



# Health Product InfoWatch

October 2018

## HEALTH PRODUCTS MENTIONED IN THIS ISSUE

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### REPORTING ADVERSE REACTIONS

Canada Vigilance Program  
 Online: [Adverse Reaction and Medical Device Problem Reporting](#)  
 Telephone: 1-866-234-2345  
 Fax or mail: Form available online

### SUBSCRIBE

To receive the Health Product InfoWatch and notifications of health product advisories electronically, subscribe to [MedEffect™ e-Notice](#) or to [MedEffect™ Canada RSS feeds](#).

### Pharmaceuticals and Biologics

- Beta-lactam antibiotics
- EpiPen and EpiPen Jr (epinephrine)
- Fibristal (ulipristal acetate)
- Hydroquinone
- Lenvima (lenvatinib)
- Marvelon 28
- Ocaliva (obeticholic acid)
- Tecentriq (atezolizumab)
- Tromboject (sodium tetradecyl sulfate)
- Valsartan-containing drugs

### Natural Health Products

- “Dr. King’s” homeopathic products

### Other

- Health products containing 2,4-dinitrophenol
- Unauthorized health products

This monthly publication is intended primarily for healthcare professionals and includes information on pharmaceuticals, biologics, medical devices and natural health products. It provides a summary of key health product safety information published in the previous month by Health Canada, as well as a selection of new health product safety information meant to raise awareness. New information contained in this issue is not comprehensive but rather represents a selection of clinically relevant items warranting enhanced dissemination.

## MONTHLY RECAP OF HEALTH PRODUCT SAFETY INFORMATION

The following is a list of [health product advisories](#), [type I recalls](#) as well as [summaries of completed safety reviews](#) published in September 2018 by Health Canada.

<b>Beta-lactam antibiotics</b> <a href="#">Summary Safety Review</a>	<p>This safety review evaluated the risk of Severe Cutaneous Adverse Reactions (SCAR) associated with beta-lactam antibiotics. Health Canada's review of the available information found a possible link. Health Canada will be working with the manufacturers to update the Canadian product monographs of beta-lactam antibiotics (that do not already include SCAR) to inform healthcare professionals and patients about this potential risk.</p>
<b>"Dr. King's" homeopathic products</b> <a href="#">Advisory</a>	<p>Health Canada advised consumers not to use homeopathic and veterinary products made by King Bio Inc. and labelled as "Dr. King's," "Dr King's Natural Pet" or "Natural Pet", due to potential microbial contamination. The products are being recalled by the Canadian distributor, Ecotrend Ecologics Ltd., and include products for children, adults and pets. They are promoted for various uses, including flu relief, respiratory care, stress control, arthritis and joint pain.</p>
<b>EpiPen and EpiPen Jr (epinephrine)</b> <a href="#">Advisory</a>	<p>In a very small number of cases, some EpiPen (0.3 mg) and EpiPen Jr (0.15 mg) auto-injector devices may not slide out of their carrier tube easily, or at all. This could delay or prevent emergency treatment. The issue is with the device label, and not with the device itself or the epinephrine that it delivers. Products are not being recalled by Pfizer, as the risk can be mitigated by pharmacists and patients by checking devices before an emergency situation arises to make sure they slide easily out of their carrier tube.</p>
<b>Fibristal (ulipristal acetate)</b> <a href="#">Summary Safety Review</a>	<p>This safety review evaluated the risk of serious liver injury associated with Fibristal (ulipristal acetate). Health Canada's review of the available information concluded that there may be a link. Health Canada is working with the manufacturer to better understand the effects of Fibristal on the liver and to update the Canadian product monograph with new restrictions for use and recommendations to monitor liver function. This information will also be communicated to healthcare professionals and Canadians.</p>

