

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 77-801

BIOEQUIVALENCE REVIEW

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	77-801
Drug Product Name	Oxcarbazepine Tablets
Strength	150, 300 mg and 600 mg
Applicant Name	Taro Pharmaceuticals, Inc.
Submission Date(s)	July 14, 2005
First Generic	No
Reviewer	Patrick Nwakama
File Location	V:\firmsnz\Taro\ltrs&rev\77801D0705.doc
Clinical Site	SFBC Anapharm Inc., Montreal, Quebec, Canada
Analytical Site	Anapharm Inc., Sante-Foy, Quebec, 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 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 Ref. No.	Product ID/Lot No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved				Study Report Location
					15 min.	30 min.	45 min.	60 min.	
	Oxcarbazepine 600 mg Tablets Lot #780755	Tablet p.o.	Apparatus: USP Paddle Speed: 60 rpm Medium: 1% w/v Sodium Dodecyl Sulphate Volume: 900 mL	12	73	96	103	105	Section VI.2, page 010A – 010G
	Trileptal® 600 mg Tablets Lot #312H1506	Tablet p.o.		12	87	94	95	99	
	Oxcarbazepine 300 mg Tablets Lot #780814	Tablet p.o.		12	64	97	101	102	
	Trileptal® 300 mg Tablets Lot #212E2527	Tablet p.o.		12	80	93	97	98	
	Oxcarbazepine 150 mg Tablets Lot #780756	Tablet p.o.		12	87	100	101	101	
	Trileptal® 150 mg Tablets Lot #128E3036	Tablet p.o.		12	80	93	97	99	

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:

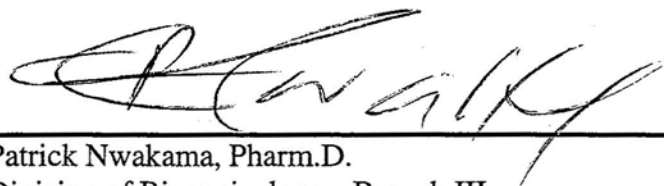
1. The firm conducted dissolution testing on all three strengths using the dissolution medium recommended by the FDA for only the 600 mg (Water + 1% SDS). The dissolution testing on the 600 mg is acceptable and meets FDA specifications of NLT ^{(b) (4)} (Q) in 30 minutes and NLT ^{(b) (4)} (Q) in 60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

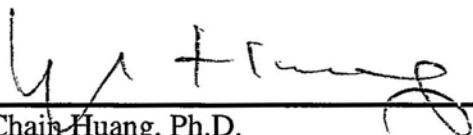
RECOMMENDATIONS:

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



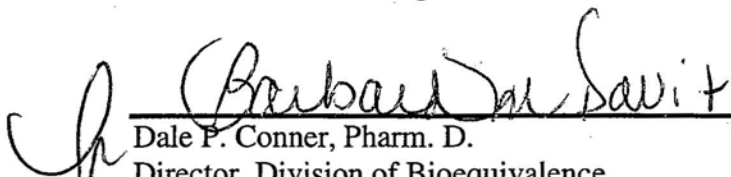
11/21/05

Patrick Nwakama, Pharm.D.
Division of Bioequivalence, Branch III
Office of Generic Drugs



11/21/2005

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



11/29/05

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

BIOEQUIVALENCE DEFICIENCY

ANDA: 77-801

APPLICANT: Taro Pharmaceuticals, 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:

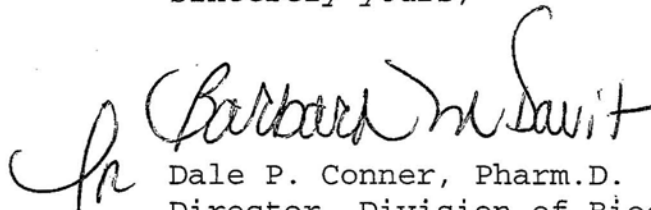
You conducted dissolution testing on all three strengths using the method recommended only for the 600 mg and did not propose any dissolution specifications. Your dissolution data for the 600 mg is acceptable. Your dissolution testing on the 150 mg and 300 mg is incomplete. Therefore, the Division of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



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

CC: ANDA 77-801
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Drug File
HFD-658/ Reviewer
HFD-658/ Team Leader

Endorsements:

HFD-658/ P. Nwakama

HFD-658/ YC Huang

HFD-650/ D. Conner

Handwritten signatures and dates:
P 11/21/05
YC 11/23/2005
D 11/29/05

DISSOLUTION – Incomplete

Submission date: 07/14/05

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

1. DISSOLUTION (Dissolution Data) *oic*

Strength: 600 mg
Outcome: AC

2. DISSOLUTION (Dissolution Data) *oic*

Strength: 150 mg & 300 mg
Outcome: IC

Outcome Decisions: IC – Incomplete (Dissolution data)

WinBio Comments: IC

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	77-801
Drug Product Name	Oxcarbazepine Tablets
Strength	150, 300 mg and 600 mg
Applicant Name	Taro Pharmaceuticals USA, Inc.
Submission Date(s)	December 29, 2005
First Generic	No
Reviewer	Patrick Nwakama
File Location	V:\firmsnz\Taro\ltrs&rev\77801a1205.doc
Clinical Site	SFBC Anapharm Inc., Montreal, Quebec, Canada
Analytical Site	Anapharm Inc., Sante-Foy, Quebec, Canada

EXECUTIVE SUMMARY

This is a review of an amendment to dissolution testing data submitted (7/14/2005) with the original ANDA.

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] for this drug product. The firm's original dissolution testing in 900 mL, Water (plus 1% SDS), Paddle, at 60 rpm was only acceptable for the 600 mg. Therefore, the firm was requested to repeat dissolution testing for the 150 mg and 300 mg using Water plus 0.3% and 0.6% SDS, respectively.

In the current amendment, the firm conducted dissolution testing using the FDA-recommended method for the 150 mg and 300 mg. The firm's dissolution testing data with the FDA method are acceptable (at S1 level). The firm also meets the FDA-recommended specifications [NLT (b) (4) (Q) in 30 minutes and NLT (b) (4) (Q) in 60 minutes]. The firm has accepted the FDA-recommended method and specifications.

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 (b) (4)	(Q) in 60 minutes

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

Reviewer's Note: The firm has accepted the above dissolution specifications (12/29/2005).

Table 1: Summary of In Vitro Dissolution Data

Study Ref. No.	Product ID/Lot No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved				Study Report Location
					15 min.	30 min.	45 min.	60 min.	
	Oxcarbazepine 600 mg Tablets Lot #780755	Tablet p.o.	Apparatus: USP Paddle Speed: 60 rpm Medium: 1% w/v Sodium Dodecyl Sulphate Volume: 900 mL	12	73 (b) (4)	96	103	105	Section VI.2, page 010A – 010G
	Trileptal® 600 mg Tablets Lot #312H1506	Tablet p.o.		12	87 (b) (4)	94	95	99	
	Oxcarbazepine 300 mg Tablets Lot #780814	Tablet p.o.	Apparatus: USP Paddle Speed: 60 rpm Medium: 0.6% w/v Sodium Dodecyl Sulphate Volume: 900 mL	12	66 (b) (4)	97	99	100	
	Trileptal® 300 mg Tablets Lot #F0214	Tablet p.o.		12	84 (b) (4)	94	97	101	
	Oxcarbazepine 150 mg Tablets Lot #780756	Tablet p.o.	Apparatus: USP Paddle Speed: 60 rpm Medium: 0.3% w/v Sodium Dodecyl Sulphate Volume: 900 mL	12	77 (b) (4)	96	98	98	
	Trileptal® 150 mg Tablets Lot #F0121	Tablet p.o.		12	74 (b) (4)	87	92	94	

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:

The dissolution testing is complete. The firm submitted dissolution testing data for their Oxcarbazepine Tablets, 150 mg, 300 mg and 600 mg using the FDA-recommended method. The dissolution data meet the FDA specifications [NLT (b) (4) (Q) in 30 minutes and NLT (b) (4) (Q) in 60 minutes] at the S1 level.

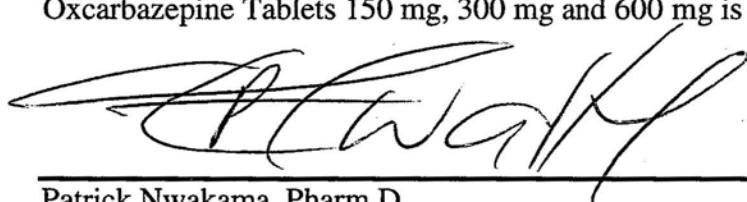
The bioequivalence studies and waiver requests are pending review.

DEFICIENCY COMMENTS:

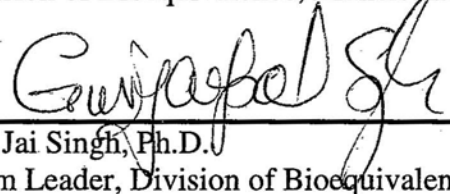
None.

