SUMMARY OF REPORT

TITLE

Protocol 051: Repeated Bioequivalence Study of US 100mg Lamictal® Tablets, US 100mg Lamictal® Dispersible/Chewable Tablets, and UK 100mg Lamictal® Dispersible/Chewable Tablets in Healthy Adult Male Volunteers.

OBJECTIVES

The primary objectives of this study were to evaluate the bioequivalence of: 1) the US 100mg Lamictal® dispersible/chewable tablet and the US 100mg Lamictal® tablet; 2) the UK 100mg Lamictal® dispersible/chewable tablet and the US 100mg Lamictal® compressed tablet; and 3) the US 100mg Lamictal® dispersible/chewable tablet and the UK 100mg Lamictal® dispersible/chewable tablet.

DESIGN

This was a single-center, randomized, open-label, three-period, three-treatment, crossover study in 18 healthy adult male volunteers.

DURATION

The study lasted approximately 80 days.

SETTING

This study was conducted at

Subjects were admitted and received Lamictal® doses as inpatients at a clinical research facility. Subjects were dosed between 15 December 1995 and 18 February 1996.

SUBJECTS

Eighteen (18) adult male subjects who were healthy and between the ages of 19 - 45 years were enrolled in the study and 16 subjects completed the study.

TREATMENTS

Each subject was assigned to receive one of three treatments during each study period and all three treatments during the study, according to a randomization schedule. All doses were administered orally after a minimum of an 8-hour fast. Study treatment was started at least two days and at most 14 days after an initial screening visit. Each dosing period began the evening prior to dosing and extended until 168 hours after dosing (Day 8). Dosing occurred at approximately 0800 hours on Day 1 of each dosing period. Serial blood samples were collected up to 168 hours following dosing for the determination of plasma lamotrigine

concentrations. Each treatment administration was separated by at least 21 days to allow for a complete washout of residual drug.

The three treatments were:
Treatment A: 1 x US 100mg Lamictal® tablet;
Treatment B: 1 x US 100mg Lamictal® dispersible/chewable tablet;
Treatment C: 1 x UK 100mg Lamictal® dispersible/chewable tablet.

The [redacted] tablet was swallowed intact with 200mL water. Dispersible/chewable tablets were first dispersed in a small cup with 5mL of water, which was then swallowed by subjects. An additional 195mL of water, used to rinse the cup, was ingested by the subjects.

MEASUREMENTS

Pharmacokinetic

The pharmacokinetics of lamotrigine were assessed by measuring plasma lamotrigine concentrations for 168 hours following dosing. Up to 23 blood samples were collected during each dosing period for lamotrigine pharmacokinetic determinations. The AUC_{last}, AUC_{∞}, C_{max}, t_{max}, λ_z, and terminal half-life ($t_{½}$) were examined.

Safety

Safety was evaluated by monitoring clinical adverse events during each treatment phase. The following were also done at screening and in the follow-up phase if they were clinically indicated:

- Physical examination;
- Clinical laboratory tests (hematology, clinical chemistry, and urinalysis); and,
- Vital signs (sitting blood pressure and sitting heart rate).

RESULTS

Pharmacokinetic

Data from all 16 subjects who completed all three periods of the study were included in the pharmacokinetic and statistical analyses. Subjects 2 and 9 completed only the first period of the study. They were included in the pharmacokinetic analysis, and in the statistical analysis for the purpose of calculation of summary statistics, but excluded from all analyses of variance, least squares means, and treatment comparisons.

Pharmacokinetic parameters for all completing subjects are summarized below:

	Treatment A US 100mg Tablet	Treatment B US 100mg Dispersible/ Chewable Tablet	Treatment C UK 100mg Dispersible/ Chewable Tablet	Ratio B:A	Ratio C:A	Ratio B:C
AUC_{last} (ng*h/mL)						
Geometric LS mean	48894	47906	47344			
95% CI (Lower)	46985	46029	45496			
(Upper)	50880	49860	49268			
Mean ratio				0.98	0.97	1.01
90% CI (Lower)				0.94	0.92	0.97
(Upper)				1.03	1.01	1.06
p-value*				0.465	0.249	0.671
AUC_{∞} (ng*h/mL)						
Geometric LS mean	51756	50317	50610			
95% CI (Lower)	49506	48122	48410			
(Upper)	54108	52613	52910			
Mean ratio				0.97	0.98	0.99
90% CI (Lower)				0.92	0.93	0.94
(Upper)				1.02	1.03	1.05
p-value*				0.365	0.468	0.851
C_{max} (ng/mL)						
Geometric LS Mean	1121	1092	1162			
95% CI (Lower)	1071	1044	1110			
(Upper)	1173	1143	1216			
Mean Ratio				0.97	1.04	0.94
90% CI (Lower)				0.92	0.98	0.89
(Upper)				1.03	1.09	0.99
p-value*				0.422	0.255	0.059
t_{max} (h)						
Median	2.00	2.00	2.50			
Range						
95% CI (Lower)	1.00	1.50	1.50			
(Upper)	2.50	3.50	3.50			
Median Difference				0.75	0.75	-0.25
90% CI (Lower)				-0.25	0.00	-1.00
(Upper)				1.50	1.50	0.75
p-value*				0.222	0.114	0.726

*P-value from ANOVA of the pairwise comparisons

The criteria for establishing bioequivalence of the three Lamictal® formulations are that the 90% confidence intervals for the ratios of log-transformed AUC_{last}, AUC_{∞}, and C_{max} for each comparison are within the range of 0.80 - 1.25. This criteria was met for all parameters and for each comparison performed. Analysis of untransformed data was consistent, with 90% confidence intervals for the ratios of AUC_{last}, AUC_{∞}, and C_{max} within 0.80 - 1.20.

Safety

The three Lamictal® tablet formulations were well tolerated in the 18 normal healthy male subjects:

- No serious adverse events or deaths occurred;
- 47 adverse events were reported throughout the course of the study, 10 were determined by the investigator to be related to drug exposure, occurrence of adverse events was similar for all treatments;
- All reported adverse events were mild or moderate in nature and none required withdrawal of a subject from the study; and
- The most frequent drug-related adverse events (as classified by the investigator) were six instances of headache (mild to moderate in intensity) in four subjects.

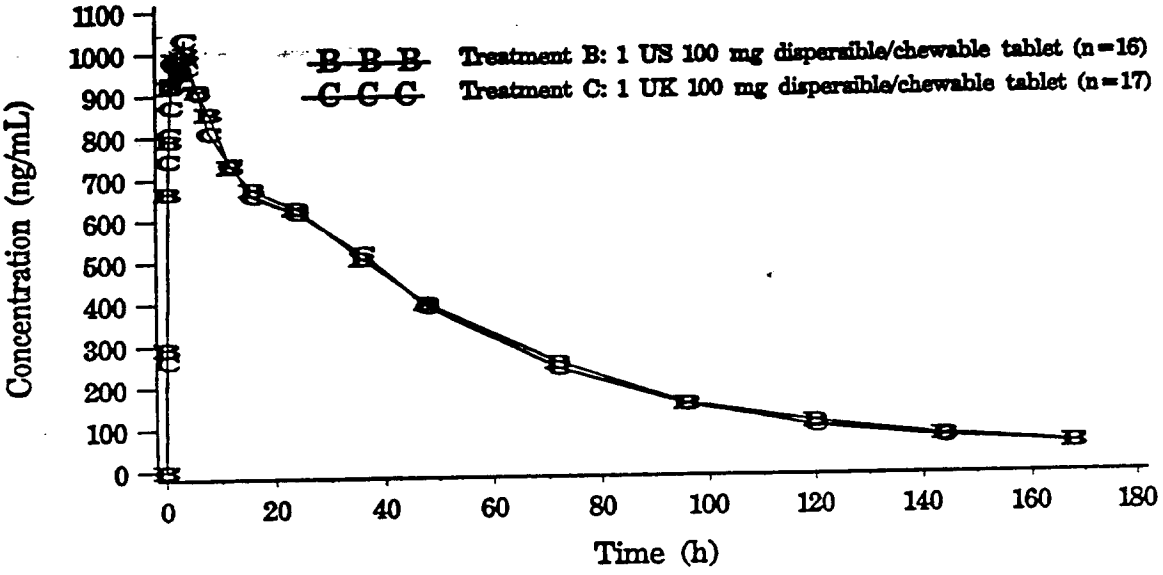
CONCLUSIONS

- The US 100mg Lamictal® dispersible/chewable tablet formulation is bioequivalent to the US 100mg tablet;
- The UK 100mg Lamictal® dispersible/chewable tablet formulation is bioequivalent to the US 100mg tablet;
- The US 100mg Lamictal® dispersible/chewable tablet formulation is bioequivalent to the UK 100mg dispersible/chewable tablet;
- The three Lamictal® formulations were well tolerated in these normal healthy male subjects.

