



LAMICTAL® (lamotrigine): Analysis of Suicidality Data

**FDA Advisory Committee
July 10, 2008**

LAMICTAL: Updated Analysis of Definitive Suicidal Behavior and Ideation

- Full updated dataset (submitted to FDA Nov 2007) consisted of:
 - Initial dataset (submitted to FDA June 2007) of 32 trials
 - (15 psychiatry, 16 neurology, 1 HVT), plus:
 - 3 additional trials completed since original FDA request
 - 2 acute bipolar depression trials
 - 1 epilepsy trial, *and*
 - Additional searches of non-databased text fields from all studies
- In total, the full updated dataset for LAMICTAL includes 35 placebo-controlled clinical trials involving 6,467 patients and 52 healthy volunteers

LAMICTAL: Updated Analysis of Definitive Suicidal Behavior and Ideation

- The additional data included in the full updated data set have contributed:
 - 706 new patients: 354 on LAMICTAL and 352 on placebo
 - 13 new classified events of suicidal ideation (none for behavior alone)
 - 9 events from the new acute bipolar depression trials:
1 on LAMICTAL and 8 on placebo
 - 4 events from non-databased text fields of the initial dataset:
3 on LAMICTAL & 1 on placebo

Number & percent of subjects with definitive suicidal behavior and ideation by treatment group and indication

Comparison of initial and updated (full) datasets

Trial		LAMICTAL	Placebo	OR (95% CI)	p-value
<i>Neurological indications</i>	Initial	5/1753 (0.29%)	3/1048 (0.29%)	1.13 (0.25, 5.95)	1.000
	Full	6/1871 (0.32%)	3/1169 (0.26%)	1.27 (0.30, 6.46)	1.000
<i>Epilepsy</i>	Initial	5/955 (0.52%)	2/684 (0.29%)	1.80 (0.34, 13.87)	0.697
	Full	6/1073 (0.56%)	2/805 (0.25%)	2.00 (0.40, 14.96)	0.478

Number & percent of subjects with definitive suicidal behavior and ideation by treatment group and indication

Comparison of initial and updated (full) datasets

Trial		LAMICTAL	Placebo	OR (95% CI)	p-value
<i>Psychiatric indications</i>	Initial	34/1556 (2.19%)	13/1404 (0.93%)	2.29 (1.21, 4.53)	0.011
	Full	37/1792 (2.06%)	22/1635 (1.35%)	1.49 (0.88, 2.59)	0.146
<i>Bipolar Disorder</i>	Initial	27/976 (2.77%)	10/823 (1.22%)	2.27 (1.10, 4.97)	0.028
	Full	29/1212 (2.39%)	19/1054 (1.80%)	1.31 (0.73, 2.39)	0.460

<i>All Indications</i>	Initial	39/3341 (1.17%)	16/2472 (0.65%)	2.06 (1.15, 3.82)	0.018
	Full	43/3695 (1.16%)	25/2824 (0.89%)	1.46 (0.89, 2.45)	0.171

Number & percent of subjects with definitive suicidal behavior by treatment group and indication

Comparison of initial and updated (full) datasets

Trial		LAMICTAL	Placebo	OR (95% CI)	p-value
<i>Neurological indications</i>	Initial	2/1753 (0.11%)	1/1048 (0.10%)	1.16 0.08,36.63)	1.000
	Full	2/1871 (0.11%)	1/1169 (0.09%)	1.16(0.08,36.63)	1.000
<i>Epilepsy</i>	Initial	2/955 (0.21%)	0/684 (0.00%)	Inf (0.17, inf)	0.498
	Full	2/1073 (0.19%)	0/805 (0.00%)	Inf (0.17, inf)	0.498

Number & percent of subjects with definitive suicidal behavior by treatment group and indication

Comparison of initial and updated (full) datasets

Trial		LAMICTAL	Placebo	OR (95% CI)	p-value
<i>Psychiatric indications</i>	Initial	12/1556 (0.77%)	4/1404 (0.28%)	2.66 (0.88,9.66)	0.125
	Full	12/1792 (0.67%)	4/1635 (0.24%)	2.66 (0.88,9.66)	0.125
<i>Bipolar Disorder</i>	Initial	10/976 (1.02%)	4/823 (0.49%)	2.16 (0.68,8.06)	0.276
	Full	10/1212 (0.83%)	4/1054 (0.38%)	2.16 (0.68,8.06)	0.276

<i>All Indications</i>	Initial	14/3341 (0.42%)	5/2472 (0.20%)	2.34 (0.85,7.34)	0.106
	Full	14/3695 (0.38%)	5/2824 (0.18%)	2.34 (0.85,7.34)	0.106

Public Presentation of LAMICTAL Suicidality Findings

- GSK Clinical Trial Registry

- Public website for GSK study results (gsk.com)

- Posted 20 Nov 2007

- Analysis of Suicidal Ideation and Behavior in Lamotrigine Clinical Trials

- International Meeting Presentations

- Title: Analysis of Suicidal Ideation and Behavior in Lamotrigine Clinical Trials

- 07 May 2008 - American Psychiatric Association (APA)

- 28 May 2008 - NCDEU: New Research Approaches for Mental Health Interventions

Excerpt from the Current LAMICTAL US Package Insert (since 2005)

Clinical Worsening and Suicide Risk Associated with Bipolar Disorder

- Patients with bipolar disorder may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviors (suicidality) whether or not they are taking medications for bipolar disorder.
- Patients should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes.

Summary

- Bipolar disorder and epilepsy are serious chronic illnesses
- Definitive interpretation of the analyses is difficult due to:
 - the small incidence and absolute numbers of events
 - the retrospective nature of the analyses
 - potentially confounding because the events of interest can be symptoms of bipolar disorder or epilepsy
- Trends from the analysis for LAMICTAL are consistent with the overall FDA anticonvulsant findings
- GSK believes the results of the FDA's analysis should be incorporated into the labelling for anticonvulsants
- GSK supports additional prospective research for a more complete understanding of the observed associations