CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-069

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	78-069
Drug Product Name	Oxcarbazepine Tablets
Strength	600 mg, 300 mg, 150 mg
Applicant Name	Breckenridge Pharmaceuticals, Inc.
Applicant Address	15 Massirio Drive, Suite 201, Berlin, CT 06037
Clinical Site	Vimta Labs Ltd 142, IDA, Phase II, Cherlapally, Hyderabad, INDA 500 051
Analytical Site	Vimta Labs Ltd. (same as above)
Submission Date(s)	22 December 2005
First Generic	No
Reviewer	Kristopher J. Bough, PhD
File Location	V:\firmsam\breckenridge\ltrs&rev\78069d1205.doc

1. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP method for this product, but there are FDA-recommended methods (one for each unit strength). Dissolution testing for the 600 mg strength product is acceptable at the S1 level; however, the firm conducted dissolution testing using non-FDA-recommended methods for the 150 and 300 mg tablets. The firm should conduct additional dissolution testing using the FDA-recommended method for the 150 mg and 300 mg strength products.

The firm should also submit electronic bio-summary tables for both in vivo BE fasted (13318) and fed (13319) studies in the attached CTD format.

The DBE will review in vivo BE studies and waiver requests at a later date.

2. DISSOLUTION METHOD

	Recommended Method			Method Used by the Firm		
Source of Method	FDA			NDA		
Tablet Strength	150	300	600	150	300	600
Media	0.3% SDS in water	0.6% SDS in water	1.0% SDS In water	1.0% SDS in water		
Volume	900 mL			900 mL		
Temperature	37 ± 0.5 °C			37 ± 0.5 °C		
Apparatus	USP 2 (paddle)			USP 2 (paddle)		
Rotational Speed	60			60		
Sampling Times	10, 20, 30, 45, 60, and 90			10, 20, 30, 45, and 60 min		
Specification(s)	NLT (b)(4)% (Q) in 30 min NLT % (Q) in 60 min			NLT (b)(4)% (Q) in 45 min		

Source of Method:

1. DBE Dissolution Database
2. Chemistry Reviews, Trileptal® (NDA 21-014, RLD for oxcarbazepine tabs), review dates: 12/14/99 & 2/17/04
   NDA Specifications: NLT (b)(4)% (Q) in 30 min
   NLT % (Q) in 60 min
3. Control #05-0381, Oxcarbazepine Tablets, 600 mg, 300 mg, & 150 mg, (b)(4) (b)(4)

3. DISSOLUTION DATA

TABLE 1. Dissolution data for Oxcarbazepine Tablets, 150 mg

TIME (min)	TEST Oxcarbazepine Tablets 150 mg Lot No. 315022			REFERENCE Trileptal® Tablets 150 mg Lot No. 204H1503		
	Mean	%CV	Min-Max	Mean	%CV	Min-Max
10	57.7	6.76	(b) (4)	68.4	4.74	(b) (4)
20	71.9	4.10		78.0	2.93	
30	77.0	3.46		80.5	2.52	
45	79.6	6.04		82.2	2.44	
60	81.5	1.84		83.1	2.43	
f_2 metric		N/A				

Reviewer's Comments: *The dissolution testing method used above is the non-FDA-recommended method for 150 mg tablets. Additional dissolution testing should be used using the FDA-recommended method of 900 mL of* ***0.3% SDS (in lieu of 1% SDS) in water****, USP apparatus 2 at 60 rpm, 37°C. Sampling times should include 10, 20, 30, 45, 60, and 90 min.*

TABLE 2. Dissolution data for Oxcarbazepine Tablets, 300 mg

TIME (min)	TEST Oxcarbazepine Tablets 300 mg Lot No. 315021			REFERENCE Trileptal® Tablets 300 mg Lot No. 589J3096		
	Mean	%CV	Min-Max	Mean	%CV	Min-Max
10	70.4	3.2	(b) (4)	70.9	7.0	(b) (4)
20	81.1	1.3		78.7	3.7	
30	85.4	1.5		80.8	2.2	
45	87.5	1.6		81.8	1.9	
60	88.8	1.6		82.4	1.7	
f_2 metric		N/A				

Reviewer's Comments: *The dissolution testing method used above is the non-FDA-recommended method for 300 mg tablets. Additional dissolution testing should be used using the FDA-recommended method of 900 mL of* ***0.6% SDS (in lieu of 1% SDS) in water****, USP apparatus 2 at 60 rpm, 37°C. Sampling times should include 10, 20, 30, 45, 60, and 90 min.*

TABLE 3. Dissolution data for Oxcarbazepine Tablets, 600 mg

TIME (min)	TEST Oxcarbazepine Tablets 600 mg Lot No. 314714			REFERENCE Trileptal® Tablets 600 mg Lot No. 006J3963		
	Mean	%CV	Min-Max	Mean	%CV	Min-Max
10	68.4	4.9	(b) (4)	69.6	11.9	(b) (4)
20	81.8	2.8		84.6	4.0	
30	86.0	2.2		86.7	2.5	
45	87.8	2.2		87.1	2.4	
60	88.7	2.5		87.3	2.6	
f_2 metric		N/A				

Reviewer's Comments: *The dissolution method used above is the FDA-recommended method. The test product meets the FDA-recommended specifications of NLT (b) (4)% (Q) in 30 min and NLT (b) (4)% (Q) in 60 min, both at the S1 level. The firm's proposed specification of NLT (b) (4)% in 45 min is not acceptable. Dissolution testing for the 600 mg tablets (lot no. 314714) is acceptable.*

TABLE 4. Dissolution data for Oxcarbazepine Tablets, 600 mg

TIME (min)	TEST Oxcarbazepine Tablets 600 mg Lot No. 316803			REFERENCE Trileptal® Tablets 600 mg Lot No. F4086		
	Mean	%CV	Min-Max	Mean	%CV	Min-Max
10	67.7	6.5	(b) (4)	83.8	3.4	(b) (4)
20	81.9	5.7		88.9	2.5	
30	85.9	2.8		89.1	2.1	
45	87.0	1.9		88.4	2.4	
60	87.3	1.9		86.3	2.1	
f_2 metric		N/A				

Reviewer's Comments: *The dissolution testing method used above is the FDA-recommended method. The test product meets the FDA-recommended specifications of NLT (b) (4)% (Q) in 30 min and NLT (b) (4)% (Q) in 60 min, both at the S1 level. The firm's proposed specification of NLT (b) (4)% in 45 min is not acceptable. Dissolution testing for the 600 mg tablets (lot no. 316803) is acceptable.*

DISSOLUTION RESULTS				
TABLET STRENGTH	**150 mg**	**300 mg**	**600 mg (lot 1)**	**600 mg (lot 2)**
Is dissolution method acceptable?	No	No	Yes	Yes
If not, why?	Non-FDA method	Non-FDA method	---	---
f2 similarity metric calculated?	No	No	No	No
If not, why?	N/A	N/A	rapidly dissolving	rapidly dissolving
If so, were results acceptable?	---	---	---	---
Are dissolution results acceptable?	**NO**	**NO**	**YES**	**YES**
If not, why?	Non-FDA method	Non-FDA method	---	---

4. IN VIVO BIOEQUIVALENCE DATA

Are the SAS files located in the EDR? (Yes/No)	
Fasting BE Study (Study No. 13318/04-05)	
Plasma Data	Yes
PK data	Yes
Fed BE Study (Study No. 13319/04-05)	
Plasma Data	Yes
PK Data	Yes
CTD Bio-Summary Tables	
Are the CTD Bio-Summary Tables in the EDR?	**NO**
If so, are they complete?	---

Reviewer's Comments: *The firm should submit electronic bio-summary tables for both in vivo BE fasted (13318) and fed (13319) studies in the attached CTD format.*

5. DEFICIENCY COMMENTS

1. Although dissolution testing for the 600 mg tablets was acceptable, the firm conducted dissolution testing using a non-FDA-recommended method for the 150 mg and 300 mg oxcarbazepine tablets.

2. The firm did not submit electronic bio-summary tables for both in vivo BE fasted (13318) and fed (13319) studies in CTD format.

6. RECOMMENDATIONS

1. Dissolution testing is incomplete for the reasons cited above. The firm should conduct comparative dissolution testing on 12 dosage units of the 150 mg and 300 mg oxcarbazepine tablets using the following FDA-recommended method:

Media:	0.3% SDS in water (150 mg)
	0.6% SDS in water (300 mg)
Volume:	900 mL
Temperature:	37±0.5°C
Apparatus:	USP 2 (paddle) at 60 rpm
Sampling times:	10, 20, 30, 45, 60, and 90 min

2. The firm should also submit electronic bio-summary tables for both in vivo BE fasted (13318) and fed (13319) studies in the attached CTD format.

05/24/06
Kristopher J. Bough, PhD — Date
Reviewer, Branch I

Moheb H. Makary — 05/24/06
Moheb H. Makary, PhD — Date
Team Leader, Branch I

5/26/06
Dale P. Conner, PharmD — Date
Director, Division of Bioequivalence
Office of Generic Drugs

CC: ANDA 78-069
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer: K. Bough
HFD/658/ TL: M. Makary

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Printed Final On: 05/24/06

Endorsements: (Final with Dates)
HFD-650/K. Bough 05/24/06
HFD-658/M. Makary 05/24/06
HFD-650/D. Conner 5/26/06

DISSOLUTION – **DEFICIENCIES**
Submission date: 22 December 2005

1. DISSOLUTION (DIS)

Strengths: 600 mg, 300 mg, & 150 mg
Outcome: **IC**

NOTE: The BE studies and waiver requests will be reviewed at a later date.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-069 APPLICANT: Breckenridge Pharmaceuticals, Inc

DRUG PRODUCT: Oxcarbazepine Tablets, 600 mg, 300 mg, & 150 mg

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

1. Please conduct comparative dissolution testing on 12 dosage units of the 150 mg and 300 mg oxcarbazepine tablets using the following FDA-recommended method:

Media:	0.3% SDS in water (150 mg) 0.6% SDS in water (300 mg)
Volume:	900 mL
Temperature:	37 ± 0.5°C
Apparatus:	USP 2 (paddle) at 60 rpm
Sampling times:	10, 20, 30, 45, 60, & 90 min

   Please refer to the DBE's dissolution database for additional information at: http://www.accessdata.fda.gov/scripts/cder/dissolution/.