RECOMMENDATIONS:

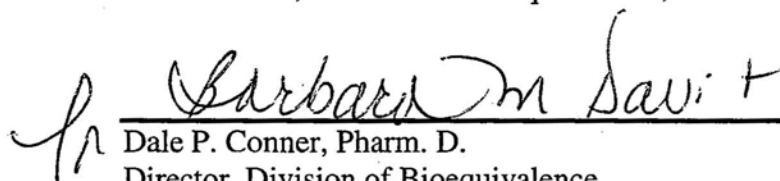
The *in vitro* dissolution testing conducted by Taro Pharmaceuticals, Inc. on its test products, Oxcarbazepine Tablets 150 mg, 300 mg and 600 mg is complete.

 1/9/06

Patrick Nwakama, Pharm.D.
Division of Bioequivalence, Branch III

 1-10-06

Gur Jai Singh, Ph.D.
Team Leader, Division of Bioequivalence, Branch III

 1/12/06

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

BIOEQUIVALENCE COMMENTS

ANDA: 77-801

APPLICANT: Taro Pharmaceuticals, Inc.

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

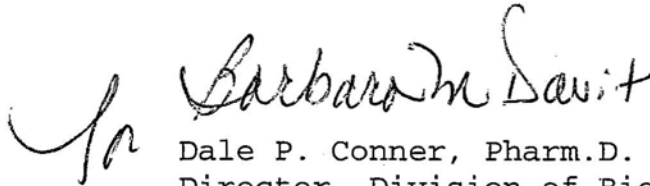
The Division of Bioequivalence has completed its review of the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the bioequivalence (BE) studies and waiver requests will be conducted later.

The Division of Bioequivalence acknowledges your acceptance of the following dissolution method and specification:

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].

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,



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

CC: ANDA 77-801
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Drug File
HFD-658/ Reviewer
HFD-658/ Team Leader

Endorsements:

HFD-658/ P. Nwakama

HFD-658/ GJP Singh

HFD-650/ D. Conner

1/9/06
Cmps 1-10-06
BMD 1/12/06

DISSOLUTION – Acceptable

Submission date: 12/29/05

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

1. DISSOLUTION (Dissolution Data)
(New Dissolution Data)

Strengths: All
Outcome: AC

Outcome Decisions: AC – Acceptable (Dissolution data)

WinBio Comments: AC

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-801
Drug Product Name	Oxcarbazepine Tablets
Strength	150 mg, 300 mg, and 600 mg tablets
Applicant Name	Taro
Address	Haifa, Israel
Submission Date(s)	07-14-05 ✓
Amendment Date(s)	12-29-05 (dissolution acknowledgement) ✓
Reviewer	Ethan M. Stier, Ph.D.
First Generic	No
File Location	V:\firmsNZ\Taro\ltrs&rev\77801N0705.Doc

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-group, two-way crossover study using male and female 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 LAUC_t 0.99, 95.72-102.39, LAUC_∞ 0.99, 95.46-102.08, and LC_{max} 1.02, 91.47-113.24.

The fed BE study is a single-dose two-way crossover study using male and female 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 LAUC_t 1.03, 97.64-107.64, LAUC_∞ 1.02, 96.82-106.54, and LC_{max} 1.04, 90.45-118.75.

The application is incomplete for several reasons. The firm did not provide the following information: 1) the content uniformity of the test product, 2) SAS data files containing the original concentration and pharmacokinetic data sets, 3) a table summarizing the pk repeats by treatment (Test or Reference), 4) chromatograms for the fasting and non-fasting studies labeled by subject number. Additionally, the firm will be asked to clarify if the subjects in the non-fasting study were dosed in two groups and will be provided with a copy of the CTD tables.

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 acceptable. However, waivers of *in vivo* bioequivalence study requirements for the 150 mg and 300 mg tablets will be granted upon the firm's satisfactory response to the deficiencies. The application is incomplete.

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III. Submission Summary

A. Drug Product Information

Test Product	Oxcarbazepine Tablet
Reference Product	Trileptal® Tablet
RLD Manufacturer	Novartis
NDA No.	21-014
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 absorption oxcarbazepine is completely absorbed

Food Effect

Food has no effect on the rate and extent of absorption
4.5 h (3-13 h)

T_{max}

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

Relevant AND, Protocols, and Controls:

History

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/Barr, 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 |
| 2. (b) (4) | | Zak |
| 3. 77794 | Sun | Jenny |
| 4. 77795 | Roxane | XJ (this review) |
| 5 (b) (4) | | Surendra |
| 6. 77801 | Taro | Ethan |
| 7. 77802 | Glenmark | Jane |

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

Volume: sulfate solution
900 mL
Temperature: 37°C
USP Apparatus: Apparatus II (paddle)
Rotation: 60 rpm
Specification: NLT^{(b) (4)} (Q) in 30 minutes
NLT^{(b) (4)} (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	No*	0

*The firm was not informed of the CTD tables in the dissolution review.

D. Pre-Study Bioanalytical Method Validation

Pre-Study Bioanalytical Method Validation:

Analyte name	oxcarbazepine
Internal Standard	(b) (4)
Method Description	LC/MS/MS
QC range	12.05 to 1405.60 ng/mL
Standard curve range	4.01 to 2006.40 ng/mL
Limit of quantitation	4.01 ng/mL
Average recovery of Drug (%)	79.40, 81.37 and 85.46%
Average Recovery of Int.Std (%)	90.76%
Intra-day accuracy range (%)	98.84 to 101.83%
Intra-day precision range (%)	3.75 to 12.05%

Inter-day accuracy range (%)	98.38 to 100.50%
Inter-day precision range (%)	5.46 to 8.49%
Bench-top stability (hrs)	24
Stock stability (days)	70 (-80°C)
Processed stability (hrs)	110
Freeze-thaw stability (cycles)	4 (-80°C)
*Long-term storage stability (days)	68 (-80°C)
Dilution integrity	105.47 for QC3 and 99.01% for DQC
Specificity	None
SOPs Submitted	ANI 8642.02
20% Chromatograms included (Y/N)	Y
Random or Serial Selection of Chromatograms	Serial

*Covers the storage period of study samples.

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary, Fasting Bioequivalence Study	
Study No.	40534
Study Design	Single-dose, 2-group, 2-way crossover, fasting
No. of subjects enrolled	60
No. of subjects completing	59
No. of subjects analyzed	59
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 45 Female: 15
Test product	Oxcarbazepine Tablet
Reference product	Trileptal®
Strength tested	600 mg
Dose	1 X 600 mg

Oxcarbazepine

N = 59

Bioavailability Parameters	A Oxcarbazepine Mean (CV %) [†]	B Trileptal [‡] Mean (CV %) [†]	Ratio of Means (%)	ANOVA [‡] p-value Treatment factor	90% C.I. Limits (%)		Minimum (%) Detectable Difference 80% Power	Power (%) to detect 20% difference $\alpha=0.05$, $\beta=0.20$
(Geometric means, ln-transformed data)								
AUC ₀₋₂₄ (ng·h/mL)	5851.63 (26.95)	5912.49 (28.69)	98.97	0.6100 NS	95.69	102.37	6.63	>99.99

AUC _{0-inf} (ng·h/mL)	5967.62 (26.45)	6047.29 (28.02)	98.68	0.5124 NS	95.42	102.06	6.59	>99.99
C _{max} (ng/mL)	1755.84 (43.18)	1728.35 (48.51)	101.59	0.8027 NS	91.45	112.86	19.06	85.55
(Arithmetic means, observed data)								
T _{max} (h)	1.45 (0.70)	1.61 (1.23)	89.97	0.3181 NS				
K _{el} (h ⁻¹)	0.0632 (0.0100)	0.0621 (0.0105)	101.82	0.2457 NS				
T _{1/2 el} (h)	11.25 (1.86)	11.49 (2.00)	97.89	0.2169 NS				

[‡]The ANOVA model has group, sequence, sequence within group, subject (sequence within group), period (group), treatment and treatment within group as factors.

[†] The CV% for geometric means was estimated as SD of ln-transformed data *100

NS = (treatment effect) not significant at p = 0.05 level.

Differences based on least-squares means.

Repeat Assays Project No. 40534

Analyte	Oxcarbazepine
Appropriate SOPs	ANI 156.08
Number of Samples Re-assayed	111
Number of Pharmacokinetic Repeats	None
Were the re-assays consistent with objective criteria in SOP?	All reassays were performed according to ANI 156.08 (Samples reassays and reporting of final concentrations), 5 codes B (0.20%) according to section 4.1.2, 91 codes D (3.69%) according to section 4.1.4, 13 codes E (0.53%) according to section 4.1.5, 2 codes G (0.08%), according to section 4.1.6
Impact of Repeat-assays on the study outcome	None

Did use of recalculated plasma concentration data change study outcome? No. The results of the fasting BE study (point estimate, 90% CI) for Oxcarbazepine using the original values are LAUC_t 0.99, 95.56-102.21, LAUC_∞ 0.99, 95.39-102.02, and LC_{max} 1.02, 91.47-113.24.