Form, Dosage, and Place of Manufacture	% Labeled Strength (mean)	Batch Number	Formulation Number	Batch Size	Date of Manufacture
Tablet, 100mg, US		1Z2701	BOM-01A3		29 April 1992
Dispersible/Chewable Tablet, 100mg, US		4M2784	BZU-01A2		9 Feb 1994
Dispersible/Chewable Tablet, 100mg, UK		3W2702	BZU-01A1		11 Feb 1994

APPENDIX 8.5.14

LINEAR AND SEMI-LOGARITHMIC PLOTS OF THE MEAN SERUM CONCENTRATION-TIME PROFILES FOR LAMOTRIGINE (TREATMENTS B AND C)



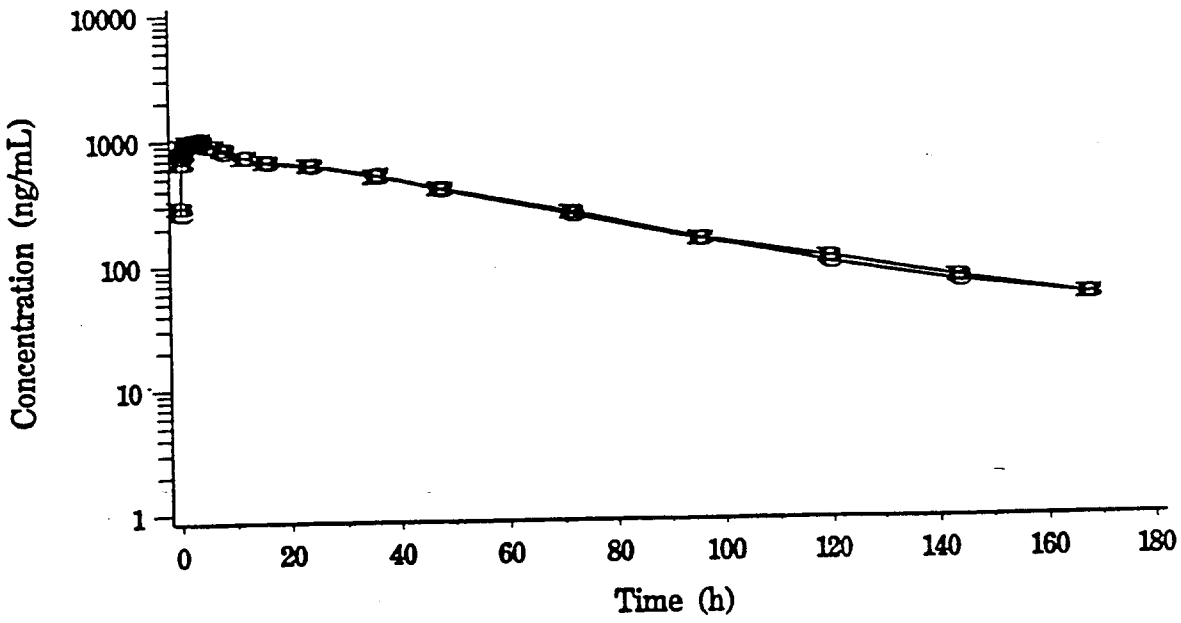
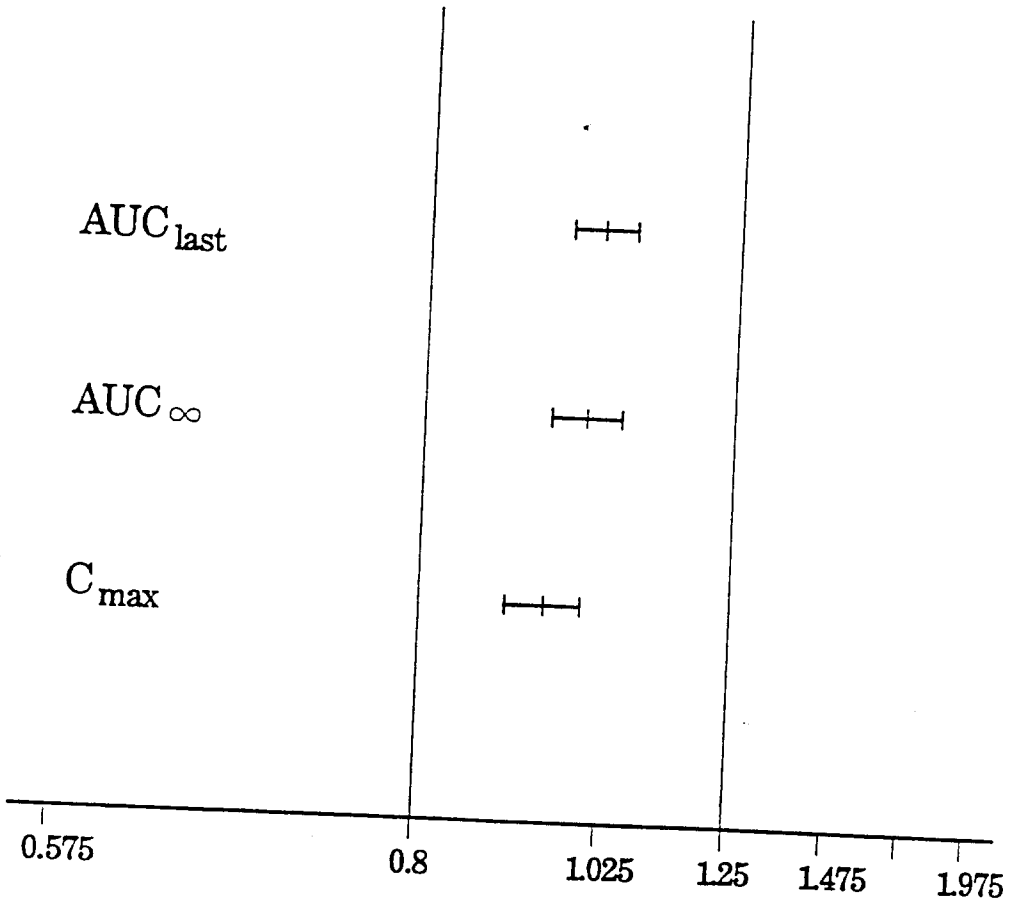


FIGURE 21

SEMI-LOGARITHMIC PLOT OF THE GEOMETRIC LS MEAN RATIOS
AND ASSOCIATED 90% CONFIDENCE INTERVALS
(LOG-TRANSFORMED DATA)

