Health Canada Santé Canada

Canada

Health Product InfoWatch

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REPORTING ADVERSE REACTIONS

Canada Vigilance Program
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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.

CORONAVIRUS DISEASE (COVID-19)

For the most up-to-date information on COVID-19, please visit the Government of Canada Coronavirus disease (COVID-19) Web site **Canada.ca/coronavirus**, which includes a dedicated section for healthcare professionals and for the health product industry.

The COVID-19 vaccines and treatments portal provides information for consumers, healthcare professionals and researchers on vaccines and treatments authorized for COVID-19.

For information about adverse events following immunization that individuals have reported after receiving a COVID-19 vaccine in Canada, new safety signals or other safety updates, please visit the COVID-19 vaccine safety in Canada webpage, which is updated weekly.

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.

Covifenz (COVID-19 Vaccine)

Covifenz was authorized by Health Canada on February 24, 2022 for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 to 64 years of age. Covifenz, which is manufactured by Medicago, is authorized as a two-dose regimen to be administered 21 days apart.

Authorization with terms and conditions

Nuvaxovid (COVID-19 Vaccine)

Nuvaxovid was authorized by Health Canada on February 17, 2022 for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older. In order to provide rapid access to Nuvaxovid in the context of the global pandemic, Novavax, Inc. will distribute product vials, cartons and package inserts that are in English-only for a period of time. The English-only vial and carton labels are missing some important Canadian-specific information normally found on Health Canada approved labels.

Health Professional Risk Communication

Omicron Variant and COVID-19 Treatments: Sotrovimab update

On March 25, 2022, the U.S. Food & Drug Administration announced that, based on available evidence, the authorized dose of sotrovimab, 500 mg, is unlikely to be effective against the SARS-CoV-2 Omicron BA.2 variant. In vitro pseudovirus neutralization assays indicate that sotrovimab retains neutralization potency against the Omicron BA.1 variant. Health Canada is working with the manufacturer to review available data, in a timely manner, and take appropriate action(s) as deemed necessary.

Spikevax (COVID-19 Vaccine Moderna)

Spikevax was authorized by Health Canada on March 17, 2022 for the extension of the indication to include active immunization to prevent coronavirus disease 2019 (COVID-19) in individuals 6 years to 11 years of age.

Authorization with terms and conditions

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 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.

Baxter Corporation's MiniCap Extended Life Peritoneal Dialysis Transfer Sets Advisory	Health Canada advised patients who use MiniCap Extended Life Peritoneal Dialysis Transfer Sets, manufactured by Baxter Corporation, that direct contact between the sets and certain cleaning products, including hand sanitizers and solvents, may damage the sets. Damaged sets could leak or crack, which may cause microbial contamination leading to the development of peritonitis in some cases.
Beovu (brolucizumab) Health Professional Risk Communication	An increased incidence of intraocular inflammation, including retinal vasculitis and retinal vascular occlusion, was observed in patients who received Beovu 6 mg with every 4 weeks dosing beyond the first 3 doses, compared to aflibercept 2 mg every 4 weeks, in neovascular (wet) age-related macular degeneration in the MERLIN study. More intraocular inflammation events were seen among patients who developed anti-brolucizumab antibodies during treatment. Retinal vasculitis and retinal vascular occlusion are immune-mediated events (BASICHR0049 study).

Certain hand sanitizers that may pose health risks Advisory	Health Canada advised Canadians that certain hand sanitizers were recalled due to various safety-related issues, including the presence of ingredients that were not permitted by Health Canada, improper labelling, unauthorized products, and missing safety information.
Methadone Summary Safety Review	This safety review evaluated the risk of hypoglycemia associated with the use of methadone. Health Canada's review of the available information found a possible link. Health Canada will be working with the manufacturers of methadone to update the Canadian product monographs to include the risk of hypoglycemia.
Rapid antigen test kits Advisory	Following an increase in reports to poison control centres, Health Canada advised Canadians about potential risks associated with the misuse, accidental ingestion, or spillage of COVID-19 rapid antigen test kit solutions on the skin.
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 similar adverse reactions.

Review articles

Oral, over-the-counter diphenhydramine-containing products and the risk of serious adverse events in children and adolescents

Key messages

- Serious adverse events have been reported in Canada and internationally with the use of oral, over-the-counter diphenhydramine-containing products in children and adolescents.
- Health Canada reviewed known and potential serious adverse events with the use of oral diphenhydramine-containing products, at both recommended and higher doses, in two pediatric populations: children under 2 (all use) and children under 18 years of age (abuse, misuse or overdose).
- No new safety concerns or changes in the type or frequency of serious adverse events were identified with the use of oral, over-the-counter diphenhydramine-containing products in children and adolescents.