2. Please also submit electronic CTD bio-summary tables for both in vivo BE fasted (13318) and fed (13319) studies. This will facilitate the BE review process. Templates for these eight tables are attached.

Sincerely yours,

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

Table 1. Summary of Bioavailability Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (units/mL)	T_{max} (hr)	AUC_{0-t} (units)	AUC_{∞} (units)	$T_{½}$ (hr)	K_{el} (hr^{-1})	
Study #	Fasting study title	Randomized, single-dose, crossover	Test product, strength, Tab./Cap./Susp., p.o. [Batch #] Ref. product, strength, Tab./Cap./Susp., p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean age (range)	M ± S.D. M ± S.D.	Mn or Md No SD	M ± S.D. M ± S.D.	M ± S.D. M ± S.D.	Mean No SD	Mean No SD	Vol. # p. #
Study #	Fed study title	Randomized, single-dose, crossover	Test product, strength, Tab./Cap./Susp., p.o. [Batch #] Ref. product, strength, Tab./Cap./Susp., p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean y (range)	M ± S.D. M ± S.D.	Mn or Md No SD	M ± S.D. M ± S.D.	M ± S.D. M ± S.D.	Mean No SD	Mean No SD	Vol. # p. #

Table 2. Statistical Summary of the Comparative Bioavailability Data

Drug Dose (# x mg) Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t}				
AUC_{∞}				
C_{max}				
Fed Bioequivalence Study				
Parameter	**Test**	**Reference**	**100*Ratio**	**90% C.I.**
AUC_{0-t}				
AUC_{∞}				
C_{max}				

Table 3. Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	Provide the volume(s) and page(s)
Analyte	Provide the name(s) of the analyte(s)
Internal standard (IS)	Identify the internal standard used
Method description	Brief description of extraction method; analytical method
Limit of quantitation	LOQ, units
Average recovery of drug (%)	%
Average recovery of IS (%)	%
Standard curve concentrations (units/mL)	Standard curve range and appropriate concentration units
QC concentrations (units/mL)	List all the concentrations used
QC Intraday precision range (%)	Range or per QC
QC Intraday accuracy range (%)	Range or per QC
QC Interday precision range (%)	Range or per QC
QC Interday accuracy range (%)	Range or per QC
Bench-top stability (hrs)	hours @ room temperature
Stock stability (days)	days @ 4°C
Processed stability (hrs)	hours @ room temperature; hours @ 4°C
Freeze-thaw stability (cycles)	# cycles
Long-term storage stability (days)	17 days @ -20°C (or other)
Dilution integrity	Concentration diluted X-fold
Selectivity	No interfering peaks noted in blank plasma samples

Table 4. Summary of In Vitro Dissolution Studies

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean %Dissolved (Range)				Study Report Location
					min	min	min	min	
Diss. study report #	Test prod name/ #	mg Tab./Cap./Susp.	Dissolution: Apparatus Speed of Rotation: rpm Medium: Volume: mL Temperature: °C	12					
Diss. study report #	Ref prod name/ #	mg Tab./Cap/Susp.		12					

Table 5. Formulation Data

Ingredient	Amount (mg) / Tablet		Amount (%) Tablet	
	Lower strength	Higher strength	Lower strength	Higher strength
Cores				
Coating				
Total			100.00	100.0

Table 6. Demographic Profile of Subjects Completing the Bioequivalence Study

Study No.		
	Treatment Groups	
	Test Product N =	Reference Product N =
Age (years)		
Mean ± SD	50 ± 15	
Range	20-85	
Groups		
< 18	N(%)	N(%)
18 – 40	N(%)	N(%)
40 – 64	N(%)	N(%)
65 – 75	N(%)	N(%)
> 75	N(%)	N(%)
Sex		
Female	N(%)	N(%)
Male	N(%)	N(%)
Race		
Asian	N(%)	N(%)
Black	N(%)	N(%)
Caucasian	N(%)	N(%)
Hispanic	N(%)	N(%)
Other	N(%)	N(%)
Other Factors		

Table 7. Incidence of Adverse Events in Individual Studies

Body System/Adverse Event	Reported Incidence by Treatment Groups					
	Fasted Bioequivalence Study Study No.		Fed Bioequivalence Study Study No.		Other Bioequivalence Study Study No.	
	Test	Reference	Test	Reference	Test	Reference
Body as a whole						
Dizziness	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Etc.	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Cardiovascular						
Hypotension						
Etc.						
Gastrointestinal						
Constipation						
Etc.						
Other organ sys.						
Total	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

Table 8. Reanalysis of Study Samples

Study No. Additional information in Volume(s), Page(s)								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]								
Reason A (e.g. below LOQ)								
Reason B								
Reason C								
Etc.								
Total								

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout table

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-069
Drug Product Name	Oxcarbazepine Tablets
Strength	150 mg, 300 mg, and 600 mg
Applicant Name	Breckenridge Pharmaceutical, Inc.
Address	1141 South Rogers Circle, Suite 3, Boca Raton, FL 33487
Contact Information	Judy-Lynn Reidinger, Manager of Technical Services, 15 Massirio Drive, Suite 201, Berlin, CT 06037
Phone Number	(860) 828-8140, ext 231
Fax Number	(860) 828-8142
Submission Date(s)	**December 22, 2005**
Amendment Date(s)	**June 12, 2006** (Dissolution Amendment)**, September 12, 2006** (Dissolution Acknowledgement)**, November 15, 2006** (Telephone Amendment), **December 18, 2006** (Telephone Amendment - new SAS data), **January 8, 2007** (Telephone Amendment)
Reviewer	Parthapratim Chandaroy, Ph.D.
First Generic	No

I. Executive Summary

In the original submission dated December 22. 2005, the firm submitted fasting and fed bioequivalence (BE) studies comparing its test product, Oxcarbazepine Tablets, 600 mg to the reference listed drug (RLD), Novartis's Trileptal® (oxcarbazepine) Tablets, 600 mg. The firm also submitted comparative *in vitro* dissolution data for 150 mg, 300 mg, and 600 mg strengths of the test and reference product and requested for waiver of *in vivo* bioequivalence requirements for the lower two strengths of the test product.

The study design for each of the BE studies is a two-way, crossover in normal healthy subjects (n=60 for fasting, n=100 for fed). Statistical analyses of the plasma concentration data for oxcarbazepine demonstrate bioequivalence for both the studies. For the fasting BE study, oxcarbazepine results (point estimate, 90% CI) are: $\ln AUC_{0-t}$ of 1.02, 98.0-105.8; $\ln AUC_{0-\infty}$ of 1.02, 98.5-106.0; and $\ln C_{max}$ of 1.02, 93.7-111.4. For the fed BE study, oxcarbazepine results (point estimate, 90% CI) are: $\ln AUC_{0-t}$ of 0.99, 96.7-101.5; $\ln AUC_{0-\infty}$ of 0.99, 97.1-101.7; and $\ln C_{max}$ of 0.92, 86.4-97.6. Metabolite plasma concentrations were comparable for the test and reference products in both the studies.

There is no USP method for this product but there is an FDA-recommended method. The firm conducted comparative dissolution testing using the FDA-recommended method. The firm's dissolution data met the FDA-recommended dissolution specifications at the S1 level. In an amendment dated September 12, 2006, the firm accepted the FDA-recommended method and specifications. The dissolution testing study is **acceptable**.

The application is **acceptable** with no deficiencies. The waivers of *in vivo* bioequivalence study requirements for the 150 mg and 300 mg strengths are **granted**.

II. Table of Contents

III. Submission Summary

A. Drug Product Information[1]

Test Product	Oxcarbazepine Tablets, 150 mg, 300 mg, and 600 mg
Reference Product	Trileptal® (Oxcarbazepine) Tablets, 600 mg
RLD Manufacturer	Novartis
NDA No.	21-014
RLD Approval Date	January 14, 2000
Indication	Indicated for use as monotherapy or adjunctive therapy in the treatment of partial seizures in adults and children ages 4-16 with epilepsy.

B. PK/PD Information[2]

Bioavailability	Following oral administration of Trileptal® tablets, oxcarbazepine is completely absorbed in the gastrointestinal tract.
Food Effect	Food has no effect on the rate and extent of absorption.
T_{max}	4.5 hours (range 3-13 hours)
Metabolism	Oxcarbazepine is extensively metabolized in the liver to the 10-monohydroxy metabolite (MHD), which is primarily responsible for the pharmacological effect of Trileptal®. 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).
Excretion	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%).
Half-life	oxcarbazepine: 2 hours; MHD: 9 hours
Relevant OGD or DBE History	The following bioequivalence documents were reviewed (or currently under review/in queue for ANDAs) by the Division of Bioequivalence (DBE) for Oxcarbazepine Tablets: **<u>Control:</u>** 03-154 ((b) (4); 03-179 (b) (4); 03-191 ((b) (4)); 03-214 ((b) (4); 03-408 ((b) (4)); 03-610 (b) (4); 03-737 ((b) (4)); 04-094 (Teva); 04-605 ((b) (4); 04-672 ((b) (4); 04-699 ((b) (4)); 04-1072 ((b) (4)); 04-1173 ((b) (4); 05-0381 ((b) (4); 05-0466 ((b) (4)) and 05-1553 (Novartis)

[1] Entry for oxcarbazepine in the Orange Book, 2006
[2] PDR® (Physician's Desk Reference) 2006 entry for Trileptal®

Protocol:
02-034 (Roxane) and 04-059 (b) (4))

ANDAs:
77-747 (Apotex); (b) (4); 77-794 (Sun); 77-795 (Roxane); (b) (4); 77-801 (Taro); 77-802 (Glenmark); 77-805 (Teva); (b) (4); (b) (4); 78-069 (Breckenridge–current application) and (b) (4)

The DBE currently recommends the following for Oxcarbazepine Tablets, 150 mg, 300 mg, and 600 mg[3]:

1. A single-dose, two-way crossover fasting *in-vivo* bioequivalence study comparing Oxcarbazepine Tablets, 600 mg, to the reference listed drug (RLD), Trileptal® (oxcarbazepine) Tablets, 600 mg.