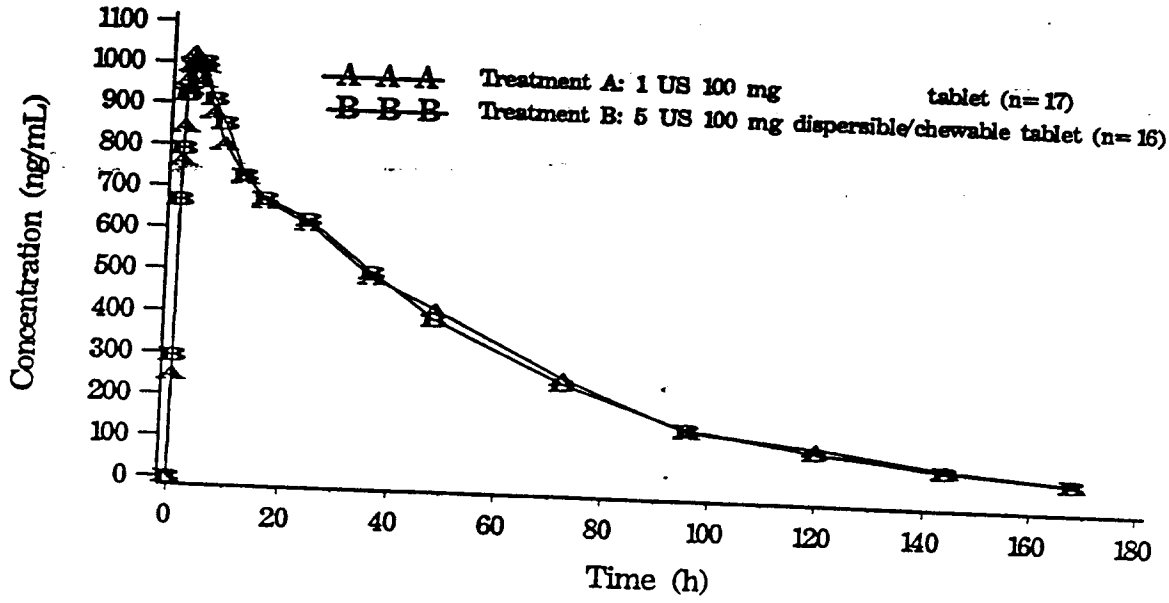
TREATMENT B RELATIVE TO TREATMENT C (N=16)



Note: Data from Subjects 2 & 9 are not included on the comparison graph. Each subject received only one Treatment; A and C, respectively.

APPENDIX 8.5.2

LINEAR AND SEMI–LOGARITHMIC PLOTS OF THE MEAN SERUM CONCENTRATION–TIME PROFILES FOR LAMOTRIGINE (TREATMENTS A AND B)



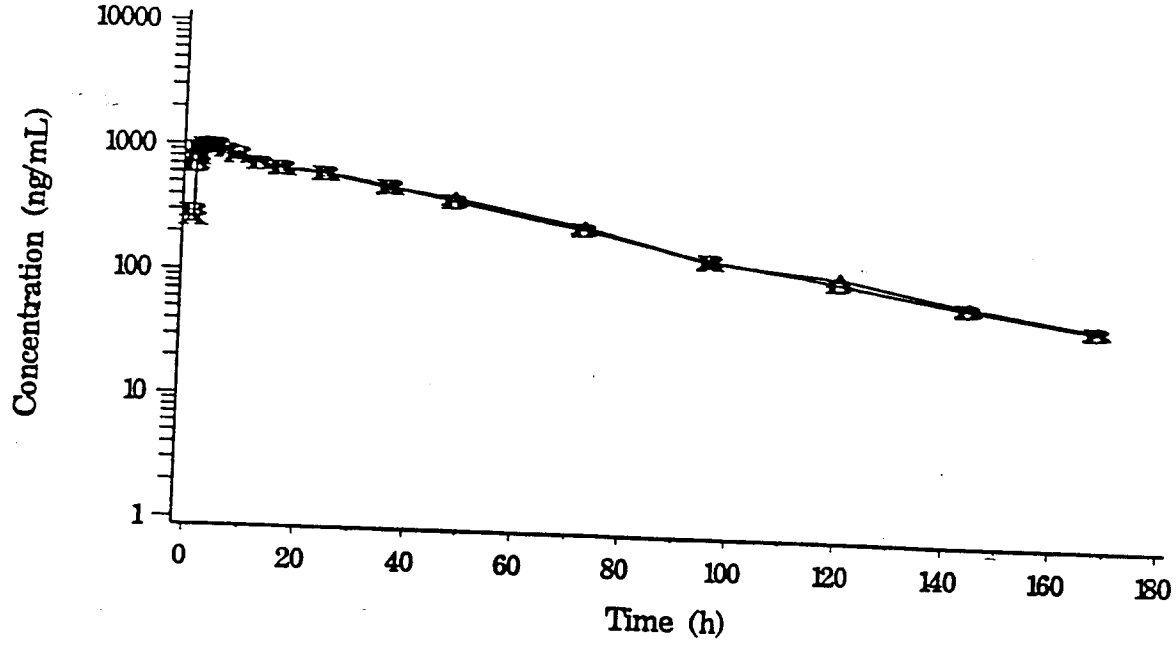
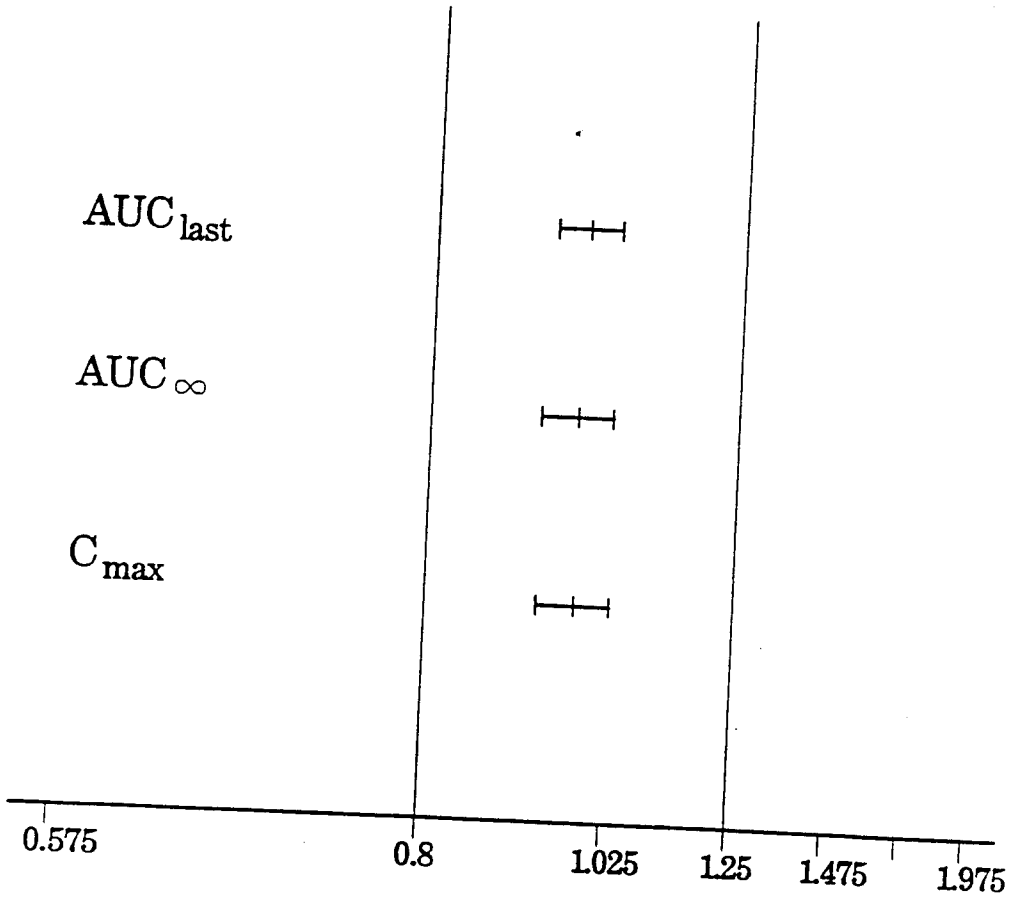


FIGURE 7

SEMI-LOGARITHMIC PLOT OF THE GEOMETRIC LS MEAN RATIOS
AND ASSOCIATED 90% CONFIDENCE INTERVALS
(LOG-TRANSFORMED DATA)

TREATMENT B RELATIVE TO TREATMENT A (N=16)



Note: Data from Subjects 2 & 9 are not included on the comparison graph. Each subject received only one Treatment; A and C, respectively.

