DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

REVIEW AND EVALUATION OF CLINICAL DATA

NDA Number	20,241
Generic (Brand) Name	Lamictal (lamotrigine)
Sponsor	GlaxoWellcome, Inc.
Indication	Response to Information Request
Correspondence Date	2 July 1998
Date Received	7 July 1998
Review Completed	21 July 1998

INTRODUCTION The Agency sent an approvable letter to GlaxoWellcome, dated 24 February 1998, in reference to its Lamictal (LTG) sNDA for monotherapy treatment of partial-onset seizures in adults. Approval was pending submission of information concerning (1) SUDEP; (2) serious dermatologic events (type and number or rashes occurring in this population); (3) other adverse events (for the transition and monotherapy phases); and (4) safety data for all on-going trials, dropouts, worldwide experience, and deaths or premature withdrawals. The present submission reviews exposure data and adverse events for the ≥450 and ≥500 mg/d dose (500 mg/d was the recommended dose in the controlled trial, US 30/31).

EXPOSURE DATA The table provided by the sponsor for the safety data base for LTG *monotherapy* in doses ≥500 mg (the monotherapy dose set by protocol US30/31) is appended; according to Betty McConnell (GlaxoWellcome, phone conversation, 7/21/98), the population includes the controlled study US30/31 (18 patients for 3 months) and the open-label extensions. A total of 103 patients were on LTG monotherapy ≥500 mg/d involves for 3 months, 75 for 6 months, 67 for 9 months, 55 for 1 year, 42 for 2 years, and 26 for 3 years.

TREATMENT-EMERGENT ADVERSE EVENTS Treatment-emergent adverse events were nearly identical for the monotherapy phase of study US30/31 (Table 2) and monotherapy at ≥500 mg/d for all studies (Table 6). The most frequent symptoms (occurring with an incidence ≥5%) that were common to both studies: headache, coordination abnormality, dizziness, anxiety, insomnia, tremor, dyspepsia, nausea, vomiting, and rhinitis. Similarly, these are the symptoms with higher incidence on the list of treatment-emergent adverse events found in current labeling.

Although there was no category for hospitalized rash, generalized rash occurred in no more than 4% of the population on ≥450 mg/d (see Table 4) and was graded no higher than "moderate." The two cases of hospitalized rash (one of which was diagnosed as Stevens-Johnson), found in US30/31, occurred during the titration phase when patients were on LTG and a second anticonvulsant; the examples were therefore not included in the monotherapy tables (per Betty McConnell, GlaxoWellcome, phone conversation, 7/21/98).

SUMMARY Because of an inadequate safety population data base at the dose

recommended for monotherapy in the sponsor's controlled trial (500 mg/d), I do not recommend approval of LTG for the indication of monotherapy in the treatment of adult partial-onset seizures.

/S/

Richard M. Tresley MD
Medical Reviewer

NDA 20,241Response to Approvable Letter (Monotherapy) div file/Katz R/Ware J/Tresley R/21 July 1998

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

REVIEW AND EVALUATION OF CLINICAL DATA

NDA Number	20,241
Generic (Brand) Name	Lamictal (lamotrigine)
Sponsor	Glaxo Wellcome, Inc.
Indication	Response to Approvable Letter for Monotherapy
Correspondence Date	15 April 1998
Date Received	15 April 1998
Review Completed	25 June 1998

INTRODUCTION The Agency sent an approvable letter to Glaxo Wellcome, dated 24 February 1998, in reference to its Lamictal (LTG) sNDA for monotherapy treatment of partial-onset seizures in adults. Approval was pending submission of information concerning (1) SUDEP; (2) serious dermatologic events (type and number or rashes occurring in this population); (3) other adverse events (for the transition and monotherapy phases); and (4) safety data for all on-going trials, dropouts, worldwide experience, and deaths or premature withdrawals.

FINAL UPDATE: CHEWABLE FORMULATION No new information since the 23 Feb 1998 submission on rash in adults and children for the period 31 Dec 1996 through 31 Oct 1997, to be reviewed by Dr. John Feeney.

DOSE JUSTIFICATION: MONOTHERAPY IN EPILEPSY For the pivotal monotherapy study, US30/31, the LTG mean modal and average doses during the add-on (LTG titration) phase were 452 and 379 mg, respectively; and for the maintenance (monotherapy) phase, 493 and 491, respectively (v 37.1, p 108). At these doses, only 37% of randomized subjects completed the trial: 22/75 (29%) met escape criteria and an additional 5/75 (7%) withdrew because of inadequate response. Together 27/75, or 36%, of all LTG-treated patients dropped out for lack of efficacy. 15/75, 20%, withdrew because of adverse events.

