Health Canada Santé Canada

Canada

Health Product InfoWatch

November 2024

Contents

REPORTING ADVERSE REACTIONS

Canada Vigilance Program
Online: Adverse Reaction and Medical Device Problem Reporting
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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.

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 drug recalls and summaries of completed safety reviews published in October 2024 by Health Canada.

Apo-Amitriptyline and Elavil

Affected lots of Apo-Amitriptyline and Elavil were recalled as they exceeded or may have exceeded the interim acceptable intake limit for *N*-nitroso-nortriptyline (NNORT), an impurity.

Type 1 drug recall: Apo-Amitriptyline
Type 1 drug recall: Elavil

Methotrexate Injection BP

Given the shortage of Methotrexate Injection BP (without preservative), 25 mg/mL in Canada, and to maintain continuity of supply, Health Canada has authorized the exceptional, temporary importation and sale of US-authorized Methotrexate for Injection, USP (preservative free) with English-only labels by Fresenius Kabi Canada Ltd. There are differences in the dosage form, the need for reconstitution and concentration, among other characteristics, which are important to note.

Health Product Risk Communication: Methotrexate Injection BP

Unauthorized Health Products

Health Canada advised Canadians about various unauthorized health products being sold at retail locations across Canada or online that may pose serious health risks.

Advisory: Unauthorized sexual enhancement products

NEW HEALTH PRODUCT SAFETY INFORMATION

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

Review article

Pseudoephedrine-containing products and the risk of posterior reversible encephalopathy syndrome and reversible cerebral vasoconstriction syndrome

Key points

- Health Canada's review of the available information confirmed that there is a rare risk of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS) associated with the use of pseudoephedrine-containing products, supporting the findings from the European Medicines Agency's assessment.
- Health Canada recommends that the labels of natural health products and non-prescription drugs containing pseudoephedrine include information on the risks of PRES and RCVS and measures to reduce

the risks. These risks are adequately labelled on prescription pseudoephedrine-containing products in Canada.
- Although considered rare, in the absence of early intervention, these conditions can have serious consequences, such as intracranial hemorrhage, ischemic stroke and death. Uncontrolled or severe hypertension and kidney disease or failure are considered important risk factors.
- Healthcare professionals should advise patients to discontinue the use of any pseudoephedrine-containing products immediately and seek medical attention if they develop signs or symptoms of PRES or RCVS, such as severe headaches with sudden onset or thunderclap headaches, nausea, vomiting, confusion, seizures, and visual disturbances.
- Healthcare professionals are encouraged to report any adverse reactions suspected of being associated with pseudoephedrine-containing products to the Canada Vigilance Program.

Pseudoephedrine is a decongestant found in marketed natural health products, non-prescription and prescription drugs. It works by stimulating alpha-adrenergic receptors, resulting in vasoconstriction in respiratory tissues.[1] It has a lesser effect on beta-adrenergic receptors. Pseudoephedrine is commonly used, alone or in combination with other medicines, to relieve nasal congestion associated with acute, upper respiratory tract infections and allergic rhinitis.

Posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS) are rare and distinct neurological syndromes with some overlapping features.[2-4] They are serious conditions affecting the cerebral blood vessels. PRES is primarily associated with reversible cerebral edema and symptoms like headaches, seizures, visual disturbances, and symptoms of encephalopathy such as confusion and altered consciousness. RCVS is characterized by reversible arterial constriction, leading to a variety of neurological symptoms including severe “thunderclap” headaches (which peak rapidly), and potentially intracranial hemorrhage, ischemic stroke and rarely, death. Their pathophysiology is linked to the dysregulation of cerebral vascular tone, possibly caused by sudden increases in blood pressure or exposure to certain vasoactive agents. Uncontrolled or severe hypertension and kidney disease or failure are considered important risk factors. PRES and RCVS can occur simultaneously.

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) conducted a safety review in 2023 which concluded that pseudoephedrine-containing products are associated with the risks of PRES and RCVS.[5,6] This conclusion was made after an evaluation of all available evidence, including pharmacovigilance databases and the medical literature. The review found 34 cases where there was a ‘probable’ or ‘possible’ link between individuals using pseudoephedrine-containing products and the development of PRES or RCVS. There were no fatal cases reported, and most cases resolved following discontinuation of the medication and appropriate treatment.

