ATTACHMENT 3

GlaxoWellcome

August 3, 1998

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 20852

Re: NDA 20-764; LAMICTAL® CD (lamotrigine) Chewable Dispersible Tablets
NDA 20-241/S-002; LAMICTAL® (lamotrigine) Tablets
Amendment to Pending Application
Response to FDA Request/Comment

Dear Dr. Leber:

Reference is made to a July 15, 1998 request from Vijay Tammara, Ph.D., Biopharmaceutics Reviewer, regarding the aforementioned applications. Specifically, Dr. Tammara requested a comparison of actual observed plasma concentration data at currently recommended doses of LAMICTAL in adults and children. The purpose of this additional information is to aid in his review of our June 23, 1998 proposal to revise the pediatric initial dosing and escalation recommendations based on the recently validated pediatric population pharmacokinetic model for LAMICTAL.

Attachment 1 contains the information requested by Dr. Tammara, including a summary and explanation of the tables and graphs provided.

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

A desk copy of this submission is being provided to Dr. Tammara under separate cover. If you have any questions regarding this submission, please do not hesitate to contact me at 919-483-6466.

Sincerely,

Elizabeth McConnell

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

Cc: Vijay Tammara, Ph.D., HFD-860 (via Jacqueline Ware, Pharm.D.)
Jacqueline Ware, Pharm.D., Regulatory Management Officer, HFD-120 (cover letter only)

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SUMMARY

Glaxo Wellcome Inc. submitted a request to the agency on June 23, 1998 for revision of the currently recommended doses for children with epilepsy. The proposed revision included reduction of the initial doses and the rate of dose ascension to the suggested therapeutic dose range, but not the therapeutic dose range. Part of the rationale for such dose reduction was based on findings from a pharmacokinetic analysis. A population pharmacostatistic model established using plasma lamotrigine concentrations collected from clinical trials suggested that plasma concentrations of lamotrigine in children would be much higher than those in adults following respective dosage recommendations. The discrepancy was greatest in patients receiving enzyme-inducing antiepileptic drugs (EIAEDs) without valproic acid (VPA), although a difference was also seen in those receiving VPA. On July 15, 1998, the Agency requested a comparison between children and adults of the actual plasma concentrations collected during the initial weeks of dose escalation following the current dosage recommendations as summarized in Table 1.

Plasma concentrations of lamotrigine were routinely collected in 7 adult or pediatric adjunctive therapy studies during the dose escalation phase (first 6 weeks) of the treatment. As patients receiving VPA were not enrolled in the adult studies, the plasma concentration comparison between adults and children can only be made for those patients receiving EIAEDs without VPA. This is the group of patients in which the pharmacokinetic model suggested the greatest discrepancy between the concentrations in children and those in adults. Plasma concentrations collected from patients receiving enzyme-inducing AEDs during dose escalation phase along with dosing information are summarized in Table 2 and the mean concentrations are presented in Figure 1. On day 28 of the treatment, the only sampling occasion common to both adults and children, the mean concentrations in children are lower than those in adults. The dosage regimens summarized in Table 1 were not used in any of the studies.

Since plasma concentrations of lamotrigine is proportional to dose, the mean concentrations were adjusted by the recommended doses to facilitate the comparison between adults and children. The dose-adjusted mean concentrations are listed in Table 3 and depicted in Figure 2. The plasma concentrations in children would be 2 to 3 fold higher than that of those in adults following the respective dosage recommendations. This finding was in general agreement with the suggestions by the population pharmacostatistical model submitted to the Agency on June 23, 1998.

Table 1 Current LAMICTAL Dosage Recommendations for Adults and Children

LAMICTAL Added to VPA With or Without EIAEDs in Patients 2 to 12 Years of Age

Weeks 1 and 2	0.2 mg/kg/day in one or two divided doses
Weeks 3 and 4	0.5 mg/kg/day in one or two divided doses
Usual maintenance dose: 1 to 15 mg/kg/day (maximum 400 mg/day in one or two divided doses). To achieve maintenance, doses may be increased by 0.5 to 1 mg/kg/day every 1 to 2 weeks. Patients adding LAMICTAL to VPA alone usually have maintenance dosages of 1 to 7 mg/kg/day (maximum 200 mg/day).	

LAMICTAL Added to EIAEDs Alone (Without VPA) in Patients 2 to 12 Years of Age

Weeks 1 and 2	2 mg/kg/day in two divided doses
Weeks 3 and 4	5 mg/kg/day in two divided doses
Usual maintenance dose: 5 to 15 mg/kg/day (maximum 400 mg/day in two divided doses). To achieve maintenance, doses may be increased by 2 to 3 mg/kg/day every 1 to 2 weeks.	

LAMICTAL Added to VPA With or Without EIAEDs in Patients Over 12 Years of Age

Weeks 1 and 2	25 mg every *other* day
Weeks 3 and 4	25 mg every day
Usual maintenance dose: 100 to 400 mg/day (1 or 2 divided doses). To achieve maintenance, doses may be increased by 25 to 50 mg/day every 1 to 2 weeks. The usual maintenance dose in patients adding LAMICTAL to VPA alone ranges from 100 to 200 mg/day.	

LAMICTAL Added to EIAEDs Alone (Without VPA) in Patients Over 12 Years of Age

Weeks 1 and 2	50 mg/day
Weeks 3 and 4	100 mg/day in two divided doses
Usual maintenance dose: 300 to 500 mg/day (in two divided doses). To achieve maintenance, doses may be increased by 100 mg/day every 1 to 2 weeks.	

Table 2. Summary of Lamotrigine Plasma Concentrations during Dose Escalation in Patients receiving Enzyme-Inducing AEDs in Clinical Trials

			Concentration (ug/mL)					Daily Dose (mg for adults and mg/kg for children)					
Study	Patients	Days on LTG[a]	n	Med	Min	Max	Mean	SD	Med	Min	Max	Mean	SD	Days on Dose[b]
16	Adult	28	232	3.30			3.41	1.68	400			392	81.28	7
30/31	Adult	14	50	2.32			2.81	2.23	300			300	0.00	7
		28	46	3.66			4.37	3.02	500			500	0.00	14
40	Pediatric	42	6	4.40			4.63	1.44	9.92			10.6	2.00	14
73	Pediatric	28	12	0.83			0.83	0.35	1.93			2.19	0.93	28
98[c]	Pediatric	28	1	0.40			0.40	-	4.41			4.41	-	14
102	Pediatric	28	43	1.60			2.40	4.45	4.69			4.31	1.13	14
123	Pediatric	28	10	0.89			0.97	0.46	3.09			2.74	0.95	14

[a]Protocol specified sampling days. Concentrations collected within ±3 day windows were included in the caluclations.