2. Single-dose Fed Bioequivalence Study

Study Summary, Fasting Bioequivalence Study	
Study No.	40231
Study Design	Single-dose, two-way crossover, randomized
No. of subjects enrolled	42+4 alternates
No. of subjects completing	46
No. of subjects analyzed	42
Subjects (Healthy or Patients?)	healthy
Sex(es) included (how many?)	Male: 42 Female: 4
Test product	Oxcarbazepine Tablet
Reference product	Trileptal®
Strength tested	600 mg
Dose	1 X 600 mg

40231:

Summary of Statistical Analysis

Taro oxcarbazepine 600 mg tablet Or Trileptal® 600 mg tablet

Mean (CV %) Bioavailability Parameters

Oxcarbazepine

N = 42

Bioavailability Parameters	A Oxcarbazepine Mean (CV %) [†]	B Trileptal [®] Mean (CV %) [†]	Ratio of Means (%)	ANOVA [§] p-value Treatment factor	90% C.I. Limits (%)		Minimum (%) Detectable Difference 80% Power	Power (%) to detect 20% difference $\alpha=0.05$, $\beta=0.20$
(Geometric means, ln-transformed data)								
AUC ₀₋₄ (ng·h/mL)	7838.33 (25.35)	7645.88 (24.25)	102.52	0.3960 NS	97.64	107.64	9.18	>99.99
AUC _{0-inf} [*] (ng·h/mL)	7974.25 (25.32)	7851.24 (24.61)	101.57	0.5870 NS	96.82	106.54	9.01	>99.99
C _{max} (ng/mL)	3269.99 (46.13)	3155.13 (42.69)	103.64	0.6606 NS	90.45	118.75	23.56	53.61
(Arithmetic means, observed data)								
T _{max} (h)	1.64 (0.73)	1.77 (1.07)	92.95	0.4506 NS				
K _{el} [*] (h ⁻¹)	0.0512 (0.0141)	0.0534 (0.0137)	95.90	0.1931 NS				
T _{1/2 el} [*] (h)	14.91 (5.73)	13.87 (3.74)	107.52	0.1375 NS				

[§]The ANOVA model has treatment, period, sequence and subject(sequence) as factors.

[†] The CV% for geometric means was estimated as SD of ln-transformed data *100

^{*}For these parameters, N = 40

NS = (treatment effect) not significant at p = 0.05 level.

Differences based on least-squares means.

Repeat Assays Project No. 40231

Analyte	Oxcarbazepine
---------	---------------

Appropriate SOPs	ANI 156.08
Number of Samples Re-assayed	465 (25.20%)
Number of Pharmacokinetic Repeats	Not Applicable
Were the re-assays consistent with objective criteria in SOP?	All reassays were performed according to ANI 156.08 (Samples reassays and reporting of final concentrations), 2 codes A (0.11%) were performed according to section 4.1.1, 21 codes B (1.14%) according to section 4.1.2, 5 codes C (0.27%) according to section 4.1.3, 198 codes D (10.73%) according to section 4.1.4, 146 codes G (7.91%) according to section 4.1.6, 22 codes H (1.19%) according to section 4.1.7, 66 codes L (3.58%) according to section 4.3 and 5 codes P (0.27%) according to section 4.1.9.
Impact of Repeat-assays on the study outcome	None

Analyte	10-OH-carbamazepine
Appropriate SOPs	ANI 156.08
Number of Samples Re-assayed	266 (14.42)
Number of Pharmacokinetic Repeats	Not applicable
Were the re-assays consistent with objective criteria in SOP?	All reassays were performed according to ANI 156.08 (Samples reassays and reporting of final concentrations), 19 codes B (1.03%) according to section 4.1.2, 1 code C (0.05%) according to section 4.1.3, 33 codes D (1.79%) according to section 4.1.4, 1 code E (0.05%) according to section 4.1.5, 137 codes G (7.43%) according to section 4.1.6, 71 codes L (3.85%) according to section 4.3 and 4 codes P (0.22%) according to section 4.1.9.
Impact of Repeat-assays on the study outcome	None

Did use of recalculated plasma concentration data change study outcome? The reviewer could not perform a statistical analysis because the firm did not provide SAS transport files containing the original data set. The firm will be requested to provide the datasets.

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?

Yes. The firm has acknowledged the FDA recommended method and specification for this product.

Is proposed specification acceptable?

Yes

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?

Yes

Waiver granted?

No

If not then why?

Refer to deficiencies section

Oxcarbazepine Tablets

I. Deficiency Comments

1. The firm did not provide SAS data files containing the original concentration and pharmacokinetic data sets for the parent and metabolite fasting and non-fasting bioequivalence studies.
2. The firm did not provide a table summarizing the pk repeats by treatment.
3. The firm did not provide the content uniformity of the test product.
4. The firm provided chromatograms for the fasting and non-fasting study, but did not label the chromatograms by subject number.
5. The firm did not state the criteria for determining the order of completion of subjects participating in the non-fasting study.
6. The firm did not state if subjects were dosed in two groups in the non-fasting study.

J. Recommendations

1. The in vivo bioequivalence study conducted under fasting conditions by Taro comparing its oxcarbazepine tablets 600 mg to the reference product Trileptal® 600 mg tablet (Novartis) is incomplete due to deficiencies # 1-4.
2. The in vivo bioequivalence study conducted under non-fasting conditions by Taro comparing its oxcarbazepine tablets 600 mg to the reference product Trileptal® 600 mg tablet (Novartis) is incomplete due to deficiencies # 1-6.
3. The dissolution testing conducted by Taro on its oxcarbazepine tablets, 150 mg, 300 mg, and 600 mg is acceptable. 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 Taro'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. Waivers 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 #1-6.

The application is incomplete.

Ethan M. Stier 4-05-06

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

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

4/5/2006

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

Dale P. Conner, Pharm. D.

4/5/06

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	40534
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	SFBC Anapharm Québec, Canada
Principal Investigator	Benoit Girard, M.D. Richard Larouche, M.D.
Study/Dosing Dates	I: 12-14-04 II: 12-21-04
Analytical Site	SFBC Anapharm Québec, Canada
Analytical Director	(b) (6), B.S.
Analysis Dates	12-23-04 to 12-29-04
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	15

Test or Reference	Test	Reference
Treatment ID	A	B
Product Name	Oxcarbazepine	Trileptal®
Manufacturer	Taro	Novartis
Batch/Lot No.	780755	312H1506
Manufacture Date	10-03	N.A.
Expiration Date	N.A.	08/06
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%)*	99.2	101.4
Content Uniformity (mean, %CV)	Not provided	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:1-30 and Group II:31-60)
Washout Period	7
Randomization Scheme	AB: 3,5,6,7,9,12,14,16,17,19,22,23,27,28,29,31,32,34,39,40,42,43,44,45,49,51,54,56,57,59 BA:1,2,4,8,10,11,13,15,18,20,21,24,25,26,30,33,35,36,37,38,41,46,47,48,50,52,53,55,58,60
Blood Sampling Times (h)	Pre-dose, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, and 60
Blood Volume Collected/Sample	3 mL (total did not exceed 161 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 24 hour blood draw
Safety Monitoring	Subjects were monitored by qualified personnel

Comments on Study Design: The firm did not provide the content uniformity of the test product.

b) Clinical Results

Table 1 Demographics of Study Subjects

Age		Weight		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0			Caucasian	93.3
Mean	44	Mean	75.2	18-40	37	Male	25	Afr. Amer.	1.6
SD	13	SD	10.1	41-64	59.7	Female	75	Hispanic	5
Range	20-70	Range	149- 188.5	65-75	3.3			Asian	0
				>75	0			Others	0

Table 2 Dropout Information

Subject No	Reason	Period	Replaced?
49	Person Reasons	I	no

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Oxcarbazepine Tablets

Table 3 Study Adverse Events

Incidence of treatment-emergent post-dose adverse events

Treatment Test (A)	Severity at onset				Relationship to study drug				Resolution		
	Mild	Mod.	Sev.	N/AP	Prob.	Poss.	Rem.	Unrel.	Spont.	With Trtmt	Unres.
Asthenia	1					1			1		
Diarrhea	1					1			1		
Dizziness		1						1	1		
Edema	1						1		1		
Fructal	1					1			1		
Headache	1				1				1		
Pain abdo	1					1			1		
Pain back	1					1			1		
Pain inject site	2							2	2		
Paresthesia	1					1			1		
Pharyngitis	1					1			1		
Rhinitis	1						1		1		
Somnolence	5	1			1	5			6		
TOTAL (A)	17	2			2	12	2	3	19		
Reference (B)	Mild	Mod.	Sev.	N/AP	Prob.	Poss.	Rem.	Unrel.	Spont.	With Trtmt	Unres.
Chills	2						2		2		
Diarrhea	1					1			1		
Dizziness	1					1			1		
Dry mouth	1						1		1		
Echymosis	1							1	1		
Headache	3	2				4	1		2	2	1
Myalgia	1						1		1		
Nausea	1					1			1		
Pain	2							2	1		1
Pain abdo		1				1			1		
Pain inject site	1							1	2		
Pain neck	1						1			1	
Paresthesia	2					2			2		
Rhinitis	1					1			1		
Somnolence	5				1	4			5		
Vomit			1			1			1		
TOTAL (B)	23	3	1		1	16	6	4	22	3	2
Clinically Significant Laboratory Results	Mild	Mod.	Sev.	N/AP	Prob.	Poss.	Rem.	Unrel.	Spont.	With Trtmt	Unres.
SGPT inc				1			1				1
Hypoglycem				1			1		1		
Hematoma				1			1		1		
TOTAL (Lab Results)				3			3		2		1

Mod. = Moderate; Sev. = Severe; N/AP = Not applicable; Prob. = Probable; Poss. = Possible; Rem. = Remote; Unrel. = Unrelated; Spont. = Spontaneous; With Trtmt = With treatment; Unres. = Unresolved

Table 4 Protocol Deviations

Oxcarbazepine Tablets

14.4 Summary of protocol deviations

See also Section 14.3, Deviations in blood sampling schedule.

