Report)								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	Test	Reference	Test	Reference	Test	Reference	Test	Reference
Pharmacokinetic[1]	0	0	0.00	0.00	0	0	0.00	0.00
Code A (Rejected Analytical Batch)	50	50	2.86	2.86	49	50	2.80	2.86
Code B (Lost in Processing/ Analysis)	1	0	0.06	0.00	1	0	0.06	0.00
Code I (Internal standard variation)	0	3	0.00	0.17	0	2	0.00	0.17
Code K (Error in Sample Processing)	1	1	0.06	0.06	1	1	0.06	0.06

10-Hydroxy Carbazepine

Study No. 228_OXCAR_06 Additional information in Appendix 16.3 (Module 5, BE Study Report)								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	Test	Reference	Test	Reference	Test	Reference	Test	Reference
Pharmacokinetic[1]	0	0	0.00	0.00	0	0	0.00	0.00
Code A (Rejected Analytical Batch)	175	175	10.01	10.01	174	175	9.95	10.01
Code B (Lost in Processing/ Analysis)	1	0	0.06	0.00	1	0	0.06	0.00
Code I (Internal standard variation)	0	1	0.00	0.06	0	1	0.00	0.06
Code K (Error in Sample Processing)	1	0	0.06	0.00	1	0	0.06	0.00

FED Study:

Oxcarbazepine

Study No. 233_OXCAR_06 Additional information in Appendix 16.3 (Module 5, BE Study Report)								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	Test	**Reference**	**Test**	**Reference**	**Test**	**Reference**	**Test**	**Reference**
Pharmacokinetic[1]	0	0	0.00	0.00	0	0	0.00	0.00
Code B (Lost in Processing/ Analysis)	1	5	0.05	0.27	1	5	0.05	0.27
Code E (Above Upper Limit of the Standard Curve)	0	1	0.00	0.05	0	1	0.00	0.05
Code I (Internal standard variation)	3	4	0.16	0.22	3	4	0.16	0.22

10-Hydroxy Carbazepine

Study No. 233_OXCAR_06 Additional information in Appendix 16.3 (Module 5, BE Study Report)								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	Test	**Reference**	**Test**	**Reference**	**Test**	**Reference**	**Test**	**Reference**
Pharmacokinetic[1]	0	0	0.00	0.00	0	0	0.00	0.00
Code B (Lost in Processing/ Analysis)	1	5	0.05	0.27	1	5	0.05	0.27
Code E (Above Upper Limit of the Standard Curve)	0	1	0.00	0.05	0	1	0.00	0.05
Code I (Internal standard variation)	3	4	0.16	0.22	3	4	0.16	0.22

Did use of recalculated plasma concentration data change study outcome? No.

Comments: The in vivo BE studies under fasting and fed conditions are **incomplete** pending the firm's response to the deficiencies listed below.

3.7 Formulation

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

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DFS
Source of Method (USP, FDA or Firm)	FDA[1]
Medium	Water with 1% SDS
Volume (mL)	900 mL
USP Apparatus type	USP 2 (paddle)
Rotation (rpm)	75 rpm
DBE-recommended specifications	NLT (b)(4)% (Q) in 30 min
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	Rapidly dissolving oral suspension
Is method acceptable?	**ACCEPTABLE** [2]
If not then why?	N/A

3.9 Waiver Request(s)

Not applicable.

[1] DBE Dissolution Database
[2] The firm acknowledged the DBE-recommended dissolution specification in the Study Amendment submitted 03 Aug 2007.

3.10 Deficiency Comments

1. Potency (assay) data were not provided for the reference (lot # H5144) product.

2. The QC values reported in the firm's original submission for fasted oxcarbazepine (study #228_OXCAR_006) do not coincide with those provided in its study amendment (electronic biosummary Table 14, submission date: 03 August 2007). The number of observations (n) and the percent nominal values (accuracy) calculated by the reviewer for oxcarbazepine do not agree with those reported by the firm (Vol. 1.9, p. 2407).

3.11 Recommendations

1. The single-dose, crossover BE studies under fasting (study #228_OXCAR_06) and fed (study #233_OXCAR_06) conditions submitted by Ranbaxy comparing its test product, Oxcarbazepine Oral Solution, 300 mg/5 mL, lot #6530601, to the RLD, Trileptal® (oxcarbazepine) Oral Suspension, 300 mg/5 mL, lot #H5144, manufactured by Novartis, are incomplete.

2. Dissolution testing is acceptable. The firm acknowledged the DBE-recommended dissolution specification [NLT (b)(4)% (Q) in 30 min] in its study amendment (submission date: 03 August 2007).

3. The product formulation is acceptable.

4. The firm should respond to the deficiencies outlined above. Specific recommendations are given the letter below.

5. In future submissions, the firm should include the mean concentrations for both QC and standard samples in place of the nominal values. These values should be included in both pre- and within-study assay biosummary tables (i.e., Table 4 and 14).

6. The application is **incomplete** with deficiencies and pending DSI inspection.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
DSI	Pending Initial DSI Inspection

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	228_OXCAR_06
Study Title	An open label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, crossover bioequivalence study comparing oxcarbazepine 300 mg/5 mL oral suspension of Ohm Laboratories (a subsidiary of Ranbaxy Pharmaceuticals Inc) with Trileptal® 300 mg/5 mL) of Novartis Pharmaceutical Corporation in healthy, adult, male, human subjects under fasting conditions.
Clinical Site (Name & Address)	Ranbaxy – Clinical Pharmacology Unit Majeedia Hospital (2nd Floor), Jamia Hamdard (Hamdard University) Hamdard Nagar, New Delhi 110 062 India
Principal Investigator	Dr. Nilanjan Saha
Dosing Dates	Period 1: 28 Sep 2006 Period 2: 12 Oct 2006
Analytical Site (Name & Address)	Ranbaxy – Clinical Pharmacology & Pharmacokinetics Plot No. 20, Sector 18, Udyog Vihar Industrial Area Gurgaon 122 015, Haryana India
Analytical Director	Dr. Tausif Monif
Analysis Dates	28 Oct 2006 – 05 Dec 2006
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	68 days

Table 5. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Oxcarbazepine Oral Suspension	Trileptal® Oral Suspension
Manufacturer	Ohm Labs (a subsidiary of Ranbaxy)	Novartis
Batch/Lot No.	6530601	H5144
Manufacture Date	Jul 2006	
Expiration Date		Aug 2007
Strength	300 mg/5 mL	300 mg/5 mL
Dosage Form	Oral Suspension	Oral Suspension

Product	Test	Reference
Bio-Batch Size	(b) (4) liters	
Production Batch Size	liters	
Potency (Assay)	(b) (4)	Not provided
Content Uniformity (mean, %CV)	N/A for oral suspension	
Dose Administered	2 x 300 mg/5 mL (600 mg in a single dose)	2 x 300 mg/5 mL (600 mg in a single dose)
Route of Administration	Oral	Oral

Comments on Product Information: Potency data for the reference product were not included; the firm should submit these data. **Incomplete**.

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

Number of Subjects	40 subjects (35 complete & analyzed)
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme	**AB:** 3, 4, 6, 7, 10, 11, 13, 14, 19, 20, 21, 24, 25, 26, 27, 31, 32, 34, 35, 36 **BA:** 1, 2, 5, 8, 9, 12, 15, 16, 17, 18, 22, 23, 28, 29, 30, 33, 37, 38, 39, 40
Blood Sampling Times	Pre-dose (0), 0.167, 0.333, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 48 and 72 hours post-dosing
Blood Volume Collected/Sample	1 x 5 mL per sample
Blood Sample Processing/Storage	Samples were collected into tubes containing EDTA and centrifuged under refrigeration to separate plasma. Plasma samples were then divided into two aliquots, labeled, and stored at -15°C or colder until they were transferred to the lab for analysis.
IRB Approval	Yes (final approval = 26 Sep 2006, 1 day prior to study onset)
Informed Consent	Yes
Length of Fasting	10 hours prior to dose administration
Length of Confinement	10 hours prior to dose administration until after the 24-hour blood sampling point
Safety Monitoring	In addition to adverse-event monitoring, safety measures included clinical laboratory tests and vital signs. Hematological and biochemical blood measures were completed at the beginning and end of the study. Vitals signs (i.e., blood pressure, pulse, oral temperature) were monitored at admission, pre-dose, and 4, 8, 12, 24, 36, 48 and 72 hours post administration.

Comments on Study Design: The study design is acceptable.

[3] DFS N78734 Chemistry Review

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

	Treatment Groups	
	Test Product N = 35	**Reference Product N = 35**
Age (years)		
Mean ± SD	26.20 ± 6.39	26.20 ± 6.39
Range	18 – 44	18 – 44
Groups		
< 18	0 %	0 %
18 – 40	33 (94.29%)	33 (94.29%)
41-64	2 (5.71%)	2 (5.71%)
65-75	0 %	0 %
>75	0 %	0 %
Sex		
Female	0 %	0 %
Male	100%	100%
Race		
Asian	100 %	100 %
Black	0 %	0 %
Caucasian	0 %	0 %
Hispanic	0 %	0 %
Other	0%	0%
Height (cm)		
Mean ± SD	166.74 ± 7.36	166.74 ± 7.36
Range	153 – 182	153 – 182
Weight (Kg)		
Mean ± SD	57.46 ± 7.48	57.46 ± 7.48
Range	45 – 70	45 – 70
Smokers		
Yes	12 (34.29%)	12 (34.29%)
No	23 (65.71%)	23 (65.71%)

Table 8. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
02	Withdrawn due to error in dosing	1	No
06	Withdrawn due to adverse event (fever)	1	No
09	Withdrawn due to adverse event (fever)	1	No
19	Withdrawn due to adverse event (fever)	1	No
34	Withdrew due to personal reasons prior to dosing	2	No

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups Fasting Bioequivalence Study Study No. 228_OXCAR_06		Pre-dose adverse events
	Test (N = 38)	Reference (N = 37)	
General Disorders/ Body as a whole			
Fever	02 (5.26%)	01 (2.70%)	-
Malaise	01 (2.63%)	-	
Total	**03 (7.89%)**	**01 (2.70%)**	-

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Subject 25 did not report for the 72-hour sampling point	25	

Comments on Dropouts/Adverse Events/Protocol Deviations:

- There were 4 reported adverse events (ADEs) in three (3) of the 40 dosed subjects; three followed test treatment and one followed reference treatment; overall, these data suggest there was an equal incidence of ADEs for both test and reference treatments.
- 7.5% of subjects exhibited at least one adverse event (although they were only thought to be remotely associated with drug treatment).
- No subjects vomited during the study.
- There were 14 reported deviations to the blood-draw schedule, representing 0.8% of the total study samples (1749); six (6) occurred following test treatment and eight (8) were after reference treatment. Eight (8) of the 14 deviated appreciably (i.e., $\geq$ 10%) from the scheduled sampling time; however, the firm corrected for each sampling-point deviation by using the actual time in the final PK analyses for both parent and metabolite analytes.
- The firm's handling of dropouts, adverse events, and protocol deviations are **acceptable.**

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Oxcarbazepine (parent)								
Parameter (n=30)	**Standard Curve Samples**							
Concentration (ng/mL)	58.79	114.90	226.18	381.96	966.92	2298.98	5020.46	6173.44
Inter day Precision (%CV)	2.9	4.3	5.6	5.4	4.5	4.5	4.6	6.0
Inter day Accuracy (%Actual)	100.3	100.1	98.5	99.8	101.0	100.9	97.0	102.5
Linearity	0.9954 – 0.9996							
Linearity Range (ng/mL)	58.79 – 6173.44							
Sensitivity/LOQ (ng/mL)	58.79							

Parameter (n=71-72)	**Quality Control Samples**			
Concentration (ng/mL)	147.75	749.4	2290.96	5028.84
Inter day Precision (%CV)	8.1	7.3	7.6	8.6
Inter day Accuracy (%Actual)	93.0	94.9	95.9	**123.5**

Comments on Oxcarbazepine Assay Validation: Values obtained from the electronic biosummary tables submitted with the study amendment (submission date: 03 Aug 2007) were cross-checked with original submission (Vol. 1.9). The firm reported the nominal concentration instead of the mean standard values for both QC and standard samples. The reviewer included the mean values taken from the original submission in the table above.

The QC values reported in the original submission do NOT agree with those provided in the electronic biosummary tables submitted with the study amendment (08/03/07). The number of observations (n) and the percent nominal values (i.e., accuracy) calculated by the reviewer for oxcarbazepine do not agree with those reported by the firm (Vol. 1.9, p. 2407), nor do they coincide with those values provided by the firm in the study amendment (03 Aug 2007). **The firm should explain these discrepancies.**

The within-fasting-study assay validation for oxcarbazepine is **incomplete**.

MHC (metabolite)								
Parameter	**Standard Curve Samples**							
Concentration (µg/mL)	0.1513	0.3202	0.6269	1.0398	2.6294	6.1675	12.8266	15.7615
Inter day Precision (%CV)	3.3	4.8	4.5	5.9	4.5	5.3	4.9	7.9
Inter day Accuracy (%Actual)	97.0	104.3	102.3	101.7	102.9	101.4	92.8	98.0
Linearity	0.9920 – 0.9990							
Linearity Range (µg/mL)	0.1513 – 15.7615							
Sensitivity/LOQ (µg/mL)	0.1513							

Parameter (n=69-70)	**Quality Control Samples**			
Concentration (µg/mL)	0.3322	1.7078	5.1814	11.1279
Inter day Precision (%CV)	10.2	10.8	8.9	9.9
Inter day Accuracy (%Actual)	100.7	103.4	98.8	100.8

Comments on Study Assay Validation: As above, values obtained from the electronic data tables submitted with the study amendment (submission date: 03 Aug 2007) were cross-checked with original submission (Vol. 1.9). The firm reported the nominal concentrations instead of the mean standard and QC values for MHC. As above, the reviewer included the mean values from the original submission in the table above.

All the QC values for MHC are within acceptable limits and the mean, precision and accuracy values DO coincide with those reported in the biosummary tables submitted with the study amendment.

The within-fasting-study assay validation for MHC is **complete**.

Any interfering peaks in chromatograms?	No. Peaks are clear for both oxcarbazepine and M(b)C.
Were 20% of chromatograms included?	Yes (20%, subjects 1-10)
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms: Acceptable.

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

SOP No.	Effective Date of SOP	SOP Title
PK-L51-02	07 Dec 2005	Repeat Analysis

Table 13. Additional Comments on Repeat Assays

Oxcarbazepine (parent)	
Were all SOPs followed?	No (see comment below)
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays:

- All samples were received at the bioanalytical facility in good condition on dry ice.
- There were two repeated batches including subjects 25 and 31.
- There were six (6) individual repeats representing <1% of the total study samples analyzed (1749); two were performed after test treatment, while four followed reference treatment.
- All repeats were reassayed due to analytical reasons.
- All values obtained during repeat analysis were used in final PK analysis, except for the one sample from the repeated analytical batch (subject 31, period 1, pre-dose); this sample was repeated twice and the value from the 2nd repeat was used for PK analysis. Apart from this one pre-dose sample, however, all repeats were conducted as per the firm's SOP #PK-L51-02.

The bioanalytical methodology for oxcarbazepine is **incomplete**.

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

Summary/Conclusions, Study Assays:

- There were seven failed batches including subjects 3, 11, 14, 21, 24, 25, and 31.
- There were three (3) individual repeats representing <1% of the total study samples analyzed (1749); two were performed after test treatment, while one followed reference treatment.
- All repeats were reassayed due to analytical reasons.

The bioanalytical methodology for MHC is **acceptable.**

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 18 and Figure 1

Oxcarbazepine (parent)										
		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng*hr/mL	5529.24	34.88	2089.54	10058.57	5963.72	36.81	2911.93	12839.32	0.93
AUCI	ng*hr/mL	6750.33	30.01	3180.22	11493.77	6822.39	33.39	3101.18	13483.37	0.99
CMAX	ng/mL	1787.11	41.19	784.20	3680.60	1637.02	42.38	609.00	3507.40	1.09
TMAX*	hr	1.00	.	0.50	2.50	1.50	.	0.33	3.00	0.67
KE	hr-1	0.12	59.91	0.02	0.30	0.14	50.67	0.06	0.35	0.86
THALF	hr	8.12	65.00	2.33	30.81	6.15	40.39	1.98	11.83	1.32

* Tmax values are presented as median, range

10-Monohydroxyoxcarbazepine (metabolite)										
		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	mcg*hr/mL	136.19	26.85	70.54	200.23	148.04	24.38	69.29	212.07	0.92
AUCI	mcg*hr/mL	145.11	25.93	75.87	208.06	159.24	23.63	73.52	223.24	0.91
CMAX	mcg/mL	5.47	25.14	3.07	8.08	6.00	29.77	3.10	12.02	0.91
TMAX	hr	5.00	.	2.50	12.00	5.00	.	3.00	16.00	1.00
KE	hr-1	0.06	16.78	0.04	0.08	0.06	18.30	0.03	0.08	1.01
THALF	hr	11.99	16.28	8.45	16.48	12.18	19.90	8.61	20.59	0.98

* Tmax values are presented as median, range

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

Oxcarbazepine (228_OXCAR_06) Dose (300 mg/5mL Oral Suspension) Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting bioequivalence study				
Oxcarbazepine				
Parameter	**Test**	**Reference**	**Ratio**	**90% CI**
AUC_{0-t} (ng.h/mL)	5190.4368	5598.0363	92.54	88.09 – 97.21
$AUC_{0-\infty}$ (ng.h/mL)	6446.2251	6462.6121	96.01	91.88 – 100.32
C_{max} (ng/mL)	1646.78	1501.46	109.19	99.22 – 120.17
10-hydroxy carbazepine				
Parameter	**Test**	**Reference**	**Ratio**	**90% CI**
AUC_{0-t} (µg.h/mL)	131.0597	143.3401	91.54	N/AP
$AUC_{0-\infty}$ (µg.h/mL)	139.9556	154.2913	90.81	N/AP
C_{max} (µg/mL)	5.2947	5.7710	91.79	N/AP

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

Oxcarbazepine (parent), 300 mg/5 mL
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	5186.30	5604.49	0.93	88.09	97.21
AUC∞ (hr *ng/ml)	6163.38	6419.41	0.96	91.89	100.31
Cmax (ng/ml)	1646.13	1507.53	1.09	99.22	120.17

10-Monohydroxyoxcarbazepine (metabolite), 300 mg/5 mL
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (µg*hr/ml)	131.10	143.21	0.92	87.87	95.38
AUC∞ (µg*hr/ml)	139.99	154.15	0.91	87.08	94.70
Cmax (µg/ml)	5.30	5.77	0.92	86.47	97.44

Table 17. Additional Study Information

Oxcarbazepine (parent)		
Root mean square error, AUC0-t	0.1216	
Root mean square error, AUC∞	0.1033	
Root mean square error, Cmax	0.2367	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	32	33
Do you agree or disagree with firm's decision?	Disagree	
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	None	None
Were the subjects dosed as more than one group?	No	

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	32	0.85	0.58	0.95
Reference	33	0.88	0.71	0.95

Comments on Pharmacokinetic and Statistical Analysis:

- The mean AUCt/AUC∞ ratio >0.80 indicates that the firm's sampling schedule for oxcarbazepine was carried out for a sufficiently long period of time. The wide range of range of the AUCt/AUCi ratios from 0.58-0.95 likely reflects the PK properties of the parent drug; that is, oxcarbazepine has a rapid absorption, extensive first-pass metabolism, and rapid half life of ~1.5 hours making sufficient sampling more difficult.
- PK endpoints were recalculated after re-determination of Kel using SAS. The PK values determined by the reviewer were in accordance with those reported by the firm; study outcome was not changed.
- The 90% CI for the least-squares geometric means of $\ln AUC_t$, $\ln AUC_\infty$, and $\ln C_{max}$ calculated by the reviewer agree with the firm's calculations and meet the CI criteria for BE (80.00-125.00%).

10-Monohydroxyoxcarbazepine (metabolite)		
Root mean square error, AUC0-t	0.1013	
Root mean square error, AUC∞	0.1035	
Root mean square error, Cmax	0.1475	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	35	35
Do you agree or disagree with firm's decision?	Agree	
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	None	None
Were the subjects dosed as more than one group?	No	

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	35	0.94	0.85	0.99
Reference	35	0.93	0.86	0.99

Comments on Pharmacokinetic and Statistical Analysis:

- The mean AUCt/AUC∞ ratio >0.80 for both test and reference products indicates that the firm's sampling schedule was satisfactory.
- Although not required for the determination of BE, the 90% CI for the least-squares geometric means of $\ln AUC_t$, $\ln AUC_\infty$, and $\ln C_{max}$ calculated by the reviewer meet the CI criteria for acceptable BE (80.00-125.00%).