2. A single-dose, two-way crossover fed *in-vivo* bioequivalence study comparing Oxcarbazepine Tablets, 600 mg, to the RLD.

3. Measurement of both the parent compound, oxcarbazepine, and its 10-hydroxy metabolite, in plasma[4].

4. Oxcarbazepine Tablets, 150 mg and 300 mg, may be considered for a waiver of *in-vivo* bioequivalence testing based on (1) acceptable bioequivalence studies on the 600 mg strength, (2) acceptable dissolution testing of the 150 mg, 300 mg, and 600 mg strengths, and (3) proportional similarity in the formulations of the 150 mg, 300 mg, and 600 mg strengths.

5. Comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the following FDA-recommended method:

Apparatus:	USP apparatus II (paddle)
Speed:	60 rpm
Medium:	Aqueous sodium dodecyl sulfate (SDS) solution
Volume:	900 mL at 37°C
Sampling times:	10, 20, 30, 45, 60, 75, and 90 minutes or until at least (b) (4)% of the label content is dissolved.

[3] Control correspondence #04-1173 to (b) (4)(\\cdsnas\ogds11\firmsnz\(b) (4)controls\04-1173)
[4] In case of measurement of both parent and metabolite in plasma, the DBE recommends the firm to subject only the parent drug data to the 90% confidence interval criteria. For the metabolite, the firm should tabulate the data and provide descriptive statistics.

	The firm is also suggested to vary the amount of SDS in the dissolution medium as follows: Strength — % SDS 600 mg — 1.0% 300 mg — 0.6% 150 mg — 0.3% Dissolution specifications are set at the time of the ANDA review. Since oxcarbazepine has low aqueous solubility, it may be necessary to set a two-point specification.
Agency Guidance	None
Drug Specific Issues (if any)	None

C. Contents of Submission

Study Types	**Yes/No?**	**How many?**
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	---
In vitro dissolution	Yes	6
Waiver requests	Yes	2
BCS Waivers	No	---
Vasoconstrictor Studies	No	---
Clinical Endpoints	No	---
Failed Studies	No	---
Amendments	Yes	2

D. Pre-Study Bioanalytical Method Validation

Reported in the Fasting Study section:

Information Requested	Data
Bioanalytical method validation report location	Volume 1/12: Pages 1080 – 1264 (fasted data presented below, fed data presented on following page)
Analyte(s)	Oxcarbazepine and its metabolite MHD (10-monohydroxy-carbamazepine)
Internal standard (IS)	(b) (4)
Method description	LC-MS/MS method; The samples were prepared by extracting the drug substance from plasma samples using an (b) (4)
Limit of quantitation (ng/mL)	Oxcarbazepine: 20.300; MHD: 98.900
Average recovery (%)	Oxcarbazepine: 89.71%; MHD: 89.17%
Average recovery of IS (%)	92.34
Standard curve concentrations (ng/mL)	Oxcarbazepine: 20.200, 40.400, 80.800, 151.500, 303.000, 606.000, 1211.950 and 2423.900 MHD: 98.200, 196.400, 392.750, 736.400, 1472.850, 2945.650, 5891.300 and 11782.600
QC concentrations (ng/mL)	Oxcarbazepine: 60.900 (LQC), 964.200 (MQC), 1826.900 (HQC) MHD: 296.700 (LQC), 4697.500 (MQC), 8900.550 (HQC)
QC Intraday precision range (%)	Oxcarbazepine: 3.55 - 8.36 (LQC), 1.94 - 5.48 (MQC) and 3.87 - 3.93 (HQC) MHD: 4.56 - 9.67 (LQC), 2.86 - 4.11 (MQC) and 2.57 - 3.59 (HQC)
QC Intraday accuracy range (%)	Oxcarbazepine: 93.79 - 93.82 (LQC), 89.32 - 93.34 (MQC) and 93.97 - 95.02 (HQC) MHD: 100.09 - 101.94 (LQC), 88.93 - 97.80 (MQC) and 92.51 - 96.65 (HQC)
QC Interday precision range (%)	Oxcarbazepine: 6.12 (LQC), 4.60 (MQC) and 4.11 (HQC) MHD: 7.23 (LQC), 5.97 (MQC) and 3.74 (HQC)
QC Interday accuracy range (%)	Oxcarbazepine: 93.80 (LQC), 91.33 (MQC) and 93.94 (HQC) MHD: 101.02 (LQC), 93.37 (MQC) and 94.58 (HQC)
Bench top stability (hr)	12 hr. @ ambient temperature (Oxcarbazepine and MHD)
Stock stability (days)	23 days @ 2-8° C (Oxcarbazepine and MHD)
Processed stability (hr)	31 hours @ ambient temperature (Oxcarbazepine and MHD)
Freeze-thaw stability (cycles)	3 cycles (Oxcarbazepine and MHD)
Long-term storage stability (days)	102 days @ -20° C (Oxcarbazepine and MHD)
Dilution integrity	Oxcarbazepine: 2 times CC9 concentration (5029.800 ng/mL) diluted in a 1:4 ratio MHD: 2 times CC9 concentration (25048.800 ng/mL) diluted in a 1:4 ratio
Selectivity	No interfering peaks noted in blank plasma samples

Reported in the Fed Study section:

Information Requested	Data
Bioanalytical method validation report location	Volume 4/18: pages 1602-1664 (fed data presented below, fasted data presented on previous page)
Analyte(s)	Oxcarbazepine and its metabolite MHD (10-monohydroxy-carbamazepine)
Internal standard (IS)	(b) (4)
Method description	LC-MS/MS method; The samples were prepared by extracting the drug substance from plasma samples using an (b) (4)
Limit of quantitation (ng/mL)	Oxcarbazepine: 20.300; MHD: 99.700
Average recovery (%)	Oxcarbazepine: 89.71; MHD: 89.17
Average recovery of IS (%)	92.34
Standard curve concentrations (ng/mL)	Oxcarbazepine: 20.100, 40.250, 100.600, 251.500, 503.000, 1005.950, 2011.900, 3017.900 and 5029.800 MHD: 99.300, 198.600, 496.450, 1241.100, 2482.200, 4964.350, 9928.750 and 24821.850
QC concentrations (ng/mL)	Oxcarbazepine: 60.950 (LQC), 2539.800 (MQC), 4063.700 (HQC) MHD: 299.050 (LQC), 12459.950 (MQC), 19935.950 (HQC)
QC Intraday precision range (%)	Oxcarbazepine: 2.35 – 6.46 (LQC), 1.33 – 2.64 (MQC) and 1.75 – 2.06 (HQC) MHD: 3.12 - 9.80 (LQC), 3.19 – 5.25 (MQC) and 1.17 – 2.95 (HQC)
QC Intraday accuracy range (%)	Oxcarbazepine: 100.72 – 103.59 (LQC), 106.55 – 109.13 (MQC) and 98.09 – 104.12 (HQC) MHD: 105.83 - 107.36 (LQC), 102.85 – 107.01 (MQC) and 98.68 – 102.51 (HQC)
QC Interday precision range (%)	Oxcarbazepine: 4.81 (LQC), 2.34 (MQC) and 3.61 (HQC) MHD: 6.93 (LQC), 4.60 (MQC) and 2.94 (HQC)
QC Interday accuracy range (%)	Oxcarbazepine: 102.16 (LQC), 107.84 (MQC) and 101.11 (HQC) MHD: 106.59 (LQC), 104.93 (MQC) and 100.59 (HQC)
Bench top stability (hr)	12 hr. @ ambient temperature (Oxcarbazepine and MHD)
Stock stability (days)	23 days @ 2-8° C (Oxcarbazepine and MHD)
Processed stability (hr)	31 hours @ ambient temperature (Oxcarbazepine and MHD)
Freeze-thaw stability (cycles)	3 cycles (Oxcarbazepine and MHD)
Long-term storage stability (days)	102 days @ -20° C (Oxcarbazepine and MHD)
Dilution integrity	Oxcarbazepine: 2 times CC9 concentration (5029.800 ng/mL) diluted in a 1:4 ratio MHD: 2 times CC9 concentration (25048.800 ng/mL) diluted in a 1:4 ratio
Selectivity	No interfering peaks noted in blank plasma samples

Reviewer's note:

- The "QC Intraday accuracy range" for HQC, submitted in the pre-study method validation data reported in the fasting study section, is from pp. 1257-1258, unlike the corresponding LQC and MQC values (pp1249-1250).
- For the pre-study Bioanalytical Method Validation report (fed study):
  - Long-term (freezer) storage stability of samples established for a period of 102 days at -20ºC was reported in the fasting study section.
  - The page reference for the report should be pp. 1524 to 1664 (including all addendums).

Comments on Pre-Study Bioanalytical Method Validation:
The pre-study bioanalytical method validation is **acceptable**.

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary, Fasting Bioequivalence Study	
Study No.	13318/04-05
Study Design	Randomized, single-dose, 2-treatment, 2-period, 2-sequence crossover bioavailability study under fasting conditions.
No. of subjects enrolled	60 + 4 (standby)
No. of subjects completing	59 + 4 (standby)
No. of subjects analyzed	60, as per protocol
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 60 Female: 0
Test product	Oxcarbazepine Tablets
Reference product	Trileptal® (oxcarbazepine) Tablets
Strength tested	600 mg
Dose	1 x 600 mg tablet with 240 mL water under fasting condition.

Fasting Study Statistical Summary (n=60**):**

Oxcarbazepine 600 mg Tablets single tablet dose Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasted Bioequivalence Study				
Parameter	**Test**	**Reference**	**100*Ratio**	**90% C.I.**
Oxcarbazepine				
AUC_{0-t}	7201.854 ± 27.23	7073.346 ± 25.02	101.82	98.98; 105.81
AUC_{∞}	7635.084 ± 26.68	7470.973 ± 24.91	102.20	98.51; 106.02
C_{max}	1878.968 ± 36.39	1839.427 ± 33.32	102.15	93.69; 111.37
10-monohydroxy derivative of oxcarbazepine (MHD)				
AUC_{0-t}	182269.190 ± 18.49	178772.380 ± 17.57	101.96	98.45; 105.64
AUC_{∞}	207601.920 ± 21.05	201432.140 ± 18.42	103.06	99.84; 106.38
C_{max}	6986.271 ± 18.99	6817.680 ± 19.36	102.47	98.35; 106.76

Reviewer's note: The values presented in the above table were calculated by the firm (n=60). The lower limit of AUC_{0-t} C.I. should be 97.98, instead of 98.98. In an amendment, submitted on November 15, 2006, the firm corrected this error.

