CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078115

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-115
Drug Product Name	Carbamazepine Extended-Release Tablets, USP
Strengths	100mg, 200mg & 400mg
Applicant Name	Taro Pharmaceutical Industries Ltd.
Address	3 Skyline Drive Hawhorne NY 10532
Submission Date(s)	December 29th, 2005
Amendment Date(s)	No Amendment
Reviewer	S. Christopher Jones Pharm.D., M.S.
First Generic	**No:** 200mg & 400mg strengths **Yes**: 100mg strength
Firm Liaison	Kalpana Rao, Regulatory Affairs 3 Skyline Drive Hawhorne NY 10532 (914) 345-9001 phone (914) 593-0078 fax

I. Executive Summary

The firm submitted a total of four studies. Three of these were bioequivalence studies [pilot-fast (Study R05-0184), pilot-fed (Study R05-0185), and pivotal-fed (Study R04-1364),] comparing its test product, carbamazepine extended release tablets, 400mg to the reference listed drug (RLD), Tegretol® XR (carbamazepine) extended release tablets, 400mg (Novartis). According to the firm, their 100 mg test tablet did not have a dissolution profile similar to the 100 mg reference tablet using the USP dissolution method and Taro consequently submitted a fourth study (pivotal-fast, Study R05-1389) comparing its test product, carbamazepine extended release tablets, 100mg to Tegretol® XR (carbamazepine) extended release tablets, 100mg (Novartis). Additionally, dissolution data on all strengths of the test and reference products were included.

Each pilot BE study ($n_{pilot\text{-}fast}$=15, $n_{pilot\text{-}fed}$=16) is designed as a single-dose, randomized, three-treatment, three-sequence, crossover study in healthy adult subjects comparing 400 mg strength tablets. The three treatments include two test formulations and the reference listed drug. The results provided are for the comparison of Test A formulation (intended for marketing) and Reference products. For the pilot-fasting study, carbamazepine results (point estimate, 90% CI) are: LAUCT of 110.03, 99.75 – 121.38%; LAUCI 111.49, 110.84 – 123.27%; and LCmax 104.84, 94.26 – 116.61%. The 90% CI for the metabolite were within acceptable limits. For the pilot-fed study, carbamazepine results (point estimate, 90% CI) are: LAUCT of 118.36, 114.64 – 121.21%; LAUCI 117.13, 112.38 – 122.07%; and LCmax 114.16, 109.97 – 118.52%. For the pilot-fed study, the firm calculated 90% CI for the metabolite were outside the acceptable limits. Therefore, the firm conducted another, larger pivotal-fed study.

Each pivotal bioequivalence (BE) study [$n_{pivotal\text{-}fast}$=20 (100 mg strength tablets), $n_{pivotal\text{-}fed}$=34 (400 mg strength tablets)] is designed as an single-dose, randomized, two-treatment, two-sequence, crossover study in healthy adult subjects. For the pivotal-fasting study, carbamazepine results (point estimate, 90% CI) are: LAUCT of 100.98, 94.17 – 108.27%; LAUCI 100.77, 93.47 – 108.65% and LCmax 96.57, 91.70 – 101.69%. For the pivotal-fed study, carbamazepine results (point estimate, 90% CI) are: LAUCT of 114.83, 110.75 – 119.05%; LAUCI 114.50, 110.37 – 118.78%; and LCmax 111.59, 108.88 – 114.36%.

The comparative dissolution testing in three different media is incomplete and the firm inconsistently reported the dose administered to subjects in the pivotal-fasting study. Additional dissolution testing and dose clarification has been requested.

Both the 100mg and 200mg tablets are proportional to the 400 mg tablet, which underwent *in vivo* testing under fasting and fed conditions. The DBE may deem lower strengths of the test product bioequivalent to the RLD based on CFR 320.24(b)(6), upon resolution of the cited deficiencies. The application is incomplete.

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III. Submission Summary

A. Drug Product Information

Test Product	Carbamazepine Extended Release Tablet 400mg
Reference Product	Tegretol-XR® Tablet 400mg
RLD Manufacturer	Novartis
NDA No.	020234
RLD Approval Date	March 25, 1996
Indication	Carbamazepine extended release tablets are indicated for use as an anticonvulsant drug. Evidence supporting efficacy of the drug as an anticonvulsant is derived from active drug-controlled studies that enrolled patients with partial seizures with complex symptomatology, generalized tonic-clonic seizures and mixed seizure patterns. Carbamazepine extended release tablets are also indicated in the treatment of the pain associated with true trigeminal neuralgia.

B. PK/PD Information[1]

Bioavailability Bioavailability is roughly 85%.

Food Effect Drug may be administered with food to minimize the GI side effects. Levy et al report that food may increase the bioavailability of carbamazepine.[2]

T_{max} & $T_{½}$ The T_{max} is estimated to be 3-12 hours. The elimination half life of carbamazepine is about 25-65 hours upon initial dosing. Because carbamazepine induces its own metabolism, the half-life is reduced to 12-17 hours on repeated doses after 3-5 weeks of a fixed dosage regimen.

Metabolism Carbamazepine is metabolized in the liver. Cytochrome P450 3A4 has been identified as the major isoform responsible for the formation of carbamazepine-10,11-epoxide metabolite (equipotent as an anticonvulsant to carbamazepine in animal studies).

Excretion After oral administration of ^{14}C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged Tegretol.

Relevant OGD or DBE History The Division of Bioequivalence (DBE) has reviewed the following documents for Carbamazepine Extended Release Tablets:

ANDAs:

- (b) (4) Application Withdrawn
- (b) (4) Application Withdrawn
- (b) (4) Application Withdrawn
- (b) (4) Not assigned
- (b) (4) Application Withdrawn

Controlled Documents:

- **00-172** (b) (4)
- **05-1506** (b) (4)
- **00-337** (b) (4)
- **02-146**
- **05-0047** (b) (4)
- **06-1082**
- **99-084** (b) (4)
- **05-1142** (b) (4)
- **05-0337**

Protocols:

- **01-056** (b) (4)

[1] All data taken from online PDR, Micromedex & Clinical Pharmacology Online.

[2] Levy RH, Pitlick WH, Troupin AS, et al. Pharmacokinetics of carbamazepine in normal man. Clin Pharmacol Ther 1975; 17:657-668.

Agency Guidance

The following are recommended to establish bioequivalence (BE) of Carbamazepine Extended Release tablets:

- A single-dose, two-way crossover fasting *in-vivo* bioequivalence study comparing Carbamazepine Extended Release tablets, 400mg, with the reference listed drug (RLD), Tegretol XR® (carbamazepine) tablets, 400mg.
- A single-dose, two-way crossover fed *in-vivo* bioequivalence study comparing Carbamazepine Extended Release tablets, 400mg, with the RLD, Tegretol XR® (carbamazepine) tablets, 400mg.
- Female subjects should not be enrolled in bioequivalence studies of carbamazepine if they are pregnant.
- Measure only the parent compound, carbamazepine.
- Carbamazepine Extended Release Tablets, 100mg and 200mg may be deemed bioequivalent per 21CFR 320.24(b)(6) to the RLD when the following conditions apply (1) Acceptable bioequivalence studies on the 400mg strength (2) Acceptable dissolution testing of the 100mg, 200mg and 400mg strengths and (3) Proportional similarity in the formulations of the 100mg, 200mg and 400mg strengths.
- Conduct comparative dissolution testing using 12 dosage units of all strengths of the test and reference products using the following USP method:

Medium: water
Volume: 1800ml for 400mg tablet, 900ml all lower strengths
Apparatus: USP Apparatus I (Basket)
Rotational speed: 100 rpm
Sampling Times: 3, 6, 12 and 24 hours until 75% dissolved
Specification:

Time (hrs)	Amount Dissolved
3	Between 10-35%
6	Between 35-65%
12	Between 65-90%
24	Not less than 75%

** Taken from online USP 29 monograph made official 4/1/2006**

Drug Specific Issues

The reviewer notes four withdrawn applications prior to this one.

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fasting pilot	Yes	1
Single-dose fed	Yes	1
Single-dose fed pilot	Yes	1
Steady-state	No	0
In vitro dissolution	Yes	3
Waiver requests	Yes	1
BCS Waivers	No	0
Vasoconstrictor Studies	No	0
Clinical Endpoints	No	0
Failed Studies	No	0
Amendments	No	0

It is noted that the firm analyzed assay samples for the metabolite (carbamazepine-10,11 epoxide). However, the reviewer did not provide details or analysis of the metabolite since it is not necessary to demonstrate bioequivalence of this product as noted in Agency Guidance.

D. Pre-Study Bioanalytical Method Validation

	Parent
Analyte name	Carbamazepine
Internal Standard	(b) (4)
Method description	LC/MS/MS with solid phase extraction
QC range	100-4000 ng/ml
Standard curve range	50-5000 ng/ml
Limit of quantitation	50.00 ng/ml
Average Recovery of Drug (%)	70.8%
Average Recovery of Int. Std (%)	84.3%
QC Intraday precision range (%CV)	0.82 to 1.56%
QC Intraday accuracy range (%)	102.4 to 106.3%
QC Interday precision range(%CV)	1.17 to 1.56%
QC Interday accuracy range (%)	96.0 to 102%
Bench-top stability (hrs)	13 hours 59 minutes @ RT
Stock stability	Analyte: 6 days @ 4°C (MeOH) IS: 9.1 days @ 4°C (MeOH)
Processed stability (hrs)	72 hours 6 minutes at RT
Freeze-thaw stability (cycles)	4 cycles
Long-term storage stability (days)	84 days @ -20°C
Dilution integrity (% accuracy)	(4 – Fold)
Specificity	Yes
SOPs submitted	Yes
Bioanalytical method is acceptable	Yes

*Control (blank matrix) human plasma with EDTA was purchased from the (b) (4) (b) (4).

E. In Vivo Studies

1. Single-Dose Fasting Bioequivalence Study (Pivotal)

Study Summary	
Study No.	Protocol/Project (# R05-1389)
Study Design	Randomized, single-dose, two-way crossover study under fasting conditions
No. of subjects enrolled	24
No. of subjects completing	21
No. of subjects analyzed (statistically)	20
Subjects (Healthy or Patients?)	Healthy male adults
Sex(es) included	Male: 20 Female: 0
Test product	Carbamazepine ER US Tablets 100mg
Reference product	Tegretol XR Tablets 100mg
Strength tested	100mg
Dose	2 x 100mg

Summary of Statistical Analysis (Fasted Study-Carbamazepine)§ Ln-Transformed Geometric Means				
Parameter	**Test**	**Reference**	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t} (ng*hr/ml)	107114.73	106079.17	100.98	(94.17-108.27)
AUC_{∞} (ng*hr/ml)	117116.55	116.217.17	100.77	(93.47-108.65)
C_{max} (ng/ml)	1369.94	1418.64	96.57	(91.70-101.69)

§These results were calculated and provided by the firm (n=20).

Summary of Statistical Analysis (Fasted Study-Carbamazepine-10,11 epoxide)§ Ln-Transformed Geometric Means				
Parameter	**Test**	**Reference**	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t} (ng*hr/ml)	7624.32	7580.32	100.58	(93.22-108.52)
AUC_{∞} (ng*hr/ml)	8541.18	8373.02	102.01	(95.72-108.71)
C_{max} (ng/ml)	90.35	92.59	97.59	(91.79-103.75)

§These results were calculated and provided by the firm (n=20).

Reanalysis of Study Samples (Fasting Study: R05-1389) †

Additional information in Appendix, Table 6 and Table 28

Fasting Bioequivalence Study R05-1389				
Reason for Reanalysis	**Number of Samples Reanalyzed**		**Number of Recalculated Values Used After Reanalysis**	
	Actual Number (% of Total Samples)		**Actual Number (% of Total Samples)**	
	Test N=541	**Reference N=543**	**Test N=541**	**Reference N=543**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Pharmacokinetic	0.0	0.0	0.0	0.0
Total	0	0	0	0

† A total of 1084 samples were analyzed in this study (8 samples were missing). The samples were extracted and analyzed in 11 runs (11 runs for individual subjects & 0 sample repeat runs). The firm explicitly stated that there were no individual subject repeats for any reasons.

Did use of recalculated plasma concentration data change study outcome? N/A

2. Single-Dose Fasting Pilot Study

Study No.	Protocol/Project (# R05-0184)
Study Design	Randomized, single dose, three-period, three-treatment, crossover bioequivalence study under fasting conditions.
No. of subjects enrolled	16
No. of subjects completing	15
No. of subjects analyzed (statistically)	15
Subjects (Healthy or Patients?)	Healthy male adults
Sex(es) included	Male 15 Female 0
Test Product A (Batch 780980)	Carbamazepine ER 400mg Tablet (Firm seeks approval of this formulation)
Test Product B (Batch 780988)	Carbamazepine ER 400mg Tablet
Reference Product (Treatment C)	Tegretol® XR 400mg Tablet
Strength tested	400mg
Dose	1 x 400mg

This study was designed to compare the relative bioavailability (rate and extent of absorption) of two formulations of 400mg Carbamazepine Extended Release Tablets by Taro Pharmaceuticals with that of 400mg Tegretol XR Tablets manufactured by Novartis

following a single dose (400mg) administered to healthy adult male volunteers under fasting conditions. The firm concluded that test product A (Batch 780980) and the RLD is bioequivalent under fasting conditions. However test product B (Batch 780988) and the RLD is ***not*** bioequivalent under fasting conditions. It is noted that the firm seeks approval of test product A (Batch 780980).

Summary of Statistical Analysis (Fasting Pilot Study-Carbamazepine)§ Ln-Transformed Geometric Means				
Parameter	**Test**	**Reference**	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t} (ng*hr/ml) (CxA)	167575.34	152292.94	110.03	(99.75-121.38)
AUC_{0-t} (ng*hr/ml) (CxB)	144637.55	152292.94	94.97	(86.10-104.76)
AUC_{∞} (ng*hr/ml) (CxA)	212051.21	190191.47	111.49	(100.84-123.27)
AUC_{∞} (ng*hr/ml) (CxB)	181427.35	190191.47	95.39	(86.08-105.71)
C_{max} (ng/ml) (CxA)	2733.45	2607.26	104.84	(94.26-116.61)
C_{max} (ng/ml) (CxB)	2299.63	2607.26	**88.20**	(**79.30**-98.10)

§These results were calculated and provided by the firm (n=15).

Summary of Statistical Analysis (Fasting Pilot Study-Carbamazepine-10,11 epoxide)§ Ln-Transformed Geometric Means				
Parameter	**Test**	**Reference**	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t} (ng*hr/ml) (CxA)	12693.21	11800.60	107.56	(95.56-121.08)
AUC_{0-t} (ng*hr/ml) (CxB)	10444.30	11800.60	88.51	(78.63-99.63)
AUC_{∞} (ng*hr/ml) (CxA)	17683.20	16742.86	105.62	(90.81-122.84)
AUC_{∞} (ng*hr/ml) (CxB)	15390.42	16742.86	91.92	(79.04-106.91)
C_{max} (ng/ml) (CxA)	195.95	186.00	105.35	(92.32-120.21)
C_{max} (ng/ml) (CxB)	159.08	186.00	85.53	(74.95-97.59)

§These results were calculated and provided by the firm (n=15).

Fasting Pilot Bioequivalence Study R05-0184				
Reason for Reanalysis	**Number of Samples Reanalyzed**		**Number of Recalculated Values Used After Reanalysis**	
	Actual Number (% of Total Samples)		**Actual Number (% of Total Samples)**	
	Test N=344	**Reference N=345**	**Test N=344**	**Reference N=345**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Pharmacokinetic	0.0	0.0	0.0	0.0
Low IS Response	1 (0.29%)	-	1 (0.29%)	-
Total	1 (0.29%)	-	1 (0.29%)	-

† A total of 1033 samples were analyzed in this study (2 samples were missing) from 15 subjects. The samples were extracted and analyzed in 12 runs (10 runs for individual

subjects & 2 sample repeat runs). The repeat was conducted for a valid analytical reason and should not alter the outcome of the study.

3. Single-Dose Fed Bioequivalence Study (Pivotal)

Study No.	Protocol/Project (# R04-1364)
Study Design	Randomized, single-dose, two-way crossover study under non-fasting conditions
No. of subjects enrolled	36
No. of subjects completing	34
No. of subjects analyzed (statistically)	34
Subjects (Healthy or Patients?)	Healthy male adults
Sex(es) included	Male 34 Female 0
Test product	Carbamazepine ER US Tablets 400mg
Reference product	Tegretol XR Tablets 400mg
Strength tested	400mg
Dose	1 x 400mg

Summary of Statistical Analysis (Fed Study-Carbamazepine)§ Ln-Transformed Geometric Means				
Parameter	**Test**	**Reference**	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t} (ng*hr/ml)	254704.30	221816.62	114.83	(110.75-119.05)
AUC_{∞} (ng*hr/ml)	273875.74	239196.08	114.50	(110.37-118.78)
C_{max} (ng/ml)	3492.33	3129.65	111.59	(108.88-114.36)

§These results were calculated and provided by the firm (n=34).

Summary of Statistical Analysis (Fed Study-Carbamazepine-10,11 epoxide)§ Ln-Transformed Geometric Means				
Parameter	**Test**	**Reference**	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t} (ng*hr/ml)	23521.81	19848.94	118.50	(114.62-122.52)
AUC_{∞} (ng*hr/ml)	25651.32	21434.20	119.67	(116.15-123.31)
C_{max} (ng/ml)	280.97	235.88	119.12	(114.98-123.40)

§These results were calculated and provided by the firm (n=34).

Reanalysis of Study Samples (Fed Study: R04-1364) †
Additional information in Appendix, Table 6 and Table 28

Non-Fasting Bioequivalence Study R04-1364				
Reason for Reanalysis	**Number of Samples Reanalyzed**		**Number of Recalculated Values Used After Reanalysis**	
	Actual Number (% of Total Samples)		**Actual Number (% of Total Samples)**	
	Test N=899	**Reference N=901**	**Test N=899**	**Reference N=901**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Pharmacokinetic	0.0	0.0	0.0	0.0
Above the Limit of Quantitation	6 (0.67%)	-	6 (0.67%)	-
Total	6 (0.67%)	-	6 (0.67%)	-

† A total of 1793 samples were analyzed in this study (27 samples were missing) from 35 subjects. The samples were extracted and analyzed in 20 runs (19 runs for individual subjects & 1 sample repeat run). These repeats were conducted for valid analytical reasons and should not alter the outcome of the study.

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

4. Single Dose Fed Pilot Study

Study No.	Protocol/Project (# R05-0185)
Study Design	Randomized, single dose, three-period, three-treatment, crossover bioequivalence study under fed conditions.
No. of subjects enrolled	16
No. of subjects completing	16
No. of subjects analyzed (statistically)	16
Subjects (Healthy or Patients?)	Healthy male adults
Sex(es) included	Male 16 Female 0
Test Product A (Batch 780980)	Carbamazepine ER 400mg Tablet (Firm seeks approval of this formulation)
Test Product B (Batch 780988)	Carbamazepine ER 400mg Tablet
Reference Product (Treatment C)	Tegretol® XR 400mg Tablet
Strength tested	400mg
Dose	1 x 400mg

This study was designed to compare the relative bioavailability (rate and extent of absorption) of two test formulations of 400mg Carbamazepine ER Tablets by Taro Pharmaceuticals with that of 400mg Tegretol XR Tablets manufactured by Novartis following a single dose (400mg) administered to healthy adult male volunteers under fed conditions. The firm concluded that both test product A (Batch 780980) and test product B (Batch 780988) are bioequivalent when compared to the RLD under fed conditions. The reviewer notes that the confidence intervals for the active metabolite do not fall within 80-125% range applied to parent compounds. The firm submitted a larger fed study (# R04-1364) in which the point estimates and confidence intervals for both the parent compound and the metabolite met bioequivalence criteria.

Summary of Statistical Analysis (Fed Pilot Study-Carbamazepine)§ Ln-Transformed Geometric Means				
Parameter	**Test**	**Reference**	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t} (ng*hr/ml) (CxA)	215647.87	182194.05	118.36	**(114.64-122.21)**
AUC_{0-t} (ng*hr/ml) (CxB)	193600.94	182194.05	106.26	(102.92-109.71)
AUC_{∞} (ng*hr/ml) (CxA)	267046.59	228001.33	117.13	**(112.38-122.07)**
AUC_{∞} (ng*hr/ml) (CxB)	249474.53	228001.33	109.42	(104.99-114.03)
C_{max} (ng/ml) (CxA)	3658.33	3204.42	114.16	**(109.97-118.52)**
C_{max} (ng/ml) (CxB)	3110.63	3204.42	97.07	(93.50-100.78)

§These results were calculated and provided by the firm (n=16).

Summary of Statistical Analysis (Fed Pilot Study-Carbamazepine-10,11 epoxide)§ Ln-Transformed Geometric Means				
Parameter	**Test**	**Reference**	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t} (ng*hr/ml) (CxA)	15658.05	12453.21	125.74	**(120.20-131.52)**
AUC_{0-t} (ng*hr/ml) (CxB)	13172.25	12453.21	105.77	(101.1-110.66)
AUC_{∞} (ng*hr/ml) (CxA)	21628.04	18000.54	120.15	**(111.09-129.96)**
AUC_{∞} (ng*hr/ml) (CxB)	19260.36	18000.54	107.00	(98.85-115.82)
C_{max} (ng/ml) (CxA)	247.78	199.13	124.43	**(118.79-130.35)**
C_{max} (ng/ml) (CxB)	203.29	199.13	102.09	(97.44-106.96)

§These results were calculated and provided by the firm (n=16).

Since this a pilot study, details of this study are not provided in appendix.