Subject Number	Period	Treatment	Protocol Deviation	Excluded from Analysis due to Deviation(s)	
				Safety	PK
01-60	N/AP	N/AP	These subjects' eligibility was signed although the protocol final version approval was not received. However, eligibility was signed according to final version. All subjects met the inclusion criteria and none presented any exclusion criteria prior to dosing.	No	No
			Contrary to regulations, the study medication for this study was received by the clinical facility prior to receipt of the letter of non-objection from Health Canada.	No	No
	1, 2	A	During medication storage at the SFBC Fort Myers Facility, the temperature of the storage room rose above the accepted range specify by the manufacturer for the test medication, to as high as 24.9°C, between June 19, 2004 and December 7, 2004.	No	No
			During medication transfer from SFBC Anapharm's Ste-Foy to Montreal clinical facility, the temperature of the storage box rose above the accepted range specify by the manufacturer for the test medication, to as high as 23.8°C, on December 9, 2004.	No	No
	1, 2	A, B	Subjects in Group 1 (Subjects No. 01-30) were served 300 mL of juice with their pre-dose and post-dose suppers; subjects in Group 2 (Subjects No. 31-60) were served 341 mL of juice with these meals.	No	No
01-30	2	A, B	These subjects' 36.0- and 48.0-hour plasma samples were mixed with an expired buffer solution during sample processing, in error (maximum time of expiration: 19 hours 42 minutes). There is no impact since L-ascorbic acid (20%) is stable at 4°C for 44 hours.	No	No
			Whether these subjects' 36.0-hour plasma samples were flash-frozen cannot be confirmed (data not recorded). However, there is no impact since the time between centrifugation of blood samples and storage at -80°C was within the 24-hour bench top stability at room temperature for both analytes.	No	No
			Whether these subjects' 36.0-hour plasma samples were vortexed cannot be confirmed (data not recorded). However, there is no impact since the transfer of plasma into polypropylene tubes implies some mixing between the plasma and the ascorbic acid solution.	No	No
19, 20	2	B, A	Whether these subjects' 36.0-hour blood collection tubes were centrifuged at the scheduled time cannot be confirmed (due to conflicting data). Samples were not considered for statistical analysis.	No	Yes

Subject Number	Period	Treatment	Protocol Deviation	Excluded from Analysis due to Deviation(s)	
				Safety	PK
01	1, 2	A, B	The Period 1-2 washout for this subject was 6 days 23 hours 58 minutes.	No	No
15	N/AP	N/AP	This subject's screening urine pregnancy test was not performed, in error. However, a test performed prior to Period 1 drug administration, yielded a negative result.	No	No
29	2	B	No aliquots were produced for this subject's 0.750-hour post-dose due to technical error.	No	Yes
41	2	A	Approximately 2 mL of water was spilled at the time of drug administration.	No	No
48	1	B	The subject consumed 1 bite of chocolate cake 2 days 8 hours 56 minutes after study drug administration.	No	No
57	1	A	The subject consumed 2 sips of coffee 2 days 7 hours 53 minutes after study drug administration.	No	No
59	1	A	The subject consumed 1 sip of beer (5% alcohol content) 1 day 9 hours 4 minutes after study drug administration.	No	No

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)	12.04	300.96	601.92	1404.48	1404.48(5*)	20064.0 (20*)		
Inter day Precision (%CV)	4.14	4.48	4.38	4.32	3.90	5.25		
Inter day Accuracy (%)	98.34	97.85	97.22	97.57	95.43	96.08		
Cal. Standards Conc. (ng/mL)	4.01	8.02	80.19	400.96	801.92	1202.88	1603.84	2004.80
Inter day Precision (%CV)	4.18	4.24	3.37	3.19	3.65	3.93	2.82	3.83
Inter day Accuracy (%)	101.5	97.13	100.87	99.38	102.19	101.15	100.79	97.05
Linearity Range (range of R² values)	0.9939-0.9990							

*Dilution Factor

Comments on Study Assay Quality Control: Acceptable

Any interfering peaks in chromatograms?	See below
Were 20% of chromatograms included?	See below
Were chromatograms serially or randomly selected?	Se below

Comments on Chromatograms: Incomplete. The firm provided chromatograms but did not label them by subject number. Therefore, the reviewer could not determine the number of subjects that were represented in the submitted chromatograms.

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

SOP No.	Date of SOP	SOP Title
ANI	12-11-02	Sample Reassay and Reporting of Final

156.08	Concentrations
--------	----------------

Table 7 Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays: Yes

d) Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters

Oxcarbazepine

PARAMETER	UNITS	TEST		REFERENCE		RATIO T/R
		MEAN1	%CV	MEAN2	%CV	
AUC _{0-∞}	ng·hr/mL	6167.99	26.30	6281.61	27.86	0.98
AUC _{0-t}	ng·hr/mL	6055.33	26.75	6151.92	28.43	0.98
C _{MAX}	ng/mL	1910.27	41.13	1920.77	45.39	0.99
KE	hour ⁻¹	0.06	15.80	0.06	16.94	1.02
LAUCI	ng·hr/mL	5962.58	0.00	6047.25	0.00	0.99
LAUCT	ng·hr/mL	5846.52	0.00	5912.22	0.00	0.99
LC _{MAX}	ng/mL	1751.52	0.02	1724.47	0.03	1.02
THALF	hour	11.25	16.53	11.49	17.44	0.98
T _{MAX}	hour	1.45	48.34	1.61	76.30	0.90

PARAMETER	UNITS	TEST		REFERENCE		RATIO T/R
		MEAN1	%CV	MEAN2	%CV	
AUC _{0-∞}	ng·hr/mL	170289.54	21.94	171248.09	22.17	0.99
AUC _{0-t}	ng·hr/mL	165546.70	21.10	166169.28	21.35	1.00
C _{MAX}	ng/mL	7410.04	19.04	7288.08	21.51	1.02
KE	hour ⁻¹	0.07	19.10	0.07	20.08	1.00
LAUCI	ng·hr/mL	166525.74	0.00	167450.16	0.00	0.99
LAUCT	ng·hr/mL	162133.89	0.00	162718.39	0.00	1.00
LC _{MAX}	ng/mL	7279.06	0.00	7125.87	0.00	1.02
THALF	hour	10.13	21.02	10.17	20.82	1.00
T _{MAX}	hour	4.97	34.57	5.01	35.44	0.99

Table 9 Geometric Means and 90% Confidence Intervals

PARAMETER	TEST	REFERENCE	RATIO T/R	90 % CI	
	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
AUC _{0-∞}	6172.82	6278.38	0.98	95.15	101.48
AUC _{0-t}	6060.26	6148.83	0.99	95.38	101.74
C _{MAX}	1916.67	1921.61	1.00	90.04	109.45
LAUCI	5968.50	6046.40	0.99	95.46	102.08
LAUCT	5852.58	5911.53	0.99	95.72	102.39
LC _{MAX}	1757.44	1726.77	1.02	91.47	113.24

Table 10 Additional Study Information

Root mean square error, LAUC _{0-t}	0.1093
Root mean square error, LAUC _∞	0.1088
Root mean square error, LC _{max}	0.3465
Kel and AUC _∞ determined for how many subjects?	59
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. The subjects were dosed in

	two groups.
--	-------------

Comments on Pharmacokinetic and Statistical Analysis:

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.

The results of the fasting BE study (point estimate, 90% CI) for the metabolite are LAUCT 1.00, 97.96-101.35, LAUC ∞ 0.99, 97.71-101.23, and LCmax 1.02, 98.94-105.46.

The firm will be requested to submit SAS transport files containing the original data for the parent and metabolite.

