Health Canada Endorsed Important Safety Information on
PrSEBIVO® (telbivudine)

NOVARTIS

March 07, 2008

Dear Health Care Professional:

Subject: **Risk of peripheral neuropathy in patients treated with telbivudine (SEBIVO®) and interferon**

Novartis Pharmaceuticals Canada Inc., in consultation with Health Canada, would like to inform you of an increased risk of peripheral neuropathy observed in chronic hepatitis B patients treated with telbivudine (SEBIVO®) in combination with peginterferon alfa-2a (Pegasys®), compared to the interferon or telbivudine alone, during a controlled pilot clinical trial. An increased risk cannot be ruled out for treatments combining telbivudine with other interferon products (pegylated or standard).

- An increased risk of peripheral neuropathy has been observed in patients receiving telbivudine and peginterferon alfa-2a in combination, compared to the interferon or telbivudine alone.
- Treatment with telbivudine should be reconsidered if peripheral neuropathy is suspected.
- The benefit to patients with chronic hepatitis B of combined treatment with telbivudine and interferon has not been established.

Telbivudine is currently indicated in Canada as monotherapy for the treatment of chronic hepatitis B in adult patients with compensated liver disease, with evidence of viral replication and active liver inflammation.

In a small ongoing clinical trial, serious peripheral neuropathy has appeared as a common adverse event (5/48; 10%) in patients treated with both telbivudine (600 mg/d) and pegylated-interferon alfa-2a (Pegasys®, 180 micrograms/wk). Non-serious peripheral neuropathy was reported in an additional 3 cases (total number of events 8/48 patients; 17%). Peripheral neuropathy occurred with a time to onset of about 1 to 6 months (median: 3 months) in the five serious cases, for which study treatments have been discontinued. For the 8 reported cases the clinical outcomes are currently unknown, or unresolved 1-6 months after treatment discontinuation. Symptoms include weakness and paraesthesias and pain in the legs that was disabling in one case. In all 8 patients the diagnosis was confirmed by a neurologist and/or electromyography and/or a nerve conduction test.

Peripheral neuropathy has been observed as an uncommon event in clinical trial patients receiving telbivudine monotherapy (5/2000; 0.3%). Two of the 5 events were serious with one event detected within 3 months of the start of treatment. Discontinuation of telbivudine has sometimes led to symptom improvement although the reversibility of the peripheral neuropathy is currently unknown due to the short follow-up periods to date. Peripheral neuropathy has also occurred in the post-market setting with 4 cases reported after an estimated 6500 patient-years of exposure to telbivudine monotherapy.

Peripheral neuropathy is a common (≥1% to <5%) adverse reaction of peginterferon alfa-2a, as described in its Product Monograph. The risk of developing peripheral neuropathy appears to be increased when the

patient receives both telbivudine and pegylated-interferon alfa-2a.

Novartis Pharmaceuticals Canada Inc. is in the process of updating the Product Monograph and Consumer Information for telbivudine to reflect this new safety finding.

Patients are being advised to talk to their doctors if they are taking both telbivudine and an interferon product (see http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/public/2008/index_e.html).

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 serious peripheral neuropathy, or other serious or unexpected adverse reactions in patients receiving telbivudine should be reported to Novartis Pharmaceuticals Canada Inc., or Health Canada at the following addresses:

Novartis Pharmaceuticals Canada Inc.
385 Bouchard Blvd.
Dorval, Quebec H9S 1A9
Phone: (514) 631-6775

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 or Fax: 866-678-6789 or email 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/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:
Marketed Health Products Directorate (MHPD)
E-mail: MHPD_DPSC@hc-sc.gc.ca
Tel: 613-954-6522 Fax: 613-952-7738

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 telbivudine please contact Novartis Pharmaceuticals Canada Inc., at 1-800-363-8883 from 8:30 to 4:30 Monday to Friday EST.

Novartis Pharmaceuticals Canada Inc.

original signed by

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