Fasting Study Sample Reanalysis:

Study No. 13318/04-05 (Fasted) Additional Information in Volume 3/12 , Pages 1045 ~ 1050								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual Number		% of total assays		Actual Number		% of total assays	
	T*	R**	T	R	T	R	T	R
Oxcarbazepine								
QC results were not within acceptance range	19	21	1.51	1.67	19	21	1.51	1.67
ISTD was not added	21	21	1.68	1.67	21	21	1.67	1.67
Concentration of subject sample is higher than CC point	31	22	2.48	1.75	31	22	2.47	1.75
Reconfirmation of earlier results	1	2	0.08	0.16	1	2	0.08	0.16
Sample not analyzed due to acquisition error	1	-	0.08	--	1	-	0.08	-
Total	**73**	**66**	**5.83**	**5.25**	**73**	**66**	**5.82**	**5.26**
MHD (10-monohydroxy-carbamazepine)								
QC results were not within acceptance range	40	42	3.2	3.35	40	42	3.20	3.35
ISTD was not added	21	21	1.68	1.67	21	21	1.67	1.67
Reconfirmation of earlier results	1	1	0.08	0.08	1	1	0.08	0.08
Sample not analyzed due to acquisition error	1	-	0.08	-	1	-	0.08	-
Total	**63**	**64**	**5.04**	**5.10**	**63**	**64**	**5.02**	**5.10**

* Test Drug
** Reference Drug

Total number of samples assayed = **2506**

Did use of recalculated plasma concentration data change study outcome? No. There were a total of 266 sample repeat analyses (parent: 139, metabolite: 127). None of them was classified as pharmacokinetic repeat. According to the reviewer, there were a total of five (parent: 3, metabolite: 2) pharmacokinetic repeats (termed by the firm as "reconfirmation of earlier results). All repeat analyses were conducted following the SOP for sample reanalysis.

2. Single-dose Fed Bioequivalence Study

Study Summary, Fed Bioequivalence Study	
Study No.	13319/04-05
Study Design	Randomized, single-dose, 2-treatment, 2-period, 2-sequence crossover bioavailability study under fed conditions.
No. of subjects enrolled	100 + 6 (standby)
No. of subjects completing	98 + 6 (standby)
No. of subjects analyzed	100, as per protocol
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 100 Female: 0
Test product	Oxcarbazepine Tablets
Reference product	Trileptal® (oxcarbazepine) Tablets
Strength tested	600 mg
Dose	1 x 600 mg tablet with 240 mL water under fed condition.

Fed Study Statistical Summary:

Oxcarbazepine 600 mg Tablets single tablet dose Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study				
Parameter	Test	Reference	100*Ratio	90% C.I.
Oxcarbazepine				
AUC_{0-t}	10273.377 ± 23.33	10370.091 ± 23.82	99.07	96.68; 101.51
AUC_{∞}	10875.309 ± 22.61	10947.678 ± 23.36	99.34	97.06; 101.67
C_{max}	3813.174 ± 37.11	4151.302 ± 33.60	91.86	86.42; 97.63
10-monohydroxy derivative of oxcarbazepine (MHD)				
AUC_{0-t}	193441.386 ± 16.05	190781.390 ± 15.94	101.39	99.64; 103.18
AUC_{∞}	214730.079 ± 17.78	213343.106 ± 18.29	100.65	98.86; 102.47
C_{max}	8779.222 ± 14.25	8732.652 ± 13.70	100.53	99.16; 101.92

Reviewer's note: The values presented in above table were calculated by the firm (n=100).

Fed Study Sample Reanalysis:

Study No. 13319/04-05 (Fed) Additional Information in Volume 3/18, Pages 1485 ~ 1491								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual Number		% of total assays		Actual Number		% of total assays	
	T*	R**	T	R	T	R	T	R
Oxcarbazepine								
QC results were not within acceptance range	41	42	1.96	2.01	40	42	1.91	2.01
ISTD was not added	1	-	0.05	-	1	-	0.05	-
Concentration of subject sample is higher than CC point	31	36	1.48	1.72	31	36	1.48	1.72
ISTD area changes due to sample processing error	1	1	0.05	0.05	1	1	0.05	0.05
Reconfirmation of earlier results	2	9	0.10	0.43	2	8	0.10	0.38
Poor chromatography	2	5	0.10	0.24	2	5	0.10	0.24
Total	78	93	3.73	4.45	77	92	3.68	4.40
MHD (10-monohydroxy-carbamazepine)								
QC results were not within acceptance range	104	105	4.97	4.02	104	105	4.97	5.02
ISTD was not added	1	-	0.05	-	1	-	0.05	-
ISTD area changes due to sample processing error	1	1	0.05	0.05	1	1	0.05	0.05
Reconfirmation of earlier results	2	9	0.10	0.43	1	8	0.05	0.38
Total	108	115	5.16	5.50	107	114	5.11	5.45

* Test Drug
** Reference Drug

Total number of samples assayed = **4184**

Did use of recalculated plasma concentration data change study outcome? No. A total of 171 oxcarbazepine samples (test: 78, reference: 93) and 223 MHD samples (test: 108, reference: 115) were reanalyzed. According to the reviewer, there were a total of eleven (both parent and metabolite) pharmacokinetic repeats (termed by the firm as "reconfirmation of earlier results). The remaining repeats were all analytical repeats. All repeat analyses were conducted following the SOP for sample reanalysis.

F. Formulation

Location in appendix	Section IV.B, page 34
Are inactive ingredients within IIG limits?	Yes
If no, list ingredients outside of limits	N/A
If a tablet, is the product scored?	Yes
If yes, which strengths are scored?	150 mg, 300 mg, and 600 mg
Is scoring of RLD the same as test?	Yes
Is the formulation acceptable?	Yes
If not acceptable, why?	N/A

G. In Vitro Dissolution[5]

Source of Method (USP, FDA or Firm)	FDA
Medium	Water (at 37ºC) with: 1.0% SDS for the 600 mg strength 0.6% SDS for the 300 mg strength 0.3% SDS for the 150 mg strength
Volume (mL)	900 mL
USP Apparatus type	II (paddle)
Rotation (rpm)	60
Firm's proposed specification(s)	NLT (b) (4) (Q) in 45 min
FDA-recommended specification(s)	NLT (Q) in 30 min, and NLT (Q) in 60 min
F2 metric calculated?	Yes (see below)
Is method acceptable?	Yes
If not then why?	

F2 metric, lower strengths compared to highest strength			
Low strength	Highest strength	F2 metric for test	F2 metric for RLD
150 mg	600 mg	57.94	48.62
300 mg	600 mg	63.81	48.97

F2 metric, test compared to reference	
Strength	F2 metric
150 mg	63.26
300 mg	55.71
600 mg	58.14

Reviewer's note: There is no USP method for this product but there is an FDA-recommended method. The firm initially conducted comparative dissolution testing for all the strengths using the FDA-recommended method for the 600 mg strength. The firm

[5] Original dissolution review (\\cdsnas\ogds11\firmsam\breckenridge\ltrs&rev\78069d1205.doc)

was asked to repeat the comparative dissolution testing for the 150 mg and 300 mg strengths. In an amendment submitted on June 12, 2006, the firm provided new comparative dissolution testing data for the 150 mg and 300 mg strengths, obtained using the FDA-recommended method for those strengths[6]. The firm's dissolution data for all three strengths met the FDA-recommended dissolution specifications at the S1 level. The firm was asked to indicate if it accepts the FDA-recommended method and specifications. In an amendment dated September 12, 2006, the firm acknowledged acceptance of the FDA-recommended method and specifications. The dissolution testing study is **acceptable**.

The reviewer calculated F2 metric values for all the three strengths of both test and reference products, presented in the two tables above. All the test products have F2 values greater than 50 (both test vs. test and test vs. reference). The F2 values calculated for the reference products (reference vs. reference) are very close to 50, as seen in the tables above.

H. Waiver Request(s)

Strengths for which waivers are requested	150 mg and 300 mg
Regulation cited	21 CFR 320.22(d)(2)
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	Yes
Waivers granted?	Yes
If not then why?	N/A

I. Deficiency Comment

None

J. Recommendations

1. The single-dose, fasting bioequivalence study (#13318/04-05) conducted by Breckenridge Pharmaceutical, Inc. on its Oxcarbazepine Tablets, 600 mg (Lot #316803; manufactured by Anabolic Laboratories), comparing it to Novartis' Trileptal® Tablets, 600 mg (Lot #F4086), is **acceptable**.

2. The single-dose, non-fasting bioequivalence study (#13319/04-05) conducted by Breckenridge Pharmaceutical, Inc. on its Oxcarbazepine Tablets, 600 mg (Lot #316803; manufactured by Anabolic Laboratories), comparing it to Novartis' Trileptal® Tablets, 600 mg (Lot #F4086), is **acceptable**.

3. The *in vitro* dissolution testing conducted by Breckenridge Pharmaceutical, Inc. on its Oxcarbazepine Tablets, 150 mg (Lot #316805), 300 mg (Lot #316804), 600 mg (Lot

[6] Dissolution Amendment review (\\cdsnas\ogds11\firmsam\breckenridge\ltrs&rev\78069a0606.doc)

#316803), comparing it to Novartis' Trileptal® Tablets, 150 mg (Lot #204H1503), 300 mg (Lot #589J3096), 600 mg (Lot #F4086), is **acceptable**.

The dissolution testing should be conducted in 900 mL water (with 0.3% SDS in water for the 150 mg strength; 0.6% SDS in water for the 300 mg strength; and 1% SDS in water for the 600 mg strength) at 37°C using USP apparatus II (paddle) at 60 rpm. The test products should meet the following specifications:

Not less than (b) (4)% (Q) of the labeled amount of oxcarbazepine in the dosage form is dissolved in 30 minutes;

Not less than (b) (4)% (Q) of the labeled amount of oxcarbazepine in the dosage form is dissolved in 60 minutes.