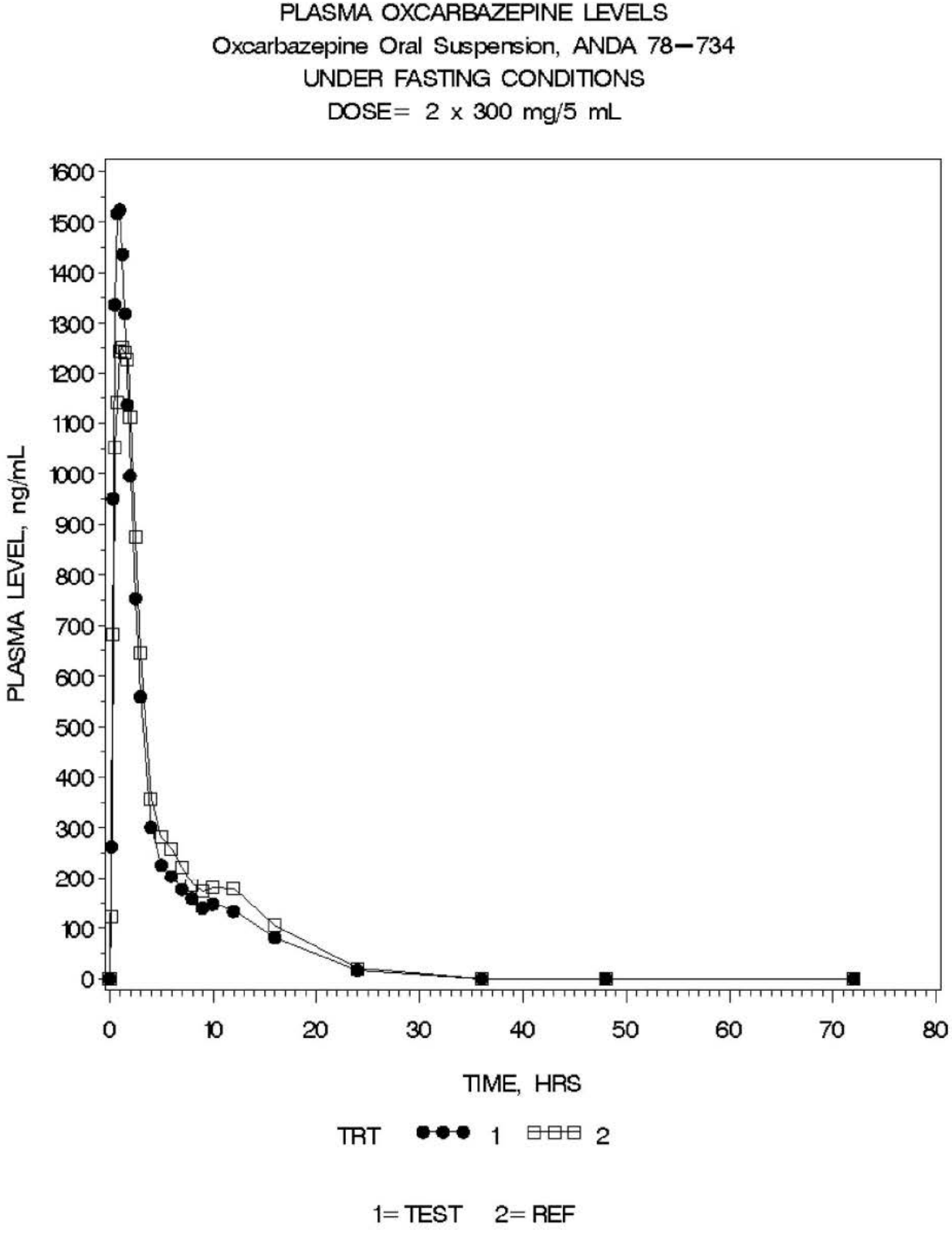
Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

- The PK parameters measured for oxcarbazepine (parent) meet the statistical criteria for BE.
- Although not required to determine BE, the MHC metabolite data also meet the statistical criteria for acceptable BE.
- However, the in vivo BE study under fasting conditions is **incomplete** pending the firm's response to the deficiencies listed above.

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

Oxcarbazepine (parent)					
	Test (n=35)		Reference (n=35)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.17	262.99	113.25	123.56	106.56	2.13
0.33	951.73	66.34	682.51	69.06	1.39
0.50	1336.93	48.98	1051.49	63.05	1.27
0.75	1517.18	45.12	1141.69	58.43	1.33
1.00	1524.26	45.35	1243.66	53.08	1.23
1.25	1436.37	49.49	1249.39	53.91	1.15
1.50	1318.92	44.84	1240.51	52.07	1.06
1.75	1136.95	44.01	1226.62	52.24	0.93
2.00	995.71	41.02	1111.67	54.58	0.90
2.50	754.07	37.53	875.55	55.59	0.86
3.00	559.48	46.03	647.00	58.58	0.86
4.00	301.01	44.24	357.05	48.25	0.84
5.00	226.23	42.64	282.52	35.84	0.80
6.00	203.58	42.50	257.60	42.08	0.79
7.00	177.21	39.86	221.27	44.05	0.80
8.00	158.58	44.04	186.53	40.80	0.85
9.00	139.82	42.91	173.49	42.15	0.81
10.00	147.94	42.83	180.05	45.79	0.82
12.00	133.61	45.39	178.39	53.96	0.75
16.00	81.48	71.77	106.05	68.84	0.77
24.00	17.16	210.18	20.49	175.25	0.84
36.00	0.00	.	0.00	.	.
48.00	0.00	.	0.00	.	.
72.00	0.00	.	0.00	.	.

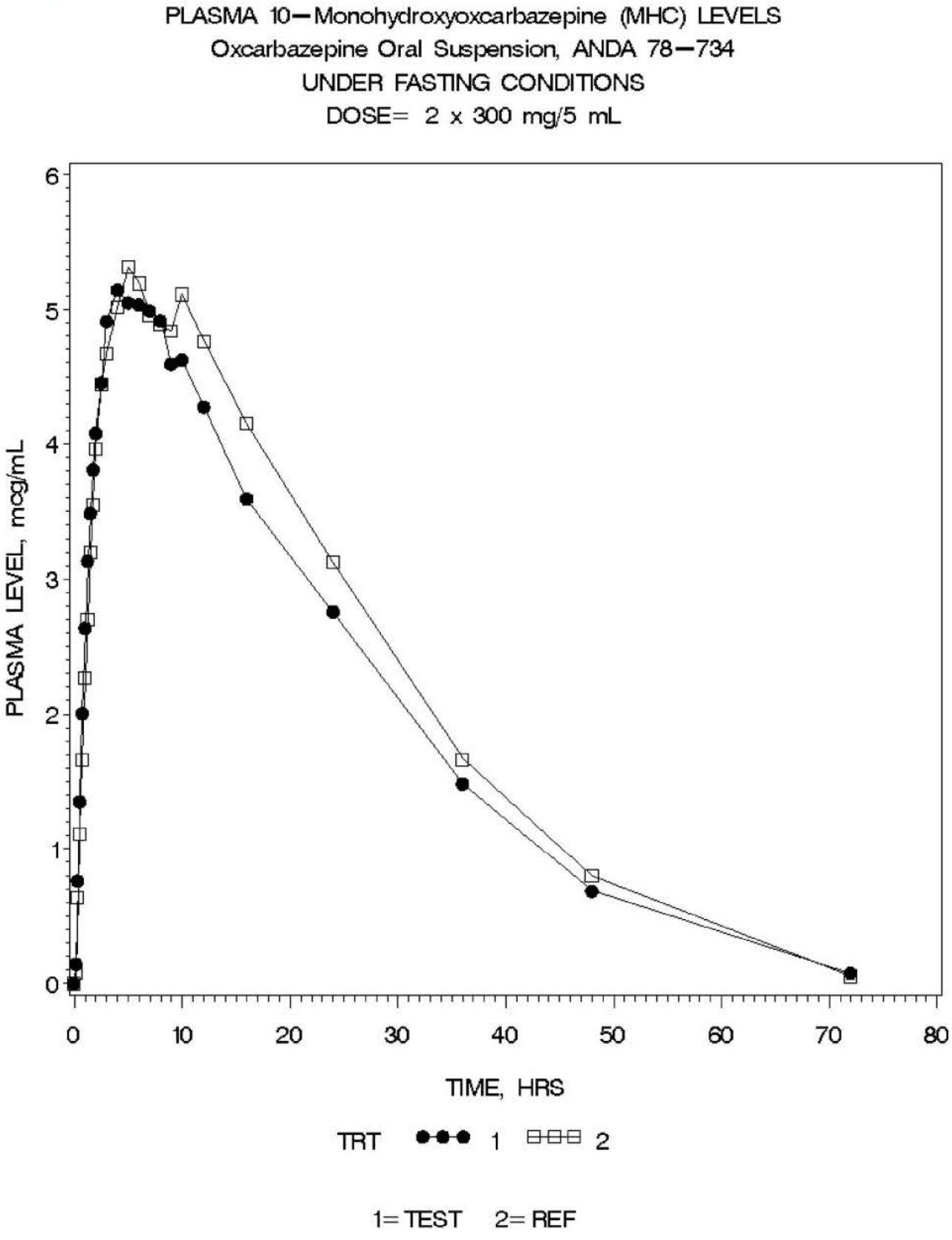
Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

10-Monohydroxyoxcarbazepine (metabolite)					
	Test (n=35)		Reference (n=35)		Ratio
Time (hr)	Mean (mcg/mL)	CV%	Mean (mcg/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.17	0.14	121.83	0.07	164.45	1.95
0.33	0.76	41.40	0.64	44.88	1.19
0.50	1.35	35.96	1.12	35.82	1.21
0.75	2.00	28.93	1.66	33.60	1.20
1.00	2.64	27.59	2.27	33.68	1.16
1.25	3.13	30.45	2.70	39.23	1.16
1.50	3.49	27.07	3.20	35.91	1.09
1.75	3.81	29.39	3.55	34.54	1.07
2.00	4.08	27.85	3.97	31.76	1.03
2.50	4.45	26.92	4.44	34.11	1.00
3.00	4.92	26.54	4.67	29.67	1.05
4.00	5.15	26.09	5.02	30.70	1.02
5.00	5.05	26.63	5.32	29.32	0.95
6.00	5.04	27.73	5.20	27.64	0.97
7.00	4.99	27.49	4.96	27.47	1.01
8.00	4.92	27.83	4.90	25.52	1.00
9.00	4.59	27.95	4.84	22.79	0.95
10.00	4.62	26.02	5.12	33.65	0.90
12.00	4.28	25.22	4.76	22.22	0.90
16.00	3.59	27.01	4.15	25.60	0.87
24.00	2.76	27.90	3.12	26.96	0.88
36.00	1.49	33.80	1.67	29.60	0.89
48.00	0.68	43.79	0.80	36.80	0.86
72.00	0.07	163.75	0.05	197.29	1.44

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



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 19. Study Information

Study Number	233_OXCAR_06
Study Title	An open label, balanced, randomised, two-treatment, two-period, two-sequence, single-dose, crossover bioavailability study comparing oxcarbazepine 300 mg/5mL oral suspension of OHM Laboratories (a subsidiary of Ranbaxy Pharmaceuticals Inc.) with Trileptal® 300 mg/5mL oral suspension (containing oxcarbazepine 300 mg/5mL) of Novartis Pharmaceutical Corporation in healthy, adult, male, human subjects under fed condition.
Clinical Site (Name, Address, Phone #)	**Clinical Pharmacology Unit** Clinical Pharmacology Unit B-22, Sector 62 Noida- 201 301 Uttar Pradesh India Tel: (+91-120) 2403988 Fax: (+91-120) 2403989
Principal Investigator	**Dr. Nilanjan Saha** Clinical Pharmacology & Development Medical Affairs and Clinical Research Ranbaxy Research Laboratories, Plot No. 77B, Sector 18, IFFCO Road Gurgaon 122 015, Haryana, India Tel: (91-124) 4107003 Fax: (91-124) 2342018
Dosing Dates	PERIOD I : 14th October 2006 PERIOD II: 31st October 2006
Analytical Site (Name, Address, Phone #)	Clinical Pharmacology & Pharmacokinetics Ranbaxy Research Laboratories Plot No. 20, Sector 18, Udyog Vihar Industrial Area Gurgaon 122 015, Haryana India Tel.: (91-124) 2346501 Fax: (91-124) 4012520
Analysis Dates	18th November 2006 – 07th December 2006
Analytical Director	Dr. Tausif Monif
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	54 Days

Table 20. Product Information

Product	Test	Reference
Treatment ID	T	R
Product Name	Oxcarbazepine oral suspension 300 mg/5mL	Trileptal® (oxcarbazepine) oral suspension 300 mg/5mL
Manufacturer	OHM Laboratories Inc., 34 West Fulton Street, Gloversville, NY 12078 (a subsidiary of Ranbaxy Pharmaceuticals Inc.)	Novartis Pharma S.A.S. Huningue, France
Batch/Lot No.	6530601	H5144
Manufacture Date	August 2006	*
Expiration Date	July 2008	August 2007
Strength	300 mg/5mL	300 mg/5mL
Dosage Form	Oral Suspension	Oral Suspension
Bio-batch Size	(b) (4) litres	*
Production Batch Size	(b) (4) liters	*
Potency	300 mg/5 ml	300 mg/5 ml
Content Uniformity (mean, %CV)	NA	NA
Dose Administered	600 mg	600 mg
Route of Administration	Oral	Oral

Comments on Product Information: Potency data for the reference product were not included; the firm should submit these data. **Incomplete**.

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

No. of Subjects	40 subjects (33 complete & analyzed)
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	17 days
Randomization Scheme	**AB:** 2, 3, 7, 9, 10, 12, 13, 14, 16, 20, 23, 24, 26, 28, 30, 33, 37, 38, 39, 40 **BA:** 1, 4, 5, 6, 8, 11, 15, 17, 18, 19, 21, 22, 25, 27, 29, 31, 32, 34, 35, 36
Blood Sampling Times	Pre-dose (0), 0.5, 1, 1.33, 1.67, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.33, 4.67, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 48 and 72 hours post-dosing
Blood Volume Collected/Sample	1 x 5 mL per sample
Blood Sample Processing/Storage	Samples were collected into tubes containing EDTA and centrifuged under refrigeration to separate plasma. Plasma samples were then divided into two aliquots, labeled, and stored at -15°C or colder until they were transferred to the lab for analysis.
IRB Approval	Yes (final approval = 12 Oct 2006, 2 days prior to study onset)
Informed Consent	Yes
Length of Fasting Before Meal	10 hours prior to dose administration
Length of Confinement	10 hours prior to dose administration until after the 24-hour blood sampling point
Safety Monitoring	In addition to adverse-event monitoring, safety measures included clinical laboratory tests and vital signs. Hematological and biochemical blood measures were completed at the beginning and end of the study. Vitals signs (i.e., blood pressure, pulse, oral temperature) were monitored at admission, pre-dose, and 4, 8, 12, 24, 36, 48 and 72 hours post administration.
Standard FDA Meal Used?	No [4]

Composition of Meal Used in Fed Bioequivalence Study		
Composition	**Percent**	**Kcal**
Fat	55.4	531
Carbohydrate	26.0	250
Protein	18.6	178
TOTAL		959

Comments on Study Design: The study design is **acceptable.**

[4] The study meal included the following: 60 g of chicken (146 Kcal – 14 g pro, 10 g fat); 240 mL of whole milk (152 Kcal – 12 g CHO, 8 g pro, 8 g fat); 120 g of Hash brown potatoes (162 Kcal – 15 g CHO, 3 g pro, 10 g fat); 2 medium eggs fried in 3 g of butter (267 Kcal – 15 g protein, 23 g fat); 2 large slices of bread with 8 g of butter (232 Kcal – 35.5 g CHO, 4.5 g pro, 8 g fat).

4.1.2.2 Clinical Results

Table 22. Demographics Profile of Subjects Completing the Bioequivalence Study

	Treatment Groups	
	Test Product N = 33	**Reference Product N = 33**
Age (years)		
Mean ± SD	25.18 ± 5.42	25.18 ± 5.42
Range	18 – 40	18 – 40
Groups		
< 18	0%	0%
18 – 40	33 (100%)	33 (100%)
41-64	0%	0%
65-75	0%	0%
>75	0%	0%
Sex		
Female	0 %	0 %
Male	100%	100%
Race		
Asian	100 %	100 %
Biracial	0 %	0 %
Black	0 %	0 %
Caucasian	0 %	0 %
Hispanic	0 %	0 %
Other	0 %	0 %
Height (cm)		
Mean ± SD	167.70 ± 6.31	167.70 ± 6.31
Range	159 – 181	159 – 181
Weight (Kg)		
Mean ± SD	57.73 ± 6.78	57.73 ± 6.78
Range	46 – 70	46 – 70
Smokers		
Yes	05 (15.15%)	05 (15.15%)
No	28 (84.85%)	28 (84.85%)

Table 23. Dropout Information

Study No. 233_OXCAR_06				
Subject No	**Reason for dropout/ withdrawal**	**Period**	**Replaced ?**	**Replaced with**
18	Withdrawn due to failure to comply with study requirements	I	-	-
22	Withdrawn due to adverse event (fever)	I	-	-
26	Withdrawn due to adverse event (fever)	I	-	-
40	Withdrawn due to adverse event (fever)	II	-	-
14	Withdrawn due to adverse event (vomiting)	II		
12	Withdrawn due to adverse event (vomiting)	II		
32	Dropped out (did not report for admission in period II)	II	-	-

Table 24. Study Adverse Events

Body system/Adverse Event	**Post-dose Adverse Events**		**Pre dose Adverse Events (Period I & II)**
	Reported Incidence by Treatment Groups		
	Test (N = 37)	**Reference (N = 34)**	
General Disorders/ Body as a whole			
Fever	01 (2.70%)	-	03
Gastrointestinal Disorders			
Vomiting	-	-	02
Total	**01 (2.70%)**	-	**05**

Table 25. Protocol Deviations

Study No. 233_OXCAR_06		
Type	**Subject # (Test)**	**Subject # (Ref.)**
Vital signs		
36 hours post dose blood sample (did not report)	-	03, 21
48 hours post dose blood sample (did not report)	-	03
72 hours post dose blood sample (did not report)	39	-
Blood Sample Collections		
36 hours post dose blood sample (did not report)	-	03, 21
48 hours post dose blood sample (did not report)	-	03
48 hours post dose blood sample (late by 13 minutes)	13	13
48 hours post dose blood sample (late by 09 minutes)	16	-
48 hours post dose blood sample (late by 15 minutes)	-	16
48 hours post dose blood sample (late by 05 minutes)	34	-
48 hours post dose blood sample (late by 54 minutes)	-	40
72 hours post dose blood sample (late by 04 minutes)	13, 34	-
72 hours post dose blood sample (late by 12 minutes)	16	16
72 hours post dose blood sample (late by 03 minutes)	28	-
72 hours post dose blood sample (did not report)	39	-

Comments on Adverse Events/Protocol Deviations:

- There were six (6) reported adverse events in five (5) of the 40 dosed subjects, all followed test treatment except one, which was pre-dose.
- Accordingly, 12.5% of subjects exhibited at least one adverse event (although they were thought to be only remotely associated with drug treatment).
- Subjects 12 and 14 vomited within 2x the median Tmax; they were dropped from the study.
- There were 15 reported deviations to the blood-draw schedule, representing 0.6% of the total study samples (1844); eight (8) followed test treatment and seven (7) were after reference treatment. None deviated significantly (i.e., > 5%) from the scheduled sampling time; nevertheless, the firm corrected for each sampling-point deviation by using the actual time in the final PK analyses for both parent and metabolite analytes.
- The firm's handling of dropouts, adverse events, and protocol deviations are **acceptable.**

4.1.2.3 Bioanalytical Results

Table 26. Assay Validation – Within the Fed Bioequivalence Study

Oxcarbazepine (parent)								
Parameter (n=33-34)	**Standard Curve Samples**							
Concentration (ng/mL)	58.6	110.09	218.12	360.58	961.76	2149 96	4718.81	5869.68
Inter day Precision (%CV)	2.4	4.1	5.1	5.7	4.2	2.1	2.5	2.1
Inter day Accuracy (%Actual)	100.7	99.5	98.7	97.8	104.4	98.0	103.3	97.6
Linearity	0.9965 – 0.9996							
Linearity Range (ng/mL)	58.6 – 5869.68							
Sensitivity/LOQ (ng/mL)	58.6							

Parameter (n=68)	**Quality Control Samples**			
Concentration (ng/mL)	176.17	832.80	2349.14	4617.13
Inter day Precision (%CV)	5.3	4.8	4.3	6.6
Inter day Accuracy (%Actual)	102.6	101.8	103.4	101.6

Comments on Study Assay Validation: Values obtained from the electronic biosummary tables submitted with the study amendment (submission date: 03 Aug 2007) were cross-checked with original submission (fed study, Vol. 1.18). The firm again reported the nominal concentrations instead of the mean standard values for both QC and standard samples. The reviewer included the mean values taken from the original submission in the table above.

