Carbamazepine
Tegretol[R], 200mg tablet
NDA 16-608
Reviewer: Nhan Le Tran, Ph.D.
Wang [redacted]
(1-S, 2-D)

Ciba-Geigy Co.
Summit, NJ
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Review of a Submission: A Bioavailability Study
and a Dissolution Study

I. Background

Carbamazepine is presently marketed in white tablet dosage form (200mg/tab) by Ciba-Geigy under the trade name Tegretol[R]. The firm now wishes to change the shape (from regular tablet shape to capsule shape) and the color (from white to pink) of the currently marketed tablet.

II. Objective of the Submission

The objective of the present submission is to determine the relative bioavailability of the new pink capsule-shaped tablet to the current marketed Tegretol[R] tablet.

III. Methodology

This study was performed according to the protocol #26 (see Appendix I). A summary of the study is given as follows:

1. Principal Investigator/ Site of the Study
Principal Investigator: W.E. Wagner, MD.
Site: In-House Clinical Pharmacology Unit, Ciba-Geigy, Summit, NJ

2. Study Design
This was 2 way cross-over study, single dose, in 10 subjects with a 3 week washout period between treatments.

3. Drug Administration
Each subject received a single oral dose of two tablets (200 mg/tablet) of either reference (white tablet) or test (capsule shaped, pink) products according to the randomization schedule (Append. 2). Subjects were fasted for at least 10 hours before and 4 hours after drug administration.

4. Subject Selection
10 subjects age between 28 to 50 y/o participated in this study. Subjects were selected based on inclusion characteristics such as ideal weight for height plus or minus 10%, normal physical examination, normal laboratory values. Subjects with history of diseases e.g., cardiovascular, asthma, hepatic or renal, and history of drug dependence were excluded. Detail of the inclusion and exclusion can be found in the Appendix 1.

5. Sampling Procedure
Blood samples (10 ml) were taken at 0, 1, 2, 4, 6, 8, 12, 24, 32, 48, 72, 96, 168, and 216 hours following drug administration. Heparinized blood samples were centrifuged and plasma was separated and frozen until assay. The assay was carried out by the [redacted]

IV. RESULTS:

1. Analytical Methodology
Carbamazepine (CBZ) and its major metabolite: carbamazepine-10, 11 -epoxide (CBZE) were assayed by HPLC equipped with a UV detector. The wavelength was 212 nm. Cyheptamide was used as internal standard for both CBZ and CBZE. The following is the brief summary of the assay validation. Complete description of the assay procedure and the validation can be found in the Appendix III.

a. Specificity The method appears to be specific. Under the described chromatographic condition, no interfering peak was observed (Fig 1, App. III).

b. Sensitivity
The sensitivity of the method which was published in the Clinical Chemistry 28: 2106, 1982 was reported as 20 mcg/L for both compounds i.e., CBZ and CBZE in 0.5 ml of plasma sample.

c. Linearity
Standard curves appear to be linear in the concentration range from [redacted] mg/L to [redacted] mg/L for CBZ and 0.02 mg/L to 1 mg/L for CBZE (Table 1 and 2 and Fig. 2 and 3, App. III).

d. Accuracy, Precision and Reproducibility:
The assay was reported as precise, accurate and reproducible in the concentration range from [redacted] mg/L to [redacted] mg/L for CBZ and [redacted] mg/L to [redacted] mg/L for CBZE. However, results submitted by the firm indicate that the method appears to be inaccurate for the concentrations below [redacted] mg/L for CBZ and [redacted] mg/L for CBZE. In fact, the %CV for [redacted] mg/L for CBZ was 32.4% (n=10) and for concentration of [redacted] mg/L for CBZE was 22% (n=10) (Tables 3 and 4, App. III).

e. Conclusion on the Assay Methodology
The assay used in the present study (developed by [redacted], [redacted]) is judged to be acceptable from the Division of Biopharmaceutics point of view.