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

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

Time (h)	Test (n=59)		Reference (n=59)		T/R
	Mean Conc. (ng/mL)	%CV	Mean Conc. (ng/mL)	%CV	
0	0.00	.	0.00	.	.
0.25	186.44	157.77	177.16	194.30	1.05
0.5	796.17	96.09	781.68	89.97	1.02
0.75	1272.88	71.95	1305.66	65.81	0.97
1	1503.01	60.46	1477.48	67.09	1.02
1.5	1373.97	50.10	1389.05	63.90	0.99
2	1146.36	44.73	1106.33	55.24	1.04
2.5	919.84	47.01	851.90	51.74	1.08
3	669.13	49.82	635.58	56.08	1.05
4	377.89	57.83	380.39	73.25	0.99
5	308.95	69.32	385.79	120.02	0.80
6	208.17	49.74	235.88	79.56	0.88
7	149.94	42.67	165.50	50.54	0.91
8	116.80	36.61	125.10	39.61	0.93

10	96.81	40.93	101.50	37.47	0.95
12	82.85	42.70	84.24	38.72	0.98
16	60.78	39.07	61.59	42.99	0.99
24	37.12	47.40	39.55	43.31	0.94
36	18.61	47.13	19.65	45.54	0.95
48	8.17	57.02	8.60	59.58	0.95
60	1.88	167.57	1.87	174.11	1.01

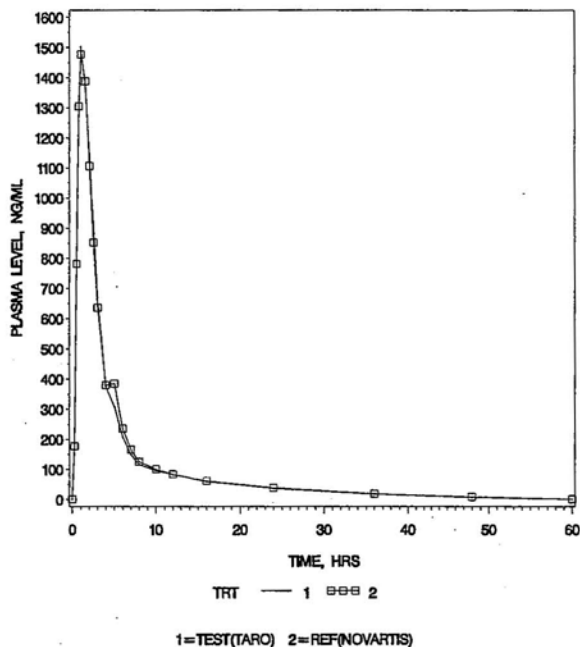
Figure 1 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Plasma Oxcarbazepine Levels
Oxcarbazepine Tablets, 600 mg
ANDA 77-801
Under Fasting Conditions
1 X 600 mg

Plasma
Levels
(ng/mL)

1=Test (Taro), 2=Reference (Novartis)

PLASMA oxcarb LEVELS
oxcarb OXCARBAZEPINE, 600 mg , ANDA #77-801
UNDER Fasting CONDITIONS
DOSE=1 X 600 mg



2. Single-dose Fed Bioequivalence Study

a) Study Design

Study Information	
Study Number	40231
Study Title	Randomized, Single Dose 2-Way Crossover Study of Oxcarbazepine 600 mg Tablet and Trileptal® Following a 600 mg Dose in Healthy Subjects Following a Standard Meal
Clinical Site	SFBC Anapharm Québec, Canada
Principal Investigator	Antonio Pizarro, M.D.
Study/Dosing Dates	I: 07-21-04 II: 07-28-04
Analytical Site	SFBC Anapharm Québec, Canada
Analytical Director	(b) (6), B.S.
Analysis Dates	12-23-04 to 12-29-04
Storage Period (no. of days from the first	15

day of sample collection to the last day of sample analysis)	
--	--

Test or Reference	Test	Reference
Treatment ID	A	B
Product Name	Oxcarbazepine	Trileptal®
Manufacturer	Taro	Novartis
Batch/Lot No.	780755	312H1506
Manufacture Date	10-03	N.A.
Expiration Date	N.A.	08/06
Strength	600 mg	600 mg
Dosage Form	Tablet	Tablet
Batch Size	(b) (4)	N.A.
Production Batch Size		N.A.
Potency	99.2	101.4
Content Uniformity	Not provided	
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 (for study subjects)	AB: 2,4,6,10,11,12,13,14,15,16,23,24,28,29,32,33,34,36, 39,41,42,43,46,48 BA:1,3,5,7,8,9,17,18,19,22,25,26,27,30,31,35,37,38, 40,44,45,47
Blood Sampling Times	Pre-dose, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, and 60
Blood Volume Collected/Sample	7 mL (total did not exceed 350 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 24 hour blood draw
Safety Monitoring	Subjects were monitored by qualified personnel
Standard FDA Meal Used?	Yes

Comments on Study Design: The firm did not provide the content uniformity of the test product.

b) Clinical Results

Table 12 Demographics of Study Subjects

Age		Weight		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0			Caucasian	28.2
Mean	35.8	Mean	76.0	18-40	67.3	Male	93.4	Afr. Amer.	4.3
SD	15.3	SD	11.6	41-64	28.6	Female	6.6	Hispanic	67.5
Range	18-73	Range	51.4-101.7	65-75	4.3			Asian	0
				>75	0			Others	0

Table 13 Dropout Information

Subject No	Reason	Period	Replaced?
26	Unable to draw 36.0 h sample	I	Yes

Table 14 Study Adverse Events

Incidence of treatment-emergent post-dose/post-study adverse events

Treatment	Severity at onset			Relationship to study drug					Resolution				
Test (A)	Mild	Mod.	Sev.	Def.	Prob.	Poss.	Unl.	NR	Cont.	Dec. SD	Stop. Temp.	Con Med	CM Red.
Item	1							1	1				
Herpes Simplex	2							2	2				
Hypesthesia	1							1	1				
Nausea		1						1	1				
Somnolence	1					1			1				
Syncope		1						1	1				
Vertigo	3						1	2	3				
TOTAL (A)	8	2				1	1	8	10				
Reference (B)	Mild	Mod.	Sev.	Def.	Prob.	Poss.	Unl.	NR	Cont.	Dec. SD	Stop. Temp.	Con Med	CM Red.
Asthenia	1							1	1				
Hypertens	1							1	1				
Pain, Catheter Site		1						1	1				
Paresth Circumoral	2							2	2				
Vertigo	4							4	4				
TOTAL (B)	8	1						9	9				
Unknown (Post-Study Labs)	Mild	Mod.	Sev.	Def.	Prob.	Poss.	Unl.	NR	Cont.	Dec. SD	Stop. Temp.	Con Med	CM Red.
Hematuria	1						1		1				
TOTAL (Unknown)	1						1		1				

Mod. = Moderate; Sev. = Severe; Def. = Definite; Prob. = Probable; Poss. = Possible;
Unl. = Unlikely; NR = Not Related; Cont. = Continued Study; Dec. SD = Decreased study drug dose;
Stop. Temp. = Stopped study drug temporarily; Con Med = Concomitant medication; CM Red. =
Concomitant medication dose reduced

Oxcarbazepine Tablets

Table 15 Protocol Deviations

See also Section 14.3, Deviations in blood sampling schedule.

Subject Number	Period	Deviation
1, 24, 37, 38	1	Belongings search was not done or is missing.
2, 3, 23, 37, 38	Screening	Drug screen and phosphorus labs were not done.
2, 3, 4	N/A	ECG, vitals, and physical were done 26 days prior to dosing.
4	Screening	BMI 31.6.
5	2	Belongings search was not done or is missing.
5	N/A	Subject smokes cigarettes.
8	1	Subject did not return for blood samples for 36, 48, and 60 hour; no samples were obtained.
10	Screening	Pregnancy test was not done.
17	Screening	Vitals were not done.
24	Screening	Screened 27 days prior to dosing.
25	Screening	Screened 26 days prior to dosing.
26	Screening	Screened 25 days prior to dosing.
27	Screening	Screened 22 days prior to dosing.
38	1	Blood sample for 0.25 hour was obtained, but is invalid, as no time was recorded on the source document.

Comments on Adverse Events/Protocol Deviations: There was one dropout. The number of adverse events observed in the test group was greater than the number observed in the reference 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)	12.21	305.10	610.2	1423.81				
Inter day Precision (%CV)	6.12	6.26	4.61	8.18				
Inter day Accuracy (%)	99.67	98.53	98.13	99.34				
Cal. Standards Conc. (ng/mL)	4.06	8.13	81.3	406.49	812.98	1219.46	1625.95	2032.44
Inter day Precision (%CV)	6.36	5.11	4.39	2.94	3.64	4.67	4.03	4.14
Inter day Accuracy (%)	100.91	98.38	97.63	99.97	101.02	98.56	98.23	105.32
Linearity Range (range of R² values)	0.9960-0.9997							

Comments on Study Assay Quality Control: Acceptable

Any interfering peaks in chromatograms?	See below
Were 20% of chromatograms included?	See below
Were chromatograms serially or randomly selected?	See below

Comments on Chromatograms: Incomplete. The firm provided chromatograms but did not label them by subject number. Therefore, the reviewer could not determine the number of subjects that were represented in the submitted chromatograms.

Table 17 SOP's dealing with analytical repeats

SOP No.	Date of SOP	SOP Title
ANI 156.08	12-11-02	Sample Reassay and Reporting of Final Concentrations

Table 18 Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	The firm did not submit the SAS transport files containing the original data. Therefore, the reviewer could not determine if the reassay values affected the outcome of the study.
Does the reviewer agree with the outcome of the repeat assays?	See above
If no, reason for disagreement	N.A.

