Health Canada Endorsed Important Safety Information on PrGILENYA* (fingolimod)

NOVARTIS

August 21, 2012

Dear Health Care Professional:

Subject: GILENYA* (fingolimod) – Stronger recommendations regarding first-dose cardiovascular monitoring and use in patients with pre-existing cardiovascular conditions

Novartis Pharmaceuticals Canada Inc. ("Novartis"), in collaboration with Health Canada, would like to inform you about important new safety and use recommendations which have been added to the Product Monograph for GILENYA* (fingolimod), a drug indicated for the treatment of relapsing-remitting multiple sclerosis.

Isolated delayed-onset cardiovascular events, including transient asystole and unexplained death, have occurred within 24 hours of the first dose of GILENYA*. Health Canada has completed its review, which included a number of international reports of deaths, several of which were considered possibly associated with GILENYA*. No deaths have been reported in Canada. Fifty-four (54) Canadian case reports of serious cardiovascular adverse events, possibly associated with GILENYA* have been reported between March 09, 2011 and January 31, 2012. The majority of these cases have occurred within 6 hours of the first dose and consisted of bradycardia, hypertension, hypotension and dizziness/malaise/palpitations. The Canadian patient exposure to GILENYA* from April 1, 2011 to December 31, 2011 was estimated at 155.3 patient-years[1] from at least 621 patients[2].

New recommendations to reduce the risk of cardiovascular events in patients taking GILENYA* have been included in the *WARNINGS AND PRECAUTIONS* section of the Product Monograph.

- Initiation of GILENYA* treatment results in reversible heart rate decrease and has also been associated with atrio-ventricular (AV) conduction delays and isolated cases of serious cardiovascular events and unexplained death.
- An electrocardiogram (ECG) should be performed and blood pressure measured prior to and 6 hours after the first dose.
- All patients should be monitored for signs and symptoms of bradyarrhythmia, with hourly pulse and blood pressure measurement for at least 6 hours after the first dose.
- Circumstances where GILENYA* should not be prescribed and which require extended monitoring beyond 6 hours are detailed on the following page.

GILENYA* is indicated as monotherapy for the treatment of adult patients with the relapsing-remitting form of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the progression of physical disability. GILENYA* is generally recommended in MS patients who have had an inadequate response to, or are unable to tolerate, one or more therapies for multiple sclerosis.

The Product Monograph for GILENYA* has been updated to include additional new recommendations. **For complete prescribing information and conditions of use, please review the revised Product Monograph before prescribing GILENYA*.**

Conditions when GILENYA* should not be used:

- In patients with a history or currently experiencing second-degree Mobitz type II or higher AV block, sick-sinus syndrome, sino-atrial heart block, a history of recurrent syncope or symptomatic bradycardia, significant QT prolongation (QTc >470 msec in females or >450 msec in males) or in patients with relevant risk factors for QT prolongation (e.g. hypokalemia, hypomagnesemia or congenital QT prolongation), due to the risk of serious rhythm disturbances.

- In patients with known ischemic heart disease (including angina pectoris), history of myocardial infarction, congestive heart failure, history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension or severe untreated sleep apnea since significant bradycardia may be poorly tolerated in these patients.

- GILENYA* should not be initiated in patients on concurrent therapy with beta-blockers, with heart-rate-lowering calcium channel blockers or with other substances which may decrease heart rate. If treatment with GILENYA* is considered necessary, advice from a cardiologist should be sought regarding a switch to a non heart-rate-lowering drug or for appropriate monitoring (e.g., at least overnight monitoring) during treatment initiation, if such a switch cannot be implemented.

- Class Ia and Class III antiarrhythmic drugs have been associated with torsades de pointes in patients with bradycardia. Because initiation of GILENYA* treatment results in decreased heart rate, GILENYA* should not be used concomitantly with these drugs.

Extended Monitoring:

- Should a patient require pharmacologic intervention during the first dose observation, continuous overnight monitoring (e.g., continuous ECG monitoring) in a medical facility should be instituted and the first dose monitoring strategy should be repeated when the second dose of GILENYA* is administered.

  Additional monitoring until the finding has resolved is also required:

  - if the heart rate at 6 hours post-dose is <45 bpm (or is the lowest value post-

dose),

- if the ECG at 6 hours after the first dose shows new-onset second-degree or higher grade AV block, or
- if the ECG shows a QTc interval ≥500 msec at any time.

Re-initiation of Therapy Following Discontinuation

If GILENYA* therapy is discontinued for more than 2 weeks, after the first month of treatment, the effects on heart rate and AV conduction may recur on reintroduction of GILENYA* treatment and the same precautions as for initial dosing should apply (i.e., monitor for at least 6 hours after the first dose). Within the first 2 weeks of treatment, first dose procedures are recommended after interruption of one day or more, during week 3 and 4 of treatment first dose procedures are recommended after treatment interruption of more than 7 days.

This communication follows up a 2012-02-27 Health Canada information update (see http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2012/2012_28-eng.php). For the complete changes to prescribing information, see the full Product Monograph, which may be accessed on the Health Canada website, at http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php.

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 cardiovascular event or other serious or unexpected adverse reactions in patients receiving GILENYA* should be reported to Novartis or Health Canada.

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Phone: 1-800-363-8883 (Medical Information)

To correct your mailing address or fax number, contact Novartis Pharmaceuticals Canada Inc.

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario K1A 0K9

The Reporting Forms, postage paid labels, and Guidelines can be found on the MedEffect™ Canada Web site in the Adverse Reaction Reporting section (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php). The Reporting Form is also in the *Canadian Compendium of Pharmaceuticals and Specialties.*

For other health product inquiries related to this communication, please contact Health Canada at:
Marketed Health Products Directorate
E-mail: mhpd_dpsc@hc-sc.gc.ca
Telephone: 613-954-6522
Fax: 613-952-7738

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

Sincerely,

Jean Godin, M.D.
Chief Scientific Officer and Vice-President Clinical and Regulatory Affairs

*GILENYA is a registered trademark.

References:

1. Calculation of patient-years derived from data supplied by IMS Health Canada Inc. – IMS Santé Canada Inc. (IMS)
2. Patient number derived from data supplied by the GILENYA* Go Program™