The sponsor now argues for even lower, likely subtherapeutic, doses to avoid the side effects resulting from the high dose used in the pivotal trial (500 mg/d). Two basic arguments are provided to support lower doses (200-500 mg/d), claiming that "the same doses of LTG used with combination therapy of VPA plus enzyme-inducing AED may be adequate for LTG monotherapy" [v 1, p 68]):

(1) "the similarity in LTG pharmacokinetics between subjects taking LTG alone and those taking VPA in addition to enzyme-inducing AEDs indicates that comparable exposures can be achieved in the two groups after the same dose"; and

(2) "the lack of consistent effects of concomitant AED on ED_{50} of LTG in animals suggested that the concentrations for effective seizure control in human may be similar in adjunctive therapy and monotherapy."

Neither argument has merit. As to the first, the actual LTG level, when used in combination, bears little relation to that in monotherapy; this appears to be true of all anticonvulsants whose levels are frequently altered by the addition of a second or third drug. Furthermore, the patients typically require higher levels when treated with only one drug, without the added protection of another on board. The second reason, which deals with ED_{50} in animals, is irrelevant to dose and effect in humans.

DEATHS See the accompaning Table 1. Between 1 Sep 1996 and 31 Oct 1997, nine deaths were reported in the clinical trials (see Table 1), "all of which were considered by investigators to be unlikely to be related to the use of LTG" (v 2, p 2): cancer (2), ALS (1), suicide (2), trauma (2), and stroke (2).

SERIOUS ADVERSE EVENTS Between 1 Sep 1996 and 31 Oct 1997, 71 serious adverse events (see Table 2) were reported in clinical trials, "of which 14 were considered by investigators to be possibly or probably related to LTG" (v 2, p 2). Despite 7 fatal outcomes, none was attributed to LTG; there were no reports of SUDEP. There was one report of rash, not identified as Stevens-Johnson (SJ); there were no reports of multi-organ failure.

New serious adverse events (not appearing in current labeling or in the monotherapy trial sNDA) involve psychiatric conditions, which make up two-thirds of the reports in the current submission and are likely due to the large enrollment of patients with depression or bipolar disorder in LTG-monotherapy psychiatric clinical studies now ongoing: Study 601, an open-label trial evaluating LTG monotherapy in 75 bipolar patients, saw serious adverse events occurring in 22 patients, including 7 episodes of mania, 7 suicide attempts, and 1 rash not described as hospitalized or SJ (see v 2, p 2). See the accompanying Table 5.

In ongoing double-blind monotherapy trials in depression and bipolar disease (see the accompanying Appendix A), from which adverse events have been preliminarily tabulated, there are 294 known LTG-treated subjects (studies 2001, 20002, 2003) plus an unknown percentage of 428 either on LTG or placebo (studies 2005, 2010, 3001). (Note: there appears to be a discrepancy in the actual numbers: elsewhere in the same volume [p 3], the sponsor speaks of bipolar and depression trials, ongoing or completed as of 31 Oct 1997, as containing 512 patients, 358 of whom received LTG.)

It appears that the blind has been broken for subjects in the double-blind psychiatric trials who have presumably withdrawn prematurely and whose adverse events have been reported. Preliminary reports number, among the LTG-treated population, 8 reports of suicide attempts, 2 completed suicides, 2 psychotic episodes, and 7 episodes of mania and 2 of depression. Information on placebo patients, if indeed it is available, has not been provided. Why the blind has been broken for some patients is not known. Note that my counts have been made from the narratives provided (v 2, pp 41-85); the sponsor's Table 5 (v 2, p 27-28), in comparison, seems incomplete (for both the open-label and blinded trials, only 5 episodes of mania are listed, 3 suicide attempts, 2 completed suicides, and 3 episodes of depression).

WITHDRAWALS DUE TO ADVERSE EVENTS Adverse events leading to withdrawal in adults from ongoing monotherapy trials (UK 126, UK 136, and SCAA 4001) followed the known adverse event profile.

For the bipolar and depression trials which were ongoing or completed as of 31 Oct 1997 (358 of 512 patients received LTG), the adverse-event profile is only preliminary and by type (there are no incidences) seems generally similar (with the exception of the psychiatric events) to the adverse-event profile found in current labeling.