All the QC values for oxcarbazepine are within acceptable limits and the mean, precision and accuracy values DO coincide with those reported in the biosummary tables submitted with the study amendment.

The within-fed-study method validation for oxcarbazepine is **satisfactory**.

MHC (metabolite)								
Parameter (32-34)	**Standard Curve Samples**							
Concentration (µg/mL)	0.1514	0.3034	0.6113	0.9697	2.5738	5.7401	12.1701	15.2158
Inter day Precision (%CV)	2.8	4.8	3.1	5.2	3.1	2.6	2.8	3.7
Inter day Accuracy (%Actual)	97.6	102.8	103.6	98.6	104.7	98.1	99.8	94.8
Linearity	0.9954 – 0.9995							
Linearity Range (µg/mL)	0.1514 – 15.2158							
Sensitivity/LOQ (µg/mL)	0.1514							

Parameter (n=68)	**Quality Control Samples**			
Concentration (µg/mL)	0.4483	2.0995	5.9906	11.9161
Inter day Precision (%CV)	6.9	6.0	6.0	6.3
Inter day Accuracy (%Actual)	97.9	96.3	98.9	98.4

Comments on Study Assay Validation: As above, values obtained from the electronic data tables submitted with the study amendment (submission date: 03 Aug 2007) were cross-checked with original submission (fed study, Vol. 1.18). The firm again reported the nominal concentration instead of the mean standard and QC values for MHC. As above, the reviewer included the mean values taken from the original submission in the table.

All the QC values for MHC are within acceptable limits and the mean, precision and accuracy values DO coincide with those reported in the biosummary tables submitted with the study amendment.

The within-fed-study assay validation for MHC is **satisfactory**.

Any interfering peaks in chromatograms?	No. Peaks for both oxcarbazepine and MHC were sharp & clear.
Were 20% of chromatograms included?	Yes (20%, subjects 30-38)
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms: Acceptable.

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

SOP No.	Effective Date of SOP	SOP Title
PK-L51-02	07 Dec 2005	Repeat Analysis

Table 28. Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays:

- All samples were received at the bioanalytical facility in good condition on dry ice.
- There were no reported failed batches.
- There were 14 individual repeats representing <1% of the total study samples analyzed (1844); four were performed after test treatment, while 10 followed reference treatment.
- All repeats were reassayed due to analytical reasons.

The bioanalytical methodology for oxcarbazepine is **acceptable**.

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

Summary/Conclusions, Study Assays:

- There were no failed batches.
- As with oxcarbazepine, there were 14 individual repeats representing <1% of the total study samples analyzed (1844); four were performed after test treatment, while 10 followed reference treatment.
- All repeats were reassayed due to analytical reasons.

The bioanalytical methodology for MHC is **acceptable.**

4.1.2.4 Pharmacokinetic Results

Table 29. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 33 and Figure

Oxcarbazepine (parent)										
		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng*hr/mL	10072.47	30.80	4452.91	18609.11	11074.56	35.40	4087.49	21750.13	0.91
AUCI	ng*hr/mL	10809.99	30.09	4652.33	19674.82	12326.39	34.96	4329.28	22612.70	0.88
CMAX	ng/mL	2324.39	37.29	649.20	4965.40	2621.77	39.44	908.50	6076.30	0.89
TMAX	hr	1.67	.	0.50	6.00	2.25	.	0.50	5.00	0.74
KE	hr-1	0.16	58.21	0.05	0.36	0.14	65.68	0.01	0.30	1.15
THALF	hr	6.29	58.98	1.91	13.96	9.52	128.87	2.29	65.87	0.66

* Tmax values are presented as median, range

10-Monohydroxyoxcarbazepine (metabolite)										
		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	mcg*hr/mL	226.75	18.91	123.53	296.00	241.72	21.41	131.23	344.61	0.94
AUCI	mcg*hr/mL	237.62	18.86	130.98	338.27	251.38	20.88	137.97	358.43	0.95
CMAX	mcg/mL	9.58	18.20	5.37	14.52	10.15	19.71	5.85	17.04	0.94
TMAX	hr	6.00	.	3.75	10.00	7.00	.	3.25	12.00	0.86
KE	hr-1	0.06	18.69	0.03	0.08	0.06	16.89	0.04	0.08	1.00
THALF	hr	11.65	23.45	8.23	20.17	11.57	19.23	8.98	17.94	1.01

* Tmax values are presented as median, range

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

Oxcarbazepine (233_OXCAR_06) Dose (300 mg/5mL Oral Suspension) Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed bioequivalence study				
Oxcarbazepine				
Parameter	**Test**	**Reference**	**Ratio**	**90% CI**
AUC_{0-t} (ng.h/mL)	9599.0274	10413.5336	92.33	87.53 – 97.39
$AUC_{0-\infty}$ (ng.h/mL)	10315.5987	11557.6395	88.93	83.37 – 94.85
C_{max} (ng/mL)	2159.94	2437.94	88.75	80.26 – 98.13
10-hydroxy carbazepine				
Parameter	**Test**	**Reference**	**Ratio**	**90% CI**
AUC_{0-t} (µg.h/mL)	222.4559	235.6732	94.41	N/AP
$AUC_{0-\infty}$ (µg.h/mL)	233.1824	245.3980	94.99	N/AP
C_{max} (µg/mL)	9.4110	9.9544	94.52	N/AP

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

Oxcarbazepine (parent), 300 mg/5 mL
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	9596.81	10394.30	0.92	87.53	97.39
AUC∞ (hr *ng/ml)	10209.02	11480.12	0.89	83.20	95.04
Cmax (ng/ml)	2159.57	2433.29	0.89	**80.26**	98.13

10-Monohydroxyoxcarbazepine (metabolite), 300 mg/5 mL
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (µg*hr/ml)	222.67	235.85	0.94	91.11	97.84
AUC∞ (µg*hr/ml)	233.46	245.76	0.95	91.40	98.72
Cmax (µg/ml)	9.42	9.96	0.95	91.71	97.41

Table 32. Additional Study Information

Oxcarbazepine (parent)		
Root mean square error, AUC0-t	0.1277	
Root mean square error, AUC∞	0.1493	
Root mean square error, Cmax	0.2407	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	32	31
Do you agree or disagree with firm's decision?	Agree	
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	1	5
Were the subjects dosed as more than one group?	No	

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	32	0.94	0.81	0.97
Reference	31	0.91	0.55	0.98

Comments on Pharmacokinetic and Statistical Analysis:

- The mean AUCt/AUC∞ ratio >0.80 for both test and reference products indicates that the firm's sampling schedule for oxcarbazepine was adequate.
- The 90% CI for the least-squares geometric means of $\ln AUC_t$, $\ln AUC_\infty$, and $\ln C_{max}$ calculated by the reviewer agree with the firm's calculations and meet the CI criteria for BE (80.00-125.00%).

10-Monohydroxyoxcarbazepine (metabolite)		
Root mean square error, AUC0-t	0.0853	
Root mean square error, AUC∞	0.0866	
Root mean square error, Cmax	0.0721	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	33	31
Do you agree or disagree with firm's decision?	Agree	
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	None	None
Were the subjects dosed as more than one group?	No	

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	33	0.95	0.78	0.99
Reference	31	0.96	0.90	0.99

Comments on Pharmacokinetic and Statistical Analysis:

- The mean AUCt/AUC∞ ratio >0.80 for both test and reference products indicates that the firm's sampling schedule was adequate.
- Although not required for the determination of BE, the 90% CI for the least-squares geometric means of $\ln AUC_t$, $\ln AUC_\infty$, and $\ln C_{max}$ calculated by the reviewer meet the CI criteria for acceptable BE (80.00-125.00%).

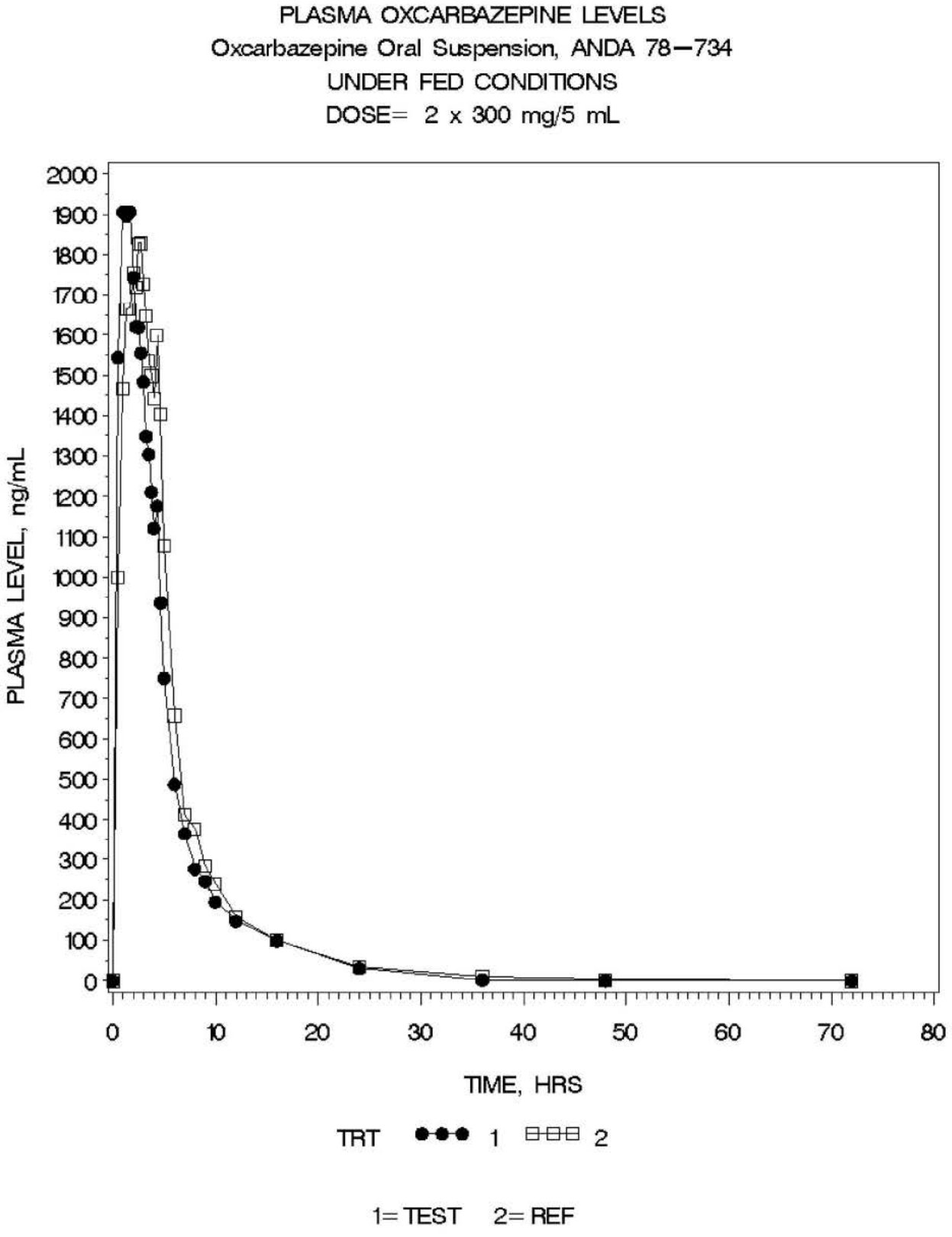
Summary and Conclusions, Single-Dose Fed Bioequivalence Study:

- The PK parameters measured for oxcarbazepine (parent) meet the statistical criteria for BE.
- Although not required to determine BE, the MHC metabolite data also meet the statistical criteria for acceptable BE.
- The in vivo BE study under fed conditions is **incomplete** pending the firm's response to the deficiencies listed above.

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

Oxcarbazepine (parent)					
	Test (n=33)		Reference (n=33)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.50	1543.86	46.17	999.90	78.67	1.54
1.00	1905.52	50.14	1465.35	69.52	1.30
1.33	1897.05	47.51	1664.79	68.11	1.14
1.67	1906.48	46.87	1665.61	53.69	1.14
2.00	1743.52	44.00	1756.26	67.14	0.99
2.25	1619.94	42.03	1718.43	62.34	0.94
2.50	1618.11	39.64	1828.10	53.88	0.89
2.75	1554.38	42.19	1828.78	47.62	0.85
3.00	1483.62	34.71	1727.99	45.36	0.86
3.25	1348.55	37.39	1647.95	39.09	0.82
3.50	1303.66	33.74	1535.70	46.29	0.85
3.75	1210.46	37.22	1497.72	41.23	0.81
4.00	1120.69	39.39	1443.05	42.88	0.78
4.33	1176.02	46.84	1597.94	39.04	0.74
4.67	937.52	49.12	1402.08	40.55	0.67
5.00	750.64	52.06	1079.11	43.63	0.70
6.00	487.27	52.20	658.48	54.41	0.74
7.00	365.05	54.00	413.95	46.52	0.88
8.00	276.40	56.75	376.52	78.82	0.73
9.00	246.15	46.93	284.86	56.67	0.86
10.00	194.77	40.64	238.18	61.05	0.82
12.00	147.09	46.37	156.58	53.47	0.94
16.00	99.07	28.16	100.18	42.31	0.99
24.00	30.58	112.74	33.98	115.22	0.90
36.00	1.78	574.46	9.86	265.53	0.18
48.00	0.00	.	2.62	565.69	0.00
72.00	0.00	.	0.00	.	.

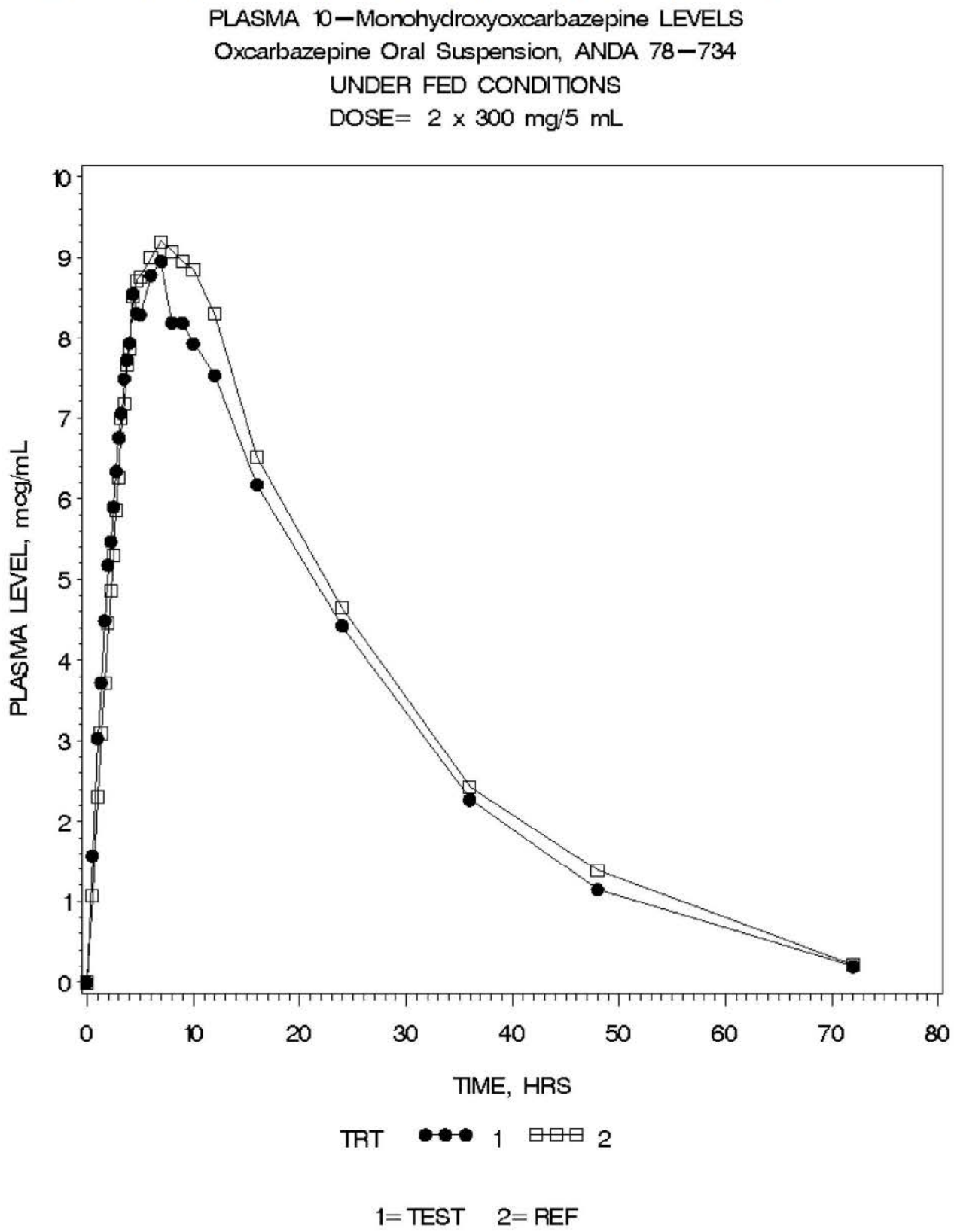
Figure 3. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

10-Monohydroxoxcarbazepine (metabolite)					
	Test (n=33)		Reference (n=33)		Ratio
Time (hr)	Mean (mcg/mL)	CV%	Mean (mcg/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.50	1.58	41.92	1.07	58.82	1.47
1.00	3.03	37.35	2.31	53.61	1.31
1.33	3.72	33.39	3.10	48.27	1.20
1.67	4.49	32.62	3.72	45.85	1.21
2.00	5.17	31.20	4.45	40.92	1.16
2.25	5.47	29.84	4.87	37.58	1.12
2.50	5.90	28.35	5.30	35.57	1.11
2.75	6.34	28.09	5.86	32.01	1.08
3.00	6.75	26.06	6.26	32.46	1.08
3.25	7.06	25.87	7.00	36.24	1.01
3.50	7.49	23.56	7.18	29.04	1.04
3.75	7.72	23.67	7.66	26.42	1.01
4.00	7.93	22.92	7.86	24.74	1.01
4.33	8.55	21.82	8.52	21.93	1.00
4.67	8.31	22.14	8.72	20.89	0.95
5.00	8.29	20.86	8.77	20.26	0.95
6.00	8.78	19.32	9.00	17.58	0.98
7.00	8.95	20.23	9.20	19.50	0.97
8.00	8.19	16.75	9.08	17.58	0.90
9.00	8.19	15.79	8.96	17.28	0.91
10.00	7.92	15.98	8.85	17.95	0.90
12.00	7.53	16.50	8.31	18.47	0.91
16.00	6.17	17.62	6.52	20.29	0.95
24.00	4.43	19.02	4.65	22.90	0.95
36.00	2.27	26.54	2.43	28.01	0.93
48.00	1.15	40.17	1.39	70.32	0.82
72.00	0.19	160.98	0.22	116.20	0.88

Figure 4. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



4.2 Formulation Data

Ingredients	mg/5 mL	% w/v
Oxcarbazepine[1]	300.00	(b) (4)
Microcrystalline Cellulose/ Carboxymethyl Cellulose Sodium, NF (b) (4)	(b) (4)	
Colloidal Silicon Dioxide, NF		
Hydroxyethyl Cellulose, NF (b) (4)		
Povidone, USP (b) (4)		
Copovidone, NF (b) (4)		
Polyoxyl 8 Stearate (b) (4)		
Methylparaben, NF		
Propylparaben, NF		
Sorbic Acid, NF		
Propylene Glycol, USP		
Saccharin Sodium, USP		
Ascorbic Acid, USP		
Noncrystallizing Sorbitol Solution, NF		
Artificail Cherry Flavor # (b) (4)		
Purified Water, USP		

[1] The quantity of Oxcarbazepine is based on (b) (4) The actual quantity will be based on actual assay and (b) (4)

Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Maximum Daily Dosing for Oxcarbazepine Oral Suspension	2400 mg/day[5]
Based on the max dosage, are all inactive ingredients within acceptable limits?	Yes (but, see comments)

Comments: The amount of hydroxyethyl cellulose exceeds that of any previously approved oral dosage form. Based on a maximum daily dosage of 2400 mg, the maximum amount of this excipient would be: (b) (4) mg. However, ingested doses are not toxic until levels exceed 2 g/kg/d. If an average adult weighs 70 kg, oral doses less than ~140 g daily should be satisfactory. Since the current formulation would only reach a maximum level of (b) (4) g/day, the levels of hydroxyethyl cellulose in the firm's formulation are satisfactory.

Two other excipients also exceeded the maximum recommended daily allowance. Including hydroxyethyl cellulose (described above), all three excipients are reviewed individually in the table below:

Ingredient	Amount in Formulation	Max Daily Dose	Toxic Dose	Ref
Hydroxyethyl Cellulose	(b) (4)	(b) (4) mg/day	> 2 g/kg (~140 g/day)	6
Povidone (b) (4)		g/day	> 5 g/kg (350 g/day)	7
Polyoxyl 8 Stearate (b) (4)		g/day	>2 g/kg (~140 g/day)	8,9

There is no API overage.

