Important Safety Information on PrREVOLADE® (eltrombopag) and Risk of Severe Hepatotoxicity

NOVARTIS

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Audience
Healthcare Professionals (medical hematologists, hepatologists, and pharmacists) pharmacy associations, nurse associations, medical associations, chiefs of medicine in hospitals, hospital pharmacy chiefs and patient groups.

Key messages

- **REVOLADE administration can cause severe hepatotoxicity and potentially fatal liver injury. Cases of severe drug-induced liver injury with REVOLADE have been reported in patients during clinical trials and post-marketing.**
- **To mitigate the risk of severe hepatotoxicity and potentially fatal liver injury, healthcare professionals should:**
  - **measure serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin prior to initiation of REVOLADE, every 2 weeks during the dose adjustment phase, and then monthly following establishment of a stable dose.**
  - **discontinue REVOLADE if ALT levels:**
    - **increase greater than or equal to 3x upper limit of normal (ULN) in patients with normal liver function or;**
    - **increase greater than or equal to 3x baseline or greater than 5x ULN, whichever is the lower, in patients with elevations in transaminases before treatment.**
- **The Canadian Product Monograph for REVOLADE has been updated to reflect this new safety information**

What is the issue?
A recent review of all clinical trial and post-marketing cases identified five (5) cases fulfilling Hy's law criteria (severe drug-induced liver injury).

Products affected
REVOLADE® (eltrombopag) tablets

Background information
REVOLADE (eltrombopag) tablets are indicated:

- For adult chronic immune thrombocytopenia purpura (cITP) to increase platelet counts in splenectomized patients who are refractory to first-line treatments (e.g. corticosteroids, immunoglobulins). REVOLADE may be considered as second line treatment for adult non-splenectomized patients where surgery is contraindicated,
- To increase platelet counts in thrombocytopenic patients with chronic hepatitis C virus (HCV) infection to allow the initiation and maintenance of interferon-based therapy, and
- For the treatment of adult patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.

A systematic analysis of the different trials in the clinical database (across the entire REVOLADE development program) and the post-marketing safety database was conducted by Novartis Pharmaceuticals Canada Inc. to identify cases fulfilling Hy's Law criteria for drug-induced liver injury (www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/hepatotox_guide_ld-eng.php#a213).

Based on this review, two (2) cases fulfilling Hy's law criteria were identified in adult cITP patients; three (3) further cases were identified in patients treated for other, non-approved indications. The elevation of laboratory values typically occurred within three (3) months of initiation; in all five (5) cases the event resolved following REVOLADE discontinuation. In clinical trials in patients with chronic HCV infection, 11 patients treated with REVOLADE (1%) experienced drug-induced liver injury.

Information for consumers
REVOLADE may damage your liver and cause serious, even life-threatening, illness.

Talk to your doctor, pharmacist or nurse before taking REVOLADE (eltrombopag) and let them know if you have liver problems, as this can increase the risk of liver injury. REVOLADE should not be used if you have severe liver impairment.

You must have blood tests to check your liver before you start taking REVOLADE and during treatment. Your doctor will order the blood tests and any other tests required. In some cases, REVOLADE treatment may need to be stopped.

Information for healthcare professionals
The Canadian Product Monograph for REVOLADE has been updated to reflect the risk of severe hepatotoxicity (i.e., severe hepatotoxicity and potentially fatal liver injury) in the existing Hepatotoxicity section under the Warnings and Precautions and to add an adverse drug reaction to the Adverse Reactions section.

In addition, an upper limit on the extent of ALT elevation in patients with elevated ALT at baseline was added, to prohibit continuation of REVOLADE in patients with

pre-existing hepatic disease, and in line with discontinuation criteria in the pivotal trials conducted in the approved indications.

Healthcare professionals should measure serum ALT, AST and bilirubin prior to initiation of REVOLADE, every 2 weeks during the dose adjustment phase, and then monthly following establishment of a stable dose. Healthcare professionals should discontinue REVOLADE if ALT levels:

- increase greater than or equal to 3x ULN in patients with normal liver function or;
- increase greater than or equal to 3x baseline or greater than 5x ULN, whichever is the lower, in patients with elevations in transaminases before treatment and that are:
    - progressive, or
    - persistent for greater than or equal to 4 weeks, or
    - accompanied by increased direct bilirubin, or
    - accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation.

Action taken by Health Canada

Health Canada, in collaboration with Novartis Pharmaceuticals Canada Inc. has updated the Canadian Product Monograph to reflect this new safety information. Health Canada is communicating this information to healthcare professionals via the Recalls and Safety Alerts Database on the Healthy Canadians Web Site (www.healthycanadians.gc.ca/recall-alert-rappel-avis/index-eng.php). This communication will be further distributed through the MedEffect™ e-Notice email notification system.

Report health or safety concerns

Managing marketed health product-related side effects depends on health care professionals and consumers reporting them. Any case of drug-induced liver injury or other serious or unexpected side effects in patients receiving REVOLADE should be reported to Novartis Pharmaceuticals Canada Inc. or Health Canada.

Novartis Pharmaceuticals Canada Inc.
385 Bouchard Blvd.
Dorval, Quebec, H9S 1A9
1-800-363-8883
www.novartis.ca

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 (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php)

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

Marketed Health Products Directorate
E-mail: mhpd_dpsc.public@hc-sc.gc.ca
Telephone: 613-954-6522
Fax: 613-952-7738

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