Health Canada Endorsed Important Safety Information on PrGLEEVEC (imatinib mesylate)*

NOVARTIS

September 21, 2006

Dear Health Care Professional:

Subject: Recent safety information regarding reports of significant Left Ventricular Ejection Fraction reduction and Congestive Heart Failure with GLEEVEC* (imatinib mesylate)

After discussions with Health Canada, Novartis wishes to provide you with recent safety information regarding reports of significant left ventricular ejection fraction reduction and congestive heart failure with GLEEVEC*.

GLEEVEC* (imatinib mesylate) is indicated for the treatment of adult patients with Philadelphia chromosome-positive, chronic myeloid leukemia (CML) and for the treatment of adult patients with unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).

A recently published article in Nature Medicine[1] reported ten patients treated with imatinib who developed significant left ventricular ejection fraction reduction and congestive heart failure (CHF). Although several of these individuals had pre-existing conditions including hypertension, diabetes and prior coronary artery disease, and had received other drugs, they were subsequently diagnosed with CHF.

The same article reports an animal study that examined the effects of imatinib mesylate on cardiac cells from the mouse. The authors hypothesize that development of cardiac dysfunction may be related to inhibition of the Abl kinase which triggers the stress response in cardiomyocytes and induces cell death.

In addition, recently obtained data from a pre-clinical carcinogenicity study of GLEEVEC* has demonstrated an incidental finding of cardiomyopathy in rats.

Subsequent to the publication of the article in Nature Medicine, Novartis has further evaluated all available data from clinical trials and spontaneous reporting. While the frequency of reported cardiac events remains less than 1% in the current prescribing information for GLEEVEC*, CHF and left ventricular dysfunction have occasionally been reported.

Pending further information on this issue, it is recommended that:

- **Any patients using GLEEVEC*, with known cardiac disease or risk factors for cardiac failure, should be monitored carefully.**
- **Any patient using GLEEVEC* who has symptoms or signs suggestive of Congestive Heart Failure (i.e., edema, dyspnea, pleural effusion or pericardial effusion) should receive timely and thorough evaluation and treatment.**
- **In patients with known underlying heart disease or in elderly patients, a baseline evaluation of Left Ventricular Ejection Fraction is recommended prior to initiation of GLEEVEC* therapy.**

Novartis will continue to review the pre-clinical and clinical data as well as post-marketing safety database for GLEEVEC*. Reports of cardiac adverse events, including cardiac failure, are noted in the current prescribing information for GLEEVEC* Novartis will be working with Health Canada to further integrate new safety information in the official Canadian Product Monograph as it becomes 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 cardiac or other serious or unexpected adverse events in patients receiving GLEEVEC* should be reported to Novartis or Health Canada at the following addresses:

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

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 Metabolism, Oncology and Reproductive Sciences (BMORS)
E-mail: bmors_enquiries@hc-sc.gc.ca
Tel: (613) 941-3171

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

Should you have any questions or require additional information regarding the use of GLEEVEC* please contact Novartis Pharmaceuticals Canada Inc., at 1-800-363-8883 from 8:30 AM to 4:30 PM Monday to Friday Eastern Standard Time.

Novartis Pharmaceuticals Canada Inc.

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Reference:

1. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. Kerkela R, Grazette L, Yacobi R et al. *Nature Medicine*; advance online publication July 23rd, 2006.

PrGLEEVEC* is a registered trademark