[5] PDR®, Dosing & Administration information for Trileptal® (oxcarbazepine) Oral Suspension
[6] National Library of Medicine, TOXNET (http://toxnet.nlm.nih.gov); cellulose gums have for several decades been considered non-irritating & non-sensitizing.
[7] (b) (4)

From the OGD Chemistry Review:[10]

Does any excipient exceed the IIG limit for this route of administration?

Firm's Response:

Quantity of inactive ingredients being used in Oxcarbazepine Oral Suspension, 300 mg/5 mL, *vis-à-vis* the quantities in eIID–2006 /quantities previously approved/accepted by the Agency for use in oral drug products is presented below:

Ingredients	mg/5 mL	Maximum Quantity Accepted by FDA in Oral Drug Products (mg)	Basis
Microcrystalline Cellulose/ Carboxymethyl Cellulose Sodium, NF (b) (4)	50.00	160 mg	(b) (4)
Colloidal Silicon Dioxide, NF		(b) (4)	
Hydroxyethyl Cellulose, NF (b) (4)			
Povidone, USP (b) (4)			
Copovidone, NF (b) (4)			
Polyoxyl 8 Stearate (b) (4)			
Methylparaben, NF			
Propylparaben, NF			
Sorbic Acid, NF			
Propylene Glycol, USP			
Saccharin Sodium, USP			
Ascorbic Acid, USP			
Noncrystallizing Sorbitol Solution, NF			
Artificial Cherry Flavor # (b) (4)			

eIID Last Updated: October 5, 2006

(Chemistry) Reviewer's Comment: Acceptable

The product formulation is **acceptable**.

[10] DFS N78734 Chemistry Review (Reviewer: Mujahid L Shaikh)

4.3 Dissolution Data

Dissolution Review Path DFS N78734 Bioequivalence Dissolution Review

Table 34. Dissolution Data

Dissolution Conditions	**Apparatus:**	USP II
	Speed of Rotation:	75 rpm
	Medium:	1 % Sodium Lauryl Sulfate in water
	Volume:	900 ml
	Temperature:	37°C
Firm's Proposed Specifications	NLT (b)(4)%(Q) of labeled amount of Oxcarbazepine is dissolved in 30 min.	
Dissolution Testing Site (Name, Address)	Ohm Laboratories Inc. 34 West Fulton Street, Gloversville NY 12078	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours) 10 min	15 min.	20 min.	30 min.	Study Report Location
Study Report #: NA	09/06	Oxcarbazepine Oral Suspension, 300 mg/5ml Batch No. – 6530601 Mfg. Date – August 2006	300 mg/ 5ml Oral suspension	12	Mean	88	91	92	93	Module 5 Page: 6466
					Range	84-91	87-94	91-93	91-95	
					%CV	2.03	2.50	0.93	1.38	
Study Report #: NA	09/06	Trileptal® (Oxcarbazepine) Oral Suspension, 300 mg/5ml Batch No. –H5144 Exp. Date – August 2007	300 mg/ 5ml Oral suspension	12	Mean	99	99	99	99	Module 5 Page: 6466
					Range	97-102	97-102	98-102	98-102	
					%CV	1.69	1.54	1.52	1.46	

Comments: As per the dissolution review, there is no USP method for this product but there is an FDA-recommended method. The DBE recommends a data-driven specification of NLT (b)(4)% (Q) in 30 minutes for the firm's test product. The dissolution testing with the FDA-recommended method is acceptable at the S_1 level. The firm's proposed liberal specification of NLT (b)(4)% (Q) in 30 minutes is not acceptable.

The firm acknowledged the FDA-recommended method and specification in a study amendment submitted 03 Aug 2007.

Dissolution is now **acceptable.**

4.4 Detailed Regulatory History (If Applicable)

The DBE has reviewed the following ANDA's regarding oxcarbazepine **TABLETS**:
77-747 (Apotex, 7/14/05)
77-795 (Roxane, 7/14/05)
(b) (4)
(b) (4)
77-801 (Taro, 7/14/05)
77-802 (Glenmark, 7/15/05)
78-005 (Teva, 11/25/05)
(b) (4)
78-069 (Breckenridge, 12/22/05)

This is a first generic application for an oral suspension.

4.5 Consult Reviews

None.

4.6 SAS Output

4.6.1 Fasting Study Data

4.6.1.1 Fasting Study Data – Oxcarbazepine (parent)

Obs	SUB	SEQ	PER	TREAT	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
1	1	(b) (4)																		
2	1																			
3	3																			
4	3																			
5	4																			
6	4																			
7	5																			
8	5																			
9	7																			
10	7																			
11	8																			
12	8																			
13	10																			
14	10																			
15	11																			
16	11																			
17	12																			
18	12																			
19	13																			
20	13																			
21	14																			
22	14																			

30 Pages have been Withheld as b4 (CCI/TS) immediately following this page

Obs	SUB	SEQ	PER	TREAT	GRP	AUCT	AUCI	CMAX	TMAX	KE	THALF
41	25	(b) (4)									
42	25										
43	27										
44	27										
45	28										
46	28										
47	29										
48	29										
49	30										
50	30										
51	31										
52	31										
53	33										
54	33										
55	34										
56	34										
57	35										
58	35										
59	36										
60	36										
61	37										
62	37										
63	38										
64	38										
65	39										
66	39										

4.7 Additional Attachments

None.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-734

APPLICANT: Ranbaxy Laboratories, Ltd.

DRUG PRODUCT: Oxcarbazepine Oral Suspension, 300 mg/5 mL

The Division of Bioequivalence has completed its review and has identified the following deficiencies:

1. Please submit potency (assay) data for the reference listed product (lot # H5144). In future submissions, please be sure to include potency data for both test and reference products within the bioequivalence section of your application.

2. The QC values reported in your original submission for the fasted oxcarbazepine (study #228_OXCAR_006) do not coincide with those you provided in your study amendment (electronic biosummary Table 14, submission date: 03 August 2007). Please explain which observations (n) were used to determine your mean concentrations and how you calculated the percent nominal values for each QC sample. In future submissions, please include the mean concentrations for both QC and standard samples instead of listing the nominal values; mean concentrations should be included in the biosummary tables for the pre- and within-study assay reports (e.g., Tables 4 and 14).

Sincerely yours,

{See appended electronic signature page}

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

4.8 Outcome Page

ANDA: 78-734

(NOTE: The clinical and analytical study sites are pending initial DSI inspection.)

1.	**Fasting Study**	Strength:	300 mg/5 mL
	(STF)	Outcome:	**IC**
	Submission Date(s)	22 December 2006	
	Clinical Site:	Ranbaxy – Clinical Pharmacology Unit Majeedia Hospital (2nd Floor), Jamia Hamdard (Hamdard University) Hamdard Nagar, New Delhi 110 062 India	
	Analytical Site:	Ranbaxy – Clinical Pharmacology & Pharmacokinetics Plot No. 20, Sector 18, Udyog Vihar Industrial Area Gurgaon 122 015, Haryana India	
2.	**Fed Study**	Strength:	300 mg/5 mL
	(STP)	Outcome:	**IC**
	Submission Date(s)	22 December 2006	
	Clinical Site:	Same as fasted site above	
	Analytical Site:	Same as fasted site above	
3.	**Study Amendment**	Strength(s):	300 mg/5 mL
	(STA)	Outcome:	**WC**
	Submission Date(s)	03 August 2007	
	Clinical Site:	Same as fasted site above	
	Analytical Site:	Same as fasted site above	

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

---

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

/s/

Kristopher Bough
8/22/2007 08:48:41 AM
BIOPHARMACEUTICS

Moheb H. Makary
8/22/2007 09:13:23 AM
BIOPHARMACEUTICS

Barbara Davit
8/22/2007 04:52:38 PM
BIOPHARMACEUTICS

BIOEQUIVALENCY AMENDMENT

ANDA 78-734

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Ranbaxy Laboratories Limited
U.S. Agent: Ranbaxy Inc.

TEL: 609-720-5666

FAX: 609-514-9797

ATTN: Abha Pant

FROM: Keri Suh

PROJECT MANAGER: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on December 22, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Oxcarbazepine Oral Suspension, 300 mg/5 mL.

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

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-734 APPLICANT: Ranbaxy

DRUG PRODUCT: Oxcarbazepine Oral Suspension, 300 mg/5 mL

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

1. Please provide a statement of your acceptance of the following dissolution method and specification:

Medium:	1% SDS in water
Volume:	900 mL
Temperature:	37°C
Apparatus:	USP Apparatus II (paddles)
Rotation:	75 RPM
Specification:	NLT (b)(4)% (Q) in 30 minutes

2. The Division of Bioequivalence has developed new data summary tables in a concise format consistent with the Common Technical Document (CTD). Please provide complete tables and send them with the rest of the bioequivalence submission. The tables are available in Word and PDF format under the title "Model Bioequivalence Data Summary Tables" in our website at http://www.fda.gov/cder/ogd/index.htm. To improve the efficiency of the Division, these tables should be provided in the ANDA submission.

Sincerely yours,

{See appended electronic signature page}

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

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

/s/

Barbara Davit
7/25/2007 06:42:55 PM
Signing for Dale P Conner

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	78-734		
Drug Product Name	Oxcarbazepine Oral Suspension		
Strength (s)	300 mg/5 mL		
Applicant Name	Ranbaxy		
Address	600 College Road Princeton, NJ		
Applicant's Point of Contact	Abha Pant		
Contact's Phone Number	609-720-5666		
Contact's Fax Number	609-516-9797		
Submission Date(s)	12-22-06		
First Generic	Yes		
Reviewer	Ethan M. Stier, R.Ph., Ph.D.		
Study Number (s)	**228_OXCAR_06 (FASTING)**	**228_OXCAR_06 (Fed)**	-
Study Type (s)	**Fasting**	**Fed**	-
Strength(s)	**300 mg/5 mL**	**300 mg/5 mL**	-
Clinical Site	Clinical Pharmacology Unit		
Clinical Site Address	Ranbaxy Research Laboratories Majeedia Hospital Hamdard Nagar, New Delhi, India		
Analytical Site	Ranbaxy Research Laboratories		
Analytical Address	Plot No 20, Sector 18, Udyog Vihar Industrial Area Gurgaon 122 015, Haryana, India		

EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP method for this product but there is an FDA-recommended method. The DBE recommends data driven specification (NLT (b)(4)% (Q) in 30 minutes) for the firm's test product. The dissolution testing with the FDA-recommended method is acceptable at the S1 level. The firm's proposed liberal specification (NLT (b)(4) % (Q) in 30 minutes) is not acceptable. The firm should acknowledge the FDA-recommended method and specification.

Note: the specification proposed for this test product is identical to the specification in the "OGD dataset".

The DBE will review the fasted and fed BE studies 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 all eight electronic summary biotables present			☒	☐	☐
Are electronic summary biotables in pdf format			☒	☐	☐

If the answer to either of the last two questions is no, indicate which summary biotables are

n/a

FDA METHOD

Oxcarbazepine

Dosage Form: Suspension

Medium: 1% SDS in water

Apparatus: II (Paddle)

Speed/RPMs: 75

Modify Date: 2/12/2004

Sampling Times: 10, 20, 30 and 45

Volume: 900

Notes:

Specification: NLT (b)(4)%, 30 min

Source: DBE DATABASE

TABLE 2. SUMMARY OF IN VITRO DISSOLUTION DATA

Table 4. Summary of In Vitro Dissolution Studies

Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)				Study Report Location
				10 min.	15 min.	20 min.	30 min.	
Oxcarbazepine Oral Suspension, 300 mg/5 mL; Batch 6530601	Oral Suspension	Medium: 1% SLS in water Volume: 900 mL Apparatus: USP Apparatus II RPM: 75 Temperature: 37° C	12	88 (84-91)	91 (87-94)	92 (91-93)	93 (91-95)	Module 5 Page: 6466
Trileptal® Oral Suspension, 300 mg/5 mL Batch H5144	Oral Suspension		12	99 (97-102)	99 (97-102)	99 (98-102)	99 (98-102)	Module 5 Page: 6466

COMMENTS:

1. The dissolution testing conducted by the firm is acceptable.

2. The firm's proposed specification is not acceptable. The firm will be requested to accept the data driven specification of NLT (b)(4)% (Q) in 30 minutes.

DEFICIENCY COMMENTS:

1. The firm should acknowledge the FDA recommended method and data driven specification.

2. In order to improve the review process, the Division of Bioequivalence requests that you provide the in-vivo study data summary, dissolution data and formulation data in the format specified in the attached template. This template incorporates some elements of the CTD format. We request that you provide the study summaries in this template in an electronic file. We hope to improve the efficiency of our review process and your cooperation is greatly appreciated. It would be helpful if you could provide this information for any other applications pending in the Division and in applications to be submitted in the future.

RECOMMENDATIONS:

1. The dissolution testing conducted by Ranbaxy on its Oxcarbazepine Oral Suspension, 300 mg/5 mL is incomplete due to deficiency #1.

BIOEQUIVALENCE DEFICIENCIES

ANDA:78-734 APPLICANT: Ranbaxy

DRUG PRODUCT: Oxcarbazepine Oral Suspension
300 mg/5 mL

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

1. Please provide a statement of your acceptance of the following dissolution method and specification:

Medium:	1% SDS in water
Volume:	900 mL
Temperature:	37°C
Apparatus:	USP Apparatus II (paddles)
Rotation:	75 RPM
Specification:	NLT (b)(4)% (Q) in 30 minutes

2. The Division of Bioequivalence has developed new data summary tables in a concise format consistent with the Common Technical Document (CTD). Please provide complete tables and send them with the rest of the bioequivalence submission. The tables are available in Word and PDF format under the title "Model Bioequivalence Data Summary Tables" in our website at http://www.fda.gov/cder/ogd/index.htm. To improve the efficiency of the Division, these tables should be provided in the ANDA submission.

Sincerely yours,

{See appended electronic signature page}

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

BIOEQUIVALENCE - DISSOLUTION INCOMPLETE Submission date: 12-22-06

[NOTE: The in vitro testing is incomplete. The fasting and fed BE studies are pending review]

1. DISSOLUTION (Dissolution Data)	Strength:	300 mg/5 mL
	Outcome:	**IC**

Outcome Decisions: IC –Incomplete

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

/s/

Ethan Stier
7/25/2007 10:11:04 AM
BIOPHARMACEUTICS

Shriniwas G. Nerurkar
7/26/2007 08:30:19 AM
BIOPHARMACEUTICS

Barbara Davit
7/27/2007 03:18:56 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-734

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 78-734 Applicant Ranbaxy Laboratories Limited
Drug Oxcarbazepine Oral Suspension Strength(s) 300 mg/5 mL

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

REVIEWER: **DRAFT Package** **FINAL Package**

1. **Martin Shimer** Date 26 May 2009 Date 6/26/09
Chief, Reg. Support Branch Initials MHS Initials rlw

Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD = Trileptal NDA# 21-285
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked Granted
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☒ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☒ Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☒ No ☐
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☒ No ☐
Type of Letter: Full Approval.
Comments: ANDA submitted on 12/26/2006, BOS=Trileptal NDA 21-285, PIV to '525, applicant originally addressed the I-478+ped with a carve-out. ANDA ack for filing with PIV on 12/26/2006 (LO dated 3/29/2007). Patent Amendment submitted on 5/17/2007-RR from Novartis in Florham Park NJ signed and dated 4/23/2007, RR from Novartis AG in Basel CH signed and dated 5/2/2007. Patent Amendment submitted on 7/2/2007-Ranbaxy asserts that they were not sued within 45 days.

If they haven't already the sponsor will need to submit revised labeling which includes reference to the I-478+ped exclusivity which expired on 4/28/2009. OGD had previously disseminated a labeling template to address this exclusivity.

Application is eligible for Full Approval with 180 day exclusivity. In order to retain eligibility for exclusivity this application must be approved by no later than 6/26/2009.

2. Project Manager, Lisa Kwok Team 11 Review Support Branch Date 5/22/09 Date 6/10/09
Initials LK Initials lk

Original Rec'd date 12/26/06
Date Acceptable for Filing 12/26/06
Patent Certification (type) IV
Date Patent/Exclus.expires
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐
Priority Approval Yes ☒ No ☐
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio reviews tabbed Yes ☐ No ☐
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 3/17/08
Date of Office Bio Review 9/27/07
Date of Labeling Approv. Sum 6/10/09
Date of Sterility Assur. App. _____
Methods Val. Samples Pending Yes ☐ No ☐
MV Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☐

Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement
Reviewer: Labeling Team Leader:
Date6/10/09 Date6/10/09
Name/Initialslk for MS Name/Initialslk for lg
Comments:

From: Golson, Lillie D
Sent: Wednesday, June 10, 2009 9:10 PM
To: Kwok, Lisa; Golson, Lillie D
Subject: FW: Labeling sign-off: ANDA 78-734 Ranbaxy Oxcarbazepine Susp

Hi Lisa,

From a labeling standpoint, this application is acceptable for approval. please endorse the AP routing slip on behalf of Melaine and me.

Thanks

From: Shin, Melaine M
Sent: Wednesday, June 10, 2009 3:28 PM
To: Kwok, Lisa
Cc: Golson, Lillie D
Subject: FW: Labeling sign-off: ANDA 78-734 Ranbaxy Oxcarbazepine Susp

Hi Lisa,

The labeling is acceptable. Please wait for Lillie's concurrence.

Thanks,
Melaine

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 10Jun09
OGD Regulatory Counsel, Post-MMA Language Included ☐ InitialsDTR
Comments:Changes to AP ltr saved to V drive. reviewed again on 25Jun09.

5. Div. Dir./Deputy Dir. Date6/25/09
Chemistry Div. III InitialsDSG

Comments:cmc acceptable.

6. Frank Holcombe **First Generics Only** Date6/26/09
Assoc. Dir. For Chemistry Initials RMP Comments: (First generic drug review)
CMC is satisfactory based on some commitments provided by the applicant post AP of this ANDA.

7. Vacant Date_____ Deputy Dir., DLPS
Initials_____
RLD = Trileptal Oral Suspension, 300 mg/5 mL
Novartis Pharmaceuticals Corp. NDA 21-285

8. Peter Rickman Date 6/26/09
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes□ No□;Pending Legal Action: Yes □ No □; Petition: Yes□ No□ Comments: Bioequivalence studies (fasting and non-fasting) on 2X300 mg/5 mL
(600 mg) found acceptable. In-vitro dissolution testing also found acceptable. DSI inspection of sites under ANDA (b) (4) found acceptable. Office-level bio endorsed 9/27/07 and 8/18/08.

Final-printed labeling (FPL) found acceptable for approval 6/10/09.

CMC found acceptable for approval (Chemistry Review #3).

First-generic CMC audit completed - R.Patel, Ph.D.

OR

8. Robert L. West Date 6/26/09
Deputy Director, OGD Initials RLWest
Para.IV Patent Cert: Yes☒ No□; Pending Legal Action: Yes□ No☒; Petition: Yes□ No☒
Press Release Acceptable □
Comments: Acceptable EES dated 3/17/08 (Verified 6/26/09). No "OAI" Alerts noted.

Ranbaxy submitted a paragraph IV certification to the '525 patent, but was not sued within the 45-day period. There are no additional patents or exclusivity listed in the current "Orange Book" for this drug product.

Ranbaxy is eligible for 180-day generic drug exclusiviry for this drug product.

This ANDA is recommended for approval.