[b]Protocol-specified dosing schedules.

[c]Not plotted due to the sample size of 1.

$\frac{400}{70} = 5.7$

$.83 \times \frac{5.7}{2.19} = 2.16 \times 2 = 4.4$

two fold

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Table 3. Lamotrigine Plasma Concentrations during Dose Escalation Adjusted by the Recommend Doses

Study	Patients	Days on LTG[a]	n	Daily Dose (mg for adults and mg/kg for children)		Mean Concentration (ug/mL)	
				Actual	Recommended	Actual	Dose-Adjusted
16	Adult	28	232	392	100	3.41	0.87
30/31	Adult	14	50	300	50	2.81	0.47
		28	46	500	100	4.37	0.87
40[b]	Pediatric	42	6	10.6	-	4.63	-
73	Pediatric	28	12	2.19	5.00	0.83	1.89
98[c]	Pediatric	28	1	4.41	5.00	0.40	0.45
102	Pediatric	28	43	4.31	5.00	2.40	2.78
123	Pediatric	28	10	2.74	5.00	0.97	1.77

[a]Protocol specified sampling days. Concentrations collected within ±3 day windows were included in the caluclations.
[b]Dose-adjusted mean concentrations were not calculated as dose on day 42 was not specified in the dose recommendations.
[c]Not plotted due to the sample size of 1.

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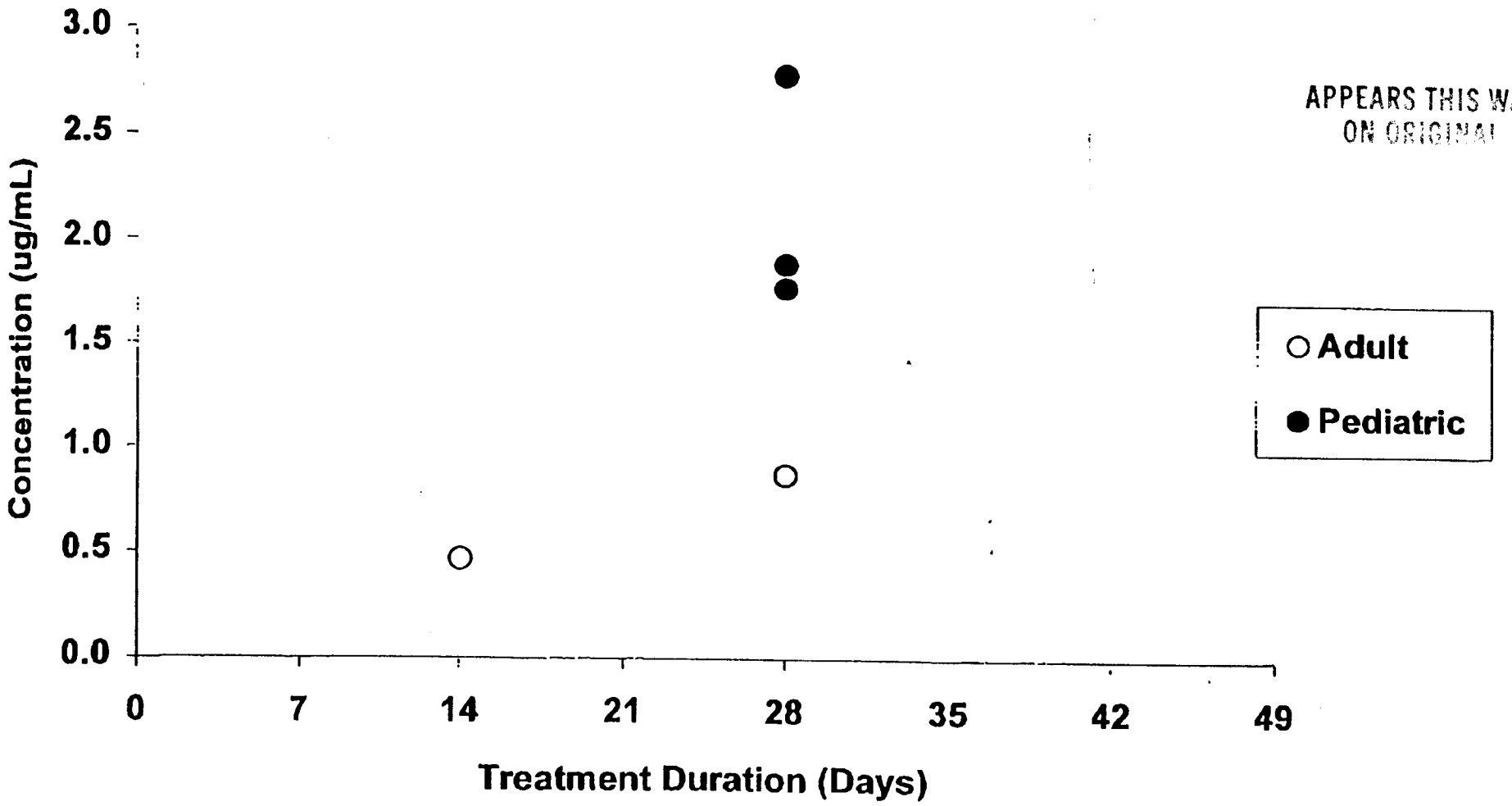
Figure 2. Mean Plasma Concentrations of Lamotrigine during Dose Escalation Adjusted by the Recommended Doses



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OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20,764
Lamotrigine (Lamictal®)
5, 25, and 100 mg Chewable/Dispersible Tablets

GlaxoWellcome Inc.
Five Moore Drive
Research Triangle Park, NC

Reviewer: Vijay K. Tammara, Ph. D.

Submission Dates;
September 16, 1996
March 11, 1997
April 8, 1997
April 9, 1997
April 11, 1997
April 18, 1997

Indication: Lennox-Gastaut Syndrome

Type of Submission: NDA

SYNOPSIS

Lamictal (Lamotrigine) is an antiepileptic drug of the phenyltriazine class.

Original NDA consisting of compressed Tablets (25, 100, 150, and 200 mg) was approved on December 27, 1994 for adjunctive therapy of partial seizures in adults with epilepsy.

In the present submission, the sponsor is proposing to market Chewable Dispersible (CD) Tablets 5, 25, and 100 mg for the adjunctive treatment of Lennox-Gastaut syndrome in pediatric and adult patients and for adjunctive treatment of secondarily generalized tonic-clonic seizures in adults with epilepsy. The sponsor is interested in marketing a chewable/dispersible tablet as an alternative formulation for patients who may have difficulty swallowing the compressed tablet (e.g., children and elderly).

As per the labeling, the therapy is initiated with 25 mg every alternate day for 2 weeks, followed by 25 mg once a day for 2 weeks. Thereafter, the dose should be increased to achieve optimal response.