SUMMARY

Title of Study:

A study to investigate the comparative bioavailability of a reference lamotrigine 100 mg capsule, lamotrigine 100 mg dispersible tablet dispersed in water, lamotrigine 100 mg dispersible tablet chewed and lamotrigine 100 mg dispersible tablet swallowed whole. (UK 134)

Publication (Reference):

None

Period of Study:

11 July 1994 to 30th April 1995

Clinical Phase:

I

Study Objectives:

To compare the relative bioavailability of a reference 100 mg lamotrigine capsule and 100 mg dispersible lamotrigine tablets dispersed, chewed or swallowed whole in terms of non–compartmental $AUC_{0-\infty}$, C_{max} and t_{max}.

Summary of Study Design and Methodology:

A 4 occasion, open, randomised cross–over design in 12 healthy male and female volunteers. Each volunteer received a single oral dose of 100 mg lamotrigine as one capsule, one dispersible tablet dispersed in water, one dispersible tablet chewed and swallowed and one tablet swallowed whole. Each dose was taken after overnight fasting with 14 days between occasions. Plasma samples for analysis were taken pre–dose and at intervals up to 168 h.

Plasma lamotrigine levels were determined using a direct procedure. The method has a limit of quantification all concentrations within the assay range.

$AUC_{0-\infty}$, $t_{½}$, CL/f and V_z/f were calculated using non–compartmental pharmacokinetic methods. C_{max} and t_{max} were taken directly from the plasma concentration versus time profiles. The main determinant of relative bioavailability was lamotrigine $AUC_{0-\infty}$.

Number of Subjects (Total and Per Treatment):

12

Key Inclusion Criteria:

Healthy volunteers of either sex who were aged between 18 and 55 years and weighed between 55 and 95 kg.

Name, Batch Number, Dose and Mode of Administration of Test Product:

Lamotrigine 100 mg capsules, Lot No 938B (swallowed) and lamotrigine 100 mg dispersible tablets, Lot No 120C.

Evaluation Criteria:

Lamotrigine $AUC_{0-\infty}$, C_{max} and t_{max} were compared between the different methods of administration of the dispersible tablet and the reference capsule formulation.

Statistical Methods:

$AUC_{0-\infty}$ and C_{max} were subjected to analysis of variance taking into account sources of variation due to subject, occasion, treatment and treatment x occasion interaction. The data were log transformed prior to analysis and 90% confidence intervals calculated for the difference between each of the dispersible tablet treatments and the capsule. Medians and ranges for t_{max} were determined and 90% confidence intervals calculated using the Wilcoxon Signed Rank Test.

Summary of Results:

Subject 5 withdrew from the study after the second occasion for reasons not associated with the study drug. Data from the first 2 occasions for this subject, which included the reference capsule treatment, were included in the results.

There were 2 AEs recorded as possibly or reasonably related to the study drug, a feeling of tiredness (possibly) and a period of nausea (reasonably). No action was taken.

Summary of Lamotrigine Pharmacokinetic Parameters. Arithmetic Means ± SD

	Capsule (n=12)	Dispersed (n=12)	Chewed (n=11)	Swallowed (n=11)
$AUC_{0-\infty}$ (µg/mL.h)	60.2 ± 21.8	62.7 ± 25.2	71.9 ± 27.0	68.7 ± 29.3
C_{max} (µg/mL)	1.49 ± 0.20	1.48 ± 0.34	1.62 ± 0.27	1.49 ± 0.22
t_{max} (h)[a]	2.0	1.5	1.5	2.5
$t_{½}$ (h)	31.5 ± 14.7	32.2 ± 11.3	34.7 ± 14.1	32.7 ± 13.3
CL/f (mL/min)	30.4 ± 11.0	31.8 ± 15.4	26.8 ± 11.7	28.4 ± 12.9
V_z/f (L)	72.6 ± 11.3	78.1 ± 15.8	70.5 ± 10.8	69.5 ± 8.1

[a] Medians and ranges are shown for t_{max}

Summary of Lamotrigine Pharmacokinetic Parameters – Dispersible/Capsule Ratio (as %) Point Estimates (with 90% Confidence Intervals)

	Dispersed/Capsule		
	Dispersed	Chewed	Swallowed
$AUC_{0-\infty}$ (µg/mL.h)	102 (95 , 109)	111 (104 , 120)	107 (100 , 115)
C_{max} (µg/mL)	98 (93 , 103)	104 (99 , 110)	97 (92 , 102)
C_{max}[a] (µg/mL)	107 (100 , 115)	112 (104 , 120)	103 (96 , 111)

[a] Without occasion 1

The 90% CI of $AUC_{0-\infty}$ ratios for all modes of ingestion of the tablet were within the 80–125% range. Similarly, 90% CI of C_{max}, with or without occasion 1, were within 80–125% for all modes of ingestion of the tablet.

Summary of Lamotrigine t_{max} – Treatment Medians and Differences between Medians (with 90% Confidence Intervals)

	Capsule (n=12)	Dispersed (n=12)	Chewed (n=11)	Swallowed (n=11)
Median (h)	2.0	1.5	1.5	2.5
Min				
Max				
Difference[a]	-	0	-0.5	1.5
90% CI	-	-0.8 , 1.1	-1.3 , 0.8	-0.1 , 3.0

[a] Median difference (test – capsule)

Conclusions:

The dispersible tablet formulation, dispersed in water, chewed or swallowed whole, is bioequivalent to the reference capsule formulation.

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Table 2 - Study 105-134 (UK 134) using dispersible tablet dispersed in water as the reference
Comparisons of geometric means and estimated test/reference ratios(1) for AUCinf, Cmax, and CL/f or comparison of medians and median differences for Tmax.

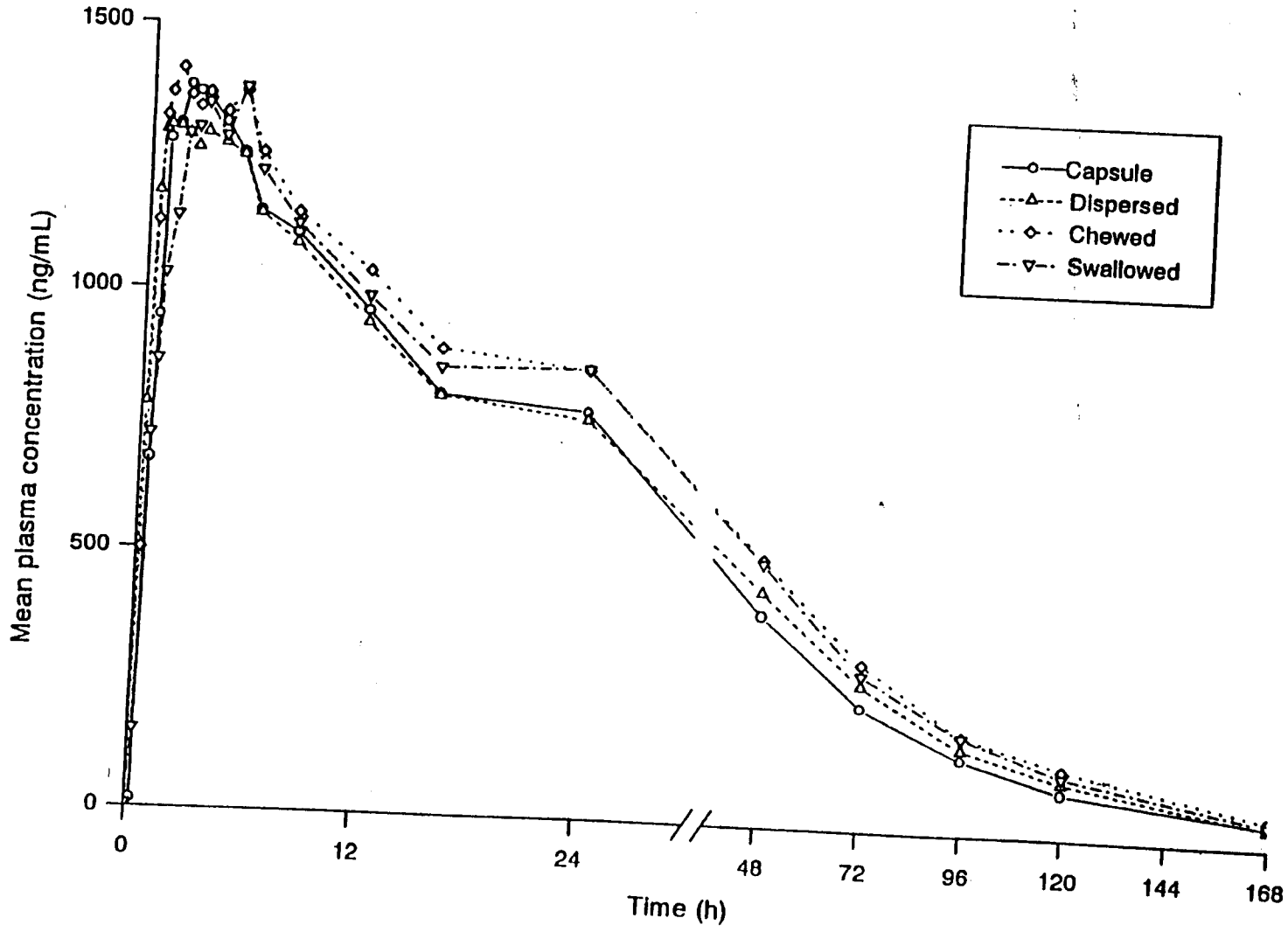
	Capsule / Dispersed	Chewed / Dispersed	Swallowed / Dispersed
AUCinf	98 (92, 105)	110 (102, 118)	106 (98, 114)
Cmax	102 (97, 108)	107 (101, 113)	99 (94, 105)
Cmax(2)	95 (88, 101)	105 (96, 113)	98 (91, 105)
Tmax(3)	0.0 (-1.1, 0.9)	0.0 (-1.5, 1.1)	1.2 (0.4, 2.6)
CL/f	99 (93, 106)	91 (85, 98)	95 (88, 102)