9. Gary Buehler Date 6/26/09
Director, OGD Initials rlw/for

Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Lisa Kwok Team 11 Date6/26/09

Review Support Branch Initials lk
_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
11:55amTime notified of approval by phone
11:57amTime approval letter faxed

FDA Notification:
6/26/09Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
6/26/09Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

EER DATA:

EES Data for: 078734

****** Compliance Recommendations ******

App No	Doc Seq No	Date	OC Recommendation
078734	000	3/17/2008	ACCEPTABLE

****** EER Table ******

CFN	Name	Profile Code	Last Milestone Name	Last Milestone Date	Last Status	Last Status Date	OAI Alert/ Effective Date
2248121	OHM LABORATORIES INC	CTL	OC RECOMMENDATION	3/17/2008	AC	3/17/2008	None
(b) (4)		CSN	OC RECOMMENDATION	(b) (4)	AC	(b) (4)	None

[redacted] (b) (4)	CTL	OC RECOMMENDATION	[redacted] (b) (4)	AC	[redacted] (b) (4)	None
1320750 OHM LABORATORIES INC	LIQ	OC RECOMMENDATION	4/2/2007	AC	4/2/2007	None
[redacted] (b) (4)	CTL	OC RECOMMENDATION	[redacted] (b) (4)	AC	[redacted] (b) (4)	None

COMIS TABLE:

Comis Application Table Data for Application No: 078734

***** Note: For Enterprise Search Files you may have to click and close the new window on first use***

Back to Search Form ***COMIS Pool Reviewers*** **ES DFS Files Only** **ES - All Files** **EDR** **Cycles**

Drug Name: OXCARBAZEPINE

Potency: 300 MG/5 ML Dosage Form: SUS APPL Type: N

Applicant: RANBAXY LABS

Status Code: PN Status Date: 6/25/2009 Clock Date: 12/26/2006 USP: N Org: 600

Therapeutic Drug Class: ANTICONVULSANTS

Patent Certification: 4 Patent Expiration Date: PEPFAR:

Incom Doc Type		*Supp Mod Type*			*Decision Code*		*Status code*	
N *Volume Locator*	000	XP	5/15/2007	5/17/2007	CL	5/17/2007		3100024
N *Volume Locator*	000	AM	7/30/2007	7/31/2007	NM	8/28/2008		3136682

N Volume Locator	000	MC	7/9/2007	7/10/2007	CL	7/10/2007				3127303		
N Volume Locator	000	AB	8/3/2007	8/6/2007	OP	8/6/2007				3139189		
N Volume Locator	000	AF	8/17/2007	8/20/2007	OP	8/20/2007				3145249		
N Volume Locator	000		12/22/2006	12/26/2006	NM	6/20/2007	PN	6/25/2009	-1	3035975	12/2/2008	
N Volume Locator	000	XP	6/29/2007	7/2/2007	CL	7/2/2007				3123454		
N Volume Locator	000	AF	9/17/2007	9/18/2007	OP	9/18/2007				3158657		
N Volume Locator	000	AB	9/11/2007	9/13/2007	OP	9/13/2007				3156689		
N Volume Locator	000	AM	6/16/2008	6/17/2008	NM	8/28/2008				3969183		
N Volume Locator	000	AM	12/1/2008	12/2/2008	OP	12/2/2008				4052150		
N Volume Locator	000	AX	5/11/2009	5/11/2009	GR	5/11/2009				4133350		
N Volume Locator	000	AF	5/21/2009	5/22/2009	OP	5/22/2009				4139814		
N Volume Locator	000	AM	6/25/2009	6/25/2009	OP	6/25/2009				4156188		

Comis Document Table Data

ORANGE BOOK PRINT OFF:

Patent and Exclusivity Search Results from query on Appl No 021285 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
021285	001	7037525	Feb 12, 2018			U-724	
021285	001	7037525*PED	Aug 12, 2018				

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021285	001	PED	Apr 28, 2009
021285	001	I-478	Oct 28, 2008

Additional information:

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

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

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:

- Orange Book Data - **Monthly**
- Generic Drug Product Information & Patent Information - **Daily**
- Orange Book Data Updated Through May, 2009
- Patent and Generic Drug Product Data Last Updated: June 25, 2009

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

/s/

Lisa Kwok

6/26/2009 11:59:58 AM

COMPLETE RESPONSE -- MINOR

ANDA 78-734

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

APPLICANT: Ranbaxy Laboratories Limited
U.S. Agent: Ranbaxy Inc.

ATTN: Usha Sankaran

FROM: Lisa Kwok

TEL: 609-720-8061

FAX: 609-514-9797

FDA CONTACT PHONE: 240-276-8494

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 22, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Oxcarbazepine Oral Suspension, 300 mg/5 mL.

Reference is also made to your amendments dated July 30, 2007 and June 16, 2008.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

We have completed the review of your ANDA and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (__2__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. Upon OGD's acceptance for filing of your ANDA, it was determined that an adequate amount of information was submitted to allow for review of your Bioequivalence and Microbiology data. You will be notified in a separate communication of any further deficiencies identified during our review of your Bioequivalence and Microbiology data If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-734 APPLICANT: Ranbaxy Laboratories Limited

DRUG PRODUCT: Oxcarbazepine Oral Suspension, 300 mg/5 mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

(b) (4)

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

Please submit any additional stability data for the exhibit batches that may be available.

Sincerely yours,

{See appended electronic signature page}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Aloka Srinivasan

8/28/2008 10:27:59 AM

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

FROM: Cecelia M. Parise
Regulatory Policy Advisor to the Director
Office of Generic Drugs (HFD-600)

THROUGH: Gary Buehler
Director
Office of Generic Drugs

TO: The Files for all Pending ANDAs for Antiepileptic Drug Products

SUBJECT: Generic Drug Products for the Treatment of Epilepsy

UCB, Inc. (UCB) submitted a citizen petition (2006P-0405) on October 3, 2006, regarding the safe and effective use of antiepileptic drugs. The petition does not request that FDA delay generic antiepileptic drug approval, but instead requests labeling changes for the entire antiepileptic drug class, including brand-name drugs. This memorandum is based upon a preliminary review of UCB's petition; it is not intended to be a response to the petition and may not address all information set forth in UCB's petition.

Specifically, the petition requests that the Agency:

1. Require that the full prescribing information of all antiepileptic drugs contain the following language under "Warnings" or "Warnings and Precautions," as applicable: "Physicians and pharmacists should exercise extreme caution when switching patients who are seizure free or whose seizures are well controlled on a given antiepileptic drug. In general, switches in patients who are well controlled and have achieved stability on a given antiepileptic drug should be undertaken only when medically necessary and with full disclosure to the treating physician and the patient." This warning should also appear in the "Highlights" section, as applicable, for labels subject to FDA's final labeling rule of January 24, 2006 (21 C.F.R. 201.56 and 201.57);

2. Add a discussion of antiepileptic drugs to Section 1.8 (Description of Special Situations) of the Orange Book. This discussion should highlight the particular risks associated with substitution of antiepileptic drugs. It should also recommend against switches of antiepileptic drugs in patients who are seizure free or whose seizures are well controlled; and

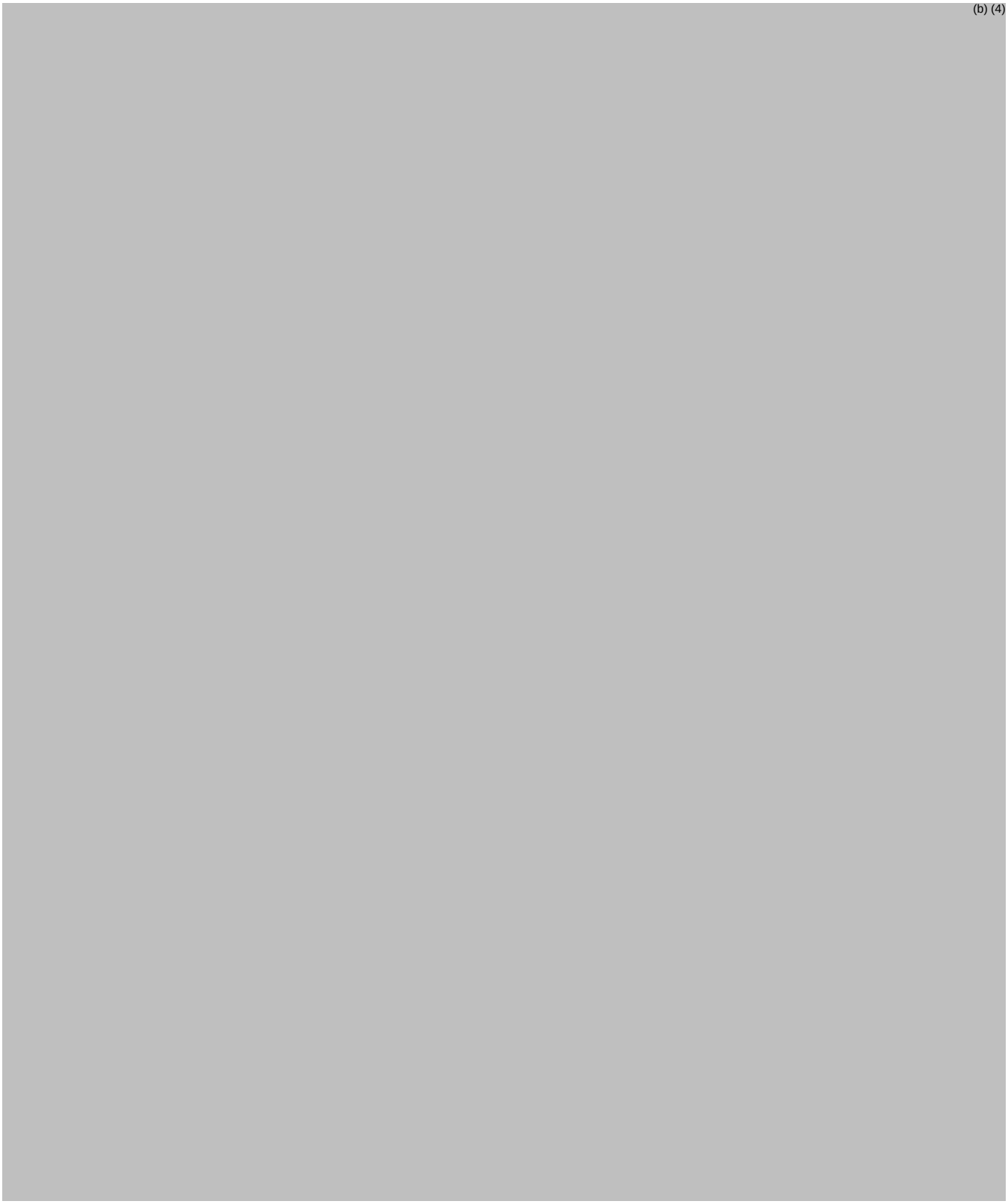
3. Narrow FDA's bioequivalence range for generic versions of antiepileptic drugs to require a showing, at the 90% confidence interval, that the lower limit is at least 90% of its reference listed drug.

Petition at 1-2.

UCB is the holder of NDAs 21-035, 21-505, and 21-872 for Keppra (levetiracetam). UCB's petition pertains to levetiracetam as well as other antiepileptic agents such as ethosuximide, primidone, topirimate, divalproex, oxcarbazepine, and carbamazepine.

Based upon a preliminary review, it (b) (4)

(b) (4)


(b) (4)

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

/s/

Patricia L. Downs
4/18/2008 10:37:56 AM
SECRETARY

Cecelia Parise
4/18/2008 10:43:30 AM
CSO

Gary Buehler
4/18/2008 02:43:40 PM
DIRECTOR

Telephone Fax

ANDA 78-734
OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8976

TO: Ranbaxy Laboratories Limited

TEL: 609-720-5666

ATTN: Abha Pant

FAX: 609-514-9797

FROM: Melaine Shin, Labeling Reviewer

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 Oxcarbazepine Oral Suspension

Pages (including cover): 4

SPECIAL INSTRUCTIONS:

Labeling Comments: See Attached

*****Please send me an email confirming the receipt of this fax and I will provide the generic labeling template for Oxcarbazepine.**

Email: melaine.shin@fda.hhs.gov

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

ANDA Number:	78-734
Date of Submission:	December 22, 2006
Applicant's Name:	Ranbaxy Laboratories Limited
Established Name:	Oxcarbazepine Oral Suspension, 300 mg/5 mL.
Proposed Proprietary Name:	None

Labeling Deficiencies:

CONTAINER: 250 mL

- Delete "Each 5 mL contains…" statement from the principal display panel.

CARTON: 250 mL.

- Relocate "Each 5 mL contains…." statement to the side display panel.

PROFESSIONAL PACKAGE INSERT

- Please note that the reference listed drug Trileptal®, has a marketing exclusivity, I-478: FOR USE AS ADJUNCTIVE THERAPY IN THE TREATMENT OF PARTIAL SEIZURES IN CHILDREN WITH EPILEPSY AGED 2-4 YEARS which expires on April 28, 2009. We consulted the New Drug Division and the Pediatric and Maternal Health Staff and the Division of Neurology Products, and now have a generic labeling template reflecting the carve outs of the information protected by exclusivity I-478 and applicable disclaimers. Please revise your insert labeling according to the attached generic labeling template.

- In the DESCRIPTION section, revise "Oxcarbazepine oral suspension contain…." To read "Oxcarbazepine oral suspension cotains…" and "hydroxy ethylcellulose" to read "hydroxyethyl cellulose"

Please revise your labeling, as instructed above, and submit the revised labeling in final print.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please

provide a side-by-side comparison of your proposed labeling with attached generic labeling template 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

Attachment: Generic oxcarbazepine model labeling

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

/s/

Lillie Golson
7/30/2007 07:05:21 PM
Lillie Golson for Wm. Peter Rickman

MINOR AMENDMENT

ANDA 78-734

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Ranbaxy Laboratories Limited
U.S. Agent: Ranbaxy Inc.

ATTN: Abha Pant

FROM: Lisa Kwok

TEL: 609-720-5666

FAX: 609-514-9797

PROJECT MANAGER: (301) 827-5739

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 22, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Oxcarbazepine Oral Suspension, 300 mg/5 mL.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__2__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments provided.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-734 APPLICANT: Ranbaxy Laboratories Limited

DRUG PRODUCT: Oxcarbazepine Oral Suspension, 300 mg/5 mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

(b) (4)

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

1. Please submit any additional stability data for the exhibit batches that may be available.

2. Labeling and bioequivalence portions of the ANDA are pending review.

3. An acceptable compliance evaluation for the firms referenced in the ANDA is required for approval.

Sincerely yours,

{See appended electronic signature page}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Shing Hou Liu
6/20/2007 03:33:17 PM
For Vilayat A. Sayeed, Ph.D.

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
***** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ *****

ANDA #: 78-734 **FIRM NAME**: RANBAXY LABORATORIES LIMITED

PIV: YES **Electronic or Paper Submission:** CTD FORMAT PAPER

RELATED APPLICATION(S):

First Generic Product Received? YES

DRUG NAME: OXCARBAZEPINE
DOSAGE FORM: ORAL SUSPENSION, 300 MG/5 ML

Bio Assignments:		
☒ **BPH**	☐ **BCE**	☐ **Micro Review (No)**
☐ **BST**	☒ **BDI**	

Random Queue: 11
Chem Team Leader: Liu, Shing Hou PM: Lisa Kwok Labeling Reviewer: Melaine Shin

Letter Date: DECEMBER 22, 2006 **Received Date**: DECEMBER 29, 2006

Comments: EC- 1 YES **On Cards:** YES
Therapeutic Code: 2010300 ANTICONVULSANTS

Archival copy: CTD FORMAT PAPER **Sections** I
Review copy: YES E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Stanley Shepperson	**Recommendation:**
Date 28-Mar-07	☒ **FILE** ☐ **REFUSE to RECEIVE**

Supervisory Concurrence/Date: Martin Shimer **Date: ____**

ADDITIONAL COMMENTS REGARDING THE ANDA:

Bio first-generic audit is acceptable.

MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2** **Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: DECEMBER 22, 2006	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) YES	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) or Disclosure Statement **(Form FDA 3455)** - YES	☒
1.3.5	**1.3.5.1** **Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations- U.S. PATENT No. 7,037,525 **1.3.5.2** **Patent Certification** 1. Patent number(s) '525 patent 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☐ PIII ☐ PIV ☒ No Relevant Patents ☐ 3. Expiration of Patent(s): 2-12-2018 a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES I-478 (expires 4-28-2009)	☒
1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient YES- DMF # (b) (4) b. Type III DMF authorization letter(s) for container closure -YES 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) -YES	☒
1.12.11	**Basis for Submission** NDA# : 21-285 Ref Listed Drug: TRILEPTAL Firm: NOVARTIS ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use SAME 2. Active ingredients SAME 3. Inactive ingredients JUSTIFIED 4. Route of administration SAME 5. Dosage Form SAME 6. Strength SAME	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): NO	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) -YES **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained -YES **1.14.1.3** 1 package insert (content of labeling) submitted electronically -YES ***Was a proprietary name request submitted? NO (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained -YES **1.14.3.3** 1 RLD label and 1 RLD container label -YES **HOW SUPPLIED:** 300 mg/5 mL Oral Suspension: 250 mL bottles	☒

ACCEPTABLE

2.3	**Quality Overall Summary** **E-Submission: __x__PDF (archive) __x_ Word Processed e.g., MS Word** A model Quality Overall Summary for an immediate release table and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ **Question based Review (QbR) __x__ YES _____ NO** **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient) YES** **2.3.S.1** **General Information** **2.3.S.2** **Manufacture** **2.3.S.3** **Characterization** **2.3.S.4** **Control of Drug Substance** **2.3.S.5** **Reference Standards or Materials** **2.3.S.6** **Container Closure System** **2.3.S.7** **Stability** **2.3.P** **Drug Product -YES** **2.3.P.1** **Description and Composition of the Drug Product** **2.3.P.2** **Pharmaceutical Development** **2.3.P.2.1** **Components of the Drug Product** **2.3.P.2.1.1** **Drug Substance** **2.3.P.2.1.2** **Excipients** **2.3.P.2.2** **Drug Product** **2.3.P.2.3** **Manufacturing Process Development** **2.3.P.2.4** **Container Closure System** **2.3.P.3** **Manufacture** **2.3.P.4** **Control of Excipients** **2.3.P.5** **Control of Drug Product** **2.3.P.6** **Reference Standards or Materials** **2.3.P.7** **Container Closure System** **2.3.P.8** **Stability**	☒

2.7	**Clinical Summary (Bioequivalence)** **E-Submission: __X__PDF (archive) _X__ Word Processed e.g., MS Word** **2.7.1** **Summary of Biopharmaceutic Studies and Associated Analytical Methods -YES** **2.7.1.1** **Background and Overview -YES** **2.7.1.2** **Summary of Results of Individual Studies -YES** **2.7.1.3** **Comparison and Analyses of Results Across Studies -YES** 1. Summary Bioequivalence tables: Table 1. Summary of Comparative Bioavailability (BA) Studies -YES Table 2. Statistical Summary of the Comparative BA Data -YES Table 4. Summary of In Vitro Dissolution Studies -YES **2.7.1.4** **Appendix -YES**	☒

MODULE 3

3.2.S DRUG SUBSTANCE

ACCEPTABLE

3.2.S.1	**General Information -YES** **3.2.S.1.1** **Nomenclature -YES** **3.2.S.1.2** **Structure -YES** **3.2.S.1.3** **General Properties -YES**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Addresses of bulk manufacturers YES 2. Manufacturing Responsibilities YES 3. Type II DMF number for API –YES. DMF (b) (4) 4. CFN or FEI numbers -YES	☒
3.2.S.3	**Characterization- SEE DMF #** (b) (4)**.**	☒

3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1** **Specification** Testing specifications and data from drug substance manufacturer(s) -YES **3.2.S.4.2** **Analytical Procedures** -YES **3.2.S.4.3** **Validation of Analytical Procedures- YES** **1.** Spectra and chromatograms for reference standards and test samples YES 2. Samples-Statement of Availability and Identification of: a. Drug Substance YES b. Same lot number(s) **3.2.S.4.4** **Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) -YES 2. Applicant certificate of analysis -YES **3.2.S.4.5** **Justification of Specification- REFER TO DMF #** (b) (4)	☒
3.2.S.5	**Reference Standards or Materials YES**	☒
3.2.S.6	**Container Closure Systems- SEE DMF #** (b) (4)	☒
3.2.S.7	**Stability- SEE DMF** (b) (4)	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1) Unit composition YES 2) Inactive ingredients are appropriate per IIG . Excipients acceptable per IIG and filing regulations.	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report YES	☒
3.2.P.3	**Manufacture** **3.2.P.3.1** **Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) YES 2. CGMP Certification: YES 3. Function or Responsibility YES 4. CFN or FEI numbers YES **3.2.P.3.2** **Batch Formula** Batch Formulation YES **3.2.P.3.3** **Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process -YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES 3. If sterile product: Aseptic fill / Terminal sterilization N/A 4. Reprocessing Statement YES **3.2.P.3.4** **Controls of Critical Steps and Intermediates- YES** **3.2.P.3.5** **Process Validation and/or Evaluation** 1. Microbiological sterilization validation 2. Filter validation (if aseptic fill) **PROPOSED COMMERCIAL BATCH SIZE:** (b) (4)	☒