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects[1] No. (M/F) Type Age: Mean (Range)	Arithmetic Mean (± SD) Pharmacokinetic Parameters					
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng-hr/mL)	$AUC_{0-\infty}$ (ng-hr/mL)	$t_{1/2}$ (hr)	k_e (1/hr)
R05-0184	**A Relative Bioavailability Pilot Study of 400 mg Carbamazepine Extended-Release Tablets Under Fasting Conditions**	Open, randomized, three-way crossover, single 400 mg dose	Test: Carbamazepine CR US Tablets 400 mg (F3), Oral [Batch No. 780980] Reference: Tegretol® - XR Tablets 400 mg, Oral [Lot No. F4109]	15 (15/0) Healthy male subjects 24.27 yr (18 - 42 yr)	2793.563 ± 477.113	25.400	172214.503 ± 36782.119	219057.870 ± 55511.314	38.268	0.019
					2667.669 ± 617.995	25.600	155755.687 ± 35857.980	194924.824 ± 49923.459	36.831	0.019
R05-0185	**A Relative Bioavailability Pilot Study of 400 mg Carbamazepine Extended-Release Tablets Under Non-Fasting Conditions**	Open, randomized, three-way crossover, single 400 mg dose	Test: Carbamazepine CR US Tablets 400 mg (F3), Oral [Batch No. 780980] Reference: Tegretol® - XR Tablets 400 mg, Oral [Lot No. F4109	16 (16/0) Healthy male subjects 24.44 yr (18 - 41 yr)	3673.584 ± 418.620	15.063	217813.408 ± 34938.827	273302.827 ± 61532.538	37.429	0.020
					3213.063 ± 363.241	17.250	183349.440 ± 24725.882	233674.764 ± 57252.698	38.322	0.020

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects[1] No. (M/F) Type Age: Mean (Range)	Arithmetic Mean (± SD) Pharmacokinetic Parameters					
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng-hr/mL)	$AUC_{0-\infty}$ (ng-hr/mL)	$t_{1/2}$ (hr)	k_e (1/hr)
R04-1364	**A Relative Bioavailability Study of 400 mg Carbamazepine Extended-Release Tablets Under Non-Fasting Conditions**	Open, randomized, two-way crossover, single 400 mg dose	Test: Carbamazepine CR US Tablets 400 mg (F3), Oral [Batch No. 780980] Reference: Tegretol® - XR Tablets 400 mg, Oral [Lot. No F4109]	34 (34/0) Healthy male subjects 29.53 yr (19 - 57 yr)	3532.46 ± 529.29	21.29	260296.35 ± 51644.51	280602.69 ± 59242.05	38.73	0.0186
					3185.76 ± 569.10	19.26	228092.79 ± 48925.16	247020.65 ± 57313.18	41.64	0.0174
R05-1389	**A Relative Bioavailability Study of 100 mg Carbamazepine Extended-Release Tablets Under Fasting Conditions**	Open, randomized, two-way crossover, single 200 mg dose	Test: Carbamazepine CR US Tablets (F3) 100 mg, Oral [Batch No. 781064] Reference: Tegretol® - XR 100 mg Tablets, Oral [Lot No. F4089]	20 (20/0) Healthy male subjects 28.80 yr (19 - 47 yr)	1386.09 ± 220.47	26.00	109534.16 ± 23910.76	120450.88 ± 29440.84	42.81	0.0167
					1433.37 ± 215.13	25.30	108300.25 ± 22366.68	119326.25 ± 28374.94	44.28	0.0163

F. Formulation

Location in appendix	Page 47
Are inactive ingredients within IIG limits?	Yes
If no, list ingredients outside of limits	N/A
If a tablet, is the product scored?	No
If yes, which strengths are scored?	N/A
Is scoring of RLD the same as test?	Yes
Is the formulation acceptable?	Yes
If not acceptable, why?	N/A

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	USP
Medium	Water (37°C)
Volume (mL)	1800ml for 400mg tablet, 900 ml all lower strengths
USP Apparatus type	Apparatus I (basket)
Rotation (rpm)	100 rpm
Firm's proposed specifications	Hour 3: (b) (4) Hour 6: Hour 12: Hour 24: NLT 75%
USP-recommended specifications	Hour 3: 10%-35% Hour 6: 35%-65% Hour 12: 65%-90% Hour 24: NLT 75%
F2 metric calculated?	Yes
If no, reason why F2 not calculated	N/A
Is method acceptable?	No
If not then why?	Missing dissolution data comparing test versus reference in three different media.

*The DBE has not previously reviewed the dissolution data. Upon review it was determined that certain dissolution tests (test versus reference) of each strength in three different media were lacking. These are recommended to determine the dose dumping capacity test of the dosage form. The dissolution testing is incomplete.

H. Waiver Request(s)

Strengths for which waivers are requested	200mg
Regulation cited	21 CFR §320.22(d)(2) DBE will use §320.24(b)(6)
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	No
Waivers granted?	No
If not then why?	Waiver is pending acceptable dissolution testing

I. Deficiency Comments

1. The DBE recommends that the firm conduct additional dissolution testing. A total of nine additional tests should be performed, consisting of each strength of test versus reference in three different media (pH 1.2, 4.5 & 6.8). For instance, test 100mg versus reference 100mg at pH 1.2, 4.5 and 6.8 should be conducted and the testing repeated for the 200mg and 400mg strengths.

2. In study #R05-1389, the number of tablets given in this fasting study was reported as 2x100mg in the clinical report and protocol yet in other documents in the submission it was reported as 1x100mg. The firm should clarify the dose each subject received in each period of this study.

3. For future reference, the DBE does not currently recommend measurement of a metabolite (10,11-epoxide metabolite) for carbamazepine extended release tablets.

J. Recommendations

1. The bioequivalence study (#R05-1389) under fasting conditions conducted by the PRACS Institute on behalf of Taro Phamaceuticals on its carbamazepine extended release tablets, 100mg, Lot #781064, comparing it to Novartis' Tegretol®-XR, 100mg, Lot #F4089, is incomplete due to the deficiency noted above.

2. The pilot bioequivalence study (#R05-0184) under fasting conditions conducted by the PRACS Institute on behalf of Taro Phamaceuticals on its carbamazepine extended release tablets, 400mg, Lot #780980 comparing it to Novartis' Tegretol®-XR, 400mg, Lot #F4109, is acceptable.

3. The bioequivalence study (#R04-1364) under fed conditions conducted by the PRACS Institute on behalf of Taro Phamaceuticals on its carbamazepine extended release tablets, 400mg, Lot #780980, comparing it to Novartis' Tegretol®-XR, 400mg, Lot #F4109, is acceptable.

4. The *in vitro* dissolution testing conducted by the firm on its carbamazepine extended release tablets, 400mg-lot #780980, carbamazepine extended release tablets, 200mg-lot #781066 and carbamazepine extended release tablets, 100mg-lot #781064 comparing it to Tegretol®-XR 400mg (carbamazepine extended release tablet)-lot #F4109, Tegretol®-XR 200mg (carbamazepine extended release tablet)-lot #F0219 and Tegretol®-XR 100mg (carbamazepine extended release tablet)-lot #F4089 is incomplete.

5. The dissolution testing should be conducted using the following USP dissolution method: 900ml (1800ml for 400mg tablets) of water (37°C) using USP apparatus I (basket) at 100 rpm.

6. The test 400mg, 200mg and 100mg tablets are proportionally formulated. The DBE may deem lower strengths of the test product bioequivalent to the RLD based on CFR 320.24(b)(6), upon resolution of the cited deficiencies.

   The firm should be informed of the deficiencies and recommendations.

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information	
Study Number	Protocol/Project #: R05-1389
Study Title	A Relative Bioavailability Study of 100mg Carbamazepine Extended Release Tablets under Fasting Conditions
Clinical Site	PRACS Institute Ltd. 625 Demers Ave East Grand Forks, MN 57621
Principal Investigator	James D. Carlson, Pharm.D.
Study/Dosing Dates	Period I: October 29th, 2005 Period II: November 19th, 2005
Analytical Site	PRACS Institute Ltd. 4801 Amber Valley Parkway Fargo ND 58104 (701) 239-4750
Analytical Director	(b) (6)
Analysis Dates	December 1st – 5th 2005
Storage Period	38 days (stability demonstrated for 84 days at -20°C)

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Carbamazepine ER US Tablets 100mg	Tegretol XR Tablets 100mg
Manufacturer	Taro Pharmaceutical Industries Ltd.	Novartis Pharma GmbH
Batch/Lot No.	781064	F4089
Manufacture Date	8/2005	N/A
Expiration Date	N/A	4/2008
Strength	100mg	100mg
Dosage Form	Extended Release Tablet	Extended Release Tablet
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	102.4%	101.8%
Content Uniformity	102.4% (RSD 1.1%)	N/A
Formulation	See Appendix	
Dose Administered*	2x100mg	2x100mg
Route of Administration	Oral	

* The firm has been asked to clarify whether the dose administered was 1 x 100 mg tablet or 2 x 100 mg tablets.

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	21 days
Randomization Scheme	AB: 1, 3, 5, 7, 8, 10, 15, 16, 17, 20, 22, 24. BA: 2, 4, 6, 9, 11, 12, 13, 14, 18, 19, 21, 23.
Blood Sampling Times	0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 22, 24, 27, 30, 36, 48, 72, 96, 120, 144 and 168 hours.
Blood Volume Collected/Sample	6 mL/sample and 26 samples collected per period in vacutainers containing EDTA. Approximately 312ml of total blood was obtained from each subject during the course of the study.
Blood Sample Processing/Storage	The samples were centrifuged at 2400 rpm for 15 minutes at 4°C. The plasma was then pipetted into polypropylene tubes, frozen and stored at -20°C or colder until transferred for analysis.
IRB Approval	Yes, originally approved 10/26/2005
Informed Consent	Yes, approved 10/26/2005
Subjects Demographics	See Table 1
Length of Fasting	Following an overnight fast of about ten hours, the subjects were dosed with 240ml of room temperature water. The subjects continued to fast until 4.25 hours after dosing. Clear fluids, such as water were allowed during fasting.
Length of Confinement	≈46.5 hours (10.5 hours before dosing and 36 hours after)
Safety Monitoring	To ensure only healthy subjects were enrolled, all subjects underwent pre-trial screening consisting of a physical examination, medical & medication history, ECG, sitting HR, RR, temperature & BP. Subjects underwent laboratory evaluation which included hematology, clinical chemistry, HIV, HepB, HepC, urinalysis and urine drug screen. During the study, a sitting blood pressure and HR were measured prior to dosing and at 12, 24 and 36 hours post dose. Upon exiting the study, subjects underwent another physical examination and vital sign measurement. Exit labs consisted of hematology and clinical chemistry.

Comments on Study Design: The reviewer notes that the DBE typically recommends a fasting study to be carried out on the highest strength (400mg) for carbamazepine extended release tablets. This sponsor chose to conduct the study using a single dose of 2x100mg of carbamazepine extended tablets. The firm provided the following rationale to support this decision (volume 15, page 2156), "Since the carbamazepine 400mg, 200mg and 100mg extended release tablets are proportionally similar in their active and

inactive ingredients and in the drug release mechanism, a waiver can be granted based upon dissolution profiles. The dissolution profiles in all three media were not similar (based upon the f2 test) between the highest and the lowest strengths. Due to the fact that the *in vitro* dissolution is not always predictive of *in-vivo* behavior in extended release products, Taro decided to conduct a fasted study on the 100mg strength to confirm bioequivalence." The reviewer concludes, the design of the fasting BE study is acceptable to establish the bioequivalence of the 100mg carbamazepine extended release dosage form under fasting conditions.

b) Clinical Results

Table 1 Demographics of Subjects Completing BE Study #R05-1389 (Fast)

Fasting Bioequivalence Study R05-1389		
	Treatment Groups	
	Test Product N=20	**Reference Product N=20**
Age (years)		
Mean ± SD	28.80 ± 9.90	28.80 ± 9.90
Range	19 - 47	19 - 47
Groups		
<18	-	-
18-39	15 (75.00%)	15 (75.00%)
40-64	5 (25.00%)	5 (25.00%)
65-75	-	-
>75	-	-
Sex		
Female	-	-
Male	20 (100.00%)	20 (100.00%)
Hispanic or Latino		
Race		
N	-	-
A	-	-
B	-	-
I	-	-
W	-	-
Not Hispanic or Latino		
Race		
N	1 (5.00%)	1 (5.00%)
A	-	-
B	-	-
I	-	-
W	19 (95.00%)	19 (95.00%)

N=American Indian or Alaskan native, A=Asian, B=Black or African American, I=Native Hawaiian or other Pacific Islander, W=White.

Table 2 Dropout Information

Subject No	Reason	Period	Replaced?
Subject #13 (b) (6)	Voluntarily withdrew from study participation prior to period II check-in for personal reasons.	washout	No
Subject #14 (b) (6)	Voluntarily withdrew from study participation prior to period II check-in for personal reasons.	washout	No
Subject #16 (b) (6)	Voluntarily withdrew from study participation prior to study hour 1 of period I for personal reasons.	Period I	No

Table 3 Study Adverse Events (Study #R05-1389-Fasting) ‡

Body System Adverse Event	Reported Incidence by Treatment Group Fasting Bioequivalence Study R05-1389	
	Test (N=22) N (%)	**Reference (N=23)** N (%)
Vomiting	1 (4.55%)	1 (4.35%)
Contusion	1 (4.55%)	1 (4.35%)
Dizziness	2 (9.09%)	1 (4.35%)
Headache	2 (9.09%)	2 (8.70%)
Total Adverse Events	**6**	**5**

‡Note: There were no serious adverse events reported. There were a total of 11 adverse events reported by 4 subjects over the course of the study. The most frequently occurring AE following the oral administration of the test product were headache and dizziness. The most common AE following the oral administration of the reference product was headache. There were five adverse events considered to be probably related, three were unrelated, one was remotely related and two were possibly related to the drug.

Table 4 Protocol Deviations

Type	Subject #s (Test)	Subject #s (Ref.)
Missing blood samples for 8 subjects.	5	3
Subject #11 (b) (6) and #24 (b) (6) were given ibuprofen 400mg early in both periods of the study. Subject #11 (b) (6) took ibuprofen in both periods.	2	1
There were a total of 8 late blood draws during the study. The times ranged from 2-6 minutes late.	-	-
Total:	**7**	**4**

Comments on Dropouts/Adverse Events/Protocol Deviations:
The number of dropouts, adverse events and protocol deviations are not significant to compromise the integrity of the study.

c) Bioanalytical Results

Table 5 Assay Quality Control – Within Study

	Carbamazepine			
QC Conc. (ng/mL)	100.00	2000.00	4000.00	250.00 (Blind)

Inter day Precision (%CV)	2.18			1.91			1.99			2.11	
Inter day Accuracy (%)	99.8			101.1			99.9			100.8	
Cal. Standards Conc. (ng/ml)	50	100	250	500	1000	2000	2800	3500	4200	5000	n/a
Inter day Precision (%CV)	2.41	1.61	1.81	1.14	1.56	1.57	1.24	1.72	1.74	1.76	n/a
Inter day Accuracy (%)	97.6	100.2	101.3	100.0	101.1	100.3	100.4	99.8	99.2	100 2	n/a
Linearity Range (R^2 values)	0.9990-0.9999										

Comments on Study Assay Quality Control: Acceptable. The QC and calibration standard concentrations are appropriate relative to the concentrations of the study samples.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serial, subject #s 1,2,3,4,5 & 6.

Comments on Chromatograms: The chromatography is acceptable.

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

SOP No.	Date of SOP	SOP Title
#405_03 Version 01	8/15/2005	Calibration/Standard Curves for Studies
#405_04 Version 01	8/15/2005	Quality Control Samples for Studies
#405_05 Version 01	8/15/2005	Study Subject Sample Analysis

Table 7 Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays: The study assays are acceptable.

d) Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 11 and Figure 1

Carbamazepine (n=20)

	Test	CV1	Ref	CV2	T/R
PARAMETER					
AUCT (ng*hr/ml)	109534.88	21.83	108461.03	20.37	1.01
AUCI (ng*hr/ml)	120454.75	24.44	119274.00	23.88	1.01
CMAX (ng/ml)	1386.09	15.91	1433.37	15.01	0.97
TMAX (hr)	26.00	26.76	25.30	24.50	1.03
KE (hr^{-1})	0.02	18.05	0.02	19.81	1.03
THALF (hr)	42.82	18.12	44.29	21.57	0.97

Table 9 Least Squares Geometric Means and 90% Confidence Intervals

Summary of Statistical Analysis (Fasted Study-Carbamazepine)§ N=20				
Parameter	**Test**	**Reference**	**Point Estimate**	**90% Confidence Interval**
$LAUC_{0-t}$ (ng*hr/ml)	107115.53	106316.83	100.75	(94.09-107.88)
$LAUC_{\infty}$ (ng*hr/ml)	117119.72	116132.73	100.84	(93.50-108.78)
LC_{max} (ng/ml)	1369.94	1418.64	96.57	(91.70-101.69)

§These results were calculated by the reviewer and corroborate those reported by the firm. See comments under "Pharmacokinetic Analysis" for further details.

Table 10 Additional Study Information

	Carbamazepine
Root mean square error, LAUCT	0.124649
Root mean square error, LAUCI	0.138017
Root mean square error, LCmax	0.094228
Ke and AUC_{∞} determined for how many subjects?	20
Do you agree or disagree with firm's decision?	agree
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	0
-first measurable drug concentration as Cmax	0
Were the subjects dosed as more than one group?	no

Comments on Pharmacokinetic Analysis:
According to the firm, "Subject #24 (b) (6) was excluded from the statistical analysis secondary to vomiting following dose administration within the labeled dosing interval for Tegretol XR tablets 100mg." Subject #24 vomited on the dosing day (10/29/05) at 1755 and was therefore excluded from the final statistical analysis. The reviewer agrees with the firm's decision to exclude data from subject #24 in the final analysis. A second subject, (#22 (b) (6) vomited on 11/21/05 at 2330, over 60 hours after dosing. The firm retained the data from this subject for their statistical analysis. When the reviewer excluded this subject from the analysis, the outcome of the study was unchanged. The reviewer agrees with the decision to retain subject #22 in the final analysis. There were no subjects with detectable predose plasma concentrations or first reportable plasma concentration as the C_{max}.

Note subject #13, #14 and #16 did not complete the study and were not included in the final statistical analysis.

The RMSE are relatively small suggesting the carbamazepine extended release tablet formulation has pharmacokinetics with low variability with respect to intra-subject performance.

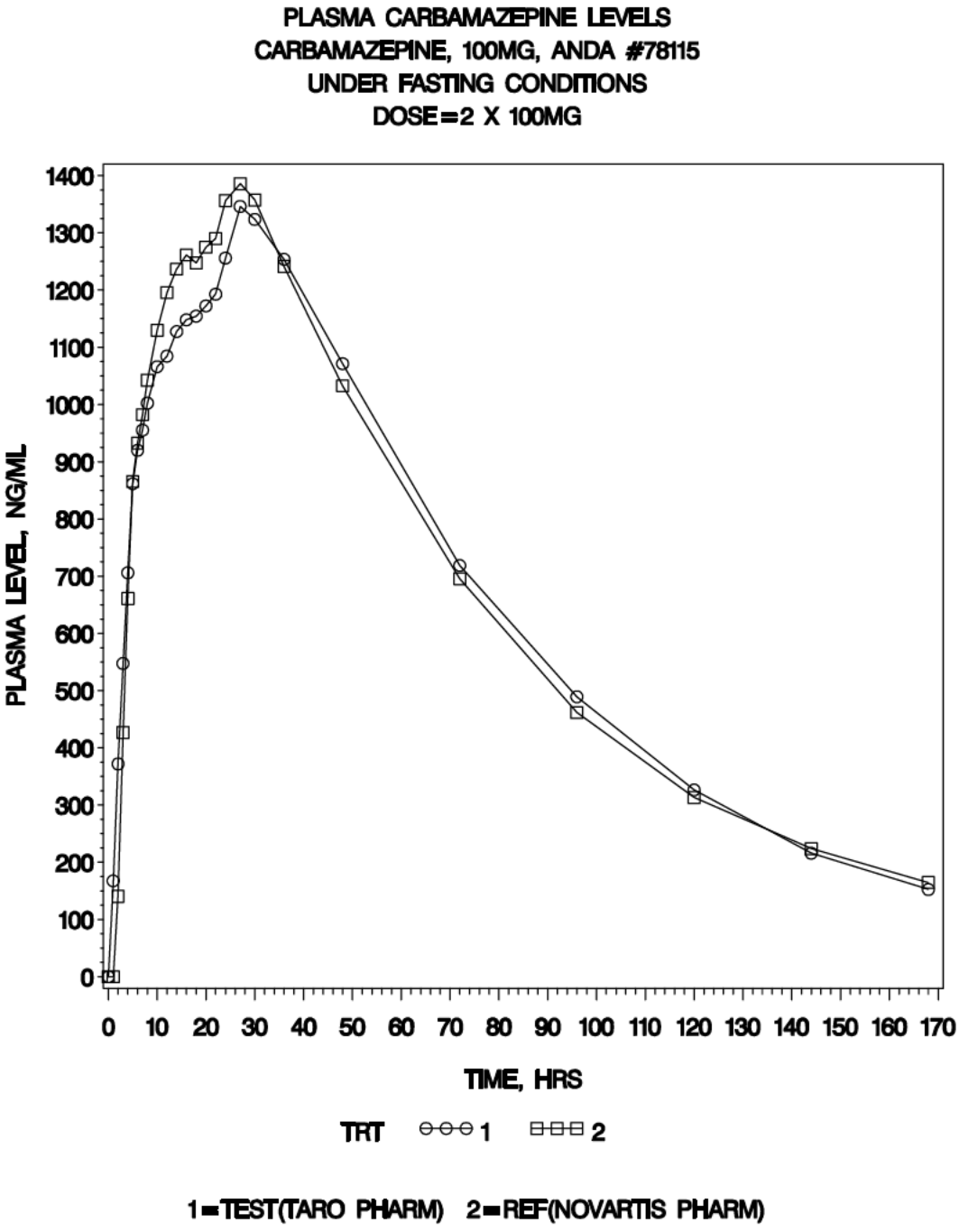
Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:
The bioequivalence study is incomplete pending clarification of the dose administered to the subjects.

