CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-005

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	78-005	
Drug Product Name	Oxcarbazepine Tablets	
Strength	150 mg, 300 mg and 600 mg	
Applicant Name	Teva Pharmaceuticals, USA	
Submission Date(s)	November 23, 2005	
First Generic	No	
Reviewer	Yi Zhang, Ph.D.	
File Location	**V:\firms\Teva\ltrs&rev\78005D1105.doc**	
Clinical Site	Pharma Medica Research Inc. 966 Pantera Drive, Unit 31 Mississauga, Ontario L4W 2S1 (For Fasted Study 2005-917 and Fed Study 205-918)	Anapharm 2050, Boul. Rene-Levesque Ouest Sainte-Foy (Quebec) Canada, G1V 2K8 (For Fed Study 50370)
Analytical Site	Pharma Medica Research Inc. 966 Pantera Drive, Unit 31 Mississauga, Ontario L4W 2S1 (For Fasted Study 2005-917 and Fed Study 205-918)	Anapharm 2050, Boul. Rene-Levesque Ouest Sainte-Foy (Quebec) Canada, G1V 2K8 (For Fed Study 50370)
Dissolution Testing Site	Teva Pharmaceutical Industries, Ltd. Hashikma Street, Industrial Area Kfar-Saba 44102, ISRAEL	

EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP method for this product but there is an FDA-recommended method. The firm's dissolution testing data with the FDA-recommended method are acceptable (at the S1 level). All strengths of the test products met the specifications of NLT (b) (4)% (Q) in 30 minutes and NLT (b) (4)% (Q) in 60 minutes. However, the firm's proposed specification of NLT (b) (4)% (Q) in 90 minutes is not the FDA-recommended specification. Therefore, the dissolution testing is incomplete pending the firm's acceptance of the above FDA-recommended specifications.

The firm has submitted all 8 electronic summary tables in the Division of Bioequivalence (DBE)-recommended format which are located in the EDR. No additional tables are needed.

The DBE will review the fasted and fed BE studies and waiver requests at a later date.

RLD METHOD

Medium/ Volume	900 mL water + 0.3% SDS (for the 150 mg strength); 900 mL water + 0.6% SDS (for the 300 mg strength); 900 mL water + 1% SDS (for the 600 mg strength);
Temperature	37 °C
Apparatus	II (Paddle)
Rotational Speed	60 rpm
Sampling Time	10, 20, 30, 45, 60 and 90 minutes
Specifications	NLT (b) (4)% (Q) in 30 minutes; NLT (b) (4)% (Q) in 60 minutes

Source of Method: OCPB review NDA 21-014/SCF-014, dated April 27, 2005, Protocol 04-059, ANDA 77-747, DBE Dissolution Database accessed on 03/30/2006.

Table 1. Summary of In Vitro Dissolution Data

Study Ref. No.	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	45 min	60 min	75 min	90 min	
CDP-1248/01	Oxcarbazepine K-34924	150 mg Tablets	**Dissolution:** Apparatus 2 (Paddles) **Speed of Rotation:** 60 rpm **Medium:** For 150 mg strength: 0.3% (w/v) sodium lauryl sulphate in water For 300 mg strength: 0.6% (w/v) sodium lauryl sulphate in water For 600 mg strength: 1.0% (w/v) sodium lauryl sulphate in water **Volume:** 900 mL **Temperature:** 37°C ± 0.5°C **Tolerance:** NLT (b) (4)% (Q) dissolved in 90 minutes	12	89	93	95	96	96	96	96	96 (b) (4)	Original ANDA pgs 113-124
	Trileptal® F0102	150 mg Tablets		12	78	87	91	95	98	99	100	100 (b) (4)	
CDP-1248/01	Oxcarbazepine K-34925	300 mg Tablets		12	86	94	95	97	99	98	98	98 (b) (4)	
	Trileptal® F0135	300 mg Tablets		12	87	95	97	99	99	100	99	99 (b) (4)	
CDP-1225/01	Oxcarbazepine K-34926	600 mg Tablets		12	82	89	99	101	101	101	102	102 (b) (4)	
	Trileptal® 295H9442	600 mg Tablets		12	77	89	93	95	97	100	97	99 (b) (4)	

Table 2. SAS Transport Files

Are the SAS files located in the EDR ? (Yes/No)	
Fasting BE Study	
Plasma Data	Yes
PK data	Yes
Fed BE Study	
Plasma Data	Yes
PK Data	Yes

COMMENTS:

1. Dissolution profiles were generated on 12 tablets each for the test and reference products.

Drug Product		Batch No.	Manufacture Date	Expiration Date	Analysis Date
Oxcarbazepine Tablets	150 mg	K-34924	03/28/2005		04/11/2005
	300 mg	K-34925	03/28/2005		04/04/2005
	600 mg	K-34926	03/28/2005		04/04/2005
Trileptal® Tablets	150 mg	F0102		11/2007	04/13/2005
	300 mg	F0135		09/2007	04/12/2005
	600 mg	295H9442		05/2006	04/05/2005

2. The firm conducted the dissolution testing using the FDA-recommended method. The dissolution data for the test and reference products are acceptable. However, the firm's proposed specification is not the FDA-recommended specification. Therefore, the dissolution testing is incomplete pending the firm's acceptance of the FDA-recommended specifications of NLT (b) (4)% (Q) in 30 minutes and NLT (b) (4)% (Q) in 60 minutes.

3. The firm has provided all 8 electronic summary tables in the DBE-recommended format which are located in the EDR.

DEFICIENCY COMMENTS:

The firm's proposed dissolution specification of NLT (b) (4)% (Q) of the labeled amount of oxcarbazepine in the dosage form dissolved in 90 minutes is not acceptable. The firm should be advised to acknowledge the FDA-recommended dissolution specifications of NLT (b) (4)% (Q) in 30 minutes and NLT (b) (4)% (Q) in 60 minutes.

RECOMMENDATIONS:

1. The dissolution testing conducted by Teva Pharmaceuticals on its test and the reference products is incomplete pending the firm's acknowledgement of its acceptance of the FDA-recommended dissolution specifications. The firm should conduct the dissolution testing 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.

2. The firm's proposed dissolution specification of NLT (b) (4)% (Q) in 90 minutes is not acceptable. The firm should acknowledge its acceptance of the above FDA-recommended dissolution specifications.

04/10/2006

Yi Zhang, Ph.D., Review Branch IV
Division of Bioequivalence
Office of Generic Drugs

4/10/2006

Yih-Chain Huang, Ph.D.
Team Leader, Review Branch IV
Division of Bioequivalence
Office of Generic Drugs

4/10/06

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

BIOEQUIVALENCE DEFICIENCY

ANDA: 78-005 APPLICANT: Teva Pharmaceuticals, USA

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

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

Your dissolution testing 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 with USP apparatus II (paddle) at 60 rpm is acceptable. However, your proposed dissolution specification of NLT (b) (4)% (Q) of the labeled amount of oxcarbazepine in the dosage form dissolved in 90 minutes is not acceptable. 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 acknowledge your acceptance of the above FDA-recommended dissolution specifications.

Sincerely yours,

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

CC: ANDA 78-005
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Bio Drug File
HFD-650/ Yi Zhang
HFD/650/ Beth Fabian-Fritsch

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Printed in final on 04/10/06

Endorsements: (Final with Dates)
HFD-650/ Yi Zhang YZ 04/10/06
HFD-650/ Yih-Chain Huang YH 4/10/2006
HFD-650/ D . P. Conner BMD 4/10/06

DISSOLUTION – Incomplete Submission date: November 23, 2005

[NOTE: The *in vitro* testing is incomplete. The fasting and fed BE studies and waiver requests are pending review]
(The firm needs to acknowledge the current FDA-recommended dissolution specifications.)

1. DISSOLUTION (Dissolution Data)	Strength:	150 mg
	Outcome:	**IC**
2. DISSOLUTION (Dissolution Data)	Strength:	300 mg
	Outcome:	**IC**
3. DISSOLUTION (Dissolution Data)	Strength:	600 mg
	Outcome:	**IC**

Outcome Decisions: IC – Incomplete
WinBio Comments: IC

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-005	
Drug Product Name	Oxcarbazepine Tablets	
Strength	150 mg, 300 mg, and 600 mg	
Applicant Name	Teva Pharmaceuticals USA	
Address	1090 Horsham Road, PO Box 1090, North Wales, PA 19454 Philip Erickson, R.Ph., PH (215) 591-3141 Fax (215) 591-8812	
Clinical Site(s)	Study Nos. 2005-917 and 2005-918 Pharma Medica Research, Inc., 966 Pantera Drive, Unit 31, Mississauga, Ontario L4W 2S1	Study No. 50370 SFBC Anapharm, 2050, Boul. Rene-Levesque Ouest, Sainte-Foy (Quebec), Canada G1V 2K8
Analytical Site(s)	Study Nos. 2005-917 and 2005-918 Pharma Medica Research, Inc., 966 Pantera Drive, Unit 31, Mississauga, Ontario L4W 2S1	Study No. 50370 SFBC Anapharm, 2050, Boul. Rene-Levesque Ouest, Sainte-Foy (Quebec), Canada G1V 2K8
Submission Date(s)	November 23, 2005	
Amendment Date(s)	August 02, 2006 (Dissolution amendment) August 31, 2006 (Complete study reports and SAS data files) October 06, 2006 (Stability Data)	
First Generic	No	
Reviewer	April C. Braddy, Ph.D.	

Review of Three Bioequivalence Studies and Waiver Requests

I. Executive Summary

In this application, the firm, Teva Pharmaceuticals USA, submitted two acceptable bioequivalence (BE) studies, one under fasting and the other under fed conditions, and dissolution data on all the test and reference products. The studies were conducted on the 600 mg tablets comparing them to Novartis' Trileptal® Tablets, 600 mg. The BE studies were conducted as two-way, crossover studies in healthy male and female subjects (N = 57 and N = 116 for the fasting and fed studies, respectively) given a dose of one tablet in each study. Statistical analyses of plasma concentration data of the parent drug, oxcarbazepine and its active metabolite, 10-hydroxy-carbazepine demonstrate bioequivalence in both studies.

For the fasting BE study, oxcarbazepine results (point estimate, 90% CI) are: $LAUC_T$ of 1.02, 98.78-105.71%, $LAUC_\infty$ of 1.03, 99.26-105.93%, and LC_{max} of 0.98, 88.98-109.00%. 10-Hydroxy-Carbazepine results (point estimate, 90% CI) are: $LAUC_T$ of 1.00, 97.50-102.15%, $LAUC_\infty$ of 1.00, 97.75-102.18%, and LC_{max} of 1.01, 97.03-104.65%.

For the fed BE study (N = 116), oxcarbazepine results (point estimate, 90% CI) are: $LAUC_T$ of 0.99, 96.79-101.11%, $LAUC_\infty$ of 0.99, 96.86-101.05%, and LC_{max} of 0.92, 86.11-97.80%. 10-Hydroxy-Carbazepine results (point estimate, 90% CI) are: $LAUC_T$ of 1.00, 99.01-101.74%, $LAUC_\infty$ of 1.00, 99.11-101.69%, and LC_{max} of 0.99, 96.75-100.57%.

The firm also submitted a failed fed BE study conducted on the 600 mg strength. Teva indicated that the study was under powered. The observation that the failed fed BE study enrolled 59 subjects whereas the acceptable fed BE study enrolled 116 subjects support's Teva's hypothesis.

The firm submitted waiver requests from *in vivo* BE study requirements for its oxcarbazepine 150 mg, and 300 mg strength tablets. The formulations for the 150 mg and 300 mg tablets are proportionally similar to the formulation of the 600 mg tablet. The Division of Bioequivalence (DBE) previously reviewed the dissolution testing method and data. The firm conducted comparative dissolution testing using the FDA-recommended method (V:\FIRMSNZ\TEVA\LTRS&REV\78005D1105.DOC). The firm acknowledged the FDA-recommended dissolution method and specifications for its Oxcarbazepine Tablets, 150 mg, 300 mg, and 600 mg. The firm's dissolution testing data with the FDA-recommended method is acceptable.

The waivers for the Oxcarbazepine Tablets, 150 mg, and 300 mg are granted based on 21 CFR §320.22(d)(2).

The application is acceptable with no deficiencies.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Oxcarbazepine Tablet
RLD	Trileptal® Tablet
RLD Manufacturer	Novartis Pharma AG
NDA No.	21-014
NDA 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 to 16 with epilepsy.

PK/PD Information[1]

Bioavailability	Following oral administration of Trileptal® Tablet, the parent drug, oxcarbazepine is completely absorbed. Food has no effect on the rate or extent of absorption of oxcarbazepine.
Metabolism	The parent drug, oxcarbazepine is rapidly and extensively metabolized in the liver by cytosolic enzymes to its pharmacologically active, 10-monohydroxy metabolite (MDH). MDH is metabolized by conjugation with glucoronic acid and further oxidized to the inactive 10, 11-dihydroxy metabolite (DHD) – (4% of dose).
Half Life	The elimination half-life for oxcarbazepine and 10-monohydroxy metabolite is 2 and 9 hours, respectively.
Tmax	After a single oral dose of Trileptal® Tablets, the T_{max} is 4.5 hrs (range 3 to 13 hrs).
Excretion	Oxcarbazepine is mostly cleared from the body and excreted by the kidneys in the form of its metabolites. More than 95% of the administered oral dose appears in the urine with less than 1% appearing as unchanged oxcarbazepine. Fecal excretion accounts for less than 4% of the administered oral dose. Approximately 80% of the dose is excreted in urine either as glucuronides of the 10-monohydroxy metabolite (MDH) (49%) or as unchanged MDH (27%); the inactive 10, 11-dihydroxy metabolite (DHD) accounts for approximately 3% and conjugates of MHD and oxcarbazepine account for 13% of the dose.

[1] 1. Online-Physicians' Desk Reference Electronic Library™. (2006). http://www.thomsonhc.com. Thomson Micromedex: Keyword Search: Trileptal® Tablets. Last accessed: 09/20/2006.
2. Online-Clinical Pharmacology (2006). http://cpip.gsm.com . World-Class Drug Information: Monographs: Trileptal® Tablets. Last updated: 12/18/2005: Last accessed: 09/20/2006.