Lamictal is rapidly and completely absorbed after oral administration, with maximal concentrations being achieved in 2-4 hours. It displays linearity over the dose range of 50-400 mg following either single or multiple dose administration.

The sponsor had conducted clinical/pharmacokinetic studies using the chewable/dispersible tablets manufactured at Dartford, UK. The eventual to-be-marketed dosage form will be manufactured in US at Greenville or Zebulon, North Carolina. In this regard, the sponsor has performed single dose bioequivalence studies for 5 mg chewable/dispersible caplet and 100 mg chewable/dispersible tablet involving the two sites of manufacture, Dartford, UK vs Greenville, NC, US. Since the 25 mg strength Chewable/dispersible tablet is compositionally proportional to 100 mg strength Chewable/dispersible tablet, the sponsor has requested a bio waiver for 25 mg strength Chewable/dispersible tablet and also provided dissolution data to show that the 25 and 100 mg Chewable/dispersible tablets are identical. For the other site, Zebulon, NC, the sponsor [redacted]. The chewable/dispersible tablets (5 and 100 mg) manufactured at different sites (Dartford, UK and Greenville, NC, US)

Pharmacokinetics of Lamictal following a single dose (2 mg/kg) was evaluated in two studies in pediatric patients with epilepsy (n=25 for patients aged 2 months-5 years and n=18 for patients aged 5-11 years). All patients were receiving concomitant therapy with other AEDs. The children were divided into 4 groups according to the concomitant medication they received: Group 1: Children receiving enzyme inducers; Group 2: Children receiving enzyme inhibitors; Group 3: Children receiving combination of either enzyme inducers and inhibitors (balanced); and Group 4: children receiving neither enzyme inducer nor inhibitor. It was observed from the results that Lamotrigine pharmacokinetics in children receiving concomitant therapy with other AEDs are highly dependant on the nature of effect of the concomitant AEDs on hepatic enzyme activity, in a similar manner to adults. In this study, it was observed that mean CL/F in children was higher and mean half-life was shorter in both pediatric groups than in adults. Thus, it can be concluded that the clearance of Lamotrigine is higher in children than that in adults. Further, it was observed that mean CL/F was higher and mean half-life was shorter in younger children than in older children.

Population pharmacokinetic analysis of lamotrigine by NONMEM indicated that oral clearance of Lamotrigine is a function of both body weight and concomitant AED's. Further it was observed that potential covariates such as age, height, and race were found to have no additional effect on oral clearance of lamotrigine.

Lamotrigine was quantified in plasma, whole blood, urine, and feces by radioimmuno assay (RIA), immunoflourometric assay (IFA), and high performance liquid chromatography (HPLC), and the limit of quantitation (LOQ) was 0.4 ng/mL. Overall, the analytical validation was found to be satisfactory in terms of specificity, sensitivity, linearity, precision, and accuracy.

RECOMMENDATION:

This submission (NDA 20-764) has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics' and has been found to be acceptable for meeting the Offices' requirements, provided the sponsor incorporates all the labeling changes and responds satisfactorily to all enclosed **Comments**. The sponsor is requested to adopt the dissolution methodology and specification as outlined in **Comment 2.** Please forward **Comments 1-6** and this **Recommendation** to the sponsor.

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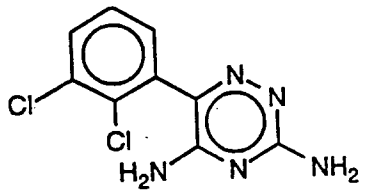
I. BIOAVAILABILITY/BIOEQUIVALENCE

II. PHARMACOKINETICS

INTRODUCTION:

Lamictal, an antiepileptic drug of the phenyltriazine class, is chemically unrelated to existing antiepileptic drugs. Its chemical name is 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine. Its molecular formula is $C_9H_7N_5Cl_2$, and its molecular weight is 256.09. Lamotrigine is a white to pale cream-colored powder and has a pKa of 5.7. It is very slightly soluble in water (0.17 mg/mL) and slightly soluble in 0.1M HCl (4.1 mg/mL). The structural formula is:



DOSAGE FORMS AND ADMINISTRATION

Pharmacokinetic studies were carried out after oral administration of Chewable/dispersible tablets. Tablets manufactured at different sites were used in the clinical studies.

MANUFACTURERS: Manufactured by Glaxo Wellcome Inc., Greenville and Zebulon, North Carolina, USA.

SUMMARY OF HUMAN BIOAVAILABILITY AND PHARMACOKINETICS

I.A. BIOAVAILABILITY/BIOEQUIVALENCE:

In the bioequivalence study (US 50) , the UK 5 mg chewable/dispersible (CD) caplet (treatment C) used in the pivotal clinical trials (UK 123, 46, and 86) and also used in well-controlled pediatric trials (US 40, 44, and UK 123) was compared with the US 5 mg CD caplet (treatment B) produced at Greenville, NC, USA and with the US 25 mg approved Lamictal tablet (treatment A), respectively. This study was conducted as a single-dose randomized, open-label, three-period, three-treatment, cross over study in 17 healthy male subjects, but only 15 subjects completed the study. Using the UK 5 mg CD caplet as the reference treatment for statistical comparisons, the US 5 mg CD caplet (to be marketed (TBM)) was found to be bioequivalent in terms of log transformed $AUC_{0-\infty}$ (90% CI=96-112) and C_{max} (90% CI=93-103%); no statistically significant difference in T_{max} was found between the two treatments (p=0.386). Similarly, using the US 25 mg tablet as the reference treatment, the US 5 mg CD caplet was found to be bioequivalent in terms of log transformed $AUC_{0-\infty}$ (90% CI=90-105) and C_{max} (90% CI=88-98%); no statistically significant difference in T_{max} was found between the two treatments (p=0.155) .

In another bioequivalence study (US 51), the UK 100 mg chewable/dispersible tablet (treatment C) used in the pivotal clinical trials (UK 123, 46, and 47) were compared with the US 100 mg chewable/dispersible tablet (treatment B) produced at Greenville, NC, USA and with the US 100 mg Lamictal tablet (treatment A), respectively. This study was conducted as a single-dose randomized, open-label, three-period, three-treatment, cross over study in 18 healthy male subjects, but only 16 subjects completed the study. Using the UK 100 mg chewable/dispersible tablet as the reference treatment for statistical comparisons, the US 100 mg chewable/dispersible tablet was found to be bioequivalent in terms of log transformed $AUC_{0-\infty}$ (90% CI=94-105) and C_{max} (90% CI=89-99%); no statistically significant difference in T_{max} was found between the two treatments (p=0.726). Similarly, using the US 100 mg compressed tablet as the reference treatment, the US 100 mg chewable/dispersible tablet was found to be bioequivalent in terms of log transformed $AUC_{0-\infty}$ (90% CI=92-102) and C_{max} (90% CI=92-103%); no statistically significant difference in T_{max} was found between the two treatments (p=0.222).

