Important Safety Information
OFEV (nintedanib) – Risk of Drug-Induced Liver Injury and the Need for Regular Monitoring of Liver Function

Boehringer Ingelheim

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Audience
Healthcare professionals including respirologists, internal medicine physicians, gastroenterologists, hepatologists, family physicians, emergency room physicians and pharmacists.

Key messages

- **Cases of drug-induced liver injury (DILI), including one fatal outcome, have been reported in patients treated with OFEV (nintedanib). In most of these cases, the DILI was reversible when the dose was reduced or treatment was stopped. The majority of the cases occurred within the first three months of starting OFEV. Therefore, particular attention is recommended during this initial period.**

- **Healthcare professionals are advised to monitor patients' liver transaminases and bilirubin levels:**
  - **just before starting treatment;**
  - **at regular intervals (e.g., monthly) during the first three months of treatment; and**
  - **periodically thereafter (e.g., at each patient visit) or as clinically indicated.**

- **Healthcare professionals are reminded that:**
  - **If the transaminase (AST or ALT) levels are greater than three times the upper limit of normal (ULN), OFEV dosage should be reduced or treatment interrupted.**
  - **OFEV therapy should be permanently discontinued if any liver test elevations are associated with clinical signs or symptoms of liver injury (e.g., jaundice).**

- **Health Canada is working with the manufacturer to include this safety information in the Canadian Product Monograph.**

What is the issue?
Drug-induced liver injuries (DILIs) have been reported in patients treated with OFEV, including one fatal outcome. In most of these cases, the DILI was reversible

when the dose was reduced or treatment was stopped.

Product affected

Brand Name	Medicinal Ingredient	Manufacturer
OFEV®	nintedanib (as nintedanib esilate)	Boehringer Ingelheim (Canada) Ltd.

Background information
OFEV (nintedanib) is used to treat idiopathic pulmonary fibrosis (IPF).

Cases of DILI have been observed with OFEV treatment in the post-marketing setting since the product was launched in 2014. The overall cumulative IPF patient exposure to OFEV from marketing experience is estimated to be over 32,000 patient-years. As of October 15, 2017, 32 cases of DILI have been reported worldwide in patients treated with OFEV, including one in Canada. In 24 of the 32 cases, the outcome of the DILI events was reported. In the majority (17) of these cases, the DILI event resolved when the dose was reduced or treatment was stopped. In 6 cases, the patient had not recovered at the time of reporting. One case resulted in fatal outcome.

Information for consumers
OFEV is a prescription medicine used to treat idiopathic pulmonary fibrosis (IPF). IPF is a condition in which the tissue in the lungs becomes scarred over time making it difficult to breathe.

In some patients, OFEV has been associated with drug-induced liver injuries (DILIs), which can be serious and life-threatening. Before taking the drug, patients should discuss with their healthcare professional if they have or have had liver problems. Before and during the treatment, patients should have blood tests done to check their liver function.

If patients experience signs of liver injury such as yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, or loss of appetite, they need to stop taking OFEV and seek immediate medical attention. Patients receiving OFEV should also inform their healthcare professional if they experience any side effects.

Information for healthcare professionals
Healthcare professionals are advised to monitor liver transaminases and bilirubin levels:

- just before treatment starts;
- at regular intervals (e.g., monthly) during the first three months of treatment; and
- periodically thereafter (e.g., at each patient visit) or as clinically indicated.

Healthcare professionals are also reminded to:

- reduce OFEV dose or interrupt the therapy when the transaminase (AST

or ALT) levels are greater than 3 times the upper limit of normal (ULN); and
- o permanently discontinue OFEV therapy if any liver test elevations are associated with clinical signs or symptoms of liver injury (such as jaundice).

Action taken by Health Canada
Health Canada is working with the manufacturer to update the Canadian Product Monograph with this safety information.

Health Canada is communicating this important safety information update to healthcare professionals and Canadians 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 update 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 healthcare professionals and consumers reporting them. Any case of drug-induced liver injury (DILI) or other serious or unexpected side effects in patients receiving OFEV should be reported to Boehringer Ingelheim (Canada) Ltd. or to Health Canada.

Boehringer Ingelheim (Canada) Ltd.
5180 South Service Rd.
Burlington, ON, L7L 5H4
Tel: 1 (800) 263-5103 Ext. 87233
Email: PV_local_Canada@boehringer-ingelheim.com

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: mhpd_dpsc@hc-sc.gc.ca
Telephone: 613-954-6522
Fax: 613-952-7738

Sincerely,

Original signed by

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Vice President, Medical and Regulatory Affairs
Boehringer Ingelheim (Canada) Ltd.