POSTMARKETING EXPERIENCE Between 1 Sep 1996 and 31 Oct 1997, there were 55 reports of serious adverse events in adults: 5 deaths, including 2 related to seizure events (SUDEP), 2 to cardiopulmonary arrest, and 1 to intrauterine causes; 4 cases of SJ; 1 case of TEN; 2 cases of erythema multiforme; 2 cases hypersensitivity (rash, fever, sore throat, other/systemic); No new adverse events, not found in current labeling, were noted. There were 4 attempted suicides, all of whom had a past history of suicide attempts.

PREGNANCY REGISTRY Established in 1992, the LTG pregnancy registry is composed of both prospective and retrospective data, but uses only prospective data to determine the risk of birth defects (see the accompanying Tables 2-5). As of 30 Sep 1997, there were 87 infants without birth defects and 5 with major malformations after first-trimester LTG exposure. 69% of the 92 exposures involved polytherapy (e.g., LTG + CBZ, LTG +VPA). There were no deaths among 40 patients with first-trimester LTG monotherapy exposure. The risk of birth defects following first-trimester exposure to LTG (5/92, or 5.4% [CI=2-13%]) does not differ from other anticonvulsants (6.2-9.6%), but the sample size is too small to derive definite conclusions about the safety of LTG in pregnancy.

Retrospective reporting has turned up 14 cases of LTG monotherapy and polytherapy. The data are not always certain. However, a review of both prospectively and retrospectively reported birth defects fails to identify a particular pattern or syndrome.

Given the small numbers of reports from exposed pregnant women, few new guidelines or recommendations can be made. Continued caution about LTG use in pregnancy is strongly warranted, and close monitoring through the Pregnancy Registry is called for.

SUDEP The sNDA population base for completed monotherapy trials consisted of 868 LTG-treated subjects with a total patient-years exposure of 589.6. There were two deaths classified as SUDEP, resulting in a incidence of 0.0034 SUDEPs per patient-year, which is similar to the 20 SUDEPs per 5747 patient years (0.0035 SUDEPs per patient-year) in the approved US label.

There are 905 additional LTG-treated patients from monotherapy trials that were ongoing at the time of the sNDA submission, constituting an estimated total of 326.4 patient-years of exposure. There was one sudden death in this population not classified as SUDEP by the investigator: 74-year-old male, with a history of stroke, asthma, and partial seizures, who, after 4 months on LTG 200 mg/d, experienced "decompensation cordis" necessitating the addition of furosemide to his regimen of verapamil, levothyroxine, and salmeterol. Three days later, he was found dead, the cause of which was attributed to heart attack. Even if this death is included with the other two, there is a SUDEP rate of only 0.0030 per patient-year exposure (3 SUDEPs per 916 patient-years; the combined population, n = 905 + 868 = 1773, for 589.6 + 326.4 = 916 total patient-years exposure). This rate is within the range of those reported in the current LTG US label, as well as in patients with epilepsy not receiving LTG.

RASH During a Feb 1998 telecon with the sponsor, the Agency requested additional information on exposure at the ≥500-mg daily dose level used in its pivotal monotherapy epilepsy trial, as well as on the incidences of SUDEP and rash. But the sponsor in the present submission really appears only to have recapitulated its sNDA review of rash in monotherapy studies (which does not, however, group patients by dose). There is little that is new here. The sNDA population of completed monotherapy trials consisted of 868 subjects, divided into two groups based on trial design: (a) initial-monotherapy studies (conducted in Europe, usually as active control trials, blinded or open-label), containing a total of 453 subjects; and (b) withdrawal-to-monotherapy studies (including the pivotal US30/31), with a total of 415 subjects. Although an additional 905 patients have received LTG monotherapy in ongoing trials, 744 of whom were enrolled in initial-monotherapy protocols, the sponsor only provides tabulated data for the original cohort of 868 patients. Subsequent to the present response and at the Agency's request, the sponsor has submitted a new tables of exposure on 10 Jun 1998, with n=283 for those receiving ≥400 mg/d, (the 24 Jun 1998 submission provided duration of exposure for this cohort). Nonetheless, this new submission failed to speak specifically to the question of monotherapy at daily doses ≥500 mg (the sNDA population for ≥500-mg dose consisted of 58 subjects).