4. The 150 mg and 300 mg strengths are proportionally formulated to the 600 mg strength which underwent acceptable bioequivalence studies. The waivers of *in vivo* bioequivalence study requirements for the 150 mg and 300 mg strengths of the test product are **granted**.

   The firm should be informed of the above recommendations.

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information	
Study Number	13318/04-05
Study Title	An open label, randomized, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study to compare Oxcarbazepine 600 mg tablets (Breckenridge Pharmaceutical Inc., USA) with Trileptal® (containing Oxcarbazepine 600 mg) film-coated tablets (Novartis Pharmaceuticals Corporation, USA) in 60+4 (standby) healthy, adult, human subjects under fasting conditions
Clinical Site	Vimta Labs Ltd., 142, IDA, Phase II, Cherlapally, Hyderabad 500 051, India
Principal Investigator	Manoj K. Bose, M.D.
Study/Dosing Dates	Period I: September 12, 2005 Period II: September 19, 2005
Analytical Site	Room No. 331, Clinical Research Division, Central Laboratory, Vimta Labs Ltd., 142, IDA, Phase II, Cherlapally, Hyderabad 500 051, India
Analytical Director (Group Leader)	(b) (6) M.Sc.
Analysis Dates	September 23, 2005 – October 5, 2005
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	24 days[7]

[7] The firm submitted long-term (freezer) storage stability data for 102 days (at -20ºC)

Treatment ID	**A**	**B**
Test or Reference	Test	Reference
Product Name	Oxcarbazepine Tablets	Trileptal® (oxcarbazepine) Tablets
Manufacturer	Anabolic Laboratories for Breckenridge Pharmaceutical, Inc.	Novartis
Batch/Lot No.	316803	F4086
Manufacture Date	4/2005	N/A
Expiration Date	N/A	3/2008
Strength	600 mg	600 mg
Dosage Form	Tablets	Tablets
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	97%	98.7%
Content Uniformity (mean, %CV)	100.2%, 0.8	N/A
Formulation	See **Table 23**	N/A
Dose Administered	1 x 600 mg	1 x 600 mg
Route of Administration	Oral	Oral

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	AB: 2, 4, 6, 8, 9, 10, 15, 16, 17, 22, 23, 24, 25, 27, 30, 31, 32, 34, 37, 39, 41, 44, 46, 48, 49, 50, 51, 55, 57, 60, 61, 62 BA: 1, 3, 5, 7, 11, 12, 13, 14, 18, 19, 20, 21, 26, 28, 29, 33, 35, 36, 38, 40, 42, 43, 45, 47, 52, 53, 54, 56, 58, 59, 63, 64
Blood Sampling Times	0, 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 12.0, 18.0, 24.0, 36.0, and 48.0 hours post-dose
Blood Volume Collected/Sample	5 mL collected in K_3 EDTA containing Vacutainer® tubes
Blood Sample Processing/Storage	After collection, blood samples were centrifuged within 30 minutes at approximately 3800 rpm (at 10º±2ºC) for 10-12 minutes. The resulting plasma was separated from centrifuged samples and transferred to two labeled tubes for freezing. The vials were stored between -18.4ºC to -24.1ºC.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See **Table 1**
Length of Fasting	At least 10 hours pre-dose until 4.0 hours post-dose
Length of Confinement	At least 12 hours pre-dose until 24 hours post-dose. Subjects returned for the 36 and 48 hour blood sample collection.
Safety Monitoring	Vital signs (blood pressure and pulse rate) were measured at

	screening, at the time of admission, 1 hour prior to dosing, and at 2, 4, 6, 12, and 24 hours post-dose in each period. Temperature was recorded at screening, at the time of admission, prior to dosing, and at 12 and 24 hours post-dose in each period. Adverse events were monitored throughout the study.

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

b) Clinical Results

Table 1: Demographics of Study Subjects

	Study No. 13318/04-05(Fasted) Treatment Groups		Study No. 13319/04-05 (Fed) Treatment Groups	
	Test Product N = 63	Ref. Product N = 63	Test Product N = 104	Ref. Product N = 104
Age (years)				
Mean ± SD	25.38 ± 5.19 yrs	25.38 ± 5.19 yrs	26.2 ± 4.99 yrs	26.2 ± 4.99 yrs
Range	19 to 39	19 to 39	19 to 44yrs	19 to 44yrs
Groups				
< 18	0	0	0	0
18 – 40	63	63	102	102
40 – 64	0	0	2	2
65 – 75	0	0	0	0
>75	0	0	0	0
Sex				
Female	0	0	0	0
Male	63	63	104	104
Race				
Asian	63	63	104	104
Black	0	0	0	0
Caucasian	0	0	0	0
Hispanic	0	0	0	0
Other	0	0	0	0
Height				
Mean	166.37 cm	166.37 cm	167.27 cm	167.27 cm
Range	149-184	149-184	152-187	152-187
Weight				
Mean	59.25 kg	59.25 kg	60.65 kg	60.65 kg
Range	50 - 75	50 - 75	51 - 78	51 - 78
Notes A=Test B=Reference	Subject #07 (Sequence BA) was found to have developed swelling on his left cheek on the day prior to admission and was withdrawn from the study		Subject #38 (Sequence AB) had a positive urine drug screen for drugs of abuse at the time of admission in Period II Subject #82 (Sequence AB) was dropped from the study prior to Period II dosing due to dizziness	

Reviewer's note: The firm also submitted following summary demographic data for the subjects included in the statistical analysis (n=60): Age: 25.38±5.19 (s.d.); BMI: 21.41±1.85 (s.d.); Groups: 18-40 years (100%); Sex: Male (100%); Race: Asian (100%).

Table 2: Dropout Information

Subject #	Reason	Period	Replaced?
7	Withdrawn from the study because of swollen left cheek	Before check-in for period II	#63

Reviewer's note: Subject #7 was replaced by standby subject #63 with same treatment sequence.

Table 3: Study Adverse Events

Body System/ Adverse Event	Reported Incidence by Treatment Groups			
	Fasted Bioequivalence Study Number: 13318/04-05		Fed Bioequivalence Study Number: 13319/04-05	
	Test Product N = 63	Ref. Product N = 64	Test Product N = 106	Ref. Product N = 104
Body as a whole				
Fever			1 (0.94%)	
Swelling	1 (1.59%)*			
Cardiovascular				
Gastrointestinal				
Abdominal pain				1 (0.96%)
Diarrhea				1 (0.96%)
Hematological				
Inc. eosinophil ct.	3 (4.76%) **		3 (2.88%)*	
Inc. monocyte ct.			1 (0.96%)*	
Neurological				
Dizziness	1 (1.59%)		1 (0.94%)	2 (1.92%)
Metabolic				
Elev. Bilirubin	2 (3.17%) **		2 (1.92%)*	
Elev. AST	1 (1.59%) **		1 (0.96%)*	
Elev. ALT	1 (1.59%) **			
Dec. Glucose	3 (4.76%) **		2 (1.92%)*	
Elev. GGT	1 (1.59%) **			
Elev. Serum Potassium	2 (3.17%) **		1 (0.96%)*	
Elev. Serum Creatinine			1 (0.96%)*	
Total	1 (1.59%)		2 (1.89%)	3 (2.88%)
Notes	* Subject #07 was found to have developed swelling on the left cheek associated with mild pain on the day prior to admission and was withdrawn from the study. The event was declared as mild and unrelated to study drug ** Post clinical laboratory assessment performed after completion of Period II.		* Post clinical laboratory assessment performed after completion of Period II.	

Reviewer's note: Subject #12 could not comply with the post-dosing posture due to "discomfort" in period II (see in protocol deviation), but that adverse event was not included in the above table and also not mentioned in the clinical study report.

Table 4: Protocol Deviations

Type	Subject #s (Test)	Subject #s (Ref.)
Blood sampling time deviations (samples drawn late)	Several	Several
Subject could not comply with the post-dosing posture due to dizziness (period I) and **discomfort** (period II)	#12	#12
Blood samples were not collected as subjects did not show up during the ambulatory visit*	5, 12, 34, 50, 57	31, 41, 42, 45, 57

*A deviation in blood draw was considered if: blood was drawn beyond 2 minutes of actual time till the 24-hour time point (housed), or beyond 1 hour of actual time for the 36 and 48-hour time points (ambulatory).

Comments on Dropouts/Adverse Events/Protocol Deviations:

- There were a total of 15 post-dose adverse events, including 13 post-clinical events, reported by 11 subjects. All events were "mild" in severity. Subject #7 had swollen left cheek (pre-check-in, period II) and was removed from the study. Seven of the adverse

events (hypoglycemia, swelling left cheek, increased eosinophil count) were considered "unrelated" or "remotely related" to the study treatments. The remaining eight adverse events (dizziness, increased bilirubin/potassium/AST/ALT/GGT level) were considered "remotely" or "possibly" related to the study treatments.

- There were several blood draw deviations in the study (samples drawn late) with a maximum deviation of 190 minutes (48 hour time point). All pharmacokinetic parameters were calculated using the actual sampling time.
- **The adverse events and protocol deviations did not compromise the integrity of the study**.

c) Bioanalytical Results

Table 5: Assay Quality Control – Within Study

	Parent (Oxcarbazepine)							
QC Conc. (ng/mL)	1826.900		964.200		60.900			
Inter day Precision (%CV)	10.17		9.96		10.01			
Inter day Accuracy (%)	98.84		96.42		95.00			
Cal. Standards Conc. (ng/mL)	20.20	40.40	80.80	151.50	303.0	606.0	1211.95	2423.90
Inter day Precision (%CV)	2.61	5.33	2.87	2.74	3.75	4.24	4.12	4.77
Inter day Accuracy (%)	97.80	102.17	103.81	103.13	99.84	97.43	96.89	99.12
Linearity Range (range of r values)	0.9962-0.9998							

Comments on Study Assay Quality Control: None

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms: None

Table 6: SOPs dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
23/13, version 7.0	September 7, 2005	Repeat Analysis of Samples & Reintegration of Chromatograms

Table 7: Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays:

- There were a total of 2506 study samples analyzed. 139 oxcarbazepine samples (test: 73, reference: 66) and 127 MHD samples (test: 63, reference: 64) were reanalyzed, including both parent and metabolite sample reanalysis for all the available samples from subject #40 and #50 (82 samples). The sample reanalysis represents 5.31% of the total study assays. According to the reviewer, there were a total of five (parent: 3, metabolite: 2) pharmacokinetic repeats (termed by the firm as "reconfirmation of earlier results). The remaining repeats were all analytical repeats. All repeat analyses were done following the SOP for sample reanalysis.
- The analytical method and data are **acceptable**.

d) Pharmacokinetic Results

Table 8: Arithmetic Mean Pharmacokinetic Parameters (n=60)

Mean plasma concentrations are presented in **Table 11 a**nd **Figure 1**.

