CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077747

BIOEQUIVALENCE REVIEWS

DEC 12 2005

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	77-747
Drug Product Name	Oxcarbazepine Tablets
Strength	150, 300 mg and 600 mg
Applicant Name	Apotex Inc.
Submission Date(s)	July 14, 2005
First Generic	No
Reviewer	Patrick Nwakama
File Location	V:\firmsam\Apotex\ltrs&rev\77747D0705.doc
Clinical Site	Apotex Inc., Biomedical Division, Toronto, Ontario, Canada
Analytical Site	Apotex's Analytical Development Laboratory, Ontario, Canada
Dissolution Site	Apotex's Analytical Development Laboratory, Ontario, Canada

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 (900 mL, Water (plus 0.3% SDS for 150 mg; 0.6% SDS for 300 mg and 1% SDS for 600 mg), Paddle, at 60 rpm. The firm conducted the dissolution testing for all three strengths using the method recommended for the 600 mg [900 mL, Water (plus **1% SDS**), Paddle, at 60 rpm]. The firm's dissolution testing data for the 600 mg passes the FDA-recommended specifications [NLT (b) (4)% (Q) in 30 minutes at the L2 level and NLT (b) (4)% (Q) in 60 minutes at L1 level] and is acceptable. The firm should repeat dissolution testing for the 150 mg and 300 mg using Water plus 0.3% and 0.6% SDS, respectively.

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

RLD METHOD:

Dissolution method
Medium:
900 mL water + 0.3% SDS (150 mg)
900 mL water + 0.6% SDS (300 mg)
900 mL water + 1% SDS (600 mg)
Apparatus
Paddle at 60 rpm
Specifications
NLT (b) (4) % (Q) in 30 minutes
NLT % (Q) in 60 minutes

Source of Method: [NDA 21-014/SCF-014, dated April 27, 2005]

Table 1: Summary of In Vitro Dissolution Data

Study Reference Number	Product ID Batch No.	Dosage Form	Conditions	Number of Dosage Units	Collection Times Mean %Dissolved (Range) 5	10	15	20	30	45	60	90	Study Report Location
N/A	Oxcarbazepine Tablets 025-21	150 mg tablets	Apparatus: USP Apparatus 2 (paddles) Agitation speed: 50 rpm Medium: 1.0% SDS in water, 900 mL Temperature: 37 ± 0.5°C	12	12	32	50	66	85	96	98	98 (b) (4)	Section 5.3.1.3
N/A	Trileptal Tablets 214H3125			12	24	62	79	87	93	97	98	99 (b) (4)	
N/A	Oxcarbazepine Tablets 025-20	300 mg tablets		12	9	24	41	54	73	89	96	97 (b) (4)	Section 5.3.1.3
N/A	Trileptal Tablets 560J3095			12	21	48	76	84	91	96	96	97 (b) (4)	
N/A	Oxcarbazepine Tablets 025-19	600 mg tablets		12	8	22	34	48	64	83	92	97 (b) (4)	Section 5.3.1.3
N/A	Trileptal Tablets 019J4374			12	39	75	86	90	94	96	97	97 (b) (4)	

COMPARATIVE DISSOLUTION RATES
OXCARBAZEPINE TABLETS 150 MG, 300 MG & 600 MG

Figure 1: Dissolution Rate Profile.

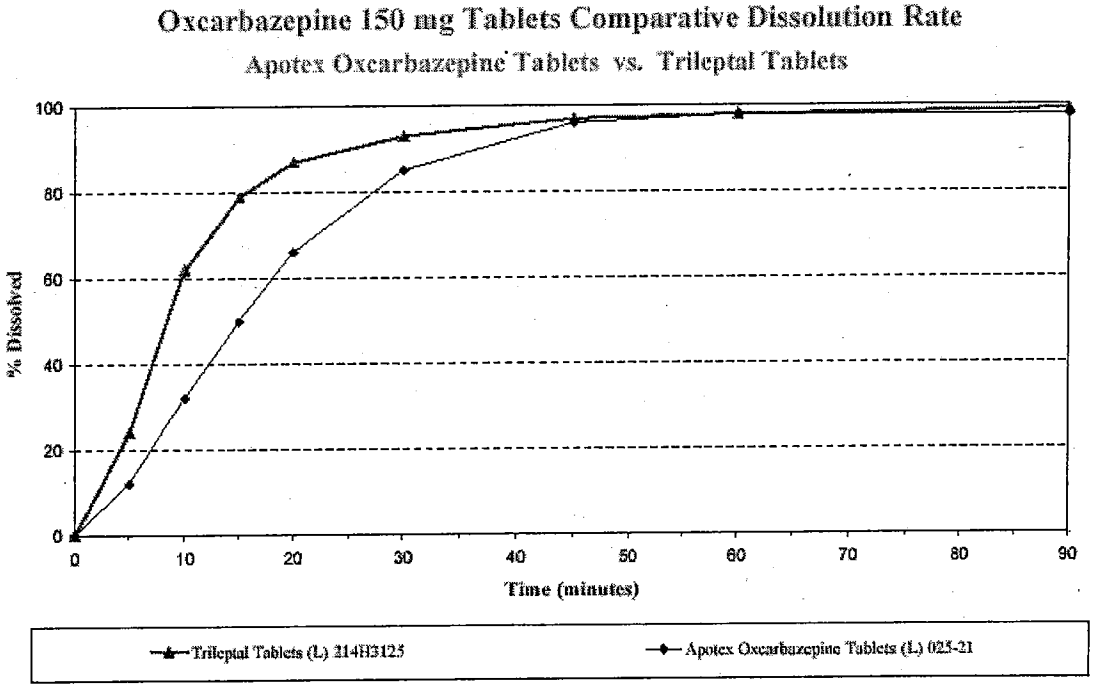


Figure 2: Dissolution Rate Profile.

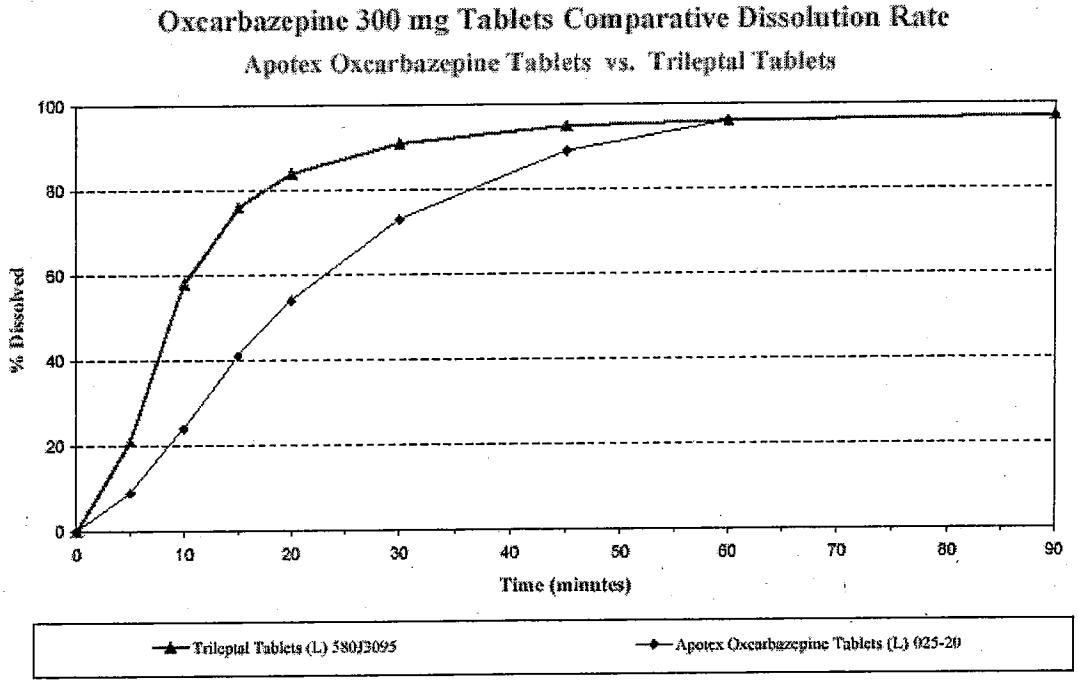


Figure 3: Dissolution Rate Profile.

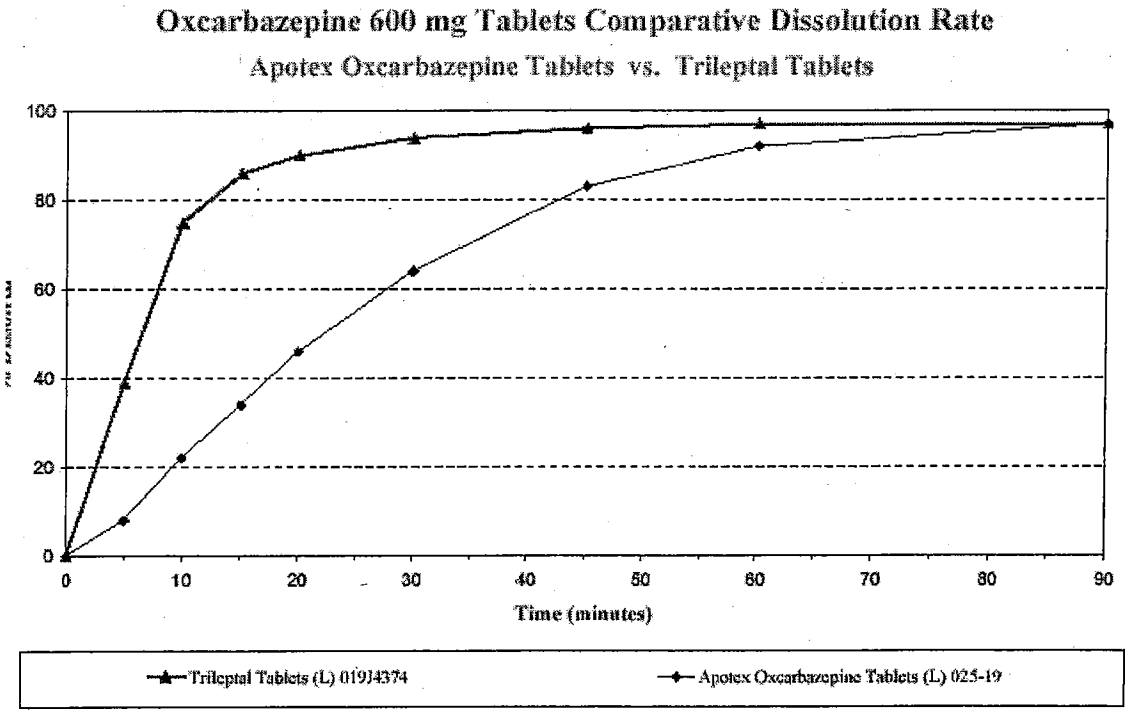


Figure 4: Comparative Dissolution Profiles of Apotex's Oxcarbazepine Tablets, 150 mg, 300 mg and 600 mg