- Health Canada is reminding healthcare professionals that some caregivers may not be aware of the known risks associated with diphenhydramine use. Caregiver education on safe storage and proper supervision is important to prevent accidental unsupervised ingestion and misuse.
- Healthcare professionals are encouraged to report to Health Canada any serious adverse reactions suspected of being associated with the use of diphenhydramine-containing products in children and adolescents, at both recommended and higher doses, to support the ongoing monitoring of this safety issue.

Diphenhydramine is a first-generation antihistamine.[1] Oral, over-the-counter diphenhydramine is authorized for sale in Canada as single ingredient or multi-ingredient products, and is commonly used for the symptomatic relief of seasonal and year-round allergies, the temporary relief of dry cough due to the common cold, and as sleep aids.[2]

Pediatric indications vary depending on patient age and product strength. In 2008, Health Canada announced that cough and cold products, including those containing diphenhydramine, should not be used in children under the age of 6 due to safety concerns. Diphenhydramine-containing products are still authorized for allergy indications in children less than 6 years old.[2] As well, sleep aid products containing diphenhydramine are authorized for children 12 and above.

In recent years, additional concerns have been raised regarding the safety of diphenhydramine. In 2019, the Canadian Society of Allergy and Clinical Immunology published a position statement, recommending the use of newer-generation over first-generation antihistamines for the treatment of allergic rhinitis and urticaria because of the unfavourable risk–benefit profile of first-generation antihistamines.[3]

In September 2020, the U.S. Food & Drug Administration warned that taking higher than recommended doses of diphenhydramine could lead to serious heart problems, seizures, coma, or even death. This Drug Safety Communication followed social media videos posted on the TikTok platform that encouraged the ingestion of large amounts of diphenhydramine to cause hallucinations.[4]

As a precaution, Health Canada carried out a safety review to determine if there was a change in the type and/or frequency of adverse events associated with the use of diphenhydramine-containing products in children and adolescents. The review focused on known and potential serious adverse events in children less than 2 years of age (all use) and in children less than 18 years of age (abuse, misuse or overdose).

Health Canada reviewed the available information from domestic case reports in the Canada Vigilance database, published literature, and information received from industry.

A small number of Canadian case reports contained sufficient information to allow for an assessment. These reports were found to be possibly or probably associated with the use of diphenhydramine, and described adverse reactions such as dyskinesia, delusions, hallucinations, disorientation, dizziness, hyperactivity, dilated pupils, tachycardia, vomiting and seizure. None of the Canadian cases reported a fatal outcome.

Health Canada also reviewed the scientific literature. Many of the serious adverse events reported in children and adolescents involved accidental unsupervised ingestions, caregiver error, and intentional

misuse/overdose.[5-11] These events involved single ingredient diphenhydramine and cough and cold remedies containing diphenhydramine. Doses as low as 2 to 3 times the maximum daily dose were reported to cause severe toxicity resulting in an anticholinergic toxidrome, seizures, rhabdomyolysis, and death from cardiac arrhythmias in children.[12]

The adverse events reported in the Canadian cases and in the literature were consistent with the known safety profile for diphenhydramine.

CONCLUSION

Health Canada's review of the available information found no change in the type or frequency of serious adverse events associated with the use of diphenhydramine-containing products in children and adolescents. There are no new safety concerns to warrant regulatory action at this time.

Caregiver error, accidental unsupervised ingestion, and intentional misuse/overdose of diphenhydramine may lead to serious adverse events in children and adolescents. Caregivers may not be aware of the known risks of diphenhydramine use. Therefore, healthcare professionals are encouraged to discuss with parents and caregivers on safe storage and proper supervision as they are important in preventing accidental unsupervised ingestion and misuse.[8] Parents and caregivers should also be reminded to select child-resistant packaging and to make sure that the cap is properly closed after each use. Medicines should be locked up to prevent accidental poisonings by children and misuse by teens.

Healthcare professionals are encouraged to report to Health Canada any serious adverse reactions suspected of being associated with the use of oral, over-the-counter diphenhydramine-containing products in children and adolescents to support the ongoing monitoring of this safety issue. Information such as dosage, duration of exposure to diphenhydramine, concomitant medications, medical history, and time to onset of adverse reactions are important to be included in the reports, to help Health Canada better assess the safety issue.