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

Carbamazepine (n=20)

	MEAN1	CV1	MEAN2	CV2	RMEAN12
TIME HR					
0	0.00	.	0.00	.	.
1	167.54	65.67	0.00	.	.
2	371.98	50.43	140.69	45.59	2.64
3	547.48	39.20	426.76	27.49	1.28
4	706.00	32.23	660.92	25.63	1.07
5	861.67	24.02	865.72	21.31	1.00
6	920.04	23.47	932.61	19.38	0.99
7	955.20	22.62	982.05	16.98	0.97
8	1002.60	21.62	1042.51	15.13	0.96
10	1066.19	20.60	1129.76	15.54	0.94
12	1084.59	18.30	1195.78	14.62	0.91
14	1127.58	16.71	1236.70	13.06	0.91
16	1148.04	16.23	1261.36	14.33	0.91
18	1154.58	17.90	1247.63	13.67	0.93
20	1172.33	17.03	1275.19	14.73	0.92
22	1192.95	16.19	1290.31	15.29	0.92
24	1256.00	16.31	1356.68	16.92	0.93
27	1346.16	17.02	1386.00	16.64	0.97
30	1323.52	19.57	1357.71	16.13	0.97
36	1253.81	20.36	1241.60	17.25	1.01
48	1071.36	22.27	1032.72	19.42	1.04
72	718.72	27.20	695.49	25.58	1.03
96	489.29	33.74	461.92	29.24	1.06
120	326.53	36.72	313.21	35.66	1.04
144	215.78	43.54	223.83	41.14	0.96
168	152.46	51.41	164.69	41.56	0.93

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



2. Single-dose Fasting Pilot Bioequivalence Study

a) Study Design

Study Information	
Study Number	Protocol/Project #: R05-0184
Study Title	A Relative Bioavailability Pilot Study of 400mg Carbamazepine Extended Release Tablets under Fasting Conditions
Clinical Site	PRACS Institute Ltd. 625 Demers Ave East Grand Forks, MN 57621
Principal Investigator	James D. Carlson, Pharm.D.
Study/Dosing Dates	Period I: February 19th, 2005 Period II: March 12th, 2005 Period III: April 2nd 2005
Analytical Site	PRACS Institute Ltd. 4801 Amber Valley Parkway Fargo ND 58104 (701) 239-4750
Analytical Director	(b) (6) Associate Director for Bioanalytical Services
Analysis Dates	April 12th-29th 2005
Storage Period	70 days (stability demonstrated for 84 days at -20°C)

Treatment ID	A	B*	C
Test or Reference	Test	Test	Reference
Product Name	Carbamazepine ER US Tablets 400mg	Carbamazepine ER US Tablets 400mg	Tegretol XR Tablets 400mg
Manufacturer	Taro Pharmaceutical Industries Ltd.	Taro Pharmaceutical Industries Ltd.	Novartis Pharma GmbH
Batch/Lot No.	780980	780988	F4109
Manufacture Date	1/2005	1/2005	N/A
Expiration Date	N/A	N/A	5/2007
Strength	400mg	400mg	400mg
Dosage Form	Extended Release Tablet	Extended Release Tablet	Extended Release Tablet
Batch Size	(b) (4)	Not provided*	N/A
Production Batch Size		Not provided*	N/A
Potency	100.9%	Not provided*	101.6%
Content Uniformity	100.9% (RSD 0.2%)	Not provided*	N/A
Formulation	See Appendix	Not applicable*	See Appendix
Dose Administered	400mg	400mg	400mg
Route of Administration	Oral		

* Treatment B is a test formulation used in the pilot study, not intended for marketing, therefore, batch size, potency, and content uniformity of treatment B is not necessary.

No. of Sequences	3
No. of Periods	3
No. of Treatments	3
No. of Groups	1
Washout Period	21 days
Randomization Scheme	ABC: 1,10,12,14,16 BCA: 2,5,7,11,15 CAB: 3,4,6,8,9,13
Blood Sampling Times	0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 22, 24, 27, 30, 36, 48, 72 and 96 hours.
Blood Volume Collected/Sample	7 mL/sample and 23 samples collected per period in vacutainers containing EDTA. Approximately 483ml of total blood was obtained from each subject during the course of the study.
Blood Sample Processing/Storage	The samples were centrifuged at 2400 rpm for 15 minutes at 4°C. The plasma was then pipetted into polypropylene tubes, frozen and stored at -20°C or colder until transferred for analysis.
IRB Approval	Yes, originally approved 2/16/2005
Informed Consent	Yes, approved 2/16/2005
Subjects Demographics	See Table 1
Length of Fasting	Following an overnight fast of about ten hours, the subjects were dosed with 240ml of room temperature water. The subjects continued to fast until 4.25 hours after dosing. Clear fluids, such as water were allowed during fasting.
Length of Confinement	≈40 hours (10 hours before dosing and 30 hours after)
Safety Monitoring	To ensure only healthy subjects were enrolled, all subjects underwent pre-trial screening consisting of a physical examination, medical & medication history, ECG, sitting HR, RR, temperature & BP. Subjects underwent laboratory evaluation which included hematology, clinical chemistry, HIV, HepB, HepC, urinalysis and urine drug screen. During the study, a sitting blood pressure and HR were measured prior to dosing and at 12, 24 and 30 hours post dose. Upon exiting the study, subjects underwent vital sign measurement. Exit labs consisted of hematology and clinical chemistry if requested by the clinical investigator.

Comments on Study Design: The design of the fasting BE study is acceptable to establish the bioequivalence of the most suitable of two test dosage forms. Based on the outcome of the study, the firm may use this pilot study as evidence of bioequivalence of the test 400mg carbamazepine extended release dosage form (Batch #780980) under fasting conditions.

e) Clinical Results

Table 12 Demographics of Subjects Completing BE Study #R04-0184 (Fasting Pilot)

Fasting Bioequivalence Study R04-0184		
	Treatment Groups	
	Test A (Batch No. 780980) N=15	**Reference Product N=15**
Age (years)		
Mean ± SD	24.27 ± 7.39	24.27 ± 7.39
Range	18 - 42	18 - 42
Groups		
<18	-	-
18-39	14 (93.33%)	14 (93.33%)
40-64	1 (6.67%)	1 (6.67%)
65-75	-	-
>75	-	-
Sex		
Female	-	-
Male	15 (100.00%)	15 (100.00%)
Race		
Asian	-	-
Black	-	-
Caucasian	15 (100.00%)	15 (100.00%)
Hispanic	-	-
Native American	-	-
Other	-	-

Table 13 Dropout Information

Subject No	**Reason**	**Period**	**Replaced?**
Subject #05 (b) (6)	Voluntarily withdrew prior to period II dosing for personal reasons.	washout	No

Table 14 Study Adverse Events (Fast Pilot: Study #R05-0184)‡

Body System Adverse Event	**Reported Incidence by Treatment Group** Fasting Pilot Bioequivalence Study R05-0184		
	Test (N=15) (Batch 780980) N (%)	**Test (N=16) (Batch 780988)** N(%)	**Reference (N=15)** N (%)
Dermatitis	-	-	1 (6.67%)
Dizziness	-	3 (18.75)	
Syncope	-	1 (6.25)	
Total Adverse Events	**0**	**4**	**1**

‡Note: There were no serious adverse events reported. There were a total of 5 events reported among all subjects who received all three dosage forms. There were no adverse events reported during the administration of carbamazepine extended release tablets 400mg batch #780980. One subject experienced dermatitis during the administration of the RLD and there were four adverse events reported by subjects receiving carbamazepine extended release tablets 400mg batch #780988. This batch did not demonstrate bioequivalence. Dermatitis, dizziness and syncope are believed to be unrelated to the drug therapy.

Table 15 Protocol Deviations

Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Missing blood samples for 2 subjects.	2	0
There were a total of 9 late blood draws during the study. The times ranged from 1-8 minutes late.	-	-
Total:	2	0

Comments on Adverse Events/Protocol Deviations:
The number of dropouts, adverse events and protocol deviations are not significant to compromise the integrity of the study.

b) Bioanalytical Results

Table 16 Assay Quality Control – Within Study

	Carbamazepine										
QC Conc. (ng/mL)	100			2000			4000			250 (Blind)	
Inter day Precision (%CV)	2.3			2.1			2.3			2.1	
Inter day Accuracy (%)	98.9			100.7			98.8			98.1	
Cal. Standards Conc. (ng/ml)	50	100	250	500	1000	2000	3500	5000	n/a	n/a	n/a
Inter day Precision (%CV)	3.17	1.86	2.84	2.44	2.44	1.94	2.82	2.22	n/a	n/a	n/a
Inter day Accuracy (%)	98.5	101.2	99.5	99.8	100.8	100.8	99.6	99.9	n/a	n/a	n/a
Linearity Range (R^2 values)	0.9965-0 9998										

Comments on Study Assay Quality Control: Acceptable. The QC and calibration standard concentrations are appropriate relative to the concentrations of the study samples.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serial, subject #s 1,2,3 & 4.

Comments on Chromatograms: The chromatography is acceptable.

Table 17 SOP's dealing with analytical repeats and others

SOP No.	Date of SOP	SOP Title
#113-01	3/15/2005	Calibration/Standard Curves for Studies
#004-17	3/15/2005	Quality Control Samples for Studies
#007-25	3/18/2005	Study Subject Sample Analysis

Table 18 Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays: Acceptable.

c) Pharmacokinetic Results

Table 19 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 33 and Figure 2

Carbamazepine (n=15)

	MEAN1 Test Batch 780980	SD1	MEAN2 Test Batch 780988	SD2	MEAN3 Reference Listed Drug	SD3	RMEAN12	RMEAN13	RMEAN23
PARAMETER									
AUCI	219057.87	55511.31	183401.39	49392.26	194924.82	49923.46	1.19	1.12	0.94
AUCT	172214.50	36782.12	147659.03	36072.21	155755.69	35857.98	1.17	1.11	0.95
CMAX	2793.56	477.11	2323.36	407.90	2667.67	618.00	1.20	1.05	0.87
KE	0.02	0.00	0.02	0.00	0.02	0.00	1.02	0.96	0.94
THALF	38.27	6.22	38.84	6.82	36.83	6.22	0.99	1.04	1.05
TMAX	25.40	6.24	26.20	8.21	25.60	6.31	0.97	0.99	1.02

Table 20 Least Squares Geometric Means and 90% Confidence Intervals

Summary of Statistical Analysis (Fasting Pilot Study-Carbamazepine)§ Ln-Transformed Geometric Means (N=15)				
Parameter	**Test**	**Reference**	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t} (ng*hr/ml) (CxA)	***167575.34***	***152292.94***	***110.03***	***(99.73-121.41)***
AUC_{0-t} (ng*hr/ml) (CxB)	144637.55	152292.94	94.97	(86.08-104.79)
AUC_{∞} (ng*hr/ml) (CxA)	***212059.30***	***190133.47***	***111.53***	***(100.87-123.33)***
AUC_{∞} (ng*hr/ml) (CxB)	182245.40	190133.47	95.85	(86.68-105.71)
C_{max} (ng/ml) (CxA)	***2733.45***	***2607.26***	***104.84***	***(94.24-116.64)***
C_{max} (ng/ml) (CxB)	2299.63	2607.26	88.20	(79.28-98.12)

§These results were calculated by the reviewer and reasonably corroborate those reported by the firm. The data bolded, italicized and underlined above are the reviewer calculated geometric means, point estimates and 90% confidence intervals for the test formulation intended to be marketed by the firm.

Treatment A = Carbamazepine Extended Release Tablets 400mg (Batch #780980)
Treatment B= Carbamazepine Extended Release Tablets 400mg (Batch #780988)
Treatment C= Tegretol® XR Tablets 400mg (Batch #F4109)

Table 21 Additional Study Information

	Carbamazepine
Root mean square error, LAUCT	0.156472
Root mean square error, LAUCI	0.169646
Root mean square error, LCmax	0.159685
Ke and AUC_∞ determined for how many subjects?	15 subjects for Test Batch 780980 (A) & RLD 14 subjects for Test Batch 780988 (B)
Do you agree or disagree with firm's decision?	Agree
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	0 subjects
-first measurable drug concentration as Cmax	0 subjects
Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic Analysis:
There were no subjects who vomited, had detectable predose plasma concentrations or first reportable plasma concentration as the C_{max} in this study. Note subject #05 did not complete the study and was not included in the final statistical analysis. The reviewer agrees with measuring K_e and AUC_∞ for 14 subjects for Test Batch 780988 as there were several data points missing in the plasma concentration profile making an accurate characterization of the elimination constant difficult.

The reviewer notes more variability in the 90% confidence interval fasting pilot study than the full fasting study. This is consistent with what is expected as the pilot study had fewer subjects enrolled.

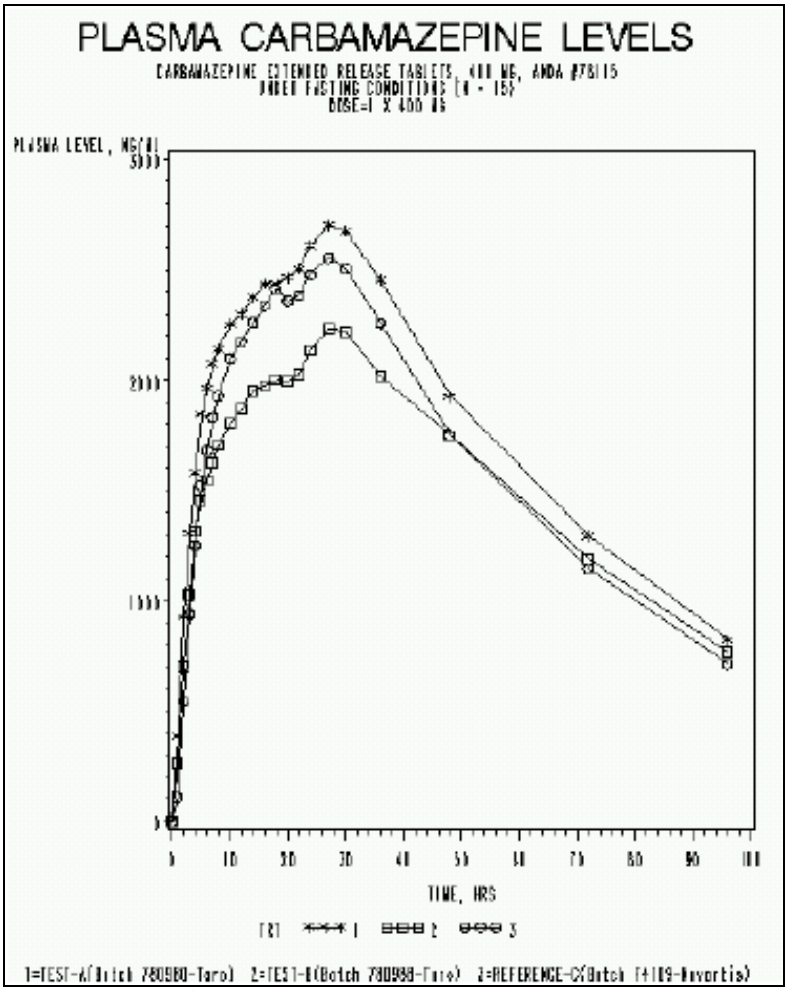
Summary/Conclusions, Single-Dose Fasting Pilot Bioequivalence Study: The BE study is acceptable.

Table 22 Mean Plasma Concentrations, Single-Dose Fasting Pilot Bioequivalence Study

Carbamazepine (n=15)

	MEAN1 Test Batch 780980	SD1	MEAN2 Test Batch 780988	SD2	MEAN3 Reference Listed Drug	SD3	RMEAN12	RMEAN13	RMEAN23
TIME HR									
0	0.00	0.00	0.00	0.00	0.00	0.00	.	.	.
1	388.88	266.27	268.27	212.53	108.57	108.69	1.45	3.58	2.47
2	927.89	481.63	704.80	350.71	542.79	151.02	1.32	1.71	1.30
3	1301.87	474.27	1028.61	385.27	938.78	254.22	1.27	1.39	1.10
4	1575.33	431.39	1313.12	345.36	1252.79	318.40	1.20	1.26	1.05
5	1841.45	399.34	1458.95	318.78	1523.74	418.67	1.26	1.21	0.96
6	1960.05	461.69	1545.87	292.76	1682.79	389.00	1.27	1.16	0.92
7	2074.45	414.85	1628.75	248.47	1830.83	465.08	1.27	1.13	0.89
8	2140.96	423.23	1706.21	261.38	1927.67	469.45	1.25	1.11	0.89
10	2252.56	434.89	1801.60	262.14	2096.04	489.51	1.25	1.07	0.86
12	2299.11	481.66	1868.85	316.67	2175.17	534.23	1.23	1.06	0.86
14	2374.12	474.99	1953.43	340.27	2260.44	544.40	1.22	1.05	0.86
16	2435.85	460.72	1972.75	352.80	2338.93	569.01	1.23	1.04	0.84
18	2433.71	455.78	2003.20	364.71	2412.92	573.63	1.21	1.01	0.83
20	2464.84	440.09	1994.92	358.60	2359.74	538.05	1.24	1.04	0.85
22	2502.92	453.78	2022.20	366.47	2384.16	537.59	1.24	1.05	0.85
24	2610.19	447.20	2135.02	363.63	2479.06	542.67	1.22	1.05	0.86
27	2701.17	499.22	2229.30	420.10	2553.25	589.50	1.21	1.06	0.87
30	2673.23	524.53	2220.34	444.43	2503.27	637.69	1.20	1.07	0.89
36	2454.61	525.36	2016.37	404.37	2257.75	587.16	1.22	1.09	0.89
48	1924.20	474.55	1747.93	542.59	1749.47	461.74	1.10	1.10	1.00
72	1293.61	377.35	1190.90	483.00	1143.99	347.47	1.09	1.13	1.04
96	823.33	276.83	766.78	341.08	711.95	243.93	1.07	1.16	1.08

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



1=Test A (Batch 780980-Taro)
2=Test B (Batch 780988-Taro)
3=Reference (Batch F4109-Novartis

3. Single-dose Fed Bioequivalence Study

a) Study Design

Study Information	
Study Number	Protocol/Project #: R04-1364
Study Title	A Relative Bioavailability Study of 400mg Carbamazepine Extended Release Tablets under Non-Fasting Conditions
Clinical Site	PRACS Institute Ltd. 4801 Amber Valley Parkway Fargo ND 58104 (701) 239-4750
Principal Investigator	James D. Carlson, Pharm.D.
Study/Dosing Dates	Period I: July 30th, 2005 Period II: August 20th, 2005
Analytical Site	PRACS Institute Ltd. 4801 Amber Valley Parkway Fargo ND 58104 (701) 239-4750
Analytical Director	(b) (6)
Analysis Dates	September 6th - 15th 2005
Storage Period	48 days (stability demonstrated for 84 days at -20°C)

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Carbamazepine ER US Tablets 400mg	Tegretol XR Tablets 400mg
Manufacturer	Taro Pharmaceutical Industries Ltd.	Novartis Pharma GmbH
Batch/Lot No.	780980	F4109
Manufacture Date	1/2005	N/A
Expiration Date	N/A	5/2007
Strength	400mg	400mg
Dosage Form	Extended Release Tablet	Extended Release Tablet
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	100.9%	101.6%
Content Uniformity	100.9% (RSD 0.2%)	N/A
Formulation	See Appendix	
Dose Administered	400mg	400mg
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	21 days
Randomization Scheme	AB: 1,3,4,7,10,12,15,16,19,20,23,24,25,28,29,30,31,32. BA: 2,5,6,8,9,11,13,14,17,18,21,22,26,27,33,34,35,36
Blood Sampling Times	0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 22, 24, 27, 30, 36, 48, 72, 96, 120, 144 and 168 hours.
Blood Volume Collected/Sample	7 mL/sample and 26 samples collected per period in vacutainers containing EDTA. Approximately 364ml of total blood was obtained from each subject during the course of the study.
Blood Sample Processing/Storage	The samples were centrifuged at 2400 rpm for 15 minutes at 4°C. The plasma was then pipetted into polypropylene tubes, frozen and stored at -20°C or colder until transferred for analysis.
IRB Approval	Yes, originally approved 7/6/2005
Informed Consent	Yes, approved 7/6/2005
Subjects Demographics	See **Table 23**
Length of Fasting before Meal	Following an overnight fast of about ten hours, subjects consumed a high fat breakfast. Subjects were dosed 30 minutes after the completion of the breakfast. The dosage form was then administered with 240ml of room temperature water.
Length of Confinement	≈46 hours (10 hours before dosing and 36 hours after)
Safety Monitoring	To ensure only healthy subjects were enrolled, all subjects underwent pre-trial screening consisting of a physical examination, medical & medication history, ECG, sitting HR, RR, temperature & BP. Subjects underwent laboratory evaluation which included hematology, clinical chemistry, HIV, HepB, HepC, urinalysis and urine drug screen. During the study, a sitting blood pressure and HR were measured prior to dosing and at 12, 24 and 36 hours post dose. Upon exiting the study, subjects underwent another physical examination and vital sign measurement. Exit labs consisted of hematology and clinical chemistry.
Standard FDA Meal Used?	Yes**

** Two eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, eight ounces of whole milk.

Comments on Study Design: The design of the non-fasting BE study is acceptable.

b) Clinical Results

Table 23 Demographics of Subjects Completing BE Study #R04-1364 (Fed)

Non-Fasting Bioequivalence Study R04-1364		
	Treatment Groups	
	Test Product N=34	**Reference Product N=34**
Age (years)		
Mean ± SD	29.53 ± 11.68	29.53 ± 11.68
Range	19 - 57	19 - 57
Groups		
<18	-	-
18-39	27 (79.41%)	27 (79.41%)
40-64	7 (20.59%)	7 (20.59%)
65-75	-	-
>75	-	-
Sex		
Female	-	-
Male	34 (100.00%)	34 (100.00%)
Hispanic or Latino		
Race		
N	-	-
A	1 (2.94%)	1 (2.94%)
B	-	-
I	-	-
W	1 (2.94%)	1 (2.94%)
Not Hispanic or Latino		
Race		
N	-	-
A	2 (5.88%)	2 (5.88%)
B	1 (2.94%)	1 (2.94%)
I	-	-
W	29 (85.29%)	29 (85.29%)

N=American Indian or Alaskan native, A=Asian, B=Black or African American, I=Native Hawaiian or other Pacific Islander, W=White.