In a comparative bioavailability and bioequivalence study (UK 134), a reference 100 mg chewable/dispersible (CD) tablet administered was compared with 100 mg CD tablet administered as chewed and swallowed, and swallowed whole, respectively. This study was conducted as a single-dose, open-label, randomized, four-period, cross over study in 12 healthy male and female subjects. Using the 100 mg chewable/dispersible tablet administered as the reference for statistical comparisons, the comparative bioavailability of dispersible tablet administered as either chewed and swallowed or swallowed as whole tablet was found to be 110 and 106%, respectively and were also found to be bioequivalent in terms of log transformed $AUC_{0-\infty}$ (90% CI=102-118 and 98-114) and C_{max} (90% CI=101-113% and 94-105%), respectively. No statistically significant difference in T_{max} was found between the various methods of ingestion of the dispersible tablet formulation.

In another bioequivalence study (US 39), a US 25 mg Lamictal tablet (Treatment 1) was compared with UK 25 mg and UK 5X5 mg Lamictal chewable/dispersible (CD) tablets administered as either dispersed in water (Treatment 2 and Treatment 3, respectively) or UK 25 mg Lamictal CD tablet chewed and swallowed (Treatment 4), respectively. This study was conducted as a single-dose, open-label, randomized, four-period, cross over study in 20 healthy male subjects, but only 18 completed all four treatment periods. Using Treatment 1 as the reference for statistical comparisons, the comparative bioavailability of Treatments 2, 3 and 4 was found to be 102, 92, and 104%, respectively. Further, they were also found to be bioequivalent in terms of log transformed $AUC_{0-\infty}$ (90% CI=91-114; 82-102 and 93-116) and C_{max} (90% CI=88-107%; 80-96 and 87-106%), respectively. No statistically significant difference in T_{max} was found between the treatments in comparison to the reference treatment 1 (p=0.13 and 0.11 for treatments 2 and 4, respectively) except for Treatment 3 (p=0.006). Using Treatment 2 as the reference for statistical comparisons, the comparative bioavailability of Treatments 3 and 4 was found to be 90 and 102%, respectively. Further, they were also found to be bioequivalent in terms of log transformed $AUC_{0-\infty}$ (90% CI= 80-100 and 91-114) and C_{max} (90% CI= 82-99 and 90-109), respectively. No statistically significant difference in T_{max} was found between the treatments (p=0.1 and 0.69 for treatments 3 and 4, respectively).

I B. BIO-WAIVER

The sponsor has requested for a waiver to conduct an in vivo study evaluating bioequivalence between Lamictal 25 mg CD tablet manufactured at Greenville or Zebulon, North Carolina, USA. To support the waiver request, the sponsor provides justification and rationale that the 25 mg strength CD tablet is compositionally proportional to 100 mg strength CD tablet, and the dissolution data show that the 25 and 100 mg CD tablets are identical. For the other site, Zebulon, NC, the sponsor has provided dissolution profiles, since the formulations are compositionally similar. Based on the results provided, a waiver to conduct an in vivo study

to demonstrate bioequivalence can be granted for the 25 mg CD tablet.

II. PHARMACOKINETICS

In a pharmacokinetic study in pediatrics aged 2 months-5 years (UK 9001), the pharmacokinetics of Lamotrigine at a dose of 2 mg/kg at steady state was determined when coadministered with other antiepileptic drugs (AEDs). This study was conducted as an open 48 week trial in which Lamotrigine was added to a regimen of standard antiepileptic drugs in 27 children of age 2 months-5 years with refractory seizures, but two of them were withdrawn from the analysis. The dosage form used to administer the drug was capsule, available in strengths of 12.5, 25, 50 and 100 mg; manufactured at Dartford, UK. The children were divided into 3 groups according to the concomitant medication they received: Group 1: Infants and Children (age: 2 months to 5 years) receiving enzyme inducers (e.g., carbamazepine, phenytoin, primidone, and phenobarbitone); Group 2: Children (age: 2 to 5 years) receiving enzyme inhibitors (e.g.., sodium valproate); and Group 3: Children (age: 2 to 5 years) receiving combination of either enzyme inducers and inhibitors or others (e.g.., clonazepam, ethosuximide, nitrazepam, vigabatrin, progabide, lorazepam, and clobazam). It was observed from the results that the Lamotrigine pharmacokinetics in children receiving concomitant therapy with other AEDs are highly dependant on the nature of effect of the concomitant AEDs on hepatic enzyme activity, in a similar manner to adults. In this study, it was observed that mean CL/F in children receiving enzyme inducers was 3.62 ± 0.82 mL/min/kg (n=10), in children receiving inhibitors was 0.47 ± 0.18 mL/min/kg (n=8), and in children receiving a combination of either inducers and inhibitors or other AEDs was 1.20 ± 0.58 mL/min/kg (n=7). Where as, the mean values of CL/F in adult patients receiving enzyme inducers, inhibitors, and a combination of either inducers and inhibitors or other AEDs were reported in original NDA as 1.10 (n=24), 0.28 (n=4), and 0.53 (n=25) mL/min/kg, respectively . Thus, it can be concluded that the clearance of Lamotrigine is higher in children than that in adults.

In another pharmacokinetic study in pediatrics aged 5-10 years (UK 61), the pharmacokinetics of Lamotrigine following a single dose (2 mg/kg) was evaluated. The pediatric patients in this study were stabilized for at least two months on other antiepileptic drugs (AEDs). This study was conducted as an open 48h trial in which Lamotrigine was added to a regimen of standard antiepileptic drugs in 20 patients (8M, 12 F) of mean age 7 yrs (range 5-11 yrs) with refractory seizures, but one of them was withdrawn from the analysis as they received lower doses than specified. The dosage form used to administer the drug was capsule available in strengths of 12.5, 25, 50 and 100 mg; manufactured at Dartford, UK. The children were divided into 4 groups according to the concomitant medication they received: Group 1: Children (age: 5 to 8 years) receiving enzyme inducers (e.g.., carbamazepine, phenytoin, primidone, and phenobarbitone); Group 2: Children (age: 5 to 7 years) receiving enzyme inhibitors (e.g.., sodium valproate); Group 3:

Children (age: 5 to 11 years) receiving combination of either enzyme inducers and inhibitors (balanced; e.g.., clonazepam, ethosuximide, nitrazepam, vigabatrin, progabide, lorazepam, and clobazam); and Group 4: children (age: 5 to 7 years) receiving neither enzyme inducer nor inhibitor. It was observed from the results that the Lamotrigine pharmacokinetics in children receiving concomitant therapy with other AEDs are highly dependant on the nature of effect of the concomitant AEDs on hepatic enzyme activity, in a similar manner to adults. In this study, it was observed that mean CL/F in children receiving enzyme inducers was 2.66 ± 1.47 mL/min/kg (n=7), in children receiving inhibitors was 0.24 ± 0.03 mL/min/kg (n=3), in children receiving a combination of either inducers and inhibitors was 0.91 ± 0.49 mL/min/kg (n=8), and in children receiving neither enzyme inducer nor inhibitor was 1.03 mL/min/kg (n=1). Where as, the mean values of CL/F in adult patients receiving enzyme inducers, inhibitors, a combination of either inducers and inhibitors or other AEDs, and in healthy adult volunteers receiving neither enzyme inducer nor inhibitor were reported in original NDA as 1.10 (n=24), 0.28 (n=4), 0.53 (n=25), and 0.44 (n=1) mL/min/kg, respectively. Thus, it can be concluded that the clearance of Lamotrigine is higher in children than that in adults.

Population PK Analysis: Plasma sample data from 271 patients enrolled in three open label trials of lamotrigine (Studies UK 73, UK 98, and UK 102) as add-on therapy in treatment resistant epileptic children were pooled for NONMEM analysis. Patients enrolled in the studies were years of age and had seizure frequency of at least 2 seizures per month.

The lamotrigine plasma concentration time data were fitted to a one-compartment model with first order absorption and elimination using NONMEM. The apparent oral clearance (CL/F), apparent volume of distribution (V/F), absorption rate constant (Ka), age, gender, body weight, and race were modeled. It was observed from NONMEM analysis that oral clearance of Lamotrigine is a function of both body weight and concomitant AED's. Further it was observed that age, height, and race were found to have no additional effect on oral clearance of lamotrigine.

From the results it can be concluded that the daily dose of lamotrigine in pediatric patients may be adjusted based on patient's body weight and the concomitant AED's.

APPENDIX IV: IN VITRO DISSOLUTION

The sponsor provided *in vitro* dissolution information of chewable/dispersible Lamictal tablets (bio-batches and the to-be-marketed dosage form manufactured at two sites) at 3 time points in 0.1 N HCl. From the data it was observed that dissolution for the chewable/dispersible Lamictal tablets is in 0.1 N HCl

Based on the results provided, the following dissolution methodology and specification is recommended for Lamictal 5 mg CD caplet and 25 and 100 mg CD tablets:

Medium:	900 mL 0.1 N HCl at 37 ± 0.5°C
Apparatus:	USP Apparatus II (paddle)
Specification:	

Comments To Be Sent To The Firm:

1) Based on the data and rationale provided by the sponsor, a bio-waiver is granted for the 25 mg CD tablets. Further, a site change from Greenville, North Carolina to Zebulon, North Carolina is also granted based on dissolution data.

2) The sponsor is requested to adopt the following dissolution methodology and specification for Lamictal 5 mg CD caplet and 25 and 100 mg CD tablets:

Medium:	900 ml 0.1 N HCl at 37 ± 0.5°C
Apparatus:	USP Apparatus II (paddle)
Specification:	

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LABELING COMMENTS

The firm is requested to perform the following revisions on the submitted annotated draft labeling:

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/S/ 5/15/97

Vijay K. Tammara, Ph. D.
Division of Pharmaceutical Evaluation I

First Draft prepared on February 12, 1997
First Draft Initialed by M. Hossain on February 28, 1997
Second Draft prepared on March 28, 1997
Second Draft Initialed by M. Hossain on April 17, 1997
Third Draft Prepared on April 28, 1997
Third Draft Initialed by M. Hossain on May 6, 1997

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Intra-Division CP/B Briefing Date: May 15, 1997
Attendees: Hank Malinowski, Mehul Mehta, John Feeney, Richard Tresley, Russell Katz, Paul Leber, Ene Ette, Ajaz Hussain, Mohammad Hossain, and Vijay Tammara.

RD/FT Initialed by M. Hossain, Ph. D. /S/ 5/15/97

CC: NDA 20,690 (orig.), HFD-120, HFD-860 (Tammara, Hossain, Malinowski), HFD-340 (Vish), HFD-019, CDR (Barbara Murphy, for Drug Files).

PS: Dr. Mohammad Hossain helped in verifying the NONMEM analysis.

APPENDIX I

SUMMARY OF REPORT

TITLE

Protocol 050: Repeated Bioequivalence Study of US 25mg Lamictal® Tablets, US 5mg Lamictal® Dispersible/Chewable Tablets, and UK 5mg 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 5mg Lamictal® dispersible/chewable tablets and the US 25mg Lamictal® tablets when administered in equal doses; 2) the UK 5mg Lamictal® dispersible/chewable tablets and the US 25mg Lamictal® tablets when administered in equal doses; and 3) the US 5mg Lamictal® dispersible/chewable tablets and the UK 5mg Lamictal® dispersible/chewable tablets.

DESIGN

This was a single-center, randomized, open-label, three-period, three-treatment, crossover study in 17 healthy adult male subjects.

DURATION

The study lasted approximately three and a half months.

SETTING

This study was conducted at Subjects were admitted and received Lamictal® doses as inpatients at a clinical research facility. Subjects were dosed between 11 November 1995 and 11 February 1996.

SUBJECTS

Seventeen (17) adult male subjects who were healthy and between the ages of 20 - 43 years were enrolled in the study and 15 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 25mg Lamictal® tablet;
Treatment B: 5 x US 5mg Lamictal® dispersible/chewable tablets (caplets);
Treatment C: 5 x UK 5mg Lamictal® dispersible/chewable tablets (caplets).

The 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, followed by 195mL of water.

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:

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

RESULTS

Pharmacokinetic

Fifteen subjects completed all three periods of the study and two subjects (Subjects 2 and 8) completed only two periods of the study. Data from all seventeen subjects were included in the pharmacokinetic and statistical analyses.