<p><b>Health products containing 2,4-dinitrophenol</b></p> <p>Advisory</p>	<p>Canadians should not buy or use health products that contain 2,4-dinitrophenol, more commonly known as DNP, because it is toxic and can cause death. Products containing DNP are primarily marketed towards bodybuilders and are promoted online as a "fat burner" or "shredder" and for weight loss. There are currently no health products containing DNP approved by Health Canada; however some Canadians may have purchased products containing DNP online.</p>
<p><b>Hydroquinone</b></p> <p>Information Update</p>	<p>Health Canada recommended that products for topical use on the skin that contain high concentrations of hydroquinone be used with caution and only under the supervision of a healthcare professional. As of June 30, 2019, products containing hydroquinone greater than 2% will require a prescription from a healthcare practitioner to be sold in Canada.</p>
<p><b>Marvelon 28</b></p> <p>Advisory</p>	<p>Packages of certain lots of Marvelon 28 do not include day-of-the-week stickers. The stickers may be used by women to help them remember if they took their daily pill on a given day. Without these stickers, there may be an increased chance of missing a dose. This issue does not impact the safety or effectiveness of the pills. Merck Canada has distributed day-of-the-week stickers to pharmacies for their customers.</p>
<p><b>Tecentriq (atezolizumab)</b></p> <p>Health Professional Risk Communication</p>	<p>Cases of immune-related nephritis have been reported in patients receiving Tecentriq (atezolizumab) for the treatment of urothelial and lung cancers. Healthcare professionals are advised to monitor kidney function during treatment and withhold treatment in patients who develop moderate (Grade 2) immune-related nephritis; permanently discontinue treatment in patients with severe (Grade 3 and 4) immune-related nephritis; administer corticosteroids and/or additional immunosuppressive agents as clinically indicated to patients who develop immune-related nephritis; and refer patients who develop immune-related nephritis to a kidney specialist. Health Canada is currently working with the manufacturer to include the risk of immune-related nephritis in the Tecentriq Canadian product monograph.</p>
<p><b>Tromboject (sodium tetradecyl sulfate)</b></p> <p>Health Professional Risk Communication</p>	<p>This update replaces the information previously communicated on <a href="#">July 17, 2018</a>, regarding the presence of visible and insoluble particles in Tromboject 1% and 3% vials. When the products must be used for reasons of medical necessity, it is recommended to administer Tromboject 1% and 3% with sterile medical grade polyethersulfone (PES) filters of 0.22 micrometer pore size, and 25 or 33 mm diameter.</p>

<p><b>Unauthorized health products</b></p> <p>Update - Multiple unauthorized health products</p>	<p>Health Canada advised Canadians about various unauthorized health products being sold at retail locations across Canada or online that may pose serious health risks.</p>
<p><b>Valsartan-containing drugs</b></p> <p>Information Update - Estimates of health risks</p> <p>Information Update - Second impurity</p>	<p>Several drugs containing valsartan were recalled by their manufacturers. Impurities, N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA), both classified as probable human carcinogens, were found in the valsartan used in these products. The valsartan was supplied by Zhejiang Huahai Pharmaceuticals. Health Canada also advised Canadians of its health risk assessment related to valsartan products containing NDMA.</p>

## NEW HEALTH PRODUCT SAFETY INFORMATION

*The following topics have been selected to raise awareness and, in some cases, to stimulate reporting of similar adverse reactions.*

### DOSE PRESCRIBING ERROR ALERT

#### Ocaliva (obeticholic acid) – hepatic decompensation and hepatic failure related to dose prescribing errors

Primary biliary cholangitis (PBC) is a rare progressive autoimmune cholestatic liver disease, affecting approximately 11,000 Canadians in 2015.<sup>1</sup> PBC causes the bile ducts to become inflamed, in turn causing a bile build-up in the liver, damaging the liver over time, and eventually leading to cirrhosis.<sup>2</sup> Despite available treatments, PBC progresses to end-stage liver disease in approximately 10% of patients.<sup>1</sup>

Ocaliva (obeticholic acid) is an agonist for the farnesoid X receptor (FXR) and is available on the Canadian market as 5 mg and 10 mg tablets (marketed since May 2017).<sup>3</sup> It is indicated for the treatment of PBC in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. In Canada, Ocaliva has received conditional approval under the Notice of Compliance with Conditions policy, pending the results of trials to verify its clinical benefit.

The dosage of Ocaliva depends on the severity of hepatic impairment. The recommended starting dose is **5 mg once a day** for less severe conditions (non-cirrhotic or compensated Child-Pugh Class A), or **5 mg once a week** for more severe conditions (Child-Pugh Class B or C or patients with a prior decompensation event).<sup>3</sup> Hepatic decompensation and hepatic failure have been reported in patients with PBC when Ocaliva was prescribed at higher doses or administered more frequently than recommended.

As of October 10, 2018, Health Canada received 8 Canadian post-market cases of drug dose prescribing error (3 serious and 5 non-serious) suspected of being associated with Ocaliva. In 4 of these reported cases, Ocaliva was initiated at a 10 mg dose (instead of 5 mg); in the other 4 cases, Ocaliva was administered daily instead of weekly in patients with more severe hepatic conditions.

A *Serious Warnings and Precautions Box* highlighting the risk of **hepatic decompensation and failure** in patients with moderate and severe hepatic impairment has recently been included in the Canadian product monograph for Ocaliva. The *Warnings and Precautions, Adverse Reactions (Post-Market Adverse Drug Reactions), Dosage and Administration, and Patient Medication Information* sections have also been updated in relation to this issue. In addition, the package labels will be updated.

