Health Canada Santé Canada

Canada

Health Product
InfoWatch

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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

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

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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.

DRUG AND VACCINE AUTHORIZATIONS AND COMMUNICATIONS FOR COVID-19

New information and recent communications related to authorized COVID-19 vaccines and treatments are highlighted in this section.

Evusheld (tixagevimab and cilgavimab)

Evusheld (tixagevimab and cilgavimab) may not be effective against certain SARS-CoV-2 Omicron subvariants when used as a prophylaxis or treatment for COVID-19. Neutralization data for the following SARS-CoV-2 Omicron subvariants have been added to the Canadian product monograph: Omicron BA.2.75.2, BF.7, BJ.1, BN.1, BQ.1, BQ.1.1, and XBB.

Health Product Risk Communication

Spikevax (COVID-19 Vaccine Moderna)

On January 12, 2023, Health Canada authorized the extension of a booster dose of Spikevax to include adolescents (12 through <18 years of age). A booster dose of 50 mcg may be administered intramuscularly at least 4 months after completion of the primary series in individuals 12 years of age and older.

Authorization with terms and conditions

Safety brief

Paxlovid (nirmatrelvir and ritonavir) and COVID-19 rebound

Paxlovid (nirmatrelvir and ritonavir) is an oral combination antiviral drug that was authorized by Health Canada on January 17, 2022.[1] It is indicated for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Health Canada is aware of cases of "COVID-19 rebound" reported worldwide following the use of Paxlovid.[2] COVID-19 rebound is characterized by a recurrence of COVID-19 symptoms or a new positive viral test after having tested negative. COVID-19 rebound appears to be generally mild in severity and may be a consequence of the natural course of SARS-CoV-2 infection in some people. It has also been observed following treatment with other SARS-CoV-2 antiviral products and in placebo recipients in COVID-19 treatment clinical studies.[2-4]

As of January 4, 2023, Health Canada has received 23 Canadian case reports of potential COVID-19 rebound with the use of Paxlovid in the Canada Vigilance database. Health Canada reviewed these case reports as well as findings from clinical trials and observational studies. Overall, there is no clear evidence to indicate that COVID-19 rebound is Paxlovid-induced. The available information also suggests that COVID-19 rebound does not change the benefits of Paxlovid, which include a reduction in hospitalization or death. The use of Paxlovid continues to be a safe and effective treatment for COVID-19 in outpatients at high-risk for progression to

severe disease. Please consult the following link for more information on the interpretation of suspected adverse reaction data collected by the Canada Vigilance Program.

Healthcare professionals are encouraged to report adverse reactions suspected of being associated with COVID-19 treatments to the Canada Vigilance Program. Health Canada will continue to monitor the safety of Paxlovid and will take appropriate action should new health risks be identified.

References

1. *Paxlovid (nirmatrelvir and ritonavir)* [product monograph]. Kirkland (QC): Pfizer Canada ULC; 2022.
2. COVID-19 Rebound After Paxlovid Treatment. Centers for Disease Control and Prevention; May 24, 2022. Accessed December 13, 2022.
3. Wang L, Berger NA, Davis PB, et al. COVID-19 rebound after Paxlovid and Molnupiravir during January-June 2022. *medRxiv*. Preprint posted online June 22, 2022. Accessed December 22, 2022.
4. Deo R, Choudhary MC, Moser C., et al. Viral and Symptom Rebound in Untreated COVID-19 Infection. *medRxiv.* Preprint posted online August 2, 2022. Accessed December 22, 2022.

ANNOUNCEMENT

Accuracy of pulse oximeters

Health Canada has published safety information on the limitations of the accuracy of pulse oximeter readings, including skin pigmentation limitations. The overview also includes other factors that may affect the accuracy of pulse oximeters, such as how the device is used, environmental conditions and patient medical conditions.

For more information, please visit Health Canada's pulse oximeter webpage.

MONTHLY RECAP OF HEALTH PRODUCT SAFETY INFORMATION

The following is a list of health product advisories, type I recalls and summaries of completed safety reviews published in December 2022 by Health Canada.