3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified – YES (SECTION 3.2.R) P. 56. **3.2.P.4.1** **Specifications** 1. Testing specifications (including identification and characterization) YES 2. Suppliers' COA (specifications and test results) YES **3.2.P.4.2** **Analytical Procedures- YES** **3.2.P.4.3** **Validation of Analytical Procedures- YES** **3.2.P.4.4** **Justification of Specifications** Applicant COA - YES	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1** **Specification(s)** -YES **3.2.P.5.2** **Analytical Procedures** -YES **3.2.P.5.3** **Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form -YES 2. Same lot numbers YES. LOT # 6530601 **3.2.P.5.4** **Batch Analysis** Certificate of Analysis for Finished Dosage Form -YES **3.2.P.5.5** **Characterization of Impurities- SEE DMF** (b) (4) **3.2.P.5.6** **Justification of Specifications- YES**	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) -YES 2. Components Specification and Test Data -YES 3. Packaging Configuration and Sizes -YES 4. Container/Closure Testing -YES 5. Source of supply and suppliers address -YES	☒
3.2.P.8	**3.2.P.8.1** **Stability (Finished Dosage Form)** 1. Stability Protocol submitted YES 2. Expiration Dating Period YES- 24 MONTHS **3.2.P.8.2** **Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments -YES **3.2.P.8.3** **Stability Data** 1. 3 month accelerated stability data -YES 2. Batch numbers on stability records the same as the test batch **-YES**	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S** **Executed Batch Records for drug substance (if available) NO** **3.2.R.2.S** **Comparability Protocols NO** **3.2.R.3.S** **Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation -YES **<u>300 mg/5 mL Oral Suspension (Lot # 6530601)</u>** Theoretical Yield - (b) (4) Actual Yield - (b) (4) Packaged Yield - (b) (4) **3.2.R.1.P.2** **Information on Components** -YES **3.2.R.2.P** **Comparability Protocols** -NO **3.2.R.3.P** **Methods Validation Package** -YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5

CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies- YES**	☒
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same? 1 STRENGTH ONLY** a. Comparison of all Strengths (check proportionality of multiple strengths) b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **2. Lot Numbers of Products used in BE Study(ies):** RLD: H5144 ANDA: (b) (4) **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below) YES	☒

5.3.1.2

Comparative BA/BE Study Reports

1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC)- YES
2. Summary Bioequivalence tables:

Table 6. Demographic Profile of Subjects Completing the Comparative BA Study -YES
Table 7. Incidence of Adverse Events in Individual Studies -YES
Table 8. Reanalysis of Study Samples -YES

5.3.1.3

In Vitro-In-Vivo Correlation Study Reports

1. Summary Bioequivalence tables:

Table 4. Summary of In Vitro Dissolution Studies -YES

Table 5. Formulation Data -YES

5.3.1.4

Reports of Bioanalytical and Analytical Methods for Human Studies

1. Summary Bioequivalence table:

Table 3. Bioanalytical Method Validation -YES

5.3.7

Case Report Forms and Individual Patient Listing - YES

5.4 Literature References

Possible Study Types:

Study Type

IN-VIVO PK STUDY(IES) (i.e., fasting/fed/sprinkle) FASTING AND FED ON 300 MG/ 5 ML

1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC)- YES
2. EDR Email: Data Files Submitted: YES SENT TO EDR
3. In-Vitro Dissolution: YES

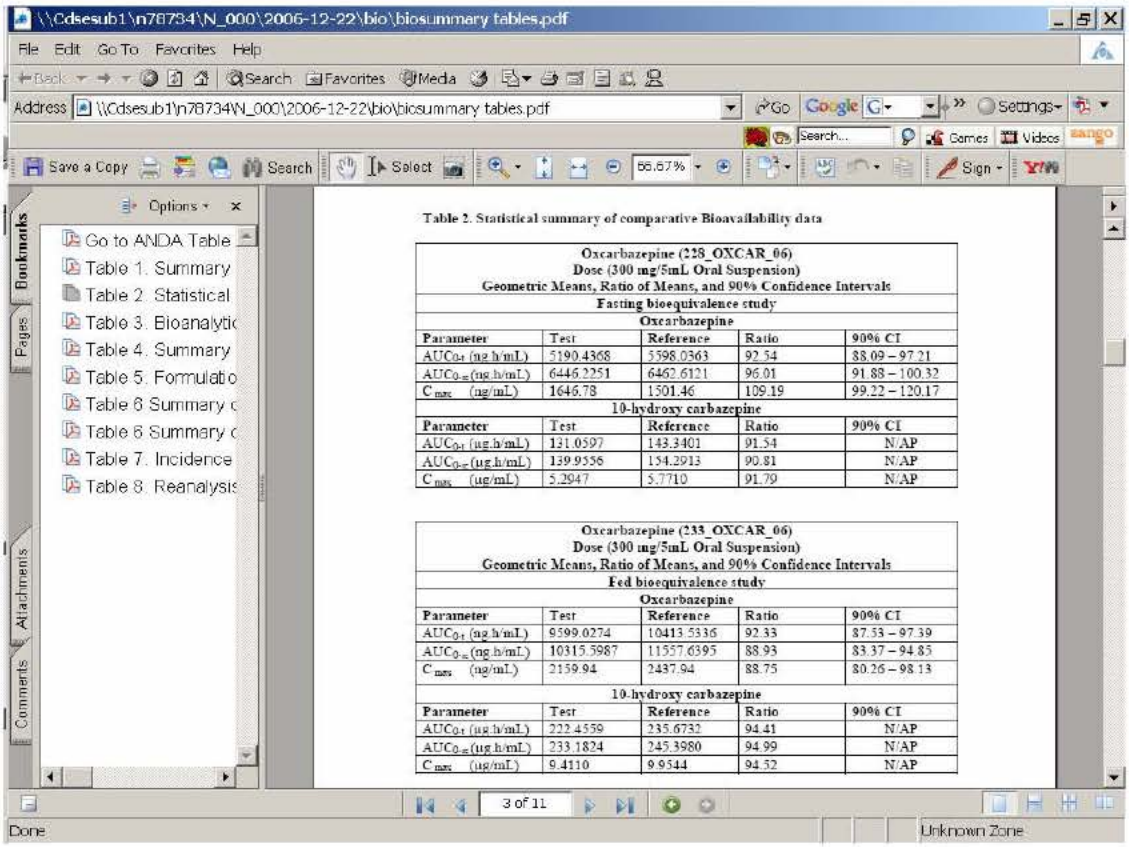


Table 2. Statistical summary of comparative Bioavailability data

Oxcarbazepine (228_OXCAR_06) Dose (300 mg/5mL Oral Suspension) Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting bioequivalence study				
Oxcarbazepine				
Parameter	Test	Reference	Ratio	90% CI
AUC_{0-t} (ng.h/mL)	5190.4368	5598.0363	92.54	88.09 – 97.21
$AUC_{0-\infty}$ (ng.h/mL)	6446.2251	6462.6121	96.01	91.88 – 100.32
C_{max} (ng/mL)	1646.78	1501.46	109.19	99.22 – 120.17
10-hydroxy carbazepine				
Parameter	Test	Reference	Ratio	90% CI
AUC_{0-t} (µg.h/mL)	131.0597	143.3401	91.54	N/AP
$AUC_{0-\infty}$ (µg.h/mL)	139.9556	154.2913	90.81	N/AP
C_{max} (µg/mL)	5.2947	5.7710	91.79	N/AP

Oxcarbazepine (233_OXCAR_06) Dose (300 mg/5mL Oral Suspension) Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed bioequivalence study				
Oxcarbazepine				
Parameter	Test	Reference	Ratio	90% CI
AUC_{0-t} (ng.h/mL)	9599.0274	10413.5336	92.33	87.53 – 97.39
$AUC_{0-\infty}$ (ng.h/mL)	10315.5987	11557.6395	88.93	83.37 – 94.85
C_{max} (ng/mL)	2159.94	2437.94	88.75	80.26 – 98.13
10-hydroxy carbazepine				
Parameter	Test	Reference	Ratio	90% CI
AUC_{0-t} (µg.h/mL)	222.4559	235.6732	94.41	N/AP
$AUC_{0-\infty}$ (µg.h/mL)	233.1824	245.3980	94.99	N/AP
C_{max} (µg/mL)	9.4110	9.9544	94.52	N/AP

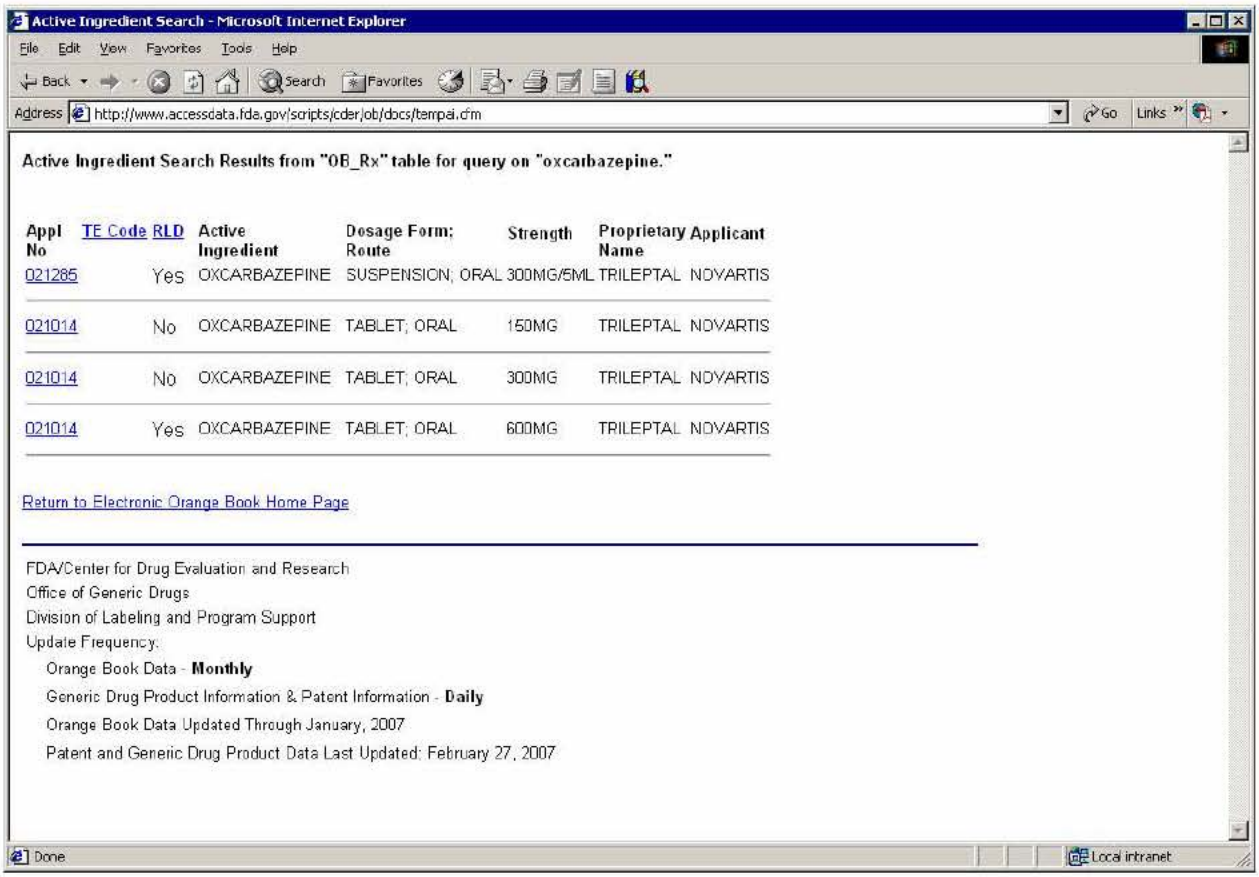
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% or 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐

TRANSDERMAL DELIVERY SYSTEMS NO

Study Type

1. In-Vivo PK Study
    1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC)
    2. In-Vitro Dissolution
    3. EDR Email: Data Files Submitted
2. Adhesion Study
3. Skin Irritation/Sensitization Study

Updated 10/10/2006 C. Bina



Active Ingredient Search - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Search Favorites

Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm Go Links

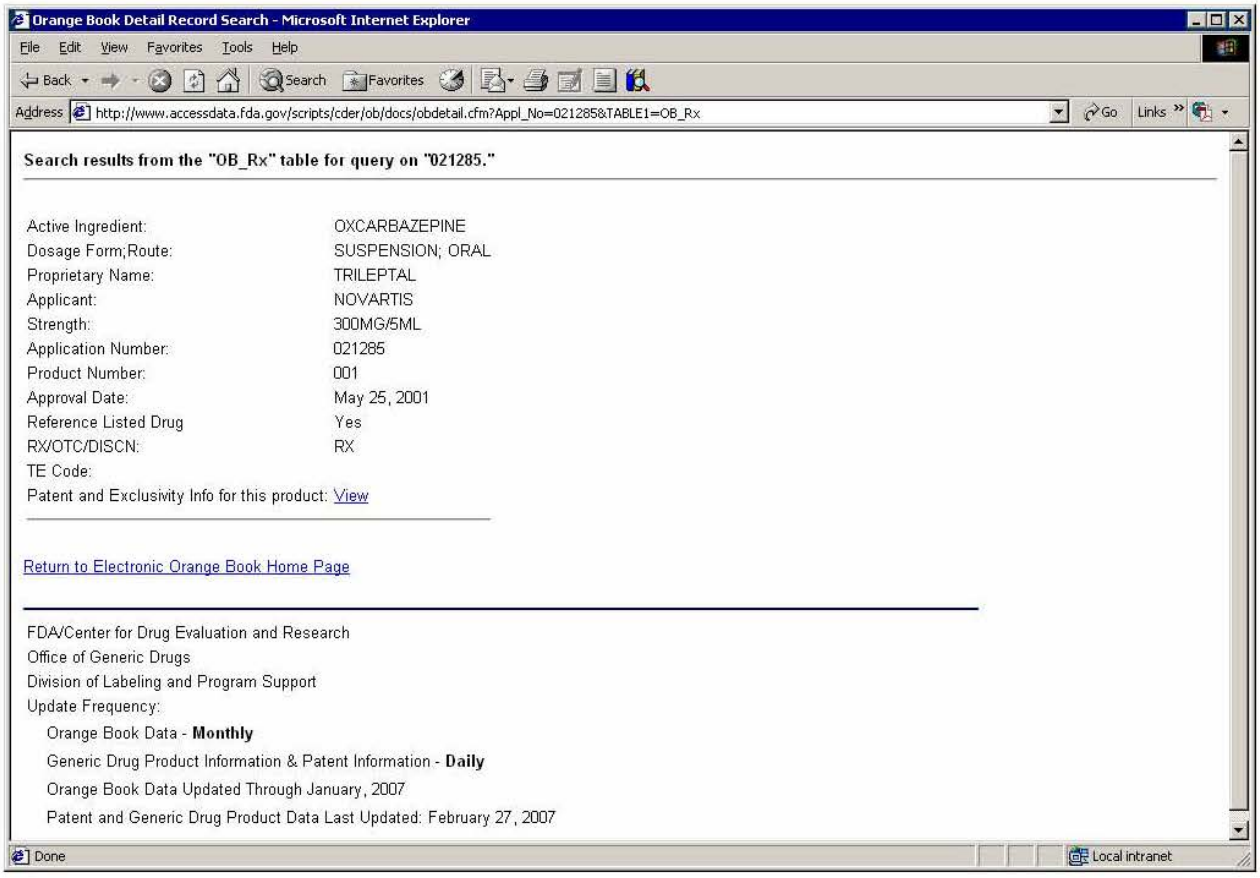
Active Ingredient Search Results from "OB_Rx" table for query on "oxcarbazepine."

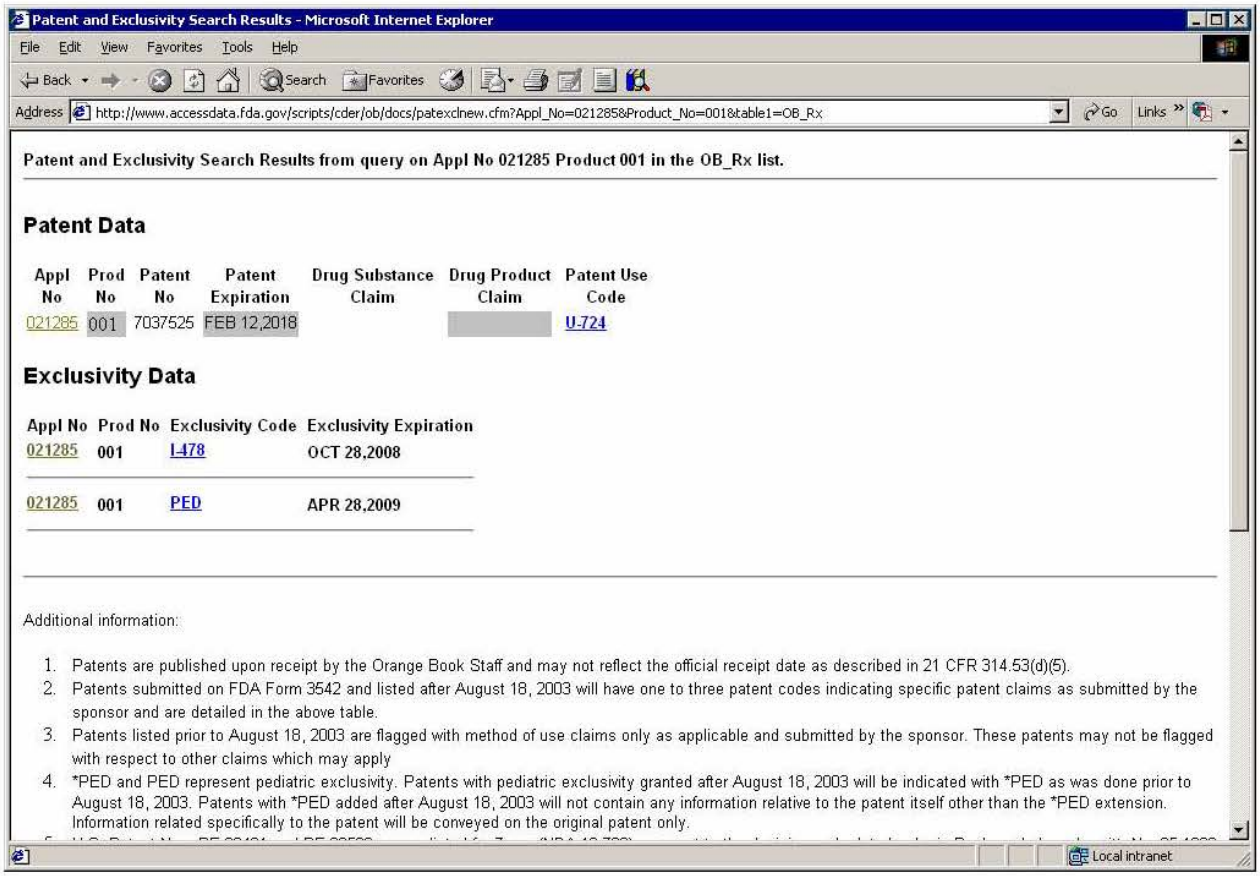
Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
021285		Yes	OXCARBAZEPINE	SUSPENSION; ORAL	300MG/5ML	TRILEPTAL	NOVARTIS
021014		No	OXCARBAZEPINE	TABLET; ORAL	150MG	TRILEPTAL	NOVARTIS
021014		No	OXCARBAZEPINE	TABLET; ORAL	300MG	TRILEPTAL	NOVARTIS
021014		Yes	OXCARBAZEPINE	TABLET; ORAL	600MG	TRILEPTAL	NOVARTIS

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through January, 2007
Patent and Generic Drug Product Data Last Updated: February 27, 2007

Done Local intranet


Orange Book Detail Record Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=021285&TABLE1=OB_Rx
Go Links
Search results from the "OB_Rx" table for query on "021285."
Active Ingredient: OXCARBAZEPINE
Dosage Form;Route: SUSPENSION; ORAL
Proprietary Name: TRILEPTAL
Applicant: NOVARTIS
Strength: 300MG/5ML
Application Number: 021285
Product Number: 001
Approval Date: May 25, 2001
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through January, 2007
Patent and Generic Drug Product Data Last Updated: February 27, 2007
Done
Local intranet



Patent and Exclusivity Search Results from query on Appl No 021285 Product 001 in the OB_Rx list.