Relevant DBE History	There are presently no generic drug products on the market for the reference-listed drug, Trileptal® Tablets by Novartis. To establish bioequivalence of Oxcarbazepine Tablets, 600 mg to the RLD, Trileptal® Tablets, 600 mg the Division of Bioequivalence (DBE) recommends the following studies: 1. Based on the CDER BA/BE General Guidance and the CDER Guidance "Food-Effect Bioavailability and Fed Bioequivalence Studies" the firm should conduct the following bioequivalence studies: **a.** A single-dose, two-way crossover fasting *in vivo* BE study comparing Oxcarbazepine Tablet, 600 mg to the reference-listed drug (RLD), Trileptal® Tablet, 600 mg. **b.** A single-dose, two-way crossover fed *in vivo* BE study comparing Oxcarbazepine Tablets, 600 mg to the reference-listed drug (RLD), Trileptal® Tablets, 600 mg. **c.** The firm should measure both the parent compound, oxcarbazepine; and can also measure its metabolite, 10-hydroxy-carbazepine, to provide supportive evidence of comparable therapeutic outcome in plasma using an achiral assay. 2. The firm should conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the following FDA method: Apparatus: USP 26 apparatus II (Paddle) Speed: 60 rpm Medium: Aqueous Sodium Codicil Sulfate (SDS) solution Volume: 900 mL Temperature: 37˚C ± 0.5˚C Sampling times: 10, 20, 30, 45, 60, 75, and 90 minutes or until at least (b) (4) of the label content is dissolved. The concentration of SDS is varied for the tablets: ▪ 0.3% for 150 mg ▪ 0.6% for 300 mg ▪ 1.0% for 600 mg

	Note: SDS is required due to the poor solubility of oxcarbazepine Dissolution specification will be determined at the time of the ANDA review. Since, oxcarbazepine has low aqueous solubility, it may be necessary to set a two-point specification. 3. The lower strengths of Oxcarbazepine Tablets, 150 mg, and 300 mg may be eligible for a waiver of *in vivo* BE study requirements based on (1) demonstration of acceptable bioequivalence on the proposed 600 mg strength, (2) acceptable dissolution testing for 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. The DBE has reviewed several ANDAs for Oxcarbazepine Tablets, 150 mg, 300 mg, and 600 mg: (b) (4) ((b) (4) 05/17/2005), (b) (4) (b) (4) 07/13/2005), #77-747 (Apotex, 07/14/2005), #77-795 (Roxane Laboratories, 07/14/2005), #77-794 (Sun Pharmaceuticals Industries, Ltd., 07/14/2005), #77-801 (Taro, 07/14/2005), #77-802 (Glenmark Pharmaceuticals, Limited, 07/15/2005), (b) (4) ((b) (4) 11/30/2005) Also, the DBE has reviewed numerous controlled documents and protocols for Oxcarbazepine Tablets, 150 mg, 300 mg, and 600 mg (since 01/01/2004): #04-094 (Teva Pharmaceuticals, Inc., 01/26/2004), #04-605 ((b) (4) (b) (4) 06/04/2004), #04-672 ((b) (4) (b) (4) 06/25/2004), #04-699 (b) (4) (b) (4) 07/14/2004), #04-1072 ((b) (4) 11/17/2004), #04-1173 (b) (4) 12/13/2004), #05-0381 ((b) (4) 03/22/2005), #05-0546 – ((b) (4) 04/22/2005); and #04-059 ((b) (4) 12/21/2004)
Dosage and Administration	Trileptal® Tablets should be given in a BID (twice-a-day) regimen.
Agency Guidance	2002 Food-Effect BA/BE Studies and 2003 General BA/BE Guidance Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations (issued Mar 2003)
Drug Specific Issues (if any)	Trileptal® should not be used in patient with a known hypersensitivity to oxcarbazepine or to any of its components.

	In addition, Trileptal® should be withdrawn gradually to minimize the potential of increased seizure frequency.

B. Contents of Submission

Study Type(s)	Yes/No?	How many?
Single-dose fasting study	Yes	1
Single-dose fed study	Yes	2 (Includes a failed study)
Steady-state study	No	--
In vitro dissolution testing	Yes	3
Waiver requests	Yes	2
BCS waivers	No	--
Vasocontrictor studies	No	--
Clinical endpoints	No	--
Failed studies	Yes	1
Amendments	Yes	3

C. Bioanalytical Method Validation

1. Pre-Study: 2005-917 (Fasting)

Number of Analytes: 2

Report Location of the Validation Report Study No. 2005-917	**(Volume 6, Pages 495-562)**	**(Volume 6, Pages 495-562)**
Analyte	***Oxcarbazepine***	***10-Hydroxy Carbazepine***
Internal standard (IS)	(b) (4)	(b) (4)
Method description	Protein precipitation; LCMS/MS	Protein precipitation; LCMS/MS
Limit of quantitation (units)	20.0 ng/mL	100 ng/mL
Average recovery of analyte (%)	92.8 % - 96.6 %	96.2 % - 99.5 %
Average recovery of IS (%)	106.5 %	106.5 %
Standard curve concentrations (units)	20.0, 40.0, 100, 200, 396, 594, 990, 1980 ng/mL	100, 200, 400, 800, 1000, 2000, 5000, 10000 ng/mL
QC concentrations (units)	60.0, 743, 1485 ng/mL	300, 3500, 7500 ng/mL
QC intra-day precision range (%)	0.9 % - 5.3 %	0.8 % - 8.7 %
QC intra-day accuracy range (%)	93.3 % - 113.0 %	93.3 % - 114.3 %
QC inter-day precision range (%)	4.2 % - 6.0 %	4.6 % - 7.3 %
QC inter-day accuracy range (%)	98.3 % - 105.0 %	97.4 % - 108.7 %
Bench-top stability (hrs)	6.00 hours @ room temperature	6.00 hours @ room temperature
Stock stability (days)	160 Days	152 Days
Processed stability at 5º C (hrs)	50.50 hours @ 5º C	50.50 hours @ 5º C
Freeze-thaw stability (cycles)	3 cycles	3 cycles
Long-term storage stability (days)	112 days @ -20±5º C	112 days @ -20±5º C
Dilution integrity	Concentration diluted 5-fold	Concentration diluted 5-fold
Selectivity	No interfering peaks noted in blank plasma samples	No interfering peaks noted in blank plasma samples
SOPs submitted*	Yes	Yes
Bioanalytical method is acceptable*	Yes	Yes
20% Chromatograms included*	Yes	**Serially Selected?*** Yes

[1] Table provided by firm
*: Reviewer added the information to the table

2. Pre-Study: 50370 (Fed)

Number of Analytes: 2

Study No. 50370 (Fed) - Section 16.6, Pages 1-191 of 191				
Analytical Site: SFBC Anapharm, Sainte-Foy (Quebec), Canada, G1V 2K8				
	Parent (1)		**Metabolite (2)**	
Analyte name	Oxcarbazepine		10-Hydroxycarbamazepine	
Internal Standard	(b) (4)		(b) (4)	
Method description	Solid-phase extraction; LC/MS/MS		Solid-phase extraction; LC/MS/MS	
QC range (ng/mL)	11.95 ng/ml, 597.60 ng/mL, and 1394.40 ng/mL		60.50 ng/mL, 3025.00 ng/mL, and 10192.00 ng/mL	
Standard curve range	3.96 ng/mL to 1977.60 ng/mL		20.39 ng/mL to 10192.00 ng/mL	
Limit of quantitation (ng/mL)	3.96 ng/mL		20.38 ng/mL	
Average recovery of Drug (%)	79.40% to 85.46%		88.33% to 106.76%	
Average Recovery of Int. Std (%)	90.76%		90.76%	
Intraday precision range (%)	3.03% to 6.07%		3.93% to 6.40%	
Intraday accuracy range (%)	105.01% to 110.30%		103.81% to 106.43%	
Interday precision range (%)	3.63% to 5.47%		3.46% to 4.42%	
Interday accuracy range (%)	102.10% to 103.10%		102.12% to 103.61%	
Bench-top stability (hours)	24 hours @ RT		24 hours @ RT	
Stock stability (days)	24 days @ -20˚C and 70 days @ -80˚C		46 days @ -20˚C and 74 days @ -80˚C	
Processed stability at RT (hrs)	110 hours @ RT		110 hours @ RT	
Freeze-thaw stability (cycles)	4 cycles @ -20˚C 4 cycles @ -80˚C		4 cycles @ -20˚C 4 cycles @ -80˚C	
Long-term storage stability (days)	365 days @ -80˚C		365 days @ -80˚C	
Dilution integrity	Concentration diluted 2-fold and 20 fold		Concentration diluted 2-fold and 20 fold	
Specificity	Yes		Yes	
SOPs submitted	Yes		Yes	
Bioanalytical method is acceptable	**Yes**		**Yes**	
20% Chromatograms included	No	**Serially Selected?**		Yes

Reviewer's Comments: In the original ANDA submission, the firm did not provide the stability data for oxcarbazepine and its metabolite, 10-hydroxy-carbazepine in plasma. On September 27, 2006, the firm was notified of this deficiency via telephone. The firm amended their application on October 6, 2006 and provided the necessary stability data from the respective analytical sites, Pharma Medica Research, Inc (Study No. 2005-917 and 2005-918) and SFBC Anapharm (Study No. 50370). The bioanalytical method is acceptable.

D. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study (2005-917)

Study No.	2005-917
Study Design	An open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover study
No. of subjects enrolled	60
No. of subjects completing	58
No. of subjects analyzed	57
Subjects (Healthy/Patients?)	Healthy, non-smoking
Sex(es) included (how many?)	**Male:** 38 **Female:** 22
Test product	Oxcarbazepine Tablets
Reference product	Trileptal® Tablets
Strength tested	600 mg
Dose	1 x 600 mg

Summary of Statistical Analysis

Summary of Statistical Analysis, Fasting Bioequivalence Study *Additional Information in Appendix A,* Table A1-9, Table A1-10, Table A1-13, and Table A1-14		
OXCARBAZEPINE		
Parameter	**Point Estimate**	**90% Confidence Interval**
$LAUC_T$	1.02	98.78-105.71%
$LAUC_\infty$	1.03	99.26-105.93%
LC_{max}	0.98	88.98-109.00%
10-HYDROXY-CARBAZEPINE		
Parameter	**Point Estimate**	**90% Confidence Interval**
$LAUC_T$	1.00	97.50-102.15%
$LAUC_\infty$	1.00	97.75-102.18%
LC_{max}	1.01	97.03-104.65%

Reviewer's Comments: Sixty (60) healthy male and female subjects were enrolled in the fasting study. Fifty-eight (58) subjects completed the study and the data from fifty-seven (57) subjects were used for BE statistical evaluations. Two (2) subjects voluntarily withdrew from the study during the wash out period due to the occurrence of adverse events (unrelated the study drug) and for personal reasons, respectively. Also, one (1) subject did not return for some of the scheduled blood sampling time collections and was therefore not included in the data set. These subjects were not replaced in the study.

Study No. 2005-917 (Fasting) Additional Information on pages 2078-2088 of 2902								
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								
Pharmacokinetic[1]	**1**	**2**	**0.08**	**0.15**	**0**	**0**	**0**	**0**
Reason A	1	2	0.08	0.15	0	0	0	0
Analytical	**60**	**47**	**4.59**	**3.59**	**60**	**47**	**4.59**	**3.59**
Reason AULOQ	44	35	3.36	2.67	44	35	3.36	2.67
Reason EE	0	1	0	0.08	0	1	0	0.08
Reason PC	4	4	0.31	0.31	4	4	0.31	0.31
Reason UISR	12	7	0.92	0.53	12	7	0.92	0.53
Total	**61**	**49**	**4.67**	**3.74**	**60**	**47**	**4.59**	**3.59**
10-Hydroxy-carbazepine								
Pharmacokinetic[1]	**6**	**6**	**0.46**	**0.46**	**1**	**4**	**0.08**	**0.31**
Reason A	0	1	0	0.08	0	1	0	0.08
Reason B	6	5	0.46	0.38	1	3	0.08	0.23
Analytical	**30**	**20**	**2.29**	**1.53**	**30**	**20**	**2.29**	**1.53**
Reason AULOQ	15	10	1.15	0.76	15	10	1.15	0.76
Reason AULOQ/UISR	3	0	0.23	0	3	0	0.23	0
Reason EE	0	1	0	0.08	0	1	0	0.08
Reason PC	3	1	0.23	0.08	3	1	0.23	0.08
Reason PC/AULOQ	0	1	0	0.08	0	1	0	0.08
Reason UISR	9	7	0.69	0.53	9	7	0.69	0.53
Total	**36**	**26**	**2.75**	**1.99**	**31**	**24**	**2.37**	**1.84**

*: Table provided by the firm

Reason A: Lack of fit in the linear regression of data points of the terminal elimination phase
B: Outside the expected concentration range based on neighboring data
AULOQ: Above the upper limit of quantitation
EE: Extraction error
PC: Poor chromatography
UISR: Unacceptable internal standard response
[1]If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout table.

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

Reviewer's Comments: A total of one-hundred and seventy-two (172) plasma samples were reassayed during this fasting study. Fifteen (15) plasma samples were reassayed for pharmacokinetic (PK) reasons. The reviewer recalculated the PK parameters using the original values. It was determined that the use of the recalculated plasma concentration data did not change the outcome of this fasting study. The analytical and PK reasons provided for reanalysis are in accordance with their SOPs and are acceptable.

Reviewer's Comments: The 90% confidence intervals are within the acceptable range of 80% - 125% for log transformed AUC_T, AUC_∞ and C_{max} for oxcarbazepine and its metabolite, 10-hydroxy-carabzepine. The fasting study is acceptable.

2. Single-dose Fed Bioequivalence Study (50370: Qualifying Study - Passed)

Study No.	50370
Study Design	An open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover study
No. of subjects enrolled	120
No. of subjects completing	116
No. of subjects analyzed	116
Subjects (Healthy/Patients?)	Healthy
Sex(es) included (how many?)	**Male**: 68 **Female:** 52
Test product	Oxcarbazepine Tablets
Reference product	Trileptal® Tablets
Strength tested	600 mg
Dose	1 x 600 mg

Summary of Statistical Analysis

Summary of Statistical Analysis, Fed Bioequivalence Study *Additional Information in Appendix A,* Table A2-10, Table A2-11, Table A2-14, and Table A2-15		
OXCARBAZEPINE		
Parameter	**Point Estimate**	**90% Confidence Interval**
$LAUC_T$	0.99	96.79-101.11%
$LAUC_\infty$	0.99	96.86-101.05%
LC_{max}	0.92	86.11-97.80%
10-HYDROXYCARBAMAZEPINE		
Parameter	**Point Estimate**	**90% Confidence Interval**
$LAUC_T$	1.00	99.01-101.74%
$LAUC_\infty$	1.00	99.11-101.69%
LC_{max}	0.99	96.75-100.57%

Reviewer's Comments: A total of one-hundred and twenty (120) healthy male and female subjects were enrolled in this fed study. Four (4) subjects were withdrawn/dropped-out of the study. Two (2) subjects were dropped from the fed study because they did not show up for Period 2 dosing. One (1) subject was withdrawn from the study after Period 1, due to missing blood samples at various time points. Also, during Period 1, one (1) subject experienced emesis as was subsequently dropped from

the study. It occurred before 2x the median T_{max}. The data from one-hundred and sixteen (116) subjects were used for BE statistical evaluations.