For health product advisories related to COVID-19 vaccines and treatments, please see the Drug and vaccine authorizations and communications for COVID-19 section.

Now Kids Vitamin D-3 Type 1 drug recall	One lot of Now Kids Vitamin D-3 was recalled as the affected lot contained active ingredient (cholecalciferol) levels outside of the labelled claim.
Ocaliva (obeticholic acid) Health Product Risk Communication	Ocaliva received a Notice of Compliance with Conditions in May 2017 for the treatment of primary biliary cholangitis (PBC), pending the results of trials to verify its clinical benefit. Clinical studies were not able to confirm the efficacy and safety of Ocaliva in PBC patients with decompensated

	cirrhosis. In addition, cases of hepatobiliary disorders, including hepatic failure and hepatic cirrhosis, have been reported in PBC patients treated with Ocaliva. As a result, Ocaliva is now contraindicated in PBC patients with decompensated cirrhosis (including Child-Pugh Class B or C) or a prior decompensation event, as well as compensated cirrhosis who have evidence of portal hypertension. The Canadian Product Monograph for Ocaliva has been updated to reflect the new contraindication and to include additional warnings based on newly available safety data.
Unauthorized health products Advisory	Health Canada advised Canadians about various unauthorized health products being sold at retail locations across Canada or online that may pose serious health risks.

NEW HEALTH PRODUCT SAFETY INFORMATION

The following topics have been selected to raise awareness and encourage reporting of adverse reactions.

Review article

Methotrexate and hemolytic anemia

Methotrexate has been available in Canada since December 31, 1955. It belongs to a group of medicines known as antimetabolites used to treat certain types of cancers.[1] Methotrexate is also used as an antirheumatic in the treatment of severe forms of psoriasis/psoriatic arthritis, rheumatoid arthritis and seronegative arthritides.

Hemolytic anemia is a condition in which red blood cells (RBCs) are destroyed faster than they can be made.[2] Blood tests usually show an increased number of reticulocytes (immature RBCs) and may also show an increase in unconjugated serum bilirubin and lactate dehydrogenase (LDH) and decreased (or absent) serum haptoglobin.[3,4]

Drug-induced hemolytic anemia is a very rare but potentially lethal adverse drug reaction.[5] The exact incidence is difficult to ascertain because of the difficulty in establishing a clear diagnosis and relationship to a specific agent.[6]

Health Canada looked at the potential risk of hemolytic anemia with methotrexate use as part of the Department's routine surveillance activities. As of November 23, 2022, Health Canada had received 7 reports of hemolytic anemia suspected of being associated with methotrexate use in Canada. Most of the cases did not report information regarding indication, dosage, or formulation used. Overall, these reports provided limited information for assessment and some were confounded by concomitant medications that are already known to cause hemolysis or hemolytic anemia.

Given the limited evidence available at this time, more detailed reports are needed to assess this potential risk involving methotrexate use. Healthcare professionals are encouraged to report to Health Canada any cases of hemolytic anemia suspected of being associated with methotrexate to support continued monitoring and assessment of this risk.

References

1. *Methotrexate tablets (methotrexate)* [product monograph]. Kirkland, (QC): Pfizer Canada ULC, 2019.
2. Hemolytic Anemia. Conditions and diseases. Johns Hopkins Medicine. Accessed January 16, 2023. https://www.hopkinsmedicine.org/health/conditions-and-diseases/hemolytic-anemia
3. Bankowski Z, Bruppacher R, Crusius I, et al, eds. Reporting adverse drug reactions: definitions of terms and criteria for their use. Council for International Organizations of Medical Sciences (CIOMS); 1999.
4. Phillips J, Henderson AC. Hemolytic Anemia: Evaluation and Differential Diagnosis. *Am Fam Physician*. 2018; 98(6):354-61. Accessed January 16, 2023.
5. Renard D, Rosselet A. Drug-induced hemolytic anemia: Pharmacological aspects. *Transfus Clin Biol*. 2017;24(3) :110-14. Accessed January 16, 2023.
6. Greene EM, Hagemann TM. Drug-Induced Hematologic Disorders. In: DiPiro JT, Talbert RL, Yee GC, et al. eds. *Pharmacotherapy: A Pathophysiologic Approach, 10e*. McGraw Hill; 2017. Accessed January 16, 2023.