Pharmacokinetic parameters for all completing subjects are summarized below:

	Treatment A US 25mg Tablet	Treatment B US 5 x 5mg Dispersible/ Chewable Tablet	Treatment C UK 5 x 5mg Dispersible/ Chewable Tablet	✓ Ratio B:A	Ratio C:A	✓ Ratio B:C
AUC_{last} (ng*h/mL)						
Geometric LS mean	11691	11672	11278			
95% CI (Lower)	10948	10855	10591			
(Upper)	12486	12550	12009			
Mean ratio				1.00	0.96	1.03
90% CI (Lower)				0.92	0.89	0.96
(Upper)				1.08	1.04	1.12
p-value*				0.973	0.423	0.467
AUC_{∞} (ng*h/mL)						
Geometric LS mean	12700	12313	11902			
95% CI (Lower)	11920	11480	11202			
(Upper)	13532	13205	12646			
Mean ratio				0.97	0.94	1.03
90% CI (Lower)				0.90	0.87	0.96
(Upper)				1.05	1.01	1.12
p-value*				0.509	0.140	0.457
C_{max} (ng/mL)						
Geometric LS Mean	273	253	259			
95% CI (Lower)	261	242	248			
(Upper)	286	265	271			
Mean Ratio				0.93	0.95	0.98
90% CI (Lower)				0.88	0.90	0.93
(Upper)				0.98	1.00	1.03
p-value*				0.023	0.098	0.458
t_{max} (h)						
Median	1.50	2.50	3.50			
Range						
95% CI (Lower)	0.75	2.00	2.00			
(Upper)	3.00	3.50	4.00			
Median Difference				0.81	1.19	-0.25
90% CI (Lower)				-0.25	0.25	-1.00
(Upper)				1.88	1.88	0.50
p-value*				0.155	0.032	0.386

* p-value from ANOVA of the pairwise comparisons.

The criteria for establishing bioequivalence was that the 90% confidence intervals for the ratios of AUC_{last}, AUC_{∞}, and C_{max} for both treatments should be within the range of 0.80 - 1.25 for the following comparisons:

- 5 x 5mg Lamictal® US dispersible/chewable tablets (Treatment B; test) versus 1 x 25mg Lamictal® tablet (Treatment A; reference)

- 5 x 5mg Lamictal® UK dispersible/chewable tablets (Treatment C; test) versus 1 x 25mg Lamictal® tablet (Treatment A; reference)
- 5 x 5mg Lamictal® US dispersible/chewable tablets (Treatment B; test) versus 5 x 5mg Lamictal® UK dispersible/chewable tablets (Treatment C; reference)

Analysis of the ln-transformed data showed AUC_{last}, AUC_{∞} and C_{max} met this criteria. Analysis of the untransformed data was consistent, with 90% confidence intervals for the ratios of AUC_{last}, AUC_{∞}, and C_{max} within 0.80 - 1.20.

Safety

All three Lamictal® tablet formulations were well tolerated in the 17 healthy male subjects:

- No serious adverse events or deaths were reported;
- 77 adverse events were reported throughout the course of the study, 16 were determined by the investigator to be related to drug exposure.
- 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 were five incidents of headache in three subjects, which were mild in intensity.

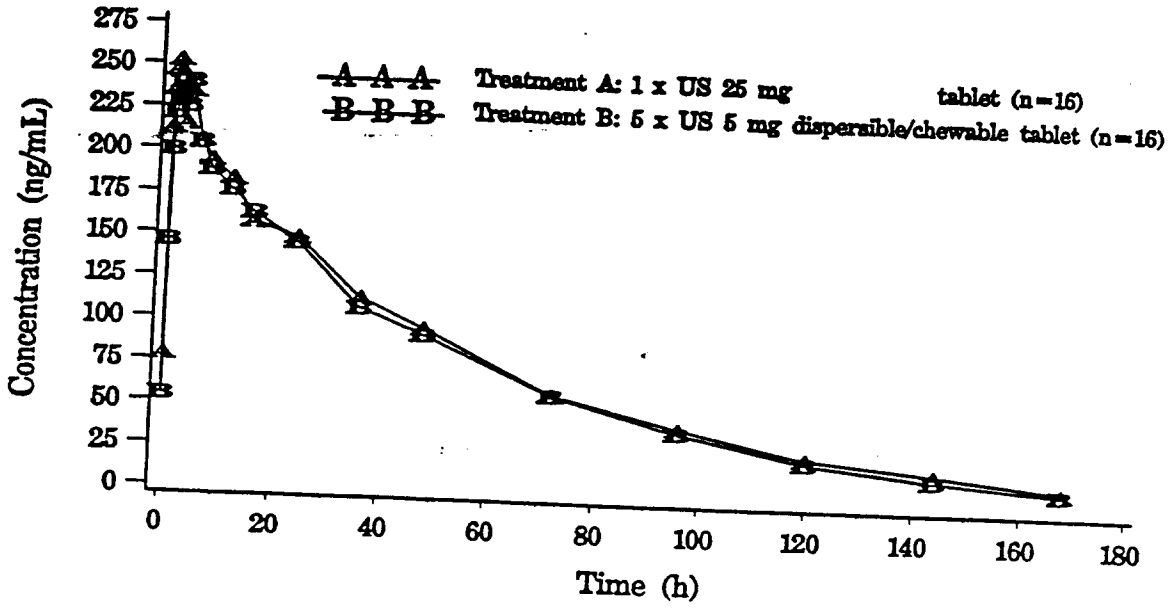
CONCLUSIONS

- The 5 x 5mg Lamictal® US dispersible/chewable tablets are bioequivalent to the 1 x 25mg Lamictal® tablet.
- The 5 x 5mg Lamictal® UK dispersible/chewable tablets are bioequivalent to the 1 x 25mg Lamictal® tablet.
- The 5 x 5mg Lamictal® US dispersible/chewable tablets are bioequivalent to the 5 x 5mg Lamictal® UK dispersible/chewable tablets.
- All three formulations were well tolerated in these healthy male subjects.

Form, Dosage, and Place of Manufacture	% Labeled Strength (mean)	Batch Number	Batch Size	Date of Manufacture
Tablet, 25mg, US		2W2707		7 Dec 1992
Dispersible/Chewable Tablet, 5mg, US		4N2712		28 Feb 1994
Dispersible/Chewable Tablet, 5mg, UK		2W2796		2 Apr 1993

