Health Canada Santé Canada

Canada

Health Product InfoWatch

August 2023

CONTENTS

Monthly recap 2

New information

- ***Review articles***

  Domperidone and psychiatric withdrawal events when used off-label for lactation stimulation 3

  Medication errors with specific mineral supplements: calcium, iron, magnesium, and zinc 4

- ***Product monograph updates***

  Third generation aromatase inhibitors: Arimidex (anastrozole), Aromasin (exemestane), and Femara (letrozole) 7

  Topamax (topiramate) 8

- ***Notice of market authorization with conditions***

  Lynparza (olaparib) 9

  Tecvayli (teclistamab) 9

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

Pharmaceuticals and biologics

0.4% Lidocaine Hydrochloride and 5% Dextrose Injection
0.9% and 3% Sodium Chloride Injection, USP
5% Dextrose Injection, USP
Arimidex (anastrozole)
Aromasin (exemestane)
Domperidone
Femara (letrozole)
Gentamicin(E) Sulfate
Lactated Ringer's Injection
Lynparza (olaparib)
Metronidazole Injection, USP
Tagrisso (osimertinib)
Tecvayli (teclistamab)
Topamax (topiramate)

Natural and non-prescription health products

Mineral Supplements
Rhinaris Nasal Mist

Other

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 and summaries of completed safety reviews published in July 2023 by Health Canada.

Rhinaris Nasal Mist Advisory	The Pendopharm Division of Pharmascience Inc. recalled one lot of Rhinaris Nasal Mist due to the risk of microbial growth.
Tagrisso (osimertinib) Summary Safety Review	This safety review evaluated the risk of rhabdomyolysis and other myopathy-related events including myositis and elevated creatine phosphokinase associated with Tagrisso (osimertinib). Health Canada's review found a possible link. Health Canada is working with the manufacturer to update the Canadian product monograph for Tagrisso to include a warning about reported cases of rhabdomyolysis, myositis and elevated creatine phosphokinase.
Unauthorized health products Unauthorized health products seized from T&T Supermarket in North York, Ontario Unauthorized health products seized from two Facebook Marketplace sellers, Pinas-Sabay Canada and Y&Y Online Retail Unauthorized nicotine buccal pouches Unauthorized Santen brand eye drops at stores in the Greater Toronto Area Unauthorized sexual enhancement products Unauthorized skin lightening and skin treatment 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.
Various Solution bags Type 1 drug recalls: 0.4% Lidocaine Hydrochloride and 5% Dextrose Injection 0.9% and 3% Sodium Chloride Injection, USP 5% Dextrose Injection, USP	Baxter Corporation recalled affected lots of: 0.4% Lidocaine Hydrochloride and 5% Dextrose Injection; 0.9% and 3% Sodium Chloride Injection, USP; 5% Dextrose Injection, USP; Gentamicin(E) Sulfate; Lactated Ringer's Injection; and Metronidazole Injection, USP; as the solution bags may be leaking.

Gentamicin(E) Sulfate
Lactated Ringer's Injection
Metronidazole Injection, USP

NEW HEALTH PRODUCT SAFETY INFORMATION

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

Review articles

Domperidone and psychiatric withdrawal events when used off-label for lactation stimulation

Key messages

- Health Canada's review of available information found an association between abruptly discontinuing or tapering domperidone, used off-label for lactation stimulation, and psychiatric withdrawal events including, but not limited to, depression, anxiety, and insomnia. Most patients had been taking daily doses of domperidone greater than 30 mg. In some case reports, individualized (slower) tapering regimens helped to manage withdrawal symptoms.
- Health Canada has not authorized domperidone for lactation stimulation. The maximum recommended daily dose for authorized indications is 30 mg. Domperidone should be used at the lowest possible dose for the shortest duration necessary. [1]
- Healthcare professionals are encouraged to report any adverse reactions suspected of being associated with domperidone to the Canada Vigilance Program.

Domperidone is a prescription drug that has been marketed in Canada since 1985. It is indicated for the symptomatic management of upper gastrointestinal motility disorders associated with chronic and subacute gastritis and diabetic gastroparesis, and prevention of gastrointestinal symptoms associated with the use of dopamine agonist antiparkinsonian agents.[1] Although domperidone has not been authorized by Health Canada for lactation stimulation, data derived from Canadian sources indicate that it has been prescribed for this off-label indication at doses exceeding the maximum recommended daily dose of 30 mg. [2]

Health Canada reviewed the potential risk of psychiatric withdrawal events, including depression, anxiety, and insomnia, following abrupt discontinuation or tapering of domperidone when it was used for lactation stimulation. A comprehensive review of available evidence identified a total of 9 relevant case reports (4 Canadian and 5 international).[3-8] Psychiatric withdrawal events developed in patients with or without a personal history of psychiatric illness. Most patients had been taking daily doses of domperidone greater than 30 mg, and all patients had been taking domperidone for longer than 4 weeks prior to the initial discontinuation or tapering attempt. The psychiatric withdrawal events were mostly refractory to commonly

prescribed medications used to treat depression and anxiety. In some case reports, individualized (slower) tapering regimens helped to manage symptoms. Two limitations were noted in the case series: there was a small number (9) of relevant case reports, and there was a lack of information regarding patients' concomitant breastfeeding patterns relative to domperidone usage. Discontinuation of breastfeeding may be independently associated with psychiatric symptoms.