### Key messages for healthcare professionals from the Canadian product monograph:<sup>3</sup>

- In post-marketing reports, hepatic decompensation and failure, in some cases fatal, have been reported in patients with PBC with decompensated cirrhosis or Child-Pugh Class B or C hepatic impairment when Ocaliva was dosed more frequently than recommended.
- Treatment with Ocaliva in patients with moderate and severe hepatic impairment should be initiated and monitored by a healthcare provider with experience managing PBC.
- Prior to the initiation of Ocaliva in patients with suspected cirrhosis, the patient's Child-Pugh classification (A, B, or C) should be assessed in order to determine the appropriate starting dose.
  - A modified dosing regimen of Ocaliva is required for patients with moderate and severe hepatic impairment (Child-Pugh Class B and C) and decompensated cirrhosis.
  - No dosage modification is needed in patients with mild hepatic impairment (Child-Pugh Class A).
- The recommended starting dosage of Ocaliva is 5 mg once weekly for patients with Child-Pugh Class B or C hepatic impairment or a prior decompensation event (see Table 1).
- Patients should be routinely monitored with laboratory and clinical assessments during Ocaliva treatment to determine whether a dosage adjustment is needed. The dosing frequency should be reduced in patients who progress from Child-Pugh A to Child-Pugh Class B or C.

In order to avoid dose prescribing errors between the daily and weekly dosing regimens resulting in potential serious adverse events, prescribers are reminded of the appropriate dosing regimen based on the Child-Pugh classification, and pharmacists are encouraged to confirm that the correct dosage and directions for use are being provided to the patient.

**Table 1: Dosage regimen of Ocaliva by PBC patient population and disease stage**

Staging / classification	Non-cirrhotic or compensated Child-Pugh class A	Child-Pugh class B or C or patients with a prior decompensation event <sup>a</sup>
Starting dosage	5 mg <b>once daily</b>	5 mg <b>once weekly</b>
Dosage titration	For patients who have not achieved an adequate reduction in ALP and/or total bilirubin after <b>first 6 months of treatment</b> and who are tolerating Ocaliva <sup>b</sup> , titrate up to 10 mg <b>once daily</b> to improve response.	For patients who have not achieved an adequate reduction in ALP and/or total bilirubin after <b>first 3 months of treatment</b> and who are tolerating Ocaliva <sup>b</sup> , titrate up to 5 mg <b>twice weekly</b> (at least 3 days apart). Subsequently titrate to 10 mg <b>twice weekly</b> (at least 3 days apart) based on response and tolerability.
Maximum dosage	10 mg <b>once daily</b>	10 mg <b>twice weekly</b> (at least 3 days apart)

<sup>a</sup> Gastro-oesophageal variceal bleeding, new or worsening jaundice, spontaneous bacterial peritonitis, etc.

<sup>b</sup> Prior to dosage adjustment, re-calculate the Child-Pugh classification.

Note: ALP = alkaline phosphatase

#### References

1. Yoshida EM, Thiele S, A Fischer A, et al. Prevalence of primary biliary cholangitis in Canada: First national study (abstract A197). *JCAG* 2018; 1 (Suppl.1) March: 344–5.
2. [Primary Biliary Cholangitis](#). Markham (ON): Canadian Liver Foundation. (accessed 2018 October 1).
3. *Ocaliva (obeticholic acid)* [product monograph]. San Diego (CA): Intercept Pharmaceuticals Inc.; 2018.

## PRODUCT MONOGRAPH UPDATES

The following safety labelling updates, which were recently made to the Canadian product monograph, have been selected for your awareness. A complete list of safety labelling updates is available on Health Canada's [Product Monograph Brand Safety Updates](#). Canadian product monographs can be accessed through Health Canada's [Drug Product Database](#).

### Lenvima (lenvatinib)

The risk of **pneumothorax** has been included in the *Warnings and Precautions*, *Post-Market Adverse Drug Reactions* and *Patient Medication Information* sections of the Canadian product monograph for Lenvima.

#### Key messages for healthcare professionals:<sup>1</sup>

- Fistulas (e.g., gastrointestinal, bronchopleural, tracheo-oesophageal, oesophageal, cutaneous, pharyngeal, female genital tract) have been reported in lenvatinib clinical trials and in post-marketing experience. In addition, pneumothorax has been reported with and without clear evidence of a bronchopleural fistula.
- Some reports of pneumothorax occurred in association with tumor regression or necrosis.

#### Reference

1. *Lenvima (lenvatinib)* [product monograph]. Mississauga (ON): Eisai Limited; 2018.

## HELPFUL LINKS

- [MedEffect™ Canada](#)
- [Recalls and Safety Alerts Database](#)
- [New Safety Reviews](#)
- [Canada Vigilance Adverse Reaction Online Database](#)
- [Drug Product Database](#)
- [Medical Devices Active Licence Listing](#)
- [Licensed Natural Health Products Database](#)
- [The Drug and Health Product Register](#)
- [Drug Shortages Canada](#)

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## Suggestions?

Your comments are important to us. Let us know what you think by reaching us at [HC.infowatch-infovigilance.SC@canada.ca](mailto:HC.infowatch-infovigilance.SC@canada.ca)

Health Canada  
Marketed Health Products Directorate  
Address Locator 1906C  
Ottawa ON K1A 0K9  
Telephone: 613-954-6522  
Fax: 613-952-7738

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*Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.*

*Due to time constraints relating to the production of this publication, information published may not reflect the most current information.*

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