Notes:

Capsule = 1 x 100 mg lamotrigine capsule, swallowed whole with 200mL water,
Dispersed = 1 x 100 mg lamotrigine dispersible tablet, dispersed in 200mL water,
Chewed = 1 x 100 mg lamotrigine dispersible tablet, chewed and swallowed with 200mL water
Swallow = 1 x 100 mg lamotrigine dispersible tablet, swallowed whole with 200mL water.

(1) The ratios and 90% confidence intervals are summarized as percentages.
(2) Analyzed without period 1 data.
(3) The comparisons for Tmax are estimated median diferences: Capsule - Dispersed, Chewed - Dispersed, and Swallowed - Dispersed, as opposed to ratios. 90% confidence intervals for median differences are presented.

Figure 1. Mean Plasma Profiles for Individual Treatments



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CLINICAL STUDY SUMMARY

TITLE OF STUDY

A Bioequivalence Study of the US 25 mg LAMICTAL† (lamotrigine) . Tablets, UK 25 mg LAMICTAL Dispersible/Chewable Tablets, and UK 5 mg LAMICTAL Dispersible/Chewable Caplets in Normal Volunteers (US 39)

PUBLICATION (REFERENCE)

Not applicable

PERIOD OF STUDY:

30 November 1993 – 1 February 1994

CLINICAL PHASE

Phase I Study

STUDY OBJECTIVES

The objectives of this Phase I study (105–039 were to evaluate the bioequivalence of:

1. UK LAMICTAL dispersible/chewable tablets, and caplets, compared to US LAMICTAL tablets,
2. UK 25 mg LAMICTAL dispersible/chewable tablets and UK 5 mg LAMICTAL dispersible/chewable caplets when administered in equal doses, and
3. UK 25 mg LAMICTAL dispersible/chewable tablets when administered after dispensing in water versus administration by chewing.

† This is a Trade Mark of Wellcome group companies. Registered in U.S. Patent and Trademark Office.

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SUMMARY OF STUDY DESIGN AND METHODOLOGY

This investigation was an open–label, single–dose, randomized, four–period, four–treatment crossover study in twenty healthy adult, male volunteers. Each volunteer received:

- Treatment 1 (reference formulation): one US 25 mg LAMICTAL tablet,
- Treatment 2 (test formulation): one UK 25 mg LAMICTAL dispersible/chewable tablet dispersed in water,
- Treatment 3 (test formulation): five UK 5 mg LAMICTAL dispersible/chewable caplets dispersed in water, or
- Treatment 4 (test formulation): one UK 25 mg LAMICTAL dispersible/chewable tablet chewed thoroughly,

in each of four dosing periods (one Treatment per dosing period) according to a randomization schedule. Administration of each treatment was separated by at least 14 days to allow for complete washout of residual lamotrigine from the previous dose. Serial blood samples were collected for 7 days after each dose. Vital signs were monitored and volunteers were evaluated for adverse experiences at protocol–specified times during the Treatment Phase.

NUMBER OF SUBJECTS (TOTAL AND PER TREATMENT)

Twenty healthy volunteers were enrolled and eighteen completed all four treatment periods. Analysis of variance (ANOVA) for bioequivalence was performed on all eighteen subjects who completed all four treatment periods. Data from one subject had much lower than expected plasma concentrations in one treatment period but this subject was included in the analyses.

DIAGNOSIS AND KEY INCLUSION CRITERIA

Not applicable

NAME, BATCH NUMBER, DOSE AND MODE OF ADMINISTRATION OF TEST AND REFERENCE PRODUCT(S)

Treatment, Dosage Form, Strength and Reference or Test Products	Batch Number	Formulation Number	Mode of Administration
No.1 Tablet, 25 mg; Reference	2W2707	BOI–01A2	Swallowed intact
No.2:Dispersible/Chewable Tablet (Dispersed), 25 mg; Test (and Reference)	2W2798	BZS–01A1	Dispersed in water
No.3:Dispersible/Chewable Caplet (Dispersed), 5x5mg; Test	2W2796	BZQ–01A1	Dispersed in water
No.4:Dispersible/Chewable Tablet (Chewed), 25 mg; Test	2W2798	BZS–01A1	Chewed

Parameter	Treatment 1	Treatment 2	Treatment 3	Treatment 4
$AUC_{0\rightarrow\infty}$ (ng·hr/mL)	15522 (30)	15741 (27)	14911 (37)	16044 (28)
$AUC_{0\rightarrow t}$ (ng·hr/mL)	14749 (27)	14964 (25)	14182 (35)	15245 (25)
C_{max} (ng/mL)	382 (18)	369 (13)	343 (21)	364 (10)
T_{max} (hr)	1.4 (55)	2.0 (67)	3.0 (73)	2.2 (73)
CL/F (ml/min)	29 (28)	28 (26)	36 (85)	28 (25)
λ_z (1/hr)	0.022 (24)	0.022 (23)	0.021 (20)	0.021 (22)
$t_{½}$ (hr)	33.4 (26)	33.9 (24)	34.5 (23)	35.1 (24)

Treatment geometric LS mean ratios (treatment ratios) and corresponding 90% confidence intervals are summarized below. In addition the ANOVA p–values from the Two One–Sided Tests Procedure for principal bioequivalence parameters are listed below for each test–to–reference comparison. Mean treatment ratios for $AUC_{0\rightarrow\infty}$, $AUC_{0\rightarrow t}$ and C_{max} and the associated 90% confidence intervals were within the 80–125% acceptance range for bioequivalence when Treatments 2, 3 and 4 were compared to Treatment 1.