Oxcarbazepine:

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC_{0-t}	ng/mL x hr	7449.95	27.23	7287.48	25.02	1.02
AUC_{∞}	ng/mL x hr	7889.07	26.68	7695.00	24.91	1.03
C_{max}	ng /mL	1995.09	36.39	1945.26	33.32	1.03
T_{max}	hr	1.53	43.72	1.86	56.43	0.82
$T_{1/2}$	hr^{-1}	9.77	38.05	9.06	37.10	1.08
K_e	hr	0.08	31.18	0.09	40.56	0.89

MHD:

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC_{0-t}	ng/mL x hr	185310.98	18.49	181512.38	17.57	1.02
AUC_{∞}	ng/mL x hr	211963.99	21.05	204576.42	18.42	1.04
C_{max}	ng /mL	7110.16	18.99	6942.70	19.36	1.02
T_{max}	hr	6.33	36.61	7.08	40.08	0.89
K_e	hr^{-1}	0.05	20.43	0.05	16.76	0.99
$T_{1/2}$	hr	13.39	22.01	12.99	16.69	1.03

Table 9: Geometric Means and 90% Confidence Intervals for Oxcarbazepine (n=60)

Parameter	Test	Reference	T/R	90% CI
AUC_{0-t}	7201.85	7073.35	1.02	97.98-105.81
AUC_{∞}	7635.08	7470.97	1.02	98.51-106.02
C_{max}	1878.97	1839.43	1.02	93.69-111.37

Reviewer's note: The values in the above tables were calculated by the reviewer.

Table 10: Additional Study Information (n=60)

	Oxcarbazepine
Root mean square error, $lnAUC_{0-t}$	0.125924
Root mean square error, $lnAUC_{0-\infty}$	0.120430
Root mean square error, lnC_{max}	0.283220
K_{el} and $AUC_{0-\infty}$ determined for how many subjects?	60
Do you agree or disagree with firm's decision?	Agree
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as C_{max}	None
Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic and Statistical Analysis:

- The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with the firm's calculations.

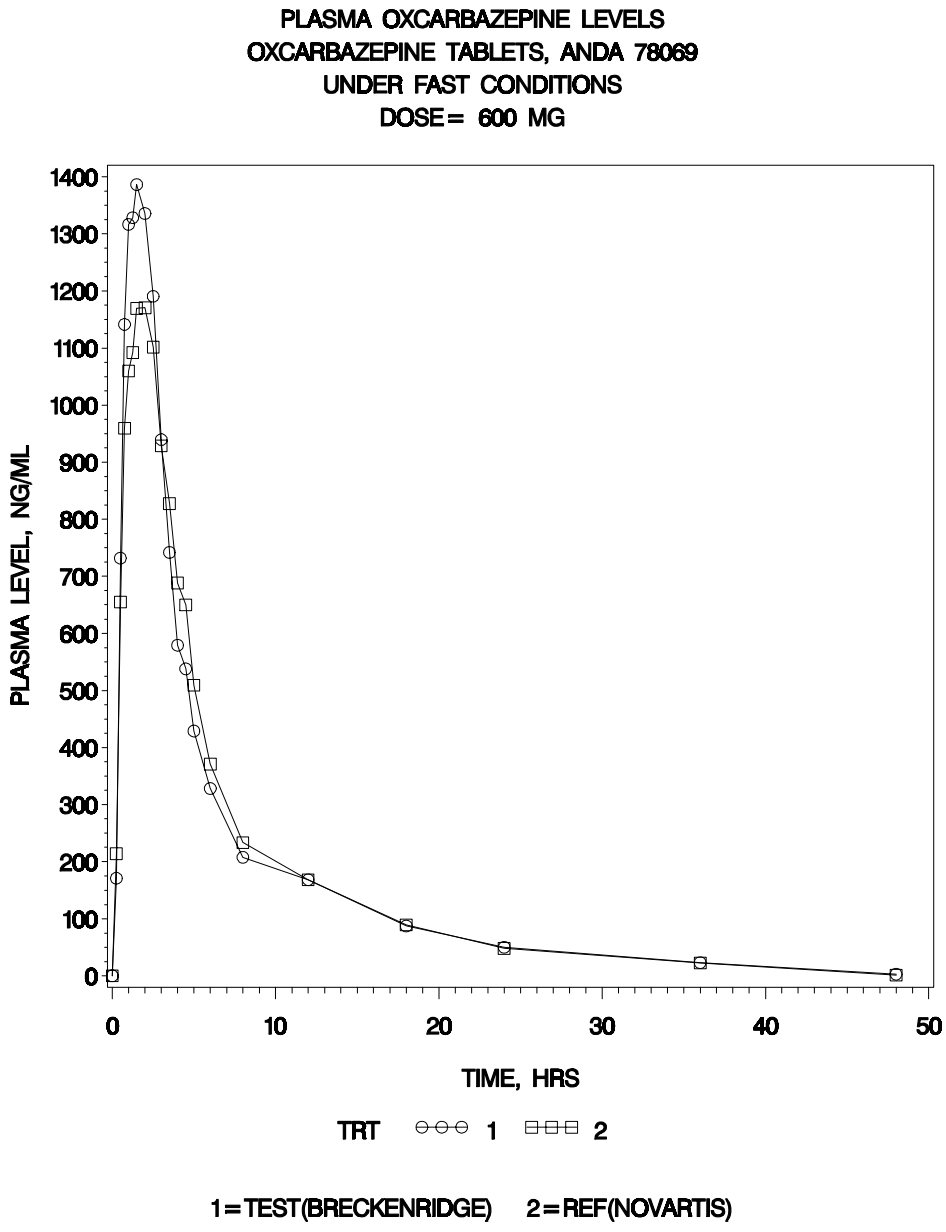
- The 90% confidence intervals for $lnAUC_{0-t}$, $lnAUC_{0-\infty,}$ and lnC_{max} are within the acceptable limits of 80-125%.
- According to the reviewer, there were five sample repeats which can be termed as pharmacokinetic repeats (termed by the firm as "reconfirmation of original results"). The three parent (oxcarbazepine) repeat values remained unchanged after the repeat. The reviewer replaced the two metabolite (MHD) repeat values with the original values and repeated the pharmacokinetic analysis. The 90% confidence intervals for $lnAUC_{0-t,}$ $lnAUC_{0-\infty,}$ and lnC_{max} were still within the acceptable limits of 80-125%.
- For the fasting study, there was discrepancy between the firm's electronic copy and paper copy of the parent (oxcarbazepine) data. Firm's submission of an amendment on November 15, 2006 was inadequate to correct the discrepancy. On December 18, 2006, the firm submitted new electronic data which matches, excluding few exceptions, the paper copy of the above-mentioned data provided in the original submission. The reviewer ran the pharmacokinetic analysis using both datasets (without using firm's pharmacokinetic parameters). For both datasets, the 90% confidence intervals for $lnAUC_{0-t,}$ $lnAUC_{0-\infty,}$ and lnC_{max} were still within the acceptable limits of 80-125%.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:
The single-dose fasting study is **acceptable**.

Table 11: Mean Plasma Concentrations for Oxcarbazepine (ng/mL), Single-Dose Fasting Bioequivalence Study

Time (Hr)	Test (n=60)		Reference (n=60)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.00	N/A	0.00	N/A	N/A
0.25	170.93	170.84	213.98	143.60	0.80
0.5	731.94	101.27	655.03	98.37	1.12
0.75	1141.43	82.37	959.50	83.65	1.19
1	1316.64	74.20	1059.69	74.87	1.24
1.25	1328.44	58.00	1091.94	68.74	1.22
1.5	1386.29	46.60	1169.50	58.90	1.19
2	1335.68	38.17	1170.64	60.46	1.14
2.5	1190.69	42.41	1101.43	62.07	1.08
3	939.48	46.96	928.63	59.27	1.01
3.5	741.98	52.47	827.28	70.00	0.90
4	579.18	59.05	688.22	84.73	0.84
4.5	538.05	54.65	649.89	82.95	0.83
5	428.98	52.51	509.31	78.47	0.84
6	328.28	50.84	370.86	77.66	0.89
8	207.72	50.66	233.66	73.94	0.89
12	168.43	43.27	168.24	51.61	1.00
18	87.35	42.95	89.28	60.44	0.98
24	50.09	56.82	48.12	51.11	1.04
36	23.24	79.72	22.74	82.10	1.02
48	2.97	378.64	1.42	444.42	2.08

Figure 1 Mean Plasma Concentrations for Oxcarbazepine, Single-Dose Fasting Bioequivalence Study (n=60)



2. Single-dose Fed Bioequivalence Study

a) Study Design

Study Information	
Study Number	13319/04-05
Study Title	An open label, randomized, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study to compare Oxcarbazepine 600 mg tablets (Breckenridge Pharmaceutical Inc., USA) with Trileptal® (containing Oxcarbazepine 600 mg) film-coated tablets (Novartis Pharmaceuticals Corporation, USA) in 100 (+6 standby) healthy, adult, human subjects under fed conditions
Clinical Site	Vimta Labs Ltd., 142, IDA, Phase II, Cherlapally, Hyderabad 500 051, India
Principal Investigator	Manoj K. Bose, M.D.
Study/Dosing Dates	Period I: July 23, 2005 Period II: July 30, 2005
Analytical Site	Room No. 331, Clinical Research Division, Central Laboratory, Vimta Labs Ltd., 142, IDA, Phase II, Cherlapally, Hyderabad 500 051, India
Analytical Director (Group Leader)	(b) (6) M.Sc.
Analysis Dates	August 2, 2005 – August 20, 2005
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	29 days[8]