APPENDIX 8.5.2

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



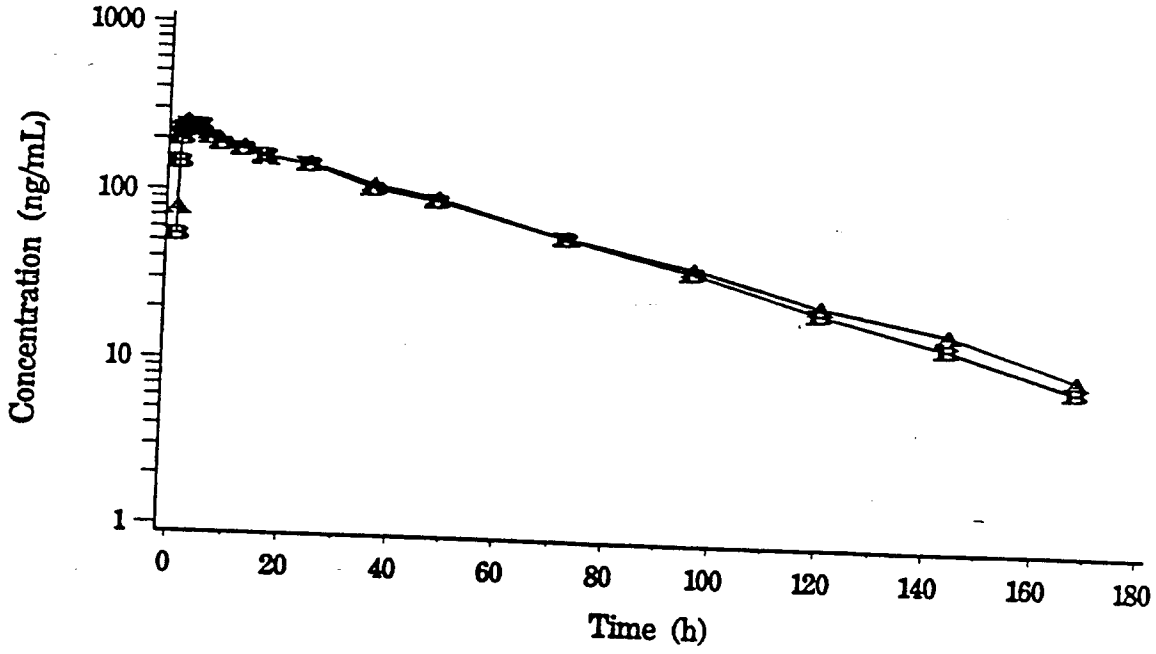
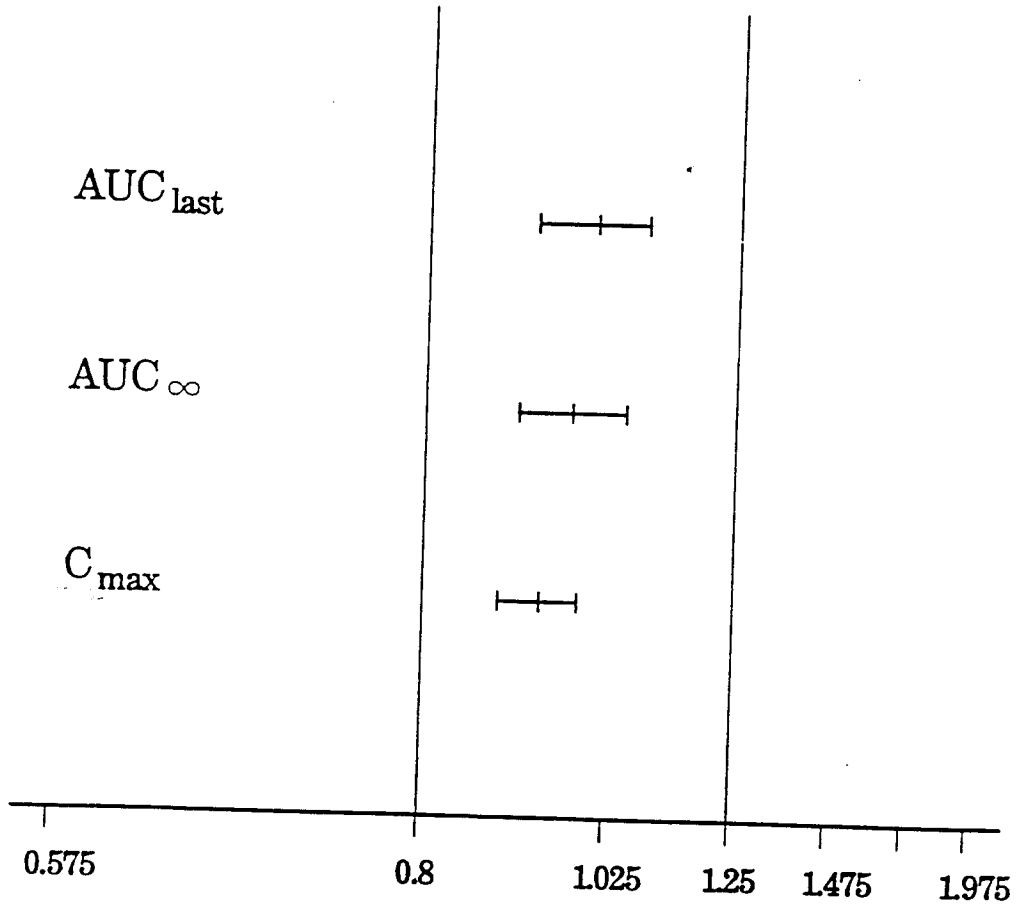


FIGURE 7

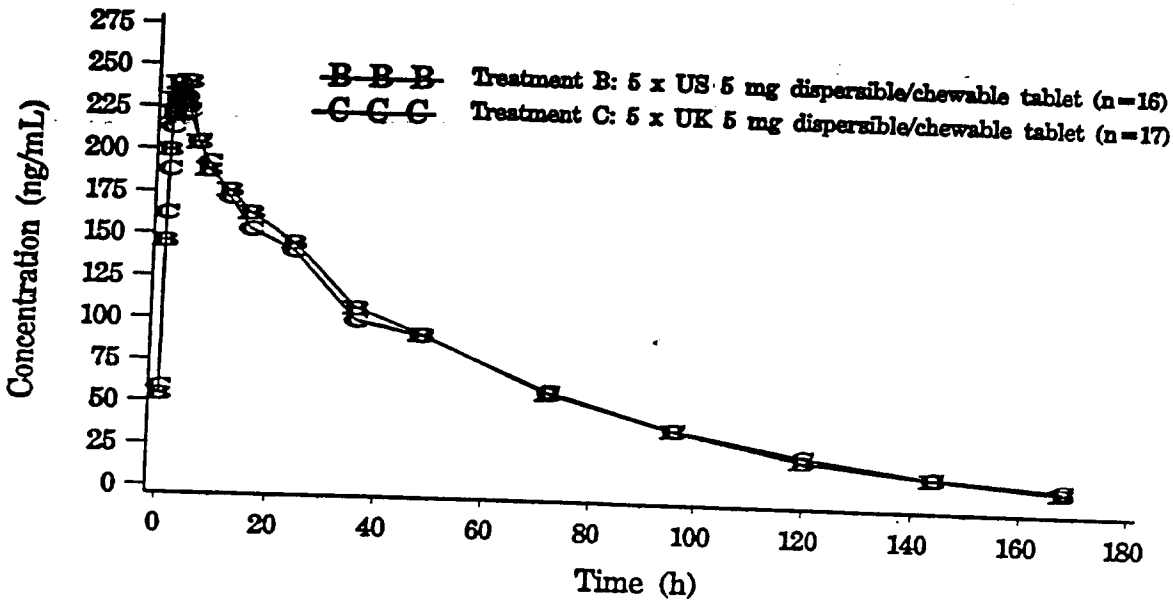
SEMI-LOGARITHMIC PLOT OF THE GEOMETRIC LS MEAN RATIOS
AND ASSOCIATED 90% CONFIDENCE INTERVALS*
(LOG-TRANSFORMED DATA)