See the accompanying graphs entitled Table 1-11. The present review analyzes incidence

of rash with LTG use by reference to the two mechanisms the sponsor has postulated for the development of rash with LTG use: (1) "incorrect dosing," either too high a dose or too-rapid a titration; and (2) combination therapy with Depakote. The Agency had earlier obtained a Dermatology consult Dr. John A. Messenheimer (Glaxo-Wellcome) blamed the higher incidence of hospitalized rash in US30/31 on the 500-mg daily dose, comparing the infrequent number of case of hospitalized rash in the European active-control initial-monotherapy trials (daily LTG doses of 100 or 200 mg). An Agency consult from Dermatology (dated 8 Dec 1994; by Hon-Sum Ko MD) would also support a dose relationship between LTG and the incidence of skin rash, possibly based on increased LTG plasma levels.

The sponsor further divides rash into four categories: any rash, rash leading to LTG discontinuation, rash associated with hospitalization, and possible SJ. The terms rash and any rash include the COSTART terms rash, urticaria, rash vesiculobullous, erythema multiforme, rash maculopapular, and Stevens-Johnson syndrome. A case was classified as SJ or TEN if reported as such by the investigator or clinical information indicated mucous membrane involvement or blistering skin lesions. The category of rash leading to hospitalization did NOT include cases in which "LTG was not discontinued in relation to the hospitalization." According to the sponsor, the "term 'serious rash' as used in this document includes any rash associated with hospitalization or considered to be possible SJS" (v 2, p 212), and all cases of serious rash were examined by the same expert who reviewed the cases of serious rash in pediatric patients. Finally, the sponsor distinguishes between "correct" dosing -- or dosing according to recommendation in labeling -- and "incorrect" dosing -- too rapid titration or use of higher than recommended doses.

The sponsor's tables, reproduced at the end, showing the incidence of rash in completed monotherapy trials (n=868); as divided by correct (n=517) and incorrect dosing (n=351); as compared to CBZ and PHT in the active-control initial-monotherapy trials (LTG doses were 100 or 200 mg per day); during the adjunctive and monotherapy portions of the withdrawal-to-monotherapy trials (including the pivotal US30/31 and well as other trials in which doses were much lower than 500 mg/d); and the latter then divided again into correct and incorrect dosing.

With reference to Table 1 (all completed monotherapy trials), there are 3 cases of hospitalized rash for a rate of 3/868 (3%, or about 1/282), and 2 cases of SJ for a rate of 2/868 (2%, or 1/424). In pivotal study US30/31 (500 mg/d dose), there were 2/75 cases of hospitalized rash and 1/75 SJ. The other tables show -- as recognized previously from other empiric evidence -- that the highest incidence of rash during the adjunctive phase of treatment occurred with the addition of LTG to VPA, while the lowest incidence was associated with the addition of LTG to enzyme-inducing anticonvulsants (EIAED). Patients receiving LTG initial monotherapy experienced higher incidences of rash and discontinuation for rash than did those on the withdrawal-to-monotherapy regimen. Furthermore, correct and incorrect dosing does not appear to have had a significant impact on the incidence of rash in initial-monotherapy studies.

Finally, the sponsor has not presented (as requested) a list of adverse events, including rash, showing the incidence for subjects in the ≥500-mg daily dose cohort.

There have been two published reports of serious dermatologic reactions (TEN and hypersensitivity), confirmed by skin biopsy, both of which the sponsor cites. Both cases have relevance to the sponsor's sNDA under consideration, since the dose in one and the titration schedule in the other are similar to those found in the US30/31, the study submitted to obtain approval for monotherapy.

TEN was diagnosed in a 24-year-old female (with no personal or family history of skin diseases) who was started on LTG, after her baseline anticonvulsant (CBZ) was withdrawn, at 50 mg/d, then increased by 50 mg/d every 4 days until she was on LTG monotherapy 100 mg bid and seizure free. On the day 20 (17 days after LTG monotherapy initiation), she developed cutaneous symptoms, and was at that time immediately taken off LTG and placed on phenobarbital (150 mg/d), with clobazame (25 mg/d) added later. (See Fogh K et al, "Toxic epidermal necrolysis after treatment with LTG," *Seizure* 6 (1997):63-5.)

The hypersensitivity reaction occurred in a 24-year-old white male with poorly controlled epilepsy on a regimen of acetazolamide and nitrazepam. LTG 200 mg bid was begun (titration schedule not provided). After 1 week, he developed a progressively worsening rash (with fever, transaminase elevation, and possibly mild renal insufficiency [Cr 2.2]; skin biopsy consistent with a "hemorrhagic drug eruption"), requiring hospitalization and resolving with IV steroids. (See Jones D, "Phenytoin-like hypersensitivity associated with LTG," *J Am Acad Derm* 36 [1997]:1016-8).

