

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020241/S003 AND 020764/S001

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Lamictal® NDA 20-241
Vijay Tammara

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OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20,241
Lamotrigine (Lamictal®)
25, 100, 150, and 200 mg Tablets

GlaxoWellcome Inc.
Five Moore Drive
Research Triangle Park, NC

Reviewer: Vijay K. Tammara, Ph. D.

Submission Dates:
February 24, 1997
June 06, 1997

Indication: Monotherapy for Partial Seizures in Adults

Type of Submission: Efficacy Supplement

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 seeking approval for a new indication of Lamictal tablets as monotherapy for the treatment of partial seizures in adult patients with epilepsy.

As per the labeling, the therapy is initiated with 25 mg every day for 2 weeks, followed by 50 mg/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 a well controlled, 28-week pivotal efficacy study (US 30/31) using the tablets to evaluate Lamictal as monotherapy in adult outpatients refractory to at least one AED e.g., phenytoin or carbamazepine. This study compared Lamictal monotherapy (500 mg/day) to a low dose of valproate monotherapy (1000 mg/day) and was designed to demonstrate a statistically significant difference between Lamictal and the control treatment.

This pivotal efficacy study is a multi center, double-blind, parallel, active control comparison study (Attachment 1). A total of 156 patients (91F, 65M; Age: 13-73 years) were randomized to receive Lamictal (N=76) or Valproate (N=80). Of these, 114 patients

completed the study (28 completed Lamictal monotherapy treatment and 22 escaped in the Lamictal Group; 13 completed the Valproate monotherapy treatment and 51 escaped in the Valproate group).

Blood samples were collected at the end of weeks 8, 10, 12, 14, 16, 20, 24, and 28 to determine plasma concentrations of Lamictal and Valproate and at end of weeks 0, 4, 8, 10, 12, 14, and 16 to determine plasma concentrations of carbamazepine and phenytoin. All samples were collected immediately prior to the next dose in order to obtain trough plasma concentrations, except for week 20, 24, and 28 which were collected randomly throughout the dosing interval.

Mean plasma concentrations of Lamictal increased from baseline through study week 12 during Lamictal dose escalation (2.6 to 4.0 $\mu\text{g/mL}$). Further, the mean concentrations of Lamictal continued to increase through study week 16 (4.0 to 5.7 $\mu\text{g/mL}$) during gradual reduction in dosage of concomitant enzyme inducing AEDs (Table 1). Lamictal was administered alone as monotherapy from study week 17 through 28. Based on the available plasma concentration data, a new steady state for Lamictal was observed to be reached at week 24, 12 weeks after the dose reduction of concomitant AEDs and 8 weeks after complete withdrawal of concomitant AEDs (Table 1). Further, mean steady state plasma concentrations of Lamictal were higher (8.0 to 10.0 $\mu\text{g/mL}$) when administered alone as monotherapy compared to when given with concomitant AEDs (4.0 to 6.0 $\mu\text{g/mL}$). In addition, once at Lamictal monotherapy, it was also observed that mean plasma concentrations of Lamictal were comparable between the completers and escapers. Therefore, patient escape from the study did not appear to be caused by lower or higher plasma concentrations of Lamictal and concomitant AEDs (Table 3).

It was also observed that mean trough plasma concentrations of carbamazepine and phenytoin did not change appreciably until after study week 12 when the reduction of the daily dosage of these concomitant AEDs initiated (Table 2). Thus, it can be concluded that the pharmacokinetics of carbamazepine and phenytoin were not affected by dose escalation of Lamictal during the first 4 weeks of treatment transition.

Overall, it can be concluded that mean plasma concentrations of Lamictal appeared to reach a new steady state (8.0 to 10.0 $\mu\text{g/mL}$) between 4 and 8 weeks after complete withdrawal of concomitant AEDs compared to the steady state concentrations of 4-6 $\mu\text{g/mL}$ in the presence of enzyme inducing AEDs. Further, mean plasma concentrations of Lamictal and those of concomitant AEDs were comparable between their respective completers and escapers of the study.

Comment to the Clinical Division: 1) Mean steady state plasma concentrations of Lamictal were higher (8.0 to 10.0 $\mu\text{g/mL}$) when administered alone as monotherapy compared to when

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given with concomitant AEDs (4.0 to 6.0 µg/mL). In addition, it was also observed that mean plasma concentrations of Lamictal were comparable between the completers and escapers during Lamictal monotherapy phase. Therefore, patient escape from the study did not appear to be caused by lower or higher plasma concentrations of Lamictal and concomitant AEDs. Further, pharmacokinetics of carbamazepine and phenytoin were not affected by dose escalation of Lamictal during the first 4 weeks of treatment transition. This inference may be incorporated into the labeling of this drug.

