

UK-61

SUMMARY

Title of the Study

Pharmacokinetic Analysis of Lamotrigine in an Open Trial of Lamotrigine as Add-on Therapy in Treatment-Resistant Epilepsy in Children (H34-061)

Study Period

Pharmacokinetic period of study 22nd July 1987-20th January 1991

Study Design (Pharmacokinetics)

Paediatric patients stabilised for at least 2 months on antiepileptic medication, single dose pharmacokinetic assessment for 48h before continuous lamotrigine (LTG) dosing.

Pharmacokinetic Objective

To examine the pharmacokinetic properties of LTG in children aged 5-10 years.

Key Inclusion Criteria

Age 5-10 years.

Antiepileptic comedication unchanged for the previous 2 months (patients totally unresponsive to established drugs and no longer on any medication could be entered).

Test Product

Four strengths, 12.5, 25, 50 and 100mg, of lamotrigine in identical,

Pharmacokinetic and Statistical Methods

Venous plasma concentrations of LTG were measured with an internally standardised method followed by

Non-compartmental, compartmental and directly observed pharmacokinetic parameters were determined and the influence of concomitant AEDs evaluated by ANOVA.

Results

Eight male and 12 female patients of mean age 7 y and mean weight 23.5 kg were included in the pharmacokinetic analysis. Two

female patients (#2 and #14) received lower doses than specified in the protocol and were excluded from calculation of mean directly observed pharmacokinetic parameters.

Seven patients (4M, 3F) received enzyme-inducing AEDs (phenytoin and/or carbamazepine), 4 patients (1M, 3F) received an enzyme-inhibiting AED (valproate), 8 (2M, 6F) received the inhibitor and an inducer (balanced) and 1 male patient received neither.

Results are shown below grouped by enzyme-inducing or -inhibiting AEDs.

Mean Parameter (range)	Unit	Induced (n=7)	Inhibited (n=4)	Balanced (n=8)	None (n=1)
Age	y	6 (5-8)	6 (5-7)	7 (5-11)	7
Weight	kg	25.9 (17.5-50)	20.0 (17-25)	22.9 (12.7-39)	24.4
Dose	mg kg ⁻¹	2.0	2.1	1.9	2.0
Non-Compartmental Parameters					
C _{max}	µg ml ⁻¹	1.40	1.80	1.55	1.35
t _{max}	h	1.57	4.50	3.30	3.00
AUC	µg ml ⁻¹ h	16.2	146.7	44.5	34.2
CL/F	ml min ⁻¹ kg ⁻¹	2.54	0.31	0.89	1.00
Compartmental Parameters					
Lag Time	h	0.27 (0.01-0.93)	0.57 (0.01-0.91)	0.42 (0.0-1.13)	0.5
k _a	h ⁻¹	9.1	6.3	6.5	4.5
k _e	h ⁻¹	0.111	0.015	0.043	0.042
t _{1/2}	h	7.0	55.4	19.1	16.4
V _c /F	L kg ⁻¹	1.40	1.28	1.26	1.46
CL/F	ml min ⁻¹ kg ⁻¹ ±SD	2.66 ± 1.47	0.24 ± 0.3 0.31 ± 0.26	0.91 ± 0.47	1.03

* Dose, C_{max}, T_{max} and AUC have n=2 for the inhibited group. All other parameters have n=4.

POPULATION - PHARMACO KINETIC ANALYSIS

2.2.3.3 Population Pharmacokinetic Analysis Employing Data from UK-Sponsored Uncontrolled Add-On LAMICTAL Studies (UK 73, UK 98 and UK 102) in Pediatric Patients.

Objectives: to investigate the population pharmacokinetics of lamotrigine in pediatric patients with epilepsy; to explore the potential factors that may contribute to the variability in pharmacokinetics of lamotrigine in children; and to make dosage suggestions for this patient population.