PORPHYRIA INDUCTION The sponsor, citing a recently published *in vitro* study, reports that LTG (along with felbamate and tiagabine) have been to induce porphyrin synthesis in cultured chick embryos liver cells, a model used to demonstrate potential porphyrogenic properties (Hahn M et al, "Effects of new anticonvulsant medications on porphyrin synthesis in cultured liver cells," *Neurology* 49 [1997]:97-106). The study suggests that LTG may "induce porphyric synthesis. . .in a dose-dependent manner, which may be a predictor of inducing porphyria in patients with defects in heme synthesis" (v 2, p 7).

LABELING The sponsor recommends daily doses of 200-500 mg for monotherapy treatment of adult partial-onset seizures and includes sections on both the scenario of withdrawal-to-LTG monotherapy and initial-LTG monotherapy. The pivotal monotherapy trial (US30/31), employing a withdrawal-to-monotherapy design, does not support the use of doses lower than 500 mg/d or the use of LTG as initial monotherapy; see my discussion above about the sponsor's justification for the lower doses. Moreover, the sponsor's newly proposed titration over a period of 4-8 weeks would leave patients dangerously unprotected by subtherapeutic doses.

SUMMARY Because of an inadequate safety population data base (n=58 in the sNDA, and no additional information to enlarge the population) -- lacking as well a table of adverse events specifically relating daily doses ≥500 mg -- I do not recommend approval of LTG for the indication of monotherapy in the treatment of adult partial-onset seizures.

RECOMMENDATIONS

(1) Request specific exposure and adverse event data for daily doses ≥500 mg, with a formal review of rash in this cohort.

(2) Epidemiology consult to review Pregnancy Registry data.

(3) Psychiatry consult to review suicide and mania data in bipolar and depression clinical trials.

(4) Add to labeling (under "Warnings" or "Precautions") the potential for LTG to induce porphyria, based on *in vitro* studies.

/S/

Richard M. Tresley MD
Medical Reviewer

NDA 20,241Response to Approvable Letter (Monotherapy) div file/Katz R/Ware J/Tresley R/25 June 1998

Table 1
Deaths in Lamictal Clinical Trials
Reporting period 9-1-96 to 10-31-97
> 16 years

Body System	Protocol	Case ID Number	Sub.ID/ Tx. No.	Age	Sex	Country	Study Drug, Unit Dose,	Frequency	Time/ Onset	Adverse Events	Dur	Outcome	Relation
CARDIOVASCULAR	105124	B0045438	02909 02909	79Y	F	United Kingdom	Lamotrigine 25 MG	1N	7D	Poss.cerebrovasc.accident Slurred speech Dysphagia Headache Decreased consciousness Lower respiratory infect.	11D	Fatal	Unlikely
DRUG INTERACTION OVERDOSE & TRAUMA	105124	B0041863	01006 01006	79Y	F	United Kingdom	Lamotrigine		74D	Hip fracture Hip surgery Falling Hypostatic pneumonia		Resolved	Unlikely
DRUG INTERACTION OVERDOSE & TRAUMA	105136	B0046530	16387 OPEN	31Y	M	Netherlands	Lamotrigine		54D	Road traffic accident Poss.epileptic convulsion	1D	Fatal	Unlikely
DRUG INTERACTION OVERDOSE & TRAUMA	SCAB3001	B0045657	01908 01291	40Y	M	Finland	Lamotrigine 500 MG		62D	Epidural hematoma Head injury Epileptic convulsions	7D	Fatal	Unlikely
LOWER RESPIRATORY	1051010	B0045207	00028 00028	50Y	M	Sweden	Lamotrigine Placebo			Respiratory insufficiency Amyotrophic lat.sclerosis	1D	Fatal	Unlikely
LOWER RESPIRATORY	105136	B0045810	16681 OPEN	69Y	F	Netherlands	Lamotrigine		18D	Pneumonia Neoplasm of brain Non-Hodgkin's lymphoma	2D	Fatal	Unlikely