RECOMMENDATION:

The Clinical Division is requested to incorporate the technical aspects of **Comment 1** into the labeling of this drug.

APPEARS THIS WAY
ON ORIGINAL

/S/

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

RD/FT Initialed by R. Baweja, Ph. D. --

/S/

- 9/15/97.

CC: NDA 20,241 (suppl.), HFD-120, HFD-860 (Tammara, Baweja, Malinowski), CDR
(Barbara Murphy for Drug Files).

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT 1

The study consisted of four phases: (1) Screen, (2) Baseline, (3) Treatment, and (4) Follow-up. The Screen Phase consisted of a period of up to two weeks during which the eligibility of patients was evaluated. The Baseline Phase consisted of an 8-week observation period during which baseline data on seizure frequency and safety parameters were obtained. The Treatment Phase was divided into the following two periods: (1) Treatment Transition (8 weeks) and (2) Monotherapy (12 weeks). During the 8-week Treatment Transition Period, patients had study medication (either LTG and corresponding VPA placebo or VPA and corresponding LTG placebo) added to the concomitant AED (either PHT or CBZ) during the initial four weeks. The concomitant AED was then withdrawn over the remaining four weeks of Treatment Transition. Patients who had fully converted to monotherapy continued to receive treatment for 12 additional weeks unless they met one of the criteria for "escape" (defined below) or they reported an adverse experience requiring discontinuation from the study. Patients who were unable, for whatever reason, to achieve monotherapy were discontinued from the study.

"Escape" criteria for each patient were determined upon completion of Baseline and included evaluation of simple partial, complex partial, and secondarily generalized seizures. Patients discontinued study treatment when one of the following "escape" criteria were met: (1) doubling of the average monthly seizure count relative to Baseline, (2) doubling of the highest consecutive 2-day seizure frequency relative to Baseline, (3) emergence of a new seizure type that was more severe than the current seizure type(s), or (4) clinically significant prolongation of generalized tonic-clonic seizures relative to Baseline.

Patients entered the Follow-up Phase following completion of the Treatment Phase or once conditions were met for premature discontinuation. Study medication was withdrawn under double-blind conditions; treatment with concomitant AED(s) was initiated at the same time.

NUMBER OF SUBJECTS (TOTAL AND PER TREATMENT):

A total of 156 patients, 91 females and 65 males ages 13 to 73 years, were randomized to receive LTG (n=76) or VPA (n=80). Of these, 114 patients completed the study (28 completed monotherapy treatment, and 22 escaped in the LTG group; 13 completed monotherapy treatment, and 51 escaped in the VPA group). A total of 26 patients in the LTG group and 16 patients in the VPA group were withdrawn during their participation in the study. Twenty-one (21) of these patients (15 in the LTG group and 6 in the VPA group) withdrew due to adverse experiences. Data from all 156 patients were included in the safety, intent-to-treat, and worst case analyses. Data from the 114 patients who completed the study were included in the per protocol efficacy analyses.

DIAGNOSIS AND KEY INCLUSION CRITERIA:

To be eligible for entry into this study, patients must have 1) been 13 years of age or older, 2) experienced at least four seizures (simple partial, complex partial, and/or secondarily generalized) every four weeks for the 12-week period prior to Screen, and 3) been currently taking either PHT or CBZ monotherapy. The etiology of the seizures could be idiopathic, cryptogenic, or temporally remote (central nervous system [CNS]) symptomatic (if symptomatic, must have been stable ≥ 24 weeks prior to study entry). The patient's condition must have been defined as refractory (i.e., not controlled by at least one marketed AED) as determined by history and not considered a treatment failure because of noncompliance. The patient must have demonstrated an ability to maintain a daily seizure calendar.

To continue to be eligible for randomization to study treatment, patients must have experienced during Baseline at least four simple partial, complex partial, and/or secondarily generalized seizures per 4-week period and had no more than 20 consecutive seizure-free days. Patients were allowed to repeat Baseline one time if needed to meet the continuing eligibility criteria.