Study No. 50370
Reanalysis of Study Samples for Oxcarbazepine
Randomized, Open-Label, 2-Way Crossover, Bioequivalence Study of Oxcarbazepine 600 mg Tablet and Trileptal
Following a 600 mg Dose in Healthy Subjects Under Fed Conditions
Additional Information 16-5 Analytical Report pages 43-54, 67 of 223

Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of Total Assays		Actual number		% of Total Assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Analytical repeat	305	313	5.71	5.86	291	304	5.45	5.70
Unacceptable internal standard response	59	56	1.11	1.05	58	54	1.09	1.01
Incomplete analysis	5	8	0.09	0.15	3	8	0.06	0.15
Sample concentration above upper limit of quantification	113	111	2.12	2.08	112	111	2.10	2.08
Sample reanalyzed to obtain confirming value	6	0	0.11	0.00	0	0	0.00	0.00
Rejected sample dilution	122	138	2.29	2.59	118	131	2.21	2.45
Total	**305**	**313**	**5.71**	**5.86**	**291**	**304**	**5.45**	**5.70**

*: Table provided by the firm

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout table
[T] Oxcarbazepine 600 mg film-coated tablet (1 x 600 mg tablet), (Teva Pharmaceutical Industries Ltd., Israel), Lot No: K-34926
[R] Oxcarbazepine (Trileptal®) 600 mg film-coated tablet (1 x 600 mg tablet), (Novartis Pharma AG, Switzerland), Lot No: 295H9442

Study No. 50370 **Reanalysis of Study Samples for 10-hydroxycarbamazepine** **Randomized, Open-Label, 2-Way Crossover, Bioequivalence Study of Oxcarbazepine 600 mg Tablet and Trileptal** **Following a 600 mg Dose in Healthy Subjects Under Fed Conditions** **Additional Information 16-5 Analytical Report pages 55-66, 68 of 223**								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of Total Assays**		**Actual number**		**% of Total Assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic[1]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Analytical repeat	190	182	3.56	3.41	178	167	3.34	3.13
Unacceptable internal standard response	60	50	1.12	0.94	55	44	1.03	0.82
Incomplete analysis	3	8	0.06	0.15	3	8	0.06	0.15
Sample concentration above upper limit of quantification	65	56	1.22	1.05	63	56	1.18	1.05
Sample reanalyzed to obtain confirming value	2	0	0.04	0.00	1	0	0.02	0.00
Rejected sample dilution	60	68	1.12	1.27	56	59	1.05	1.11
Total	**190**	**182**	**3.56**	**3.41**	**178**	**167**	**3.34**	**3.13**

*: Table provided by the firm

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout table
[T] Oxcarbazepine 600 mg film-coated tablet (1 x 600 mg tablet), (Teva Pharmaceutical Industries Ltd., Israel), Lot No: K-34926
[R] Oxcarbazepine (Trileptal®) 600 mg film-coated tablet (1 x 600 mg tablet), (Novartis Pharma AG, Switzerland), Lot No: 295H9442

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

Reviewer's Comments: Nine hundred and ninety (990) plasma samples (18.55%) were reassayed for analytical reasons. Six hundred and eighteen (618) oxcarbazepine plasma samples (11.58%) were reassayed; and three-hundred and seventy-two (372) 10-hydroxycarbamazepine plasma samples (6.97%) were reassayed. No plasma samples were reassayed for pharmacokinetic reasons. The analytical reasons provided for reanalysis are in accordance with their SOPs and are acceptable.

Reviewer's Comments: The 90% confidence intervals are within the acceptable range of 80% - 125% for log transformed AUC_T, AUC_∞ and C_{max} for oxcarbazepine and its metabolite, 10-hydroxycarbamazepine. The fed study is acceptable.

3. Single-dose Fed Bioequivalence Study (2005-918: Failed Fed Study)

Study No.	2005-918
Study Design	An open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover study
No. of subjects enrolled	60
No. of subjects completing	59
No. of subjects analyzed	59
Subjects (Healthy/Patients?)	Healthy
Sex(es) included (how many?)	**Male**: 36 **Female:** 24
Test product	Oxcarbazepine Tablets
Reference product	Trileptal® Tablets
Strength tested	600 mg
Dose	1 x 600 mg

Summary of Statistical Analysis

Summary of Statistical Analysis, Fed Bioequivalence Study *Additional Information in 2005-918 Report (Amendment No.1).PDF* *Electronic document room: \\CDSESUB\N78005\N_000\2006-08-31*		
OXCARBAZEPINE		
Parameter	**Point Estimate**	**90% Confidence Interval**
$LAUC_T$	0.98	94.86-101.90%
$LAUC_\infty$	0.98	94.64-101.33%
LC_{max}	0.87	**78.74-95.69%**
10-HYDROXY-CARBAZEPINE		
Parameter	**Point Estimate**	**90% Confidence Interval**
$LAUC_T$	1.00	98.17-101.58%
$LAUC_\infty$	1.00	98.30-101.88%
LC_{max}	0.99	97.50-101.24%

Reviewer's Comments: The 90% confidence interval for LC_{max} does not fall within the acceptable 80-125% range for oxcarbazepine. The fed study failed. The firm hypothesized that there initial fed study was underpowered, and the results obtained did not accurately represent their product. The firm stated, *"Please note that while this study yielded unacceptable results, these results were deemed not to be representative of our formulation as the study itself was determined to be underpowered."* The firm repeated the fed study with sufficient power by increasing the number of subjects from fifty-nine (59) to one-hundred and twenty (120).

E. Formulation

Location in Appendix	Please see Appendix II, Section B1
Are inactive ingredients within IIG limits?	Yes
If no, list ingredients outside of limits	--
If a tablet, is/are the product(s) 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?	--

Reviewer's Comments: The inactive ingredients used in Teva's formulation for Oxcarbazepine Tablets, 150 mg, 300 mg, and 600 mg are within the FDAs IIG limits. A chemistry review was performed by Leo Zadecky, in order to justify the acceptability for filing this ANDA based on IIG limits (V:\FIRMSNZ\TEVA\LTRS&REV\78005.INACTIVE INGREDIENT JUSTIFICATION.DOC), before being reviewed by Mujahid L. Shaikh (V:\FIRMSNZ\TEVA\LTRS&REV\78005.R01.DOC). The firm calculated the maximum daily dose of elemental iron in its 150 mg, 300 mg, and 600 mg strength tablets. The maximum daily dose was calculated based on regimen of QID (4x a day - 600 mg tablets). The recommended dosage is BID (twice daily). The DBE reviewer confirmed the firm results. The formulation is acceptable.

F. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	FDA
Medium	▪ 150 mg strength tablet: 0.3% (w/v) Sodium Lauryl Sulfate in Water ▪ 300 mg strength tablet-0.6% (w/v) Sodium Lauryl Sulfate in Water ▪ 600 mg strength tablet-1.0% (w/v) Sodium Lauryl Sulfate in Water
Volume	900 mL
USP Apparatus	II (Paddle)
Rotation (rpm)	60 rpm
Firm's proposed specifications	For all strengths, NLT (b) (4) (Q) in 90 minutes
FDA-recommended specifications	For all strengths, ▪ NLT (b) (4)% (Q) of the labeled amount of oxcarbazepine in the dosage form is dissolved in 30 minutes. ▪ NLT (b) (4)% (Q) of the labeled amount of oxcarbazepine in the dosage form is dissolved in 60 minutes
F2 metric calculated?	No
If no, reason why F2 not calculated	N/A
Is method acceptable?	**Yes**
If not then why?	--

Reviewer's Comments: The DBE previously reviewed the dissolution testing method, data and results for Teva's Oxcarbazepine Tablets, 150 mg, 300 mg, and 600 mg (V:\FIRMSNZ\TEVA\LTRS&REV\78005D1105.DOC). The firm used the FDA-recommended method. However, the firm's proposed specification of NLT (b) (4) (Q) in 90 minutes was unacceptable. On August 02, 2006, the firm amended their ANDA by acknowledging the FDA-recommended method and specifications for its Oxcarbazepine Tablets, 150 mg, 300 mg, and 600 mg. The *in vitro* dissolution testing method, data and results are acceptable.

G. Waiver Request

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?	--

H. Deficiency Comment

None.

I. Recommendations

1. The single-dose fasting bioequivalence (BE) study (2005-917) conducted by Teva Pharmaceuticals USA, comparing its test product, Oxcarbazepine Tablets, 600 mg, Batch No. K-34926, to the reference-listed drug (RLD), Trileptal® Tablets, 600 mg, Lot No. 295H9442, by Novartis Pharma AG, is acceptable. The *in vivo* BE under fasting conditions demonstrates that Teva's Oxcarbazepine Tablets, 600 mg is bioequivalent to the RLD, Trileptal® Tablets, 600 mg, by Novartis.

2. The single-dose fed BE study (50370) conducted by Teva Pharmaceuticals USA, comparing its test product, Oxcarbazepine Tablets, 600 mg, Batch No. K-34926, to the reference-listed drug (RLD), Trileptal® Tablets, 600 mg, Lot No. 295H9442, by Novartis Pharma AG is acceptable. The *in vivo* BE under fed conditions demonstrates that Teva's Oxcarbazepine Tablets, 600 mg is bioequivalent to the RLD, Trileptal® Tablets, 600 mg by Novartis.

3. The dissolution testing conducted by Teva Pharmaceuticals USA, on its Oxcarbazepine Tablets, 150 mg, 300 mg, and 600 mg, is acceptable.

   The dissolution testing should be conducted in 900 mL water with the following:
   a. 150 mg strength tablet, 0.3% Sodium Lauryl Sulfate (SDS)
   b. 300 mg strength tablet, 0.6% SDS
   c. 600 mg strength tablet, 1.0% SDS

   at 37°C ± 0.5 °C using USP apparatus II (paddle) at 60 rpm. The test product (all strengths) 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) f the labeled amount of oxcarbazepine in the dosage form is dissolved in 60 minutes

   The firm should be informed of the above recommendations.

IV. Appendix I

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study (2005-917)

Study Information

Study Number	2005-917
Study Title	A Single-Dose, Comparative Bioavailability Study of Two Formulations of Oxcarbazepine 600 mg Tablets Under Fasting Conditions
Clinical Site	Pharma Medica Research, Inc., 1410 Warden Avenue, Toronto, Canada, M1R 5A3
Principal Investigator	Xueyu (Eric) Chen, M.D., Ph.D., FRCP (C)
Study/Dosing Dates	Dosing Dates: Period 1: April 28, 2005 Period 2: May 05, 2005
Analytical Site	Pharma Medica Research, Inc., 966 Pantera Drive, Unit 31, Mississauga, Ontario, Canada, L4W 2S1
Analytical Director	(b) (6)
Analysis Dates	June 02, 2005 to July 12, 2005
Storage Period	75 days (April 28, 2005 to July 12, 2005)

Treatment ID	**A**	**B**
Test or Reference	Test	Reference
Product Name	Oxcarbazepine Tablets	Trileptal®
Manufacturer	Teva Pharmaceuticals Industries Ltd.	Novartis Pharma AG, Switzerland
Batch/Lot No.	K-34926	295H9442
Manufacture Date	March 28, 2005	N/A
Expiration Date	Not specified	May 2006
Strength	600 mg	600 mg
Dosage Form	Tablets	Tablets
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	100.7%	99.2%
Content Uniformity	100.8%	99.5%
Formulation	See Appendix II, Table B-1	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	Sequence AB Subject No. 2, 4, 7, 8, 9, 12, 15, 16, 18, 19, 23, 24, 27, 28, 30, 31, 34, 36, 37, 40, 42, 44, 45, 46, 50, 51, 53, 55, 58, and 59 Sequence BA Subject No. 1, 3, 5, 6, 10, 11, 13, 14, 17, 20, 21, 22, 25, 26, 29, 32, 33, 35, 38, 39, 41, 43, 47, 48, 49, 52, 54, 56, 57, and 60
Blood Sampling Times	0 (pre-dose), 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 6.5, 7, 8, 10, 12, 16, 24, 36, and 48 hours post-dose
Blood Volume Collected/Sample	7 mL (1 x 7 mL)
Blood Sample Processing/Storage	The blood samples will be collected in pre-chilled labeled 7 mL Vacutainer® tubes containing K_3-EDTA as the anticoagulant. The time of each sample collection is recorded. Blood samples are centrifuged at 3,000 rpm for 10 minutes at 4˚C, within 30 minutes of collection.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	Please see Appendix I, Table A1-1
Length of Fasting	An overnight fast of at least 10 hours
Length of Confinement	From at least 10 hours prior to drug administration until 24 hours post-dose.
Safety Monitoring	Vital signs were not measured throughout the study. However, subjects were questioned regarding their health status throughout the study.

Table A1-1. Demographic Profile of Subjects Completing the Bioequivalence Study[1]

Study No. 2005-917, Fasting	
	Treatment Groups
	Test & Reference Products* N = 57
Age (years)	
Mean ± SD	35 ± 8
Range	20 - 54
Groups	
< 18	0 (0%)
18 - 39	40 (70%)
40 - 64	17 (30%)
65 - 75	0 (0%)
> 75	0 (0%)
Sex	
Female	22 (39%)
Male	35 (61%)
Race	
Asian	12 (21%)
Black	14 (25%)
Caucasian	31 (54%)
Hispanic	0 (0%)
Other	0 (0%)
Other Factors	

* *Crossover design = Subjects completing the study received both treatments*

[1] Table provided by firm

Subject Dropout Information

Table A1-2. Study Dropout Information

Additional Information is located in 2005-917 Report (Amendment No. 1), Section 11.0, pp. 1 018

Subject Number	**33**
Reason	Experienced adverse events (sleepiness, sore throat and feeling feverish) unrelated to the study drug
Period	I (Washout period)
Treatment	A, Test Product - Oxcarbazepine Tablets, 1 x 600 mg
Withdrawal Date	May 04, 2005
Replacement	None
Subject Number	**38**
Reason	Personal reasons
Period	I (Washout period)
Treatment	B, Reference Product - Trileptal® Tablets, 1 x 600 mg
Withdrawal Date	May 02, 2005
Replacement	None

Reviewer's Comments: Two (2) subjects voluntarily withdrew from the fasting study. Subject No. 33 withdrew from the study after experiencing several adverse events in Period 1. These adverse events were reported as being unrelated to the study drug. Subject No. 38 withdrew from the study due to personal reasons. No alternates were enrolled in the study to replace the subjects that withdrew.

Was there a difference in side effects for the test versus the reference? No

Table A1-3. Incidence of Adverse Events in Individual Studies[1]

Additional Information is Located in 2005-917 Report (Amendment No. 1), pp. 1 043 - 1045

Body System/Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study Study No. 2005-917	
	Test (n = 58)	Reference (n = 60)
Body as a Whole		
Headache	2 (3.4%)	2 (3.3%)
Fever		1 (1.7%)
Pain abdo		
Pain		1 (1.7%)
Asthenia		
Photosensitivity		
Cardiovascular System		
Hypertens	1 (1.7%)	1 (1.7%)
Digestive System		
Vomit		
Nausea		
GGTP INC		1 (1.7%)
Diarrhea		
Hemic and Lymphatic System		
Ecchymosis		1 (1.7%)
Metabolic and Nutritional Disorders		
Hyperglycem		1 (1.7%)
Edema Periph		1 (1.7%)
Edema		
SGPT INC	1 (1.7%)	
SGOT INC	1 (1.7%)	
LDH INC		
Nervous System		
Emotion labil		
Depersonal		
Dry mouth		
Somnolence	8 (13.8%)	9 (15.0%)
Dizziness	5 (8.6%)	2 (3.3%)
Hypesthesia		
Paresthesia		
Respiratory System		
Rhinitis		
Pharyngitis		1 (1.7%)

[1] Table provided by the firm

continued, **Table A1-3. Incidence of Adverse Events in Individual Studies[1]**

Additional Information is Located in 2005-917 Report (Amendment No. 1), pp. 1 043 - 1045

Body System/Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study Study No. 2005-917	
	Test (n = 58)	Reference (n = 60)
Skin and Appendages		
Rash	1 (1.7%)	
Special Senses		
Tinnitus		
Ear Dis		
Amblyopia		
Eye Dis		
Urogenital System		
Glycosuria	1 (1.7%)	1 (1.7%)
Urin Abnorm	2 (3.4%)	4 (6.7%)
Total	**22 (37.9%)**	**26 (43.3%)**

[1] Table provided by the firm

Reviewer's Comments: A total of fifty-six (56) adverse events were reported by thirty (30) subjects (Subject No. 2, 3, 4, 5, 6, 7, 9, 10, 12, 13, 17, 18, 19, 20, 21, 26, 27, 29, 31, 33, 34, 35, 37, 48, 49, 50, 52, 53, 57, and 59) during the fasting study. The adverse events reported are similar between the test and reference products. Although, eight (8) of the adverse events reported could not be assigned to a treatment group. All adverse events reported were mild in severity. No incidence of emesis was reported. Seventeen (17) of the adverse events were associated with the Treatment A (test product, Teva's Oxcarbazepine Tablets, 1 x 600 mg), while thirty (30) adverse events were reported as being associated with Treatment B (reference product, Novartis', Trileptal® Tablets, 1 x 600 mg). Twenty-six (26) adverse events were unrelated to the study drug, and eight (8) adverse events were reported as being unlikely related to the study drug. Three (3) adverse events were reported as being possibly related to the study drug; and twenty-eight (28) adverse events were reported as probably related to the study drug. The table provided by the firm lists forty-eight (48) of the fifty-six (56) adverse events reported.