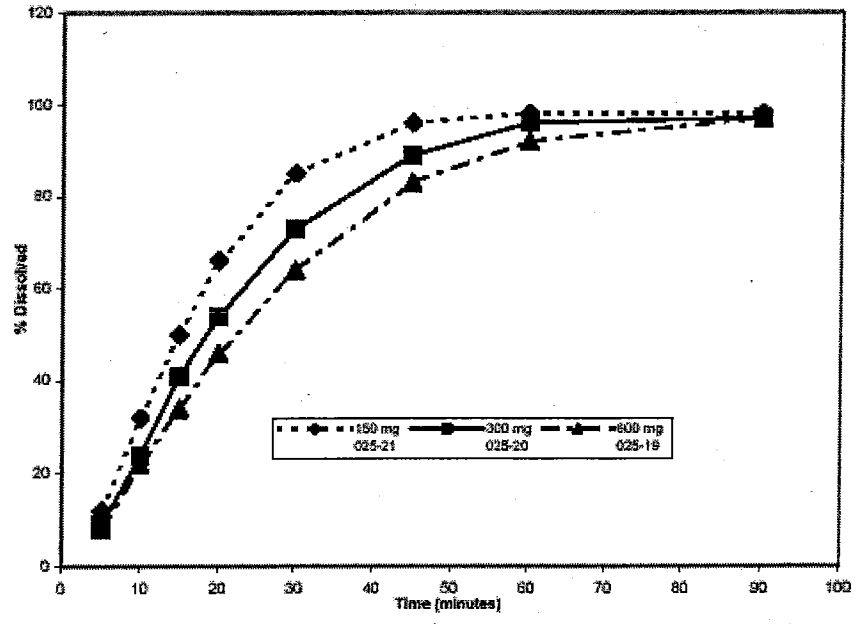


Table 2: SAS Transport Files

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. The firm conducted dissolution testing on all three strengths using the dissolution medium recommended by the FDA for only the 600 mg (Water + 1% SDS). The dissolution testing on the 600 mg is acceptable and meets FDA specifications of NLT (b) (4)% (Q) in 30 minutes and NLT (b) (4)% (Q) in 60 minutes at L2 and L1 levels, respectively.

2. The firm has submitted complete in-vivo study data summary, dissolution data and formulation data in the electronic format that are recommended by the Division of Bioequivalence.

DEFICIENCY COMMENTS:

The firm's dissolution testing data with the FDA-recommended method are acceptable for the 600 mg. However, the firm did not conduct dissolution testing on the 150 mg and 300 mg using the FDA-recommended methods for these two strengths. The firm should repeat dissolution testing for the 150 mg and 300 mg using Water plus 0.3% and 0.6% SDS, respectively.

RECOMMENDATIONS:

The *in vitro* dissolution testing conducted by Apotex Inc. on its test products, Oxcarbazepine Tablets (150 mg and 300 mg) is incomplete for the reason cited in the deficiency comment above.

12/09/05

Patrick Nwakama, Pharm.D. Branch III Date

12/11/2005

Yih-Chain Huang, Ph.D.,Team Leader Branch III Date

12/12/05

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

BIOEQUIVALENCE DEFICIENCY

ANDA: 77-747 APPLICANT: Apotex Inc.

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 (BE) studies and waiver requests will be conducted later.

The following deficiency has been identified:

You conducted dissolution testing on all three strengths using the method recommended only for the 600 mg and did not propose any dissolution specifications. Your dissolution data for the 600 mg is acceptable. Your dissolution testing on the 150 mg and 300 mg is incomplete. Therefore, the Division of Bioequivalence recommends that you repeat dissolution testing on the 150 mg and 300 mg using the following dissolution method and specifications:

The dissolution testing should be conducted in 900 mL, Water (plus 0.3% SDS for 150 mg; 0.6% SDS for 300 mg and 1% SDS for 600 mg), Paddle, at 60 rpm; NLT (b)(4)% (Q) in 30 minutes and NLT (b)(4)% (Q) in 60 minutes].

With your response to the above deficiency, please acknowledge that you have accepted the above dissolution method and specifications.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after complete review of the application.

Sincerely yours,

for Barbara M. Davit

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

CC: ANDA 77-747
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Drug File
HFD-658/ Reviewer
HFD-658/ Team Leader

Endorsements:
HFD-658/ P. Nwakama 12/09/05
HFD-658/ YC Huang 12/11/2005
HFD-650/ D. Conner 12/12/05

DISSOLUTION – Incomplete Submission date: 07/14/05

[NOTE: The *in vitro* testing is incomplete. The fasting and fed BE studies and waiver requests are pending review]

1. DISSOLUTION (Dissolution Data) Strength: 600 mg
Outcome: AC

2. DISSOLUTION (Dissolution Data) Strength: 150 mg & 300 mg
Outcome: IC

Outcome Decisions: IC – Incomplete (Dissolution data)
WinBio Comments: IC

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-747
Drug Product Name	Oxcarbazepine Tablets
Strength	150 mg, 300 mg, and 600 mg tablets
Applicant Name	Apotex
Address	150 Signet Toronto, Ontario
Submission Date(s)	07-14-05
Amendment Date(s)	02-07-06
Reviewer	**Ethan M. Stier, Ph.D.**
First Generic	**No**
File Location	**V:\firmsam\apotex\ltrs&rev\77747N0705**

I. Executive Summary

This application references Trileptal® tablets and includes one fasting and one fed BE study.

The fasting study is a single-dose, two-way crossover study using male healthy volunteers given a dose of 1 X 600 mg. The results of the fasting BE study (point estimate, 90% CI) for Oxcarbazepine tablets are LAUCt 0.98, 94.59-101.75, LAUC∞ 0.99, 94.70-102.70, and LCmax 1.00, 85.61-116.54.

The fed BE study is a single-dose, two-group, two-way crossover study using male healthy volunteers given a dose of 1 X 600 mg. The results of the fed BE study (point estimate, 90% CI) for Oxcarbazepine tablets are LAUCt 0.97, 94.44-98.97, LAUC∞ 0.96, 93.89-98.57, and LCmax 0.94, 88.94-100.16.

The bioequivalence studies are incomplete for several reasons. Please refer to the deficiencies section.

The applicant requests waivers of in vivo BE study requirements for the 150 mg and 300 mg tablets. The formulations of the 150 mg and 300 mg tablets are proportional to the 600 mg tablet, which underwent in vivo testing. The dissolution testing conducted by the firm on the 150 mg, 300 mg, and 600 mg tablets was previously reviewed, and was found incomplete. The firm submitted a study amendment (02-07-06) containing dissolution data. However, the firm will requested to provide further information. The testing is incomplete. Waivers of *in vivo* bioequivalence study requirements for the 150 mg and 300 mg tablet will be granted pending a satisfactory response to the deficiencies.

The application is incomplete.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Oxcarbazepine Tablet
Reference Product	Trileptal® Tablet
RLD Manufacturer	Novartis
NDA No.	20-014
RLD Approval Date	01-14-00
Indication	Used for treatment of partial seizures in adults and children ages 4-16 with epilepsy.

B. PK/PD Information

Bioavailability	Following administration oxcarbazepine is completely absorbed
Food Effect	Food has no effect on the rate and extent of absorption
Tmax	4.5 h (3-13 h)
Metabolism	Oxcarbazepine is metabolized in the liver to the 10-monohydroxy metabolite, which is primarily responsible for the pharmacological effect of Trileptal®.
Excretion	Oxcarbazepine is cleared from the body primarily as metabolites. More than 95% of the dose appears in the kidneys and less than 1% as unchanged as parent. Fecal excretion accounts for less than 4% of the administered dose.
Half-life	2 hours
Relevant OGD or DBE History	*Relevant AND, Protocols, and Controls:* The DBE has not previously reviewed any ANDAs for this drug product; reviewed two protocols (04-059/(b) (4) and 02-034/Roxane); reviewed multiple controls including: 03-737/(b) (4), 03-154/(b) (4), 03-610/(b) (4), 03-179/(b) (4), 03-193/(b) (4), 03-214/(b) (4), 04-699/(b) (4), and 04-672/(b) (4). A cluster of ANDAs is under review: 1. 77747 Apotex Ethan (incomplete) 2. (b) (4) Zak (incomplete) 3. 77794 Sun Jenny (acceptable) 4. 77795 Roxane XJ (incomplete) 5. (b) (4) Surendra (working) 6. 77801 Taro Ethan (this review) 7. 77802 Glenmark Jane (working) *Bioequivalence Testing and Dissolution:* Based on the protocols and controls the ANDA sponsors should conduct two BE studies (single-dose fasting and single-dose non-fasting) on the 600 mg strength tablet and the lower strengths (150 mg and 300 mg tablets) may be eligible for a biowaiver. The applicant should conduct comparative dissolution testing using the FDA-recommended method: Medium: Aqueous sodium dodecyl

	sulfate solution
Volume:	900 mL
Temperature:	37°C
USP Apparatus:	Apparatus II (paddle)
Rotation:	60 rpm
Specification:	NLT (b)(4)%(Q) in 30 minutes NLT %(Q) in 60 minutes

The concentration of SDS was varied for the tablets:

- 1.0% for 600 mg
- 0.6% for 300 mg
- 0.3% for 150 mg

Note: SDS is required due to the poor solubility of oxcarbazepine

Agency Guidance None.

Drug Specific Issues (if any) N/A

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	NA
In vitro dissolution	Yes	3
Waiver requests	Yes	2
BCS Waivers	No	NA
Vasoconstrictor Studies	No	NA
Clinical Endpoints	No	NA
Failed Studies	No	NA
Amendments	Yes	1
CTD Tables	Yes	8

D. Pre-Study Bioanalytical Method Validation

Method for fasting study

Table 3. Bioanalytical Method Validation (STUDY: OXCA-IMTB-01AB03-2FA)

Information Requested	Data for Oxcarbazepine	Data for 10-hydroxycarbazepine
Bioanalytical method validation report location	Section 16.6	Section 16.6
Internal Standard (IS)	(b) (4)	(b) (4)
Method description	Automated solid phase extraction. HPLC-MS/MS detection	Automated solid phase extraction. HPLC-MS/MS detection
Limit of quantification	10.0 ng/mL (nominal)	50.0 ng/mL (nominal)
Average recovery of drug	88.07 %	85.62 %
Average recovery of IS	97.03 %	97.03 %
Standard curve concentrations (ng/mL)	10.0 to 2000.0 (nominal)	50.0 to 10000.0 (nominal)
QC concentrations (ng/mL)	QC A: 30.0 QC B: 750.0 QC C: 1500.0	QC A: 150.0 QC B: 3750.0 QC C: 7500.0
QC Intraday precision range (CV%)	QC A: 3.1 to 8.3 % QC B: 2.4 to 7.6 % QC C: 2.3 to 9.4 %	QC A: 4.0 to 13.1 % QC B: 3.4 to 10.9 % QC C: 0.7 to 11.5 %
QC Intraday accuracy range (%Dev)	QC A: -8.0 to 9.3 % QC B: - 7.9 to 6.8 % QC C: -10.4 to 0.8 %	QC A: -4.1 to12.5 % QC B: -8.3 to 3.4 % QC C: -9.9 to 0.9 %
QC Interday precision range (CV%)	6.5 to 7.8 %	7.7 to 9.1 %
QC Interday accuracy range (%Dev)	-5.0 to 0.8 %	-4.9 to 0.9 %
Bench-top stability	2 hrs at room temperature 3 hrs on ice	2 hrs at room temperature 3 hrs on ice
Stock stability	20 days at -80°C set point freezer	20 days at -80°C set point freezer
Stock stability (IS)	13 days at -80°C set point freezer	13 days at -80°C set point freezer
Processed stability	30.5 hrs (refrigerated)	30.5 hrs (refrigerated)
Freeze-thaw stability	3 cycles	3 cycles
Long-term storage stability	56 days at -80°C set point freezer	56 days at -80°C set point freezer
Dilution integrity	Diluted 2 fold and 4 fold	Diluted 2 fold and 4 fold
Selectivity	No interfering peaks noted in blank plasma samples	No interfering peaks noted in blank plasma samples