[8] The firm submitted long-term (freezer) storage stability data for 102 days (at -20ºC)

Treatment ID	**A**	**B**
Test or Reference	Test	Reference
Product Name	Oxcarbazepine Tablets	Trileptal® (oxcarbazepine) Tablets
Manufacturer	Anabolic Laboratories for Breckenridge Pharmaceutical, Inc.	Novartis
Batch/Lot No.	316803	F4086
Manufacture Date	4/2005	N/A
Expiration Date	N/A	3/2008
Strength	600 mg	600 mg
Dosage Form	Tablets	Tablets
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	97%	98.7%
Content Uniformity (mean, %CV)	100.2%, 0.8	N/A
Formulation	See **Table 23**	N/A
Dose Administered	1 x 600 mg	1 x 600 mg
Route of Administration	Oral	Oral

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	AB: 2, 3, 5, 8, 10, 12, 14, 15, 17, 18, 23, 24, 27, 28, 30, 32, 33, 36, 37, 38, 42, 44, 46, 48, 51, 52, 53, 55, 58, 59, 62, 63, 66, 67, 70, 71, 73, 74, 77, 78, 81, 82, 85, 86, 90, 92, 94, 95, 98, 100, 103, 104, 106 BA: 1, 4, 6, 7, 9, 11, 13, 16, 19, 20, 21, 22, 25, 26, 29, 31, 34, 35, 39, 40, 41, 43, 45, 47, 49, 50, 54, 56, 57, 60, 61, 64, 65, 68, 69, 72, 75, 76, 79, 80, 83, 84, 87, 88, 89, 91, 93, 96, 97, 99, 101, 102, 105
Blood Sampling Times	0, 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 12.0, 18.0, 24.0, 36.0, and 48.0 hours post-dose
Blood Volume Collected/Sample	Same as Fasting study
Blood Sample Processing/Storage	Same as Fasting study
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See **Table 12**
Length of Fasting before Meal	After an overnight fast of at least 10 hours, subjects received a high-fat, high-calorie breakfast 30 minutes prior to drug administration. Subjects fasted for 4 hours post-dose.
Length of Confinement	Same as Fasting study
Safety Monitoring	Same as Fasting study
Standard FDA Meal Used?	No
If no, then meal is listed in table below	See below

High Fat Breakfast Menu[9]:

Name	**Weight of the sample**	**Fat (gm)**	**Protein (gm)**	**Carbohydrates (gm)**	**Total (Kcal)**
Bread/ butter	43.40 gm	15.20	3.25	19.70	**901.26**
Egg Omelet	20.30 grams	6.20	4.15	1.00	
Hash brown potatoes	85 grams	3.07	2.00	19.44	
Chicken Tikka	75 grams	22.61	31.88	0.69	
Tonned milk	246 ml	5.22	6.53	19.00	
Total		52.3	47.81	59.83	
Energy * (Kcal)		470.70	191.24	239.32	
% Total (energy)		**52.23**	**21.22**	**26.55**	

***** 1 gm of fat = 9 Kcal; 1 gm of protein = 4 Kcal; and 1 gm of carbohydrate = 4 Kcal

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

[9] Based on information provided by the firm in an amendment submitted on January 8, 2007

b) Clinical Results

Table 12: Demographics of Study Subjects

Reviewer's note:

- Demographics data from both the studies (fasting and fed) were provided together by the firm (see **Table 1**).
- The firm also submitted following summary demographic data for the subjects included in the statistical analysis (n=100): Age: 26.20±5.00 (s.d.); BMI: 21.67±2.00 (s.d.); Groups: 18-40 years (98%) and 41-64 (2%); Sex: Male (100%); Race: Asian (100%).

Table 13: Dropout Information

Subject #	Reason	Period	Replaced?
38	Removed from the study because of positive urine drug screen test	Before check-in for period II	#103
82	Withdrawn from the study because of adverse event (dizziness)	Before dosing in period II	#104

Reviewer's note: Subject #38 and 82 were replaced by standby subjects #103 and #104, respectively, with same treatment sequence.

Table 14: Study Adverse Events

Reviewer's note: Adverse event data from both the studies (fasting and fed) were provided together by the firm (see **Table 3**).

Table 15: Protocol Deviations

Type	Subject #s (Test)	Subject #s (Ref.)
Blood sampling time deviations (samples drawn late	Several	Several
There was a deviation in serving 240 mL of drinking water, instead of the protocol-specified 100 mL, to all subjects at 4 hours post-dose in both periods, as 100 mL of drinking water was not deemed sufficient for lunch.	All	All
Blood samples were not collected as subjects did not show up during the ambulatory visit*	13, 37, 42, 56, 70, 75, 78	13, 41, 42, 51, 56, 58, 76

**A deviation in blood draw was considered if: blood was drawn beyond 2 minutes of actual time till the 24-hour time point (housed), or beyond 1 hour of actual time for the 36 and 48-hour time points (ambulatory).

Comments on Dropouts/Adverse Events/Protocol Deviations:

- There were a total of 17 post-dose adverse events, including 11 post-clinical events, reported by 15 subjects. All events were "mild" in severity. Subject #82 was removed from the study before dosing due to adverse event (dizziness). Ten of the adverse events (dizziness, diarrhea, hypoglycemia, increased eosinophil/monocyte count, increased serum creatinine/potassium level) were considered "unrelated" or "remotely related" to the study treatments. The remaining seven adverse events (dizziness, fever, abdominal pain, increased bilirubin/AST level) were considered "probably" related to the study treatments.
- There were several blood draw deviations in the study (samples drawn late) with a maximum deviation of 159 minutes (48 hour time point). All pharmacokinetic parameters were calculated using the actual sampling time.
- **The adverse events and protocol deviations did not compromise the integrity of the study**.

c) Bioanalytical Results

Table 16: Assay Quality Control – Within Study

	Parent (Oxcarbazepine)								
QC Conc. (ng/mL)	4099.550			2562.200		61.500			
Inter day Precision (%CV)	7.11			6.46		10.46			
Inter day Accuracy (%)	101.45			103.68		99.45			
Cal. Standards Conc. (ng/mL)	20.30	40.550	101.40	253.50	506.95	1013.95	2027.85	3041.80	5069.65
Inter day Precision (%CV)	2.76	6.37	4.70	4.58	3.15	2.86	3.92	2.88	4.66
Inter day Accuracy (%)	100.86	98.75	97.33	99.03	99.62	99.61	102.73	101.70	99.30
Linearity Range (range of r values)	0.9967-0.9998								

Comments on Study Assay Quality Control: None

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	**No**
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms: The firm did not include 20% of the chromatograms in the fed study report, because only chromatograms from subjects #1-18 and #20 (both

oxcarbazepine and MHD) were provided amounting to approximately 19% of the total chromatograms. Chromatograms from subject #16 were provided twice.

Table 17: SOPs dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
23/13, version 6.0	March 3, 2005	Repeat Analysis of Samples & Reintegration of Chromatograms

Table 18: Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays:

- There were a total of 4184 study samples analyzed. 171 oxcarbazepine samples (test: 78, reference: 93) and 223 MHD samples (test: 108, reference: 115) were reanalyzed, including both parent and metabolite sample reanalysis for all the available samples from subject #44 and #78 (82 samples). The sample reanalysis represents 9.42% of the total study assays. According to the reviewer, there were a total of eleven (both parent and metabolite) pharmacokinetic repeats (termed by the firm as "reconfirmation of earlier results). The remaining repeats were all analytical repeats. All repeat analyses were done following the SOP for sample reanalysis.
- The analytical method and data are **acceptable**.

d) Pharmacokinetic Results

Table 19: Arithmetic Mean Pharmacokinetic Parameters (n=100)

Mean plasma concentrations are presented in **Table 22** and **Figure 2**.

Oxcarbazepine:

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC_{0-t}	ng/mL x hr	10535.42	23.33	10657.61	23.82	0.99
AUC_{∞}	ng/mL x hr	11132.15	22.61	11236.42	23.36	0.99
C_{max}	ng /mL	4053.79	37.11	4410.52	33.60	0.92
T_{max}	hr	2.10	48.11	1.99	45.06	1.06
K_e	hr^{-1}	0.06	56.92	0.06	41.67	1.02
$T_{1/2}$	hr	13.84	29.44	14.03	34.04	0.99

MHD:

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC_{0-t}	ng/mL x hr	195973.48	16.05	193117.21	15.94	1.01
AUC_{∞}	ng/mL x hr	218188.93	17.78	216785.52	18.29	1.01
C_{max}	ng /mL	8867.11	14.25	8813.53	13.70	1.01
T_{max}	hr	4.61	24.79	4.59	28.26	1.00
K_e	hr^{-1}	0.06	22.65	0.06	22.92	1.02
$T_{1/2}$	hr	12.80	21.64	13.17	28.67	0.97

Table 20: Geometric Means and 90% Confidence Intervals for Oxcarbazepine (n=100)

Parameter	Test	Reference	T/R	90% CI
AUC_{0-t}	10273.38	10370.09	0.99	96.68-101.51
AUC_{∞}	10875.31	10947.68	0.99	97.06-101.67
C_{max}	3813.17	4151.30	0.92	86.42-97.43

Reviewer's note: The values in the above table were calculated by the reviewer.