TABLE 1
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Body System	Protocol	Case ID Number	Sub.ID/ Tx. No.	Age	Sex	Country	Study Drug, Unit Dose,	Frequency	Time/ Onset	Adverse Events	Dur	Outcome	Relation
NEUROLOGY	105124	B0045131	02907 02907	77Y	F	United Kingdom	Lamotrigine			Hemiparesis Deterioration:condition Death		Fatal	Unlikely
PSYCHIATRY	SCAA2010	A0056708	3166 102	38Y	M	USA	Lamotrigine	1N	17D	Suicide	1D	Fatal	Unlikely
PSYCHIATRY	SCAB2003	B0050474	03901 OPEN	48Y	M	Denmark	Lamotrigine 50 MG		16D	Suicide	1D	Fatal	Unlikely

Table 5 Adverse Events (Raw Terms) that Resulted in a Adult Patient (>16 years old) Withdrawal from a LAMICTAL Bipolar Clinical Study by 31 October 1997.

Body System Adverse Experience	Total #Cases	# Fatal	Study Number
Blood and Lymphatic			
Neutropenia	1		SCAA2010
Cardiovascular			
Myocardial infarction	1		SCAB2001
Endocrine and Metabolic			
Sweating	1		601
Weight gain	1		SCAB2001
Gastrointestinal			
Nausea	1		601
Vomit	1		601
Ulcer(s) of oral mucosa	1		SCAB2001
Hepatobiliary Tract & Pancreas			
Hepatitis	1		SCAB2002
Neurology			
Insomnia	3		SCAA2011, SCAB2001
Headache	2		SCAB2001
Somnolence	1		601
Dizziness	1		SCAB2001
Tremor	1		601
Agitation	1		SCAB2001
Light headedness	1		SCAA2011
Memory loss	1		SCAA2011
Tingling in hands	1		SCAA2011
Cerebrovasc Acci	1		601
Speech disorder	1		601
Convuls	1		601
Dream abnormality	1		SCAB2001
Non-site Specific			
Face Edema	1		SCAB2002
Fever	1		SCAA2010
Edema	1		601

TABLE 5
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Body System Adverse Experience	Total #Cases	# Fatal	Study Number
Psychiatry			
Mania	5		601, SCAB2001, SCAB2002
Suicide Attempt	3		601, SCAB2001
Depression	3		SCAB2001
Emotional lability	3		601, SCAB2001, SCAB2002
Confusion	2		601, SCAA2011
Suicide	2	2	SCAA2010, SCAB2005
Irritability	1		SCAA2011
Anxiety	1		601
Psychotic disorder	1		SCAB2001
Depressive psychosis	1		SCAB2001
Reproductive			
Abnormal menses	1		SCAB2002
Erectile dysfunction	1		SCAA2011
Skin			
Rash	26		601, SCAB2001, SCAB2002, SCAA2010, SCAA2012
Pruritis	4		SCAB2001, SCAB2003
Exacer. of psoriasis	1		SCAA2010
Herpes zoster	1		SCAB2001
Total Number of Patients	**61**	**2**	

Appendix A. Summary of Characteristics of Studies Evaluating LAMICTAL in Adult Patients (> 16 years old) for Monotherapy Enrollment as of 31 October 1997 (Deaths, SAEs, Withdrawals Due to Adverse Events)

Protocol Number	Study[a] Objective	Study[a] Design	Control[b]	LAMICTAL Treatment Regimen & formulation[c]	LAMICTAL Treatment Duration (weeks)	LAMICTAL Treatment Doses (mg/day)	Completion Status	No. Entered	Age range	Number Exposed to LTG[d]	Patient Type
Clinical Trials for Epilepsy with Adult Patients											
US Sponsored Studies											
US 29	S	OL or DBC	None or VPA	b.i.d. Tabs	96	300-700	Completed	104		103	Partial Seizures
SCAA4001	S, E	DB-P	VPA	Tabs	32	25-500	Ongoing	42 (5 peds)[e]	≥12	21 (3 peds)[e]	Generalized Seizures
UK Sponsored Studies											
UK 126	S	SB	VPA	q.d. CD/Tabs	24	5-500	Ongoing	419 (204 peds)[e]	>2	279 (136 peds)[e]	Generalized Seizures
UK 136	S	SB	CBZ	q.d. CD	24	5-1000	Ongoing	471 (260 peds)[e]	>2	314 (173 peds)[e]	Partial Seizure
UK 133 SCAB3001	S	OL	VPA CBZ	q.d. Tabs	8(add-on) 8(withdrawal) 8(monotherapy) Total 24	200-500	Ongoing	383 (63 peds)[e]	≥2	UNK	Treatment Resistant
UK 124	S,E	DB	CBZ	b.i.d. Tabs	28	100-500	Pt. Enrollment complete	150	≥65	75	Elderly /Newly Diagnosed
Local Operating Companies Sponsored Studies											
105-405	S	OL	VPA CBZ	q.d. Tabs	20	100-500	Ongoing	712	≥12	UNK	Newly Diagnosed
105-1006 (Netherlands)	S	OL	None	q.d./b.i.d. Tabs	24	25-500	Ongoing	241[f]		241	Newly Diagnosed and Treatment Resistant
105-1010 (Sweden)	S, E	DB-CO	PBO	q.d. Tabs	46	25-300	Ongoing	50	≥40	50	Amyotrophic Lateral Sclerosis