Summary/Conclusions, Study Assays: Incomplete

d) Pharmacokinetic Results

Table 19 Arithmetic Mean Pharmacokinetic Parameters

Oxcarbazepine

PARAMETER	UNITS	TEST		REFERENCE		RATIO T/R
		MEAN1	%CV	MEAN2	%CV	
AUC _{0-∞}	ng·hr/mL	8217.61	27.19	8104.44	25.55	1.01
AUC _{0-t}	ng·hr/mL	8079.81	26.46	7884.96	25.05	1.02
C _{MAX}	ng/mL	3621.18	50.27	3434.44	40.07	1.05
K _E	hour ⁻¹	0.05	27.52	0.05	25.60	0.96
LAUCI	ng·hr/mL	7954.05	0.00	7863.89	0.00	1.01
LAUCT	ng·hr/mL	7824.03	0.00	7658.08	0.00	1.02
LC _{MAX}	ng/mL	3249.30	0.01	3157.55	0.01	1.03
THALF	hour	14.91	38.42	13.87	26.99	1.08
T _{MAX}	hour	1.64	44.20	1.77	60.77	0.93

10-OH-Carbazepine

PARAMETER	UNITS	TEST		REFERENCE		RATIO T/R
		MEAN1	%CV	MEAN2	%CV	
AUC _{0-∞}	ng·hr/mL	173334.69	21.82	174452.50	21.89	0.99
AUC _{0-t}	ng·hr/mL	166421.22	20.52	167648.29	21.23	0.99
C _{MAX}	ng/mL	8498.19	17.64	8445.79	15.64	1.01

PARAMETER	UNITS	TEST		REFERENCE		RATIO T/R
		MEAN1	%CV	MEAN2	%CV	
KE	hour ⁻¹	0.06	26.52	0.06	26.09	0.97
LAUCI	ng-hr/mL	169774.39	0.00	170810.38	0.00	0.99
LAUCT	ng-hr/mL	163350.22	0.00	164220.19	0.00	0.99
LCMAX	ng/mL	8374.03	0.00	8348.38	0.00	1.00
THALF	hour	11.93	30.54	11.51	29.40	1.04
TMAX	hour	4.11	34.49	4.48	43.47	0.92

Table 20 Geometric Means and 90% Confidence Intervals

PARAMETER	TEST	REFERENCE	RATIO T/R	90 % CI	
	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
AUC _{0-∞}	8240.74	8093.10	1.02	96.92	106.72
AUC _{0-t}	8095.59	7874.05	1.03	97.82	107.80
C _{MAX}	3651.93	3435.42	1.06	91.91	120.70
LAUCI	7974.25	7851.24	1.02	96.82	106.54
LAUCT	7838.33	7645.88	1.03	97.64	107.64
LC _{MAX}	3269.99	3155.13	1.04	90.45	118.75

Table 21 Additional Study Information

Root mean square error, LAUC _{0-t}	0.1326
Root mean square error, LAUC _∞	0.1268
Root mean square error, LC _{max}	0.3700
K _{el} and LAUC _∞ determined for how many subjects?	40
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?	The firm should clarify if the subjects were dosed in one group.

Comments on Pharmacokinetic and Statistical Analysis:

Oxcarbazepine Tablets

The results of the fasting BE study (point estimate, 90% CI) for the metabolite are LAUC_t 1.00, 96.79-102.67, LAUC_∞ 1.00, 96.62-102.64, and LC_{max} 1.00, 97.80-103.24.

The firm will be requested to submit SAS transport files containing the original data for the parent and metabolite.

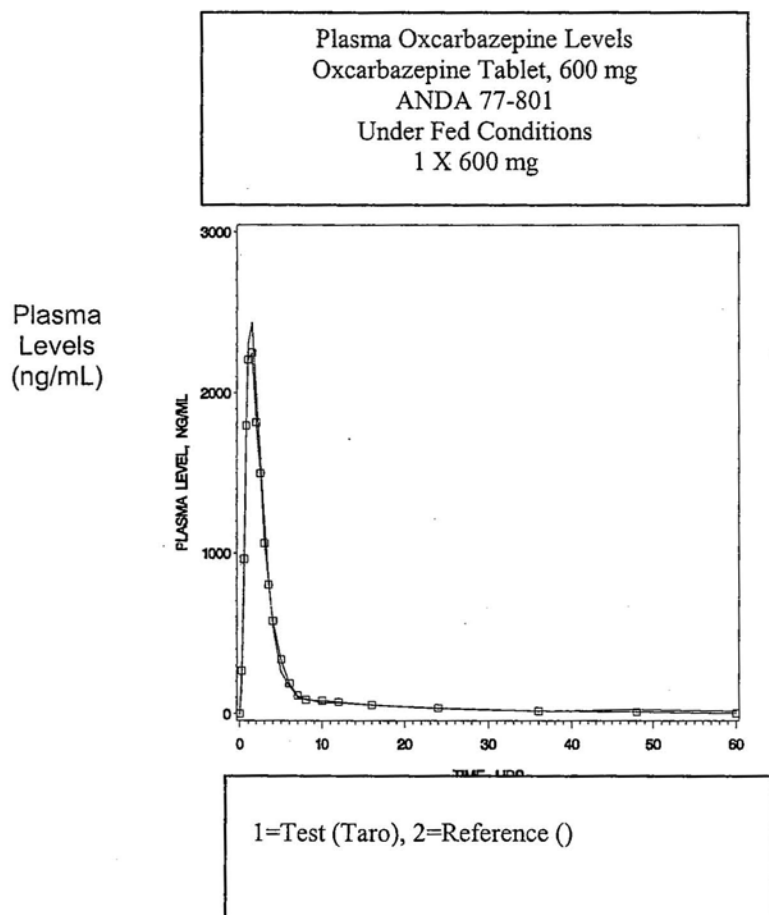
Summary/Conclusions, Single-Dose Fed Bioequivalence Study: Incomplete

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

Time (h)	Test (n=42)		Reference (n=42)		T/R
	Mean Conc. (ng/mL)	%CV	Mean Conc. (ng/mL)	%CV	
0	0.00	.	0.00	.	.
0.5	711.74	138.09	962.60	151.85	0.74
0.75	1799.02	119.44	1795.65	106.35	1.00
1	2303.66	85.33	2205.33	80.61	1.04
1.5	2435.66	72.11	2248.58	57.54	1.08
2	1988.83	43.21	1814.96	42.35	1.10
2.5	1589.86	38.25	1498.28	67.38	1.06
3	1197.71	48.10	1061.42	66.30	1.13
3.5	817.70	57.58	802.59	70.93	1.02
4	542.04	64.20	577.61	85.12	0.94
5	260.80	77.92	336.64	100.32	0.77
6	171.13	93.68	187.43	93.28	0.91
7	101.20	68.67	112.28	73.43	0.90
8	94.21	99.33	86.04	44.59	1.09
10	68.55	27.89	80.64	59.03	0.85
12	67.88	27.53	73.21	53.77	0.93
16	54.29	29.24	54.49	34.81	1.00
24	32.88	23.96	35.64	49.49	0.92
36	16.10	51.97	15.80	49.14	1.02
48	26.62	356.67	11.56	61.34	2.30
60	16.59	499.42	2.75	191.67	6.04

Oxcarbazepine Tablets

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



Oxcarbazepine Tablets

B. Formulation Data

Taro Pharmaceutical Industries Ltd. formulation of Oxcarbazepine Tablets, 150 mg, 300 mg and 600 mg consists of the following:

Ingredient	Proposed Formulation, 150 mg/ Tablet Quantity	Proposed Formulation, 300 mg/ Tablet Quantity	Proposed Formulation, 600 mg/ Tablet Quantity
Oxcarbazepine, (b) (4)	150	300	600
Microcrystalline Cellulose (PH 102)	(b) (4)		
Croscarmellose Sodium			
Hypromellose			
Colloidal Silicone Dioxide			
Yellow Iron Oxide			
Red Iron Oxide			
Purified Water ⁽¹⁾			
Microcrystalline Cellulose (PH 200)			
Magnesium Stearate			
Total Dry Weight	213.75	427.50	855.00
	Pale peach, ovaloid, slightly biconvex, scored on both sides. Imprinted with R/O on one side and O/C on the other side	Pale peach, ovaloid, slightly biconvex, scored on both sides. Imprinted with OX/C3 on one side and TA/RO on the other side	Pale peach, ovaloid, slightly biconvex, scored on both sides. Imprinted with OX/C6 on one side and TA/RO on the other side

(1) (b) (4)

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 (see below). The firm acknowledged the acceptance of the FDA-recommended dissolution method and specification (see Amendment dated 12-28-05).