Table 21: Additional Study Information for (n=100)

	Oxcarbazepine
Root mean square error, $lnAUC_{0-t}$	0.103874
Root mean square error, $lnAUC_{0-\infty}$	0.098861
Root mean square error, lnC_{max}	0.259500
K_{el} and $AUC_{0-\infty}$ determined for how many subjects?	100
Do you agree or disagree with firm's decision?	Agree
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as C_{max}	None
Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic and Statistical Analysis:

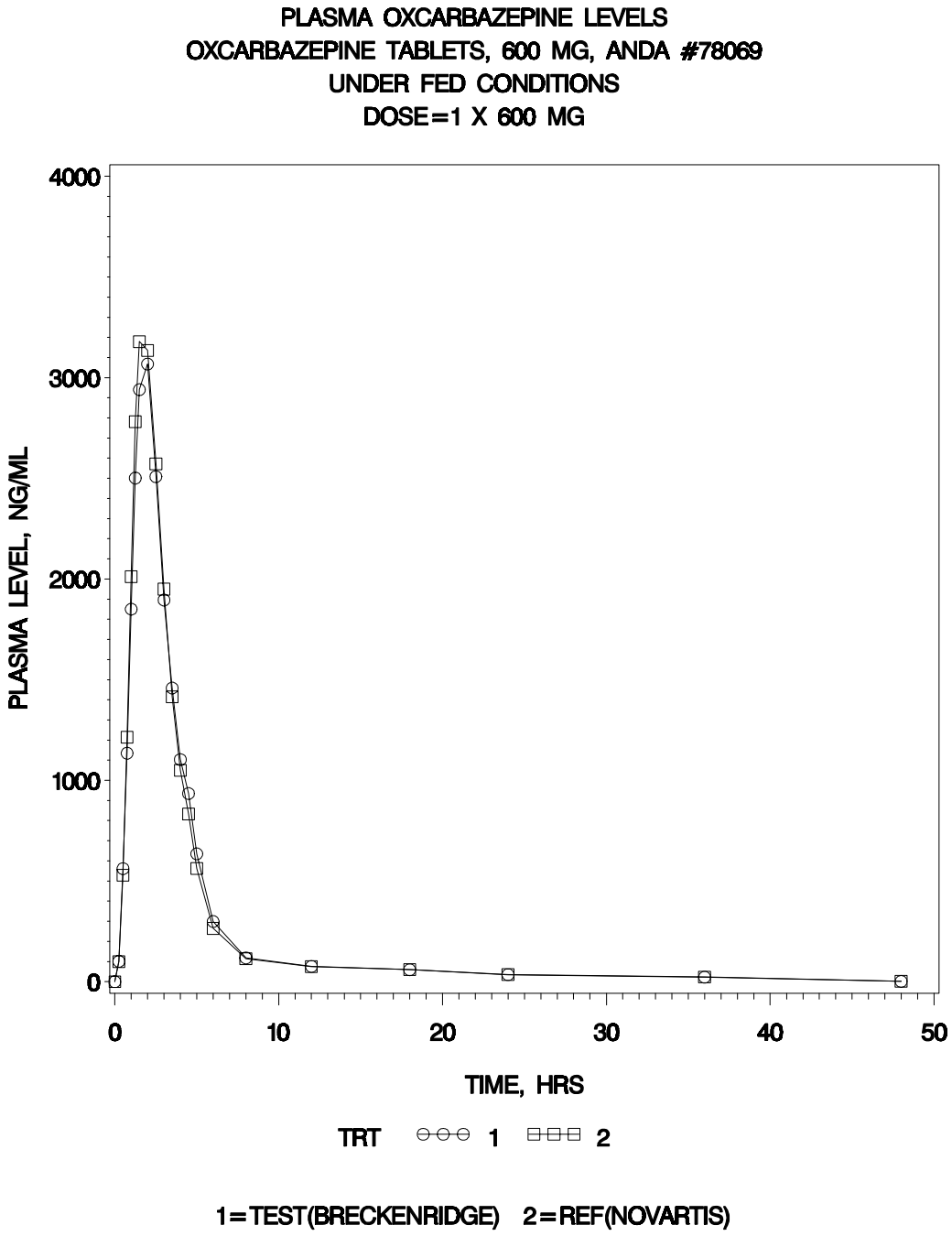
- The pharmacokinetic parameters and 90% confidence intervals for oxcarbazepine, as calculated by the reviewer, agree with the firm's calculations.
- The 90% confidence intervals for $lnAUC_{0-t}$, $lnAUC_{0-\infty,}$ and lnC_{max} for oxcarbazepine are within the acceptable limits of 80-125%.
- The pharmacokinetic analysis for both oxcarbazepine and its metabolite (MHD) were repeated after replacing the eleven PK repeat values (termed by the firm as "reconfirmation of earlier results) with the original values, for both the analytes. For oxcarbazepine, the 90% confidence intervals for $lnAUC_{0-t}$, $lnAUC_{0-\infty,}$ and lnC_{max} were still within the acceptable limits of 80-125%. For the metabolite (MHD), the mean plasma concentrations and pharmacokinetic parameters were comparable for the test and reference products.

Summary/Conclusions, Single-Dose Fed Bioequivalence Study:
The single-dose fed study is **acceptable**.

Table 22: Mean Plasma Concentrations for Oxcarbazepine (ng/mL), Single-Dose Fed Bioequivalence Study

Time (Hr)	Test (n=100)		Reference (n=100)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.00	.	0.00	.	N/A
0.25	101.35	302.50	99.32	273.30	1.02
0.5	561.53	143.56	529.10	129.49	1.06
0.75	1134.72	120.32	1214.39	103.34	0.93
1	1850.26	96.03	2011.37	85.97	0.92
1.25	2501.41	74.53	2781.93	72.53	0.90
1.5	2940.76	61.04	3179.07	63.03	0.93
2	3067.98	43.69	3135.17	45.64	0.98
2.5	2508.25	40.39	2572.00	42.49	0.98
3	1895.69	36.66	1950.08	45.80	0.97
3.5	1458.43	43.74	1415.29	55.05	1.03
4	1103.15	69.41	1050.17	73.35	1.05
4.5	934.68	105.14	833.18	101.88	1.12
5	635.05	114.90	562.44	122.21	1.13
6	299.08	132.82	264.70	120.17	1.13
8	118.18	85.81	114.03	60.60	1.04
12	75.70	23.91	74.58	21.91	1.02
18	59.40	22.01	60.98	29.76	0.97
24	35.08	31.92	35.26	27.23	0.99
36	22.51	70.26	23.08	57.77	0.98
48	1.55	396.96	1.95	365.63	0.80

Figure 2: Mean Plasma Concentrations for Oxcarbazepine, Single-Dose Fed Bioequivalence Study (n=100)



B. Formulation Data

Table 23 Formulation of Oxcarbazepine Tablets

Tablet Ingredients	Amount (mg) / Tablet	Amount (%) Tablet	Amount (mg) / Tablet	Amount (%) Tablet	Amount (mg) / Tablet	Amount (%) Tablet
Oxcarbazepine	600		300		150	
Hypromellose, USP						
Microcrystalline Cellulose, NF						
Magnesium Stearate, NF						
Crospovidone, NF						
Colloidal Silicon Dioxide, NF						
Talc, USP						
Coating Ingredients						
(b) (4) Beige (b) (4) consisting of: Polyvinyl Alcohol, USP Talc, USP Titanium Dioxide, USP Polyethylene Glycol, USP FD&C Yellow #6 FD&C Blue #2 FD&C Yellow #5 Lecithin, NF						
(b) (4)						
Total	828	100%	414	100%	207	100%

(b) (4)

Composition of (b) (4) Beige (b) (4)[10]

Ingredients	Amount (mg) 150 mg Tablets	Amount (mg) 300 mg Tablets	Amount (mg) 600 mg Tablets
Polyvinyl Alcohol, USP			(b) (4)
Talc, USP			
Titanium Dioxide, USP			
Polyethylene Glycol (b) (4) USP			
FD&C Yellow #6 FD&C Blue #2 FD&C Yellow #5			
Lecithin, NF			

[10] Composition of (b) (4) Beige (b) (4) was obtained from page 12 of the chemistry review of ANDA #78069 (\\cdsnas\ogds11\firmsam\breckenridge\ltrs&rev\78069.cr1.doc).

C. Dissolution Data

FDA-recommended method and specification

Medium	Water (at 37ºC) with: 1.0% SDS for the 600 mg strength 0.6% SDS for the 300 mg strength 0.3% SDS for the 150 mg strength
Volume (mL)	900 mL
USP Apparatus type	II (paddle)
Rotation (rpm)	60
FDA-recommended specifications	NLT (b) (4) (Q) in 30 min, and NLT (Q) in 60 min

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The dissolution amendment review is stored at:
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D. Consult Reviews

None

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BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-069 APPLICANT: Breckenridge Pharmaceutical, Inc.

DRUG PRODUCT: Oxcarbazepine Tablets, 150 mg, 300 mg, and 600 mg

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

We acknowledge that you have accepted the following dissolution method and specification:

The dissolution testing should be conducted in 900 mL water (with 0.3% sodium dodecyl sulfate (SDS) in water for the 150 mg strength; 0.6% SDS in water for the 300 mg strength; and 1% SDS in water for the 600 mg strength) at 37°C using USP apparatus II (paddle) at 60 rpm. The test products should meet the following specifications:

- Not less than (b) (4)% (Q) of the labeled amount of oxcarbazepine in the dosage form is dissolved in 30 minutes;

- Not less than (b) (4) (Q) of the labeled amount of oxcarbazepine in the dosage form is dissolved in 60 minutes.

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

Sincerely yours,

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

ANDA#: 78-069

BIOEQUIVALENCE – **ACCEPTABLE** Submission Date: **December 22, 2005**

1. **FASTING STUDY** (STF) Strength: 600 mg
   Clinical: Vimta Labs Ltd., **Outcome: AC**
   142, IDA, Phase II, Cherlapally,
   Hyderabad 500 051, India

   Analytical: Room No. 331, Clinical Research Division,
   Central Laboratory, Vimta Labs Ltd.,
   142, IDA, Phase II, Cherlapally,
   Hyderabad 500 051, India

2. **FOOD STUDY** (STP) Strength: 600 mg
   Clinical: Same as fasting study **Outcome: AC**

   Analytical: Same as fasting study

3. **Dissolution Waiver** (DIW) Strength: 150 mg
   Outcome: AC

4. **Dissolution Waiver** (DIW) Strength: 300 mg
   Outcome: AC

5. **Study Amendment** (STA) Strength: 150 mg and 300 mg
   Submitted on November 15, 2006 **Outcome: WC**

6. **Study Amendment** (STA) Strength: 150 mg and 300 mg
   New SAS data submitted on December 18, 2006 **Outcome: WC**

Outcome Decisions: AC - Acceptable

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/s/

Parthapratim Chandaroy
1/9/2007 04:14:02 PM
BIOPHARMACEUTICS

Kuldeep R. Dhariwal
1/9/2007 04:17:43 PM
BIOPHARMACEUTICS

Barbara Davit
1/10/2007 11:43:42 AM
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