Table 24 Dropout Information

Subject No	Reason	Period	Replaced?
Subject #23 (b) (6)	Dropped prior to study hour 72 during period II by the medical investigator secondary to a headache.	II	No
Subject 29 (b) (6)	Elected to withdraw prior to period II dosing due to a family emergency.	washout	No

Table 25 Study Adverse Events (Fed: Study #R04-1364)‡

Body System Adverse Event	**Reported Incidence by Treatment Group** Non-Fasting Bioequivalence Study R04-1364	
	Test (N=34) N (%)	**Reference (N=36)** N (%)
Nausea	-	1 (2.78%)
Pyrexia	-	1 (2.78%)
Back pain	1 (2.94%)	-
Pain in extremity	-	1 (2.78%)
Dizziness	2 (5.88%)	1 (2.78%)
Headache	3 (8.82%)	5 (5.56%)
Migraine	-	1 (2.87%)
Pharyngolaryngeal pain	-	2 (5.56%)
Total Adverse Events	**6**	**12**

‡Note: There were no serious adverse events reported. A total of 18 events reported by 11 subjects. The most frequently occurring AE for each dosage form was headache. There were five adverse events considered to be probably related, eight were unrelated, four were remotely related and one was possibly related to the drug.

Table 26 Protocol Deviations

Type	Subject #s (Test)	Subject #s (Ref.)
Missing blood samples for 22 subjects.	13	9
Subject #34 took acetaminophen for pharyngolaryngeal pain/pyrexia on 8/17/05 & 8/18/05.	-	-
Subject #30 took ibuprofen 400mg for a headache on 7/31/05.	-	-
Subject #23 was given metoclopramide, ketorlac, and ibuprofen during the course of the study for a migraine and was eventually withdrawn from the study.	-	-
There were a total of 10 late or early blood draws during the study. The times ranged from 2-74 minutes late.	-	-
Total:	13	9

Comments on Adverse Events/Protocol Deviations:
The number of dropouts, adverse events and protocol deviations are not significant to compromise the integrity of the study.

c) Bioanalytical Results

Table 27 Assay Quality Control – Within Study

	Carbamazepine										
QC Conc. (ng/mL)* **	100			2000			4000			250 (Blind)	
Inter day Precision (%CV)	2.5			1.6			1.7			1.6	
Inter day Accuracy (%)	98.4			99.5			100.1			99.5	
Cal. Standards Conc. (ng/ml)	50	100	250	500	1000	2000	2800	3500	4200	5000	n/a
Inter day Precision (%CV)	2.01	2.16	1.98	1.51	1.54	1.55	1.65	1.52	1.48	1.34	n/a
Inter day Accuracy (%)	97.9	100.3	102.9	100.8	97.5	100.2	100.1	100.4	100.2	99.7	n/a
Linearity Range (R^2 values)	0.9980-0 9998										

***The firm included a fifth QC concentration (5000ng/ml) for the repeat run because the samples were more concentrated.

Comments on Study Assay Quality Control: Acceptable. The QC and calibration standard concentrations are appropriate relative to the concentrations of the study samples.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serial, subject #s 1,2,3,4,5,6,7 & 8.

Comments on Chromatograms: The chromatography is acceptable.

Table 28 SOP's dealing with analytical repeats and others

SOP No.	**Date of SOP**	**SOP Title**
#405_03 Version 01	8/15/2005	Calibration/Standard Curves for Studies
#405_04 Version 01	8/15/2005	Quality Control Samples for Studies
#405_05 Version 01	8/15/2005	Study Subject Sample Analysis

Table 29 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: Acceptable.

d) Pharmacokinetic Results

Table 30 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 33 and Figure 2

Carbamazepine (n=34)

	Test	CV1	Ref	CV2	T/R
PARAMETER					
AUCT (ng*hr/ml)	261266.22	19.42	228075.05	21.45	1.15
AUCI (ng*hr/ml)	280562.36	21.11	247005.59	23.20	1.14
CMAX (ng/ml)	3532.46	14.98	3185.76	17.86	1.11
TMAX (hr)	21.29	34.56	19.26	36.87	1.11
KE (hr^{-1})	0.02	20.44	0.02	21.67	1.07
THALF (hr)	38.74	18.65	41.65	20.62	0.93

Table 31 Least Squares Geometric Means and 90% Confidence Intervals

Summary of Statistical Analysis (Fed Study-Carbamazepine)§ N=34				
Parameter	**Test**	**Reference**	**Point Estimate**	**90% Confidence Interval**
$LAUC_{0-t}$ (ng*hr/ml)	255942.17	221802.65	115.39	(111.53-119.38)
$LAUC_{\infty}$ (ng*hr/ml)	273838.10	239184.59	114.49	(110.35-118.79)
LC_{max} (ng/ml)	3492.33	3129.65	111.59	(108.88-114.36)

§These results were calculated by the reviewer and reasonably corroborate those reported by the firm. See comments under "Pharmacokinetic Analysis" for further details.

Table 32 Additional Study Information

	Carbamazepine
Root mean square error, LAUCT	0.082612
Root mean square error, LAUCI	0.089542
Root mean square error, LCmax	0.059650
Ke and AUC_{∞} determined for how many subjects?	34 subjects
Do you agree or disagree with firm's decision?	Agree
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	0 subjects
-first measurable drug concentration as Cmax	0 subjects
Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic Analysis:
There were no subjects who vomited, had detectable predose plasma concentrations or first reportable plasma concentration as the C_{max} in this study. Note subject #23 and #29 did not complete the study and were not included in the final statistical analysis.

The RMSE are relatively small suggesting the carbamazepine extended release tablet formulation has pharmacokinetics with low variability with respect to intra-subject performance.

Unlike the fasting study (PRACS #R05-1389, n=20) whose point estimates centered near one, in this fed study (PRACS #R04-1364, n=34), the point estimates were consistently higher indicating the test dosage form has a higher Cmax (11% higher) and releases more drug (14-15% increase in AUC) over the dosing interval. The fed pilot study (PRACS #R05-0185, n=16) submitted provided similar results indicating the test dosage form has a higher Cmax (14% higher) and releases more drug (17-18% increase in AUC) over the dosing interval. This finding is possible based on the differing release mechanisms of drug from the dosage forms. The RLD utilizes a release portal bored in an insoluble tablet shell to release carbamazepine over the dosing period. The test dosage form is a compressed tablet which may be more amenable to a food effect, consistent with the findings in both the fed and fed pilot studies. Despite this effect, the variability was sufficiently low in these studies to deem the dosage forms bioequivalent.

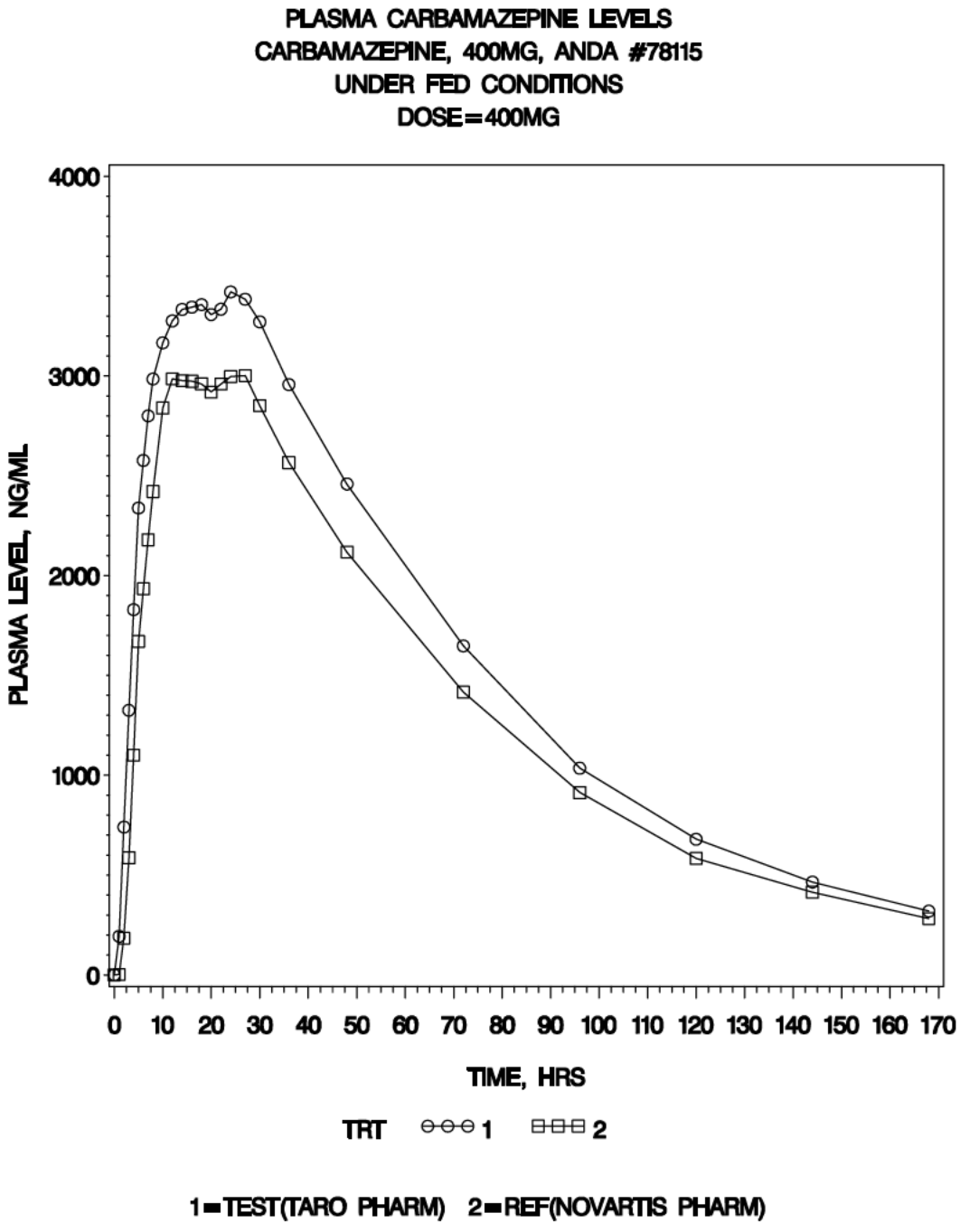
Summary/Conclusions, Single-Dose Fed Bioequivalence Study: The BE study is acceptable.

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

Carbamazepine (n=34)

	MEAN1	CV1	MEAN2	CV2	RMEAN12
TIME HR					
0	0.00	.	0.00	.	.
1	193.29	103.45	1.87	583.10	103.28
2	740.39	68.32	183.39	115.32	4.04
3	1325.54	56.18	587.30	77.14	2.26
4	1829.76	48.77	1100.77	61.45	1.66
5	2338.88	38.04	1670.43	31.79	1.40
6	2577.06	29.92	1934.48	25.28	1.33
7	2800.32	24.72	2179.38	24.34	1.28
8	2985.15	20.77	2421.67	24.32	1.23
10	3166.12	18.21	2840.09	21.84	1.11
12	3276.00	17.35	2985.55	19.52	1.10
14	3333.12	17.00	2976.52	17.90	1.12
16	3344.81	16.91	2973.37	18.32	1.12
18	3357.13	17.05	2960.53	18.96	1.13
20	3307.80	17.38	2919.16	19.26	1.13
22	3334.33	17.38	2959.38	19.65	1.13
24	3420.83	15.31	2997.85	18.19	1.14
27	3384.32	16.94	3001.30	20.44	1.13
30	3271.41	16.34	2850.62	20.21	1.15
36	2956.86	17.83	2566.41	20.54	1.15
48	2458.87	19.70	2118.01	21.56	1.16
72	1648.03	26.61	1416.74	27.40	1.16
96	1035.75	30.63	913.29	31.27	1.13
120	679.55	35.08	583.64	33.75	1.16
144	465.28	39.48	414.61	41.23	1.12
168	319.50	43.32	281.93	48.64	1.13

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



B. Formulation Data

Composition of Carbamazepine Extended Release Tablets (Taro Pharmaceuticals)

Each tablet strength is proportionally similar with respect to excipient concentrations and all ingredients are within the IIG specified limits. The formulation is a common blend. The formulation is acceptable.

Formulation Data

Ingredient	Amount (mg) / Tablet			Amount (%) / Tablet		
	100 mg	**200 mg**	**400 mg**	**100 mg**	**200 mg**	**400 mg**
Carbamazepine	100.0	200.0	400.0	58.56	58.56	58.56
Eudragit (b) (4)	(b) (4)					
Diethyl Phthalate						
Purified Water[3]						
Microcrystalline Cellulose (b) (4)						
Corn Starch						
Lactose Monohydrate (b) (4)						
Sodium Starch Glycolate, (b) (4)						
Magnesium Stearate						
Total Dry Weight	**170.8**	**341.5**	**683.0**	**100**	**100**	**100**

(b) (4)

C. Dissolution Data

Table 1

USP Method

USP Apparatus I (basket) at 100 rpm in 900 ml (1800ml for 400mg tablet) water (37°C)
Specification:

Time (hrs)	Amount Dissolved
3	Between 10-35%
6	Between 35-65%
12	Between 65-90%
24	Not less than 75%

Firm's Method

USP Apparatus I (basket) at 100 rpm in 900 ml (1800ml for 400mg tablet) water (37°C)
Specification:

Time (hrs)	Amount Dissolved
3	(b) (4)
6	
12	
24	Not less than 75%

Tablet Number	**Carbamazepine Extended Release Tablets 400mg Taro Batch # 780980 Assay 100.9%**				**Carbamazepine Extended Release Tablets 100mg Taro Batch # 781064 Assay 102.4%**			
	3 hr	**6 hr**	**12 hr**	**24 hr**	**3hr**	**6 hr**	**12hr**	**24hr**
Average	40	58	71	77	52	71	82	87
Max	(b) (4)				(b) (4)			
Min								
RSD(%)	15.9	12.9	10.7	10.4	10.1	10.6	8.4	7.2
Dissolution Method	Phosphate buffer (pH 6.8) + 0.07% SLS 1800ml (400mg) 900ml (100mg) Apparatus I (Basket) at 100 RPM				**F2 Statistic**	49.0		

Tablet Number	**Carbamazepine Extended Release Tablets 400mg Taro Batch # 780980 Assay 100.9%**				**Carbamazepine Extended Release Tablets 100mg Taro Batch # 781064 Assay 102.4%**			
	3 hr	**6 hr**	**12 hr**	**24 hr**	**3hr**	**6 hr**	**12hr**	**24hr**
Average	48	69	88	99	57	77	90	97
Max	(b) (4)				(b) (4)			
Min								
RSD(%)	3.8	2.9	2.3	2.8	3.4	3.4	2.7	2.2
Dissolution Method	Acetate buffer (pH 4.5) 1800ml (400mg) 900ml (100mg) Apparatus I (Basket) at 100 RPM				**F2 Statistic**	60.4		

Tablet Number	Carbamazepine Extended Release Tablets 400mg Taro Batch # 780980 Assay 100.9%				Carbamazepine Extended Release Tablets 100mg Taro Batch # 781064 Assay 102.4%			
	3 hr	**6 hr**	**12 hr**	**24 hr**	**3hr**	**6 hr**	**12hr**	**24hr**
Average	32	48	66	78	44	64	79	87
Max	[redacted] (b) (4)				[redacted] (b) (4)			
Min								
RSD(%)	4.8	4.8	5.8	6.9	5.8	6.5	6.2	6.8
Dissolution Method	Gastric fluid (pH 1.2) 1800ml (400mg) 900ml (100mg) Apparatus I (Basket) at 100 RPM				F2 Statistic	46.1		

Tablet Number	Carbamazepine Extended Release Tablets 400mg Taro Batch # 780980 Assay 100.9%				Carbamazepine Extended Release Tablets 200mg Taro Batch # 781066 Assay 100.3%			
	3 hr	**6 hr**	**12 hr**	**24 hr**	**3hr**	**6 hr**	**12hr**	**24hr**
Average	40	58	71	77	46	65	81	87
Max	[redacted] (b) (4)				[redacted] (b) (4)			
Min								
RSD(%)	15.9	12.9	10.7	10.4	9.6	10.3	12.0	11.9
Dissolution Method	Phosphate buffer (pH 6.8) + 0.07% SLS 1800ml (400mg) 900ml (100mg) Apparatus I (Basket) at 100 RPM				**F2 Statistic**	58.1		

Tablet Number	Carbamazepine Extended Release Tablets 400mg Taro Batch # 780980 Assay 100.9%				Carbamazepine Extended Release Tablets 200mg Taro Batch # 781066 Assay 100.3%			
	3 hr	**6 hr**	**12 hr**	**24 hr**	**3hr**	**6 hr**	**12hr**	**24hr**
Average	48	69	88	99	49	70	88	97
Max	[redacted] (b) (4)				[redacted] (b) (4)			
Min								
RSD(%)	3.8	2.9	2.3	2.8	4.4	3.9	3.1	2.5
Dissolution Method	Acetate buffer (pH 4.5) 1800ml (400mg) 900ml (100mg) Apparatus I (Basket) at 100 RPM				**F2 Statistic**	95.6		

Tablet Number	Carbamazepine Extended Release Tablets 400mg Taro Batch # 780980 Assay 100.9%				Carbamazepine Extended Release Tablets 200mg Taro Batch # 781066 Assay 100.3%			
	3 hr	**6 hr**	**12 hr**	**24 hr**	**3hr**	**6 hr**	**12hr**	**24hr**
Average	32	48	66	78	39	58	77	89
Max	[redacted] (b) (4)				[redacted] (b) (4)			
Min								
RSD(%)	4.8	4.8	5.8	6.9	5.7	3.6	4.0	5.2
Dissolution Method	Gastric fluid (pH 1.2) 1800ml (400mg) 900ml (100mg) Apparatus I (Basket) at 100 RPM				**F2 Statistic**	54.1		

Tablet Number	**Carbamazepine Extended Release Tablets 100mg Taro Batch # 781064 Assay 102.4%**				**Tegrtol XR Tablets 100mg Novartis Batch # F4089 Assay 101.8%**			
	3 hr	**6 hr**	**12 hr**	**24 hr**	**3hr**	**6 hr**	**12hr**	**24hr**
Average	53	78	98	105	16	47	81	93
Max	[redacted] (b) (4)				[redacted] (b) (4)			
Min								
RSD(%)	4.1	2.2	1.8	1.9	25.0	13.1	3.8	2.4
Dissolution Method	Deionized & degassed water 900ml Apparatus I (Basket) at 100 RPM				**F2 Statistic**	29.6		
Tablet Number	**Carbamazepine Extended Release Tablets 200mg Taro Batch # 781066 Assay 100.3%**				**Tegrtol XR Tablets 200mg Novartis Batch # F0219 Assay 101.4%**			
	3 hr	**6 hr**	**12 hr**	**24 hr**	**3hr**	**6 hr**	**12hr**	**24hr**
Average	43	65	86	99	19	51	82	94
Max	[redacted] (b) (4)				[redacted] (b) (4)			
Min								
RSD(%)	5.6	5.1	3.8	3.0	32.9	19.1	5.7	1.9
Dissolution Method	Deionized & degassed water 900ml Apparatus I (Basket) at 100 RPM				**F2 Statistic**	42.6		

Tablet Number	**Carbamazepine Extended Release Tablets 400mg Taro Batch # 780980 Assay 100.9%**				**Tegrtol XR Tablets 400mg Novartis Batch # F4109 Assay 101.6%**			
	3 hr	**6 hr**	**12 hr**	**24 hr**	**3hr**	**6 hr**	**12hr**	**24hr**
Average	44	67	88	101	25	54	79	84
Max	[redacted] (b) (4)				[redacted] (b) (4)			
Min								
RSD(%)	6.2	6.1	4.0	2.3	13.2	7.0	3.8	3.0
Dissolution Method	Deionized & degassed water 1800ml Apparatus I (Basket) at 100 RPM				**F2 Statistic**	45.3		

Tablet Number	**Carbamazepine Extended Release Tablets 400mg Taro Batch # 780980 Assay 100.9%**				**Carbamazepine Extended Release Tablets 200mg Taro Batch # 781066 Assay 100.3%**			
	3 hr	**6 hr**	**12 hr**	**24 hr**	**3hr**	**6 hr**	**12hr**	**24hr**
Average	45	67	88	101	43	65	86	99
Max	[redacted] (b) (4)				[redacted] (b) (4)			
Min								
RSD(%)	6.2	6.1	4.0	2.3	5.6	5.1	3.8	3.0
Dissolution Method	Deionized & degassed water 1800ml (400mg) 900ml (100mg) Apparatus I (Basket) at 100 RPM				F2 Statistic	85.0		

Tablet Number	Carbamazepine Extended Release Tablets 400mg Taro Batch # 780980 Assay 100.9%				Carbamazepine Extended Release Tablets 100mg Taro Batch # 781064 Assay 102.4%			
	3 hr	**6 hr**	**12 hr**	**24 hr**	**3hr**	**6 hr**	**12hr**	**24hr**
Average	45	67	88	101	53	78	98	105
Max	[redacted] (b) (4)				[redacted] (b) (4)			
Min								
RSD(%)	6.2	6.1	4.0	2.3	4.1	2.2	1.8	1.9
Dissolution Method	Deionized & degassed water 1800ml (400mg) 900ml (100mg) Apparatus I (Basket) at 100 RPM				F2 Statistic	53.5		

Dissolution Summary Table

Dosage Forms Tested	Conditions	F2 Statistic	Reviewer Interpretation of the Results
Test 400mg vs Test 100mg	pH 6.8	49.0	The 100mg strength has a dissolution profile somewhat similar to 400mg strength at pH 6.8 as 40≤F2≤50.
Test 400mg vs Test 100mg	pH 4.5	60.4	The 100mg strength has a dissolution profile similar to 400mg strength at pH 4.5 as the F2 statistic is >50.
Test 400mg vs Test 100mg	pH 1.2	46.1	The 100mg strength has a dissolution profile somewhat similar to 400mg strength at pH 1.2 as 40≤F2≤50.
Test 400mg vs Test 200mg	pH 6.8	58.1	The 200mg strength has a dissolution profile similar to 400mg strength at pH 6.8 as the F2 statistic is >50.
Test 400mg vs Test 200mg	pH 4.5	95.6	The 200mg strength has a dissolution profile similar to 400mg strength at pH 4.5 as the F2 statistic is >50.
Test 400mg vs Test 200mg	pH 1.2	54.1	The 200mg strength has a dissolution profile similar to 400mg strength at pH 1.2 as the F2 statistic is >50.
Test 100mg vs Reference 100mg	USP	29.6	The 100mg test strength does not have a dissolution profile similar to the 100mg reference strength under USP dissolution method testing conditions as the F2 statistic <50. This is the basis for the firm conducting in vivo testing on the 100mg tablet in study #R05-1389.
Test 200mg vs Reference 200mg	USP	42.6	The 200mg test strength has a dissolution profile somewhat similar to the 200mg reference strength under USP dissolution method testing conditions as 40≤F2≤50.
Test 400mg vs Reference 400mg	USP	45.3	The 400mg test strength has a dissolution profile somewhat similar to the 400mg reference strength under USP dissolution method testing conditions as 40≤F2≤50.
Test 400mg vs Test 200mg	USP	85.0	The 400mg test strength has a dissolution profile similar to the 200mg test strength under USP dissolution method testing conditions as the F2 statistic >50.
Test 400mg vs Test 100mg	USP	53.5	The 400mg test strength has a dissolution profile similar to the 100mg test strength under USP dissolution method testing conditions as the F2 statistic >50.