Method for non-fasting study

Table 3. Bioanalytical Method Validation (STUDY: OXCA-IMTB-01AB05-2FE)

Information Requested	Data for Oxcarbazepine	Data for 10-hydroxycarbazepine
Bioanalytical method validation report location	Section 16.6	Section 16.6
Internal Standard (IS)	(b) (4)	(b) (4)
Method description	Automated solid phase extraction. HPLC-MS/MS detection	Automated solid phase extraction. HPLC-MS/MS detection
Limit of quantification	10.0 ng/mL (nominal)	0.050 µg/mL (nominal)
Average recovery of drug	48.93 %	43.23 %
Average recovery of IS	57.62 %	57.62 %
Standard curve concentrations	10.0 to 6000.0 (ng/mL) (nominal)	0.050 to 10.000 µg/mL (nominal)
QC concentrations	QC A: 30.0 (ng/mL) QC B: 2250.0 QC C: 4500.0	QC A: 0.150 (µg/mL) QC B: 3.750 QC C: 7.500
QC Intraday precision range (CV%)	QC A: 3.1 to 7.5 % QC B: 2.6 to 10.4 % QC C: 2.1 to 9.2 %	QC A: 5.9 to 7.9 % QC B: 2.3 to 4.8 % QC C: 3.4 to 7.8 %
QC Intraday accuracy range (%Dev)	QC A: -6.7 to 9.3 % QC B: -5.0 to 10.5 % QC C: -6.5 to 9.0 %	QC A: 0.7 to 7.3 % QC B: -5.0 to 5.2 % QC C: -6.1 to 0.5 %
QC Interday precision range (CV%)	7.2 to 7.3 %	5.0 to 7.1 %
QC Interday accuracy range (%Dev)	-0.8 to 0.3 %	-3.1 to 3.3 %
Bench-top stability	3.5 hrs at room temperature	3.5 hrs at room temperature
Stock stability	76 days at -80°C set point freezer	34 days at -80°C set point freezer
Stock stability (IS)	76 days at -80°C set point freezer	76 days at -80°C set point freezer
Processed stability	98 hrs (refrigerated)	98 hrs (refrigerated)
Freeze-thaw stability	3 cycles	3 cycles
Long-term storage stability	61 days at -80°C set point freezer	61 days at -80°C set point freezer
Dilution integrity	Diluted 2 fold and 4 fold	Diluted 2 fold and 4 fold
Selectivity	No interfering peaks noted in blank plasma samples	No interfering peaks noted in blank plasma samples

The analytical method is acceptable.

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary, Fasting Bioequivalence Study	
Study No.	01AB03-2FA
Study Design	Single-dose, 2-way crossover, fasting
No. of subjects enrolled	20 (+4 alternates)
No. of subjects completing	20 (+3 alternates)
No. of subjects analyzed	20
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 20 Female: 0
Test product	Oxcarbazepine Tablet
Reference product	Trileptal®
Strength tested	600 mg
Dose	1 X 600 mg

Study Ref. No.	Study Objective	Study Design	Subject No. (M/F)* Type Age: mean (Range)**	Treatments Strength [Lot #]	Analyte	Arithmetic Mean Parameters (±SD) Cmax (ng/mL)[1] (mcg/mL)[2]	Tmax (h)	AUCt (ng*h/ml)[1] (mcg*h/ml)[2]	AUCinf (ng*h/ml)[1] (mcg*h/ml)[2]	Thalf (h)	Kel (1/h)	Study Report Location
OXCA-IMTB-01AB03-2FA	Comparative, Randomized, 2-way Crossover Bioavailability Study of OXCARBAZEPINE TABLETS (Apotex Inc.) and TRILEPTAL® TABLETS (Novartis), (USA) under fasting conditions	Randomized, single-dose, open label, fasting, 2-way crossover	20 (20/0) healthy subjects Age: 30.2 (18-48)	OXCARBAZEPINE TABLETS, 600 mg, [025-19A]	Oxcarbazepine	1499.0 ± 623.0	1.52	5051.3 ± 991.1	5344.4 ± 1004.3	11.49	0.06378	5.3.1.2
					# 10-Hydroxy-Carbazepine	7.308 ± 1.223	5.48	173.890 ± 24.345	176.689 ± 26.443	10.18	0.07022	
				TRILEPTAL® TABLETS, 600 mg, [019J4374]	Oxcarbazepine	1496.4 ± 470.9	1.24	5120.1 ± 817.4	5404.9 ± 852.0	11.38	0.06283	
					# 10-Hydroxy-Carbazepine	7.412 ± 1.016	5.38	179.185 ± 24.068	184.171 ± 24.091	9.78	0.07250	
OXCA-IMTB-01AB05-2FE	Comparative, Randomized, 2-way Crossover Bioavailability Study of OXCARBAZEPINE TABLETS (Apotex Inc.) and TRILEPTAL® TABLETS (Novartis), (USA) under fed conditions	Randomized, single-dose, open label, fed, 2-way crossover	113 (113/0) healthy subjects Age: 34.3 (18 - 56)	OXCARBAZEPINE TABLETS, 600 mg, [025-19A]	Oxcarbazepine	3138.8 ±1183.0	1.69	7654.1 ±1745.1	7922.3 ±1748.3	11.52	0.06195	5.3.1.2
					10-Hydroxy-Carbazepine	8.147 ±1.166	4.66	188.880 ±26.319	189.741 ±26.111	9.89	0.07160	
				TRILEPTAL® TABLETS, 600 mg, [F0107]	Oxcarbazepine	3325.2 ±1221.3	1.70	7990.4 ±1707.1	8220.1 ±1720.4	12.00	0.06052	
					10-Hydroxy-Carbazepine	8.227 ± 1.052	4.37	189.852 ± 27.607	172.788 ± 27.685	10.02	0.07073	

*Based on subjects included in pharmacokinetic/statistical analysis.
**Based on subjects dosed in period 1.

[1] Units for Oxcarbazepine data

[2] Units for 10-Hydroxy-Carbazepine data

Units for 10-Hydroxy-Carbazepine data within OXCA-IMTB-01AB03-2FA study were expressed as ng/mL in the report. For presentation purposes within this table and to facilitate comparison between the two studies, 10-Hydroxy-Carbazepine concentration data for this study were converted to mcg/mL units.

Fasting Bioequivalence Study					
Parameter	Analyte	Oxcarbazepine	Trileptal®	Ratio	90% C.I.
(ng*h/mL) AUCt	Oxcarbazepine	4957.7	5053.5	98.1	94.6 – 101.7
(mcg*h/mL)	# 10-Hydroxy-Carbazepine	172.171	177.891	96.9	94.3 – 99.6
(ng*h/mL) AUCinf	Oxcarbazepine	5253.9	5327.5	98.6	94.7 – 102.7
(mcg*h/mL)	# 10-Hydroxy-Carbazepine	175.055	179.561	97.5	95.0 – 100.0
(ng/mL) Cmax	Oxcarbazepine	1344.2	1345.7	99.9	85.6 – 116.5
(mcg/mL)	# 10-Hydroxy-Carbazepine	7.206	7.348	98.1	90.9 – 105.8
Fed Bioequivalence Study					
Parameter	Analyte	Oxcarbazepine	Trileptal®	Ratio	90% C.I.
(ng*h/mL) AUCt	Oxcarbazepine	7457.8	7714.0	96.7	94.4 - 99.0
(mcg*h/mL)	10-Hydroxy-Carbazepine	164.910	167.737	98.3	97.2 - 99.4
(ng*h/mL) AUCinf	Oxcarbazepine	7732.9	8038.0	96.2	93.9 - 98.6
(mcg*h/mL)	10-Hydroxy-Carbazepine	167.871	170.720	98.3	97.3 - 99.4
(ng/mL) Cmax	Oxcarbazepine	2927.4	3101.6	94.4	88.9 - 100.2
(mcg/mL)	10-Hydroxy-Carbazepine	8.056	8.161	98.8	97.4 - 100.3

Note: Geometric Means, Ratio of Means, and 90% CIs are based on the least squares estimates

Units for 10-Hydroxy-Carbazepine data within OXCA-IMTB-01AB03-2FA study were expressed as ng/mL in the report. For presentation purposes within this table and to facilitate comparison between the two studies, 10-Hydroxy-Carbazepine concentration data for this study were converted to mcg/mL units.

STUDY: OXCA-IMTB-01AB03-2FA Additional information in Table 16.5.8.6								
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	0	0	0	0	0	0	0	0
B: Analysis Incomplete	0	1	0	0.11	0	0	0	0
F: Outside Range	4	5	0.46	0.57	0	0	0	0
G: Highest and/or Lowest Std Missing	5	3	0.57	0.34	0	0	0	0
Total	9	9	1.02	1.02	0	0	0	0

Did use of recalculated plasma concentration data change study outcome? No, there were no PK repeats.