Reviewer's Comments: The outcome of the study was not affected by the reported adverse events.

Protocol Deviations

Additional Information is Located in 2005-917 Report (Amendment No. 1), pp. 1 025, 1 037- 1 040, 1 046, 2 477 – 2 480

Table A1-4. Protocol Deviations

Subject No.	Period	Protocol Section	Protocol Requirement	Deviation
14	2	9.2	Subjects will be instructed not to chew, break or touch the study drug.	The subject held the tablet in hand, then placed it back into the vial prior to swallowing/
58, and 59	2	10.10	Within 30 minutes of collection, the blood samples will be centrifuged at approximately 4˚C for 10 minutes at 3000 rpm.	The 48-hour blood samples (Draw 23) were centrifuged within 38 and 39 minutes of collections for Subjects 58 and 59, respectively.
21-32, 34-37, and 39	1, 2	10.10	Within 30 minutes of collection, the blood samples will be centrifuged at approximately 4˚C for 10 minutes at 3000 rpm	The following samples were spun more than 10 minutes: **Subject** / **Period** / **Draw** 25 / 1 / 7 21-32, 34-37, and 39 / 2 / 22

Table A1-5. Blood Draw Time Deviations

Blood Sampling Time Deviations		
	Period 1	**Period 2**
Subject Number	3, 7, 8, 9, 11, 12, 14, 15, 16, 18, 19, 20, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 32, 34, 35, 36, 38, 39, 42, 43, 46, 47, 49, 53, 55, 56, 57, and 59	2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 16, 17, 18, 19, 20, 21, 22, 23, 25, 26, 27, 28, 31, 32, 34, 35, 40, 45, 46, 48, 49, 50, 51, 52, 56, 58, 59, and 60
Time Range	1 minute (late) to 380 minutes (late)	1 minute (early) to 20 minutes (late)

Reviewer's Comments: The blood sampling time deviations occurring in Period 1 and Period 2 were not significant. Sixty-six (66) blood sampling time deviations occurred in Period 1. All blood sampling time deviations occurring more than 10 minutes late were at the 36- and 48-hour (post-dose) blood collection time points. Seventy-five (75) blood sampling time deviations occurred in Period 2. Blood sampling time deviations were between one minute early and twenty minutes, late. For Subjects No. 32, 49, 50, and 52, blood sampling times were missed for the 36- and 48-hour (post-dose) blood collection

time point. The firm assigned missing values "." to the analytes levels for these samples before pharmacokinetic (PK) and statistical analysis. Subject #50 was dropped from all PK and statistical analysis, because blood samples were not collected for the 36- and 48-hour (post-dose) time points.

Reviewer's Comments: Protocol deviations and blood sampling time deviations, did not have an impact on the outcome nor integrity of the study.

Table A1-6. During Study-Assay Validation for Oxcarbazepine

Accuracy and Precision Summary: Quality Control Sample Analysis			
QC Conc. (ng/mL)	**60.0**	**750**	**1500**
Interday Accuracy (%)	**98.6**	**96.5**	**100.9**
Interday Precision (%CV)	**6.6**	**4.7**	**4.8**

Accuracy and Precision Summary: Calibration Curve								
Cal. Standards Conc. (ng/mL)	**20.0**	**40.0**	**100**	**200**	**400**	**600**	**1000**	**2000**
Interday Accuracy (%)	**103.6**	**103.8**	**99.5**	**91.7**	**97.5**	**99.9**	**104.4**	**99.1**
Interday Precision (%CV)	**5.5**	**4.9**	**6.1**	**3.1**	**3.0**	**2.0**	**2.6**	**0.6**
Linearity Range (range of R^2 values) :	**$\geq$ 0.9981**							

Table A1-7. During Study-Assay Validation for 10-HydroxyCarbazepine

Accuracy and Precision Summary: Quality Control Sample Analysis								
QC Conc. (ng/mL)	**300**		**3500**			**7500**		
Interday Accuracy (%)	**100.6**		**93.9**			**100.5**		
Interday Precision (%CV)	**6.2**		**4.8**			**4.9**		
Accuracy and Precision Summary: Calibration Curve								
Cal. Standards Conc. (ng/mL)	**100**	**200**	**400**	**800**	**1000**	**2000**	**5000**	**10000**
Interday Accuracy (%)	**104.4**	**99.2**	**99.9**	**98.2**	**98.7**	**97.2**	**102.8**	**99.4**
Interday Precision (%CV)	**6.3**	**4.8**	**4.7**	**3.7**	**4.3**	**3.5**	**2.8**	**0.7**
Linearity Range (range of R^2 values) :	**≥ 0.9971**							

Table A1-8. Standard Operation Procedures Used for Sample Analysis
Additional Information is Located in 2005-917 Report (Amendment No. 1), Section 33.0, pp. 6 482 – 6 293

Firm Provided SOPs		**Yes**
SOP No.	**Effective Date of SOP**	**SOP Title**
LAB105.03	June 16, 2003	Replicate and Repeat Sample Analysis Procedure and Acceptance Criteria
LAB300.03	June 30, 2003	Calibration Standards, Quality Control Samples and Analytical Run Acceptance Criteria
Were the SOPs appropriate?		Yes
Number of Samples Re-assayed		172
Number of Pharmacokinetic Repeats		15
Were the reassays consistent with objective criteria in SOP?		Yes
Impact of Repeat-assays on the study outcome		None

Chromatograms: Acceptable.

Reviewer's Comments: A total of one-hundred and seventy-two (172) samples were reassayed for pharmacokinetic (PK) and analytical reasons. One-hundred and ten (110) oxcarbazepine plasma samples were reassayed; and sixty-two (62) plasma samples were reassayed for its metabolite, 10-hydroxy-carbazepine. Three (3) oxcarbazepine plasma samples were repeated for PK reasons. The repeated results confirmed the original results. Therefore, the original value was reported and used in all PK calculations. For, 10-hydroxy-carbazepine, twelve (12) plasma samples were reassayed for PK reasons.

Seven (7) of the samples reassayed, yielded results that confirmed the original results; therefore, the original value was used. For the other five (5) plasma samples, the repeated results were used in PK calculations. The reviewer recalculated the PK parameters using the original values. It was determined that the use of the recalculated plasma concentration data did not change the outcome of this fasting study. The analytical and PK reasons provided for reanalysis are in accordance with the the firm's SOP.

Reviewer's Comments: (on analytical study)

1. The firm provided SOPs for their analytical method and replicate sample analysis procedures.

2. The firm used five of the reassayed results for 10-hydroxy-carbazepine plasma samples. These reassayed values were used in pharmacokinetic and statistical analysis. The criteria for accepting the repeated values, according to SOP LAB105.03 is acceptable.

Conclusion: The bioanalytical method is acceptable.

1A. Pharmacokinetic/Statistical Analysis Results for Oxcarbazepine
Mean plasma loratadine concentrations are presented in Table A1-12 and Figure A1-1

Table A1-9. Arithmetic Mean Pharmacokinetic Parameters

PARAMETER	TEST		REFERENCE		RATIO T/R
	MEAN1	%CV	MEAN2	%CV	
AUC_I	5873.08	27.22	5711.70	25.78	1.03
AUC_T	5309.49	30.10	5176.78	28.87	1.03
CMAX	1630.35	40.64	1620.25	39.77	1.01
KE	0.07	29.42	0.07	27.27	0.94
THALF*	10.94	--	10.31	--	1.06
TMAX	1.72	75.69	1.52	54.87	1.13

* Pharmacokinetic data provided by firm

Table A1-10. Geometric Means and 90% Confidence Intervals

PARAMETER	TEST	REFERENCE	RATIO T/R	90% CI	
	LSM1	LSM2	RLSM12	LOWERCI12	UPPERCI12
$LAUC_I$	5605.95	5467.01	1.03	99.26	105.93
$LAUC_T$	5097.67	4988.52	1.02	98.78	105.71
LCMAX	1482.12	1505.03	0.98	88.98	109.00

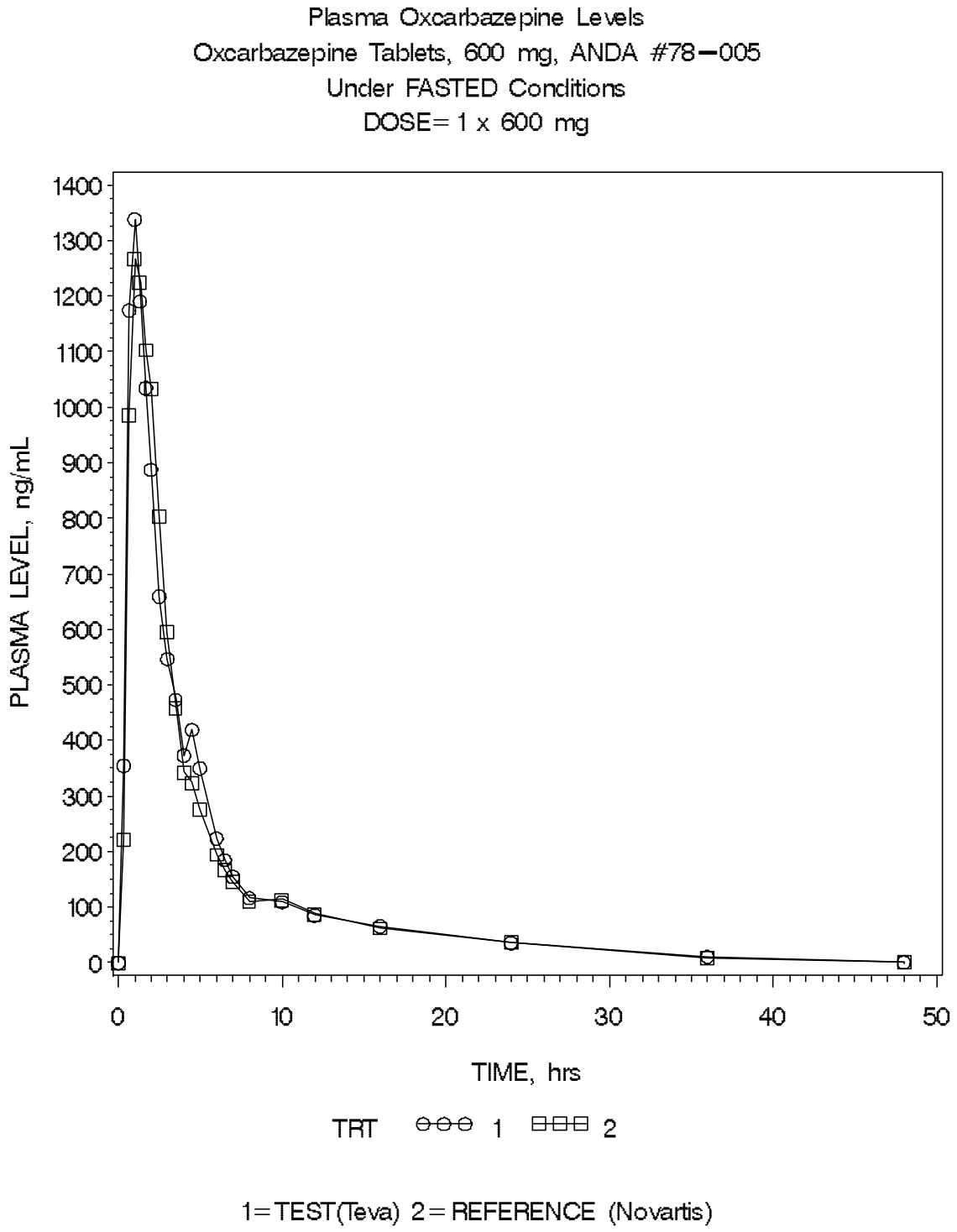
Table A1-11. Additional Study Information: Total SD and within-subject error (root MSE):

Root mean square error, $LAUC_T$	0.108	
Root mean square error, $LAUC_\infty$	0.0988	
Root mean square error, LC_{max}	0.323	
Mean ratio AUC_T/AUC_∞	Test = 0.92	Reference: = 0.92
Range of values, ratio AUC_T/AUC_∞	Test = 0.83 – 0.97	Reference: = 0.78 - 0.97

Table A1-12. Mean Plasma Oxcarbazepine Concentrations for Teva's Test Product, Oxcarbazepine Tablets, 600 mg and Novartis' Trileptal® Tablets, 600 mg – Single-Dose Fasting Study (N = 57)

Time (hr)	Test Product		Reference Product		Ratio T/R
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	--	0.00	--	--
0.33	354.80	118.64	221.47	110.55	1.60
0.67	1174.51	62.09	986.68	73.43	1.19
1	1338.25	60.92	1267.46	57.98	1.06
1.33	1190.64	54.26	1223.98	52.63	0.97
1.67	1034.73	59.00	1102.71	48.35	0.94
2	887.82	60.52	1032.60	54.02	0.86
2.5	659.53	58.48	804.47	50.90	0.82
3	546.67	62.32	595.03	54.43	0.92
3.5	473.42	70.76	457.35	64.60	1.04
4	372.91	76.40	343.11	72.28	1.09
4.5	419.34	78.27	324.36	80.49	1.29
5	349.98	85.45	276.25	58.69	1.27
6	224.39	76.81	194.33	43.93	1.15
6.5	185.10	60.26	166.56	41.12	1.11
7	154.82	47.44	146.20	36.81	1.06
8	116.56	38.48	110.64	35.73	1.05
10	109.01	42.23	113.49	57.89	0.96
12	85.26	35.11	87.48	46.45	0.97
16	65.34	39.43	61.88	41.53	1.06
24	35.64	63.98	36.67	66.79	0.97
36	10.73	142.18	8.54	176.67	1.26
48	0.91	515.06	1.39	435.60	0.66

Figure A1-1. Mean Plasma Oxcarbazepine Concentrations for Teva's Test Product, Oxcarbazepine Tablets, 600 mg and Novartis' Trileptal® Tablets, 600 mg – Single-Dose Fasting Study (N = 57)



1B. Pharmacokinetic/Statistical Analysis Results for 10-Hydroxy-Carbazepine

Mean plasma descarboethoxyloratadine concentrations are presented in Table A1-16 and Figure A1-2

Table A1-13. Arithmetic Mean Pharmacokinetic Parameters

PARAMETER	TEST		REFERENCE		RATIO T/R
	MEAN1	%CV	MEAN2	%CV	
AUC_I	173770.04	21.76	174424.37	25.60	1.00
AUC_T	157371.68	18.73	157542.35	20.25	1.00
CMAX	7119.42	23.36	7004.28	20.13	1.02
KE	0.06	23.68	0.06	23.20	1.03
THALF*	12.81	--	13.13	--	0.97
TMAX	5.65	41.36	5.52	47.98	1.02

* Pharmacokinetic data provided by firm

Table A1-14. Geometric Means and 90% Confidence Intervals

PARAMETER	TEST	REFERENCE	RATIO T/R	90% CI	
	LSM1	LSM2	RLSM12	LOWERCI12	UPPERCI12
$LAUC_I$	169983.16	170078.24	1.00	97.75	102.18
$LAUC_T$	154597.23	154912.24	1.00	97.50	102.15
LCMAX	6931.30	6878.29	1.01	97.03	104.65