Methodology: Concentrations of lamotrigine in 652 plasma samples collected from 204 pediatric patients at 1.5 to 18 years of age were included in this population pharmacokinetic analysis. The patients were enrolled in three add-on efficacy and safety trials (UK 73, UK 98 and UK 102) and were receiving no more than two concomitant AEDs in addition to lamotrigine. Plasma drug levels were obtained after 4, 8, 12, 24, 36 and 48 weeks of dosing (in study UK 73) or after 4, 12, 24, 36 and 48 weeks of dosing (in studies UK 98 and UK 102). The data were fitted to a one compartment open model with first order absorption and first order elimination using the nonlinear mixed effect modeling approach. Apparent clearance and apparent volume of distribution were estimated. The influence of covariates age, weight, height, race, sex and the type of concomitant AEDs on apparent oral clearance was evaluated. A covariate was included in the model only if its addition to the model resulted in a statistically significant difference ($p < 0.05$).

Results: The apparent oral clearance (mL/min/kg) of lamotrigine in pediatric patients was a function of both body weight (kg) and concomitant AEDs. For patients receiving enzyme-inducing AEDs, $CL = 26.8 + 0.72 \times BW$. For patients receiving valproate, $CL = (26.8 + 0.72 \times BW) \times 0.19$. For patients receiving both enzyme-inducing AED and valproate, $CL = (26.8 + 0.72 \times BW) \times 0.37$. The apparent volume of distribution (L) was also a function of body weight (kg) and could be calculated as $V = 2.1 \times BW$. Age, height, sex and race were found to have no additional effect on apparent clearance of LAMICTAL. The above equations for clearance estimation can therefore be used to calculate the daily dose of lamotrigine required to obtain a desirable plasma concentration.

Conclusion: The daily dose of lamotrigine in pediatric patients needs to be adjusted based on the patient's body weight and the concomitant AEDs.

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2.2.3.4 *Pharmacokinetics of Lamotrigine in Patients with Lennox-Gastaut Syndrome (UK 123) as Compared to That in the General Pediatric Epilepsy Patient Population (UK 73, UK 98 and UK 102)*

Objective: This analysis was performed to detect the potential difference in the apparent clearance (CL/F) of lamotrigine between pediatric patients with Lennox-Gastaut syndrome and the general patient population of pediatric epilepsy.

Methodology: Plasma concentrations, one from each patient, were obtained throughout the dosing intervals after 16 weeks of LAMICTAL once a day or twice a day administration from 62 patients with Lennox-Gastaut syndrome enrolled in Study UK 123. The concentration values were assumed to reflect average steady-state concentrations. A linear regression was performed between the observed concentrations (C_{obs}) and the steady-state average concentration (C_{pred}) predicted using the relationships derived from a prior population pharmacokinetic analysis in the general pediatric epilepsy patient population (see preceding summary of studies UK 73, UK 98 and UK 102). To determine whether the effects of body weight and concomitant AEDs on CL/F were different between the patients with Lennox-Gastaut syndrome and the general pediatric patient population, the effects of these cofactors on the difference between CL/F calculated using the observed plasma levels and CL/F calculated using the population pharmacokinetic analysis were examined graphically. In addition, plasma concentrations of concomitant AEDs including carbamazepine, clobazam, phenytoin and valproic acid were monitored before and during lamotrigine treatment.

Results: A linear relationship $C_{obs} = 1.67 + 0.80 \times C_{pred}$ was derived from the linear regression analysis (Figure 2.1). The intercept and the slope were not significantly different from 0 (95% CI: -0.64 ~ 4.04) and 1 (95% CI: 0.51 ~ 1.08), respectively, indicating that CL/F in patients with Lennox-Gastaut syndrome was comparable to that in the general pediatric patient population. Furthermore, no obvious effects of body weight (Figure 2.2) and concomitant AEDs (Figure 2.3) were shown on the difference between CL/F calculated using the observed plasma levels and CL/F calculated using the population pharmacokinetic analysis results. Therefore, the effects of the above cofactors on CL/F in patients with Lennox-Gastaut syndrome were appropriately described by the relationships derived from the general population of pediatric patients with epilepsy. The plasma levels of concomitant AEDs carbamazepine, clobazam, phenytoin and valproic acid were not changed after 4 and 16 weeks of lamotrigine dosing (results below).