2. Single-dose Fed Bioequivalence Study

Study Summary, Fasting Bioequivalence Study	
Study No.	01AB05-2FE
Study Design	Single-dose, two-group, two-way crossover, randomized
No. of subjects enrolled	116
No. of subjects completing	113
No. of subjects analyzed	113
Subjects (Healthy or Patients?)	healthy
Sex(es) included (how many?)	Male: 113 Female: 0
Test product	Oxcarbazepine Tablet
Reference product	Trileptal®
Strength tested	600 mg
Dose	1 X 600 mg

Study Ref. No.	Study Objective	Study Design	Subject No. (M/F)* Type Age: mean (Range)**	Treatments Strength [Lot #]	Analyte	Arithmetic Mean Parameters (±SD) Cmax (ng/mL)[3] (mcg/mL)[2]	Tmax (h)	AUCt (ng*h/ml)[3] (mcg*h/ml)[2]	AUCinf (ng*h/ml)[3] (mcg*h/ml)[2]	Thalf (h)	Kel (1/h)	Study Report Location
OXCA-IMTB-01AB03-2FA	Comparative, Randomized, 2-way Crossover Bioavailability Study of OXCARBAZEPINE TABLETS (Apotex Inc.) and TRILEPTAL® TABLETS (Novartis), (USA) under fasting conditions	Randomized, single-dose, open label, fasting, 2-way crossover	20 (20/0) healthy subjects Age: 30.2 (18-43)	OXCARBAZEPINE TABLETS, 600 mg, [025-19A]	Oxcarbazepine	1439.0 ± 623.0	1.52	5051.3 ± 991.1	5344.4 ± 1004.3	11.49	0.06378	5.3.1.2
					# 10-Hydroxy-Carbazepine	7.308 ± 1.223	5.46	173.690 ± 24.945	176.869 ± 26.442	10.18	0.07022	
				TRILEPTAL® TABLETS, 600 mg, [019J4374]	Oxcarbazepine	1436.4 ± 470.9	1.24	5120.1 ± 817.4	5404.9 ± 852.0	11.38	0.06283	
					# 10-Hydroxy-Carbazepine	7.412 ± 1.016	5.38	179.165 ± 24.068	181.171 ± 24.091	9.78	0.07260	
OXCA-IMTB-01AB05-2FE	Comparative, Randomized, 2-way Crossover Bioavailability Study of OXCARBAZEPINE TABLETS (Apotex Inc.) and TRILEPTAL® TABLETS (Novartis), (USA) under fed conditions	Randomized, single-dose, open label, fed, 2-way crossover	113 (113/0) healthy subjects Age: 34.3 (18 - 55)	OXCARBAZEPINE TABLETS, 600 mg, [025-19A]	Oxcarbazepine	3138.8 ±1163.9	1.69	7654.1 ±1745.1	7922.3 ±1748.3	11.52	0.06195	5.3.1.2
					10-Hydroxy-Carbazepine	8.147 ±1.166	4.68	188.880 ±26.319	189.741 ±26.111	9.86	0.07160	
				TRILEPTAL® TABLETS, 600 mg, [F0107]	Oxcarbazepine	3325.2 ±1221.3	1.70	7900.4 ±1707.1	8220.1 ±1720.4	12.00	0.05952	
					10-Hydroxy-Carbazepine	8.227 ± 1.952	4.37	189.852 ± 27.607	192.788 ± 27.885	10.02	0.07073	

*Based on subjects included in pharmacokinetic/statistical analysis.
**Based on subjects dosed in period 1.

[1] Units for Oxcarbazepine data.

[2] Units for 10-Hydroxy-Carbazepine data

Units for 10-Hydroxy-Carbazepine data within OXCA-IMTB-01AB03-2FA study were expressed as ng/mL in the report. For presentation purposes within this table and to facilitate comparison between the two studies, 10-Hydroxy-Carbazepine concentration data for this study were converted to mcg/mL units.

Fasting Bioequivalence Study					
Parameter	Analyte	Oxcarbazepine	Trileptal®	Ratio	90% C.I.
(ng*h/mL) AUCt	Oxcarbazepine	4957.7	5053.5	98.1	94.6 – 101.7
(mcg*h/mL)	# 10-Hydroxy-Carbazepine	172.171	177.691	96.9	94.3 – 99.6
(ng*h/mL) AUCinf	Oxcarbazepine	5253.9	5327.5	98.6	94.7 – 102.7
(mcg*h/mL)	# 10-Hydroxy-Carbazepine	175.055	179.581	97.5	95.0 – 100.0
(ng/mL) Cmax	Oxcarbazepine	1344.2	1345.7	99.9	85.6 – 116.5
(mcg/mL)	# 10-Hydroxy-Carbazepine	7.206	7.348	98.1	90.9 – 105.8
Fed Bioequivalence Study					
Parameter	Analyte	Oxcarbazepine	Trileptal®	Ratio	90% C.I.
(ng*h/mL) AUCt	Oxcarbazepine	7457.8	7714.0	96.7	94.4 - 99.0
(mcg*h/mL)	10-Hydroxy-Carbazepine	164.910	167.737	98.3	97.2 - 99.4
(ng*h/mL) AUCinf	Oxcarbazepine	7732.9	8038.0	96.2	93.9 - 98.6
(mcg*h/mL)	10-Hydroxy-Carbazepine	167.871	170.720	98.3	97.3 - 99.4
(ng/mL) Cmax	Oxcarbazepine	2927.4	3101.6	94.4	88.9 - 100.2
(mcg/mL)	10-Hydroxy-Carbazepine	8.056	8.161	98.8	97.4 - 100.3

Note: Geometric Means, Ratio of Means, and 90% CIs are based on the least squares estimates.

Units for 10-Hydroxy-Carbazepine data within OXCA-IMTB-01AB03-2FA study were expressed as ng/mL in the report. For presentation purposes within this table and to facilitate comparison between the two studies, 10-Hydroxy-Carbazepine concentration data for this study were converted to mcg/mL units.

STUDY: OXCA-IMTB-01AB05-2FE Additional information in Table 16.5.8.6								
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	0	0	0	0	0	0	0	0
B: Analysis Incomplete	8	12	0.16	0.24	0	0	0	0
C: Poor Chromatography	28	5	0.56	0.10	0	0	0	0
G: Highest/Lowest Std Missing	23	29	0.46	0.58	0	0	0	0
F: Outside Range	15	31	0.30	0.62	0	0	0	0
Total	74	77	1.49	1.55	0	0	0	0

Did use of recalculated plasma concentration data change study outcome? No, there were no PK repeats.

F. Formulation

Location in appendix	
Are inactive ingredients within IIG limits?	Yes
If no, list ingredients outside of limits	N.A.
If a tablet, is the product scored?	Yes
If yes, which strengths are scored?	All strengths.
Is RLD scored?	Yes. All three strengths are scored.
Is the formulation acceptable?	Yes
If not acceptable, why?	N.A.

G. In Vitro Dissolution

Firm's Method and Specification	
Medium	Water +0.3% SDS for 150 mg + 0.6% SDS for 300 mg + 1% SDS for 600 mg
Volume (mL)	900
USP Apparatus type	II
Rotation (rpm)	60
FDA Recommended Specification	NLT (b) (4)% (Q) in 30 minutes and NLT (b) (4)% (Q) in 60 minutes
F2 metric calculated?	No
If no, reason why F2 not calculated	Rapid Dissolution
Is method acceptable?	No. The firm did not specify the volume of media and rotation speed used for testing.
Is proposed specification acceptable?	N.A.
If not then why?	N.A.

H. Waiver Request(s)

Strength 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?	No
Waiver granted?	No
If not then why?	Refer to deficiencies section

I. Deficiency Comments

1. The firm used different batches of the RLD in the fasting and non-fasting studies. The firm should provide explanation for such usage.

2. The firm did not provide the potency of the RLD in the fasting study (Batch #: 019J4374) and non-fasting study (Batch #: F0107).

3. The firm provided only summary reassay tables for both studies. It should provide details of reassayed samples in tables (subject #, treatment, period, sampling time, reason for reassay, original value, reassayed value(s) and reason for the selection of the value for the statistical analysis).

4. The firm did not provide the medium, volume of medium and rotation speed used for in vitro dissolution testing. The firm used 2 different lots of 600 mg RLD tablets in the BE studies, but provided dissolution only on the lot 019J4374. It should provide dissolution testing on the 600 mg RLD lot F0107.

J. Recommendations

1. The in vivo bioequivalence study conducted under fasting conditions by Apotex comparing its oxcarbazepine tablets 600 mg to the reference product Trileptal® 600 mg tablet (Novartis) is incomplete due to deficiencies #1-3.

2. The in vivo bioequivalence study conducted under non-fasting conditions by Apotex comparing its oxcarbazepine tablets 600 mg to the reference product Trileptal® 600 mg tablet (Novartis) is incomplete due to deficiencies #1-3.

3. The dissolution testing conducted by Apotex on its oxcarbazepine tablets, 150 mg, 300 mg, and 600 mg is incomplete due to deficiency #4. The dissolution testing should be conducted in 900 mL of water (plus 0.3% SDS for 150 mg; plus 0.6% SDS for 300 mg; plus 1% SDS for 600 mg) using USP Apparatus II (Paddle) at 60 RPM. The test product 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 and not less than (b) (4)% (Q) of the labeled amount of oxcarbazepine in the dosage form is dissolved in 60 minutes and .

4. The formulations of Apotex's 150 mg and 300 mg oxcarbazepine tablets are proportional to the 600 mg strength tablet, which underwent in vivo bioequivalence testing. The firm has previously acknowledged the acceptance of the FDA recommended method and specification. A waiver of *in vivo* bioequivalence study requirements for the 150 mg and 300 mg tablets will be granted when the firm provides a satisfactory response to the deficiencies #1-4.

The application is incomplete.

Ethan M. Stier 4-25-06

Ethan M. Stier, Ph.D., Team II, Date Signed

4/25/2006

Shriniwas G. Nerurkar, Ph.D., Team II, Date Signed

Dale P. Conner 4/25/06

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

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information	
Study Number	OXCA-IMTB-01AB03-2FA
Study Title	Randomized, 2-Way Crossover Study of Oxcarbazepine 600 mg Tablet and Trileptal® Following a 600 mg Dose in Healthy Subjects Under Fasting Conditions
Clinical Site	APOTEX Weston, Ontario
Principal Investigator	D. Satok, M.D.
Study/Dosing Dates	I: 10-16-04 II: 10-23-04
Analytical Site	APOTEX Weston, Ontario
Analytical Director	(b) (6)
Analysis Dates	11-5-04 to 11-30-04
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	45 days

Test or Reference	Test	Reference
Treatment ID	**A**	**B**
Product Name	Oxcarbazepine	Trileptal®
Manufacturer	Apotex	Novartis
Batch/Lot No.	025-19A	019J4374
Manufacture Date	09-04	N.A.
Expiration Date	N.A.	06-07
Strength	600 mg	600 mg
Dosage Form	Tablet	Tablet
Batch Size	(b) (4)	N.A.
Production Batch Size		N.A.
Potency (absolute difference is less than 5%)*	99.1	Not Provided
Content Uniformity (mean, %CV)	98.4 (1.2)	N.A.
Formulation	See Table B	
Dose Administered	1 X 600 mg	1 X 600 mg
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7
Randomization Scheme	AB: 1,4,6,7,11,12,15,16,19,20 BA:2,3,5,8,9,10,13,14,17,18
Blood Sampling Times (h)	Pre-dose, 0.33, 0.66, 1, 1.33, 1.66, 2.0, 2.5, 3, 3.5, 4, 5,6,7,9,12,16,24,36,48, and 72
Blood Volume Collected/Sample	10 mL
Blood Sample Processing/Storage	-80°C
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table I
Length of Fasting	At least 10 hours
Length of Confinement	From at least 10 hours prior to drug administration till the 36 hour blood draw
Safety Monitoring	Vital signs and adverse events were monitored by qualified personnel

Comments on Study Design: The firm did not provide the potency of the RLD.

b) Clinical Results

Table 1 Demographics of Study Subjects

Table 6. Demographic Profile of Subjects Completing the Bioequivalence Study - Oxcarbazepine

Study No. OXCA-BMTB-01AB03-2FA		
	Treatment Groups	
	Test Product N = 23	Reference Product N = 23
Age (years)		
Mean ± SD	29.87 ± 8.57	29.87 ± 8.57
Range	18 – 48	18 – 48
Groups		
<18	0 (0 %)	0 (0 %)
18 – 40	20 (87 %)	20 (87 %)
41 – 64	3 (13 %)	3 (13 %)
65 – 75	0 (0 %)	0 (0 %)
>75	0 (0 %)	0 (0 %)
Sex		
Female	0 (0 %)	0 (0 %)
Male	23 (100 %)	23 (100 %)
Race		
Asian	1 (4.3 %)	1 (4.3 %)
Black	3 (13 %)	3 (13 %)
Caucasian	13 (56.5 %)	13 (56.5 %)
Hispanic	2 (8.8 %)	2 (8.8 %)
Other	4 (17.4 %)	4 (17.4 %)
Other Factors	Subject OC22 was withdrawn due to an adverse event.	