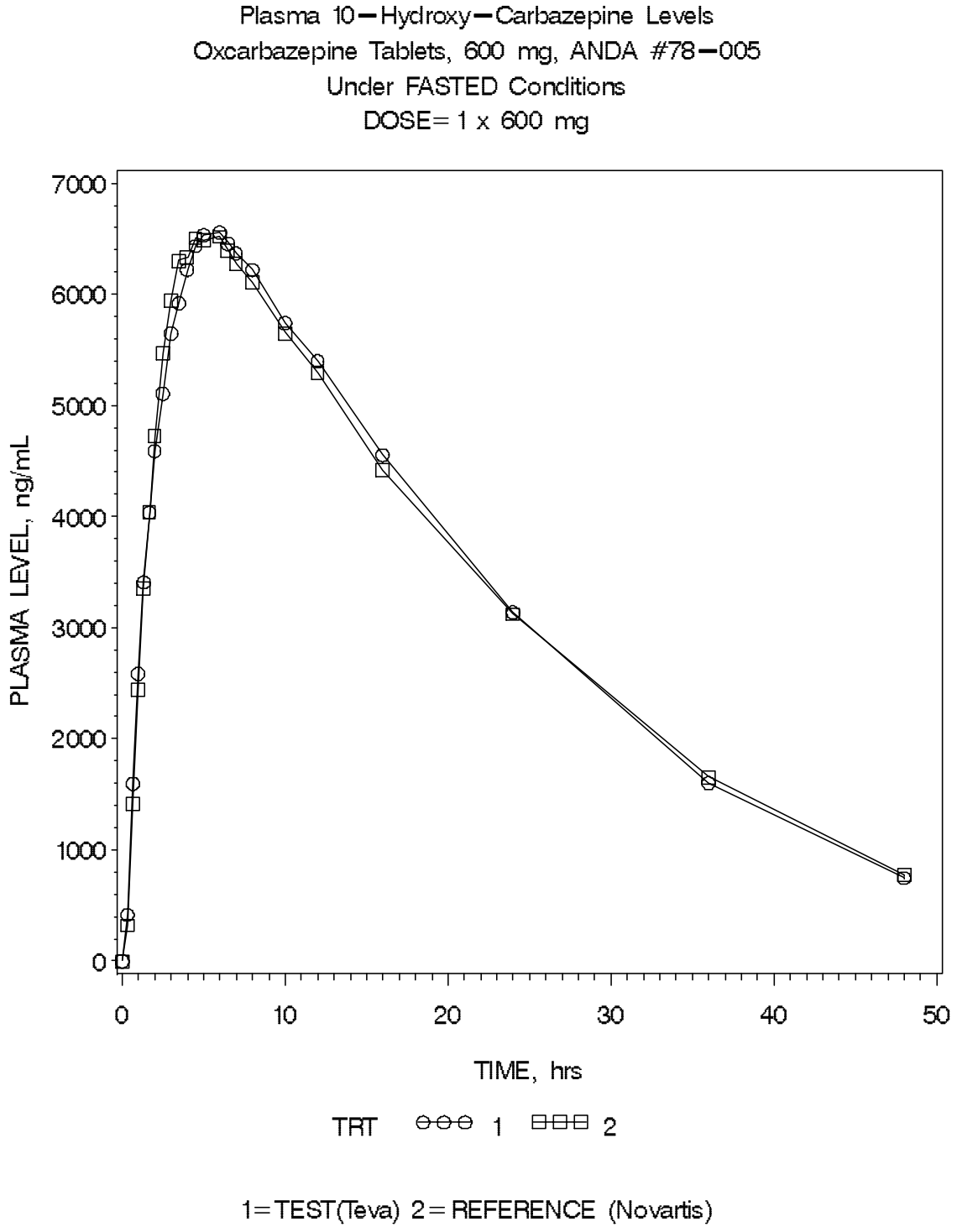
Table A1-15. Additional Study Information: Total SD and within-subject error (root MSE):

Root mean square error, $LAUC_T$	0.0743	
Root mean square error, $LAUC_\infty$	0.0707	
Root mean square error, LC_{max}	0.120	
Mean ratio AUC_T/AUC_∞	Test = 0.91	Reference: = 0.91
Range of values, ratio AUC_T/AUC_∞	Test = 0.69 – 0.99	Reference: = 0.66 – 0.99

Table A1-16. Mean Plasma 10-Hydroxy-Carbazepine Concentrations for Teva's Test Product, Oxcarbazepine Tablets, 600 mg and Novartis' Trileptal® Tablets, 600 mg – Single-Dose Fasting Study (N = 57)

Time (hr)	Test Product		Reference Product		Ratio T/R
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	--	0.00	--	--
0.33	415.86	83.92	322.00	85.75	1.29
0.67	1597.39	50.18	1418.48	52.85	1.13
1	2587.60	47.69	2441.88	42.77	1.06
1.33	3410.26	44.12	3354.70	40.71	1.02
1.67	4036.93	44.69	4038.99	37.12	1.00
2	4590.73	42.83	4730.24	35.65	0.97
2.5	5108.49	39.11	5472.74	31.00	0.93
3	5649.39	37.51	5942.18	27.19	0.95
3.5	5920.55	31.76	6305.77	25.80	0.94
4	6222.85	29.50	6333.32	23.08	0.98
4.5	6437.36	26.20	6507.50	22.33	0.99
5	6533.76	24.76	6490.13	20.94	1.01
6	6557.47	22.87	6519.40	20.33	1.01
6.5	6458.55	21.66	6395.33	19.56	1.01
7	6369.84	22.83	6272.55	16.74	1.02
8	6222.92	21.36	6110.31	18.98	1.02
10	5740.97	19.99	5655.05	18.42	1.02
12	5399.30	18.22	5292.62	17.24	1.02
16	4555.30	19.48	4422.88	20.45	1.03
24	3138.45	25.60	3125.04	29.78	1.00
36	1602.62	36.77	1656.40	43.47	0.97
48	746.97	51.52	777.87	57.77	0.96

Figure A1-2. Mean Plasma 10-Hydroxy-Carbazepine Concentrations for Teva's Test Product, Oxcarbazepine Tablets, 600 mg and Novartis' Trileptal® Tablets, 600 mg – Single-Dose Fasting Study (N = 57)



Reviewer's Comments: (on pharmacokinetic analysis)

1. The firm assayed the plasma concentration for the parent drug, oxcarbazepine and its active metabolite, 10-hydroxy-carbazepine. The firm provided the plasma profiles for oxcarbazepine and 10-hydroxy-carbazepine.

2. The firm and reviewer calculated pharmacokinetic (PK) parameters ($AUC_{\mathbf{0}-\infty}$, AUC_T, C_{max}, T_{max}, and K_{el}) for oxcarbazepine and 10-hydroxy-carbazepine. Statistical analysis was performed on the PK parameters using the GLM procedure of SAS with a 90% confidence interval. The reviewer agrees with the firm results.

3. The reviewer recalculated PK parameters ($AUC_{\mathbf{0}-\infty}$, AUC_T, C_{max}, T_{max}, and K_{el}) for 10-hydroxy-carbazepine using the original plasma concentration data. Statistical analysis was performed on the PK parameters using the GLM procedure of SAS with a 90% confidence interval.

4. The firm and reviewer used the data from fifty-seven (57) subjects to conduct bioequivalence statistical evaluations.

Conclusion: The single-dose fasting bioequivalence study is acceptable**.**

2. Single-dose Fed Bioequivalence Study (50370)

Study Information

Study Number	50370	
Study Title	Randomized, Open-Label, 2-Way Crossover, Bioequivalence Study of Oxcarbazepine 600 mg Tablet and Trileptal® Following a 600 mg Dose in Healthy Subjects under Fed Conditions	
Clinical Site	SFBC Anapharm, 2050, Boul. Rene-Levesque Ouest, Sainte-Foy (Quebec), Canada G1V 2K8	
Principal Investigator	Richard Larouche, M.D.	
Study/Dosing Dates	Study Dates: July 08, 2005 to July 25, 2005	Dosing Dates: Period 1: July 8, 2005 Period 2: July 15, 2005
Analytical Site	SFBC Anapharm, 2050, Boul. Rene-Levesque Ouest, Sainte-Foy (Quebec), Canada G1V 2K8	
Analytical Director	(b) (6) Ph.D.	
Analysis Dates	August 08, 2005 to October 07, 2005	
Storage Period	91 days	

Treatment ID	**A**	**B**
Test or Reference	Test	Reference
Product Name	Oxcarbazepine Tablets	Trileptal®
Manufacturer	Teva Pharmaceuticals Industries Ltd.	Novartis Pharma AG, Switzerland
Batch/Lot No.	K-34926	295H9442
Manufacture Date	March 28, 2005	N/A
Expiration Date	Not specified	May 2006
Strength	600 mg	600 mg
Dosage Form	Tablets	Tablets
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	100.7%	99.2%
Content Uniformity	100.8%	99.5%
Formulation	See Appendix II, Table B-1	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	Sequence AB Subject No. 4, 6, 7, 9, 10, 11, 16, 18, 19, 20, 23, 24, 26, 28, 30, 32, 33, 34, 35, 39, 41, ,43, 47, 48, 50, 51, 57, 58, 59, 60, 61, 62, 64, 65, 70, 71, 74, 75, 79, 80, 81, 82, 84, 88, 89, 91, 94, 95, 96, 97, 101, 104, 105, 107, 110, 111, 112, 113, 114 and 115 Sequence BA Subject No. 1, 2, 3, 5, 8, 12, 13, 14, 15, 17, 21, 22, 25, 27, 29, 31, 36, 37, 38, 40, 42, 44, 45, 46, 49, 52, 53, 54, 55, 56, 63, 66, 67, 68, 69, 72, 73, 76, 77, 78, 83, 85, 86, 87, 90, 92, 93, 98, 99, 100, 102, 103, 106, 108, 109, 116, 117, 118, 119, and 120
Blood Sampling Times	0 (pre-dose), 0.333, 0.667, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.0, 16.0, 24.0, 36.0, and 48.0 hours post dose
Blood Volume Collected/Sample	3 mL (1 x 3 mL)
Blood Sample Processing/Storage	All blood samples were collected in tubes containing EDTA-K_2. Blood samples were cooled in an ice bath and were centrifuged at 3,000 rpm for at least 10 minutes at approximately 4˚C. Two aliquots of at least 0.5 mL (when possible) of plasma were dispensed into polypropylene tubes (as soon as possible), containing 25 µL of L-ascorbic acid solution, resulting in a plasma: buffer of 5% v/v and were vortexed. The aliquots were flash frozen at approximately -80˚C and subsequently transferred to a -80˚C (-65 ˚C to -85˚C) freezer.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	Please see Appendix I, Table A2-1
Length of Fasting	Overnight fast of at least 10 hours
Meals Provided	Thirty minutes prior to dosing, all subjects received a standard FDA-recommended high-fat breakfast. Standard meals were provided at appropriate times with the contents of meals served identical across treatment periods.
Length of Confinement	From at least 11 hours prior to drug administration, until after the 24.0-hour post-dose blood draw, in each period

Safety Monitoring	Vitals signs (blood pressure and heart rate) were measured prior to dosing. Throughout the study, subjects were monitored for adverse events.

Table A2-1. Demographic Profile of Subjects Completing the Bioequivalence Study[1]

Study No 50370, Fed		**Safety population**	**PK population**		
Category		**Total**	**Randomization**		**Total**
			AB	**BA**	
Age (years)	Mean ± SD	43 ± 14	45 ± 14	42 ± 15	43 ± 15
	Range	20 - 82	20 – 70	20 - 82	20 - 82
	Median	45	48	39	44
	N	120	59	57	116
Age Groups	< 18	0	0	0	0
	18-40	57 (47.5%)	26 (44.1%)	30 (52.6%)	56 (48.3%)
	41-64	57 (47.5%)	31 (52.5%)	23 (40.4%)	54 (46.6%)
	65-75	5 (41.7%)	2 (3.4%)	3 (5.3%)	5 (4.3%)
	> 75	1 (8.3%)	0	1 (1.8%)	1 (0.9%)
Gender	Female	52 (43.3%)	24 (40.7%)	26 (45.6%)	50 (43.1%)
	Male	68 (56.7%)	35 (59.3%)	31 (54.4%)	66 (56.9%)
Race	Asian	0	0	0	0
	Black	8 (6.7%)	6 (10.2%)	2 (3.5%)	8 (6.9%)
	Caucasian	99 (82.5%)	47 (79.7%)	48 (84.2%)	95 (81.9%)
	American Hispanic	13 (10.8%)	6 (10.2%)	7 (12.3%)	13 (11.2%)
Height (cm)	Mean ± SD	169.7 ± 9.7	169.6 ± 9.6	169.7 ± 9.4	169.6 ± 9.4
	Range	148.5 – 193.0	151.0 – 193.0	148.5 – 192.5	148.5 – 193.0
	Median	169.5	169.3	170.5	169.5
	N	120	59	57	116
Weight (kg)	Mean ± SD	70.6 ± 10.5	70.8 ± 10.8	70.7 ± 10.1	70.7 ± 10.4
	Range	47.2 – 91.8	47.2 – 90.2	51.5 – 91.8	47.2 – 91.8
	Median	70.0	70.1	70.3	70.2
	N	120	59	57	116
BMI (kg/m2)	Mean ± SD	24.5 ± 2.7	24.6 ± 2.9	24.5 ± 2.6	24.5 ± 2.7
	Range	19.4 – 29.7	19.4 – 29.7	19.5 – 28.7	19.4 – 29.7
	Median	24.4	24.6	24.5	24.6
	N	120	59	57	116

[1] Table provide by the firm

Subject Dropout Information

Table A2-2. Study Dropout Information

Subject Number	**04**
Reason	Due to missing time points and bad veins
Period	1
Treatment	A, Test Product – Oxcarbazepine Tablets, 1 x 600 mg
Withdrawal Date	July 15, 2005
Replacement	None
Subject Number	**15**
Reason	Voluntarily withdrew - did not show up for Period 2 dosing
Period	2
Treatment	A, Test Product – Oxcarbazepine Tablets, 1 x 600 mg
Withdrawal Date	July 14, 2005
Replacement	None
Subject Number	**73**
Reason	Experienced emesis
Period	1
Treatment	B, Reference Product, Trileptal® Tablets, 1 x 600 mg
Withdrawal Date	--
Replacement	None
Subject Number	**86**
Reason	Voluntarily withdrew – did not show up for Period 2 dosing
Period	2
Treatment	A, Test Product – Oxcarbazepine Tablets, 1 x 600 mg
Withdrawal Date	July 14, 2005
Replacement	None

Reviewer's Comments: Four (4) subjects were withdrawn and/or dropped from the fed study. During Period 1, Subject No. 4 was dropped from the study due to bad veins and missing time points. Subject No. 15 and 86, both voluntarily withdrew from the fed study. They did not show up for Period 2 dosing. Subject No. 73 experienced emesis in Period 2. The subject vomited two minutes post-dose Treatment B (reference product, Novartis', Trileptal® Tablets, 1 x 600 mg). It occurred before 2x the median T_{max}. Therefore, the subject was withdrawn from the study. No alternates were used to replace the four (4) subjects that were withdrawn and/or dropped from this study.