* The firm did not make comparisons of the test and reference formulations in three different media as recommended to determine if dose-dumping occurs as a function of changing pH. Comparisons of test to test were made. The firm acknowledges that *in vitro* dissolution testing may suggest that their 100mg test dosage form releases drug at a different rate than the 100mg reference dosage form (F_2-29.6). This was the basis for the firm conducting *in vivo* testing on the 100mg tablet in study #R05-1389. The dissolution testing is incomplete.

D. Consult Reviews

None

Following this page, 118 pages withheld in full (b)(4)

I. Additional Attachments

None

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-115 APPLICANT: Taro Pharmaceuticals

DRUG PRODUCT: Carbamazepine Extended Release Tablets, USP
100mg, 200mg & 400mg

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

1. The DBE reviewed the dissolution testing data submitted. For extended release dosage forms, the DBE currently recommends dissolution testing be conducted by comparing the test and reference dosage forms in three different media. Please conduct dissolution testing comparing each strength of the test and reference tablets in three different media (pH 6.8, 4.5 and 1.2). We recommend a total of nine additional dissolution tests be conducted. These are summarized in the table below.

Test 100mg vs Reference 100mg	Phosphate buffer (pH 6.8) + 0.07% SLS 900ml Apparatus I (basket) at 100 rpm
Test 200mg vs Reference 200mg	Phosphate buffer (pH 6.8) + 0.07% SLS 900ml Apparatus I (basket) at 100 rpm
Test 400mg vs Reference 400mg	Phosphate buffer (pH 6.8) + 0.07% SLS 1800ml Apparatus I (basket) at 100 rpm
Test 100mg vs Reference 100mg	Acetate buffer (pH 4.5) 900ml Apparatus I (basket) at 100 rpm
Test 200mg vs Reference 200mg	Acetate buffer (pH 4.5) 900ml Apparatus I (basket) at 100 rpm
Test 400mg vs Reference 400mg	Acetate buffer (pH 4.5) 1800ml Apparatus I (basket) at 100 rpm
Test 100mg vs Reference 100mg	Low pH Solution (pH 1.2) 900ml Apparatus I (basket) at 100 rpm
Test 200mg vs Reference 200mg	Low pH Solution (pH 1.2) 900ml Apparatus I (basket) at 100 rpm
Test 400mg vs Reference 400mg	Low pH Solution (pH 1.2) 1800ml Apparatus I (basket) at 100 rpm

Please conduct these tests and resubmit the data.

2. In reviewing study #R05-1389, inconsistencies were noted in the dose given to each subject. The clinical report and protocol report that 2 x 100mg tablets were administered to each subject in each period, yet in other documents in the submission it was reported as 1 x 100mg tablets. Please clarify the dose each subject received in period of this study.

3. The DBE does not currently recommend measurement of a metabolite (10,11-epoxide metabolite) to establish the bioequivalence of carbamazepine extended release tablets. For future reference, you may submit your

protocol to the DBE for review prior to starting the study which may eliminate unnecessary analysis.

Sincerely yours,

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

ANDA: 78-115
BIOEQUIVALENCE – DEFICIENCIES Submission Date: 12/29/2005
Amendment Date: None

1. FASTING STUDY (STF) Strength: 100mg
Outcome: IC

Clinical: PRACS Institute Ltd.
625 Demers Ave.
East Grand Forks, MN 57621

Analytical: PRACS Institute Ltd.
4801 Amber Valley Parkway
Fargo, ND 58104

2. FASTING PILOT STUDY (STF) Strength: 400mg
Outcome: AC

Clinical: PRACS Institute Ltd.
625 Demers Ave.
East Grand Forks, MN 57621

Analytical: PRACS Institute Ltd.
4801 Amber Valley Parkway
Fargo, ND 58104

3. FOOD STUDY (STP) Strength: 400mg
Outcome: AC

Clinical: PRACS Institute Ltd.
4801 Amber Valley Parkway
Fargo, ND 58104

Analytical: PRACS Institute Ltd.
4801 Amber Valley Parkway
Fargo, ND 58104

4. FOOD PILOT STUDY (STP) Strength: 400mg
Outcome: AC

Clinical: PRACS Institute Ltd.
4801 Amber Valley Parkway
Fargo, ND 58104

Analytical: PRACS Institute Ltd.
4801 Amber Valley Parkway
Fargo, ND 58104

5. **DISSOLUTION WAIVER** (DIW) Strength: 200mg
Outcome: IC

Outcome Decisions: AC – Acceptable, IC - Incomplete

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

/s/

S Christopher Jones
12/18/2006 04:43:59 PM
BIOPHARMACEUTICS

Devvrat Patel
12/18/2006 05:05:30 PM
BIOPHARMACEUTICS
Signing for Kuldeep Dhariwal

Barbara Davit
12/19/2006 11:42:55 AM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-115
Drug Product Name	Carbamazepine Extended Release Tablets USP
Strength(s)	100mg, 200mg and 400mg
Applicant Name	Taro Pharmaceuticals Industries Ltd.
Address	3 Skyline Drive Hawthorne, NY 10532
Applicant's Point of Contact	Kalpana Rao, Regulatory Affairs
Contact's Telephone Number	914-345-9001
Contact's Fax Number	914-593-0078
Original Submission Date(s)	12/29/2005
Submission Date(s) of Amendment(s) Under Review	01/04/2007 (Amendment to the Original Review) 09/17/2007 (DSI Audit Report)
Reviewer	S. Christopher Jones PharmD, MS
Study Number (s)	Study #R05-1389
Study Type (s)	Fasting-Pivotal
Strength (s)	2X100mg
Clinical Site & Address	PRACS Institute Ltd. 625 Demers Ave East Grand Forks, MN 57621
Analytical Site & Address	PRACS Institute Ltd. 4801 Amber Valley Parkway Fargo, ND 58104
Study Number (s)	Study #R05-0184
Study Type (s)	Fasting-Pilot
Strength (s)	400mg
Clinical Site & Address	PRACS Institute Ltd. 625 Demers Ave East Grand Forks, MN 57621
Analytical Site & Address	PRACS Institute Ltd. 4801 Amber Valley Parkway Fargo, ND 58104
Study Number (s)	Study #R04-1364
Study Type (s)	Fed-Pivotal
Strength (s)	400mg
Clinical Site & Address	PRACS Institute Ltd. 4801 Amber Valley Parkway Fargo, ND 58104
Analytical Site & Address	PRACS Institute Ltd. 4801 Amber Valley Parkway Fargo, ND 58104

Review of an Amendment and a DSI Inspection Report

I. Executive Summary

The Division of Bioequivalence (DBE) completed the original review of this ANDA on December 19th 2006 and three deficiencies were cited. The DBE also requested an onsite inspection from the Division of Scientific Investigations (DSI). This document is both a review of firm's responses to deficiencies in the original review and the DSI's findings during their recent site inspection.

After the initial review of the submission, the DBE asked the firm to conduct additional dissolution testing, clarify the dose administered to subjects in the pivotal fasting bioequivalence (BE) study (#R05-1389) and the DBE further informed the firm that metabolite measurement was not recommended for this drug product. While the firm has responded satisfactorily to the deficiencies, new deficiencies were discovered during the recent DSI site inspection, where a FDA form 483 was issued. The inspector determined that the audit trail software on analytical instrumentation had been disabled; making it impossible to verify chromatograms had been integrated in an unbiased way. The DSI reviewer had further concerns regarding storage location and temperatures for stock solutions, sample extracts prior to analysis on the HPLC/MS/MS instrumentation and quality control standards used to demonstrate stability of the analytes in matrix at room temperature. As of the completion of this review the firm had not responded to the FDA form 483 issued by the DSI.

The DSI recommends that the DBE not accept these BE studies. The DBE agrees with this recommendation. Therefore, the fasting-pivotal study on the 100mg strength (#R05-1389), fasting-pilot study on the 400mg strength (#R05-0184) and fed-pivotal study on the 400mg strength (#R04-1364) are unacceptable. The firm may remedy the DSI deficiencies in one of two ways. The firm may re-assay samples from these studies if sufficient plasma volumes exist and long term storage stability has been demonstrated. Alternatively, the firm may choose to conduct new fasting and fed BE studies.

The DBE also notes that study #R05-1389 (fasting pivotal) was conducted by dosing subjects with a 2x100mg dose of the carbamazepine extended release tablets. The DBE currently recommends a single dose of the highest strength (400mg) be used in both fasting and fed bioequivalence studies. The DBE may then deem the lower strengths bioequivalent based on CFR 320.24(b)(6) provided all strengths are proportionally formulated and acceptable dissolution testing has been completed. The firm is informed of these recommendations.

II. Table of Contents

III. Review of Bio Amendment Submission from January 4th 2007

1. *The DBE reviewed the dissolution testing data submitted. For extended release dosage forms, the DBE currently recommends dissolution testing be conducted by comparing the test and reference dosage forms in three different media. Please conduct dissolution testing comparing each strength of the test and reference tablets in three different media (pH 6.8, 4.5 and 1.2). We recommend a total of nine additional dissolution tests be conducted. These are summarized in the table below.*

Test 100mg vs Reference 100mg	*Phosphate buffer (pH 6.8) + 0.07% SLS 900ml Apparatus I (basket) at 100 rpm*
Test 200mg vs Reference 200mg	*Phosphate buffer (pH 6.8) + 0.07% SLS 900ml Apparatus I (basket) at 100 rpm*
Test 400mg vs Reference 400mg	*Phosphate buffer (pH 6.8) + 0.07% SLS 1800ml Apparatus I (basket) at 100 rpm*
Test 100mg vs Reference 100mg	*Acetate buffer (pH 4.5) 900ml Apparatus I (basket) at 100 rpm*
Test 200mg vs Reference 200mg	*Acetate buffer (pH 4.5) 900ml Apparatus I (basket) at 100 rpm*
Test 400mg vs Reference 400mg	*Acetate buffer (pH 4.5) 1800ml Apparatus I (basket) at 100 rpm*
Test 100mg vs Reference 100mg	*Low pH Solution (pH 1.2) 900ml Apparatus I (basket) at 100 rpm*
Test 200mg vs Reference 200mg	*Low pH Solution (pH 1.2) 900ml Apparatus I (basket) at 100 rpm*
Test 400mg vs Reference 400mg	*Low pH Solution (pH 1.2) 1800ml Apparatus I (basket) at 100 rpm*

Please conduct these tests and resubmit the data.

Firm's Response:

"Dissolution testing of the drug product, Carbamazepine Extended-Release Tablets, 100mg, 200mg and 400mg, comparing each strength of the test and reference tablets in three different media (pH 6.8, 4.5 and 1.2) was conducted and the data is submitted in Attachment 1 of this amendment. The dissolution testing in Phosphate buffer pH 6.8 was performed without addition of 0.07% SLS as dissolution was slow (about 50% after 24 hours) for the reference product when tested in medium containing SLS. However, comparative data of the Taro and reference product in phosphate buffer (pH 6.8) + 0.07% SLS are enclosed in Attachment 2 of this amendment."

Reviewer's Response: The tables below summarize the new dissolution data submitted by the firm.

Tablet Number =12	Carbamazepine Extended Release Tablets 100mg Taro Batch # 781064 Assay 102.4%				Tegretol-XR® Tablets 100mg Batch # F4089 Assay 101.8%			
	3 hr	**6 hr**	**12 hr**	**24 hr**	**3hr**	**6 hr**	**12hr**	**24hr**
Average	43	60	75	84	16	48	60	83
Max	[redacted] (b) (4)				[redacted] (b) (4)			
Min								
RSD(%)	9.3	12.4	10.1	9.9	18.5	12.0	10.9	2.2
Dissolution Method	900 ml Phosphate buffer (pH 6.8) Apparatus I (Basket) at 100 RPM				**F2 Statistic**			

Tablet Number =12	Carbamazepine Extended Release Tablets 200mg Taro Batch # 781066 Assay 100.3%				Tegretol-XR® Tablets 200mg Batch # F0219 Assay 101.4%			
	3 hr	**6 hr**	**12 hr**	**24 hr**	**3hr**	**6 hr**	**12hr**	**24hr**
Average	42	61	76	83	12	37	68	81
Max	[redacted] (b) (4)				[redacted] (b) (4)			
Min								
RSD(%)	5.6	4.5	4.3	5.2	25.6	20.8	5.2	3.5
Dissolution Method	900 ml Phosphate buffer (pH 6.8) Apparatus I (Basket) at 100 RPM				**F2 Statistic**			

Tablet Number =12	Carbamazepine Extended Release Tablets 400mg Taro Batch # 780980 Assay 100.9%				Tegretol-XR® Tablets 400mg Batch # F4109 Assay 101.6%			
	3 hr	**6 hr**	**12 hr**	**24 hr**	**3hr**	**6 hr**	**12hr**	**24hr**
Average	32	47	61	71	21	47	72	77
Max	[redacted] (b) (4)				[redacted] (b) (4)			
Min								
RSD(%)	4.5	5.5	6.2	7.0	17.2	8.0	2.9	3.6
Dissolution Method	1800 ml Phosphate buffer (pH 6.8) Apparatus I (Basket) at 100 RPM				**F2 Statistic**			

Tablet Number =12	Carbamazepine Extended Release Tablets 100mg Taro Batch # 781064 Assay 102.4%				Tegretol-XR® Tablets 100mg Batch # F4089 Assay 101.8%			
	3 hr	**6 hr**	**12 hr**	**24 hr**	**3hr**	**6 hr**	**12hr**	**24hr**
Average	57	77	90	97	16	50	76	87
Max	[redacted] (b) (4)				[redacted] (b) (4)			
Min								
RSD(%)	3.4	3.4	2.7	2.2	19.5	8.8	2.7	4.8
Dissolution Method	900 ml Acetate buffer (pH 4.5) Apparatus I (Basket) at 100 RPM				**F2 Statistic**			

Tablet Number =12	Carbamazepine Extended Release Tablets 200mg Taro Batch # 781066 Assay 100.3%				Tegretol-XR® Tablets 200mg Batch # F0219 Assay 101.4%			
	3 hr	6 hr	12 hr	24 hr	3hr	6 hr	12hr	24hr
Average	49	70	88	97	13	39	73	86
Max	[redacted] (b) (4)				[redacted] (b) (4)			
Min								
RSD(%)	4.4	3.9	3.1	2.5	20.2	10.5	5.5	7.9
Dissolution Method	900 ml Acetate buffer (pH 4.5) Apparatus I (Basket) at 100 RPM				F2 Statistic			

Tablet Number =12	Carbamazepine Extended Release Tablets 400mg Taro Batch # 780980 Assay 100.9%				Tegretol-XR® Tablets 400mg Batch # F4109 Assay 101.6%			
	3 hr	6 hr	12 hr	24 hr	3hr	6 hr	12hr	24hr
Average	48	69	88	99	24	54	76	80
Max	[redacted] (b) (4)				[redacted] (b) (4)			
Min								
RSD(%)	3.8	2.9	2.3	2.8	15.7	9.3	10.7	10.2
Dissolution Method	1800 ml Acetate buffer (pH 4.5) Apparatus I (Basket) at 100 RPM				F2 Statistic			

Tablet Number =12	Carbamazepine Extended Release Tablets 100mg Taro Batch # 781064 Assay 102.4%				Tegretol-XR® Tablets 100mg Batch # F4089 Assay 101.8%			
	3 hr	6 hr	12 hr	24 hr	3hr	6 hr	12hr	24hr
Average	44	64	79	87	12	40	73	87
Max	[redacted] (b) (4)				[redacted] (b) (4)			
Min								
RSD(%)	5.8	6.5	6.2	6.8	23.8	16.7	8.0	4.0
Dissolution Method	900 ml Gastric Fluid (pH 1.2) Apparatus I (Basket) at 100 RPM				F2 Statistic			

Tablet Number =12	Carbamazepine Extended Release Tablets 200mg Taro Batch # 781066 Assay 100.3%				Tegretol-XR® Tablets 200mg Batch # F0219 Assay 101.4%			
	3 hr	6 hr	12 hr	24 hr	3hr	6 hr	12hr	24hr
Average	39	58	77	89	13	36	74	89
Max	[redacted] (b) (4)				[redacted] (b) (4)			
Min								
RSD(%)	5.7	3.6	4.0	5.2	17.9	16.2	5.3	10.7
Dissolution Method	900 ml Gastric Fluid (pH 1.2) Apparatus I (Basket) at 100 RPM				F2 Statistic			

Tablet Number =12	Carbamazepine Extended Release Tablets 400mg Taro Batch # 780980 Assay 100.9%				Tegretol-XR® Tablets 400mg Batch # F4109 Assay 101.6%			
	3 hr	6 hr	12 hr	24 hr	3hr	6 hr	12hr	24hr
Average	32	48	66	78	19	41	68	78
Max	(b) (4)				(b) (4)			
Min								
RSD(%)	4.8	4.8	5.8	6.9	20.0	16.9	11.4	9.0
Dissolution Method	1800 ml Gastric Fluid (pH 1.2) Apparatus I (Basket) at 100 RPM				F2 Statistic			

The reviewer notes that drug release from the test dosage form is more rapid than the reference. Despite a more rapid *in vitro* release rate, the variability was sufficiently low in the *in-vivo* studies such that bioequivalence criteria appear to have been met, albeit higher point estimates were observed. The DBE dissolution focal point was consulted to render an opinion about the dissolution method and specification for this test drug product. Because the product does not conform well to the USP specification, the DBE recommends the following dissolution method for this product:

FDA Method

Acetate Buffer, pH 4.5
1800 mL (400 mg), 900 mL (100 mg, 200 mg)
Apparatus I (Basket)/ 100 rpm

Specifications

For 400mg and 200mg
3hr: (b) (4)
6hr:
12hr
24hr

For 100mg
3hr: (b) (4)
6hr:
12hr
24hr

These dissolution data were reviewed and are presented here despite the recent DSI audit, which raised serious concerns regarding the validity of the bioanalytical results. Considering the DSI's findings, further evaluation of the dissolution data will cease until the firm is able to remedy the DSI discrepancies noted on the FDA form 483. The dissolution testing is incomplete pending resolution of these DSI discrepancies.

2. *In reviewing study #R05-1389, inconsistencies were noted in the dose given to each subject. The clinical report and protocol report that 2 x 100mg tablets were administered to each subject in each period, yet in other documents in the submission it was reported as 1 x 100mg tablets. Please clarify the dose each subject received in period of this study.*

Firm's Response: "The attached Drug Dispensing Log (Attachment 3) indicates that each subject was administered 2 x 100mg tablets. Additionally, an example Study Product Dispensed CRF page for subject #1 included as Attachment 4 also indicates that 2 x 100mg tablets were administered. The report entitled "A Relative Bioavailability Study of 100mg Carbamazepine Extended-Release Tablets Under Fasting Conditions", Study #R05-1389 has been amended to reflect the 2 x 100mg dose. The amended report has been enclosed in Attachment 5."

Reviewer's Response: The response by the firm clarifies the dose administered in Study #R05-1389, consistent with the assumptions made by the reviewer during the original review. The response is acceptable.

3. *The DBE does not currently recommend measurement of a metabolite (10,11-epoxide metabolite) to establish the bioequivalence of carbamazepine extended release tablets. For future reference, you may submit your protocol to the DBE for review prior to starting the study which may eliminate unnecessary analysis.*

Firm's Response: "Acknowledged."

Reviewer's Response: The response by the firm is acceptable.

IV. Review of DSI Inspection Report from September 17th 2007

The DSI conducted an audit of the bioequivalence studies #R05-1389 (Pivotal-Fasting) and #R04-1364 (Pivotal Fed) by visiting the PRACS Institute Fargo North Dakota location. This report has been archived in DFS (N 078115 N 000 29-Dec-2005). All clinical study records from these studies were stored at the PRACS Institute, Fargo North Dakota facility. Since these records were stored in Fargo, the DSI reviewer chose to audit these data. The analytical site for both studies was also located at the Fargo facility. After the inspection was complete, the DSI issued the FDA Form 483 to the contract research organization (CRO). The following problem list was provided by the DSI:

1) Lack of audit trail for the (b) (4) software used for chromatography integrations. The audit trail function was disabled during the conduct of studies R04-1364 and R05-1389.