Product monograph updates

The following safety labelling updates, which were recently made to the Canadian product monographs, have been selected for your awareness. A complete list of safety labelling updates for pharmaceuticals is available on Health Canada's Product monograph brand safety updates page. Canadian product monographs can be accessed through Health Canada's Drug Product Database.

Apomorphine-containing products: Kynmobi (apomorphine hydrochloride) and Movapo (apomorphine hydrochloride)

The *Warnings and Precautions*, *Adverse Reactions (Post-Market Adverse Reactions)*, and *Patient Medication Information* sections of the Canadian product monographs for apomorphine-containing products[*], have been, or will be, updated with the risk of **hemolytic anemia**.

Key messages for healthcare professionals:[1]

- Hemolytic anemia requiring hospitalization has been reported with apomorphine treatment in the post-marketing setting.
- Many of the reported cases included a positive direct antiglobulin test (Coombs test), suggesting a potential immune-mediated hemolysis.
- Hemolytic anemia can appear at any time after apomorphine treatment. If a patient develops anemia while taking apomorphine, consider a workup for hemolytic anemia. If hemolytic anemia occurs, consider discontinuing apomorphine treatment.

Reference

1. *Kynmobi (apomorphine hydrochloride)* [product monograph]. Mississauga (ON): Sunovion Pharmaceuticals Canada Inc.; 2022.

[*] At the time of publication, the Canadian product monograph update for Kynmobi has been completed. Updates for Movapo are ongoing.

Zepzelca (lurbinectedin)

The *Warnings and Precautions*, *Dosage and Administration*, *Adverse Reactions (Post-Market Adverse Reactions)*, and *Patient Medication Information* sections of the Canadian product monograph for Zepzelca have been updated with the risk of **rhabdomyolysis**.

Key messages for healthcare professionals:[1]

- Rhabdomyolysis has been reported in patients treated with Zepzelca.
- Monitor for signs and symptoms of rhabdomyolysis through plasma creatine kinase, or urinary myoglobin levels prior to initiating Zepzelca and periodically during treatment, as clinically indicated.
- If rhabdomyolysis occurs, withhold or permanently discontinue Zepzelca based on severity (see Dosage modifications table). Supportive measures such as parenteral hydration, urine alkalinization and dialysis should be promptly established, as indicated.
- Caution should be taken if medicinal products with known association with rhabdomyolysis (e.g., statins), are administered concomitantly with lurbinectedin, since the risk of rhabdomyolysis may be increased.

Dosage modifications criteria for Zepzelca for rhabdomyolysis

Adverse reaction	Severity[†]	Dosage modification
Rhabdomyolysis	Grade 2	Withhold Zepzelca until Grade ≤1 *and* Resume Zepzelca at same dose
	Grade ≥3	Permanently discontinue Zepzelca

Reference

1. *Zepzelca (lurbinectedin)* [product monograph]. Mississauga (ON): Jazz Pharmaceuticals Canada Inc., 2022.

[†] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI -CTCAE) version 4.0.

Helpful links

- MedEffect™ Canada
- Recalls and Safety Alerts Database
- New Safety and Effectiveness 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
- Medical device shortages: List of shortages and discontinuations
- Stop Illegal Marketing of Drugs and Devices
- List of drugs for exceptional importation and sale
- Coronavirus disease (COVID-19)
- COVID-19 list of authorized drugs, vaccines and expanded indications
- COVID-19 vaccines and treatments portal
- Reported side effects following COVID-19 vaccination in Canada

Suggestions?

Your comments are important to us. Let us know what you think by reaching us at: infowatch-infovigilance@hc-sc.gc.ca

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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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