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**Summary of Concomitant AED Plasma Concentrations ($\mu\text{g/mL}$) in UK 123
Protocol Specified Population**

AED	Study Phase	Lamotrigine (N=71)			Placebo (N = 72)		
		N	Mean	Std	N	Mean	Std
Carbamazepine	Screen	12	6.38	2.60	17	6.92	2.89
	Week 4	12	6.47	2.57	18	7.63	2.76
	Week 16	12	6.30	2.27	17	6.90	2.32
Clobazam	Screen	9	0.19	0.09	10	0.23	0.16
	Week 4	11	0.31	0.56	12	0.20	0.11
	Week 16	12	0.88	2.25	10	0.22	0.14
Phenytoin	Screen	10	14.65	8.00	8	8.85	4.40
	Week 4	8	13.80	7.43	7	10.41	5.98
	Week 16	8	17.34	8.08	6	13.59	7.06
Valproic Acid	Screen	46	72.23	32.11	42	80.63	31.22
	Week 4	44	83.71	31.17	40	84.84	30.07
	Week 16	46	79.30	26.34	39	81.65	32.69

Conclusion: The apparent clearance of lamotrigine in patients with Lennox-Gastaut syndrome was comparable to that in the general population of pediatric patients with epilepsy.

**Estimated Apparent Oral Clearance of Lamotrigine in Pediatric Patients
Receiving Various Regimens of Concomitant Anti-epileptic Medications
Clearance Estimates Obtained Using Final Estimates in Tables 3 and 4**

Age Group (years)	N	Mean Weight (kg)	Estimated Cl/F (ml/min/kg)		
			Induced	Balanced	Inhibited
1.5 to <6	51	16.9	2.3	0.9	0.5
6 to <13	130	31.6	1.6	0.6	0.3
≥ 13 to <18	23	47.0	1.3	0.5	0.3

**Lamotrigine Dosing Recommendations in Pediatric Patients Receiving Various
Regimens of Concomitant Anti-epileptic Medications
Clearance Estimates Obtained Using Final Estimates in Tables 3 and 4**

Age Group (years)	N	Mean Weight (kg)	Dosing Recommendations (mg/kg/day)		
			Induced	Balanced	Inhibited
1.5 to <6	51	16.9	13.2	5.2	2.9
6 to <13	130	31.6	9.2	3.4	1.7
≥ 13 to <18	23	47.0	7.5	2.9	1.7

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Table 3: Effects of Patient Covariates in the Final Model Incorporating Body Size and Patient Covariates

Parameter†	Final Estimate	%SEM	95% Confidence Interval	
			Lower	Upper
⊖ BAL CI	-0.63*	4.65	-0.68	-0.57
⊖ INH CI	-0.81*	1.54	-0.84	-0.79
⊖ Young CI	-0.06	128.96	-0.23	0.10
⊖ Old CI	0.08	138.79	-0.14	0.31
⊖ Race CI	-0.04	181.00	-0.18	0.10
⊖ Sex CI	-0.13*	39.21	-0.23	-0.03

* Statistically significant effects ($p < 0.05$).