Was there a difference in side effects for the test versus the reference? No

Table A2-3. Incidence of Adverse Events in Individual Studies[1]

Additional Information is Located in Section 14.5, pp.386 -395

System Class	**Project No. 50370***	
COSTART	**A**	**B**
Cardiac disorders		
Palpitat	1 (0.5%)	2 (1.0%)
Ear and labyrinth disorders		
Ear disorders	1 (0.5%)	
Eye disorders		
Amblyopia	1 (0.5%)	3 (1.5%)
Dry eye	1 (0.5%)	
Eye dis	1 (0.5%)	
Gastrointestinal disorders		
Constip		1 (0.5%)
Diarrhea		1 (0.5%)
Dry mouth	2 (1.0%)	2 (1.0%)
Nausea	6 (3.0%)	4 (2.0%)
Pain abdo	1 (0.5%)	1 (0.5%)
Paresthesia	5 (2.5%)	6 (3.0%)
Vomit		1 (0.5%)
General disorders and administration site conditions		
Asthenia	3 (1.5%)	3 (1.5%)
Edema	1 (0.5%)	
Fever	1 (0.5%)	
Pain inject site	1 (0.5%)	
Infections and infestations		
Herpes simplex	1 (0.5%)	
Injury, poisoning, and procedural complications		
Edema inject site	1 (0.5%)	
Hysn inject site	1 (0.5%)	2 (1.0%)
Injury accid	1 (0.5%)	
Pain inject site	3 (1.5%)	6 (3.0%)
Pruritus	1 (0.5%)	
Rash	1 (0.5%)	
Musculoskeletal and connective tissue disorders		
Pain back	1 (0.5%)	1 (0.5%)
Pain neck	1 (0.5%)	
Nervous system disorders		
Ataxia	1 (0.5%)	
Dizziness	21 (10.4%)	21 (10.4%)
Headache	5 (2.5%)	7 (3.5%)
Paresthesia	1 (0.5%)	
Somnolence	17 (8.4%)	19 (9.4%)
Tremor	1 (0.5%)	1 (0.5%)

* 18 adverse events could not be assigned to a treatment group.

[1] Table provided by the firm.

continued, **Table A2-3. Incidence of Adverse Events in Individual Studies[1]**

Additional Information is Located in Section 14.5, pp.386 -395

System Class	**Project No. 50370***	
COSTART	**A**	**B**
Psychiatric disorders		
Confus	1 (0.5%)	
Euphoria	1 (0.5%)	
Hostility	1 (0.5%)	
Thinking abnorm	2 (1.0%)	1 (0.5%)
Renal and urinary disorders		
Urin abnorm	1 (0.5%)	1 (0.5%)
Reproductive system and breast disorders		
Dysmenorrhea		1 (0.5%)
Libido inc	1 (0.5%)	
Respiratory, thoracic, and mediastinal disorders		
Pharyngitis		1 (0.5%)
Rhinitis	1 (0.5%)	2 (1.0%)
Yawn		2 (1.0%)
Skin and subcutaneous tissue disorders		
Ecchymosis		2 (1.0%)
Rash		1 (0.5%)
Vascular disorders	1 (0.5%)	1 (0.5%)
TOTAL	**87 (43.5%)**	**97 (48.5%)**

* 18 adverse events could not be assigned to a treatment group.

[1] Table provided by the firm.

Reviewer's Comments: A total of two-hundred and two (202) adverse events (post-dose) were reported by seventy-six subjects (Subject No. 2, 4 - 6, 9, 10, 12 - 18, 20, 23, 24, 29, 30-34, 36, 37, 39, 41, 43, 45 - 46, 48, 49, 50, 52, 53, 56, 57, 58, 59, 61, 63 - 67, 69, 71 – 73, 75, 78, 79, 81 – 83, 87, 89, 91 – 95, 99, 100, 103, 104, 106 – 112, 114, 117 and 119. Of the adverse events reported, only one (1) was severe in nature (Subject No. 14, emesis). All other adverse events reported were mild to moderate in severity. Sixty-nine (69) of these adverse events reported were listed as potentially being associated with Treatment A (test product, Teva's, Oxcarbazepine Tablets, 1 x 600 mg; and seventy-six (76) of these adverse events reported were listed as potentially being associated with Treatment B (reference product, Novartis', Trileptal® Tablets, 1 x 600 mg). Fifty-five (55) of the adverse events reported were listed as being unrelated to the study drug (test or reference). Eighteen (18) of these adverse events reported could not be assigned to a treatment group. The firm stated, "*The remaining 2 adverse events were associated with clinically significant post-study laboratory tests and could not be assigned to a treatment group (date and time of onset is unknown*)." Also, fifteen (15) adverse events were reported pre-dose; but are not represented in the reported value for adverse events or the table above.

Reviewer's Comments: The outcome of the study was not affected by the reported adverse events.

Protocol Deviations

Table A2-4. Summary of Protocol Deviations

Additional Information is Located in Section 16-4, pp. 2 – 35

Subject Number	Period	Treatment	Protocol Deviation	Excluded from Analysis due to Deviation(s)	
				Safety	PK
001-040	1	A, B	For these subjects' 16.0-, 24.0-, and 36.0-hour post-dose plasma aliquots 1 of 2 and 2 of 2, the buffer used was expired by as much as 2 hours and 6 minutes. According to the investigation report, there is no impact since a stability was provided for buffer expired by 3 hours and 2 minutes.	No	No
001-120	N/AP	N/AP	These subjects' post-dose vital signs were not performed, in error. However, the impact is minimal since these subjects received only two doses of the study medication and hypotension, bradycardia, postural hypotension, hypertension, and tachycardia were observed with subjects receiving larger doses of the oxcarbazepine.	No	No
	1, 2	A, B	For these subjects' plasma samples, whether the 10 seconds of vortex was respected can not be confirmed. There is no impact since the addition of plasma in the polypropylene tube permits an adequate mixing of the plasma with the buffer. Note: this deviation does not apply to all subjects and all sampling time.	No	No
021, 022, 073, 104, 105, 108-114	1, 2	A, B	The following blood samples were centrifuged as much as 73 minutes after their collection: • Subjects No. 021 and 022, time point 48.0-hour post- dose, Period 2; • Subjects No. 073, 104, and 105, time point 3.00-hour post-dose, Period 1; • Subjects No. 108 to 114, time point 5.00-hour post-dose, Period 2. Since oxcarbazepine and 10-OH-carbamazepine are stable in human blood for 50 minutes, the above samples had to be rejected.	No	Yes
041-051, 053-069	1	A, B	For these subjects' 48.0-hour plasma samples, it can not be confirmed if the buffer solution was prepared following the SFBC Anapharm SOP. Since the buffer could have an impact on samples integrity, all samples were rejected	No	Yes

continued, **Table A2-4. Summary of Protocol Deviations**

Additional Information is Located in Section 16-4, pp. 2 – 35

Subject Number	Period	Treatment	Protocol Deviation	Excluded from Analysis due to Deviation(s)	
				Safety	PK
045, 051, 059, 065	N/AP	N/AP	For these subjects, no alcohol breath test was performed at the screening session. There is no impact since a negative result was obtained from an alcohol breath test performed prior to study drug administration in Period 1.	No	No
042, 050	N/AP	N/AP	It can no be confirmed if these subjects has made donation of plasma (500 mL) within 30 days or donation or loss of whole blood prior to administration of the study medication as follow: • 50 to 300 mL of whole blood within 30 days, • 301 mL to 500 mL of whole blood within 45 days, or • more than 500 mL of whole blood within 56 days prior to drug administration However, per SFBC Anapharm CESR database, it can be confirmed that neither of these subjects participated in another study within 30 days prior to drug administration.	No	No
059, 062	N/AP	N/AP	At the time screening session, whether these subjects received a verbal explanation and a copy of the study specific and screening ICFs can not be confirmed. There is no impact since these subjects received all pertinent study information at check-in, in Period 1 and signed the ICFs.	No	No
005	2	A	During her critical breakfast, this subject dabbed her buttered toast with a napkin. There is no impact since the subject is still within the range of 800-1000 calories required for the completion of the critical breakfast.	No	No
009	2	B	This subject consumed 125 mL of Moka yogurt 1 day 22 hours 44 minutes after study drug administration.	No	No
066	2	A	This subject consumed 3 beers of 350 mL 1 day 6 hours, 40 minutes, 1 day 7 hours 10 minutes, and 1 day 7 hours 40 minutes after study drug administration, respectively.	No	No
075	2	B	Whether this subject's 4.00-hour post-dose blood sample was centrifuged within 50 minutes after blood collection can not be confirmed. This sample was rejected since oxcarbazepine and 10-hydroxycatrbamazepine are found to be stable in human EDTA K3 whole blood for a maximum of 50 minutes.	No	Yes
103	N/AP	N/AP	No urine pregnancy test was performed at the screening session for this subject. There is no impact since the subject's husband is vasectomized. Moreover, this subject's pregnancy tests performed during the study were negative.	No	No
108	N/AP	N/AP	No urine pregnancy test was performed at the screening session for this subject. However, there is no impact since all other pregnancy tests performed during the study were negative.	No	No

Reviewer's Comments: Several protocol deviations occurred in the fed study. Most were insignificant. However, for several subjects, blood samples were not centrifuged within 30 minutes of collection at varying time points. All of these samples were rejected by the firm because they could have an impact on the pharmacokinetics in this study. Blood samples that were improperly prepared were rejected as well.

Table A2-5. Blood Draw Time Deviations

Additional Information is located in Section 3 to 15, pp. 374 - 383

Blood Sampling Time Deviations		
	Period 1	**Period 2**
Subject Number	1–9, 12–28, 33–39, 40, 42–44, 47–49, 51–55, 57–60, 64–67, 70, 73–85, 88–92, 94, 95, 97, 98, 100, 102-106, 108–111, 118, and 120	3, 6–8, 11, 13, 16–19, 21, 23, 25, 26, 28, 33–36, 39–43, 45-49, 51 – 59, 62–72, 75, 77–82, 84, 85, 88–92, 95–118, and 120
Time Range	1 minute (late) to 20 minutes (late)	1 minute (late) to 38 minutes (late)

Table A2-6. Subjects Who Received Concomitant Medication:

Subject:	53
Period:	I
Reason:	Pain in the back of the neck
Medication (Dosage)[a]:	Acetaminophen (1 x 500 mg)
Start Date:	July 15, 2006
End Date:	July 15, 2005

[a] Medication was given to the patient once.

Reviewer's Comments: The blood sampling time deviations occurring in Period 1 and Period 2 were not significant. Two-hundred and forty-three (243) blood sampling time deviations occurred in Period 1. Two-hundred and twenty-four (224) blood sampling time deviations occurred in Period 2. A total of twenty-five (25) blood samples were not obtained from subjects. The majority of the blood sampling time deviations were due to difficulty drawing the blood. The firm assigned missing values "." to the analytes levels for these samples before PK and statistical analysis. Subject No. 53 received a non-scheduled medication as pharmacotherapy for an adverse event (pain in the back of the neck) which was possibly related to the study drug, Treatment B (reference product, Novartis', Trileptal® Tablets, 1 x 600 mg).

Reviewer's Comments: Protocol deviations, blood sampling time deviations, nor the administration of concomitant medication during the fed study, did not have an impact on the outcome nor integrity of the study.

Table A2-7. During Study-Assay Validation for Oxcarbazepine

Accuracy and Precision Summary: Quality Control Sample Analysis								
QC Conc. (ng/mL)		**11.95**		**597.60**			**1394.40**	
Interday Accuracy (%)		**103.26**		**103.25**			**108.79**	
Interday Precision (%CV)		**5.11**		**4.93**			**3.85**	
Accuracy and Precision Summary: Calibration Curve								
Cal. Standards Conc. (ng/mL)	**3.96**	**7.91**	**79.10**	**395.52**	**791.04**	**1186.56**	**1582.08**	**1977.60**
Interday Accuracy (%)	**100.25**	**99.75**	**96.7**	**99.1**	**102.46**	**98.53**	**100.08**	**103.16**
Interday Precision (%CV)	**5.29**	**4.69**	**3.57**	**3.28**	**3.72**	**3.00**	**3.77**	**4.27**
Linearity Range (range of R^2 values) :					**0.9974**			

Table A2-8. During Study-Assay Validation for 10-Hydroxycarbamazepine

Accuracy and Precision Summary: Quality Control Sample Analysis								
QC Conc. (ng/mL)		**60.50**		**3025.00**			**7058.20**	
Interday Accuracy (%)		**103.44**		**104.15**			**109.88**	
Interday Precision (%CV)		**4.01**		**3.64**			**3.19**	
Accuracy and Precision Summary: Calibration Curve								
Cal. Standards Conc. (ng/mL)	**20.38**	**40.77**	**407.68**	**2038.40**	**4076.80**	**6115.20**	**8153.60**	**10192.00**
Interday Accuracy (%)	**100.29**	**99.8**	**96.24**	**98.73**	**102.35**	**98.60**	**100.19**	**103.93**
Interday Precision (%CV)	**4.06**	**3.98**	**3.28**	**2.69**	**3.04**	**2.94**	**3.30**	**3.49**
Linearity Range (range of R^2 values) :					**0.9979**			

Table A2-9. Standard Operation Procedures Used for Sample Analysis

Additional Information located in Section 16-5, pp. 144 - 220

Firm Provided SOPs		**Yes**
SOP No.	**Effective Date of SOP**	**SOP Title**
ANI 153.07	Dec. 11, 2003	Preparation, Identification and Acceptance Criteria of Stock Solutions, Calibration Standards, Quality Control Samples and Reference Solutions
ANI 156.08	July 1, 2003	Sample Reassays and Reporting Final Concentration
ANI 157.04	April 28, 2003	Application of Chromatographic Methods to Routine Drug Analysis
ANI 167.05	June 30, 2005	Chromatographic Acceptance Criteria and Verification of Chromatograms
Were the SOPs appropriate?		Yes
Number of Samples Re-assayed		990
Number of Pharmacokinetic Repeats		0
Were the reassays consistent with objective criteria in SOP?		Yes
Impact of Repeat-assays on the study outcome		None

Chromatograms: Acceptable.

Reviewer's Comments: During this fed study, nine-hundred and ninety (990) plasma samples were reassayed for analytical reasons. This is 18.65% of the total number of plasma samples (5337) analyzed. For oxcarbazepine, six hundred and eighteen (618) plasma samples were reassayed; and five hundred and fifty-five (555) of the recalculated values were used in pharmacokinetic (PK) and statistical analysis. For 10-hydroxycarbamazepine, three-hundred and seventy-two (372) samples were reassayed; and three hundred and forty-five (345) recalculated values were used after reanalysis for PK and statistical analysis. The reanalysis and acceptance criteria for recalculated values for the plasma samples were all in accordance with the firm's SOPs.

Chromatograms: Acceptable.

1. The firm provided SOPs for their analytical method and replicate sample analysis procedures.

2. The firm used nine-hundred and forty (940) recalculated values for oxcarbazepine and 10-hydroxycarbamazepine plasma concentration data in pharmacokinetic (PK) and statistical analysis. The criteria for accepting the repeated values, according to SOP ANI 156.08 is acceptable. The reviewer used this data for BE statistical evaluations as well.

Conclusion: The bioanalytical method is acceptable.

2A. Pharmacokinetic/Statistical Analysis Results for Oxcarbazepine
Mean plasma loratadine concentrations are presented in Table A2-13 and Figure A2-1

Table A2-10. Arithmetic Mean Pharmacokinetic Parameters

PARAMETER	TEST		REFERENCE		RATIO T/R
	MEAN1	%CV	MEAN2	%CV	
AUC_I	9679.79	24.49	9772.18	24.05	0.99
AUC_T	9445.55	24.64	9539.53	24.04	0.99
CMAX	3537.63	37.68	3820.31	35.52	0.93
KE	0.06	20.19	0.06	19.81	1.01
THALF*	12.56	2.81	12.69	2.62	0.99
TMAX	1.89	50.89	1.86	61.77	1.01

*: Pharmacokinetic data provided by the firm.