	Treatment 1: US 25mg LAMICTAL tablet (Swallowed) (Reference)	Ratio 2:1	Treatment 2: UK 25mg LAMICTAL Dispersible/ Chewable (Dispersed) (Test)	Ratio 3:1	Treatment 3: UK 5 x 5mg LAMICTAL Dispersible/ Chewable (Dispersed) (Test)	Ratio 4:1	Treatment 4: UK 25mg LAMICTAL Dispersible/ Chewable (Chewed) (Test)
$AUC_{0\rightarrow\infty}$ (ng·h/mL)							
Geometric LS Mean	14926		15250		13682		15524
95% CI	(13583–16401)		(13879–16758)		(12451–15034)		(14127–17058)
Mean Ratio		1.02		0.917		1.04	
90% CI		(0.91–1.14)		(0.820–1.02)		(0.93–1.16)	
p value		0.747		0.195		0.557	
$AUC_{0\rightarrow t}$ (ng·h/mL)							
Geometric LS Mean	14292		14589		13024		14854
95% CI	(12900–15834)		(13168–16163)		(11756–14429)		(13407–16456)
Mean Ratio		1.02		0.911		1.04	
90% CI		(0.90–1.15)		(0.81–1.03)		(0.92–1.17)	
p value		0.777		0.203		0.595	
C_{max} (ng/mL)							
Geometric LS Mean	379		368		331		364
95% CI	(349–410)		(340–399)		(305–359)		(336–394)
Mean Ratio		0.973		0.875		0.961	
90% CI		(0.88–1.07)		(0.80–0.96)		(0.87–1.06)	
p value		0.633		0.023		0.487	

Table 9. Individual T_{max} Values (hr) and Summary Statistics for Lamotrigine Treatments 2, 3 and 4 vs. Treatment 1

Group 1 = 1x25 mg - swallowed
Group 2 = 1x25 mg - dissolved
Group 3 = 5x5 mg - dissolved
Group 4 = 1x25 mg - chewed

Subject	Group 1	Group 2	Group 3	Group 4
1(2)				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18(2)				
19				
20				
95% CI (lower)	0.9	1.3	1.9	1.1
95% CI (upper)	1.8	2.5	4.0	3.0
Median	1.0	2.0	2.8	2.0
Minimum				
Maximum				
Arithmetic Mean	1.4	2.0	3.0	2.2
SD	0.8	1.3	2.2	1.6
CV	55	67	73	73

Comparison	Est. Diff(1)	90% C.I.	p value
Group 1 - 2	0.6	(-.125-1.000)	0.1254
Group 1 - 3	1.1	(0.500-2.000)	0.0058
Group 1 - 4	0.8	(0.000-1.625)	0.1041

(1) Estimated Difference Based Upon Wilcoxon Signed Rank Test.
CI = Confidence Interval from Wilcoxon Signed Rank Test.
SD = Standard Deviation
%CV = Percent Coefficient of Variation
(2) Data Included in Listing Only, Excluded From All Analyses

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Mean treatment ratios for $AUC_{0\rightarrow\infty}$ and C_{max} and the associated 90% confidence intervals were within the 80–125% acceptance range for bioequivalence when Treatments 3 and 4 were compared to Treatment 2. $AUC_{0\rightarrow t}$ mean treatment ratios and associated 90% confidence intervals were within 80–125% for Treatment 4 when compared to Treatment 2. The 90% confidence interval for $AUC_{0\rightarrow t}$ was 79–101% for Treatment 3 compared to Treatment 2. Since one subject (Subject 6) had abnormally low plasma levels, this may have accounted for the log transformed $AUC_{0\rightarrow t}$ ratio falling just outside the 80% lower limit. In the untransformed analysis, $AUC_{0\rightarrow\infty}$, $AUC_{0\rightarrow t}$, and C_{max} treatment ratios and associated confidence intervals all met the bioequivalence criteria and were within the 80–120% range.

	Treatment 2: UK 25mg LAMICTAL Dispersible/ Chewable (Dispersed) (Reference)	Ratio 3:2	Treatment 3: UK 5 x 5mg LAMICTAL Dispersible/ Chewable (Dispersed) (Test)	Ratio 4:2	Treatment 4: UK 25mg LAMICTAL Dispersible/ Chewable (Chewed) (Test)
$AUC_{0\rightarrow\infty}$ (ng·h/mL)					
Geometric LS Mean	15250		13682		15524
95% CI	(13879–16758)		(12451–15034)		(14127–17058)
Mean Ratio		0.897		1.02	
90% CI		(0.80–1.00)		(0.91–1.14)	
p value		0.108		0.790	
$AUC_{0\rightarrow t}$ (ng·h/mL)					
Geometric LS Mean	14589		13024		14854
95% CI	(13168–16163)		(11756–14429)		(13407–16456)
Mean Ratio		0.893		1.02	
90% CI		(0.79–1.01)		(0.90–1.15)	
p value		0.122		0.804	
C_{max} (ng/mL)					
Geometric LS Mean	368		331		364
95% CI	(340–399)		(305–359)		(336–394)
Mean Ratio		0.899		0.988	
90% CI		(0.82–0.99)		(0.90–1.09)	
p value		0.068		0.826	

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Table 16. Individual T_{max} Values (hr) and Summary Statistics for Lamotrigine Treatments 3 and 4 vs. Treatment 2

Group 1 = 1x25 mg - swallowed
Group 2 = 1x25 mg - dissolved
Group 3 = 5x5 mg - dissolved
Group 4 = 1x25 mg - chewed

Subject	Group 2	Group 3	Group 4
1(2)			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18(2)			
19			
20			
95% CI (lower)	1.3	1.9	1.1
95% CI (upper)	2.5	4.0	3.0
Median	2.0	2.8	2.0
Minimum			
Maximum			
Arithmetic Mean	2.0	3.0	2.2
SD	1.3	2.2	1.6
CV	67	73	73

Comparison	Est. Diff(1)	90% C.I.	p value
Group 2 - 3	0.9	(0.000-1.875)	0.0956
Group 2 - 4	0.3	(-.750-1.250)	0.6852

(1) Estimated Difference Based Upon Wilcoxon Signed Rank Test.
CI = Confidence Interval from Wilcoxon Signed Rank Test.
SD = Standard Deviation
%CV = Percent Coefficient of Variation
(2) Data Included in Listing Only, Excluded From All Analyses

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BIO$STAT_CP:[P105F.SAS.PROGRAMS.039.PK]039SUM2X.SAS 06/26/96

7. CONCLUSIONS

- The UK dispersible/chewable LAMICTAL tablets, either dispersed or chewed (Treatment 2, 3 or 4), are bioequivalent to the US 25 mg LAMICTAL tablet (Treatment 1).
- The UK 5x5 mg LAMICTAL dispersible/chewable caplets (Treatment 3) are bioequivalent to the UK 25 mg dispersible/chewable tablet (Treatment 2).
- The UK 25 mg dispersible/chewable tablet, chewed (Treatment 4) is bioequivalent to the same tablet, dispersed prior to ingestion (Treatment 2).

Figure 1. Average (±SD) Plasma Lamotrigine Concentration–Time Profiles

(n=18)