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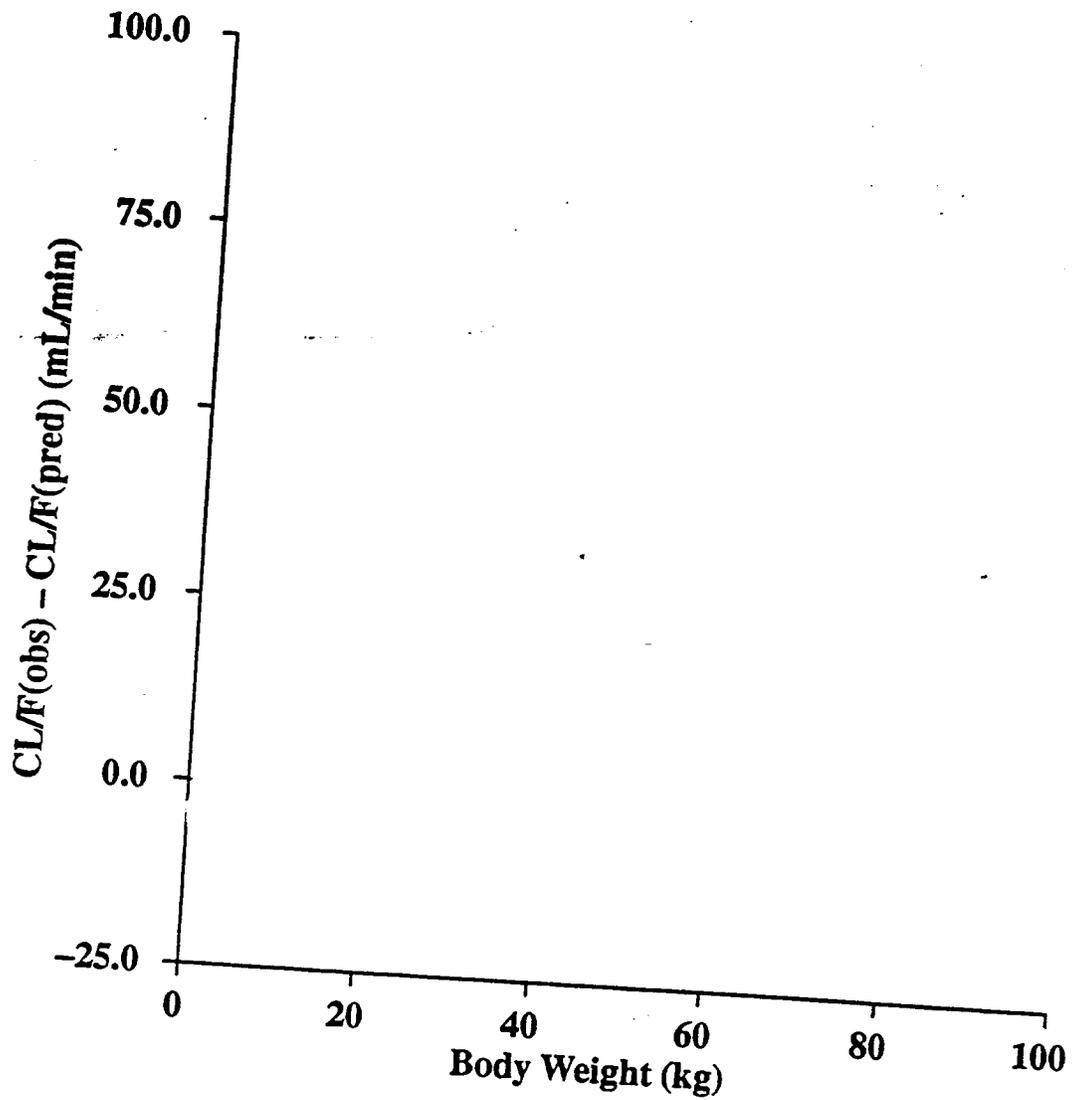


Figure 2.2. Body Weight Had No Apparent Effect on $CL/F(\text{obs}) - CL/F(\text{pred})$ in UK123

Body weight had no apparent effect on the difference between CL/F calculated using the lamotrigine concentrations observed in patients with Lennox-Gastaut syndrome and CL/F calculated using the relationships derived from the population pharmacokinetic analysis in the general population of pediatric patients with epilepsy, indicating that the effect of body weight on CL/F in Lennox-Gastaut patients was appropriately explained by the relationships derived from the general population of pediatric patients with epilepsy.

