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Important Safety Information on GILENYA (fingolimod) and the Risk of Liver Injury

NOVARTIS

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Audience
Healthcare professionals including neurologists, pediatricians, family physicians, general practitioners, nurses and pharmacists.

Key messages

- **Cases of clinically significant liver injury, including acute liver failure requiring liver transplant, have been reported in patients treated with GILENYA (fingolimod).**
- **Healthcare professionals are advised to:**
  - **perform liver function tests, including liver transaminases and bilirubin, before starting treatment, at months 1, 3, 6, 9, 12 during the first year of treatment, and at regular intervals thereafter until 2 months after GILENYA discontinuation.**
  - **monitor patients for signs and symptoms of liver injury, such as unexplained vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine, during treatment with GILENYA. Promptly check liver transaminases and bilirubin if there are signs and symptoms suggestive of liver injury.**
  - **perform more frequent liver function monitoring, or interrupt treatment with GILENYA, if liver transaminases and bilirubin rise above specific levels (see Table in the Information for healthcare professionals section).**
  - **monitor patients with mild or moderate liver disease more closely.**
- **The Canadian Product Monograph (CPM) for GILENYA has been updated to include this revised guidance for monitoring liver function and criteria for treatment interruption and/or discontinuation. Health Canada will work with the manufacturers of generic versions of fingolimod to update their respective CPMs.**

What is the issue?
Post-market cases of clinically significant liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, have been reported in multiple sclerosis (MS) patients treated with GILENYA. Some of these cases have resulted in

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acute liver failure requiring liver transplant.

Products affected
GILENYA, fingolimod capsules, 0.25 mg and 0.5 mg (as fingolimod hydrochloride).

Other products affected by this risk information include all generic fingolimod capsules 0.5 mg (as fingolimod hydrochloride).

Background information
GILENYA is indicated as monotherapy for the treatment of adults 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 MS.

GILENYA is also indicated as monotherapy for the treatment of pediatric patients between 10 and 18 years of age with relapsing MS to reduce the frequency of clinical exacerbations.

The most recent periodic review of international safety data identified cases of liver failure, some requiring liver transplant, in patients treated with GILENYA. Other cases of clinically significant liver injury were also reported in patients treated with GILENYA. Signs of liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, have appeared shortly following the initiation of treatment as well as after prolonged use.

During clinical trials, an increase in hepatic enzymes was identified as a very common adverse drug reaction associated with GILENYA. Given the seriousness and severity of recently reported post-market cases, the Canadian Product Monograph (CPM) for GILENYA has been updated to further inform on the risk of liver injury and to include revised guidance for monitoring liver function and criteria for treatment interruption and/or discontinuation.

Information for consumers

GILENYA (also known as fingolimod) is used to treat adults with the relapsing and remitting form of multiple sclerosis (MS). MS is an unpredictable, often disabling disease of the brain and spinal cord (central nervous system). GILENYA is generally recommended for MS patients who have not responded well to, or cannot tolerate, one or more of the other therapies for MS.

GILENYA is also used to treat children and adolescents between 10 and 18 years of age with the relapsing form of MS.

GILENYA may cause liver damage. Patients should have blood tests done to check their liver function before they start taking GILENYA and periodically during treatment. Patients should call their doctor immediately if they experience symptoms

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of liver injury such as nausea, vomiting, stomach pain, tiredness, loss of appetite, yellowing of the skin or eyes, or dark urine.

Patients should discuss any questions or concerns about this information with their healthcare professional.

Information for healthcare professionals

Healthcare professionals are advised to:

- perform liver function tests, including liver transaminases and bilirubin, before starting treatment with GILENYA, at months 1, 3, 6, 9, 12 during the first year of treatment, and at regular intervals thereafter until 2 months after GILENYA discontinuation.
- monitor patients for signs and symptoms of liver injury, such as unexplained vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine, during treatment with GILENYA.
- promptly check liver transaminases and bilirubin in the presence of signs and symptoms suggestive of liver injury.
- monitor patients with mild or moderate liver disease more closely as they are at an increased risk of developing elevated liver enzymes during GILENYA treatment.

Healthcare professionals are advised to take the following actions based on the laboratory values or signs or symptoms of liver injury described in the table below:

LABORATORY VALUES/SIGNS OR SYMPTOMS OF LIVER INJURY	**ACTION**
Liver transaminases elevation to >3 times ULN*	Perform more frequent liver function monitoring, including ALP measurement.
Liver transaminases elevation to >5 times ULN*(with repeated confirmation)	Interrupt treatment with GILENYA

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ALT >3 times the reference range with serum total bilirubin > 2 times the reference range	Interrupt treatment with GILENYA
A plausible alternative cause for the signs and symptoms of liver injury cannot be established	Discontinue treatment with GILENYA

*the upper limit of normal

Action taken by Health Canada

Health Canada, in collaboration with Novartis Pharmaceuticals Canada Inc., updated the Canadian Product Monograph (CPM) for GILENYA. Health Canada will work with manufacturers of generic versions of fingolimod to update their respective CPMs.

Health Canada is communicating this important safety information to healthcare professionals and Canadians via the Recalls and Safety Alerts Database on the Healthy Canadians Web Site. This communication will be further distributed through the MedEffect™ e-Notice email notification system, as well as through social media channels, including LinkedIn and Twitter.

Report health or safety concerns

Health Canada's ability to monitor the safety of marketed health products depends on healthcare professionals and consumers reporting adverse reactions and medical device incidents. Any case of liver injury or other serious or unexpected side effects in patients receiving GILENYA should be reported to Novartis Pharmaceuticals Canada Inc., to the respective generic fingolimod manufacturer, or to Health Canada.

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www.novartis.ca/en/our-products/pharmaceuticals

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 Health Canada by:

- Calling toll-free at 1-866-234-2345; or
- Visiting MedEffect Canada's Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax.

For other health product inquiries related to this communication, contact Health Canada at:

Marketed Health Products Directorate
E-mail: hc.mhpd-dpsc.sc@canada.ca
Telephone: 613-954-6522
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