Protocol Number	Study[a] Objective	Study[a] Design	Control[b]	LAMICTAL Treatment Regimen & formulation[c]	LAMICTAL Treatment Duration (weeks)	LAMICTAL Treatment Doses (mg/day)	Completion Status	No. Entered	Age range	Number Exposed to LTG[d]	Patient Type
Bipolar Studies											
105-601	E , S	OL	PBO	b.i.d. CD	24 +24 Total 48	25-500	Compl	75	≥18	75	Bipolar I & II
SCAB 2001	E, S	DB-P	PBO	b.i.d. CD	7	25-200	Compl	193	≥18	128	Bipolar I, Depressed
SCAB 2002	S	OL	None	b.i.d. CD	52	25-500	Ongoing	111 (37)[g]	≥18	111 (37)	Bipolar I, Depressed
SCAA 2010	E, S	DB-P	PBO	q.d. CD	10	25-500	Ongoing	51	≥18	Unk	Bipolar I & II
SCAA 2014	S	OL	None	q.d. CD	52	25-500	Ongoing	16	≥18	16	Bipolar I & II
SCAA 2012	E, S	RE	PBO	q.d. CD	8-16 (open) 32 (DB) Total 40-48	25-500	Ongoing	19	≥18	19	Bipolar I & II Rapid Cyclers
SCAB 2003	E, S	RE	Lithium	b.i.d. CD	8-16 (open) 52 (DB) Total 60-68	25-500	Ongoing	55	≥18	55	Bipolar I, Depressed
SCAB 2006	E, S	RE	Lithium	b.i.d. CD	8-16 (open) 52 (DB) Total 60-68	25-500	Ongoing	21	≥18	21	Bipolar I, Manic State
SCAB 2005	E, S	DB-P	Lithium	q.d. CD	32	25-500	Ongoing	14	≥18	Unk	Bipolar I & II
SCAA 2011	E, Ls	DB-P	Desipramine	q.d. CD	8	25-500	Ongoing	24		Unk	Unipolar Depression

[a]S = safety, E = efficacy, OL = open-label, DBC = double-blind continuation, DB-P = double-blind placebo controlled, RE = responder enriched, LTC = long-term continuation, SB = single blind, QOL = quality of life, DB-CO = double-blind crossover [b]PBO = placebo, VPA = valproic acid, CBZ = carbamazepine, ZSM = zonisamide
[c]b.i.d. = twice a day, q.d. = once a day, Tabs = compressed tablet, CD = LAMTICAL CD [d]Number is approximated for ongoing studies
e Peds = number of patients ≤ 16 years old [f]Cut-off date for enrollment information is 30 September 1996
[g]Approximate number of new exposures to LAMICTAL

Table 2. Prospective Registry - Lamotrigine Exposure in Pregnancy by Earliest Trimester of Exposure and Outcome

1 September 1992 - 30 September 1997

Earliest Trimester of Exposure	Birth Defects				No Birth Defects Reported[a]				Total Outcomes
	Live Birth	Spontaneous Pregnancy Loss[b]	Fetal Death[c]	Induced Abortion	Live Birth	Spontaneous Pregnancy Loss[b]	Fetal Death[c]	Induced Abortion	
First	4	0	0	1	87[d]	6	0	20	118
Second	0	0	0	0	1	0	0	0	1
Third	0	0	0	0	0	0	0	0	0
Unspecified	0	0	0	0	4[e]	0	0	0	4
Total	4	0	0	1	92	6	0	20	123

[a] Birth defect not reported but cannot be ruled out.