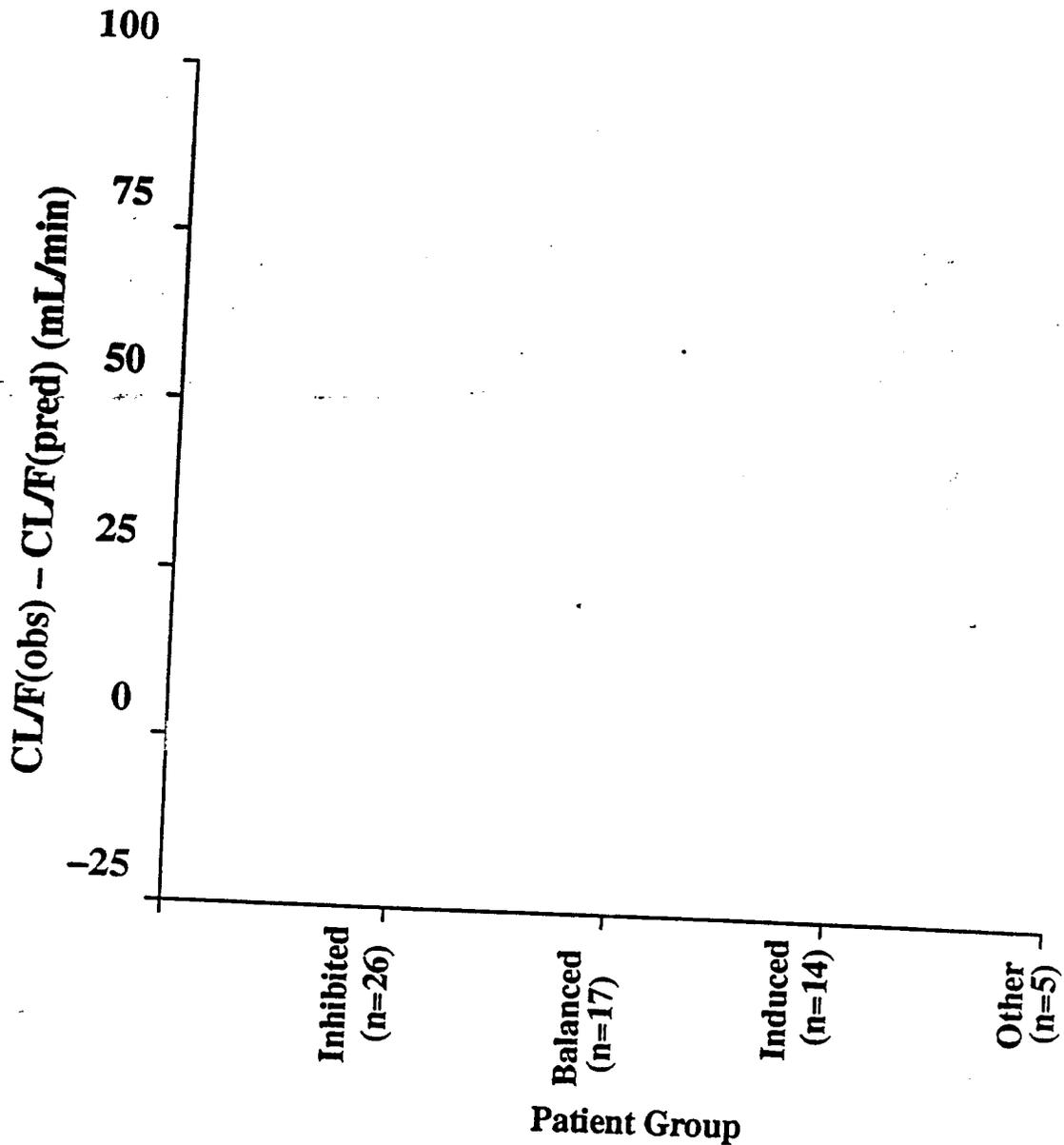


Figure 2.3. Concomitant AEDs Had No Apparent Effect on $CL/F_{(obs)} - CL/F_{(pred)}$ in UK123

Concomitant AEDs had no apparent effect on the difference between CL/F calculated using the lamotrigine concentrations observed in patients with Lennox-Gastaut syndrome and CL/F calculated using the relationships derived from the population pharmacokinetic analysis in the general population of pediatric patients with epilepsy, indicating that the effect of concomitant AEDs on CL/F in Lennox-Gastaut patients was appropriately explained by the relationships derived from the general pediatric patient population. Patients in the Inhibited group received valproate with or without AEDs with no known effects on drug metabolizing enzymes. Patients in the Balanced group received valproate and one or more enzyme-inducing AED(s). Patients in the Induced group received one or more enzyme-inducing AED(s). Patients in the Other group received no AED or AED(s) with no known effect on drug metabolizing enzymes. The enzyme-inducing AEDs were carbamazepine, phenytoin, phenobarbital and primidone. The AEDs without known effect on drug metabolizing enzymes were vigabatrin, clobazam, ethosuximide, clonazepam, oxcarbazepine, nitrazepam, diazepam, lorazepam and methsuximide.