NAME, BATCH NUMBER, DOSE AND MODE OF ADMINISTRATION OF STUDY DRUG:

Study medication (LTG 50 mg b.i.d.) was added to the current AED therapy the day following completion of the Baseline Period (Day 1 of the Treatment Phase). Patients assigned to the LTG treatment group received VPA placebo (PBO) and systematically increasing doses of active LTG (initiated at 100 mg/day and increased by weekly increments of 100 mg/day). If the target dose of study medication was not tolerated, two separate dose reductions for LTG (or matching PBO) were allowed. Patients were rechallenged with the next highest dose of LTG (or matching PBO) after the adverse experience had resolved, unless the investigator did not think that rechallenge was in the best interest of the patient. Patients who could not tolerate the lowest permitted dose of LTG (300 mg/day) were discontinued. All study medication was administered orally.

Patients assigned to the VPA treatment group received corresponding "strengths" of LTG placebo tablets and systematically increasing doses of active VPA (initiated at 500 mg/day and increased over a period of 1 week to 1000 mg/day). Dose adjustments for VPA were not permitted. Valproate was provided as valproic acid 250mg soft gelatin capsules.

Table A Dose Ascension, Maintenance, and Taper Schedule^a

Treatment Group	TREATMENT TRANSITION PERIOD						MONOTHERAPY TREATMENT PERIOD		Double-Blind Taper ^c					
	Dose Ascension						Maintenance ^b							
	Study Wk 9		Study Wk 10		Study Wk 11		Study Wks 12-16		Study Wks 17-28		Study Wk 29		Study Wk 30	
	3 Days	4 Days	3 Days	4 Days	3 Days	4 Days	3 Days	4 Days	3 Days	4 Days	3 Days	4 Days	3 Days	4 Days
LAMOTRIGINE 500 mg/day (full dose) 400 mg/day (dose reduction #1) ^d 300 mg/day (dose reduction #2) ^d	2 x 50 4 x 250	LTC VPA PBO	2 x 100 4 x 250	LTC VPA PBO	2 x 150 4 x 250	LTC VPA PBO	2 x 200 4 x 250	LTC VPA PBO	2 x 250 4 x 250	LTC VPA PBO	2 x 250 4 x 250	LTC VPA PBO	2 x 150 2 x 250	LTC VPA PBO
	2 x 250 2 x 250 2 x 50	VPA VPA PBO LTC PBO	3 x 250 1 x 250 2 x 100	VPA VPA PBO LTC PBO	4 x 250 2 x 150	VPA LTC PBO	4 x 250 2 x 200	VPA LTC PBO	4 x 250 2 x 200	VPA LTC PBO	4 x 250 2 x 200	VPA LTC PBO	2 x 250 2 x 100	VPA LTC PBO
	2 x 250 2 x 250 2 x 50	VPA VPA PBO LTC PBO	4 x 250 2 x 150	VPA LTC PBO	4 x 250 2 x 200	VPA LTC PBO	4 x 250 2 x 200	VPA LTC PBO	4 x 250 2 x 200	VPA LTC PBO	4 x 250 2 x 200	VPA LTC PBO	2 x 250 2 x 100	VPA LTC PBO
VALPROATE 1000 mg/day (full dose) 1000 mg/day (dose reduction #1) ^d 1000 mg/day (dose reduction #2) ^d	2 x 250 2 x 250 2 x 50	VPA VPA PBO LTC PBO	3 x 250 1 x 250 2 x 100	VPA VPA PBO LTC PBO	4 x 250 2 x 150	VPA LTC PBO	4 x 250 2 x 200	VPA LTC PBO	4 x 250 2 x 200	VPA LTC PBO	4 x 250 2 x 200	VPA LTC PBO	2 x 250 2 x 150	VPA LTC PBO
	2 x 250 2 x 250 2 x 50	VPA VPA PBO LTC PBO	4 x 250 2 x 150	VPA LTC PBO	4 x 250 2 x 200	VPA LTC PBO	4 x 250 2 x 200	VPA LTC PBO	4 x 250 2 x 200	VPA LTC PBO	4 x 250 2 x 200	VPA LTC PBO	2 x 250 2 x 100	VPA LTC PBO

^a All doses will be given b.i.d.

^b If an adverse experience is judged by the investigator to be related to study medication, the maintenance dose may be reduced.

^c The dose taper is not required for patients who enter Protocol 29, the double-blind continuation study of Protocol 30.

^d These doses will be used if dose reduction is needed.