FDA Recommended Method Accepted by Firm:

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

Dissolution Reviews



77801D0705.doc



77801a1205.doc

D. Consult Reviews

None

E. SAS Output

Statistical Analysis	Program file	Output file
Single dose fasting study	 OXCARBARENTNOG RPEFFECT.txt	 nogroupeffectoutput .txt
Single dose fed study	 FEDPARENTANALYSIS FIRMDATA.TXT	 PARENTOUTPUT.TXT

F. Additional Attachments

None

CC: ANDA 77-801
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer: E. Stier
HFD-655/ TL: GJP Singh

Endorsements: (Final with Dates)

HFD-650/Ethan M. Stier *EMA 4-05-06*

HFD-655/S. G. Nerurkar

HFD-617/K. Suh

HFD-650/Dale Conner *BMD 4/5/06*

DN 4/5/06

fn

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Printed in final on 04-05-06

BIOEQUIVALENCY Submission Date: 07-14-05

1. **FASTING STUDY (STF)** **Strength: 600 mg**
Clinical: SFBC Anapharm
Québec, Canada ✓ **Outcome: IC**

Analytical: SFBC Anapharm
Québec, Canada
2. **FOOD STUDY (STF)** **Strength: 600 mg**
Clinical: SFBC Anapharm
Québec, Canada ✓ **Outcome: IC**

Analytical: SFBC Anapharm
Québec, Canada
3. **DISSOLUTION WAIVER (DIW)** **Strength: 300 mg**
✓ **Outcome: IC**
4. **DISSOLUTION WAIVER (DIW)** **Strength: 150 mg**
✓ **Outcome: IC**

Outcome Decisions: IC - Incomplete

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-801

APPLICANT: Taro

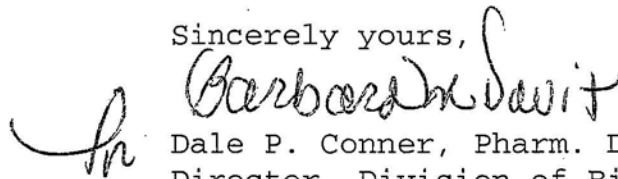
DRUG PRODUCT: Oxcarbazepine Tablets
150 mg, 300 mg, and 600 mg

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

1. Please provide the content uniformity of the test product used in the fasting and non-fasting studies.
2. You provided chromatograms for the fasting and non-fasting studies. However, you did not identify the chromatograms by subject number. Please provide sample chromatograms for at least 20% of the subjects in the fasting and non-fasting studies providing the subject, period, and sample time information.
3. Please provide SAS transport files for the fasting and non-fasting studies for the parent and metabolite containing the original data.
4. Please provide a summary table for reassayed samples classified by treatment (test or reference). Please refer to table 8 below.
5. Please clarify if subjects in the fasting study were dosed in one or two groups.
6. You stated that the data from the first 42 subject to complete the non-fasting study were used for pharmacokinetic analysis. Please describe the criteria used for determining the order of completion of subjects participating in the non-fasting study.

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

Sincerely yours,

A handwritten signature in dark ink, appearing to read "Dale P. Conner". The signature is fluid and cursive, with a large initial "D" and "C".

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

Table 1. Summary of Bioavailability Studies

Study #	Fasting study title	Randomized, single-dose, crossover	Test product, strength, Tab./Cap./Susp., p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean age (range)	M ± S.D.	Mn or Md	M ± S.D.	M ± S.D.	Mean	Mean	Vol. # p. #
			Ref. product, strength, Tab./Cap./Susp., p.o. [Batch #]		M ± S.D.	No SD	M ± S.D.	M ± S.D.	No SD	No SD	
Study #	Fed study title	Randomized, single-dose, crossover	Test product, strength, Tab./Cap./Susp., p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean y (range)	M ± S.D.	Mn or Md	M ± S.D.	M ± S.D.	Mean	Mean	Vol. # p. #
			Ref. product, strength, Tab./Cap./Susp., p.o. [Batch #]		M ± S.D.	No SD	M ± S.D.	M ± S.D.	No SD	No SD	

Table 2. Statistical Summary of the Comparative Bioavailability Data

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

Table 3. Bioanalytical Method Validation

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

Table 4. Summary of In Vitro Dissolution Studies

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

Table 5. Formulation Data

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

Please include the formulation of all strengths

Table 6. Demographic Profile of Subjects Completing the Bioequivalence Study

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

Table 7. Incidence of Adverse Events in Individual Studies

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

Table 8. Reanalysis of Study Samples

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

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

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-801
Drug Product Name	Oxcarbazepine Tablets
Strength	150 mg, 300 mg, and 600 mg tablets
Applicant Name and Contact	Taro 14 Hakitor Street Haifa Bay, 26110 Israel Kalpana Rao 914-345-9001 (phone) / 914-593-0078 (fax)
Submission Date(s)	07-14-05
Amendment Date(s)	12-29-05 (dissolution acknowledgement), 06-28-06, (reviewed below) 08-01-06, (telephone amendment) 08-14-06 (reviewed below), 11-14-06 (telephone amendment)
Reviewer	Ethan M. Stier, Ph.D.
First Generic	No

I. Executive Summary

Taro has previously submitted single-dose fasting and non-fasting bioequivalence studies comparing its test product, Oxcarbazepine Tablet, 600 mg to the RLD product, Trileptal® tablets, 600 mg, in the original application, dated 07-14-05 (V:\firmsam\taro\ltrs&rev\77801N0705).

The firm submitted the 06-28-06 amendment in response to the Division of Bioequivalence (DBE) deficiency comments requesting the firm to submit additional study information regarding the bioequivalence studies including pk repeat data for both BE studies and group assignment number for subjects in the fasting study. The reviewer reanalyzed the data and found the BE studies to be acceptable. The additional requested study information was acceptable.

The applicant has previously requested 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 acceptable. The firm has previously accepted the FDA recommended method and specification. Waiver of in vivo BE testing for the 150 mg and 300 mg tablets are granted.

The BE studies and waivers requests in the original submission are acceptable. Waivers for the lower strengths are granted.

(b) (4)



(b) (4)

The application is acceptable and complete. (Note: The firm is proposing a (b) (4) and the application can be reopened at a later time after the firm decides to make the change).

II. Table of Contents

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C. Appendix	9

III. Background:

See the review of the original submission of the study.
(V:\firmsNZ\Taro\ltrs&rev\77801N0705.Doc)

IV. Submission:

A. 06-28-06 Submission

DEFICIENCY COMMENT #1

- Please provide the content uniformity of the test product used in the fasting and non-fasting studies.*

FIRM'S RESPONSE: The results of the content uniformity testing (mean, C.V.) were 99.2%, 0.6%.

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

DEFICIENCY COMMENT #2

2. You provided chromatograms for the fasting and non-fasting studies. However, you did not identify the chromatograms by subject number. Please provide sample chromatograms for at least 20% of the subjects in the fasting and non-fasting studies providing the subject, period, and sample time information.

FIRM'S RESPONSE: The firm submitted labeled chromatograms for the fasting and non-fasting study.

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

DEFICIENCY COMMENT #3

3. Please provide SAS transport files for the fasting and non-fasting studies for the parent and metabolite containing the original data.

FIRM'S RESPONSE: The firm provided data sets containing original values.

REVIEWER'S COMMENT: The reviewer determined that the reassay values did not affect the outcome of the study.

DEFICIENCY COMMENT #4

4. Please provide a summary table for reassayed samples classified by treatment (test or reference). Please refer to table 8 below.

FIRM'S RESPONSE: The firm provided the table.

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

DEFICIENCY COMMENT #5

5. *Please clarify if subjects in the fasting study were dosed in one or two groups.*

FIRM'S RESPONSE: The firm stated that subjects were dosed in two groups.

REVIEWER'S COMMENT: The reviewer determined there was no group effect. The reviewer analyzed the data by dropping the trt*grp term from the GLM model. The firm's response is acceptable.

DEFICIENCY COMMENT #6

6. You stated that the data from the first 42 subject to complete the non-fasting study were used for pharmacokinetic analysis. Please describe the criteria used for determining the order of completion of subjects participating in the non-fasting study.

FIRM'S RESPONSE: The firm stated that numbers 20 and 21 were not assigned.

REVIEWER'S COMMENT: The firm's response accounts for the apparent discrepancy in the selection of the first 42 subjects to complete the study. The firm's response is acceptable.

B. 08-14-06 Submission

FIRM'S QUESTION:

1.