References

1. Church MK, Church DS. Pharmacology of antihistamines. *Indian J Dermatol* 2013;58(3):219-24.
2. *Guidance Document: Drug Facts Table for Non-prescription Drugs*. Ottawa (ON): Health Canada; 2017 June 6. (accessed 2021 June 28).
3. Fein MN, Fischer DA, O'Keefe AW, et al. CSACI position statement: Newer generation H1-antihistamines are safer than first-generation H1-antihistamines and should be the first-line antihistamines for the treatment of allergic rhinitis and urticaria. *Allergy Asthma Clin Immunol* 2019;15:61.
4. *Drug Safety Communication - FDA warns about serious problems with high doses of the allergy medicine diphenhydramine (Benadryl)*. Silver Spring (MD): U.S. Food and Drug Administration; 2020 Sept 24. (accessed 2021 June 28).
5. Baker AM, Johnson DG, Levisky JA et al. Fatal diphenhydramine intoxication in infants. *J Forensic Sci* 2003;48(2):425-8.
6. Cole JB, Stellpflug SJ, Gross EA, et al. Wide complex tachycardia in a pediatric diphenhydramine overdose treated with sodium bicarbonate. *Pediatr Emerg Care* 2011;27(12):1175-7.
7. Fitzgerald DP, Bennett E, Mitchell MM, et al. Successful physostigmine reversal of severe anticholinergic toxidrome in a child with diphenhydramine intoxication [abstract 311]. *J Invest Med* 2020;68(2):558.
8. Green JL, Wang GS, Reynolds KM et al. Safety profile of cough and cold medication use in pediatrics. *Pediatrics* 2017;139(6):e20163070.
9. Isbister GK, Prior F, Kilham HA. Restricting cough and cold medicines in children. *J Paediatr Child Health* 2012;48(2):91-8.

10. McKeown NJ, West PL, Hendrickson RG, et al. Survival after diphenhydramine ingestion with hemodialysis in a toddler. *J Med Toxicol* 2011;7(2):147-50.
11. Wang GS, Reynolds KM, Banner W et al. Adverse events related to accidental unintentional ingestions from cough and cold medications in children. *Pediatr Emerg Care* 2020. doi: 10.1097/PEC.0000000000002166.
12. Keshary M, Manga A, Kolovos N. Successful use of ecmo and endoscopic gastric lavage for massive diphenhydramine ingestion. *Critical Care Medicine* 2019;47(1):465.

Ketamine: Off-label use

Ketamine is authorized in Canada under the brand name Ketalar, as an injection for anesthetic-related purposes during diagnostic or surgical procedures.[1] It is also available as a generic product. Ketamine, a controlled substance, is a racemic mixture of two molecules, S-ketamine (esketamine) and R-ketamine (arketamine).[2,3]

Esketamine is authorized in Canada under the brand name Spravato, as a nasal spray, for the treatment of moderate to severe major depressive disorder where patients have not responded to other antidepressants, or where urgent psychiatric care is required.[3] Due to the well-established risks associated with its use, esketamine is only available through a controlled distribution program. The product has specific instructions for distribution in addition to requirements for medication administration and post-administration monitoring by a healthcare professional.

The Canadian product monographs, which are available on Health Canada's Drug Product Database, should be used for complete product reference.

Health Canada has become aware of an increased interest in the off-label use of ketamine for the treatment of different conditions, such as mental illnesses, utilizing various formulations, including compounded products. The risks and benefits of ketamine used for off-label conditions have not been assessed by Health Canada. There are currently clinical trials underway to further characterize the safety and efficacy of ketamine for various therapeutic uses.*

Health Canada would like to provide healthcare professionals with the following safety information for ketamine:

Safety Information

- Ketamine is known to carry the risk of abuse and misuse.[1,2,3] It is also associated with other significant risks including sedation, increased blood pressure, and dissociation or altered level of consciousness.
- Hepatobiliary toxicity as well as urinary and bladder problems have been reported with chronic use of ketamine.[1,2,3]
- Healthcare professionals are encouraged to report any adverse reactions suspected of being associated with ketamine (including off-label use) to the Canada Vigilance Program.

Health Canada will continue to monitor safety information involving ketamine, as it does for all health products on the Canadian market, to identify and assess potential harms. Health Canada will take appropriate and timely action should new health risks be identified.

**A list of ongoing and pending Canadian trials can be found at Health Canada's Clinical Trials Database.*

References

1. Ketalar (ketamine hydrochloride) [product monograph]. Montréal (QC): ERFA Canada 2012 Inc.; 2020.
2. Controlled and Illegal Drugs: Ketamine. Ottawa (ON): Health Canada; 2020 April 3. (accessed 2022 January 26).
3. Spravato (esketamine hydrochloride) [product monograph]. Toronto (ON): Janssen Inc.; 2021.

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.

Lokelma (sodium zirconium cyclosilicate)

The *Warnings and Precautions* and *Patient Medication Information* sections of the Canadian product monograph for Lokelma have been updated with the **risk of x-ray imaging interference**.

Key messages for healthcare professionals:[1]

- Lokelma may be opaque to x-rays and may therefore affect the interpretation of abdominal radiographic results.

Reference

1. *Lokelma (sodium zirconium cyclosilicate)* [product monograph]. Mississauga (ON) AstraZeneca Canada Inc., 2022.

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
- Stop Illegal Marketing of Drugs and Devices
- List of drugs for exceptional importation and sale
- COVID-19: List of authorized drugs, vaccines and expanded indications
- 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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