Patent Data

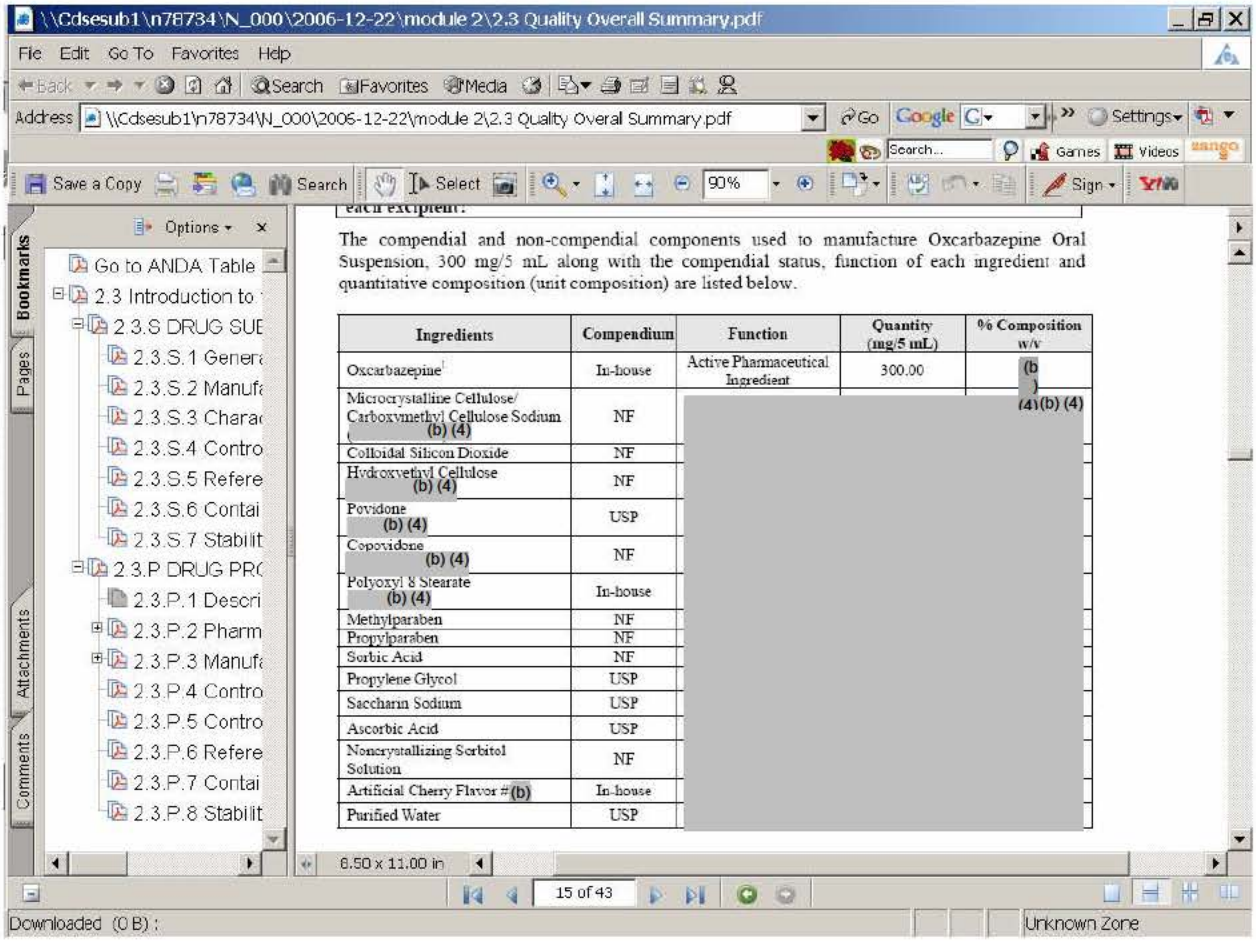
Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
021285	001	7037525	FEB 12,2018			U-724

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021285	001	I-478	OCT 28,2008
021285	001	PED	APR 28,2009

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.
3. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply
4. *PED and PED represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 18, 2003 will be indicated with *PED as was done prior to August 18, 2003. Patents with *PED added after August 18, 2003 will not contain any information relative to the patent itself other than the *PED extension. Information related specifically to the patent will be conveyed on the original patent only.



each excipient:

The compendial and non-compendial components used to manufacture Oxcarbazepine Oral Suspension, 300 mg/5 mL along with the compendial status, function of each ingredient and quantitative composition (unit composition) are listed below.

Ingredients	Compendium	Function	Quantity (mg/5 mL)	% Composition w/v
Oxcarbazepine	In-house	Active Pharmaceutical Ingredient	300.00	(b) (4)
Microcrystalline Cellulose/ Carboxymethyl Cellulose Sodium (b) (4)	NF			(b) (4)
Colloidal Silicon Dioxide	NF			
Hydroxyethyl Cellulose (b) (4)	NF			
Povidone (b) (4)	USP			
Copovidone (b) (4)	NF			
Polyoxyl 8 Stearate (b) (4)	In-house			
Methylparaben	NF			
Propylparaben	NF			
Sorbic Acid	NF			
Propylene Glycol	USP			
Saccharin Sodium	USP			
Ascorbic Acid	USP			
Noncrystallizing Sorbitol Solution	NF			
Artificial Cherry Flavor # (b)	In-house			
Purified Water	USP			

Inactive Ingredients Query
ANDA 78-734
Oxcarbazepine Oral Suspension, 300 mg/5 mL
Ranbaxy Laboratories Limited

CELLULOSE MICROCRYSTALLINE/CARBOXYMETHYLCELLULOSE SODIUM (b) (4) (b) (4)

SILICON DIOXIDE, COLLOIDAL (b) (4) (b) (4)

HYDROXYETHYL CELLULOSE ORAL; (b) (4)

POVIDONE (b) (4)

COPOVIDONE (b) (4)

POLYOXYL 8 STEARATE (b) (4)

METHYLPARABEN (b) (4)

PROPYLPARABEN (b) (4)

SORBIC ACID (b) (4)

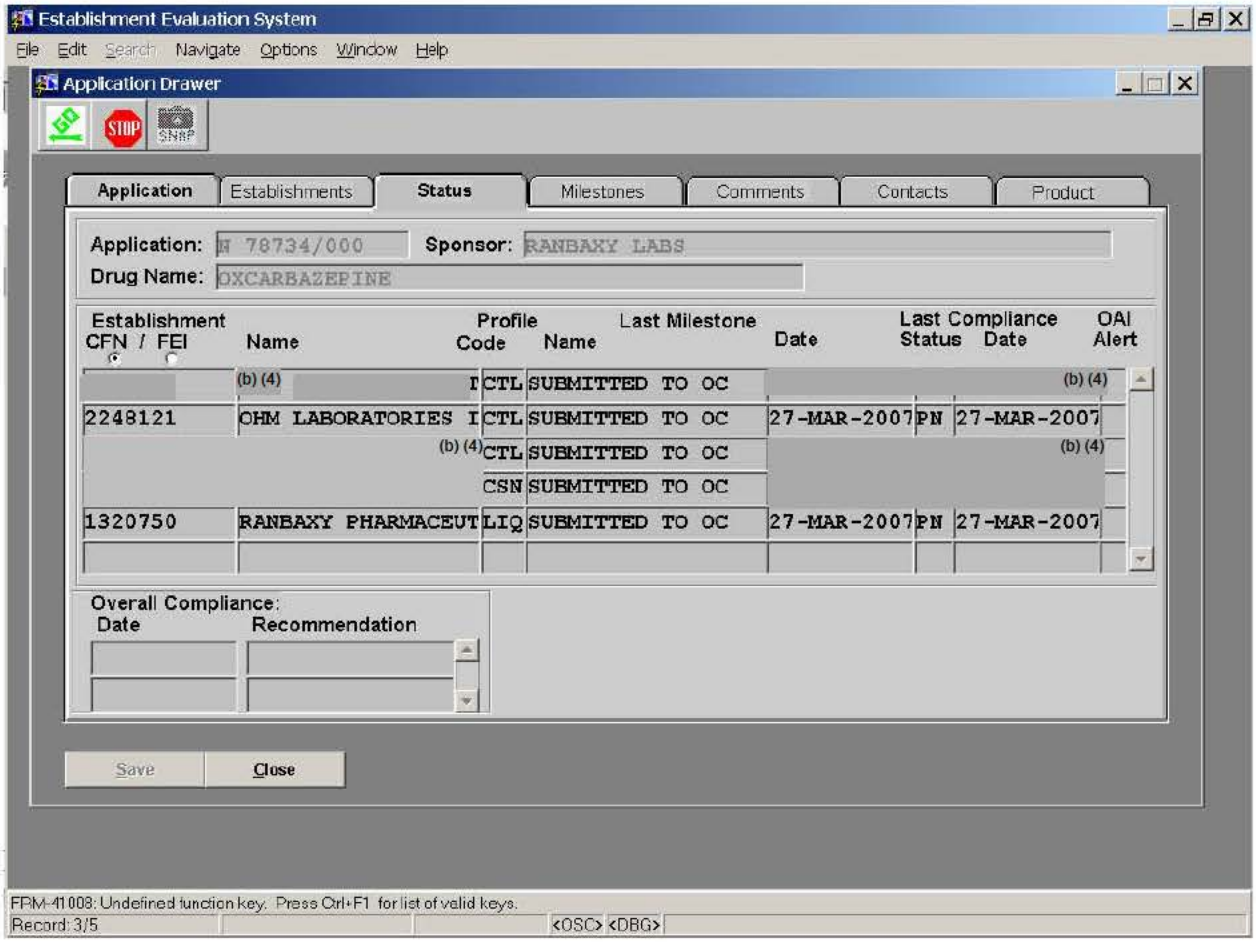
PROPYLENE GLYCOL (b) (4)

SACCHARIN SODIUM (b) (4)

ASCORBIC ACID (b) (4)

SORBITOL (b) (4)

Artificial Cherry Flavor # (b) (4).- no justification needed


Establishment Evaluation System
File Edit Search Navigate Options Window Help
Application Drawer
Application Establishments Status Milestones Comments Contacts Product
Application: N 78734/000 Sponsor: RANBAXY LABS
Drug Name: OXCARBAZEPINE
Establishment CFN / FEI Name Profile Code Last Milestone Name Last Milestone Date Last Compliance Status Last Compliance Date OAI Alert
(b) (4) I CTL SUBMITTED TO OC (b) (4)
2248121 OHM LABORATORIES I CTL SUBMITTED TO OC 27-MAR-2007 PN 27-MAR-2007
(b) (4) CTL SUBMITTED TO OC (b) (4)
CSN SUBMITTED TO OC
1320750 RANBAXY PHARMACEUT LIQ SUBMITTED TO OC 27-MAR-2007 PN 27-MAR-2007
Overall Compliance:
Date Recommendation
Save Close
FRM-41008: Undefined function key. Press Ctrl+F1 for list of valid keys.
Record: 3/5
<OSC> <DBG>

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

/s/

Martin Shimer

3/29/2007 06:46:47 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-734

Ranbaxy Inc.
U.S. Agent for: Ranbaxy Laboratories Limited
Attention: Scott Tomsky
600 College Road East
Princeton, NJ 08540

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Oxcarbazepine Oral Suspension, 300 mg/5 mL

DATE OF APPLICATION: December 22, 2006

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 26, 2006

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

  2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet “PATENT AMENDMENT” with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a 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 (301)827-0503.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Lisa Kwok
Project Manager
301-827-5746

Sincerely yours,

{See appended electronic signature page}

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

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

/s/

Martin Shimer
3/29/2007 06:42:07 AM
Signing for Wm Peter Rickman

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 78-734 **FIRM NAME** Ranbaxy Laboratories Limited

DRUG NAME Oxcarbazepine Oral Suspension, 300 mg/5 mL

DOSAGE FORM Oral Suspension, 300 mg/5 mL
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 N/A**
☐	**Waiver does NOT meet statutory requirements**
	Reason:

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

Reviewed by:

_____ Date: _____
Zakaria Wahba
Reviewer

_____ Date: _____
Chandra Chaurasia
Team Leader

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☒	☐			**Two BE studies (under fasting and fed conditions) on the 300 mg/5 mL strength (a single dose of 600 mg was administered).**
Assay Methodology	☒	☐			
Procedure SOP	☒	☐			
Methods Validation	☒	☐			
Study Results Ln/Lin	☒	☐			
Adverse Events	☒	☐			
IRB Approval	☒	☐			
Dissolution Data	☒	☐			
Pre-screening of Patients	☒	☐			
Chromatograms	☒	☐			
Consent Forms	☒	☐			
Composition	☒	☐			
Summary of Study	☒	☐			
Individual Data & Graphs, Linear & Ln	☒	☐			
PK/PD Data Disk Submitted)	☒	☐			Electronic data submitted.
Randomization Schedule	☒	☐			
Protocol Deviations	☒	☐			
Clinical Site	☒	☐			

Analytical Site	☒	☐			
Study Investigators	☒	☐			
Medical Records	☒	☐			
Clinical Raw Data	☒	☐			
Test Article Inventory	☒	☐			
BIO Batch Size	☐	☒			Not provided in the submission
Assay of Active Content Drug	☒	☐			
Content Uniformity	☐	☒			Not provided in the submission
Date of Manufacture	☒	☐			
Exp. Date of RLD	☒	☐			
BioStudy Lot Numbers	☒	☐			
Statistics	☒	☐			
Summary results provided by the firm indicate studies pass BE criteria	☒	☐			
Waiver requests for other strengths / supporting data	☐	☐			N/A

ADDITIONAL COMMENTS REGARDING THE ANDA:

1. The RLD is TRILEPTAL (OXCARBAZEPINE ORAL SUSPENSION; 300MG/5ML) by NOVARTIS; NDA #21285, approved date: 05/25/2001.
2. The application contains two BE studies (Fasted and Fed) on the 300 mg/5 mL strength (a single dose of 600 mg was administered).
3. The information on the content uniformity and bio-batch size are not provided in the ANDA volumes related to BE submission.

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

/s/

Chandra S. Chaurasia
3/7/2007 11:23:11 AM

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 : February 27, 2006

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 78-734 for Oxcarbazepine Oral Suspension, 300 mg/5 mL to determine if the application is substantially complete for filing.

Ranbaxy Laboratories Limited has submitted ANDA 78-734 for Oxcarbazepine Oral Suspension, 300 mg/5 mL. 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 Ranbaxy Laboratories Limited on December 22, 2006 for its Oxcarbazepine 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 to an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

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

/s/

Eda Howard
2/28/2007 09:54:27 AM
APPLICATIONS EXA

RR included for PIV notification to Patent holder of 1525 patent RR dated 4/19/07.

JW 5/25/07

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540, PHONE: (609) 720-9200 FAX: (609) 720-1155

May 15, 2007

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

PATENT AMENDMENT

JP

Reference: **ANDA 78-734**
Oxcarbazepine Oral Suspension, 300 mg/5 mL
Patent Amendment – Notice of certification of non-infringement of patents

Dear Sir/Madam:

Reference is made to our pending ANDA 78-734 for Oxcarbazepine Oral Suspension, 300 mg/5 mL submitted December 22, 2006. Reference is also made to the acceptance for filing letter dated March 29, 2007.

This ANDA refers to the listed drug Trileptal® Suspension of Novartis, as listed in the FDA Electronic Orange Book, *"Approved Drug Products with Therapeutic Equivalence Evaluations."*

Submitted within the original ANDA for Oxcarbazepine Oral Suspension, 300 mg/5 mL, Ranbaxy Laboratories Limited certified under FDCA Section 505(j)(2)(A)(vii), paragraph IV, that in the opinion and to the best of its knowledge, no valid or enforceable claim of U.S. Patent No. 7,037,525 will be infringed by the manufacture, use, or sale of the drug product for which ANDA 78-734 has been submitted.

With this amendment Ranbaxy Laboratories Ltd. hereby certifies that pursuant to 21 CFR 314.95(a), notice of certification of non-infringement of the above referenced patent has been provided to:

(1) Each owner of the patent which is the subject of the certification 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 that is claimed by the patent and for which the applicant is seeking approval, or, if the application holder does not reside or maintain a place of business within the United States, the application holder's attorney, agent or other authorized official.

Ranbaxy Laboratories Limited also certifies that the notice meets the content requirement as described in 21 CFR 314.95(c).

A notice was sent to the appropriate individuals on April 19, 2007. The certified receipt illustrates that the notice was received on April 23, 2007 and May 2, 2007. A copy of the notice, along with the certified mail receipts is provided in **Attachment 1** and **Attachment 2**, respectively.

If you have any questions regarding this amendment, please call me at 609-720-5617 or Scott D. Tomsky at 609-720-5609.

Sincerely,

Mike Yefimenko *(for)*
Manager, Regulatory Affairs
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-5352 FAX: (609) 720-5351

Not filed in 45-day period re: 505 patent

DWS 8/21/07

June 29, 2007

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

PATENT AMENDMENT
NO RESPONSE

N.050.
XP

Reference: **ANDA 78-734**
Oxcarbazepine Oral Suspension, 300 mg/5 mL
Patent Amendment – No Response

Dear Sir/Madam:

Reference is made to Ranbaxy Laboratories Limited pending Abbreviated New Drug Application (ANDA) 78-734 for Oxcarbazepine Oral Suspension, 300 mg/5 mL. Reference is also made to our Patent Amendment dated May 15, 2007, in which we notified the Agency that Novartis received notifications of Ranbaxy's paragraph IV certification on April 23, 2007 and May 2, 2007.

As of today, (more than 45 days since notice was received), Novartis has not filed suit against Ranbaxy Laboratories Limited regarding the submission of ANDA 78-734.

If you have any questions regarding this Amendment, please call the undersigned at 609-720-8061 or Mr. Scott D. Tomsky at 609-720-5609. Thank you.

Sincerely,

Usha Sankaran
Sr. Regulatory Affairs Associate *(for)*
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-5352 FAX: (609) 720-5351

July 9, 2007

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS
EXPEDITED REVIEW REQUEST

MC

Reference: ANDA 78-734
Oxcarbazepine Oral Suspension, 300 mg/5 mL

Dear Sir/Madam:

Reference is made to Ranbaxy Laboratories Limited's ANDA 78-734 for Oxcarbazepine Oral Suspension, 300 mg/5 mL. Reference is also made to the Office of Generic Drugs Manual of Policies and Procedures (MAPP) 5240.3, "Review Order of Original ANDAs, Amendments, and Supplements" effective October 18, 2006.

Based on the MAPP referenced above, "Certain applications may be identified at the time of submission for expedited review. These include products to respond to current and anticipated public health emergencies, products under special review programs such as PEPFAR, products for which a nationwide shortage has been identified, and ***first generic products for which there are no blocking patents or exclusivities on the referenced listed drug***."

At this time, Ranbaxy would like to request an expedited review of our ANDA 78-734 for Oxcarbazepine Oral Suspension, 300 mg/5 mL. In Ranbaxy's opinion and to the best of its knowledge, ANDA 78-734 for Oxcarbazepine Oral Suspension, 300 mg/5 mL is the first generic product in which there are no unexpired patents or exclusivities for the reference listed drug product. Please note, Ranbaxy submitted a Paragraph IV Patent Certification against the listed '525 patent and Novartis (the RLD holder) has not filed suit against Ranbaxy Laboratories Limited regarding the submission of ANDA 78-734.

Please contact either Mike Yefimenko at (609) 720-5617 or Scott D. Tomsky at (609) 720-5609 if you have any questions regarding this submission.

Sincerely,

Usha Sankaran
Sr. Regulatory Associate (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

July 30, 2007

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS

MINOR AMENDMENT
CMC

ORIG AMENDMENT
N/Am

RE: ANDA 78-734
Oxcarbazepine Oral Suspension, 300 mg/5 mL
Response to CMC deficiency dated June 20, 2007

Dear Sir or Madam:

Reference is made to our pending ANDA 78-734 for Oxcarbazepine Oral Solution, 300 mg/5 mL. Reference is also made to the FDA CMC deficiency dated June 20, 2007.

We are hereby submitting, in duplicate, a complete response to the deficiencies noted in the above referenced FDA correspondence.

FIELD COPY: We certify that a true copy of the technical sections described in 21 CFR 314.94 (d)(5) of this submission has been provided to the FDA New York District Office, Jamaica, NY since the manufacturing is done at Ohm Laboratories facility, in Gloversville, NY.

If you have any questions regarding this submission, please call Mike Yefimenko at 609-720-5617 or Scott Tomsky at 609-720-5609.

Sincerely,

Rich Leone

Rich Leone, RAC
Manager, Regulatory Affairs (*for*)
Scott Tomsky
Director, Regulatory Affairs
U.S. Agent for Ranbaxy Laboratories Limited

RECEIVED
JUL 31 2007
OGD

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0430
Expiration Date: April 30, 2009
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Ranbaxy Laboratories Limited	07/30/2007
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
91-124-4016863	609-514-9797
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
Sector 18, Ugyog Vihar Industrial Area Gurgaon - 122 001 India	Scott Tomsky, US Agent for Ranbaxy Laboratories Limited Ranbaxy Inc. 600 College Road East Princeton, NJ 08540

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 78-734

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Oxcarbazepine Oral Suspension	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Suspension	300 mg/5 mL	Oral

(PROPOSED) INDICATION(S) FOR USE:

Monotherapy or adjunctive therapy in the treatment of partial seizures in adults and children ages 4 to 16 with epilepsy

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)*
☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Trileptal Oral Suspension Holder of Approved Application Novartis

RECEIVED
JUL 31 2007
OGD

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Response to CMC deficiency dated June 20, 2007.

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

001

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☒	4. Chemistry section
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Rich Lesne	Scott D. Tomsky, US Agent for Ranbaxy Labs Ltd.	07/30/2007

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Ranbaxy Inc., 600 College Road East, Princeton, NJ 08540	(609) 720-5609

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

MINOR AMENDMENT

ANDA 78-734

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Ranbaxy Laboratories Limited
U.S. Agent: Ranbaxy Inc.