2. Pharmacokinetics
Plasma concentration-time profiles of individual subjects are presented in the App. IV. In general, plasma profiles appear to be comparable for reference (white, conventional tablet) and test (pink, capsule shaped tablet) products. Pharmacokinetic parameters derived from the plasma data namely, $AUC_{0-\infty}$, TMAX, CMAX and T1/2 are presented in the following tables:

Table 7

Summary of CBZ Plasma Levels (mg/L) following Administration of Single 400-mg Dose of CBZ, Grouped by Treatment.

Treatment A

U.S. Conventional Tablet, 2 x 200 mg.

	Subject											
time(hr)	1	2	3	4	5	6	7	8	9	10	mean (S.D.)	n
0											0 -	10
1											1.026(.593)	10
2											1.804(.709)	9
4											2.680(.598)	10
6											2.940(.669)	10
8											3.100(.736)	10
12											3.200(.558)	10
24											3.030(.442)	10
32											2.880(.424)	10
48											2.210(.367)	10
72											1.355(.335)	10
96											0.812(.262)	10
168											0.218(.131)	10
216											0.095(.068)	10

Table 2 (Continued)

Summary of CBZ Plasma Levels (mg/L) following Administration of Single 400-mg Dose of CBZ, Grouped by Treatment.

Treatment B

Pink Capsule-shaped Tablet, 2 x 200 mg.

	Subject											
Time(hr)	1	2	3	4	5	6	7	8	9	10	mean (S.D.)	n
0											0 -	10
1											1.232(.726)	10
2											1.958(.935)	10
4											2.870(.814)	10
6											3.340(.622)	10
8											3.480(.683)	10
12											3.330(.613)	10
24											3.220(.454)	10
32											3.110(.493)	10
48											2.270(.452)	10
72											1.406(.382)	10
96											0.861(.275)	10
68											0.221(.109)	10
											0.078(.048)	8

Table 4

Pharmacokinetic Parameters Determined from Plasma Levels of Carbamazepine following 400-mg Single Dose

Treatment A

U.S. Conventional Tablet, 2 x 200 mg.

Subject	C_{max} (mg/L)	T_{max} (hr)	AUC (0-inf) (mg hr/L)	$t_{\frac{1}{2}}$ (hr)
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
mean	3.3	10.84	251.0	35.8
S.D.	0.64	14.9%	47.94	8.46
	4 of 19		19	24
median		12		
range				

Table 5

Pharmacokinetic Parameters Determined from Plasma Levels of Carbamazepine following 400-mg Single Dose

Treatment B

Pink Capsule-shaped Tablet, 2 x 200 mg.

Subject	C_{max} (mg/L)	T_{max} (hr)	AUC (0-inf) (mg hr/L)	$t_{\frac{1}{2}}$ (hr)
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
mean	3.6	10.6	265.0	35.0
S.D.	0.66	7.4	50.38	7.79
	18.3	74	19	22
median		(8)		
range				

Table 8

Ratio of Pharmacokinetic Parameters for Treatment B, Pink Capsule-shaped Tablet, 2 x 200 mg, relative to Treatment A, U.S. Conventional Tablet, 2 x 200 mg, Determined from Plasma Levels of Carbamazepine following 400-mg Single Dose

Subject	C_{max} Ratio B/A	AUC (0-inf) Ratio B/A	$t_{\frac{1}{2}}$ Ratio B/A	Tmax Ratio B/A
1	1.36 *	1.23	0.86	.25 *
2	0.94	0.99	1.00	.75
3	1.21	1.25	1.00	.66 *
4	0.87	0.96	1.05	.5 *
5	1.11	1.06	1.12	1.0
6	1.33 *	1.19	0.90	1.33 *
7	0.96	1.04	1.08	1.0
8	1.12	0.99	0.90	.15 *
9	1.09	0.93	0.95	.60 *
10	0.88	0.95	0.97	1.33 *
				.75 (.40)
mean	1.09	1.06	0.98	30% BV = 5 min .75-1.25 (3 of 8)
S.D.	.18	.12	.084	
	.75 - 1.25 80%	100%	100%	

< .75

< 1 = 6

≥ 1 = 4

For a quick comparison, means CMAX, TMAX, AUC_{0-00}, T1/2 of CBZ and its metabolite (CBZE) of the test and reference products can be summarized as follows:

	CBZ			CBZE		
	Reference	Test	Ratio T/R	Reference	Test	Ratio T/R
Cmax(mg/L)	3.3 (.64)	3.60(0.7)	1.09	0.22(.04)	.22(.06)	1.0
AUC(mg*hr/L)	251.0(48)	265(50.4)	1.06	16.4(3.3)	15.8(4.4)	.97
T1/2 (hrs)	35.8(8.5)	35.0(7.8)	.98	40.8(11)	37(10)	.93
*Tmax (hrs)	17(10.84)	10.6(7.4)	.75	30(5.08)	34(5.7)	1.17

*: Tmax values are taken from Tables 4 and 5 computed by the firm.

Data submitted by the firm indicate that:

a) It appears that there is no difference between test and reference products in term of CMax, AUC_{0-00}, and T1/2.

b. ANOVA for CBZ using the model: subject, period, treament for AUC, Cmax, and T1/2 does not show significant difference between test and reference products. The power to detect 20% diffrence from the reference mean is 99% for Cmax, T1/2, and AUC_{0-00} (Append V). In addition, results of ratio analysis show that 88% for CMAX, 100% for AUC and T1/2, lie within 0.75-1.25 range.

c. In addition to ANOVA and ratio analysis, the firm also included Westlake's symetric confidence interval test for AUC, Cmax, and T1/2. Results indicate good agreement with the ANOVA and ratio tests (Append. V).

d. From the data computed by the firm in Tables 4 and 5 above, TMAX of the reference tablet appears to be longer [mean=17(10.84) hrs with n=10] than the test product [mean=10.6(7.4) hrs with n=10]. However, using raw plasma concentration-time data in Table 1 and 2 provided by the firm, the Division of Biopharmaceutics has plotted these data in an expanded scale (Appendix IV) and recomputed the Tmax, we have observed that the different in Tmax is no longer apparent. That can be seen in the table below:

Pharmacokinetic Parameters from plasma levels

Subject	Computed by Sponsor				Computed by FDA			
	Treament A		Treatment B		Treatment A		Treatment B	
	Cmax	Tmax	Cmax	Tmax	Cmax	Tmax	Cmax	Tmax
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
Mean	3.3	17.0	3.6	10.6	3.3	12.6	3.6	12.6
%CV	19	64	18	70	20	68	17	69

As can be seen from the FDA calculations for Tmax, both the old and reformulated products have similar mean Tmax, about 12.6 hours with a %CV of 68%. Ratio analysis performed on Tmax computed by the Agency revealed that 80% of the subjects pass 75/75 test.

e. Athough large variation is observed in T1/2, which may be related to the sensitivity of the assay, half-life appears to be similar for test and reference tablets (35 hrs).

f. As far as the metabolite is concerned, no statistical analysis was performed on the parameters of the metabolite (CBZE). However, using ratio analysis, the Division of Biopharmaceutics has estimated that 80% for AUC and Cmax and 60% for T1/2 of the subjects lie between 0.75-1.25 range.

g. Due to low concentrations of the metabolite and lack of sensitivi y at low concentrations, a flattening of the plasma concentration time curves were observed. Thus it is not accurate nor meaningfull to statistically compare the Cmax, Tmax, and T1/2 of the metabolite between the test and reference products.

h. Individual plasma concentration-time profiles submitted by the firm appear to show slow release characteristics of the old (reference) as well as new (test) dosage forms. In 6 subjects or about 60% of the subjects under investigation (subject # 1, 2, 6, 8, 9 and 10) high plasma levels appear to be sustained for a period up to 48 hours.

V. Conclusions on the Pharmacokinetic Portion
Study conducted by the firm yielded the following results:

1. The extent of absorption, measured by total AUC appears to be statistically comparable for reference and test tablets.

2. The rate of absorption, measured by Tmax and Cmax appears to be comparable for test and reference tablets.

3. No comparison can be made with respect to Tmax, Cmax, and T1/2 of the metabolite of the test and reference products, however the amount of the metabolite in the body as determined by AUCs of the metabolite following difference treatment appears to be similar.