Table 2 Dropout Information

Subject No	Reason	Period	Replaced?
22 (unused alternate)	Adverse Events	I	no

Table 3 Study Adverse Events

TABLE 7 Incidences of Adverse Events in Individual Studies – (Oxcarbazepine Tablets)

System/Adverse Events	Reported Incidence by Treatment Groups			
	Fasted Bioequivalence Study Study No. (OXCA-IMTB-01AB03-2FA) (Internal code: OC2062)		Fed Bioequivalence Study Study No. (OXCA-IMTB-01AB03-2FE) (Internal Code: OC2260G1, OX2260G2)	
	Test	Reference	Test	Reference
Cardiac disorders				
Atrioventricular block first degree	1 (4.2%)	1 (4.3%)		1 (0.5%)
Gastrointestinal Disorders				
Hypoaesthesia oral			2 (1.8%)	4 (3.6%)
Diarrhea	1 (4.2%)			
General disorder and administration site conditions				
Fatigue	1 (4.2%)		5 (4.4%)	3 (2.6%)
Feeling abnormal			4 (3.5%)	3 (2.6%)
Chest Discomfort				1 (0.5%)
Swollen Tongue				1 (0.5%)
Feeling Drunk			2 (1.8%)	2 (0.17%)
Application site pain	1 (4.2%)			
Catheter site edema	1(4.2%)			
Catheter site haemorrhage	1 (4.2%)			
Catheter site hematoma		1(4.3%)		1(0.5%)
Venipuncture site swelling		1(4.3%)		1(0.5%)
Injury, poisoning and procedural complications				
Contusion	1 (4.2%)	1(4.3%)		1(0.5%)
Metabolism and nutrition disorder				
Decreased Appetite			1 (0.9%)	
Musculoskeletal and connective tissue disorders				
Back pain	1 (4.2%)			
Nervous system disorders				
Dizziness	2 (8.3%)	2 (8.7%)	7 (6.2%)	6 (5.9%)
Headache		1 (4.3%)	2(1.8%)	2(0.17%)
Disturbance in attention			3 (2.7%)	2 (0.17%)
Somnolence	1 (4.2%)	1 (4.3%)	8 (7.1%)	7 (6.0%)
Paraesthesia oral			1 (0.9%)	1 (0.5%)
Syncope				1 (0.9%)
Balance disorder				1 (0.9%)

Page 1 of 1

Table 4 Protocol Deviations

Type	Subject #s (Test)	Subject #s (Ref.)
Blood samples for the 5 hour time point will stored at room temperature for 7 minutes	All	All
Error in Recording Sampling time at 72 hours by one hour (note: the plasma level of drug was zero at 48 hours, so an error in the 72 hour time point will not affect the outcome)	10	-

Comments on Dropouts/Adverse Events/Protocol Deviations: There was one dropout. The number of adverse events observed in the test group was greater than in the reference group. The protocol deviations did not compromise the outcome of this study.

Analytical Results

Table 5 Assay Quality Control – Within Study

	Oxcarbazepine		
QC Conc. (ng/mL)	30.0	750.0	1500.0
Inter day Precision (%CV)	8.2	6.6	6.3
Inter day Accuracy (%)	97.7	101.3	95.7

Cal. Standards Conc. (ng/mL)	10.0	20.0	40.0	100.0	200.0	400.0	800.0	1200.0	1600.0	2000.0
Inter day Precision (%CV)	4.1	6.3	4.4	5.4	4.4	4.2	3.5	3.7	4.3	3.8
Inter day Accuracy (%)	98.0	102.5	101.8	104.6	102.0	104.4	98.7	98.6	94.1	95.6
Linearity Range (range of R^2 values)	0.9913-0.9988									

Comments on Study Assay Quality Control: Acceptable

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

Comments on Chromatograms: Acceptable

Table 6 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
ABM-BL-0154	06-15-04	Routine Batch Analysis

Table 7 Additional Comments on Repeat Assays

Were all SOPs followed?	The firm provided only a summary reassay table. It should provides details of reassayed samples in a table (subject #, treatment, period, sampling time, reason for reassay, original value, reassayed value(s) and reason for the selection of the value for the statistical analysis).
Did recalculation of plasma concentrations change the study outcome?	No. There were no PK repeats
Does the reviewer agree with the outcome of the repeat assays?	See Above
If no, reason for disagreement	See above

Summary/Conclusions, Study Assays: Incomplete

d) Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters

Parent

PARAMETER	UNITS	TEST		REFERENCE		RATIO T/R
		MEAN1	%CV	MEAN2	%CV	
$AUC_{0-\infty}$	ng·hr/mL	5344.40	18.79	5404.92	15.76	0.99
AUC_{0-t}	ng·hr/mL	5051.27	19.62	5120.14	15.96	0.99
CMAX	ng/mL	1438.96	43.29	1436.37	32.78	1.00
KE	$hour^{-1}$	0.06	24.25	0.06	16.36	1.02
THALF	hour	11.49	23.89	11.38	17.66	1.01
TMAX	hour	1.52	43.04	1.24	39.69	1.23

Metabolite

PARAMETER	UNITS	TEST		REFERENCE		RATIO T/R
		MEAN1	%CV	MEAN2	%CV	
$AUC_{0-\infty}$	ng·hr/mL	176688.51	14.40	181171.09	13.79	0.98
AUC_{0-t}	ng·hr/mL	173690.41	14.02	179185.36	13.43	0.97
CMAX	ng/mL	7307.80	16.73	7411.73	13.71	0.99
KE	$hour^{-1}$	0.07	16.87	0.07	15.04	0.97
THALF	hour	10.18	19.35	9.78	15.77	1.04
TMAX	hour	5.48	30.42	5.38	36.20	1.02

Table 9 Geometric Means and 90% Confidence Intervals

Parent

PARAMETER	TEST	REFERENCE	RATIO T/R	90 % CI	
	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
$AUC_{0-\infty}$	5344.40	5391.72	0.99	94.91	103.33
AUC_{0-t}	5051.27	5120.14	0.99	94.93	102.38
CMAX	1438.96	1436.37	1.00	85.21	115.15
LAUCI	5253.89	5327.53	0.99	94.70	102.70
LAUCT	4957.75	5053.45	0.98	94.59	101.75
LCMAX	1344.16	1345.72	1.00	85.61	116.54

Metabolite

PARAMETER	TEST	REFERENCE	RATIO T/R	90 % CI	
	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
LAUCI	175055.50	179581.38	0.97	95.04	99.98
LAUCT	172170.59	177691.05	0.97	94.34	99.52
LCMAX	7206.26	7347.96	0.98	90.89	105.82

Table 10 Additional Study Information

Root mean square error, LAUC0-t	0.0664
Root mean square error, LAUC∞	0.0716
Root mean square error, LCmax	0.2812
Kel and AUC∞ determined for how many subjects?	19
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	0
-first measurable drug concentration as Cmax	0
Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic and Statistical Analysis:

1. The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations. The 90% confidence intervals for lnAUC0-t, lnAUC∞ and lnCmax are within the acceptable limits of 80-125%.

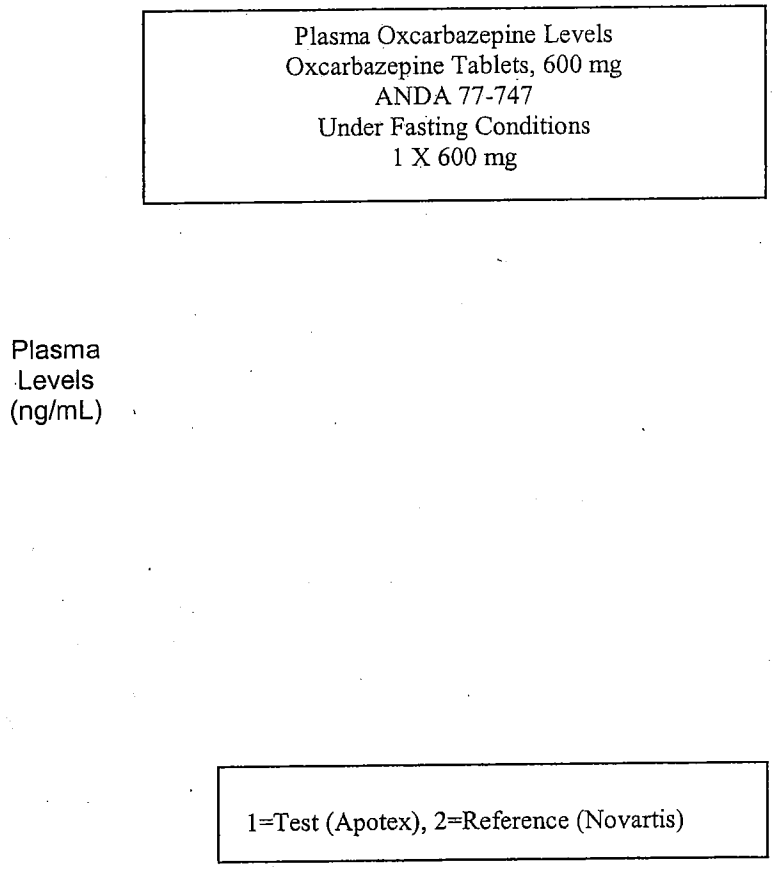
Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: Incomplete

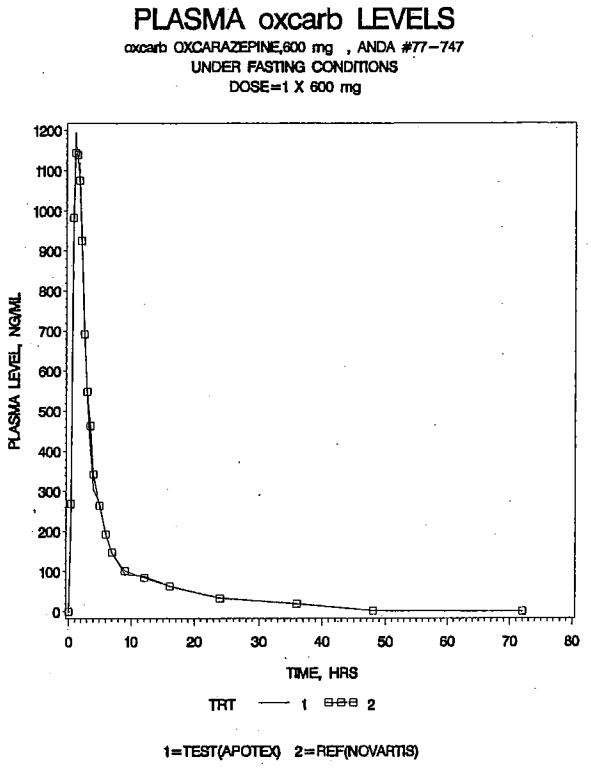
Table 11 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Time (h)	Test (n=20)		Reference (n=20)		T/R
	Mean Conc. (ng/mL)	%CV	Mean Conc. (ng/mL)	%CV	
0	0.00	.	0.00	.	.
0.33	192.00	153.35	268.66	110.03	0.71
0.66	847.47	58.40	982.80	58.63	0.86
1	1192.92	66.45	1143.80	53.86	1.04
1.33	1122.36	46.24	1138.94	42.39	0.99
1.66	1118.48	33.77	1075.29	38.93	1.04
2	959.25	38.22	925.25	32.10	1.04
2.5	710.93	42.94	692.09	44.81	1.03
3	522.73	48.54	548.41	57.15	0.95
3.5	403.98	54.19	463.25	54.36	0.87
4	304.68	56.70	342.70	58.73	0.89
5	271.46	52.57	264.12	41.17	1.03
6	196.48	35.06	192.80	27.78	1.02

7	147.92	29.12	147.61	28.39	1.00
9	92.27	23.48	101.07	29.02	0.91
12	88.45	40.04	84.22	33.40	1.05
16	63.67	40.90	63.10	28.16	1.01
24	34.42	26.24	33.13	36.39	1.04
36	18.93	62.82	19.36	33.73	0.98
48	2.38	253.80	1.97	251.66	1.21
72	0.00	.	0.00	.	.