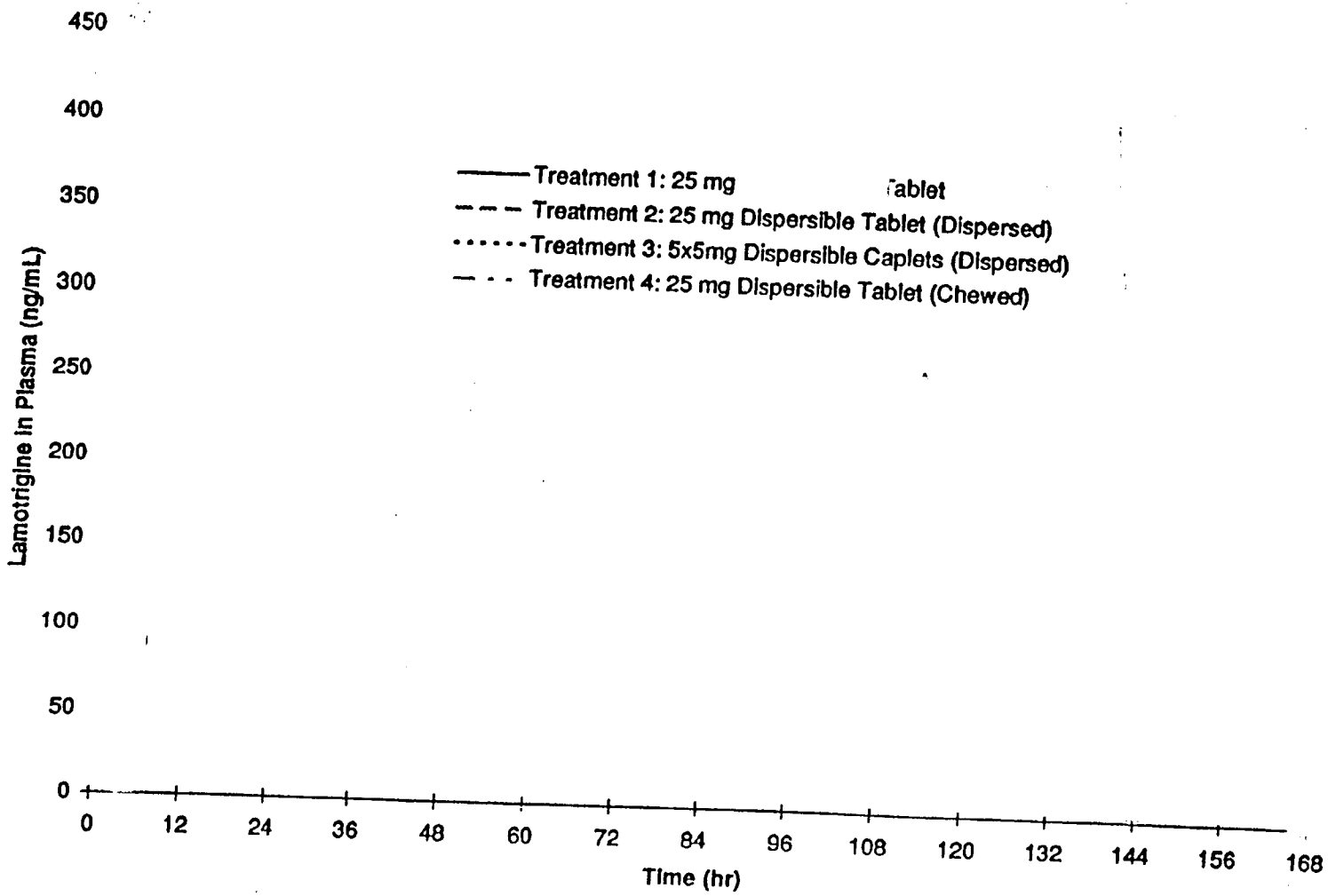
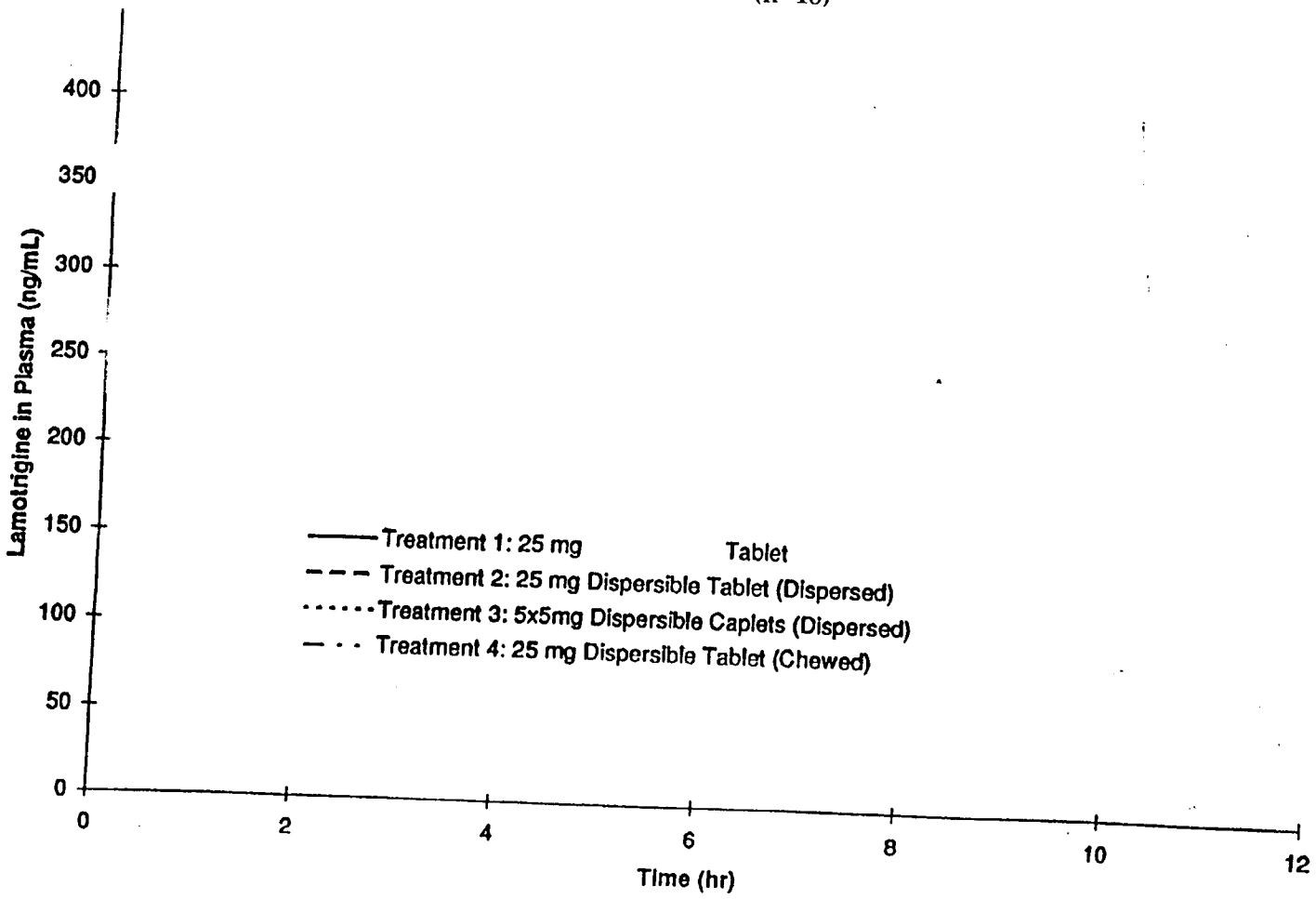


Figure 2. Average (±SD) Plasma Lamotrigine Concentration–Time Profiles (From 0 to 12 Hours)

(n=18)



GlaxoWellcome

April 8, 1997

Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
HFD-120, Woodmont II, Room 4037
1451 Rockville Pike
Rockville, MD 20857

Re: NDA 20-764; LAMICTAL CD (lamotrigine) Chewable Dispersible Tablets Amendment to Pending Application: Request for Waiver for Bioequivalence Studies

Dear Dr. Leber:

LAMICTAL (lamotrigine) Tablets (NDA 20-241) are approved in the US for use as adjunctive therapy in the treatment of partial seizures. LAMICTAL Tablets are supplied in 25, 100, 150 and 200 mg strengths for oral administration.

On September 16, 1996, Glaxo Wellcome Inc. submitted NDA 20-764 requesting approval of **(1)** a new chewable/dispersible tablet formulation of lamotrigine in three different strengths (5, 25, and 100 mg tablets), **(2)** use of lamotrigine as adjunctive therapy in the treatment of Lennox-Gastaut syndrome, a rare epilepsy syndrome in pediatric patients and **(3)** use of lamotrigine as adjunctive treatment of secondarily generalized tonic-clonic seizures in adults.

The purposes of this correspondence are **(1)** to request for a waiver from conducting an in vivo study evaluating bioequivalence between LAMICTAL 25 mg chewable/dispersible tablet and an approved formulation; and **(2)** to support bioequivalence between the products manufactured in the UK and used in pivotal trial UK 123 for Lennox-Gastaut indication and the compressed tablets approved in the US.

On the basis of 21 CFR Part 320.22 (d) (2) quoted below, Glaxo Wellcome Inc. requests for a waiver from conducting an in vivo study evaluating bioequivalence between LAMICTAL 25 mg chewable/dispersible tablet and an approved formulation.

> "The drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another drug product for which the same manufacturer has obtained approval and

Glaxo Wellcome Research and Development
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709
Telephone
919 248 2100
A Division of
Glaxo Wellcome Inc.

the conditions in paragraphs (d)(2)(i) through (d)(2)(iii) are met:

(i) The bioavailability of this other drug product has been demonstrated;

(ii) Both drug products meet an appropriate in vitro test approved by FDA; and

(iii) The applicant submits evidence showing that both products are proportionally similar in their active and inactive ingredients.