VI. REVIEW OF IN-VITRO DISSOLUTION STUDY

1. Assay Used for Dissolution Study
The drug in the dissolution medium was determined by spectrophotometric method at 284 nm. The assay validation was submitted and found to be adequate in term of accuracy (101.3% recovery), precision (% CV=103% with n=5) and linearity (linear up to 125% of the working concentration). Complete documentation of the assay can be found in the Append. VI.

2. Dissolution Method
USP Method II (paddle), with 900 ml of various media (water, SGF, SIF, alcoholic system containing 10% ethanol and 0.1% Tween 20) and speed (50, 75, 100 RPM) were used.

3. Results

Results are given in Appendix VI. Based on the solubility of the drug in various media as well as dissolution data provided by the firm, and given the fact that dissolution should be done under the "sink" conditions, it appears that the use of alcoholic/Tween media by the Sponsor is acceptable on an interim basis from the Division of Biopharmaceutics viewpoint. For a quick comparison, only dissolution data using alcoholic/Tween medium is summarized as follows: Note that values reported are the mean and range of 12 individual tablets.

LOT # E-11786 (REFERENCE)

900ml of water containing 10% ethanol+0.1% Tween 20.

	SPEED (RPM)					
	50		75		100	
Time	Mean	Range	Mean	Range	Mean	Range
30 min.	20		39		50	
60 min.	30		53		67	
120 min.	43		68		83	
180 min.	42		77		90	

LOT #E-11766 (TEST)

900 ml of water containing 10% ethanol+0.1% Tween 20.

	SPEED (RPM)					
	50		75		100	
Time	Mean	Range	Mean	Range	Mean	Range
30 min.	29		52		63	
60 min.	38		64		79	
120 min.	48		73		89	
180 min.	55		79		93	

VII. Comment:

1. Although the dissolution medium and conditions used by the firm are acceptable on an interim basis, it would be more desirable if the Sponsor should document that the method and conditions used by the Sponsor are optimal. For this purpose, as a post approval commitment, it is requested that the firm should explore the possibility of using dissolution medium containing single chemical entity. One of theses possibilities includes, but not limited to, hydro-alcoholic media. Various alcohol concentrations should be tested e.g., 10, 20 and 30%. Dissolution conditions are paddle method, 75 RPM, 900 ml of the dissolution medium at 37°C.

VIII. Recommendations:

1. The Division of Biopharmaceutics has reviewed the Bioavailability and dissolution studies for Carbamazepine tablets (Tegretol®), NDA 16-608 and found that in-vivo bioavailability study acceptable, and in-vitro dissolution study acceptable on an interim basis. The supplement is approvable and recommended for approval provided that the Sponsor agrees to conduct further dissolution testing as outlined in Comment 1.

2. The firm should be informed that final dissolution conditions and specifications can not be set at this time but will be determined when data requested in the comment 1 is submitted and reviewed by the Agency. In the interim, dissolution conditions and specifications for Tegretol® tablets can be set as follows:

Dissolution should be conducted using USP Method II (Paddle) at 75 RPM in 900 ml of dissolution medium composed of water/10% ethanol+0.1% Tween 20 at 37°C. The specifications are: at 60minutes, Q1=[redacted] and Q2=[redacted], and at 180 minutes, Q[redacted]

3. The firm is requested to submit, 1000 tablets in each lot , for the following lots: Lot# E-11786 and Lot# E-11766 to:

Vadlamini K. Prasad, Ph.D.
Chief, Biopharmaceutics Laboratories
FDA
200 C Street, S.W
FOB-8 HFN-224 Rm 6076
Washington DC 20204

Samples should be delivered in a appropriate containers with adequate information on the label such as batch size, lot, date of manufacturing and expiration date.

The firm should be informed of the comment and recommendations.

Nhan Le Tran 4/16/86

Nhan Le Tran, Ph. D.
Pharmacokinetics Evaluation Branch

RD Initialed by Paul L. Hepp, Pharm.D.
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