Table A2-11. Geometric Means and 90% Confidence Intervals

PARAMETER	TEST	REFERENCE	RATIO T/R	90% CI	
	LSM1	LSM2	RLSM12	LOWERCI12	UPPERCI12
$LAUC_I$	9401.63	9502.59	0.99	96.86	101.05
$LAUC_T$	9171.29	9270.73	0.99	96.79	101.11
LCMAX	3292.14	3587.45	0.92	86.11	97.80

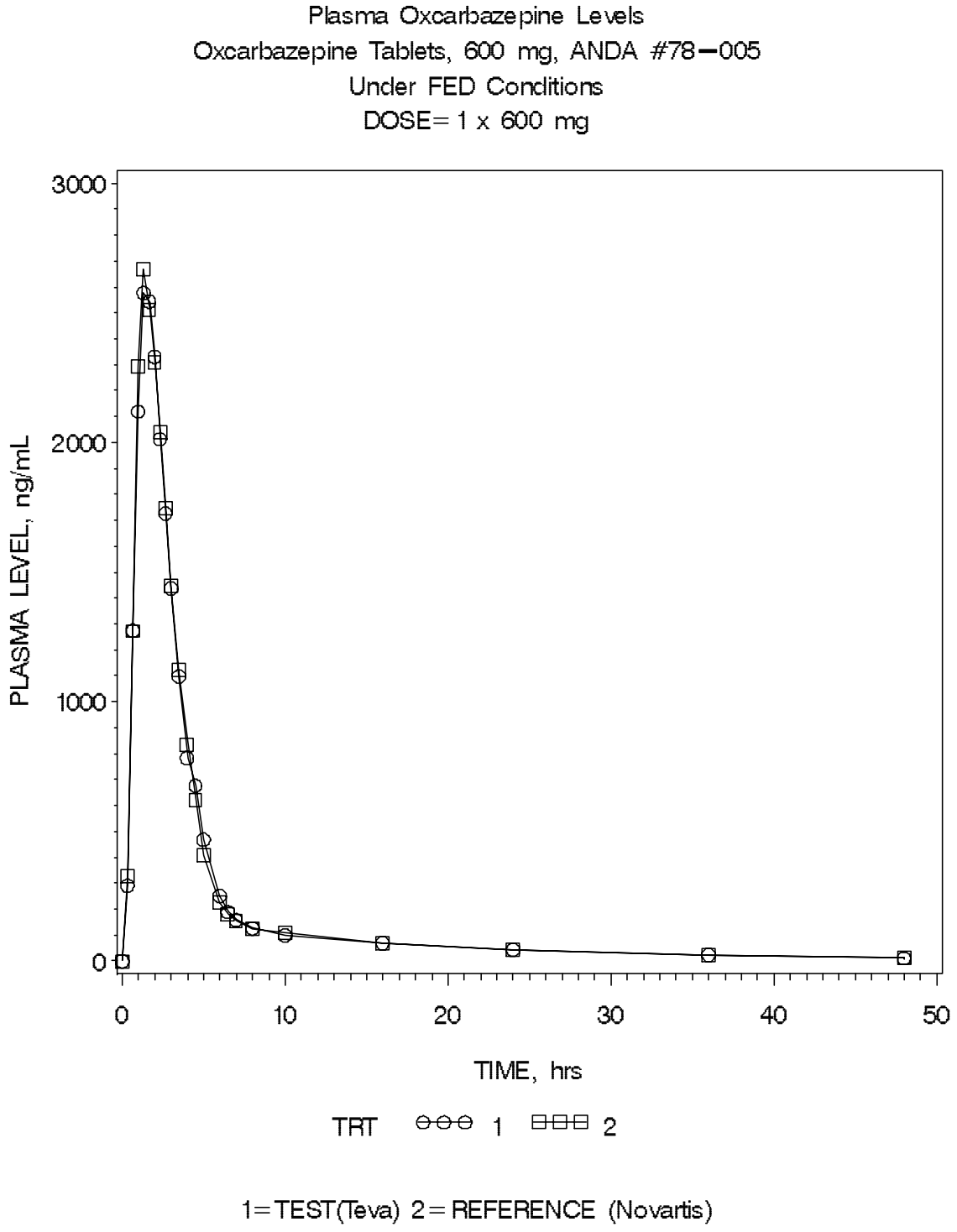
Table A2-12. Additional Study Information: Total SD and within-subject error (root MSE):

Root mean square error, $LAUC_T$	0.100	
Root mean square error, $LAUC_\infty$	0.0963	
Root mean square error, LC_{max}	0.292	
Mean ratio AUC_T/AUC_∞	Test = 0.97	Reference: = 0.97
Range of values, ratio AUC_T/AUC_∞	Test = 0.90 – 1.00	Reference: = 0.90 – 1.00

Table A2-13. Mean Plasma Oxcarbazepine Concentrations for Teva's Test Product, Oxcarbazepine Tablets, 600 mg and Novartis' Trileptal® Tablets, 600 mg – Single-Dose Fed Study (N = 116)

Time (hr)	Test Product		Reference Product		Ratio T/R
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	--	0.00	--	--
0.33	291.06	204.49	329.00	204.01	0.88
0.67	1274.66	120.87	1273.48	130.67	1.00
1	2119.84	81.35	2296.14	91.35	0.92
1.33	2577.46	63.88	2668.44	66.35	0.97
1.67	2544.34	50.32	2512.16	52.09	1.01
2	2331.62	44.80	2310.12	45.57	1.01
2.33	2013.88	45.51	2042.12	46.65	0.99
2.67	1726.82	45.85	1749.23	51.42	0.99
3	1437.85	50.25	1447.92	56.42	0.99
3.5	1098.95	62.65	1123.41	71.32	0.98
4	782.81	74.05	836.20	84.61	0.94
4.5	676.88	99.84	623.68	96.69	1.09
5	468.17	88.11	407.69	97.19	1.15
6	252.17	84.85	226.33	89.27	1.11
6.5	189.19	70.76	181.35	84.24	1.04
7	158.52	61.90	154.70	79.24	1.02
8	126.89	60.74	123.98	65.08	1.02
10	99.65	37.78	109.63	126.39	0.91
16	69.95	30.64	68.60	28.66	1.02
24	44.37	36.02	44.15	37.02	1.01
36	24.39	41.63	24.72	42.97	0.99
48	11.45	56.24	12.22	77.15	0.94

Figure A2-1. Mean Plasma Oxcarbazepine Concentrations for Teva's Test Product, Oxcarbazepine Tablets, 600 mg and Novartis' Trileptal® Tablets, 600 mg – Single-Dose Fed Study (N = 116)



2A. Pharmacokinetic/Statistical Analysis Results for 10-Hydroxycarbamazepine
Mean plasma loratadine concentrations are presented in Table A2-17 and Figure A2-2

Table A2-14. Arithmetic Mean Pharmacokinetic Parameters

PARAMETER	TEST		REFERENCE		RATIO T/R
	MEAN1	%CV	MEAN2	%CV	
AUC_I	197864.34	23.79	196607.20	22.04	1.01
AUC_T	179002.40	21.88	177979.76	19.95	1.01
CMAX	9349.83	18.61	9517.52	21.37	0.98
KE	0.06	21.31	0.06	20.42	1.02
THALF*	12.15	2.54	12.37	2.57	0.98
TMAX	4.58	35.17	4.44	36.73	1.03

*: Pharmacokinetic data provided by the firm.

Table A2-15. Geometric Means and 90% Confidence Intervals

PARAMETER	TEST	REFERENCE	RATIO T/R	90% CI	
	LSM1	LSM2	RLSM12	LOWERCI12	UPPERCI12
$LAUC_I$	193062.61	192308.10	1.00	99.11	101.69
$LAUC_T$	175269.44	174632.29	1.00	99.01	101.74
LCMAX	9199.00	9325.57	0.99	96.75	100.57

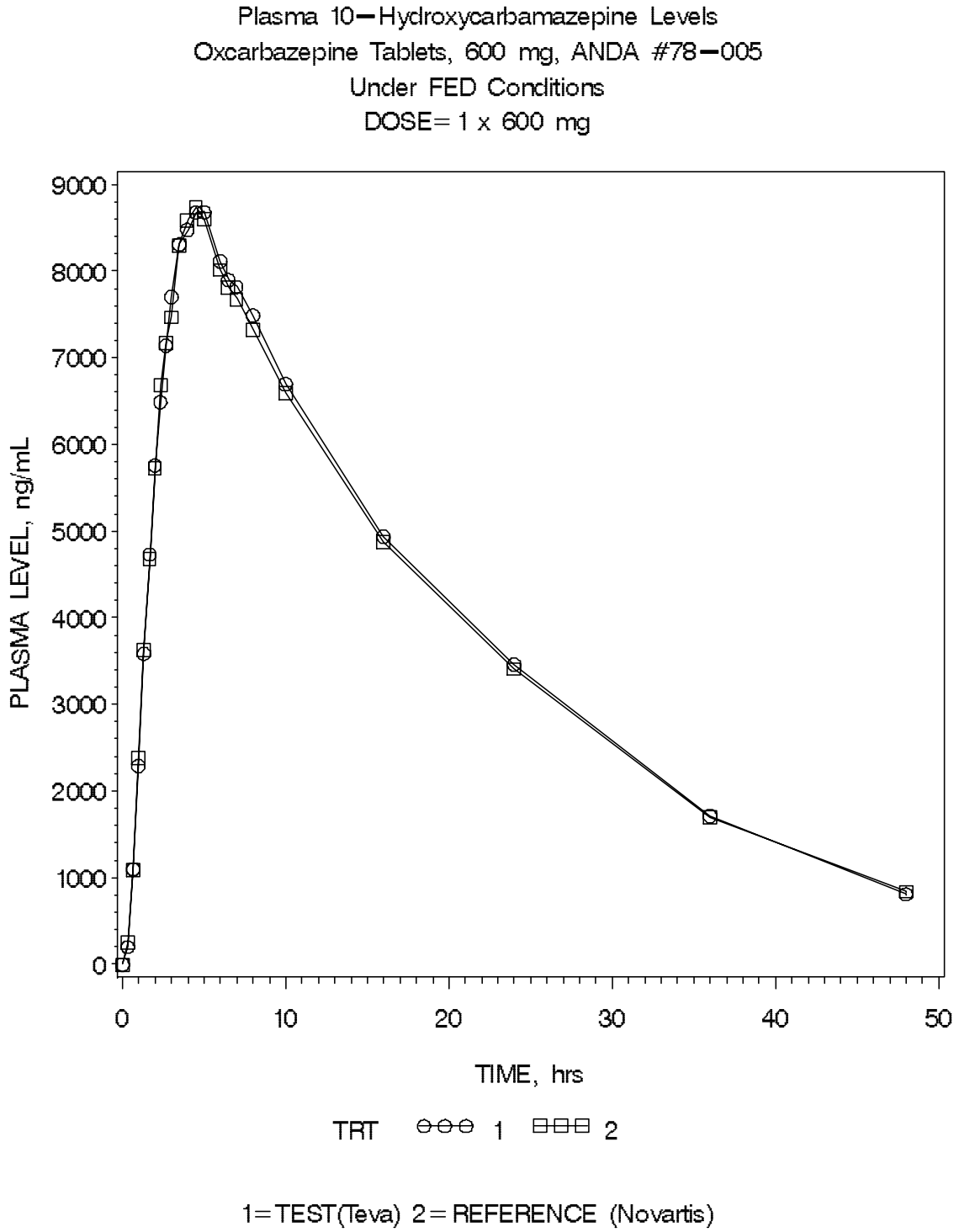
Table A2-16. Additional Study Information: Total SD and within-subject error (root MSE):

Root mean square error, $LAUC_T$		0.0624
Root mean square error, $LAUC_\infty$		0.0586
Root mean square error, LC_{max}		0.0889
Mean ratio AUC_T/AUC_∞	Test = 0.91	Reference: = 0.91
Range of values, ratio AUC_T/AUC_∞	Test = 0.68 -0.99	Reference: = 0.76 – 0.99

Table A2-17. Mean Plasma 10-Hydroxycarbamazepine Concentrations for Teva's Test Product, Oxcarbazepine Tablets, 600 mg and Novartis' Trileptal® Tablets, 600 mg – Single-Dose Fed Study (N = 116)

Time (hr)	Test Product		Reference Product		Ratio T/R
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	--	0.00	--	--
0.33	201.27	161.04	253.50	157.42	0.79
0.67	1096.35	103.12	1085.13	104.15	1.01
1	2290.47	75.31	2379.81	84.09	0.96
1.33	3587.74	61.15	3623.77	68.04	0.99
1.67	4731.70	50.86	4685.16	57.40	1.01
2	5757.61	44.69	5729.83	48.20	1.00
2.33	6490.71	39.19	6688.90	42.10	0.97
2.67	7143.14	32.83	7178.01	34.96	1.00
3	7703.76	29.13	7469.43	31.26	1.03
3.5	8309.53	23.97	8304.68	25.43	1.00
4	8478.20	23.12	8592.89	23.54	0.99
4.5	8676.94	19.02	8743.23	22.45	0.99
5	8683.98	17.33	8600.75	19.02	1.01
6	8115.05	17.65	8017.65	18.51	1.01
6.5	7900.27	18.18	7810.09	18.78	1.01
7	7817.99	18.26	7679.55	18.81	1.02
8	7488.88	19.44	7331.03	18.77	1.02
10	6696.74	19.28	6591.16	19.12	1.02
16	4940.05	24.52	4880.51	23.12	1.01
24	3464.00	29.02	3410.35	26.30	1.02
36	1711.82	37.33	1702.37	34.80	1.01
48	810.57	56.75	838.73	47.56	0.97

Figure A2-2. Mean Plasma 10-Hydroxycarbamazepine Concentrations for Teva's Test Product, Oxcarbazepine Tablets, 600 mg and Novartis' Trileptal® Tablets, 600 mg – Single-Dose Fed Study (N = 116)



***Reviewer's Comments*:** (on pharmacokinetic analysis)

1. The firm assayed the plasma concentration for the parent drug, oxcarbazepine and its active metabolite, 10-hydroxy-carbazapine. The firm provided the plasma profiles for oxcarbazepine and 10-hydroxy-carbazepine.

2. The firm and reviewer calculated pharmacokinetic (PK) parameters ($AUC_{0-\infty}$, AUC_T, C_{max}, T_{max}, and K_{el}) for oxcarbazepine and 10-hydroxycarbamazepine. Statistical analysis was performed on the PK parameters using the GLM procedure of SAS with a 90% confidence interval. The reviewer agrees with the firm results.

3. The firm and reviewer used the data from one-hundred and sixteen (116) subjects to conduct bioequivalence statistical evaluations.

Conclusion: The single-dose fed bioequivalence study is acceptable**.**

B. Appendix II

1. Formulation Data

Table B1-1. Formulation of Oxcarbazepine Tablets, 150 mg, 300 mg, and 600 mg [1]

Ingredient	Amount (mg) / Tablet			Amount (%) / Tablet		
	150 mg strength	300 mg strength	600 mg strength	150 mg strength	300 mg strength	600 mg strength
(b) (4)						
Oxcarbazepine (b) (4)	(b) (4)					
Microcrystalline Cellulose NF (b) (4)						
Hypromellose USP (b) (4)						
(b) (4)						
(b) (4)						
Crospovidone NF (b) (4)						
Colloidal Silicon Dioxide NF (b) (4) (b) (4)						
Magnesium Stearate NF						
(b) (4)						
(b) (4)						
Polyethylene Glycol (b) (4) NF						
(b) (4)						
(b) (4) Brown						
Total:	**207.0**	**414.0**	**828.0**	**100.0**	**100.0**	**100.0**

* (b) (4)
*

[1] Table provided by firm.