(iv) This subparagraph does not apply to enteric coated or controlled release dosage forms."

The approved tablet formulations and the chewable/dispersible formulations are uncoated immediate-release products. Lamotrigine is rapidly and completely absorbed after oral administration with negligible first-pass metabolism. The absolute bioavailability is 98% (Current US Package Insert, data submitted with NDA 20-241, LAMICTAL Tablets).

The compositions of 5, 25 and 100 mg chewable/dispersible tablets are summarized in Table 1. All formulations contain identical ingredients and the amounts of all ingredients are proportionally identical between the 25 mg and 100 mg formulations.

In vitro dissolution of both 25 and 100 mg chewable/dispersible tablets were assessed using the method of USP (Method # AM0632, General Chapter <711>, Apparatus 2). Dissolution tests were conducted in 900 mL of 0.1 N hydrochloric acid at 37.0 ± 0.5°C The recommended dissolution specification for both 25 mg and 100 mg formulations The dissolution data for these tablets manufactured at Greenville and Zebulon, North Carolina are shown in Table 2 and Table 3, respectively. The dissolution profiles are 25 mg and 100 mg products manufactured at both Greenville and Zebulon plants and the profiles are similar between the two sites for each strength.

The 100 mg chewable/dispersible tablet formulation manufactured at Greenville, North Carolina has been proven bioequivalent to the approved 100 mg tablet formulation (Study US 51, Item 6, NDA 20-764 submitted 16 September 1996). The geometric least square mean ratio (90% confidence interval) of 100 mg chewable/dispersible tablets to 100 mg tablets for AUC_{∞}, $AUC_{0\rightarrow t}$ and C_{max} were 0.97 (0.92 ~ 1.02), 0.98 (0.94 ~ 1.03) and 0.97 (0.92 ~ 1.03), respectively. In addition, the 25 mg chewable/dispersible tablets manufactured at containing the same components at the same amounts and produced using the same process as the 25 mg chewable/dispersible tablets manufactured at Greenville, North Carolina were shown bioequivalent to the 25 mg US commercial tablet (Study US 39, Item 6, NDA 20-764 submitted September 1996). Moreover, the 5 mg chewable/dispersible tablets

manufactured at Greenville, North Carolina were proven bioequivalent to the 25 mg commercial tablets at the same doses (Study US 50, Item 6, NDA 20-764 submitted 16 September 1996).

Therefore, Glaxo Wellcome Inc requests for a waiver from conducting an in vivo study evaluating bioequivalence between LAMICTAL 25 mg chewable/dispersible tablet manufactured at Greenville or Zebulon, North Carolina and an approved formulation because the 100 mg chewable/dispersible tablet has been demonstrated to be bioequivalent to the 100 mg tablet and the 25 mg and 100 mg chewable dispersible tablets are compositionally proportional.

The 5 mg, 25 mg and 100 mg chewable/dispersible tablets manufactured in and used in pivotal trial UK 123 for Lennox-Gastaut indication are bioequivalent to the tablets approved in the US.

Study UK 123 was the pivotal study to support the use of LAMICTAL as adjunctive therapy for treatment of Lennox-Gastaut Syndrome. LAMICTAL chewable/dispersible tablets in 5 mg, 25 mg, and 100 mg strengths manufactured at were used in this study. Both batches of the 5 mg and 25 mg chewable/dispersible tablets used in UK123 were studied in US 39. In US 39, the UK 5 and 25 mg chewable/dispersible tablets used in UK 123 were shown bioequivalent to the US 25 mg conventional tablet. In Study US 51, the same batch of the 100 mg chewable/dispersible tablets administered in UK 123 were proven bioequivalent to the US 100 mg tablets and the US 100 mg chewable/dispersible tablets. Therefore, all chewable/dispersible formulations manufactured in UK and used in Study UK 123 are bioequivalent to the US commercial tablets. Results of Studies US 39 and 51 can be found in Item 6, NDA 20-764.

We trust that this information will support our request for a waiver for conducting additional bioequivalence studies for LAMICTAL CD Chewable Dispersible Tablets. If you have any questions regarding this submission, please do not hesitate to contact me at 919-483-6466.

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Sincerely,

Elizabeth McConnell

Elizabeth A. McConnell, Pharm.D.
Project Director
Regulatory Affairs

cc: Vijay Tammara, Ph.D., Biopharmaceutics Reviewer, HFD-426
Jacqueline Ware, Pharm.D., Regulatory Management officer, HFD-120

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UK - 9001

SUMMARY

Title
Pharmacokinetics and safety of lamotrigine in young epileptic children. (UK - 9001)

Publication
None

Studied period
First inclusion : July 1990
Last inclusion : May 1992

Objectives
Primary objectives of the study were :
.to determine lamotrigine pharmacokinetic parameters after oral administration to children aged less than 5 years, presenting with refractory epilepsy.
.to investigate the relationship between plasma lamotrigine concentrations at steady state and dosage administered.

Secondary objectives were :
.to generate safety data.
.to evaluate the effects of concomitant antiepileptic drugs withdrawal after three months of lamotrigine treatment.

Methodology
An open 48-week trial in which lamotrigine was added to a regimen of standard antiepileptic drugs in children below the age of 5 years and with refractory seizures. Twenty seven children were included but two of them were withdrawn from the analysis.

Subsequent to an initial screening, patients were admitted for 48 h to determine lamotrigine pharmacokinetic parameters after a single 2.10 ± 0.38 mg/kg oral dose. Blood samples (1 ml) were collected before and at 1, 3, 6, 12, 24 and 48 h after administration. Lamotrigine concentrations were determined by Individual kinetic parameters were calculated and used for dose adjustment in order to achieve a trough level between

1.5 and 3 mg/l at steady state. Half of this calculated dose was administered for two weeks, and the full calculated dose for a further two weeks. Over the next 44 weeks the dose was adjusted to maintain a trough plasma concentration

The children were divided into 3 groups according to the concomitant antiepileptic medication: inducers (phenytoin, phenobarbital, carbamazepine), inhibitors (sodium valproate), others (drugs with no known effect on drug metabolising enzymes).

Statistical methods
Descriptive.

Results and discussion
The mean kinetic parameters were :

MEAN ± SD (range)	AGE Year	Tmax h	Cmax mg/l	AUC0->inf mg.h/l	CL/f (ml/min/kg) l/h/kg	Vz/f l/kg	T 1/2 h
Inducers (n = 10)	2.48 ± 1.21	3.04 ± 1.19	0.80 ± 0.23	9.70 ± 1.53	(3.62 ± 0.32) 0.217 ± 0.049	2.33 ± 0.44	7.66 ± 1.79
Inhibitors (n = 9)	3.38 ± 1.56	2.86 ± 1.56	1.44 ± 0.53	36.20 ± 41.34	(0.47 ± 0.15) 0.028 ± 0.011	1.75 ± 0.59	44.92 ± 8.28
Others (n = 7)	3.51 ± 1.06	5.16 ± 1.47	1.33 ± 0.63	37.13 ± 12.90	(1.20 ± 0.58) 0.072 ± 0.035	2.00 ± 1.01	19.02 ± 6.86

The final adjusted doses (mean ± sd) were as follows 21.01 ± 6.04 mg/kg (inducers), 1.88 ± 0.75 mg/kg (inhibitors) and 5.83 ± 3.85 mg/kg (others).

Conclusions
Lamotrigine pharmacokinetics in children receiving concomitant therapy with other AEDs are highly dependant on the nature of the effect of the concomitant AED on hepatic enzyme activity, in a similar manner to adults. Body weight was also an important variable, but age was not a significant additional factor. Body-weight adjusted doses in children need to be higher than in adults to achieve similar plasma concentrations.

Lamotrigine appears to have benefited a proportion of children with refractory seizures. It was well tolerated over the course of the treatment period. There were no significant changes in laboratory safety evaluation parameters that were considered related to lamotrigine.