



GlaxoSmithKline

**IMPORTANT
PRESCRIBING
INFORMATION**

GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709-3398
Tel. 919 483 2100
www.gsk.com

June 2006

Dear Health Care Professional:

Emerging data from a pregnancy registry suggest an association between LAMICTAL[®] (lamotrigine) and an increased risk of non-syndromic oral clefts. Specifically, the ongoing North American Antiepileptic Drug (NAAED) Pregnancy Registry detected an elevated prevalence of isolated, non-syndromic cleft palate deformity occurring in infants exposed to lamotrigine monotherapy during the first trimester of pregnancy compared to the reference population used in this registry.¹ Recently published data from the registry report 3 cases of isolated, non-syndromic cleft palate and two cases of isolated, non-syndromic cleft lip without cleft palate in infants from 564 first trimester lamotrigine monotherapy exposures giving a rate of 8.9 per 1000.² This compares with a prevalence rate of 0.37 per 1000 seen in the general population of the Brigham and Women's Hospital (BWH) Surveillance Program (relative risk in lamotrigine-treated patients vs BWH general population of 24; 95% CI 10.0-57.4). For reference, the overall rate of major malformations reported by the NAAED registry was 15/564 (2.7%, 27 per 1000).

The prevalence of oral clefts noted in the NAAED registry is also higher than the background prevalence of non-syndromic oral clefts reported in the literature, including studies from the United States, Australia, and Europe. While different studies have differing results due to geographic and case ascertainment variations, the reported range is 0.50 to 2.16/1000³⁻¹⁷.

GlaxoSmithKline is in discussion with the FDA and regulatory authorities around the world about these newly reported data and other relevant information, including outcomes in more than 2000 pregnancies from other pregnancy registries, to further understand the significance of this finding. GlaxoSmithKline will update prescribing information, including pregnancy category, as necessary and patient information, as appropriate, on conclusion of these discussions.

At this time, patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy. Although pregnant women and their unborn children may face significant health risks from uncontrolled epilepsy or bipolar disorder, LAMICTAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

To facilitate monitoring fetal outcomes of pregnant women exposed to lamotrigine, physicians are encouraged to register patients, **before fetal outcome (e.g., ultrasound, results of amniocentesis, birth, etc.) is known**, and can obtain information by calling the Lamotrigine Pregnancy Registry at 1-800-336-2176 (toll-free). Patients can enroll themselves in the NAAED Pregnancy Registry by calling 1-888-233-2334 (toll-free).

The medical community can further our understanding of LAMICTAL by reporting adverse events to GlaxoSmithKline at 1-888-825-5249 or to the FDA's MedWatch Adverse Event Reporting program online (at www.fda.gov/MedWatch/report.htm), by phone (1-800-FDA-1088), or by returning the postage-paid FDA form 3500 (which may be downloaded from www.fda.gov/MedWatch/getforms.htm) by mail (to MedWatch, 5600 Fisher's Lane, Rockville, MD 20852-9787) or fax (1-800-FDA-0178).

**Medication errors have occurred involving LAMICTAL.
To reduce the potential for medication errors, please write and say
"LAMICTAL" clearly.**

IMPORTANT NOTE: Medication errors have occurred between LAMICTAL and other medications, most commonly Lamisil[®],* lamivudine, Ludiomil[®],* labetalol, and Lomotil[®].* Patients who do not receive LAMICTAL would be inadequately treated and could experience serious consequences. Conversely, patients erroneously receiving LAMICTAL, especially high initial doses, would be unnecessarily subjected to a risk of serious side effects.

Please consult the enclosed Prescribing Information for LAMICTAL. Should you have any questions or require additional information, please contact our Customer Response Center at 1-888-825-5249.

Sincerely,



Michael Gold, MS, MD
VP Neurology, US Clinical
Neurosciences MDC

* Lamisil (terbinafine HCl tablets) and Ludiomil (maprotiline HCl) are registered trademarks of Novartis Pharmaceuticals Corporation. Lomotil (diphenoxylate HCl, atropine sulfate) is a registered trademark of G.D. Searle LLC.

References:

1. Nelson K., Holmes L.B. Active Malformations Surveillance Program at Brigham and Women's Hospital in Boston. *New England J Medicine*. 1989;320:19-23.
2. Holmes LB, Wyszynski, DF, Baldwin EJ, Haebecker E, Glassman LH, Smith CR. Increased risk for non-syndromic cleft palate among infants exposed to lamotrigine during pregnancy (abstract). *Birth Defects Research Part A: Clinical and Molecular Teratology*. 2006;76(5):318.
3. Tolarova MM, Cervenka J. Classification and birth prevalence of orofacial clefts. *Am J Med Genetics*. 1998;75:126-37.
4. Das S, Runnels R Jr, Smith J, et al. Epidemiology of cleft lip and cleft palate in Mississippi. *South Med J*. 1995;88:437-42.
5. Croen LA, Shaw GM, Wasserman CR, et al. Racial and ethnic variations in the prevalence of orofacial clefts in California, 1983-92. *Am J Med Genetics*. 1998;79:42-47.
6. Hashmi SS, Waller DK, Langlois P, et al. Prevalence of non-syndromic oral clefts in Texas: 1995-1999. *Am J Med Genetics*. 2005;134(A):368-72.
7. DeRoo LA, Gaudino JA, Edmonds LD. Orofacial cleft malformations. Associations with maternal and infant characteristics in Washington state. *Birth Defects Research (A)*. 2003;67:637-42.
8. Menegotto BG, Salzano FM. Epidemiology of oral clefts in a large South American sample. *Cleft Palate Craniofacial Journal*. 1991;28:373-77.
9. Vallino-Napoli LD, Riley MM, Halliday J. An epidemiologic study of isolated cleft lip, palate or both in Victoria, Australia from 1983-2000. *Cleft Palate Craniofacial Journal*. 2004;41:185-94.
10. Christensen K. The 20th century Danish facial cleft population — epidemiological and genetic-epidemiological studies. *Cleft Palate Craniofacial Journal*. 1999;36:96-104.
11. Bille C, Skytthe A, Vach W, et al. Parent's age and the risk of oral clefts. *Epidemiology*. 2005;16:311-16.
12. Kallen B. Maternal drug use and infant cleft lip/palate with special reference to corticoids. *Cleft Palate Craniofacial Journal*. 2003;40(6):624-8.
13. Becker M, Svensson H, Kallen B. Birth weight, body length, and cranial circumference in newborns with cleft lip or palate. *Cleft Palate Craniofacial Journal*. 1998;35:255-61.

14. Robert E, Kallen B, Harris J. The epidemiology of orofacial clefts. 1. Some general epidemiological characteristics. *J Craniofacial Genetics Developmental Biology*. 1996;16:234-41.
15. Stoll C, Alembik Y, Dott B, et al. Associated malformations in cases with oral clefts. *Cleft Palate Craniofacial Journal*. 2000;37:41-47.
16. Teconi R, Clementi M, Turolla L. Theoretical recurrence risks for cleft lip derived from a population of consecutive newborns. *J Med Genetics*. 1988;25:243-46.
17. Harville EW, Wilcox AJ, Lie RT, et al. Cleft lip and palate versus lip only: are they distinct defects? *Am J Epidemiol*. 2005;162:448-53.