[b] Pregnancy Loss occurring < 20 weeks gestation

[c] Pregnancy Loss occurring ≥ 20 weeks gestation

[d] Includes 1 set of twins.

[e] Represents 1 set of triplets.

Table 3. **Prospective Registry - Lamotrigine Exposure in Pregnancy Summaries of Defects by Earliest Trimester of Exposure and Polytherapy Status**

1 September 1992 - 30 September 1997

First-Trimester Lamotrigine Polytherapy Exposure

Case Report #		Exposure	Date of Report	Infant Sex	Gestational Weeks at Outcome	Outcome
2624	32	Lamotrigine 2000 mg/day from week 0-7 Carbamazepine preconception throughout pregnancy	15 Oct 90	M	40	Live infant with one extra digit on one hand.[a]
2663	46	Lamotrigine 50 mg/day from week 0-40 Valproic Acid throughout pregnancy	7 Nov 94	F	Unknown	Live infant with bilateral talipes
2693	29	Lamotrigine 400 mg/day from week 0 600 mg/day from week 12 800 mg/day from week 16 Gabapentin preconception and throughout pregnancy	9 Nov 95	M	37	Live infant with skin tags on left ear; no opening to ear canal on right ear.[b]
2689	23	Lamotrigine 600 mg/day from week 0-37 Phenytoin and Primidone preconception throughout pregnancy.	12 Dec 94	M	37	Live infant with cardiac murmur and patent foramen ovale requiring banding around pulmonary artery; baby died at 3 months following corrective surgery (bronchiolitis and seizures just prior to death).

[a] Previous infant born with cardiac septal defect, multiple extra bones in left thumb, distortion of penis.
[b] The infant also had tremors intermittently for about 5 days post birth and was jaundiced.

Table 3. Prospective Registry - Lamotrigine Exposure in Pregnancy Summaries of Defects by Earliest Trimester of Exposure and Polytherapy Status (con't)

1 September 1992 - 30 September 1997

First-Trimester Lamotrigine Polytherapy Exposure (cont'd)

Case Report #	Age	Exposure	Date of Report	Infant Sex	Gestational Weeks at Outcome	Outcome
2696	35	Lamotrigine 700 mg/day from week 0 Clobazam preconception through first trimester.	8 Dec 95	Unknown	17	Induced abortion. Lumbar neural tube defect with early evidence of ventriculomegaly and a derangement of the posterior fossa.

Table 4. **Prospective Registry - Antiepileptic Drug Polytherapy Exposure in Pregnancy, by Trimester of Exposure and Outcome**

1 September 1992 - 30 September 1997

First-Trimester Exposures: Concomitant Antiepileptic Drug Exposures	Outcomes with Birth Defects	Outcomes without Reported Birth Defects[a]			
		Live Births Without Defects	Spontaneous Pregnancy Losses/Fetal Deaths	Induced Abortions	Total
lamotrigine monotherapy	0	29	2	9	40
carbamazepine	1	11	2	3	17
clobazam	1	0	0	0	1
clonazepam	0	1	0	0	1
phenytoin	0	3	0	1	4
gabapentin	1	0	0	0	1
phenobarbital	0	3	0	1	4
primidone	0	1	0	0	1
valproate	1	12	0	2	15
vigabatrin	0	1	0	0	1
carbamazepine & clobazam	0	1	0	0	1
carbamazepine & clonazepam	0	2	0	0	2
carbamazepine & clorazepate	0	0	1	0	1
carbamazepine & methylphenobarbitone	0	1	0	0	1
carbamazepine & phenytoin	0	3	1	1	5
carbamazepine & valproate	0	3	0	0	3
carbamazepine & vigabatrin	0	3	0	1	4
clobazam & vigabatrin	0	1	0	0	1
clonazepam & phenytoin	0	1	0	0	1
clonazepam & primidone	0	1	0	0	1
diazepam & valproate	0	1	0	0	1
gabapentin & phenytoin	0	1	0	0	1
phenobarbital & phenytoin	0	1	0	0	1
phenytoin & primidone	1	1	0	0	2
phenytoin & valproate	0	3	0	0	3
barbexaclone & carbamazepine & phenytoin	0	1	0	0	1
carbamazepine & clobazam & clonazepam	0	1	0	0	1
carbamazepine & diazepam & gabapentin	0	1	0	0	1
carbamazepine & felbamate & phenytoin	0	0	0	1	1
carbamazepine & phenobarbital & primidone	0	0	0	1	1
Total	5	87	6	20	118