TEL: 609-720-5666

FAX: 609-514-9797

ATTN: Abha Pant

PROJECT MANAGER: (301) 827-5739

FROM: Lisa Kwok

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 22, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Oxcarbazepine Oral Suspension, 300 mg/5 mL.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__2__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments provided.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-734 APPLICANT: Ranbaxy Laboratories Limited

DRUG PRODUCT: Oxcarbazepine Oral Suspension, 300 mg/5 mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

(b) (4)

[redacted]

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

1. Please submit any additional stability data for the exhibit batches that may be available.

2. Labeling and bioequivalence portions of the ANDA are pending review.

3. An acceptable compliance evaluation for the firms referenced in the ANDA is required for approval.

Sincerely yours,

(See appended electronic signature page)

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

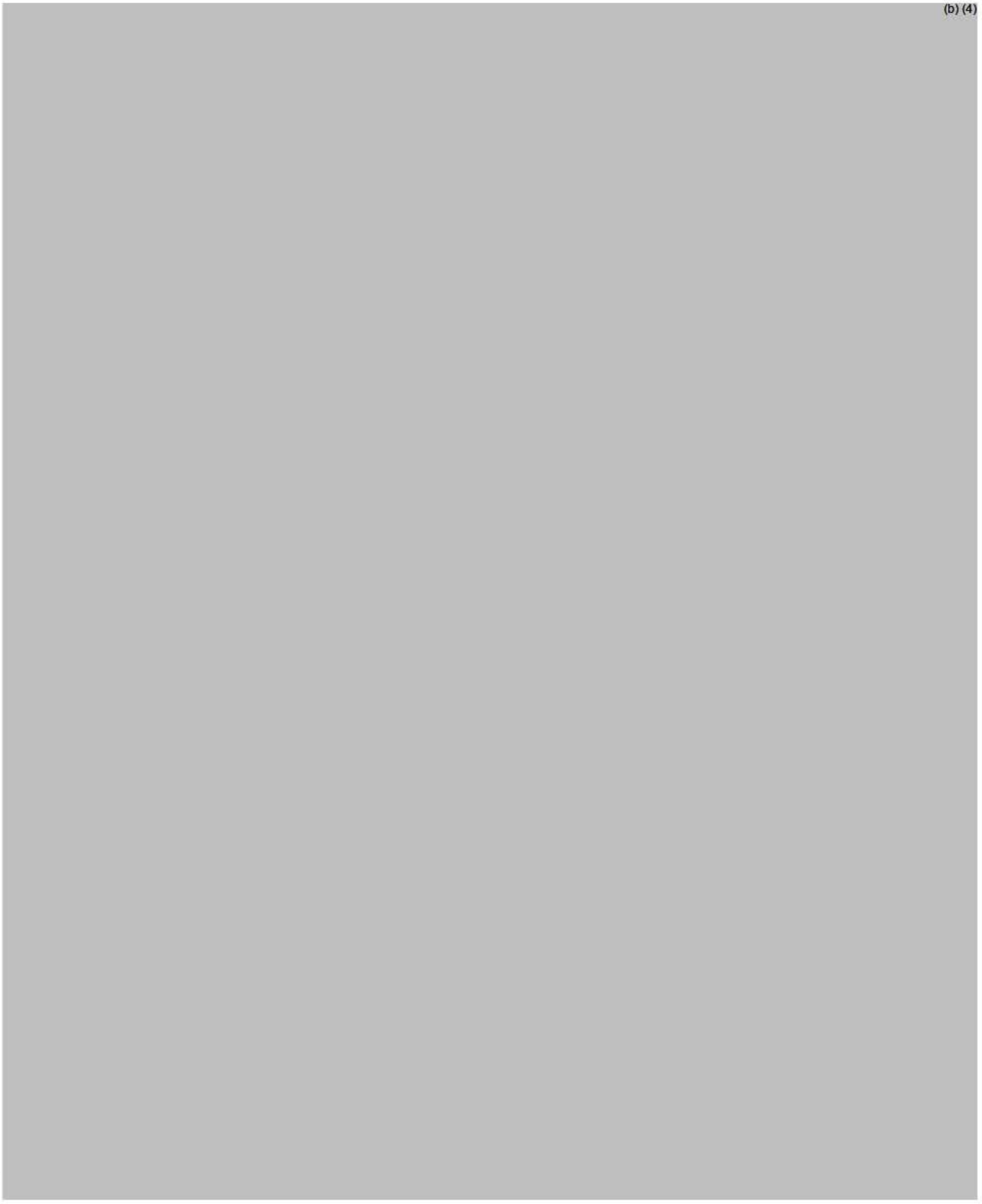
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

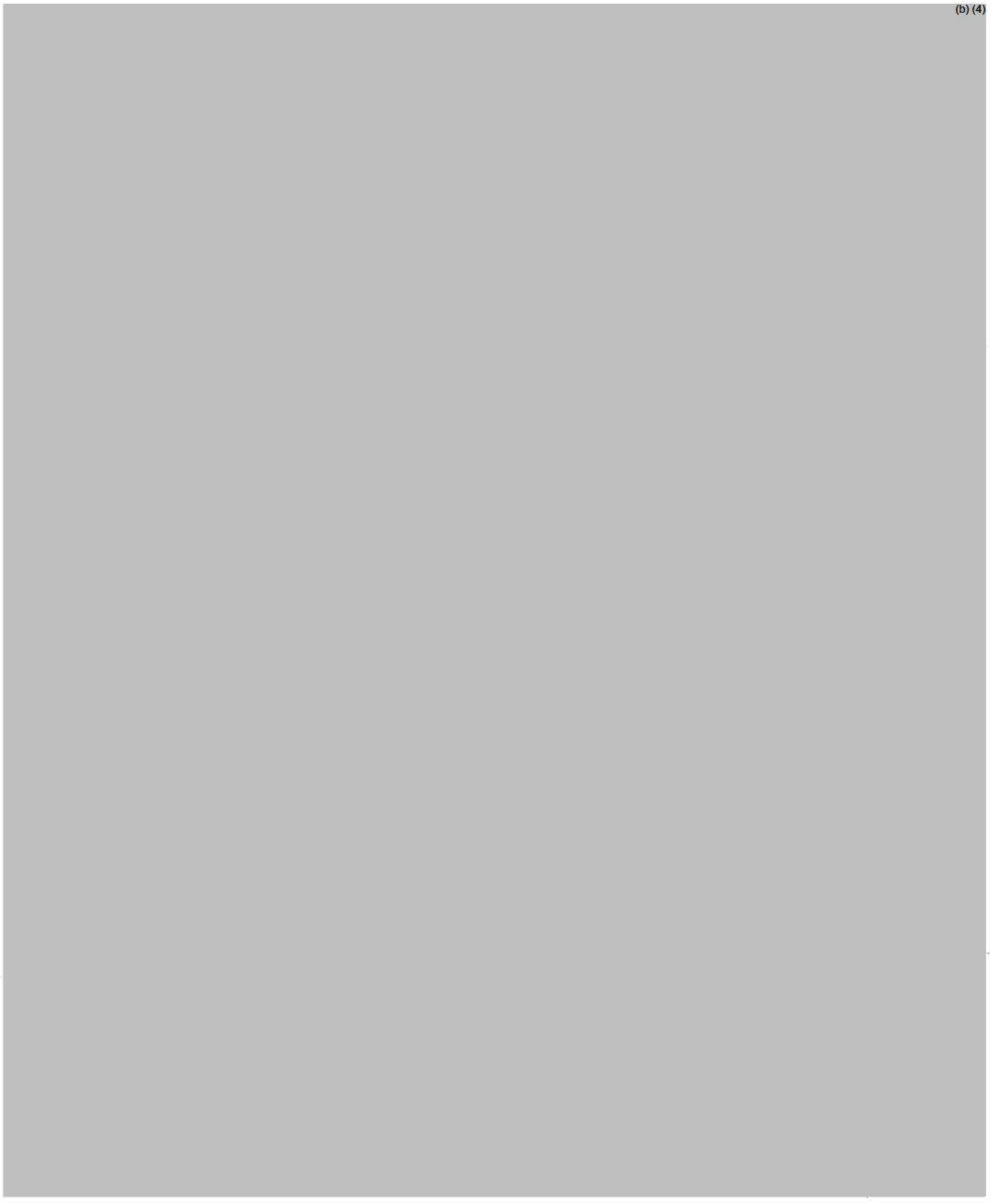
/s/

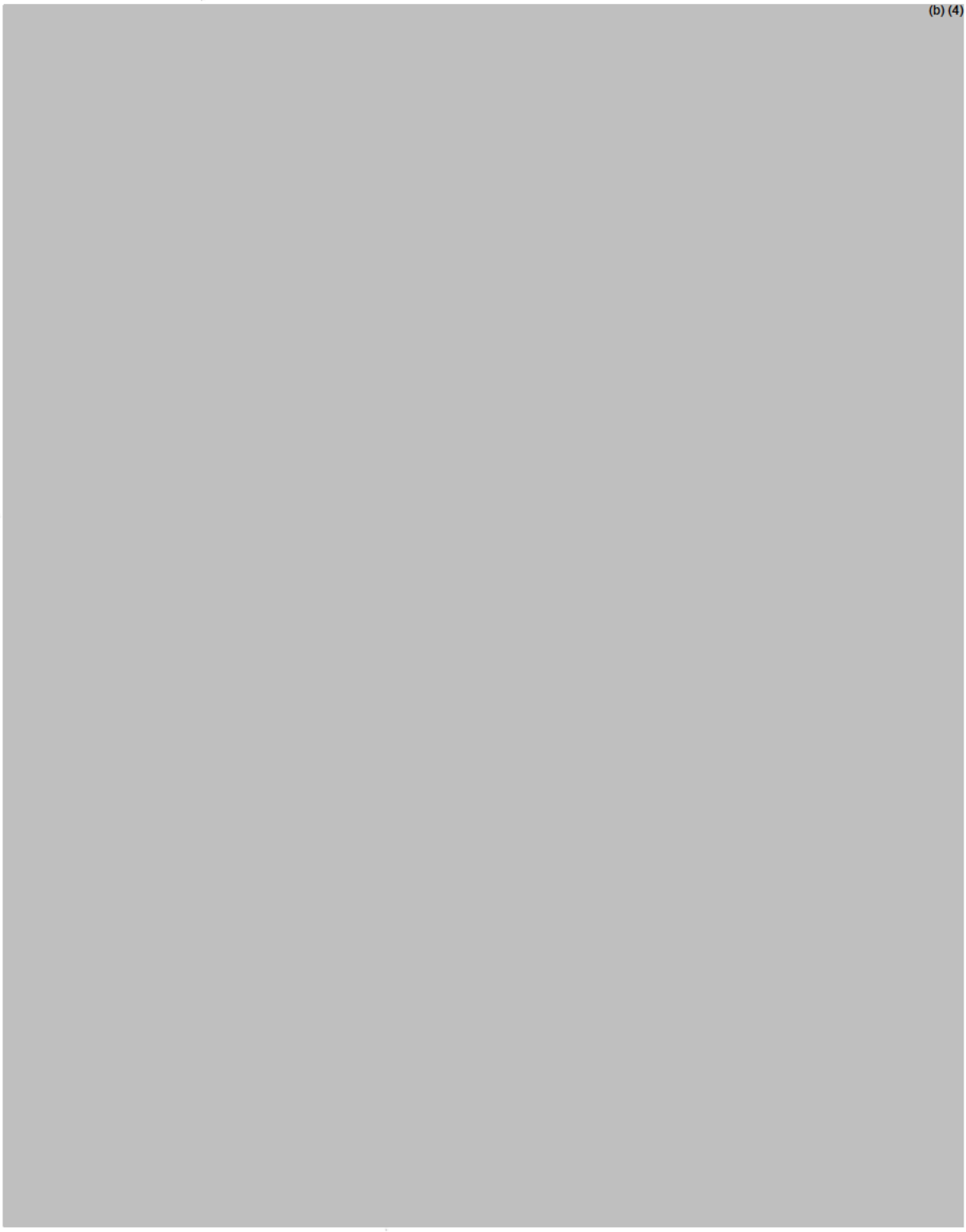
Shing Hou Liu
6/20/2007 03:33:17 PM
For Vilayat A. Sayeed, Ph.D.

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:




(b) (4)


(b) (4)

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

1. **Please submit any additional stability data for the exhibit batches that may be available.**

   The updated stability data up to 9 months at controlled room temperature condition for the exhibit batch are enclosed in **Attachment-4.**

2. **Labeling and bioequivalence portions of the ANDA are pending review.**

   We note and acknowledge the Agency's comment.

3. **An acceptable compliance evaluation for the firms referenced in the ANDA is required for approval.**

   We note and acknowledge the Agency's comment.

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

September 11, 2007

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS & FAX

BIOEQUIVALENCE AMENDMENT

N-000-AB

RE: ANDA 78-734
Oxcarbazepine Oral Suspension, 300 mg/5 mL
Response to Bioequivalence deficiency dated September 7, 2007

Dear Sir or Madam:

Reference is made to our pending ANDA 78-734 for Oxcarbazepine Oral Solution, 300 mg/5 mL. Reference is also made to the Bioequivalency amendment dated August 3, 2007 and the Bioequivalence deficiency dated September 7, 2007.

We are hereby submitting, in duplicate, a complete response to the deficiencies noted in the above referenced FDA correspondence.

If you have any questions regarding this submission, please call Usha Sankaran at 609-720-8061 or Mr. Scott D Tomsky at 609-720-5609. Thank you.

Sincerely,

Usha Sankaran
Manager, Regulatory Affairs (*for*)
Scott D Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0430
Expiration Date: April 30, 2009
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Ranbaxy Laboratories Limited	09/11/2007
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
91-124-4016863	609-514-9797
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
Sector 18, Ugyog Vihar Industrial Area Gurgaon - 122 001 India	Scott D. Tomsky, US Agent for Ranbaxy Laboratories Limited Ranbaxy Inc. 600 College Road East Princeton, NJ 08540

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 78-734

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Oxcarbazepine Oral Suspension	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Suspension	300 mg/5 mL	Oral

(PROPOSED) INDICATION(S) FOR USE:

Monotherapy or adjunctive therapy in the treatment of partial seizures in adults and children ages 4 to 16 with epilepsy

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)*
☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Trileptal Oral Suspension Holder of Approved Application Novartis

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Bioequivalence Amendment-Response to Bioequivalence deficiency dated September 7, 2007

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

RECEIVED
SEP 13 2007

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☒	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Response to Bioequivalence deficiency dated September 7, 2007

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
(for)	Scott D. Tomsky, US Agent for Ranbaxy Labs Ltd.	09/11/2007

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Ranbaxy Inc., 600 College Road East, Princeton, NJ 08540	(609) 720-5609

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

BIOEQUIVALENCY AMENDMENT

ANDA 78-734

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Ranbaxy Laboratories Limited
U.S. Agent: Ranbaxy Inc.

TEL: 609-720-5666

FAX: 609-514-9797

ATTN: Scott Tomsky

PROJECT MANAGER: (240) 276-8782

FROM: Aaron Sigler

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on December 22, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Oxcarbazepine Oral Suspension, 300 mg/5 mL.

Reference is also made to your amendment dated August 03, 2007.

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

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review,** nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (black) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-734

APPLICANT: Ranbaxy Laboratories, Ltd.

DRUG PRODUCT: Oxcarbazepine Oral Suspension, 300 mg/5 mL

The Division of Bioequivalence has completed its review and has identified the following deficiencies:

1. Please submit potency (assay) data for the reference listed product (lot # H5144). In future submissions, please be sure to include potency data for both test and reference products within the bioequivalence section of your application.

2. The QC values reported in your original submission for the fasted oxcarbazepine (study #228_OXCAR_006) do not coincide with those you provided in your study amendment (electronic biosummary Table 14, submission date: 03 August 2007). Please explain which observations (n) were used to determine your mean concentrations and how you calculated the percent nominal values for each QC sample. In future submissions, please include the mean concentrations for both QC and standard samples instead of listing the nominal values; mean concentrations should be included in the biosummary tables for the pre- and within-study assay reports (e.g., Tables 4 and 14).

Sincerely yours,

{See appended electronic signature page}

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

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

/s/

Barbara Davit
9/6/2007 06:23:38 PM
Signing for Dale P Conner

ANDA: 78-734
APPLICANT: Ranbaxy Laboratories Ltd.
DRUG PRODUCT: Oxcarbazepine Oral Suspension, 300 mg/ 5 ml

The Division of Bioequivalence has completed its review and has identified the following deficiencies:

1. **Please submit potency (assay) data for the reference listed product (lot #H5144). In future submissions, please be sure to include potency data for both test and reference products within the bioequivalence section of your application.**

   The potency (assay) for the reference listed product (lot # H5144) is (b) (4) mg (b) (4) %) as indicated in the certificate of analysis for the RLD (lot # H5144) provided in Module 5, Section 5.3.1.3, Page 6471.

   Ranbaxy commits to include potency data for both test and reference products within the bioequivalence section in all the future submissions as recommended by Agency.

2. **The QC values reported in your original submission for the fasted oxcarbazepine (study #228_OXCAR_006) do not coincide with those you provided in your study amendment (electronic biosummary Table 14, submission date: 03 August 2007). Please explain which observations (n) were used to determine your mean concentrations and how you calculated the percent nominal values for each QC sample. In future submissions, please include the mean concentrations for both QC and standard samples instead of listing the nominal values; mean concentrations should be included in the biosummary tables for the pre- and within-study assay reports (e.g., Tables 4 and 14)**

   We note and acknowledge the Agency's comments.

   The difference in the QC values for the fasted study provided in the original ANDA and in the bioequivalency amendment dated August 3, 2007 is a result of an error in the statistical calculation of the mean, percent nominal, S.D and C.V values provided in page no. 2407 (Table 1) of the original ANDA. The biosummary table 14 provided in the bioequivalency amendment dated August 3, 2007 reflects the corrected values. We inadvertently missed to clarify this in the above referenced amendment.

   The revised page 2407 (Table 1) of the original ANDA reflecting the correct values for the mean, percent nominal, S.D and C.V values for the fasted study is enclosed.

The percent nominal values for QC samples were calculated as follows.

$$\% \text{ Nominal} = \frac{\text{Mean concentration of QC sample}}{\text{Nominal concentration of QC sample}} \times 100$$

Ranbaxy commits to include the mean concentrations for both QC and standard samples instead of listing the nominal values in the biosummary tables (e.g., Tables 4 and 14) in all the future submissions as recommended by Agency.

Table 1
Quality Control Sample Data for Oxcarbazepine
(Precision and Accuracy)

Subject No.	QC -ID	Nominal Concentration (ng/mL)							
	228OX/LQC#	LOC	228OX/M1OC#	M1OC	228OX/MOC#	MOC	228OX/HOC#	HOC	(b) (4)
1									(b) (4)
1									
3									
3									
4									
4									
5									
5									
7									
7									
8									
8									
10									
10									
11									
11									
12									
12									
13									
13									
14									
14									
15									
15									
16									
16									
17									
17									
18									
18									
20									
20									
21									
21									
22									
22									
23									
23									
24									
24									
26									
26									
27									
27									
28									
28									
29									
29									
30									
30									
32									
32									
31									
31									
35									
35									
36									
36									
37									
37									
38									
38									
39									
39									
40									
40									
Repeat (25)									
Repeat (25)									
Repeat (31) & Identified repeats									
Repeat (31) & Identified repeats									
Identified repeat									
Identified repeat									
Identified repeats									
Identified repeats									
Identified repeats									
Identified repeats									
Mean		148.25		751.76		2301.87		5017.28	
SD(+/-)		11.907		54.703		175.054		442.168	
C.V.(%)		8.0		7.3		7.6		8.8	
Nominal(%)		97.8		99.2		95.8		99.0	
N		76		76		76		75	

N: Number of Observations
***: Statistical outlier**

Please process this as the AM. 12-1
The hard copy as MC. Tx, Lisa

RANBAXY

RANBAXY USA INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

June 25, 2009

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS & FAX

CMC TELEPHONE AMENDMENT

N/AM

RE: ANDA 78-734
Oxcarbazepine Oral Suspension, 300 mg/5 mL
Response to FDA Telephone contact on June 23, 2009, June 24, 2009 and June 25, 2009

Dear Sir or Madam:

Reference is made to our pending ANDA 78-734 for Oxcarbazepine Oral Solution, 300 mg/5 mL. Reference is also made to the FDA telephone contacts that Ranbaxy had with the Agency on June 23, 2009, June 24, 2009 and June 25, 2009.

Through this telephone amendment, Ranbaxy is responding to the Agency's comments in the above referenced telephone contacts.

As per the FDA's special instructions, Ranbaxy is providing this submission in an electronic PDF format. This submission is placed on a CD-ROM and is less than 3 MB in size. The contents of the CD have been scanned for viruses using McAfee VirusScan Enterprise 8.0.0 updated on June 25, 2009.

If you have any questions regarding this submission; please call me at 609-720-8061.

Thank you.

Sincerely,

Usha Sankaran
U.S. Agent for Ranbaxy Laboratories Limited