In light of the EMA’s conclusions, Health Canada conducted its own assessment for all products containing pseudoephedrine (i.e., natural health products, non-prescription and prescription drugs) to determine the need for new or modified existing measures to mitigate the risk in the Canadian context.

As of April 30, 2024, Health Canada has not received any reports of PRES or RCVS in association with the use of pseudoephedrine-containing products in Canada. Additionally, no Canadian cases were identified in the published scientific and medical literature. Although no Canadian cases were identified, Health Canada concurs with the EMA’s findings and conclusions that pseudoephedrine-containing products are associated with the risks of PRES and RCVS.

Health Canada recommends enhancing awareness of the rare, but serious, risks of PRES and RCVS through communication to stakeholders, and product labelling revisions for natural health products and non-prescription drugs containing pseudoephedrine. The Canadian Product Monographs of prescription drugs containing pseudoephedrine include warnings about the risks of PRES and RCVS and do not require revision.

Recognizing the signs, symptoms, and risk factors for PRES and RCVS is important for preventing and managing their severe complications. Early intervention, through cessation of the triggering agent, and treatment of symptoms and aggravating factors such as hypertension, may improve chances of reversibility and reduce the risks of serious sequelae, such as intracranial hemorrhage and ischemic stroke.[2-4]

Healthcare professionals are reminded to ask patients about the use of any non-prescription drugs or natural health products. They should advise patients to discontinue the use of any pseudoephedrine-containing products immediately and seek medical attention if they develop signs or symptoms of PRES or RCVS. Any adverse reactions suspected of being associated with pseudoephedrine-containing products should be reported to the Canada Vigilance Program. Health Canada will continue to monitor the risks of PRES and RCVS associated with these products and will take appropriate action, as required, to mitigate the risks to Canadians.

References

1. Pseudoephedrine drug information. Lexicomp. UpToDate. Accessed August 27, 2024.
2. Geocadin RG. Posterior reversible encephalopathy syndrome. *N Engl J Med*. 2023;388(23):2171-8. doi:10.1056/NEJMra2114482
3. Ando Y, Ono Y, Sano A, Fujita N, Ono S. Posterior reversible encephalopathy syndrome: A review of the literature. *Intern Med.* 2022;61(2):135-41. doi:10.2169/internalmedicine.7520-21
4. Nesheiwat O, Al-Khoury L. Reversible cerebral vasoconstriction syndromes. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. Updated June 14, 2024.
5. European Medicines Agency. Pseudoephedrine-containing medicinal products Article-31 referral - Assessment report. Accessed August 21, 2024.
6. European Medicines Agency. Pseudoephedrine-containing medicinal products. Accessed August 21, 2024.

Product monograph update

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

Brilinta (ticagrelor) and Crestor (rosuvastatin calcium)

The *Drug Interactions* and *Patient Medication Information* sections of the Canadian product monographs for Brilinta (ticagrelor) and Crestor (rosuvastatin calcium) have been updated with information on the risk of **myopathy including rhabdomyolysis** as a result of a drug-drug interaction involving these two products.

Key messages for healthcare professionals:[1,2]

- When co-administered, ticagrelor has been shown to increase rosuvastatin concentrations.
- The increase in rosuvastatin concentrations may increase the risk of myopathy including rhabdomyolysis.
- Consideration should be given to the benefits of prevention of major adverse cardiovascular events by use of rosuvastatin and the risks with increased rosuvastatin plasma concentrations.

References

1. *Brilinta (ticagrelor)* [product monograph]. Mississauga (ON): AstraZeneca Canada Inc.; 2024.
2. *Crestor (rosuvastatin calcium)* [product monograph]. Mississauga (ON): AstraZeneca Canada Inc.; 2024.

Helpful links

- 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 Portal
- Drug Shortages Canada
- Medical device shortages
- COVID-19 vaccines and treatments portal

Contact us

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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.

ISSN: 2368-8025
Cat.: H167-1E-PDF
Pub.: 240000