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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HEALTH PRODUCTS MENTIONED IN THIS ISSUE

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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.

Safety brief

Drug-drug interaction with Paxlovid and tacrolimus

Key messages for healthcare professionals:[1]

- Avoid use of Paxlovid in patients taking immunosuppressants when close monitoring of immunosuppressant concentrations is not feasible.
- If co-administered, dose adjustment of the immunosuppressant and monitoring for immunosuppressant concentrations and immunosuppressant-associated adverse reactions is recommended.
- Refer to the Paxlovid product label and individual immunosuppressant product label for further information and obtain expert consultation from the patient's immunosuppressive therapy specialist.
- Consider the potential for drug interactions prior to and during Paxlovid therapy; review concomitant medications during Paxlovid therapy and monitor for the adverse reactions associated with the concomitant medications.

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 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.

Paxlovid is an inhibitor of cytochrome P450 (CYP) 3A and may increase plasma concentrations of drugs that are primarily metabolized by CYP3A.[1]

Tacrolimus is an immunosuppressant drug used for the treatment or prevention of organ transplant rejection and the treatment of rheumatoid arthritis. Tacrolimus is metabolized by CYP3A.[2] It also has a narrow therapeutic index, which means that small differences in dose or blood concentration may lead to serious adverse drug reactions that may be life-threatening.[3,4]

Canadian cases of serious adverse events following a drug-drug interaction between Paxlovid and tacrolimus have been reported to Health Canada. In some cases, the tacrolimus levels were observed to go up rapidly and to very high levels. High tacrolimus levels can lead to adverse effects such as acute kidney injury and increased susceptibility to severe infections due to over-immunosuppression.[2,5] International cases have also been reported in the literature.[5,6]

The *Drug-Drug Interactions* section of the Canadian product monograph for Paxlovid has been updated with information on the risk of **Paxlovid drug-drug interaction with immunosuppressants (including cyclosporine, everolimus, sirolimus and tacrolimus).** Healthcare professionals are encouraged to report adverse reactions suspected of being associated with Paxlovid 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. *Prograf (tacrolimus)* [product monograph]. Markham (ON): Astellas Pharma Canada, Inc., 2022
3. Yu L, Jiang W, Zhang X, et al. Novel bioequivalence approach for narrow therapeutic index drugs. *Clin Pharmacol Ther*. 2015 Mar;97(3):286-291.
4. Gantar K, Škerget K, Mochkin I, Bajc A. Meeting Regulatory Requirements for Drugs with a Narrow Therapeutic Index: Bioequivalence Studies of Generic Once-Daily Tacrolimus. *Drug Healthc Patient Saf*. 2020 Sep 8;12:151-160.
5. Prikis M, Cameron A. Paxlovid (Nirmatelvir/Ritonavir) and Tacrolimus Drug-Drug Interaction in a Kidney Transplant Patient with SARS-2-CoV infection: A Case Report. *Transplant Proc*. 2022 Jul-Aug; 54(6):1557-1560.
6. Lindauer KE, Hamel AG. Case Report: Nirmatrelvir/Ritonavir and Tacrolimus in a Kidney Transplant Recipient With COVID-19. *Am Fam Physician*. 2022 Jun 1;105(6):569-570.

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 February 2023 by Health Canada.

APO-Amitriptyline Advisory	Apotex Inc. recalled 1 lot of APO-Amitriptyline 10 mg tablets due to the presence of N-nitrosodimethylamine (NDMA), a nitrosamine impurity, above the acceptable limit.
Intraocular eye lens Advisory	Health Canada warned that intraocular lenses are not licensed to replace a patient's natural, healthy lens (without cataracts) and that their use for this purpose comes with risks that may outweigh the benefits.
Rocuronium-containing products Summary Safety Review	This safety review evaluated the risk of mydriasis associated with the use of rocuronium-containing products. Health Canada's review of the available information found a link between the use of rocuronium and the risk of mydriasis in mechanically ventilated adult patients with systemic infection, and in newborn infants undergoing surgery. Mydriasis is expected to reverse when rocuronium is discontinued. Health Canada will work with the manufacturers to update the Canadian product monographs for rocuronium-containing products to include the risk of mydriasis.

Unauthorized health products Unauthorized Kobayashi Eyebon Eye Wash Unauthorized prescription and controlled drugs Unauthorized prescription drug called Solmux Unauthorized products may pose serious health risks	Health Canada advised Canadians about various unauthorized health products being sold at retail locations across Canada or online that may pose serious health risks.
Zejula (niraparib) Health Product Risk Communication	Currently available data from the Phase III, ENGOT-OV16/NOVA study is suggesting that median overall survival of patients treated with Zejula may be lower than expected in the non-g*BRCA*mut patient population. GlaxoSmithKline has notified Health Canada that the company will be submitting additional overall survival data. Health Canada will review all available overall survival data and further communicate if any actions are needed.

NEW HEALTH PRODUCT SAFETY INFORMATION

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

Product monograph update

The following safety labelling update, which was recently made to the Canadian product monograph, has 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.

Spravato (esketamine)

The *Warnings and Precautions, Adverse Reactions (Post-Market Adverse Reactions),* and *Drug-Drug Interactions* sections of the Canadian product monograph for Spravato have been updated with post-market information about the risk of **respiratory depression**.

Key messages for healthcare professionals:[1]

- Respiratory depression has been observed in rare cases with Spravato during post-marketing use.
- Most cases occurred in combination with other central nervous system (CNS) depressants and in patients with comorbidities such as obesity, anxiety, cardiovascular and respiratory conditions. These events were transient in nature and resolved after verbal/tactile stimulation or supplemental oxygen.

- Healthcare professionals are advised to closely monitor patients for respiratory depression when Spravato is used concomitantly with CNS depressants.

Reference

1. *Spravato (esketamine)* [product monograph]. Toronto (ON). Janssen Inc., 2023.

Notice of market authorization with conditions

*A Notice of Compliance with Conditions (NOC/c) is a form of market authorization with conditions granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada. Communicating a NOC/c is intended to raise awareness on the details of the drug and the type of authorization granted.*

Healthcare professionals are encouraged to report to Health Canada any adverse reactions suspected of being associated with marketed health products, including drugs authorized under the NOC/c policy.

The content of these notices reflects current information at the time of publication. Conditions associated with the NOC/c will remain until they have been fulfilled and authorized by Health Canada. For the most up-to-date information, consult Health Canada's NOC database.

Carvykti (ciltacabtagene autoleucel): Authorization with conditions

Health Canada has issued a Notice of Compliance, under the NOC/c policy, for Carvykti (ciltacabtagene autoleucel), cell suspension in infusion bag, 0.5-1.0x10^6 CAR-positive viable T-cells per kg body weight with a maximum of 1x10^8 CAR-positive viable T-cells, for intravenous infusion. Carvykti is indicated for the treatment of adult patients with multiple myeloma, who have received at least three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody, and who are refractory to their last treatment. Patients should be advised of the conditional market authorization for this indication.

For the complete prescribing information and information available for patients/caregivers, please consult the Carvykti Canadian product monograph. The product monograph can be accessed through Health Canada's Drug Product Database, the Janssen Inc. website or by contacting Janssen Inc. at 1-800-567-3331. Contact the company for a copy of any references, attachments or enclosures.

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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