Figure 1. Prediction of plasma concentrations of lamotrigine using model BASIC1

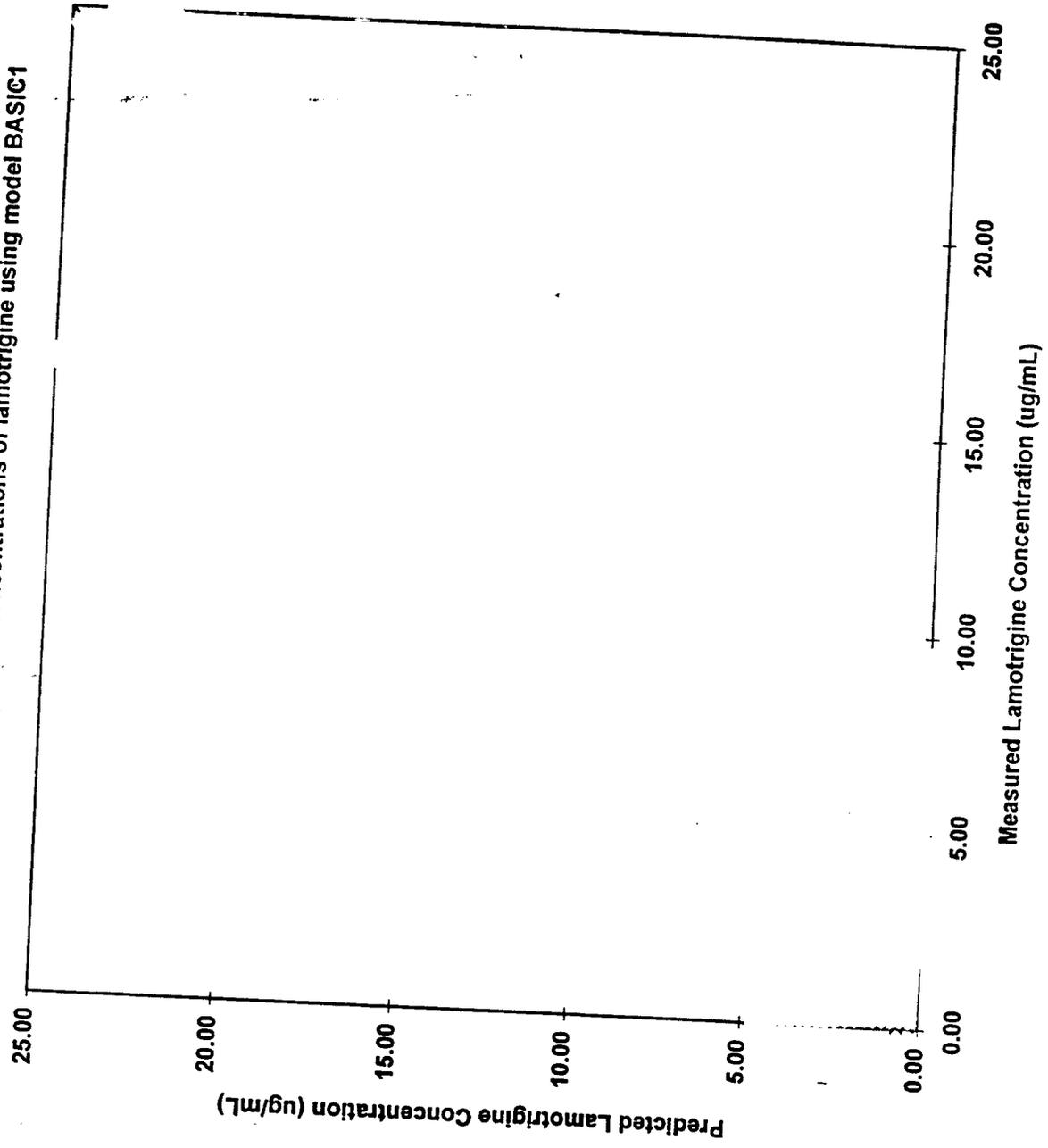


Figure 2. Prediction of plasma concentrations of lamotrigine using model BASIC2

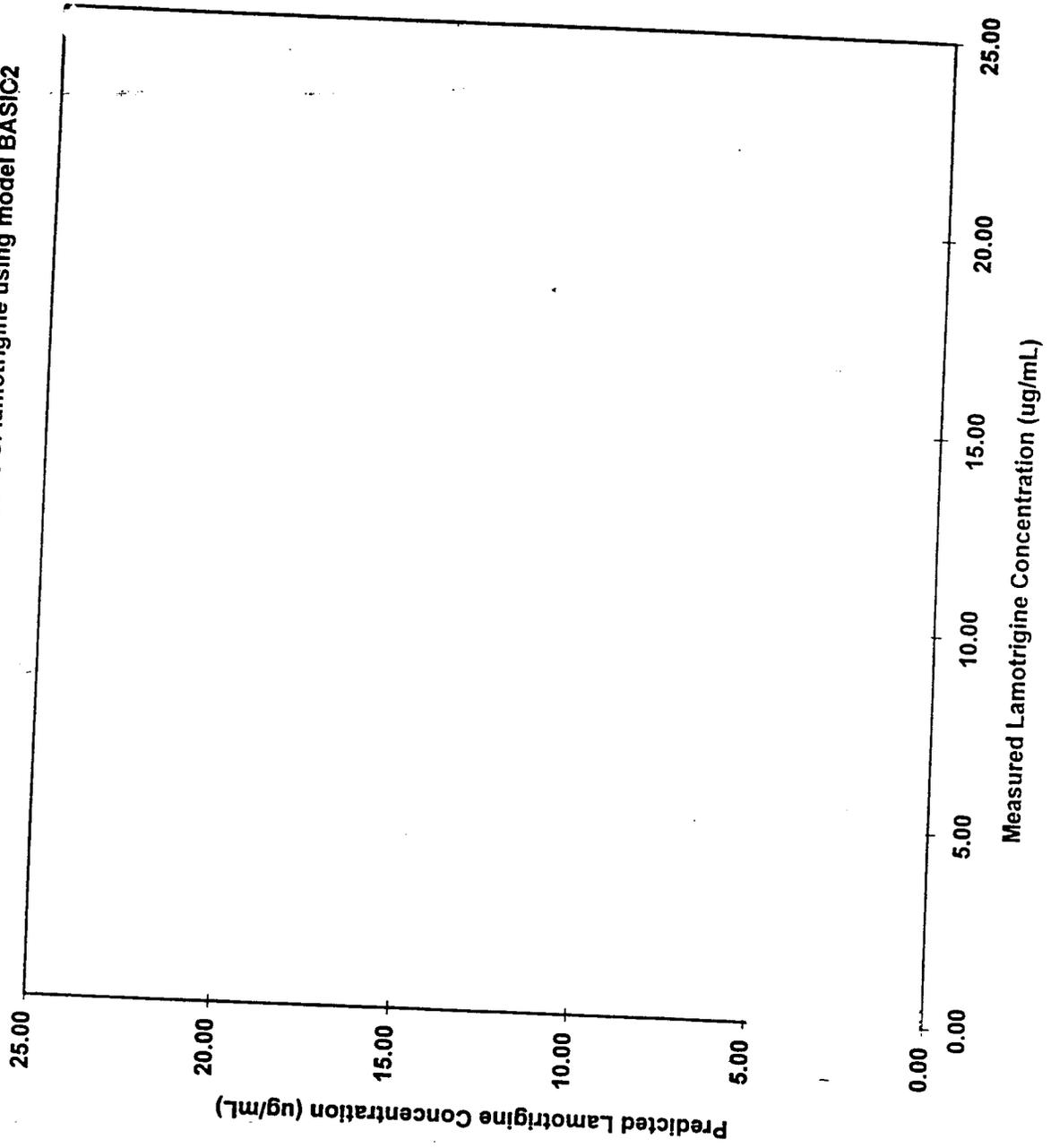
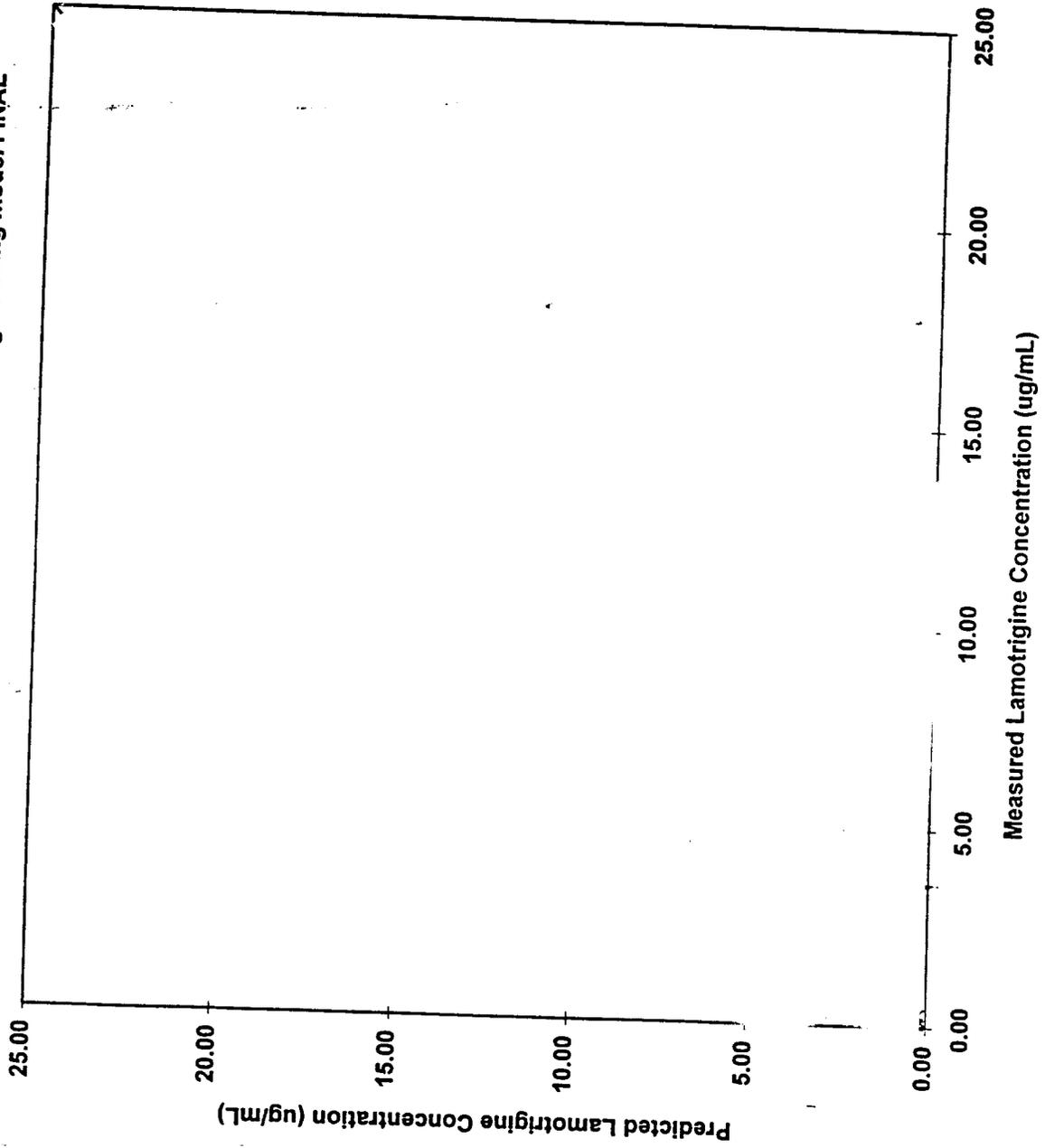


Figure 3. Prediction of plasma concentrations of lamotrigine using model FINAL



ANALYTICAL METHODOLOGY

APPENDIX II

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DRUG FORMULATION

APPENDIX III

7

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IN VITRO DISSOLUTION

APPENDIX IV

7

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PROPOSED LABELING

APPENDIX V

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STUDIES NOT REVIEWED

APPENDIX VI

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