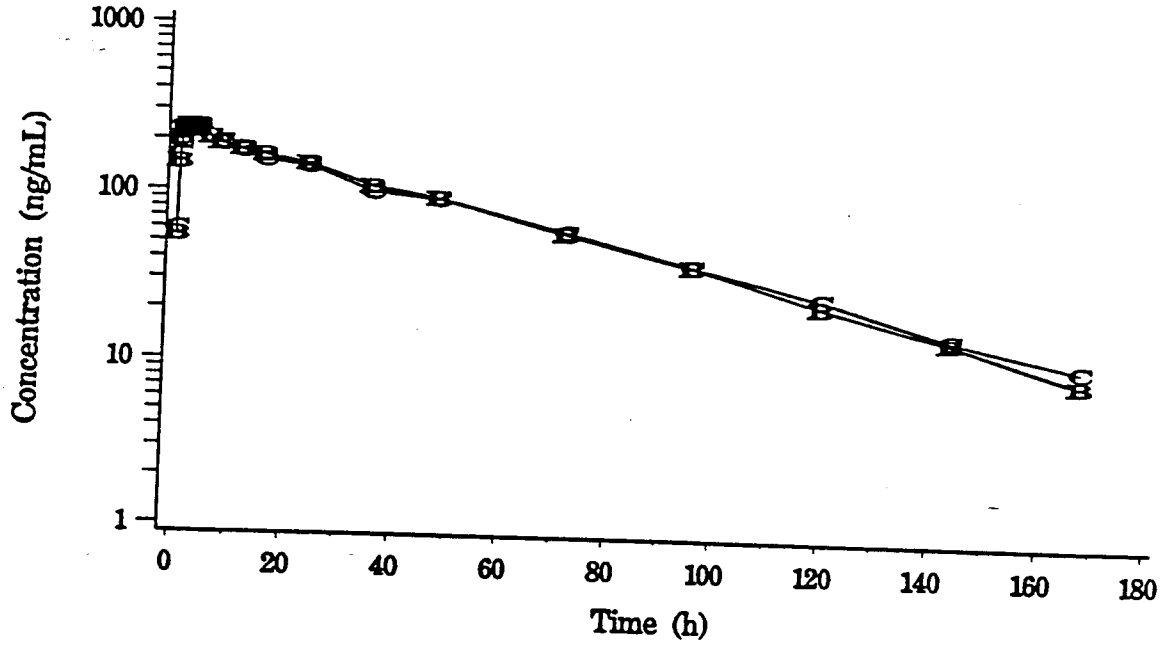


* Treatment B relative to Treatment A (n=15)

APPENDIX 8.5.18

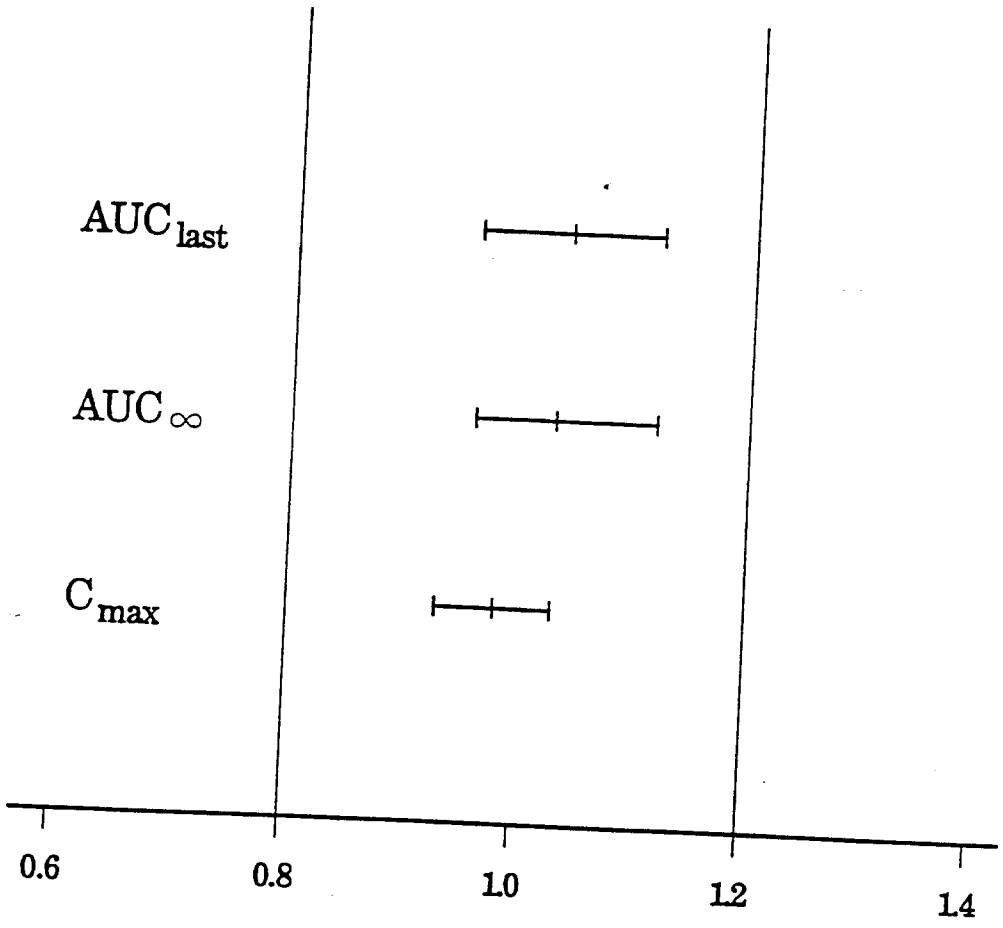
LINEAR AND SEMI-LOGARITHMIC PLOTS OF THE MEAN SERUM CONCENTRATION-TIME PROFILES FOR LAMOTRIGINE (TREATMENTS B AND C)





APPENDIX 8.5.23

LINEAR PLOT OF THE LS MEAN RATIOS AND ASSOCIATED
90% CONFIDENCE INTERVALS*
(UNTRANSFORMED DATA)



* Treatment B relative to Treatment C (n=16).