Health Canada Endorsed Important Safety Information on LAMICTAL® (lamotrigine) Tablets

August 1, 2006

Dear Healthcare Professional

Subject: Association of LAMICTAL® (lamotrigine) with an increased risk of non-syndromic oral clefts

GlaxoSmithKline Inc. (GSK), following discussions with Health Canada, would like to inform you of important new safety information concerning the antiepileptic, LAMICTAL® (lamotrigine).

- Emerging data from the North American Antiepileptic Drug (NAAED) Pregnancy Registry suggest an association between LAMICTAL® (lamotrigine) and an increased risk of non-syndromic oral clefts over the reference population for the registry (ie. Active Malformations Surveillance Program at Brigham and Women's Hospital in Boston, USA) [1]. Recently published data from the Registry report three 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 1,000, as compared to 0.37 per 1000 in the reference population for that registry.
- 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 2.16/1000 [3-17].
- To assist with the assessment of risk, analysis of data from additional pregnancy registries, with approximately 2200 additional lamotrigine monotherapy first trimester exposures has been conducted, and 4 additional non-syndromic cases of oral cleft have been identified. Follow-up information will be provided via the appropriate channels when available.
- Health-care professionals are reminded that patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy.

Recently published data from the North American Antiepileptic Drug (NAAED) Pregnancy Registry report three 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 1,000.[2] This compares with a prevalence rate of 0.37 per 1,000 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). The NAAED data did not show an increase in the overall risk of major congenital malformations associated with lamotrigine (15/564 = 2.7% or 27 per 1000).

Data from additional Pregnancy Registries

Data from additional pregnancy registries are currently being assessed to provide a more complete picture. Given the heterogeneity in data collection processes across the registries, and the variety of factors considered to play a role in the risk of oral clefts, including genetics, the optimal route for analysis of all data remains to be decided. Follow-up information will be provided via the appropriate channels when available.

Updates to Prescribing Information

GlaxoSmithKline is in discussion with regulatory authorities around the world about these newly reported data and other relevant information, including outcomes in over 2000 pregnancies from other pregnancy registries, to further understand the significance of this finding. GSK will update prescribing information as necessary and patient information, as appropriate, on conclusion of these discussions. As is currently stated in the Product Monograph, 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, 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 (800) 336-2176 (toll-free). Patients can enroll themselves in the NAAED Pregnancy Registry by calling (888) 233-2334 (toll-free).

GSK continues to work closely with Health Canada to monitor adverse event reporting and to ensure that up-to-date information regarding the use of lamotrigine is available.

Managing marketed health product-related adverse reactions depends on health care professionals and consumers reporting them. Reporting rates determined on the basis of spontaneously reported post-marketing adverse reactions are generally presumed to underestimate the risks associated with health product treatments. Any case of cleft lip and/or cleft palate or other serious or unexpected adverse reactions in patients receiving LAMICTAL® should be reported to GlaxoSmithKline Inc., or Health Canada at the following addresses:

GlaxoSmithKline Inc.
7333 Mississauga Road North
Mississauga, Ontario
L5N 6L4
Tel: 1-800-387-7374

Any suspected adverse reaction can also be reported to:
Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Marketed Health Products Directorate
HEALTH CANADA
Address Locator: 0701C
OTTAWA, Ontario, K1A 0K9
Tel: (613) 957-0337 or Fax: (613) 957-0335
To report an Adverse Reaction, consumers and health professionals may call toll free:
Tel: 866 234-2345
Fax: 866 678-6789
cadrmp@hc-sc.gc.ca

The AR Reporting Form and the AR Guidelines can be found on the Health Canada web site or in *The Canadian Compendium of Pharmaceuticals and Specialties.*

http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/form/ar-ei_form_e.html
http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/guide/ar-ei_guide-ldir_e.html

For other inquiries related to this communication, please contact Health Canada at:
Bureau of Cardiology, Allergy and Neurological Sciences
E-mail: BCANS_Enquiries@hc-sc.gc.ca
Tel: (613) 941-1499
Fax: (613) 941-1668

Your professional commitment in this regard is important to protecting the well-being of your patients by contributing to early signal detection and informed drug use.

Any questions from health care professionals may be directed to Medical Information via GSK Customer service at 1-800-387-7374.

Sincerely,

Dr John A Dillon MB BCh MFPM
VP, Medical Division and Chief Medical Officer
GlaxoSmithKline Inc.

References:

1. Nelson K., Holmes L.B. Malformations due to presumed spontaneous mutations in newborn infants. New England J Medicine 320:19-23, 1989.

2. Holmes LB, Wyszynski, DF, Baldwin EJ et al. 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 plalate in Mississisippi. 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.