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





2. Single-dose Fed Bioequivalence Study

a) Study Design

Study Information	
Study Number	OXCA-IMTB-01AB05-2FE
Study Title	Comparative, Randomized, 2-Way Crossover Bioavailability Study of Oxcarbazepine 600 mg Tablet and Trileptal® Under Fed Conditions
Clinical Site	APOTEX Weston, Ontario
Principal Investigator	D. Satok, M.D.
Study/Dosing Dates	I: 01-08-05 for Group I and 01-12-05 for Group II II: 01-15-05 for Group I and 01-19-05 for Group II
Analytical Site	APOTEX Weston, Ontario
Analytical Director	(b) (6)
Analysis Dates	01-21-05 to 03-08-05
Storage Period (no. of days from the first day of sample collection to the last day of	59

sample analysis)	

Test or Reference	**Test**	**Reference**
Treatment ID	**A**	**B**
Product Name	Oxcarbazepine	Trileptal®
Manufacturer	Taro	Novartis
Batch/Lot No.	025-19A	F0107
Manufacture Date	09-04	N.A.
Expiration Date	N.A.	08-07
Strength	600 mg	600 mg
Dosage Form	Tablet	Tablet
Batch Size	(b) (4)	N.A.
Production Batch Size		N.A.
Potency	99.1	Not Reported
Content Uniformity	98.4 (1.2)	N.A.
Formulation	See Table B	
Dose Administered	1 X 600 mg	1 X 600 mg
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	2 group I 1-61 (prefix of OC used for group I) and group II 1-58 (prefix of OX used for group II)
Washout Period	7
Randomization Scheme (for study subjects)	See Randomization Scheme in Attachments
Blood Sampling Times	Pre-dose, 0.33, 0.66, 1, 1.33, 1.66, 2.0, 2.5, 3, 3.5, 4, 5,6,7,9,12,16,24,36,48, and 72
Blood Volume Collected/Sample	10 mL
Blood Sample Processing/Storage	-80°C
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	**See Table 12**
Length of Fasting before Meal	At least 10 hours
Length of Confinement	From at least 10 hours prior to drug administration till the 36 hour blood draw
Safety Monitoring	Vital signs and adverse events were monitored by qualified personnel
Standard FDA Meal Used?	Yes

Comments on Study Design: The firm did not report the potency of the RLD. Also, the firm used a different lot of RLD than was used in the fasting study.

b) Clinical Results

Table 12 Demographics of Study Subjects

Table 6 Demographic Profile of Subjects Completing the Bioequivalence Study - Oxcarbazepine

Study No. OXCA-IMTB-01AB05-2FE		
	Treatment Groups	
	Test Product N = 59	Reference Product N = 59
Age (years) Mean ± SD Range Groups <18 18 – 40 41 – 64 65 – 75 >75	 34.24 ± 8.95 19 – 53 0 (0 %) 42 (71.1 %) 17 (28.9 %) 0 (0 %) 0 (0 %)	 34.24 ± 8.95 19 – 53 0 (0 %) 42 (71.1 %) 17 (28.9 %) 0 (0 %) 0 (0 %)
Sex Female Male	 0 (0 %) 59 (100 %)	 0 (0 %) 59 (100 %)
Race Asian Black Caucasian Hispanic Other	 4 (6.8 %) 10 (16.9 %) 35 (59.3 %) 7 (11.9 %) 3 (5.1 %)	 4 (6.8 %) 10 (16.9 %) 35 (59.3 %) 7 (11.9 %) 3 (5.1 %)
Other Factors	Subject OC14 voluntarily withdrew prior to period 2. Subject OC56 was removed prior to period 2 due an adverse event.	

Table 13 Dropout Information

Subject No	Reason	Period	Replaced?
OC14	Voluntary	Interperiod	No
OC56	Syncopal, 1st degree AV Block	Prior to Period 2	No
OX43	Elevated AST and AST	Prior to Period 2	No

Table 14 Study Adverse Events

TABLE 7 Incidences of Adverse Events in Individual Studies – (Oxcarbazepine Tablets)

System/Adverse Events	Reported Incidence by Treatment Groups			
	Fasted Bioequivalence Study Study No. (OXCA-IMTB-01AB03-2FA) (Internal code: OC2662)		Fed Bioequivalence Study Study No. (OXCA-IMTB-01AB05-2FE) (Internal Code: OC2260G1, OX2260G2)	
	Test	Reference	Test	Reference
Cardiac disorders				
Atrioventricular block first degree	1 (4.2%)	1 (4.3%)		1 (0.9%)
Gastrointestinal Disorders				
Hypoaesthesia oral			2 (1.8%)	4 (3.4%)
Diarrhea	1 (4.2%)			
General disorder and administration site conditions				
Fatigue	1 (4.2%)		5 (4.4%)	3 (2.6%)
Feeling abnormal			4 (3.5%)	3 (2.6%)
Chest Discomfort				1 (0.9%)
Swollen Tongue				1 (0.9%)
Feeling Drunk			2 (1.8%)	2 (0.17%)
Application site pain	1 (4.2%)			
Catheter site oedema	1(4.2%)			
Catheter site haemorrhage	1 (4.2%)			
Catheter site hematoma		1(4.3%)		1(0.9%)
Venipuncture site swelling		1(4.3%)		1(0.9%)
Injury, poisoning and procedural complications				
Contusion	1 (4.2%)	1(4.3%)		1(0.9%)
Metabolism and nutrition disorder				
Decreased Appetite			1 (0.9%)	
Musculoskeletal and connective tissue disorders				
Back pain	1 (4.2%)			
Nervous system disorders				
Dizziness	2 (8.3%)	2 (8.7%)	7 (6.2%)	8 (6.9%)
Headache		1 (4.3%)	3(1.9%)	2(0.17%)
Disturbance in attention			3 (2.7%)	2 (0.17%)
Somnolence	1 (4.2%)	1 (4.3%)	8 (7.1%)	7 (6.0%)
Paraesthesia oral			1 (0.9%)	1 (0.9%)
Syncope				1 (0.9%)
Balance disorder				1 (0.9%)

Page 1 of 1

Table 15 Protocol Deviations

Type	# in Test Group	# in Ref. Group
Period I Subject OC3 was served meal 54 minutes before dosing (30 minutes in protocol)	1	-
Period I Subject OX21 did not report for 72 h sample due being in a car accident unrelated to medication	1	-
Samples in period 1 and 2 were stored on ice for 1-98 minutes instead of immediately being transferred to -80°C	Multiple	Multiple
Vital signs taken 1-5 minutes earlier than scheduled in Period I and II	Multiple	Multiple
OC 35 did not show up for 72 hour blood draw	1	-
Study was initiated with less than 120 subjects	-	-
OC27 consumed water 5 minutes earlier than stated time during Period I	1	
Freezer fell to -57°C for 3 hours and 13 minutes during period II	Multiple	Multiple
The 3 hour sample for OC03 in period I was recorded at the theoretical time, because the recorded time was 26 minutes earlier than the recorded time (not at Cmax; reviewer set value to missing in data set and determined that it had no affect on the outcome of the study)	-	1
The 1.66 h sample for OC52 during Period II had a sampling time deviation, but the actual time was not known, so a deviation of 10:17 was used (not at Cmax; reviewer set value to missing in data set and determined that it had no affect on the outcome of the study)	-	1

Comments on Adverse Events/Protocol Deviations: There were three dropouts. The number of adverse events observed in the reference group was greater then the number observed in the test group. The protocol deviations did not compromise the outcome of this study.

c) Bioanalytical Results

Table 16 Assay Quality Control – Within Study

	Oxcarbazepine									
QC Conc. (ng/mL)	30.0	2250.0	4500.0							
Inter day Precision (%CV)	8.7	7.0	7.2							
Inter day Accuracy (%)	96.3	99.0	97.2							
Cal. Standards Conc. (ng/mL)	10.0	20.0	100.0	200.0	600.0	1200.0	2400.0	3600	4800	6000
Inter day Precision (%CV)	3.0	5.6	5.5	5.0	4.8	4.7	4.8	4.8	4.4	5.9
Inter day Accuracy (%)	101	98.5	102	101.6	101.0	100.4	99.7	100.1	98.3	98.0
Linearity Range (range of R^2 values)	0.9913-0.9998									

Comments on Study Assay Quality Control: Acceptable

Any interfering peaks in chromatograms?	There are no interfering peaks in the chromatogram.
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Randomly

Comments on Chromatograms: Acceptable

Table 17 SOP's dealing with analytical repeats

SOP No.	Date of SOP	SOP Title
ABM-BL-0154	06-15-04	Routine Batch Analysis

Table 18 Additional Comments on Repeat Assays

Were all SOPs followed?	The firm provided only a summary reassay table. It should provides details of reassayed samples in a table (subject #, treatment, period, sampling time, reason for reassay, original value, reassayed value(s) and reason for the selection of the value for the statistical analysis).
Did recalculation of plasma concentrations change the study outcome?	No. There were no PK repeats
Does the reviewer agree with the outcome of the repeat assays?	See Above
If no, reason for disagreement	See above

Summary/Conclusions, Study Assays: Incomplete

d) Pharmacokinetic Results

Table 19 Arithmetic Mean Pharmacokinetic Parameters

Parent

PARAMETER	UNITS	TEST		REFERENCE		RATIO T/R
		MEAN1	%CV	MEAN2	%CV	
$AUC_{0-\infty}$	ng·hr/mL	7922.32	22.07	8220.07	20.93	0.96
AUC_{0-t}	ng·hr/mL	7654.08	22.80	7900.45	21.61	0.97
CMAX	ng/mL	3138.85	37.08	3325.20	36.73	0.94
KE	$hour^{-1}$	0.06	17.06	0.06	18.46	1.02
THALF	hour	11.52	17.63	12.00	29.09	0.96
TMAX	hour	1.69	51.31	1.70	53.19	0.99

