Health Canada Endorsed Important Safety Information on TEGRETOL* (carbamazepine)

NOVARTIS

March 17, 2008

Dear Health Care Professional:

Subject: New Safety Information for the anti-epileptic drug TEGRETOL*

Novartis Pharmaceuticals Canada Inc., following discussion with Health Canada, would like to inform you about new safety information in the Product Monograph for TEGRETOL* (carbamazepine).

The TEGRETOL* Product Monograph has been revised to include the following safety information in the WARNINGS section:

- Serious and sometimes fatal dermatologic reactions, including Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome (SJS), have been reported with TEGRETOL*. Should signs and symptoms suggest a serious skin reaction such as SJS or TEN, TEGRETOL* should be withdrawn at once and alternative therapy should be considered.
- The risk of SJS and TEN exists in all patients, but these reactions are generally very rare. However, in some Asian countries the risk is estimated to be approximately 10 times higher than in Western countries.
- In studies that included small samples of patients of Han Chinese ancestry a strong association was found between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene.
- The HLA-B*1502 allele is found almost exclusively in individuals with ancestry across broad areas of Asia. Therefore, physicians should consider HLA-B*1502 genotyping as a screening tool in genetically at-risk patients. HLA-B*1502 genotyping must never substitute for appropriate clinical vigilance and patient management.
- Until further information is available, the use of TEGRETOL* and other anti-epileptic drugs associated with SJS/TEN should be avoided in patients who test positive for the HLA-B*1502 allele.

Retrospective case-control studies in patients of Han Chinese ancestry have shown a strong association between the development of these severe skin reactions and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. The prevalence of this allele is negligible in Western Caucasian populations but is approximately 5-10% in Han Chinese, and ranges from <1% to over 15% in other Asian ethnic populations.

Health care professionals should also be aware that HLA-B*1502 genotyping as a screening tool has important limitations. These limitations include the possibility that serious dermatologic reactions may still occur in some patients who test negative for HLA-B*1502 and that some patients who test positive for HLA-B*1502 may not develop serious dermatologic reactions. This suggests that the presence of the

allele may be only one of the risk factors for developing serious dermatologic reactions. Therefore, HLA-B*1502 genotyping must never substitute for appropriate clinical vigilance and patient management.

In addition, it should be kept in mind that over 90% of TEGRETOL*-treated patients (of any ethnicity) who will experience SJS/TEN typically have this reaction within the first few months of treatment. This information should be considered when deciding whether to screen genetically at-risk patients currently on TEGRETOL*.

Regardless of ethnicity or HLA-B*1502 genotype, should signs and symptoms suggest a serious skin reaction such as SJS or TEN, TEGRETOL* should be withdrawn at once. The use of other anti-epileptic drugs associated with SJS/TEN should also be avoided in patients who have shown serious dermatological reactions during treatment with TEGRETOL*.

TEGRETOL* is indicated for the treatment of epilepsy, either alone or in combination with other anticonvulsant drugs. TEGRETOL* is also indicated for the symptomatic relief of pain of trigeminal neuralgia, as well as in the treatment of acute mania and prophylaxis treatment in bipolar (manic-depressive) disorders (as monotherapy or as an adjunct to lithium).

The Product Monograph for TEGRETOL* has been updated to include information regarding an association between the presence of the allele HLA-B*1502 in patients of Asian ancestry and the risk of developing serious potentially fatal dermatologic reactions: toxic epidermal necrolysis (TEN) and Stevens-Johnson Syndrome (SJS). Please review the Product Monograph, which may be accessed on the Health Canada website, for the complete changes to prescribing information http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index_e.html.

This new safety information pertains to TEGRETOL* and all other carbamazepine products marketed in Canada.

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 serious or unexpected adverse reactions in patients receiving TEGRETOL* should be reported to Novartis Pharmaceuticals Canada Inc. or Health Canada at the following addresses:

Novartis Pharmaceuticals Canada Inc.
385 Bouchard Blvd.
Dorval, (QC) H9S 1A9
Phone: 1-800-363-8883 (Medical Information)

Any suspected adverse reaction can also be reported to:

Canada Vigilance Program
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
CanadaVigilance@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/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:
Marketed Health Products Directorate (MHPD)
E-mail: MHPD_DPSC@hc-sc.gc.ca
Tel: 613-954-6522
Fax: 613-952-7738

Should you have any questions or require additional information regarding the use of TEGRETOL*, please contact Novartis Pharmaceuticals Canada Inc., Medical Information Department at 1-800-363-8883.

Sincerely,

Original signed by

Jean-Marie Leclerc, M.D. FRCP(C)
Chief Scientific Officer and Senior Vice-President Clinical and Regulatory Affairs

[Pr]TEGRETOL* is a registered trademark.

References:

1. Chung WH et al. Medical Genetics: a Marker for Stevens-Johnson Syndrome. Nature 2004; 428 (6982): 486
2. Hung SI et al. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. Pharmacogenetics and Genomics 2006; 16 (4): 297-306
3. Lonjou C et al. A marker for Stevens-Johnson syndrome…: ethnicity matters. The Pharmacogenomics Journal 2006; 6 (4): 265-268
4. Man CB et al. Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. Epilepsia 2007; 48 (5): 1015-1018.