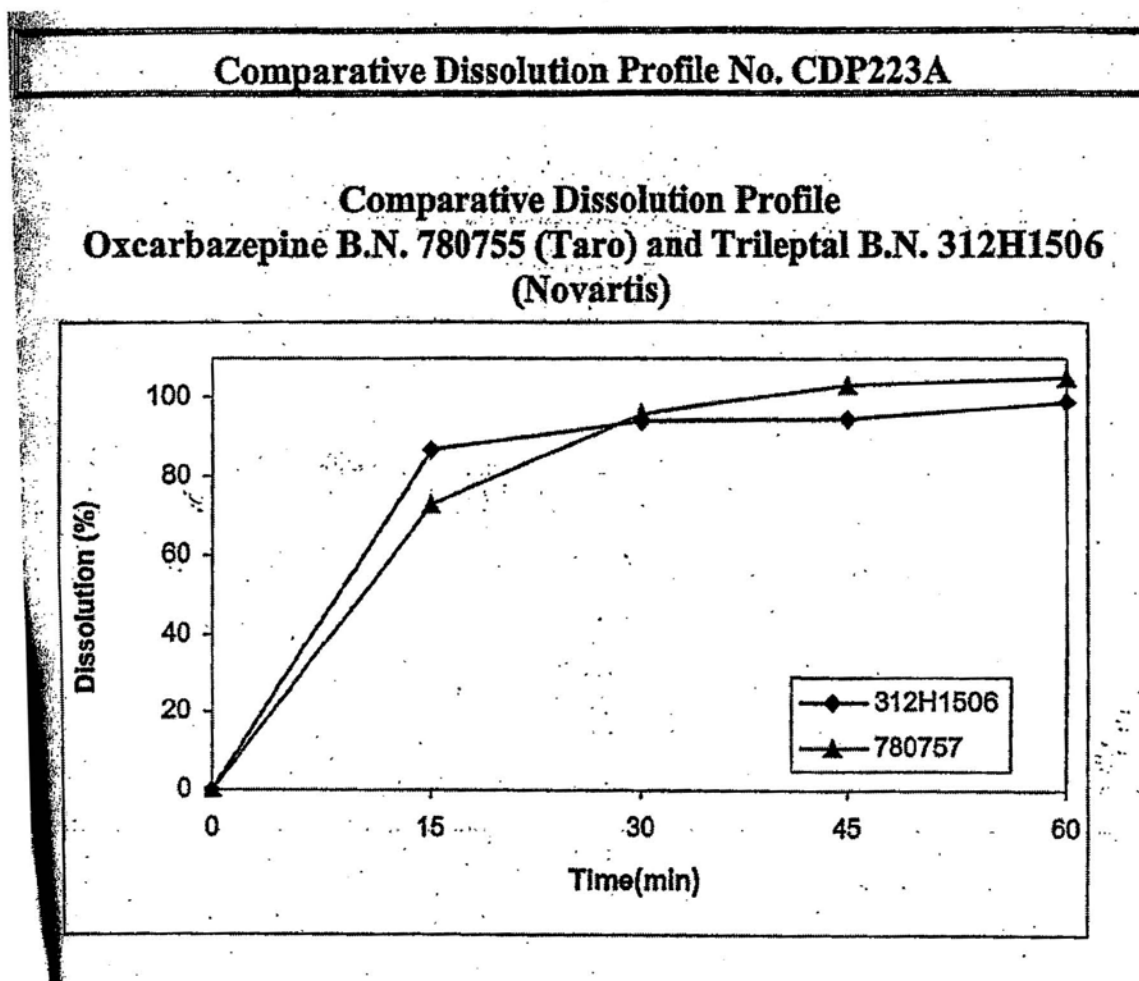
(b) (4)

REVIEWER'S COMMENT:

(b) (4)

Following this page, page #5 is withheld in full
(b)(4).

Table II. Dissolution (b) (4) vs RLD formulation



(b)
(4)

(b) (4)

A. Waiver Request ((b) (4) formulation)

Strengths for which waivers requested	150 mg and 300 mg
Proportional to strength tested in vivo (yes or no)	Yes
Dissolution is acceptable (yes or no)	Yes
Waiver granted (yes or no)	Yes

B. Deficiency Comments

06-28-06 Amendment

None

08-14-06 Amendment

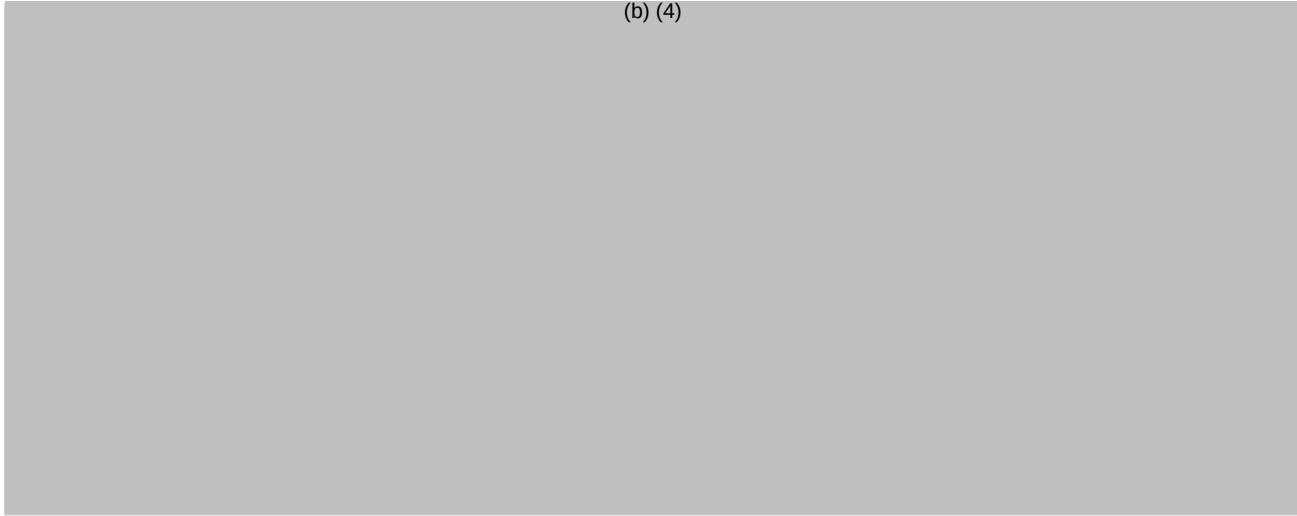
None

C. Recommendations

06-28-06 Amendment

1. The in vivo bioequivalence study previously conducted under fasting conditions by Taro comparing its oxcarbazepine tablets 600 mg to the reference product Trileptal® 600 mg tablet (Novartis) is acceptable.
2. The in vivo bioequivalence study previously conducted under non-fasting conditions by Taro comparing its oxcarbazepine tablets 600 mg to the reference product Trileptal® 600 mg tablet (Novartis) is acceptable.
3. The dissolution testing conducted by Taro on its oxcarbazepine tablets, 150 mg, 300 mg, and 600 mg is acceptable. 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.
4. The formulations of Taro'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. Waivers of in vivo bioequivalence study requirements for the 150 mg and 300 mg tablets are granted.

(b) (4)



3.

(b) (4)

D. Appendix

None

BIOEQUIVALENCE COMMENTS

ANDA: 77-801

APPLICANT: Taro

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

REVIEW OF ORIGINAL SUBMISSION AND 06-28-06 AMENDMENT:

We agree with your proposed dissolution method and specification as follows:

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), at 37°C 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 the drug in 30 minutes and not less than (b) (4) (Q) of the labeled amount of 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.

Following this page, 2 pages (#11 & 12) are withheld in full (b)(4).

5. The bioequivalence data for your Abbreviated New Drug Application (ANDA) should be provided in a diskette or CD in SAS Transport format in two separate files as described below:

- a. SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX KE THalf
- b. SUBJ SEQ PER TRT C1 C2 C3 Cn

Please separate each field with a blank space and indicate missing values with a period (.).

For additional information, please refer to the Guidance for Industry: "Providing Regulatory Submissions in Electronic Format-ANDAs" at www.fda.gov/cder/guidance/index.htm.

6. In the bioequivalence section of the ANDA, please include the address of the laboratories conducting the dissolution testing.

Sincerely yours,

{See appended electronic signature page}

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

CC: ANDA 77801

BIOEQUIVALENCY Submission Dates: 07-14-05, 12-29-05,
06-28-06, 08-01-06, 08-14-06, 11-14-06

- | | | |
|----|---|--|
| 1. | FASTING STUDY (STF-07-14-05-WC) | Strength: 600 mg |
| | Clinical: SFBC Anapharm
Québec, Canada | Outcome: AC |
| | Analytical: SFBC Anapharm
Québec, Canada | |
| 2. | FOOD STUDY (STF-07-14-05-WC) | Strength: 600 mg |
| | Clinical: SFBC Anapharm
Québec, Canada | Outcome: AC |
| | Analytical: SFBC Anapharm
Québec, Canada | |
| 3. | DISSOLUTION WAIVER (DIW-07-14-05-WC) | Strength: 300 mg
Outcome: AC |
| 4. | DISSOLUTION WAIVER (DIW-07-14-05-WC) | Strength: 150 mg
Outcome: AC |
| 5. | STUDY AMENDMENT (06-28-06) | Strength: 150 mg, 300 mg,
and 600 mg
Outcome: AC |
| 6. | STUDY AMENDMENT (08-14-06) | Strength: 150 mg, 300 mg,
and 600 mg
Outcome: AC |
| 7. | STUDY AMENDMENT (08-01-06-WC) | Strength: 150 mg, 300 mg,
and 600 mg
Outcome: AC |
| 7. | STUDY AMENDMENT (11-14-06-WC) | Strength: 150 mg, 300 mg,
and 600 mg
Outcome: AC |

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

/s/

Ethan Stier
2/28/2007 03:03:51 PM
BIOPHARMACEUTICS

Shriniwas G. Nerurkar
2/28/2007 03:14:27 PM
BIOPHARMACEUTICS

Dale Conner
2/28/2007 03:50:08 PM
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