2. Product Description[2]

Test drug product: Oxcarbazepine Tablets, 150 mg, 300 mg, and 600 mg by Teva Pharmaceuticals USA

- All strengths of the tablets are available in a brown to dark-brown color. They are film-coated and have a capsule shape. The tablets are scored in half on both sides and debossed with numbers on each side.

Reference drug product: Trileptal® Tablets, 150 mg, 300 mg, and 600 mg by Novartis Pharma AG

- All strengths are available as yellow, ovaloid, slight biconvex tablets. They are scored in half on both sides and debossed with numbers on each side.

Table B2-1. Product Description for Oxcarbazepine Tablets by Teva Pharmaceuticals', and Trileptal® Tablets by Novartis Pharma AG

	Oxcarbazepine Tablets (Teva)			Trileptal® Tablets (Novartis)		
Strength	**Color**	**Identification Information debossed on scored side of tablet**		**Color**	**Information debossed on the scored side of tablet**	
		Side 1	**Side 2**		**Side 1**	**Side 2**
150 mg	Brown to Dark Brown	9 | 3	72 | 81	Yellow	T | G	C | G
300 mg	Brown to Dark Brown	9 | 3	72 |82	Yellow	TE | TE	CG | CG
600 mg	Brown to Dark Brown	9 | 3	72 | 83	Yellow	TF | TF	CG | CG

[2] 1. ANDA 78-005. Drug Product. Archival copy, Volume 4-4, pp. 1059.
2. Online-Physicians' Desk Reference Electronic Library™. (2006). http://www.thomsonhc.com. Thomson Micromedex: Keyword Search: Trileptal® Tablets. Last accessed: 09/20/2006.

3. In Vitro Dissolution Testing

***In Vitro* Comparative Drug Release**

Testing Conditions

Medium: 150 mg strength tablet: 0.3% (w/v) Sodium Lauryl Sulfate in Water
300 mg strength tablet-0.6% (w/v) Sodium Lauryl Sulfate in Water
600 mg strength tablet-1.0% (w/v) Sodium Lauryl Sulfate in Water

Volume: 900 mL
Apparatus: II (Paddle)
Speed: 60 rpm
Temperature: 37 °C ± 0.5 °C

Specification(s) are as follows:

For all strengths,

NLT (b) (4) % (Q) of the labeled amount of oxcarbazepine in the dosage form is dissolved in 30 minutes.

NLT (b) (4) % (Q) f the labeled amount of oxcarbazepine in the dosage form is dissolved in 60 minutes

***Reviewer's Comments*:** The DBE previously reviewed the dissolution testing data and results. The dissolution review is located on the V:\ drive: V:\FIRMSNZ\TEVA\LTRS&REV\78005D1105.DOC. The firm amended their application on August 02, 2006 to acknowledge and accept the FDA-recommended dissolution method and specifications for it's Oxcarbazepine Tablets, 150 mg, 300 mg and 600.

Table B3-1. Summary of In Vitro Dissolution Studies[1]

Study Ref. No.	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	45 min	60 min	75 min	90 min	
CDP-1248/01	Oxcarbazepine K-34924	150 mg Tablets	**Dissolution:** Apparatus 2 (Paddles) **Speed of Rotation:** 60 rpm **Medium:** For 150 mg strength: 0.3% (w/v) sodium lauryl sulphate in water For 300 mg strength: 0.6% (w/v) sodium lauryl sulphate in water For 600 mg strength: 1.0% (w/v) sodium lauryl sulphate in water **Volume**: 900 mL **Temperature:** 37°C ± 0.5°C **Tolerance**: NLT (b) (4)% (Q) dissolved in 90 minutes	12	89	93	95	96	96	96	96	96 (b) (4)	Original ANDA pgs 113-124
	Trileptal® F0102	150 mg Tablets		12	78	87	91	95	98	99	100	100 (b) (4)	
CDP-1249/01	Oxcarbazepine K-34925	300 mg Tablets		12	86	94	95	97	99	98	98	98 (b) (4)	
	Trileptal® F0135	300 mg Tablets		12	87	95	97	99	99	100	99	99 (b) (4)	
CDP-1225/01	Oxcarbazepine K-34926	600 mg Tablets		12	82	89	99	101	101	101	102	102 (b) (4)	
	Trileptal® 295H9442	600 mg Tablets		12	77	89	93	95	97	100	97	99 (b) (4)	

[1] Table provided by the firm

Figure B3-1. Dissolution Profile for Teva's Oxcarbazepine Tablets, 150 mg and Novartis' Trileptal® Tablets, 150 mg

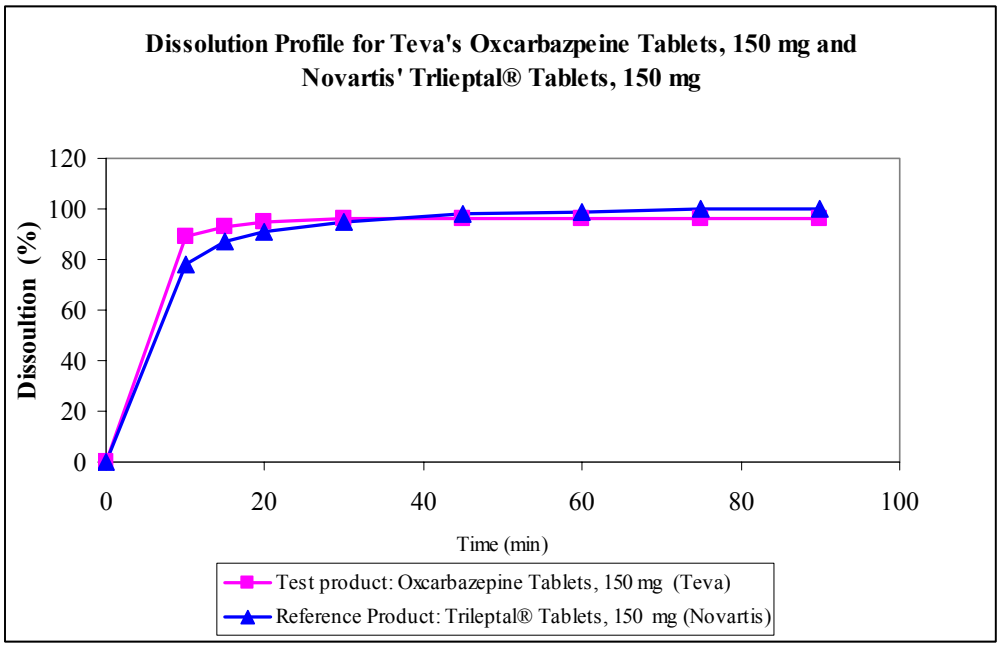


Figure B3-2. Dissolution Profile for Teva's Oxcarbazepine Tablets, 300 mg and Novartis' Trileptal® Tablets, 300 mg

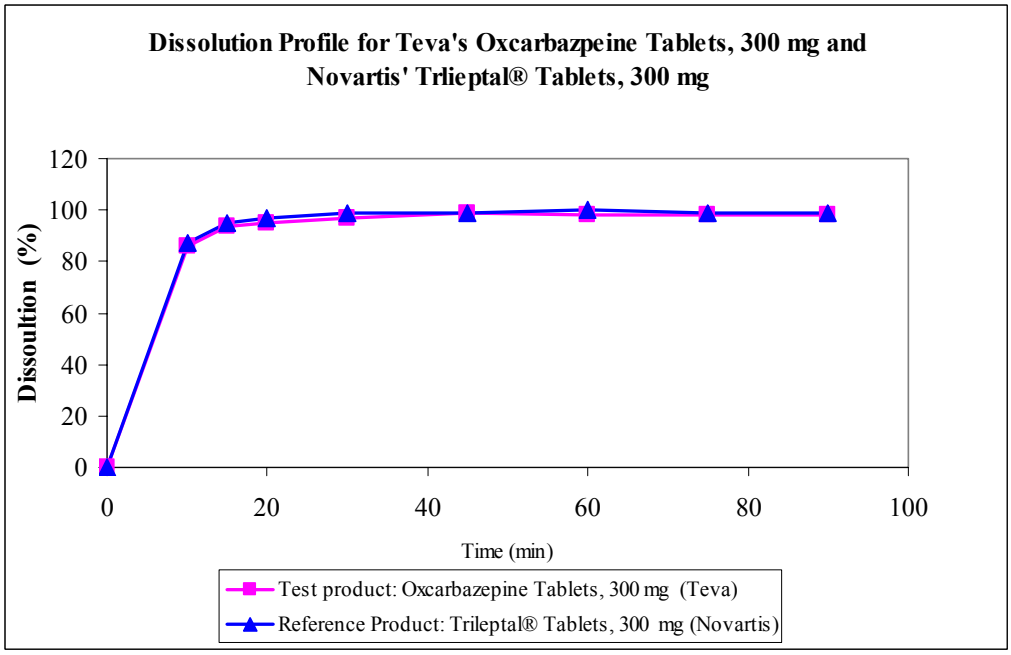
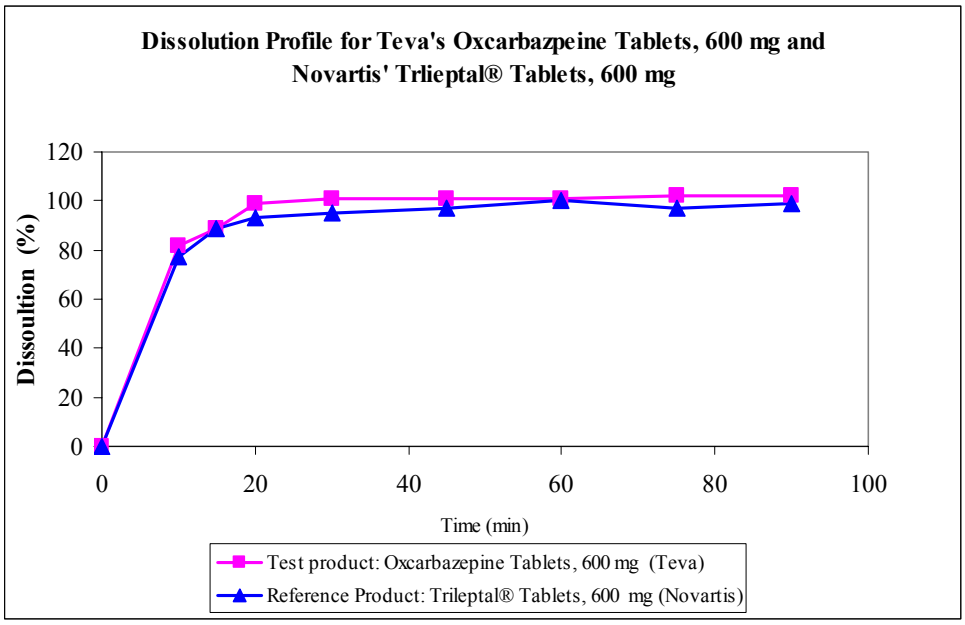


Figure B3-3. Dissolution Profile for Teva's Oxcarbazepine Tablets, 600 mg and Novartis' Trileptal® Tablets, 600 mg



C. Consult Reviews

None.

Following this page, 205 pages withheld in full- (b)(4) SAS output

E. Attachments

None.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-005

APPLICANT: Teva Pharmaceuticals, USA

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

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet 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 of 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 product (all strengths) 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,

{See appended electronic signature}

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

ANDA 78-005

BIOEQUIVALENCY –ACCEPTABLE Submission date: November 23, 2005

1. **FASTING STUDY** (STF) Strength: 600 mg
Outcome: AC

Study No. 2005-917
Clinical Site : Pharma Medica Research, Inc.,
966 Pantera Drive, Unit 31
Mississauga, Ontario L4W 2S1

Analytical Site: Pharma Medica Research, Inc.,
966 Pantera Drive, Unit 31
Mississauga, Ontario L4W 2S1

2. **FED STUDY** (STP) **S**trength: 600 mg
Outcome: AC

Study No. 50370
Clinical Site: SFBC Anapharm, 2050,
Boul. Rene-Levesque Ouest
Sainte-Foy (Quebec), Canada G1V 2K8

Analytical Site: SFBC Anapharm, 2050,
Boul. Rene-Levesque Ouest
Sainte-Foy (Quebec), Canada G1V 2K8

3. **FED STUDY- FAILED** (STP) Strength: 600 mg
Outcome: UN

Study No. 2005-918
Clinical Site: Pharma Medica Research, Inc.,
966 Pantera Drive, Unit 31
Mississauga, Ontario L4W 2S1

Analytical Site: Pharma Medica Research, Inc.,
966 Pantera Drive, Unit 31
Mississauga, Ontario L4W 2S1

4. **DISSOLUTION WAIVER** (DIW)	Strength: 150 mg **Outcome: AC**
5. **DISSOLUTION WAIVER** (DIW)	Strength: 300 mg **Outcome: AC**
6. **STUDY AMENDMENT** (STA) August 02, 2006 Dissolution Amendment	Strengths: 150 mg, 300 mg, and 600 mg **Outcome: AC** WC
7. **STUDY AMENDMENT** (STA) August 31, 2006 Complete study reports and SAS data files	Strengths: 600 mg **Outcome: AC** WC
8. **STUDY AMENDMENT** (STA) October 06, 2006 Long-term stability data	Strengths: 600 mg **Outcome: AC** WC

Outcome Decisions: **AC- Acceptable**

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/s/

April Braddy
11/7/2006 09:50:47 AM
BIOPHARMACEUTICS

Moheb H. Makary
11/7/2006 10:03:48 AM
BIOPHARMACEUTICS

Barbara Davit
11/9/2006 02:36:19 PM
BIOPHARMACEUTICS

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #:	78-005 **SPONSOR:** Teva Pharmaceuticals USA
DRUG & DOSAGE FORM:	Oxcarbazepine Tablets
STRENGTH(S):	150 mg, 300 mg, and 600 mg
TYPES OF STUDIES:	One fasting and two fed studies on Oxcarbazepine Tablets, 600 mg
CLINICAL STUDY SITE(S):	Fasting study (2005-917) and Fed Study (2005-918): Pharma Medica Research, Inc., Mississauga, Ontario Fed study (50370): SFBC Anapharm, Sainte-Foy (Quebec), Canada
ANALYTICAL SITE(S):	Fasting study (2005-917) and Fed Study (2005-918): Pharma Medica Research, Inc., Mississauga, Ontario Fed study (50370): SFBC Anapharm, Sainte-Foy (Quebec), Canada
STUDY SUMMARY:	The fasting study (2005-917) and fed study (50370) are acceptable. The fed study (2005-918) is unacceptable.
DISSOLUTION:	The dissolution testing is acceptable.
WAIVER REQUEST	Waivers for the 150 mg and 300 mg strength are granted.

DSI INSPECTION STATUS

Inspection needed:	No	**Inspection status:**	**Inspection results:**
First Generic	No		
New facility			
For cause			
Other			

Proposed Dissolution Method and Specifications from Original Submission Acceptable?
Yes _____ No X (If no, project Manager should verify and sign below when acknowledgement amendment is received)

DBE Dissolution Method and Specifications acknowledged by firm? Yes X No ___

AMENDMENT DATE: _____

PROJECT MANAGER: _____ **DATE:** _____

PRIMARY REVIEWER: April C. Braddy, Ph.D. **BRANCH:** 1
INITIAL: _____ DATE: _____

ACTING TEAM LEADER: Moheb H. Makary, Ph.D. **BRANCH:** 1
INITIAL: _____ DATE: _____

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.
INITIAL: _____ DATE: _____

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/s/

Barbara Davit
11/9/2006 02:51:51 PM
Signing for Dale P Conner