2) Failure to document:
   I. The storage location and temperature for:
      a) Solutions used to demonstrate stock stabilities during validation
      b) Sample extracts prior to analysis on the HPLC/MS/MS during validation and study conduct. Stability in extracts was reported at 4°C.

c) QCs used to demonstrate stability of the analytes in matrix at room temperature.

II. Plasma volumes used for achieving the reported dilutions to demonstrate dilution integrity during the validation.

3) Failure to ensure that subjects met all the inclusion/exclusion criteria at the time of the study check-in after a significant weight loss just prior to dosing.

The DBE agrees that these findings are problematic.[1] The lack of an audit trail on critical analytical instrumentation is worrisome in that it is unknown whether integration parameters could have been chosen to bias the outcome of analytical data. Because the audit trail was intentionally disabled, the DBE reviewer no longer has confidence in the bioanalytical portions of these studies. Therefore on the basis of finding #1 above, the results of the study #R05-1389 and #R04-1364 cannot be guaranteed as accurate and are deemed unacceptable. Moreover, since the firm is currently relying on the results from study # R05-0184 (Fasting Pilot) using a 400mg dose of carbamezepine, and the bioanalytical portion of the study was also conducted at the Fargo facility during the time that this audit trail function was disabled, study #R05-0184 is also deemed unacceptable.

The DBE notes the DSI inspector could not confirm the storage location and temperature for stock solutions, extracted samples on the LC-MS-MS or QCs that were used to demonstrate stability of the analyte in matrix at RT. Because the stability of stock solutions is critical to create accurate standards to quantify analyte, and the storage conditions of these solutions cannot be verified, it further leads the DBE reviewer to question the validity of the bioanalytical data in both studies. The DBE reviewer also notes the DSI's third concern where all subjects could not be verified as having met the inclusion/exclusion criteria at the time of study check-in. The DBE reviewer also agrees that this finding is troublesome, although no harm to any subject was incurred.

On October 2nd 2007, the DSI and DBE met to discuss the relevance and potential ramifications of the DSI audit. It was determined that the DSI auditor's findings as noted on the FDA Form 483 were significant and the bioanalytical results from the cited studies were unreliable. Therefore, the DBE reviewer finds the bioanalytical results from PRACS studies #R05-1389, #R05-0184 and #R04-1364 to be unacceptable.

V. Deficiencies

1. The Division of Scientific Investigations (DSI) conducted an audit of the analytical facility (PRACS Institute, Fargo ND) where carbamazepine samples were analyzed for the fasting pivotal (#R05-1389), fasting-pilot (#R05-0184) and fed-pivotal (#R04-1364) bioequivalence studies submitted for this ANDA. The DSI detected analytical problems, specifically a disabled audit trail function on software used to acquire and integrate chromatograms. Additionally, the PRACS Institute failed to provide documentation demonstrating proper storage temperatures and locations of stock solutions, sample

[1] See Section VII of this review which includes meeting notes where DSI and DBE met to discuss these findings.

extracts prior to analysis on HPLC/MS/MS and QCs used to demonstrate stability of analyte in matrix at room temperature. The DSI recommends that the DBE not accept these bioequivalence studies. The DBE concurs with this recommendation. Therefore, the firm's fasting pivotal (#R05-1389), fasting-pilot (#R05-0184) and fed-pivotal (#R04-1364) bioequivalence studies submitted in support of the ANDA are unacceptable.

2. The firm may elect to conduct and submit new fasting and fed bioequivalence studies using an acceptable fully-validated assay. In lieu of conducting new studies, the firm may choose to re-assay samples from these studies if sufficient plasma volumes exist and long term storage stability has been demonstrated.

3. If the firm chooses to conduct new studies, they should complete new dissolution testing using the same lot of the test and reference products as the ones used in the new fasting and fed studies.

4. The DBE notes that study #R05-1389 (fasting pivotal) was conducted by dosing subjects with 2x100mg dose of carbamazepine extended release tablets. The DBE currently recommends a single dose of the highest strength (400mg) be used in both fasting and fed bioequivalence studies. The DBE may deem the lower strengths bioequivalent based on CFR 320.24(b)(6) provided all strengths are proportionally formulated and acceptable dissolution testing has been completed.

VI. Recommendations

1. The bioequivalence study (#R05-1389) under fasting conditions conducted by the PRACS Institute on behalf of Taro Phamaceuticals on its carbamazepine extended release tablets, 100mg, Lot #781064, comparing it to Novartis' Tegretol®-XR, 100mg, Lot #F4089, is unacceptable due to recent findings from the DSI audit. The PRACS Institute has yet to respond to these findings. The firm may choose to re-conduct this study or reanalyze existing samples from the study provided long term storage stability data of analyte in matrix exists for the samples. The DBE does not currently recommend a bioequivalence study be conducted on strengths other than 400mg. Lower strengths may be deemed bioequivalent based on CFR 320.24(b)(6) provided all strengths are proportionally formulated and acceptable dissolution testing has been completed.

2. The pilot bioequivalence study (#R05-0184) under fasting conditions conducted by the PRACS Institute on behalf of Taro Phamaceuticals on its carbamazepine extended release tablets, 400mg, Lot #780980 comparing it to Novartis' Tegretol®-XR, 400mg, Lot #F4109, is unacceptable due to recent findings from the DSI audit. The PRACS Institute has yet to respond to these findings. The firm may choose to re-conduct this study or reanalyze existing samples from the study provided long term storage stability of analyte in matrix exists for the samples.

3. The bioequivalence study (#R04-1364) under fed conditions conducted by the PRACS Institute on behalf of Taro Phamaceuticals on its carbamazepine extended release tablets, 400mg, Lot #780980, comparing it to Novartis' Tegretol®-XR, 400mg, Lot #F4109, is

unacceptable due to recent findings from the DSI audit. The PRACS Institute has yet to respond to these findings. The firm may choose to re-conduct this study or reanalyze existing samples from the study provided long term storage stability data of analyte in matrix exists for the samples.

The firm should be informed of the above deficiency comments and recommendations.

VII. Appendix

A. Not to be Released Under Freedom of Information (DBE/DSI Meeting Notes)

Date: October 2, 2007 **Time**: 1:00 PM MPN I

Subject: Carbamazepine Extended-release Tablets (78-115)

Meeting Type: Internal Meeting

FDA Participants:

Bob West, Deputy Director, Office of Generic Drugs (OGD)
Dale Conner, Director, Division of Bioequivalence (DBE)
Lizzie Sanchez, Special Assistant to Director, DBE
Kuldeep Dhariwal, Team Leader, Team 5, DBE
Christopher Jones, Reviewer, Team 5, DBE
CT Viswanathan, Associate Director, Division of Scientific Investigations (DSI)
Nilufer Tampal, Reviewer, DSI
Michael Skelly, Reviewer, DSI
Jacqueline O'Shaughnessy, Reviewer, DSI

Meeting Objective:

The DSI inspection report for ANDA 78-115, Carbamazepine Extended-release Tablets was received by the DBE. The DBE would like to clarify and discuss these findings and its impact on this and other ANDAs that contain studies conducted at PRACS. The deficiencies appear significant without a recommendation to reject the study.

Discussion:

- The major finding from this inspection was the lack of audit trail for the (b) (4) software used for chromatography integrations. It is not clear how the integrations were conducted. It is unacceptable to turn off the audit trail.
- The audit trail function was disabled during the conduct of studies R04-1364 and R05-1389 for this application, without adequate justification. PRACS claims that there were technical problems. However, DSI was not able to verify their claim.
- The audit trail was turned off from April-May 2005 to April 2007. A new version of the software was installed in April 2007, with the audit trail function always "enabled".
- All studies conducted using the instrumentation with disabled audit trail software, during that period of time, should be re-evaluated. There is more than one instrument involved with audit trails turned off.
- A Form 483 was issued. PRACS has not responded to the deficiencies.

Action Items:

- The studies in this application are not considered acceptable, and a deficiency will be issued to the firm, Taro.
- (b) (5)

Drafted: Christina Thompson, Project Manager (10/4/2007)
Comments:
L. Sanchez/10/4/2007

B. Not to be Released Under Freedom of Information (DBE Dissolution Focal Point Opinion)

Hi Chris,

I just compiled and looked over all the data that you sent me. From what I can see, for the firm's product(s), I would recommend that they use a different media than USP. I suggest that the firm use the following method:

Acetate Buffer, pH 4.5
1800 mL (400 mg), 900 mL (100 mg, 200 mg)
I (Basket)/ 100 rpm

This method provides overall good discrimination across all strengths compared to other methods. I wouldn't worry about the RLD too much in this case since particularly for MR products, generics can behave very differently than RLD due to formulation issues (e.g. osmotic pump). The above recommended media still provides the best profiles even considering the RLD profiles.

As for the specificaiton, I recommend the following:

For 400mg and 200mg
3hr: (b) (4)
6hr:
12hr:
24hr:

For 100mg
3hr: (b) (4)
6hr:
12hr:
24hr:

Depending on how the biostudies look, you may want to consider giving a little more "breathing room" to the specs as per the following (its up to you and Kuldeep however) and would still be acceptable in my opinion.

For 400mg and 200mg
3hr: (b) (4)
6hr:
12hr:
24hr:

For 100mg
3hr: (b) (4)
6hr:
12hr:
24hr:

You could potentially extend the specs for the 400mg and 200 mg to include the 100 mg strength (resulting in 1 set of specs), but you would lose what discrimination you have w/ the current specs. Therefore, it looks like we can't avoid having 2 sets of specs for the 3 different strengths. This is just a recommendation, please consult your TL as well.

Thanks,
Paul

-----Original Message-----
From: Jones, Christopher
Sent: Fri 1/19/2007 10:10 AM
To: Seo, Paul
Cc: Dhariwal, Kuldeep R
Subject: Dissolution Focal Point Question

Paul:

I spoke with you briefly about ANDA 78-115 about a month and a half ago. I completed an initial review and now have an amendment to consider. The drug is Carbamazepine ER Tabs (400mg, 200mg & 100mg) by Taro. The firm conducted three successful bioequivalence studies and they would like to use dissolution data to waive the middle strength (200mg). The firm conducted a fasting pilot study on the 400mg strength, a fasting study on the 100mg strength and a fed study on the 400mg strength. They chose to conduct a fasting study on the 100mg strength because by their own admission, the dissolution data are not sufficient to support a waiver. They have completed a number of dissolution tests and submitted additional dissolution tests per our request in the amendment yesterday. In the MSWord document attached I'm including these summarized tabulated data.

The problem I'm encountering is setting a specification that is universal to all strengths. Their product doesn't meet the specification that they themselves recommend. It seems that the 100mg strength consistently dissolves at a higher rate than the 200mg strength in the same volume of media.

To further complicate the issue, the innovator product consists of an insoluble shell that delivers drug via an osmotic gradient through a laser drilled hole where as the test product is a (b) (4) tablet which is more vulnerable to changing dissolution conditions. The test product releases more drug or "dose dumps" under different conditions.

I'm asking for your advice as to what specification and/or method to set for this drug or any other pearl of wisdom you may offer with respect to the information we have thus far. Let me know if you need more information.

Thanks for your time

Chris

<<Dissolution Study Summary.doc>>

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-115 APPLICANT: Taro Pharmaceutical Industry Ltd.

DRUG PRODUCT: Carbamazepine Extended-Release Tablets, USP
100mg, 200mg and 400mg

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

1. The Division of Scientific Investigations (DSI) conducted an audit of the analytical facility (PRACS Institute, Fargo ND) where carbamazepine samples were analyzed for the fasting pivotal (#R05-1389), fasting-pilot (#R05-0184) and fed-pivotal (#R04-1364) bioequivalence studies submitted for this ANDA. The DSI detected analytical problems, specifically a disabled audit trail function on software used to acquire and integrate chromatograms. Additionally, the PRACS Institute failed to provide documentation demonstrating proper storage temperatures and locations of stock solutions, sample extracts prior to analysis on HPLC/MS/MS and QCs used to demonstrate stability of analyte in matrix at room temperature. The DSI recommends that the DBE not accept these bioequivalence studies. The DBE concurs with this recommendation. Therefore, your fasting pivotal (#R05-1389), fasting-pilot (#R05-0184) and fed-pivotal (#R04-1364) bioequivalence studies submitted in support of your ANDA are unacceptable.

2. Please conduct and submit new fasting and fed bioequivalence studies using an acceptable fully-validated assay. In lieu of conducting new studies, you may choose to re-assay samples from these studies if sufficient plasma volumes exist and long term storage stability has been demonstrated.

3. If you choose to conduct new studies, please complete new dissolution testing using the same lot of the test and reference products as the ones used in the new fasting and fed studies.

4. The DBE notes that study #R05-1389 (fasting pivotal) was conducted by dosing subjects with 2x100mg dose of carbamazepine extended release tablets. The DBE currently recommends a single dose of the highest strength (400mg) be

used in both fasting and fed bioequivalence studies. The DBE may deem the lower strengths bioequivalent based on CFR 320.24(b)(6) provided all strengths are proportionally formulated and acceptable dissolution testing has been completed.

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

ANDA: 78-115
Carbamazepine ER Tablets
Taro

VIII. *Completed Assignment for 78115 ID: 662*

Reviewer: Jones, Christopher **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description: Study Amendment from January 4th 2007 DSI Audit Report September 17th 2007

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*		
662	1/4/2007	Other	Study Amendment	1	1	Edit	Delete
662	9/17/2007	Other	DSI Inspection Report	1	1	Edit	Delete
				Bean Total:	2		

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

/s/

S Christopher Jones
10/18/2007 11:44:47 AM
BIOPHARMACEUTICS

Kuldeep R. Dhariwal
10/18/2007 11:50:51 AM
BIOPHARMACEUTICS

Dale Conner
10/18/2007 01:18:29 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-115		
Drug Product Name	**Carbamazepine Extended-Release Tablets, USP**		
Strength(s)	100mg, 200mg & 400mg		
Applicant Name	Taro Pharmaceutical Industries Ltd.		
Address	14 Hakitor Street Haifa Vay, Israel 26110 FCIS026		
Applicant's Point of Contact	Kalpana Rao Taro Pharmaceuticals U.S.A., Inc. 3 Skyline Drive Hawhorne NY 10532		
Contact's Telephone Number	914-345-9001		
Contact's Fax Number	914-593-0078		
Original Submission Date(s)	December 29, 2005		
Submission Date(s) of Amendment(s) Under Review	January 24, 2008; January 25, 2008		
Reviewer	Sherry Bous, Pharm.D.		
Study Number (s)	CRN-P7-304 (previously R05-0185)	CRN-P7-305 (previously R05-0184)	
Study Type (s)	Fed- Pilot	Fasting- Pilot	
Strength (s)	400 mg	400 mg	
Clinical Site	PRACS Institute, Ltd. Fargo, ND 58104 & East Grand Forks, MN 56721		
Clinical Site Address			
Analytical Site	(b) (4)		
Analytical Site Address			
Study Number (s)	CRN-P7-303 (previously R05-1389)	CRN-P7-306 (previously R04-1364)	
Study Type (s)	Fasting- Pivotal	Fed- Pivotal	
Strength (s)	2 x 100 mg	400 mg	
Clinical Site	PRACS Institute, Ltd. Fargo, ND 58104 & East Grand Forks, MN 56721		
Clinical Site Address			
Analytical Site	(b) (4)		
Analytical Site Address			
OUTCOME DECISION	**INCOMPLETE**		

1 EXECUTIVE SUMMARY

This is a review of the second amendment. ***To accept all three strengths, the DBE recommends 2 BE studies (fasting and fed) on the 400 mg ER tablet*** and multimedia dissolution testing on all three strengths. **In the original submission (12-29-2005),** Taro Pharmaceuticals submitted a total of four BE studies. Those were 3 BE studies on the 400 mg ER tablet [pilot-fast (Study R05-0184), pilot-fed (Study R05-0185), and pivotal-fed (Study R04-1364),] and a fourth study on the 100mg ER tablet (pivotal-fast, Study R05-1389). ***Even though the firm did not conduct fasting and fed BE study on the 400 mg ER tablet, the DBE accepted its above mentioned plan of BE studies.*** However the DBE communicated 3 deficiencies to the firm (one of the deficiencies requested additional dissolution testing).

The firm submitted the first amendment on January 4, 2007 satisfactorily addressing the three deficiencies that were communicated to the firm. However, the DBE also reviewed the DSI report along with the 1st amendment and found 4 DSI-report-related deficiencies. Of these four only the 2nd was a valid deficiency. This valid deficiency gave the firm two choices viz. i) to either pursue sample re-analysis if sufficient plasma volumes exist and long term storage stability has been demonstrated or ii) to conduct and submit new fasting and fed bioequivalence studies using an acceptable fully-validated assay. The DBE finalized dissolution testing methods and specifications for Taro's 3 carbamazepine ER tablets but did not convey those to the firm.

The firm submitted the current amendment (2nd) by electing to pursue sample re-analysis. The firm re-analyzed its samples at (b) (4) (b) (4) also determined carbamazepine long term stability of 2070 days at -20°C. **Based on the SAS analyses of the re-assayed blood samples, the fasting and fed BE studies are acceptable. The earlier data that were disallowed because of disabling of audit trail are very similar to the data in this amendment [see pages (15, 16) and (22, 23)].** The dissolution testing is acceptable but is incomplete pending an acknowledgement from the firm for the following FDA-recommended method and data driven specification:

FDA Method

Acetate Buffer, pH 4.5
1800 mL (400 mg), 900 mL (100 mg, 200 mg)
Apparatus I (Basket)/ 100 rpm

Specifications:

For 400mg and 200mg:	For 100mg:
3hr: (b) (4) 6hr: 12h 24h	3hr: (b) (4) 6hr: 12hr 24hr

The application is acceptable pending acknowledgement of the FDA recommended method and data driven specification. No DSI inspection is required at this time.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 OGD Recommendations for Drug Product

Number of studies recommended:	2, fasting and fed

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	400 mg
	Subjects:	Normal healthy males, and females that are not pregnant, general population
	Additional Comments:	

2.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	400 mg
	Subjects:	Normal healthy males, and females that are not pregnant, general population
	Additional Comments:	

Analytes to measure (in plasma/serum/blood):	Only parent compound (carbamazepine)
Bioequivalence based on:	90% CI
Waiver request of in-vivo testing:	100 mg, 200 mg
Source of most recent recommendations:	**Control #05-1506** (b) (4)

Summary of OGD or DBE History	The Division of Bioequivalence (DBE) has reviewed the following documents for Carbamazepine Extended Release Tablets: **ANDAs:** • (b) (4) Application Withdrawn • (b) (4) Application Withdrawn • (b) (4) Application Withdrawn • (b) (4) Pending • (b) (4) Application Withdrawn **Controlled Documents:** • **00-172** (b) (4) • **05-1506** • **00-337** • **02-146** • **05-0047** • **99-084** • **05-1142** • **05-0337** **Protocols:** • **01-056** (b) (4)

The firm conducted a fed pivotal study on the 400 mg ER tablet, d a fasting pivotal study on the 100 mg ER tablet (2 x 100 mg dose), a fed pilot study on the 400 mg ER tablet measuring the parent and a metabolite, and a fasting pilot on the 400 mg ER tablet.

The previous reviewer noted that the DBE typically recommends a single dose, fasting BE study on the 400mg ER tablet. This sponsor chose to conduct the study on the 100 mg ER tablet (a single dose of 2x100mg). The firm provided the following rationale to support this decision (volume 15, page 2156), "Since the carbamazepine 400mg, 200mg and 100mg extended release tablets are proportionally similar in their active and inactive ingredients and in the drug release mechanism, a waiver can be granted based upon dissolution profiles. The dissolution profiles in all three media were not similar (based upon the f2 test) between the highest and the lowest strengths. Due to the fact that the *in vitro* dissolution is not always predictive of *in-vivo* behavior in extended release products, Taro decided to conduct a fasted study on the 100mg strength to confirm bioequivalence." **The reviewer concluded that the design of a fasting BE study on the 100 mg ER tablet and fed BE study on the 400 mg ER tablet is acceptable.**

3.2 Pre-Study Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	N/AP
Analyte	Carbamazepine
Internal Standard (IS)	(b) (4)
Method description	Protein precipitation extraction; HPLC with MS/MS detection
Limit of quantitation	50.0 ng/mL
Average recovery of drug (%)	94.1%
Average recovery of IS (%)	101.5%
Standard curve concentrations (ng/mL)	50.0 ng/mL, 100.0 ng/mL, 300.0 ng/mL, 800.0 ng/mL, 1800.0 ng/mL, 3500.0 ng/mL, 4200.0 ng/mL, 5000.0 ng/mL
QC concentrations (ng/mL)	50.0 ng/mL, 150.0 ng/mL, 1200.0 ng/mL, 3800.0 ng/mL
QC Intraday precision range (%)	1.7% - 10.7%
QC Intraday accuracy range (%)	97.5% - 105.9%
QC Interday precision range (%)	2.3% - 6.7%
QC Interday accuracy range (%)	100.5% - 104.6%
Bench-top stability (hrs)	46.9 hours at a temperature of 22°C nominal
Stock stability (days)	34 days at a concentration of 1000.00 µg/mL at a temperature of 4°C nominal 11 days at a concentration of 5.00 µg/mL at a temperature of 4°C nominal
Processed stability (hrs)	141.7 hours at a temperature of 4°C nominal
Freeze-thaw stability (cycles)	6 cycles
Long-term storage stability (days)	2070 days at a temperature of -20°C nominal
Dilution integrity	10000.0 ng/mL diluted 5-fold
Selectivity	No significant interference at the retention time and mass transition of Carbamazepine or IS was observed in any of the 10 blank matrix pools screened.

N/AP: Not Applicable.