Metabolite

PARAMETER	UNITS	TEST		REFERENCE		RATIO T/R
		MEAN1	%CV	MEAN2	%CV	
$AUC_{0-\infty}$	mcg·hr/mL	169.74	15.38	172.79	16.02	0.98
AUC_{0-t}	mcg·hr/mL	166.88	15.77	169.85	16.25	0.98
CMAX	mcg/mL	8.15	14.31	8.23	12.79	0.99
KE	$hour^{-1}$	0.07	13.64	0.07	14.15	1.01
THALF	hour	9.88	15.27	10.02	16.17	0.99
TMAX	hour	4.68	30.08	4.37	32.00	1.07

Table 20 Geometric Means and 90% Confidence Intervals

Parent

PARAMETER	TEST	REFERENCE	RATIO T/R	90 % CI	
	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
$AUC_{0-\infty}$	7924.43	8221.39	0.96	94.00	98.77
AUC_{0-t}	7657.35	7902.03	0.97	94.59	99.22
CMAX	3144.96	3331.11	0.94	89.03	99.80
LAUCI	7732.88	8038.03	0.96	93.89	98.57
LAUCT	7457.84	7713.98	0.97	94.44	98.97
LCMAX	2927.41	3101.64	0.94	88.94	100.16

Metabolite

PARAMETER	TEST	REFERENCE	RATIO T/R	90 % CI	
	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
LAUCI	167.87	170.72	0.98	97.29	99.39
LAUCT	164.91	167.74	0.98	97.22	99.42
LCMAX	8.07	8.16	0.99	97.39	100.29

Table 21 Additional Study Information

Root mean square error, $LAUC_{0-t}$	0.1061
Root mean square error, $LAUC_{\infty}$	0.1096
Root mean square error, LC_{max}	0.2690
K_{el} and $LAUC_{\infty}$ determined for how many subjects?	111
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	0
-first measurable drug concentration as C_{max}	0
Were the subjects dosed as more than one group?	Yes. Subjects were dosed in two groups.

Comments on Pharmacokinetic and Statistical Analysis:

1. The subjects were dosed in 2 groups. Therefore, the following model was used for statistical analysis:

Model Y= group seq seq*group subject (seq*group) per (group) trt trt*group

Since the trt*group was not statistically significant ($p>0.05$) for LAUCT, LAUCI, and LCmax, this term was dropped from the analysis. Results given in table 8 and 9 are from this analysis.

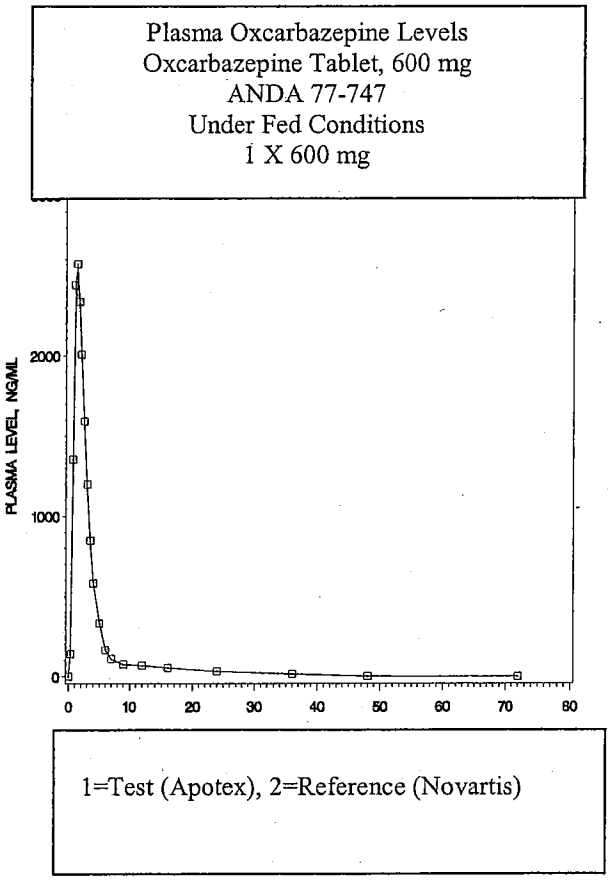
2. The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations. The 90% confidence intervals for $lnAUC_{0-t}$, $lnAUC_{\infty}$ and lnC_{max} are within the acceptable limits of 80-125%.

Summary/Conclusions, Single-Dose Fed Bioequivalence Study: Incomplete

Table 22 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Time (h)	Test (n=113)		Reference (n=113)		T/R
	Mean Conc. (ng/mL)	%CV	Mean Conc. (ng/mL)	%CV	
0	0.00	.	0.00	.	.
0.33	126.87	205.74	139.20	186.21	0.91
0.66	1077.86	118.40	1353.22	110.33	0.80
1	2185.32	73.81	2440.63	69.42	0.90
1.33	2488.49	55.68	2573.31	58.16	0.97
1.66	2349.00	45.83	2338.69	45.42	1.00
2	2105.07	40.66	2007.96	37.86	1.05
2.5	1552.48	41.27	1592.80	44.39	0.97
3	1137.40	45.40	1199.05	50.68	0.95
3.5	802.49	55.85	848.27	60.69	0.95
4	594.30	68.36	581.62	61.82	1.02
5	350.85	105.22	330.37	114.73	1.06
6	172.28	84.72	163.85	81.73	1.05
7	108.13	48.51	109.64	54.25	0.99
9	74.64	26.77	75.52	25.94	0.99
12	67.54	23.25	67.92	20.25	0.99
16	53.29	25.26	53.54	21.54	1.00
24	31.91	28.14	32.77	29.44	0.97
36	13.45	62.58	17.03	130.73	0.79
48	2.39	211.25	2.17	243.98	1.10
72	0.00	.	0.11	1063.01	0.00

Figure 2 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



B. Formulation Data

Components	Function	150 mg mg/tablet	300 mg mg/tablet	600 mg mg/tablet
		(b) (4)		
Oxcarbazepine	Active	150.0	300.0	600.0
Crospovidone, NF				
Methylcellulose (b) (4) NF				
Magnesium stearate, NF				
Colloidal silicon dioxide, NF				
		(b) (4)		
Hydroxypropyl methylcellulose (b) (4) NF				
Hydroxypropyl cellulose, (b) (4) NF				
Polyethylene glycol (b) (4) NF				
Titanium dioxide, NF				
Yellow ferric oxide				
(b) (4)				
Total tablet weight		**184.0**	**368.0**	**736.0**

Reviewer's Comment: The tablets are proportional.

C. Dissolution Data

The dissolution testing for 150 mg, 300 mg, and 600 mg tablets was previously reviewed and found to be incomplete. The firm was requested to perform testing using the FDA recommended method. The firm submitted the data (see Amendment dated 02-07-06). However, the firm did not specify the volume of medium used or the rotation speed. The firm will be requested to provide this information.

Table 1: Oxcarbazepine Tablets 150 mg Lot#025-21, Apotex Inc.

Time (minutes)	% Dissolved														
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Mean	%RSD
5												(b) (4)	(b) (4)	23	44
10														57	33
15														80	20
20														92	9
30														99	4
45														101	4
60														101	4
90														101	4

Table 2: Trileptal Tablets 150 mg Lot#214H3125, Manufacturer: Novartis, Expiry Date: 12/2006

Time (minutes)	% Dissolved														
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Mean	%RSD
5												(b) (4)	(b) (4)	39	20
10														76	8
15														85	6
20														90	5
30														94	4
45														97	3
60														98	2
90														99	1

See Figure 1 for the dissolution rate profile 150mg strength.

Table 3: Oxcarbazepine Tablets 300 mg, Lot #025-20, Apotex Inc.

Time (minutes)	% Dissolved														
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Mean	%RSD
5												(b) (4)	(b) (4)	13	43
10														36	35
15														57	31
20														74	27
30														91	13
45														98	4
60														99	2
90														99	2

Table 4: Trileptal Tablets 300 mg, Lot #580J3095, Manufacturer: Novartis, Expiry Date 01/2007

Time (minutes)	% Dissolved														
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Mean	%RSD
5												(b) (4)	(b) (4)	23	14
10														66	12
15														82	8
20														88	6
30														94	3
45														97	2
60														99	1
90														99	1

Table 5: Oxcarbazepine Tablets 600 mg, Lot #025-19, Apotex Inc.

Time (minutes)	% Dissolved														
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Mean	%RSD
5												(b) (4)	(b) (4)	8	13
10														22	14
15														34	12
20														46	11
30														64	11
45														83	8
60														92	4
90														97	1

Table 6: Trileptal Tablets 600 mg, Lot #019J4374, Manufacturer: Novartis, Expiry Date: 06/2007

Time (minutes)	% Dissolved														
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Mean	%RSD
5												(b) (4)	(b) (4)	39	13
10														75	8
15														86	3
20														90	3
30														94	2
45														96	1
60														97	1
90														97	1

See Figure 3 for the dissolution rate profile for 600 mg strength.

Dissolution Reviews

77747D0705.doc

D. Consult Reviews

None

E. SAS Output

Statistical Analysis	Program file	Output file
Single dose fasting study	FASTPARENTANALYISFIRMDATA.txt	FASTPARENTANALYISFIRMDATAOUTPUT.
Single dose fed study	FEDPARENTANALYISFIRMDATAGRPNOTIN	MFEDPARENTOUTPUTGRPNOTINMODEL.T

F. Additional Attachments

randomizationfedsch
eme.pdf

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-747 APPLICANT: Apotex

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

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

1. You have used different batches of the 600 mg RLD in the fasting and non-fasting studies. Please provide explanation for such usage.

2. Please provide the potency of the RLD in the fasting study (Batch #: 019J4374) and non-fasting study (Batch #: F0107).

3. You provided only summary reassay tables for both studies. Please provide details of reassayed samples in tables (subject #, treatment, period, sampling time, reason for reassay, original value, reassayed value(s) and reason for the selection of the value for the statistical analysis).

4. Please provide the medium, volume of medium and rotation speed used for in vitro dissolution testing. You used 2 different lots of the 600 mg RLD tablet in the BE studies, but provided dissolution only on the lot 019J4374. Please provide dissolution testing on the 600 mg RLD lot F0107.

Sincerely yours,

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

Endorsements: (Final with Dates)
HFD-650/Ethan M. Stier EMS 4-25-06
HFD-655/S. G. Nerurkar
HFD-617/K. Suh
HFD-650/Dale Conner DC 4/25/06

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Printed in final on 04/25/06

BIOEQUIVALENCY Submission Date: 07-14-05

1. **FASTING STUDY** (STF) **Strength: 600 mg**
Clinical: APOTEX
Weston, Ontario ✓ **Outcome: IC**

Analytical: APOTEX
Weston, Ontario

2. **FOOD STUDY** (STF) **Strength: 600 mg**
Clinical: APOTEX
Weston, Ontario ✓ **Outcome: IC**

Analytical: APOTEX
Weston, Ontario

3. **DISSOLUTION WAIVER (DIW)** **Strength: 300 mg**
✓ **Outcome: IC**

4. **DISSOLUTION WAIVER (DIW)** **Strength: 150 mg**
✓ **Outcome: IC**

5. **STUDY AMENDMENT (STA)** **Strengths: 150 mg, 300 mg, and 600 mg**
✓ **Outcome: IC**

Outcome Decisions: IC - Incomplete

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-747
Drug Product Name	Oxcarbazepine Tablets
Strength	150 mg, 300 mg, and 600 mg tablets
Applicant Name	Apotex
Address	150 Signet Toronto, Ontario
Submission Date(s)	07-14-05
Amendment Date(s)	02-07-06; 05-25-06
Reviewer	**Ethan M. Stier, Ph.D.**
First Generic	**No**
File Location	**V:\firmsam\apotex\ltrs&rev\77747A0506**

I. Executive Summary

Apotex has previously submitted a single-dose fasting bioequivalence study comparing its test product, Oxcarbazepine tablets, 600 mg to the RLD product, Trileptal® tablets, 600 mg, in the original application, dated 07/14/05 (**V:\firmsam\apotex\ltrs&rev\77747N0705**).

The firm submitted the current amendment in response to the Division of Bioequivalence (DBE) deficiency comments requesting the firm to submit additional study information regarding the bioequivalence studies and to conduct additional dissolution testing.

The requested study information and in vitro dissolution testing dated were submitted in the current amendment. All are acceptable. However, the firm should acknowledge the FDA recommended method and specification.

The applicant requests waivers of in vivo BE study requirements for the 150 mg and 300 mg tablets. The formulations of the 150 mg and 300 mg tablets are proportional to the 600 mg tablet, which underwent in vivo testing. The dissolution testing conducted by the firm on the 150 mg, 300 mg, and 600 mg tablets is complete. However, the firm should acknowledge the FDA recommended method and specification. Waivers of *in vivo* bioequivalence study requirements will be granted for the 150 mg and 300 mg tablets after the firm's satisfactory response to the deficiency.

The application is incomplete pending firm's acknowledgment of the dissolution method and specifications.

II. Table of Contents

III. Background:

See the review of the original submission of the study.
(V:\firmsam\apotex\ltrs&rev\77747N0705)

IV. Current Submission:

DEFICIENCY COMMENT #1

1. You have used different batches of the 600 mg RLD in the fasting and non-fasting studies. Please provide explanation for such usage.

FIRM'S RESPONSE: The firm stated that the high variability of Cmax observed in the fasting study necessitated using a larger number of number subjects than initially planned in the non-fasting study. The quantity of drug that the company had purchased prior to initiation of the BE studies was not sufficient to conduct the larger non-fasting study. Therefore, the company had to purchase more drug for the study and was not able to purchase the same lot used in the fed study.

REVIEWER'S COMMENT: The firm's response is acceptable.

DEFICIENCY COMMENT #2

2. Please provide the potency of the RLD in the fasting study (Batch #: 019J4374) and non-fasting study (Batch #: F0107).

FIRM'S RESPONSE: The potencies of the RLDs used in the fasting and non-fasting studies were 98.7% and 101.5%, respectively.

REVIEWER'S COMMENT: The firm's response is acceptable.

DEFICIENCY COMMENT #3

3. You provided only summary reassay tables for both studies. Please provide details of reassayed samples in tables (subject #, treatment, and period, sampling time, reason for reassay, original value, reassayed value and reason for the selection of the value for the statistical analysis).

FIRM'S RESPONSE: The firm provided the requested information.

REVIEWER'S COMMENT: The firm's response is acceptable.

DEFICIENCY COMMENT #4

4. Please provide the medium, volume of medium and rotation speed used for in vitro dissolution testing. You used 2 different lots of the 600 mg RLD tablet in the BE studies, but provided dissolution only on the lot 019J4374. Please provide dissolution testing on the 600 mg RLD lot F0107.

FIRM'S RESPONSE:

Part I: Comparative Testing between RLD (lot F0107) and test:

Table 1: Oxcarbazepine Tablets 600 mg Lot# 025-19, Apotex Inc.

Time (minutes)	% Dissolved														
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Mean	%RSD
5												(b) (4)	(b) (4)	8	15
10														22	14
15														34	12
20														46	11
30														64	11
45														83	8
60														92	4
90														97	1

Table 2: Trileptal Tablets 600 mg Lot# F0107, Manufacturer: Novartis, Expiry Date: 08/2007

Time (minutes)	% Dissolved														
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Mean	%RSD
5												(b) (4)	(b) (4)	31	22
10														75	8
15														87	4
20														91	2
30														95	2
45														97	2
60														97	2
90														98	2

Part II: Medium, Volume, Rotation Speed used for In Vitro Testing

Dissolution method
Medium:
900 mL water + 0.3% SDS (150 mg)
900 mL water + 0.6% SDS (300 mg)
900 mL water + 1% SDS (600 mg)
Apparatus
Paddle at 60 rpm

REVIEWER'S COMMENT:

I) The firm's response was acceptable.

II) The dissolution method and specification for Apotex's product had not been previously determined due to deficiencies in the dissolution testing. The firm has now completed satisfactory dissolution testing. The reviewer requested a dissolution consultation because the data for 600 mg tablet does not conform to the FDA recommended method and specification at the S1 or S2 level. Based on the consultation, the following method and specification are recommended (see attachments below):

Medium:	Water (0.3% SDS for 150 mg tablet; 0.6% for 300 mg tablet; 1.0% for 600 mg tablet)
Volume:	900 mL
Temperature:	37°C
USP Apparatus:	Apparatus II (paddle)
Rotation:	60 rpm
Specifications:	NLT (b)(4)% (Q) in 30 minutes and NLT (b)(4)% (Q) in 60 minutes for the 150 mg and 300 mg tablets; NLT (b)(4)% (Q) in 30 minutes and NLT (b)(4)% (Q) in 60 minutes for the 600 mg tablet

dissolutionconsult.rtf dissolution data

A. Waiver Request

Strength 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?	No
Waiver granted?	No
If not then why?	Refer to deficiencies section

B. Deficiency Comments

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

C. Recommendations

1. The in vivo bioequivalence study conducted under fasting conditions by Apotex comparing its oxcarbazepine tablets 600 mg to the reference product Trileptal® 600 mg tablet (Novartis) is acceptable.

2. The in vivo bioequivalence study conducted under non-fasting conditions by Apotex comparing its oxcarbazepine tablets 600 mg to the reference product Trileptal® 600 mg tablet (Novartis) is acceptable.

3. The dissolution testing conducted by Apotex on its oxcarbazepine tablets, 150 mg, 300 mg, and 600 mg is incomplete due to deficiency #1. The firm should accept the following FDA recommended method and specifications: 900 mL of water (plus 0.3% SDS for 150 mg; plus 0.6% SDS for 300 mg; plus 1% SDS for 600 mg) using USP Apparatus II (Paddle) at 60 RPM. The test product should meet the following specifications:

   1) 150 mg and 300 mg tablets:
   Not less than (b) (4)% (Q) of the labeled amount of oxcarbazepine in the dosage form is dissolved in 30 minutes and not less than (b) (4)% (Q) of the labeled amount of oxcarbazepine in the dosage form is dissolved in 60 minutes

   1) 600 mg tablets:
   Not less than (b) (4)% (Q) of the labeled amount of oxcarbazepine in the dosage form is dissolved in 30 minutes and not less than (b) (4)% (Q) of the labeled amount of oxcarbazepine in the dosage form is dissolved in 60 minutes

4. The formulations of Apotex's 150 mg and 300 mg oxcarbazepine tablets are proportional to the 600 mg strength tablet, which underwent in vivo bioequivalence testing. The dissolution testing is complete. However, the firm should acknowledge the acceptance of the FDA recommended method and specification. A waiver of *in vivo* bioequivalence study requirements for the 150 mg and 300 mg tablets will be granted when the firm provides a satisfactory response to the deficiency #1.

Ethan Stier, Ph.D., Branch II — Date signed: 10, 2006

Shriniwas G. Nerurkar, Ph.D., Branch II — Date signed: 7/11/2006

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs — Date signed: 7/11/06

D. Appendix

None

BIOEQUIVALENCE DEFICIENCY

ANDA: 77-747 APPLICANT: Apotex

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

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

Please provide acknowledgement for your acceptance of the following dissolution method and specification:

Medium:	water (plus 0.3% SDS for 150 mg; plus 0.6% SDS for 300 mg; plus 1% SDS for 600 mg)
Volume:	900 mL
Apparatus:	USP Apparatus II (Paddle)
Rotation Speed:	60 RPM
Specifications:	150 mg and 300 mg tablets: Not less than (b) (4)% (Q) of the labeled amount of oxcarbazepine in the dosage form is dissolved in 30 minutes and not less than (b) (4)% (Q) of the labeled amount of oxcarbazepine in the dosage form is dissolved in 60 minutes 600 mg tablets: Not less than (b) (4)% (Q) of the labeled amount of oxcarbazepine in the dosage form is dissolved in 30 minutes and not less than (b) (4)% (Q) of the labeled amount of oxcarbazepine in the dosage form is dissolved in 60 minutes

Sincerely yours,

Barbara M Davit

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

Endorsements: (Final with Dates)
HFD-650/Ethan M. Stier 6-10-06
HFD-655/S. G. Nerurkar
HFD-617/K. Suh
HFD-650/Dale Conner 7/11/06

7/11/06

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Printed in final on 07-10-06

BIOEQUIVALENCY Submission Date: 07-14-05

1. **FASTING STUDY** (STF) **Strength: 600 mg**
Clinical: APOTEX
Weston, Ontario ✗ **Outcome: IC**

Analytical: APOTEX
Weston, Ontario

2. **FOOD STUDY** (STF) **Strength: 600 mg**
Clinical: APOTEX
Weston, Ontario ✗ **Outcome: IC**

Analytical: APOTEX
Weston, Ontario

3. **DISSOLUTION WAIVER (DIW)** **Strength: 300 mg**
✗ **Outcome: IC**

4. **DISSOLUTION WAIVER (DIW)** **Strength: 150 mg**
✗ **Outcome: IC**

5. **STUDY AMENDMENT (STA)** **Strengths: 150 mg, 300 mg,**
✓ **and 600 mg**
Outcome: IC

Outcome Decisions: IC - Incomplete

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #:	77-747 **SPONSOR:** Apotex
DRUG & DOSAGE FORM:	Oxcarbazepine Tablets
STRENGTH(S):	150 mg, 300 mg, and 600 mg
TYPES OF STUDIES:	Fed and fasting
CLINICAL STUDY SITE(S):	Apotex, Weston, Ontario, Canada
ANALYTICAL SITE(S):	Apotex, Weston, Ontario, Canada
STUDY SUMMARY:	Acceptable
DISSOLUTION: WAIVER:	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: 08-04-06

PROJECT MANAGER: _____ **DATE:** _____

PRIMARY REVIEWER: Ethan M. Stier, Ph.D. **BRANCH:** II
INITIAL: Ethan M Stier DATE: 8-31-06

TEAM LEADER: Shriniwas G. Nerurkar, Ph.D. **BRANCH:**
INITIAL: DATE: 8/31/2006

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.
INITIAL: DATE: 8/31/06