Comments on the Pre-Study Method Validation:

Acceptable

3.3 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (ng/mL)	T_{max}* (hr)	AUC_{0-t} (ng·h/mL)	AUC_{∞} (ng·h/mL)	$T_{½}$ (hr)	K_{el} (hr^{-1})	
Study # CRN-P7-303 (Sponsor Study # PRACS R05-1389)	A Relative Bioavailability Study of 100 mg Carbamazepine Extended-Release Tablets under Fasting Conditions	Randomized single-dose 2-way crossover	2 X Carbamazepine CR US Tablets (F3) 100 mg p.o. [Batch # 781064]	21 completing (21 M)** Healthy subjects Age: N/A (N/A)	1443.0 (246.2)	27.00 (6.00 – 30.00)	109860.4 (23675.2)	120549.8 (28744.3)	43.10 (8.58)	0.0167 (0.0032)	N/AP
			2 X Tegretol® - XR Tablets 100 mg p.o. [Batch # F4089]		1520.0 (237.9)	27.00 (12.00 – 30.00)	109493.1 (22065.8)	120081.8 (27456.5)	43.07 (8.93)	0.0167 (0.0033)	

* Median and (range) are presented for T_{max}.

** 21 subjects completing the crossover design, i.e. received both the Test product and the Reference formulation, however 20 subjects were included in the main pharmacokinetic and statistical re-analyses, excluding subject # 024.

N/A: Not Available.

N/AP: Not Applicable.

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (ng/mL)	T_{max}* (hr)	AUC_{0-t} (ng·h/mL)	AUC_{∞} (ng·h/mL)	$T_{½}$ (hr)	K_{el} (hr^{-1})	
Study # CRN-P7-306 (Sponsor Study # PRACS R04-1364)	A Relative Bioavailability Study of 400 mg Carbamazepine Extended-Release Tablets under Non-Fasting Conditions	Randomized single-dose 2-way crossover	Carbamazepine CR US Tablets (F3) 400 mg p.o. [Batch # 780980]	34 completing (34M) Healthy subjects Age: N/A (N/A)	3398.4 (610.6)	20.00 (8.00-30.00)	242533.9 (46433.1)	262174.8 (53390.4)	39.41 (6.45)	0.0181 (0.0033)	N/AP
			Tegretol® - XR Tablets 400 mg p.o. [Batch # F4109]		2979.4 (532.3)	18.00 (10.00-30.00)	211390.7 (44193.4)	229776.8 (52363.1)	42.51 (8.90)	0.0170 (0.0036)	

* Median and (range) are presented for T_{max}.
N/A: Not Available.
N/AP: Not Applicable.

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

Carbamazepine Dose (2 x 100 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (CRN-P7-303)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (units)	107534.9	107369.9	1.00	93.52	107.26
AUC∞ (units)	117409.3	117170.8	1.00	93.08	107.87
Cmax (units)	1422.64	1502.32	0.95	88.80	100.99

Carbamazepine Dose (1 x 400 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study (CRN-P7-306)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (units)	237573.2	205818.3	1.15	111.22	119.80
AUC∞ (units)	256229.8	222726.0	1.15	110.74	119.51
Cmax (units)	3346.15	2926.88	1.14	110.30	118.49

Table 3. Reanalysis of Study Samples

Study No. CRN-P7-303								
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 Fit (PF)	0	0	0.0	0.0	0	0	0.0	0.0
Sample Lost in Processing (SLP)	0	1	0.0	0.1	N/AP	N/AP	N/AP	N/AP
Total	0	1	0.0	0.1	0	0	0.0	0.0

N/AP: Not Applicable.

Study No. CRN-P7-306								
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 Fit (PF)	0	0	0.0	0.0	0	0	0.0	0.0
Above Upper Limit of Quantitation (>ULQ)	3	0	0.2	0.0	N/AP	N/AP	N/AP	N/AP
Sample Lost in Processing (SLP)	4	3	0.2	0.2	N/AP	N/AP	N/AP	N/AP
Total	7	3	0.4	0.2	0	0	0.0	0.0

N/AP: Not Applicable.

Did use of recalculated plasma concentration data change study outcome? No, the 3 samples that were re-drawn for being above the limit of quantification are valid since it was first pre-defined in SOP LAP-3001-06.

Comments from the Reviewer:

3.4 Waiver Request(s)

Strengths for which waivers are requested	200 mg
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	Yes
Waivers granted?	**NO**
If not then why?	Acknowledgement of FDA recommended method and data driven specification required.

3.5 Deficiency Comments

1. The firm's in vitro dissolution testing is incomplete pending its acceptance and acknowledgment of the FDA-recommended method and specifications. The dissolution testing should be conducted in (900 mL for 100 mg and 200 mg strength, and 1800 mL for the 400 mg strength) of (Acetate Buffer, pH 4.5) at (temp, 37ºC + 0.5ºC) using (USP apparatus I) at (100 rpm). The test product should meet the following specification(s):

Specifications:

For 400mg and 200mg:	For 100mg:
3hr: (b) (4) 6hr: 12hr 24hr	3hr: (b) (4) 6hr: 12hr 24hr

3.6 Recommendations

Standard BE Studies

1. The Division of Bioequivalence accepts the fasting BE study (CRN-P7-303) conducted by Taro Pharmaceuticals on Carbamazepine 100 mg extended release

tablets comparing it to Tegretol® XR (carbamazepine) extended release tablets, 100 mg (Novartis).

2. The Division of Bioequivalence accepts the fed BE study (CRN-P7-306) conducted by the (Taro Pharmaceuticals on Carbamazepine 400 mg extended release tablets comparing it to Tegretol® XR (carbamazepine) extended release tablets, 400 mg (Novartis).

3. The firm's in vitro dissolution testing is incomplete pending its acceptance and acknowledgment of the FDA-recommended method and specifications. The dissolution testing should be conducted in (900 mL for 100 mg and 200 mg strength, and 1800 mL for the 400 mg strength) of (Acetate Buffer, pH 4.5) at (temp, 37ºC + 0.5ºC) using (USP apparatus I) at (100 rpm). The test product should meet the following specification(s):

Specifications:

For 400mg and 200mg:	For 100mg:
3hr: (b) (4) 6hr: 12hr 24hr	3hr: (b) (4) 6hr: 12hr 24hr

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	**CRN-P7-303**
Study Title	A Relative Bioavailability Study of 100mg Carbamazepine Extended Release Tablets under Fasting Conditions
Clinical Site (Name, Address, Phone #)	PRACS Institute Ltd. 625 Demers Ave East Grand Forks, MN 57621
Principal Investigator	**James D. Carlson, Pharm.D.**
Dosing Dates	Period I: October 29th, 2005 Period II: November 19th, 2005
Analytical Site (Name, Address, Phone #)	(b) (4)
Re-Analysis Dates	Between 2007/11/21 and 2007/12/06
Analytical Director	(b) (6) Ph.D.
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	768 days

4.1.1.2 Bioanalytical Results

Table 5. Assay Validation – Within the Fasting Bioequivalence Study

Bioequivalence Study No. CRN-P7-303 Carbamazepine								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	50.0	100.0	300.0	800.0	1800.0	3500.0	4200.0	5000.0
Inter day Precision (%CV)	5.7	4.2	3.3	4.4	2.1	3.0	4.3	2.4
Inter day Accuracy (%Actual)	91.7	99.2	103.8	104.5	101.3	105.0	98.7	96.4
Linearity	0.9950 – 0.9995							
Linearity Range (ng/mL)	50.0 – 5000.0							
Sensitivity/LOQ (ng/mL)	50.0							

Bioequivalence Study No. CRN-P7-303 Carbamazepine			
Parameter	**Quality Control Samples**		
Concentration (ng/mL)	150.0	1200.0	3800.0
Inter day Precision (%CV)	6.7	6.2	4.1
Inter day Accuracy (%Actual)	97.2	102.8	96.7

Comments on Study Assay Validation:

Acceptable

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

Comments on Chromatograms:

Acceptable

Table 6. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
LAP-3001-06	2007/09/04	Sample Coding and Re-assay

Table 7. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	Not applicable

Summary/Conclusions, Study Assays:

4.1.1.3 Pharmacokinetic Results

Table 8. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 12

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	109860.4	21.55	73479.60	167822.2	109493.1	20.15	69790.30	148846.9	1.00
AUCI	ng hr/mL	120549.8	23.84	75396.70	187123.0	120081.8	22.86	72704.90	173419.0	1.00
CMAX	ng/mL	1442.98	17.06	960.80	1881.10	1519.97	15.65	1105.70	2005.50	0.95
TMAX	hr	27.00	.	6.00	30.00	27.00	.	12.00	30.00	1.00
KE	hr-1	0.02	19.07	0.01	0.02	0.02	19.73	0.01	0.02	1.00

Arithmetic mean PK parameters from the earlier review (signed on 12-19-2006): The data were not accepted because the audit trail was disabled during the sample assay.

Carbamazepine (n=20)

	Test	CV1	Ref	CV2	T/R
PARAMETER					
AUCT (ng*hr/ml)	109534.88	21.83	108461.03	20.37	1.01
AUCI (ng*hr/ml)	120454.75	24.44	119274.00	23.88	1.01
CMAX (ng/ml)	1386.09	15.91	1433.37	15.01	0.97
TMAX (hr)	26.00	26.76	25.30	24.50	1.03
KE (hr^{-1})	0.02	18.05	0.02	19.81	1.03
THALF (hr)	42.82	18.12	44.29	21.57	0.97

Table 9. Geometric Means and 90% Confidence Intervals - Firm Calculated

Carbamazepine Dose (2 x 100 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (CRN-P7-303)					
Parameter	Test	Reference	Ratio	90% C.I.	
AUC0-t (units)	107534.9	107369.8	100.15	93.52	107.26
AUC∞ (units)	117409.3	117170.8	100.20	93.08	107.87
Cmax (units)	1422.6	1502.3	94.70	88.80	100.99

Table 10. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	107534.9	107369.9	1.00	93.52	107.26
LAUCI	117409.3	117170.8	1.00	93.08	107.87
LCMAX	1422.64	1502.32	0.95	88.80	100.99

Statistical analysis of PK parameters from the earlier review (signed on 12-19-2006): The data were not accepted because the audit trail was disabled during the sample assay.

Summary of Statistical Analysis (Fasted Study-Carbamazepine)§ N=20				
Parameter	Test	Reference	Point Estimate	90% Confidence Interval
$LAUC_{0-t}$ (ng*hr/ml)	107115.53	106316.83	100.75	(94.09-107.88)
$LAUC_{\infty}$ (ng*hr/ml)	117119.72	116132.73	100.84	(93.50-108.78)
LC_{max} (ng/ml)	1369.94	1418.64	96.57	(91.70-101.69)

§These results were calculated by the reviewer and corroborate those reported by the firm. See comments under "Pharmacokinetic Analysis" for further details.

Table 11. Additional Study Information, Fasting Study No.

Root mean square error, AUC0-t	0.1250	
Root mean square error, AUC∞	0.1345	
Root mean square error, Cmax	0.1173	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	All	All
Do you agree or disagree with firm's decision?	Yes	Yes
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Treatment	n	Mean	Minimum	Maximum
TEST	20	0.92	0.83	0.97
REFERENCE	20	0.92	0.83	0.96

Comments on Pharmacokinetic and Statistical Analysis:

- According to the firm, "Subject #24 (b) (6) was excluded from the statistical analysis secondary to vomiting following dose administration within the labeled dosing interval for Tegretol XR tablets 100 mg." Subject #24 vomited on the dosing day (10/29/05) at 1755 and was therefore excluded from the final statistical analysis. The reviewer agrees with the firm's decision to exclude data from subject #24 in the final analysis. A second subject, (#22 (b) (6) vomited on 11/21/05 at 2330, over 60 hours after dosing. The firm retained the data from this subject for their statistical analysis. When the reviewer excluded this subject from the analysis, the outcome of the study was unchanged. The reviewer agrees with the decision to retain subject #22 in the final analysis. There were no subjects with detectable predose plasma concentrations or first reportable plasma concentration as the C_{max}.

- Note subject #13, #14 and #16 did not complete the study and were not included in the final statistical analysis.

- The RMSE are relatively small suggesting the carbamazepine extended release tablet formulation has pharmacokinetics with low variability with respect to intra-subject performance.

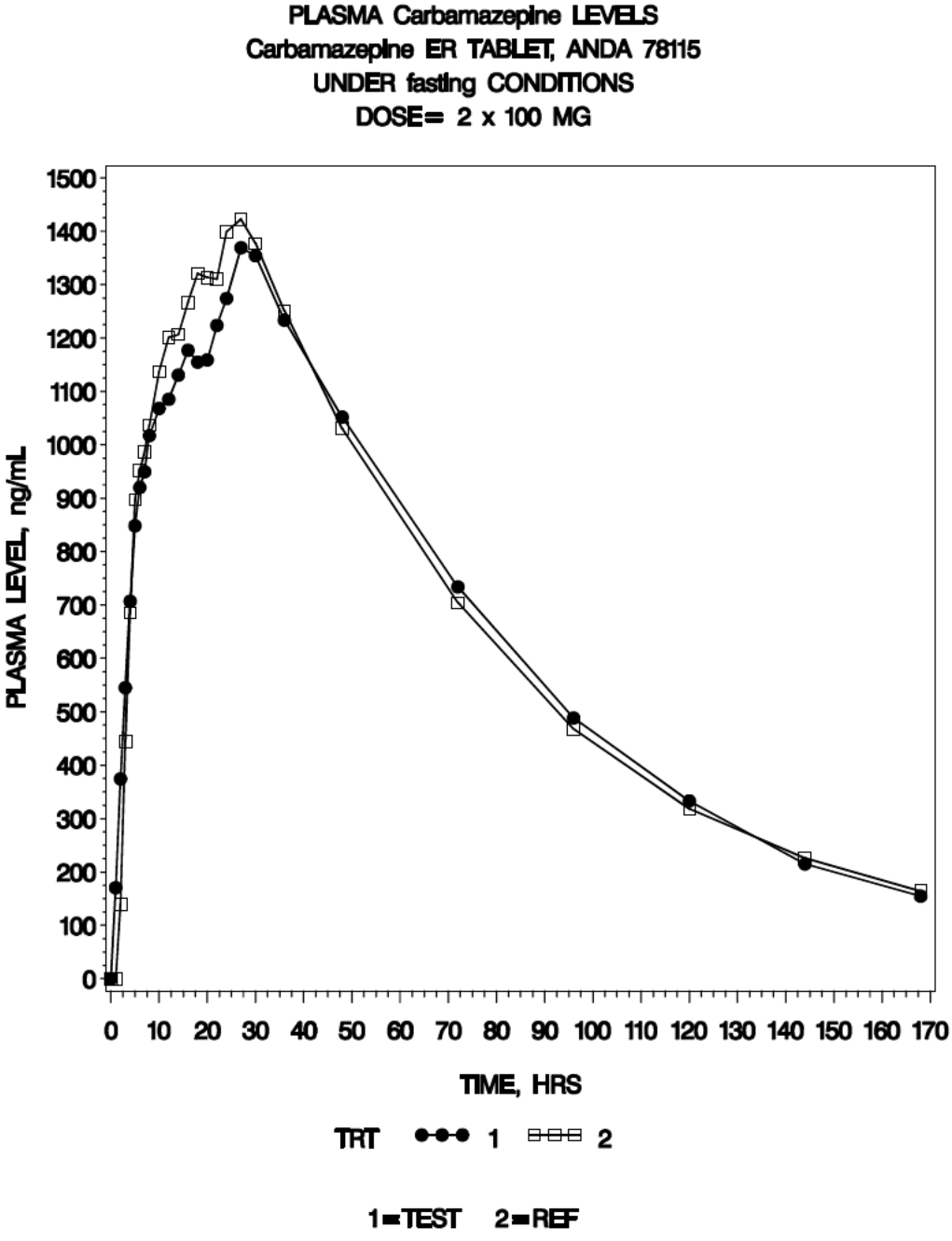
Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

Acceptable

Table 12. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

	Test (n=20)		Reference (n=20)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
1.00	170.54	66.53	0.00	.	.
2.00	374.35	49.58	139.31	45.86	2.69
3.00	544.95	40.85	444.20	29.27	1.23
4.00	706.93	31.18	685.56	29.33	1.03
5.00	848.22	24.88	897.31	23.85	0.95
6.00	920.16	21.87	951.83	20.16	0.97
7.00	949.40	24.41	986.68	17.19	0.96
8.00	1017.28	19.88	1036.89	15.98	0.98
10.00	1068.01	20.73	1136.68	15.86	0.94
12.00	1085.23	18.47	1200.97	14.21	0.90
14.00	1130.44	18.69	1206.78	15.31	0.94
16.00	1176.87	15.75	1266.91	15.91	0.93
18.00	1154.69	18.42	1320.54	17.52	0.87
20.00	1158.85	17.64	1313.49	18.11	0.88
22.00	1223.47	16.22	1310.50	15.03	0.93
24.00	1273.97	16.64	1399.02	19.10	0.91
27.00	1368.95	19.03	1422.14	19.38	0.96
30.00	1354.17	18.28	1377.20	16.04	0.98
36.00	1233.29	19.40	1250.97	16.22	0.99
48.00	1051.72	24.88	1030.29	21.56	1.02
72.00	733.84	27.86	704.58	25.05	1.04
96.00	488.25	33.35	467.72	28.39	1.04
120.00	333.06	37.20	318.41	34.83	1.05
144.00	214.93	44.23	226.07	42.56	0.95
168.00	154.76	48.26	164.16	39.55	0.94

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



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 13. Study Information

Study Number	**CRN-P7-306**
Study Title	A Relative Bioavailability study of 400 mg Carbamazepine ER tabs under Non-fasting conditions.
Clinical Site (Name, Address, Phone #)	PRACS Institute, Ltd. Fargo, ND 58104 & East Grand Forks, MN 56721 (701) 239-4750
Principal Investigator	James D. Carlson, Pharm. D.
Dosing Dates	Period 1: 2005/07/30 Period 2: 2005/08/20
Analytical Site (Name, Address, Phone #)	(b) (4)
Analysis Dates	Between 2007/11/16 and 2007/12/04
Analytical Director	(b) (6) Ph.D.
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	857 days

4.1.2.2 Bioanalytical Results

Table 14. Assay Validation – Within the Fed Bioequivalence Study

Bioequivalence Study No. CRN-P7-306 Carbamazepine								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	50.0	100.0	300.0	800.0	1800.0	3500.0	4200.0	5000.0
Inter day Precision (%CV)	7.2	5.0	4.2	5.4	4.1	5.0	4.3	4.5
Inter day Accuracy (%Actual)	97.0	96.5	104.9	102.0	99.8	101.7	101.5	97.2
Linearity	0.9935 – 0.9993							
Linearity Range (ng/mL)	50.0 – 5000.0							
Sensitivity/LOQ (ng/mL)	50.0							

Bioequivalence Study No. CRN-P7-306 Carbamazepine			
Parameter	**Quality Control Samples**		
Concentration (ng/mL)	150.0	1200.0	3800.0
Inter day Precision (%CV)	5.5	5.3	6.4
Inter day Accuracy (%Actual)	100.4	104.5	99.1

Comments on Study Assay Validation:

Acceptable

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially, subject #s 1,2,3,4,5 & 6.

Comments on Chromatograms:

Acceptable

Table 15. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
LAP-3001-06	2007/09/04	Sample Coding and Re-assay

Table 16. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	Not Applicable

Summary/Conclusions, Study Assays:

4.1.2.3 Pharmacokinetic Results

Table 17. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 21 and Figure 2

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	242533.9	19.14	153699.6	337912.5	211390.7	20.91	93587.70	300138.0	1.15
AUCI	ng hr/mL	262174.8	20.36	155880.7	377927.6	229776.8	22.79	95988.00	336964.7	1.14
CMAX	ng/mL	3398.42	17.97	2489.70	4933.20	2979.39	17.87	1989.30	4505.30	1.14
TMAX	hr	20.00	.	8.00	30.00	18.00	.	10.00	30.00	1.11
KE	hr-1	0.02	18.50	0.01	0.03	0.02	21.33	0.01	0.03	1.06

Arithmetic mean PK parameters from the earlier review (signed on 12-19-2006): The data were not accepted because the audit trail was disabled during the sample assay.

Carbamazepine (n=34)

	Test	CV1	Ref	CV2	T/R
PARAMETER					
AUCT (ng*hr/ml)	261266.22	19.42	228075.05	21.45	1.15
AUCI (ng*hr/ml)	280562.36	21.11	247005.59	23.20	1.14
CMAX (ng/ml)	3532.46	14.98	3185.76	17.86	1.11
TMAX (hr)	21.29	34.56	19.26	36.87	1.11
KE (hr^{-1})	0.02	20.44	0.02	21.67	1.07
THALF (hr)	38.74	18.65	41.65	20.62	0.93

Table 18. Geometric Means and 90% Confidence Intervals - Firm Calculated

Carbamazepine Dose (1 x 400 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study (CRN-P7-306)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (units)	237573.2	205818.3	115.43	111.22	119.80
AUC∞ (units)	256229.8	222726.0	115.04	110.74	119.51
Cmax (units)	3346.2	2926.9	114.32	110.30	118.49

Table 19. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	237573.2	205818.3	1.15	111.22	119.80
LAUCI	256229.8	222726.0	1.15	110.74	119.51
LCMAX	3346.15	2926.88	1.14	110.30	118.49

Statistical analysis of PK parameters from the earlier review (signed on 12-19-2006): The data were not accepted because the audit trail was disabled during the sample assay.

Summary of Statistical Analysis (Fed Study-Carbamazepine)§ N=34				
Parameter	Test	Reference	Point Estimate	90% Confidence Interval
$LAUC_{0-t}$ (ng*hr/ml)	255942.17	221802.65	115.39	(111.53-119.38)
$LAUC_{\infty}$ (ng*hr/ml)	273838.10	239184.59	114.49	(110.35-118.79)
LC_{max} (ng/ml)	3492.33	3129.65	111.59	(108.88-114.36)

§These results were calculated by the reviewer and reasonably corroborate those reported by the firm. See comments under "Pharmacokinetic Analysis" for further details.

Table 20. Additional Study Information

Root mean square error, AUC0-t	0.0903	
Root mean square error, AUC∞	0.0926	
Root mean square error, Cmax	0.0870	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	All	All
Do you agree or disagree with firm's decision?	Yes	Yes
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Treatment	n	Mean	Minimum	Maximum
TEST	34	0.93	0.82	0.99
REFERENCE	34	0.92	0.82	0.98

Comments on Pharmacokinetic and Statistical Analysis:

There were no subjects who vomited, had detectable predose plasma concentrations or first reportable plasma concentration as the C_{max} in this study. Note subject #23 and #29 did not complete the study and were not included in the final statistical analysis.

The RMSE are relatively small suggesting the carbamazepine extended release tablet formulation has pharmacokinetics with low variability with respect to intra-subject performance.

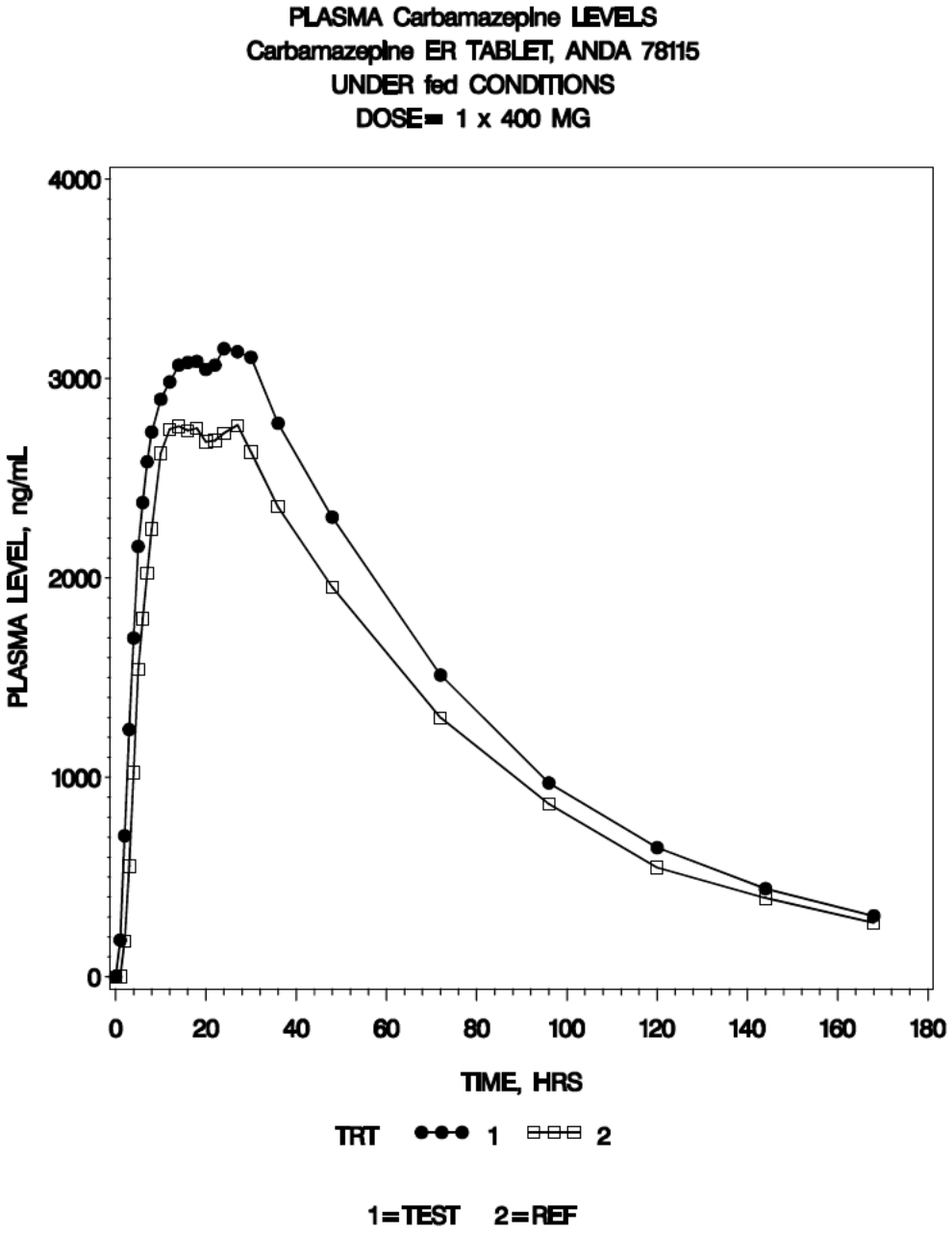
Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

Acceptable

Table 21. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

	Test (n=34)		Reference (n=34)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
1.00	184.09	103.90	1.90	583.10	96.89
2.00	707.25	68.15	177.62	117.16	3.98
3.00	1240.02	57.69	553.70	77.26	2.24
4.00	1698.72	49.69	1023.54	60.59	1.66
5.00	2157.76	39.64	1541.96	30.21	1.40
6.00	2377.96	29.31	1794.81	24.27	1.32
7.00	2582.24	25.16	2022.09	24.68	1.28
8.00	2731.64	21.78	2246.21	25.54	1.22
10.00	2895.54	18.24	2624.61	21.55	1.10
12.00	2982.82	16.31	2745.54	19.57	1.09
14.00	3067.19	18.44	2760.63	19.18	1.11
16.00	3080.27	19.20	2739.39	19.83	1.12
18.00	3085.59	19.71	2749.64	19.42	1.12
20.00	3045.36	17.06	2682.14	19.21	1.14
22.00	3066.73	16.63	2688.79	16.86	1.14
24.00	3149.49	15.26	2725.12	18.21	1.16
27.00	3134.18	16.42	2766.51	20.46	1.13
30.00	3106.33	18.83	2630.37	21.48	1.18
36.00	2775.72	17.40	2355.68	21.28	1.18
48.00	2304.58	18.49	1953.97	21.31	1.18
72.00	1512.71	24.03	1298.72	26.11	1.16
96.00	971.85	30.01	866.98	30.63	1.12
120.00	647.44	35.48	548.18	33.57	1.18
144.00	442.08	38.70	395.34	41.17	1.12
168.00	305.41	42.40	270.90	47.53	1.13

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



4.2 SAS Output

4.2.1 Fasting Study Data

(b) (4)

Following this page, 20 pages withheld in full (b)(4)-SAS Output

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78115

APPLICANT: Taro Pharmaceutical Industries Ltd.

DRUG PRODUCT: Carbamazepine ER Tablets 100 mg, 200 mg, 400 mg

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

1. Please acknowledgment the following FDA-recommended method and data driven specifications:

The dissolution testing should be conducted in (900 mL for 100 mg and 200 mg strength, and 1800 mL for the 400 mg strength) of (Acetate Buffer, pH 4.5) at (temp, 37°C + 0.5°C) using (USP apparatus I) at (100 rpm).

The test product should meet the following specification(s):

For 400mg and 200mg:	For 100mg:
3hr: (b) (4)	3hr: (b) (4)
6hr:	6hr:
12hr	12hr:
24hr	24hr:

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

Sincerely yours,

{See appended electronic signature page}

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

4.3 Outcome Page

ANDA: 78115

COMPLETED ASSIGNMENT FOR 78115 ID: 4906

Reviewer: Bous, Sherry **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Carbamazepine ER tabs, 100 mg, 200 mg, 400 mg, Taro pharma

---

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
4906	1/24/2008	Other	Study Amendment	1	1
				Bean Total:	1

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

/s/

Sherry Bous
3/5/2008 09:33:31 AM
BIOPHARMACEUTICS

Shriniwas G. Nerurkar
3/5/2008 09:42:35 AM
BIOPHARMACEUTICS

Barbara Davit
3/6/2008 05:30:08 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE DISSOLUTION ACKNOWLEDGEMENT REVIEW

ANDA No.	78-115
Drug Product Name	Carbamazepine Extended Release Tablets
Strength	100 mg, 200 mg and 400 mg
Applicant Name	Taro Pharmaceuticals U.S.A., Inc.
Submission Date	March 13, 2008
Reviewer	Nam Chun, Pharm.D.

EXECUTIVE SUMMARY

This is a review of the dissolution specification acknowledgement from the firm.

The firm has accepted the FDA-recommended dissolution method and specification.

The application is complete.

COMMENTS:

None

DEFICIENCY COMMENTS:

None

RECOMMENDATIONS:

From a bioequivalence point of view, the firm has met the requirements for *in-vivo* bioequivalence and *in-vitro* dissolution testing and the application is approvable.

I. Completed Assignment for 78115 ID: 5061

Reviewer: Chun, Nam **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
5061	3/13/2008	Dissolution Data	Dissolution Acknowledgement	1	0
				Bean Total:	0

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

/s/

Nam J Chun
3/19/2008 11:15:45 AM
BIOPHARMACEUTICS

Shriniwas G. Nerurkar
3/20/2008 07:47:57 AM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78115			
Drug Product Name	Carbamazepine Extended-Release Tablets			
Strength(s)	100 mg, 200 mg and 400 mg			
Applicant Name	Taro Pharmaceuticals USA, Inc.			
Address	3 Skyline Drive Hawthorne, NY 10532			
Applicant's Point of Contact	Kavita Srivastava Director, Regulatory Affairs			
Contact's Telephone Number	(914) 345-9001			
Contact's Fax Number	(914) 593-0078			
Original Submission Date(s)	December 29, 2005			
Submission Date(s) of Amendment(s) Under Review	July 18, 2008			
Reviewer	Kimberly W. Raines, Ph. D.			
Study Number (s)	R05-0184	R05-0185	R04-1364	R05-1389
Study Type (s)	Pilot Fasting	Pilot Fed	Pivotal Fed	Pivotal Fast
Strength(s)	400 mg	400 mg	400 mg	100 mg
Clinical Site	PRACS Institute Ltd.			
Clinical Site Address	4801 Amber Valley Parkway Fargo, ND 58104			
Analytical Site	PRACS Institute Ltd.			
Analytical Address	4801 Amber Valley Parkway Fargo, ND 58104			
OUTCOME DECISION	**INCOMPLETE**			

Review of an Amendment

I. Executive Summary

Taro Pharmaceuticals USA, Inc. submitted the current amendment in response to the Agency's Minor Deficiency Letter issued by the Division of Chemistry, for its Carbamazepine Extended-Release Tablets 100 mg, 200 mg and 400 mg. In the firm's response, reference is made to a telephone conversation on July 16, 2008 with the Division of Bioequivalence indicating that the firm wants to amend the previously accepted DBE recommended dissolution specifications for its 100 mg tablet.

In this amendment, the firm has submitted 35 month long-term stability summary data for its Carbamazepine Extended-Release Tablets, 100 mg. The firm is proposing a minor change in the

dissolution specifications at 3 and 6 hours. The firm proposes that FDA should consider: 3 hr: (b) (4) 6 hr: (b) (4); 12 hr: (b) (4); 24 hr: (b) (4) as dissolution specifications for its 100 mg tablet.

The dissolution specifications are set based on the data obtained on fresh lots and are not widened based on stability data. The dissolution data on fresh lots demonstrate that the test product meets the FDA specifications at L1 level. Furthermore, the 35 month long-term stability summary data does not support the firm's proposed specifications range. Therefore, the firm's request to change the FDA-recommended specifications is not acceptable. The firm should indicate if it accepts the FDA-recommended specifications: 3 hr: (b) (4); 6 hr: (b) (4); 12 hr: (b) (4); 24 hr: (b) (4) for its 100 mg tablet.

The application is incomplete.

II. Table of Contents

III. Background

The Division of Bioequivalence communicated the FDA-recommended dissolution specifications and dissolution method for Taro's Carbamazepine Extended Release Tablets, 100 mg, 200 mg and 400 mg in a Bioequivalence Deficiency Letter dated March 10, 2008. The firm submitted a bio-amendment dated March 13, 2008 accepting the FDA-recommended dissolution testing method and specifications.

Table 1: Dissolution Data Submitted by the firm in Bio-Amendment dated January 4, 2007

Tablet Number =12	**Carbamazepine Extended Release Tablets 100mg Taro Batch # 781064 Assay 102.4%**				**Tegretol-XR® Tablets 100mg Batch # F4089 Assay 101.8%**			
	3 hr	**6 hr**	**12 hr**	**24 hr**	**3hr**	**6 hr**	**12hr**	**24hr**
Average	57	77	90	97	16	50	76	87
Max	(b) (4)				(b) (4)			
Min								
RSD(%)	3.4	3.4	2.7	2.2	19.5	8.8	2.7	4.8
Dissolution Method	900 ml Acetate buffer (pH 4.5) Apparatus I (Basket) at 100 RPM				**F2 Statistic**			

Drug release from the test dosage form is more rapid than the reference. Despite a more rapid *in vitro* release rate, the variability was sufficiently low in the *in-vivo* studies such that

bioequivalence criteria appear to have been met, albeit higher point estimates were observed. The DBE dissolution focal point was consulted to render an opinion about the dissolution method and specifications for this test drug product. Because the product does not conform well to the USP specification, the DBE recommended the following dissolution method and specifications for this product:

FDA Method
Acetate Buffer, pH 4.5
1800 mL (400 mg), 900 mL (100 mg, 200 mg)
Apparatus I (Basket)/ 100 rpm

Specifications

For 400 mg and 200 mg
3hr: (b) (4)
6hr:
12hr
24hr

For 100 mg
3hr: (b) (4)
6hr:
12h
24h

IV. Review of Amendment

<u>*Comment 5* of Minor Deficiency Letter dated July 2, 2008 issued by the Division of Chemistry</u>

Based on the Division of Bioequivalence (DBE) recommendations on dissolution specification and dissolution method in the letter dated March 10, 2008 and your acceptance of the same in the bio-amendment dated March 13, 2008, please update the ANDA as follows:

a. Provide revised specification for the drug product release and stability, blank COAs and blank stability data sheets to reflect the revised dissolution method and specifications.

<u>Response</u>

Taro's finished product release and stability specifications for Carbamazepine Extended-Release Tablets were revised to reflect the DBE-recommended dissolution method (assigned as Taro's method M2022) and specifications for the 200 mg and 400 mg strengths.

Reference is made to Telephone conversation between Aaron Sigler, Division of Bioequivalence, FDA and Taro on July 16, 2008. As advised by the Agency, the following dissolution proposal is requested for Carbamazepine Extended-Release Tablets, USP, 100 mg:

Taro is accepting the DBE proposed dissolution method. However, Taro is proposing a minor change in the dissolution specifications at 3 and 6 hours time points for the 100 mg tablets only presented in the following table:

Taro's Proposed Specifications Carbamazepine Extended-Release Tablets, USP, 100 mg	DBE Recommended Specifications Carbamazepine Extended-Release Tablets, USP, 100 mg
3 hr: (b) (4) 6 hr: 12 hr 24 hr	3 hr: (b) (4) 6 hr: 12 hr 24 hr

The proposed limits are based on the following considerations:

1. From the initial time points it was observed that the release rate of Carbamazepine Extended-Release Tablets, 100 mg (average values) is faster than that of the 200 mg and 400 mg strengths in Acetate buffer media as shown below:

Dissolution Media	Time points (hours)	Carbamazepine Extended-Release Tablets, USP, 100 mg, Lot # 781064	Carbamazepine Extended-Release Tablets, USP, 200 mg, Lot # 781066	Carbamazepine Extended-Release Tablets, USP, 400 mg, Lot # 780980
Buffer Acetate pH 4.5	3	(b) (4)		
	6			
	12			
	24			

Therefore, Taro decided to conduct additional BE study in fasted conditions for the 100 mg tablets. The study results clearly demonstrated that Taro's Carbamazepine Extended-Release Tablets, 100 mg are bioequivalent to RLD product and that the apparent faster in vitro release rate do not impair the product bioavailability.

2. The dissolution data available for 35 months Long Term stability of the exhibit batch is consistent with the higher release rate supporting the proposed limits (See Attachment E).

   Updated finished product release and stability specifications, and a copy of the dissolution method M2022 are enclosed in Attachment C of this response.

Following this page, 1 page withheld in full (b)(4)

Bioequivalence Reviewer's Comments

The firm's proposed changes to the dissolution specifications for its Carbamazepine Extended-Release Tablet, 100 mg are not justified. The dissolution testing [FDA method: 900 mL of Acetate Buffer, pH 4.5 (37°C) using USP Apparatus I (basket) at 100 rpm] and dissolution specifications [3hr: (b) (4); 6hr: (b) (4); 12hr: (b) (4); 24hr: (b) (4) for Taro's Carbamazepine Extended Release Tablets, 100 mg, were previously reviewed. The firm was asked to indicate if it accepts the FDA-recommended testing method and specifications. In the bio-amendment dated March 13, 2008 Taro indicated the acceptance of the FDA-recommended dissolution testing method and specifications. The only additional information submitted in the current amendment is 35 month long-term stability summary data. Moreover, the 35 month long-term stability summary data for Taro's Carbamazepine Extended-Release Tablets, 100 mg does not meet the firm's proposed specifications.

Dissolution specifications are set based on the data obtained on fresh lots. The dissolution data on fresh lots demonstrate that the test product meets the FDA-recommended specifications at L1 level. Therefore, the firm's request to change the FDA-recommended specifications is not acceptable.

The firm should indicate if it accepts the FDA-recommended specifications. This application is **incomplete**.

V. Deficiency Comments

The firm proposed revised dissolution specifications at 3 and 6 hours based on observations from 35 month long-term stability data. The firm should note that dissolution specifications are set based on the data obtained from fresh lots. The dissolution data on the fresh lot indicates that the test product, Carbamazepine ER Tablets, 100 mg, meets the FDA-recommended specifications (3hr: (b) (4); 6hr: (b) (4) 12hr: (b) (4); 24hr: (b) (4)) at L1 level. Therefore, the firm's proposed specifications are not acceptable. The firm may also note that the 35 month long-term stability summary data for the 100 mg tablet does not meet the firm's proposed specifications range.

The dissolution testing should be conducted in 900 mL of Acetate Buffer, pH 4.5 using USP Apparatus I (basket) at 100 rpm. The 100 mg Carbamazepine Extended-Release Tablets should meet the following specifications:

3hr: (b) (4)
6hr:
12hr
24hr

The firm should indicate if it accepts the FDA-recommended dissolution specifications.

VI. Recommendation

1. The *in vitro* dissolution testing is incomplete. The dissolution testing was conducted using the FDA-recommended method: 900 mL of Acetate Buffer, pH 4.5 using apparatus I (basket) at 100 rpm. The firm should indicate if accepts the FDA-recommended dissolution specifications (3hr: (b) (4); 6hr (b) (4); 12hr: (b) (4); 24hr: (b) (4) for its Carbamazepine Extended Release Tablets, 100 mg.

BIOEQUIVALENCE DEFICIENCY

ANDA: 78115

APPLICANT: Taro Pharmaceutical USA, Inc.

DRUG PRODUCT: Carbamazepine Extended-Release Tablets 100 mg, 200 mg and 400 mg

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

You proposed revised dissolution specifications at 3 and 6 hours based on observations from 35 month long-term stability data. Please note that dissolution specifications are set based on the data obtained from fresh lots. The dissolution data on the fresh lot indicates that the test product, Carbamazepine Extended-Release Tablets, 100 mg, meets the FDA-recommended specifications (3hr: (b) (4); 6hr: (b) (4); 12hr: (b) (4); 24hr: (b) (4)) at L1 level. Therefore, your proposed specifications are not acceptable. You may also note that the 35 month long-term stability summary data for the 100 mg tablet does not meet your proposed specifications range.

In order to justify your proposed specifications, please submit additional dissolution data of three fresh production lots, to determine if a revision of the dissolution specifications is warranted. Alternatively, please acknowledge the FDA-recommended dissolution method and specifications given below for the 100 mg tablet:

The dissolution testing should be conducted in 900 mL of Acetate Buffer, pH 4.5 using USP Apparatus I (basket) at 100 rpm. The 100 mg Carbamazepine Extended-Release Tablets should meet the following specifications: 3hr: (b) (4); 6hr: (b) (4); 12hr: (b) (4); 24hr: (b) (4).

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

VII. OUTCOME

Completed Assignment for 78115 ID: 6036

Reviewer: Raines, Kimberly **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
6036	7/18/2008	Other	Study Amendment	1	1
				Bean Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Study Amendment (s)	
Study Amendment	1
Study Amendment Total	*1*

Grand Total	**1**

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

/s/

Kimberly W Raines
8/5/2008 09:28:35 AM
BIOPHARMACEUTICS

Kuldeep R. Dhariwal
8/5/2008 09:43:57 AM
BIOPHARMACEUTICS

Moheb H. Makary
8/9/2008 11:28:50 AM
BIOPHARMACEUTICS
For Dr. Barbara M. Davit, Acting Director, Division of Bioequivalence II

DIVISION OF BIOEQUIVALENCE DISSOLUTION ACKNOWLEDGEMENT REVIEW

ANDA No.	78-115
Drug Product Name	Carbamazepine Extended Release Tablets
Strength	100 mg, 200 mg and 400 mg
Applicant Name	Taro Pharmaceutical USA, Inc.
Submission Date	August 21, 2008
Reviewer	Christina Thompson, Pharm.D.

EXECUTIVE SUMMARY

This is a review of the dissolution specification acknowledgement from the firm.

The firm has accepted the FDA-recommended dissolution method and specification.

The bioequivalence section of the application is complete.

COMMENTS:

None

DEFICIENCY COMMENTS:

None

RECOMMENDATIONS:

From a bioequivalence point of view, the firm has met the requirements for *in-vivo* bioequivalence and *in-vitro* dissolution testing. The bioequivalence section of the application is acceptable.

Reviewer: Thompson, Christina **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
6303	8/21/2008	Dissolution Data	Dissolution Acknowledgement	1	0
				Bean Total:	0

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

/s/

Christina Thompson
8/26/2008 09:05:00 AM
BIOPHARMACEUTICS

Aaron Sigler
8/26/2008 09:12:05 AM
BIOPHARMACEUTICS