Health Canada's review of available information found an association between the abrupt discontinuation or tapering of domperidone, used for lactation stimulation, and the development of psychiatric adverse events.

Health Canada will work with manufacturers to update the Canadian product monographs for domperidone-containing products with language in line with the current level of evidence.

Health Canada will continue to monitor the safety of domperidone, 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.

References

1. *Apo-Domperidone (domperidone maleate)* [product monograph]. Toronto (ON): Apotex Inc.; 2023.
2. Moriello C, Paterson JM, Reynier P, et al. Off-label postpartum use of domperidone in Canada: a multidatabase cohort study. *CMAJ Open* 2021;9(2):E500-9.
3. Adverse Reaction Database. Health Canada. Published September 24, 2009. Accessed May 21, 2023. https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-database.html
4. Doyle M, Grossman M. Case report: Domperidone use as a galactagogue resulting in withdrawal symptoms upon discontinuation. *Archives of Women's Mental Health.* 2018;21(4):461–463.
5. Majdinasab E, Haque S, Stark A, Krutsch K, and Hale TW. Psychiatric Manifestations of Withdrawal Following Domperidone Used as a Galactagogue. *Breastfeeding Medicine.* 2022; 17(12):1018-1024.
6. Manzouri P, Mink M. Withdrawal effects from domperidone requiring prolonged tapering schedule. Pharmacotherapy. ACCP Virtual Poster Symposium; *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*. 2017;37(10): e112–e117.
7. Papastergiou J, Abdallah M, Tran A, Folkins C. Domperidone withdrawal in a breastfeeding woman. *Canadian Pharmacists Journal*. 2013; 146(4): 210-212.
8. Sharma V, Sharma S, Doobay M. Domperidone Withdrawal in a Nursing Female with Pre-existing Psychiatric Illness: A Case Report. *Current Drug Safety*. 2022;17 (3):278 – 280.

Medication errors with specific mineral supplements: calcium, iron, magnesium, and zinc

Key messages

- Healthcare professionals should be aware that dosing errors have occurred with mineral supplements in practice settings due to confusion about labelled strength.
- Medication errors leading to overdoses for single-ingredient calcium, iron, magnesium, and zinc supplements have been reported by healthcare professionals in Canada.

- These medication errors were attributed to confusion with the strength of the mineral supplement's elemental and salt content, as displayed on the product label.
- Health Canada has provided additional direction to manufacturers to reduce confusion in product labels for calcium, iron, magnesium and zinc mineral supplements.
- Healthcare professionals are encouraged to report medication errors involving mineral supplements to the **Canadian Medication Incident Reporting and Prevention System** (CMIRPS), a program in which Health Canada participates.

Minerals are essential substances that our bodies need to develop and function normally.[1] Minerals are commonly used as dietary supplements, which may be prescribed or recommended by healthcare professionals for a variety of reasons.

In Canada, mineral supplements are regulated as natural health products (NHPs) under the *Natural Health Products Regulations*. These products are widely used by Canadians. In a 2015 survey, the overall prevalence of mineral supplement/vitamin use among Canadian men and women was 38% and 53%, respectively.[2]

Health Canada has reviewed Canadian reports of medication errors, submitted by healthcare professionals, involving mineral supplements, specifically single-ingredient products containing calcium, iron, magnesium, and zinc. These errors have led to overdoses and, in some cases, serious harm.[3,4,5] Confusion with the strength of the elemental and salt content, as displayed on the mineral supplement's product label, was identified as a contributing factor for these medication errors. Misinterpretation due to confusion with the labelled strength of mineral supplements can lead to over- or under-dosing. Concerns regarding the labelling of mineral supplements have been raised by healthcare professionals and poison centres across Canada.

The following is a summary of a Canadian case report that was evaluated by Health Canada, describing an error associated with confusion about the labelled strength of a mineral supplement.

Case report

In this case, the prescription was dispensed by the pharmacy using a product labelled as "calcium carbonate 500 mg" (see representation in image 1). While preparing the patient's compliance pack, the pharmacy misinterpreted the product to contain 500 mg of calcium carbonate when each tablet actually contained 500 mg of elemental calcium. As a result, the patient received 2.5 times the intended dose and required intervention in a hospital.

After becoming aware of this medication error, Health Canada worked with the manufacturer to modify the label (see representation in image 2) to assist in reducing confusion and prevent similar incidents from happening in the future.

Image 1*: Representation of principal display panel (original)

Image 2*: Representation of principal display panel (revised)

**These images were created by Health Canada to illustrate the product labels described in the case report.*

Following a review of reported errors, Health Canada has taken steps to provide additional direction to manufacturers to improve the labelling of specific mineral supplements (calcium, iron, magnesium and zinc) to help reduce confusion between the elemental and salt content:

- The Guidance document: Labelling of natural health products was updated in 2022 with a new section that provides recommendations on best practices for labelling of these mineral supplements.
- The Multi-vitamin/Mineral Supplements Monograph has been revised to include guidance on labelling for these mineral supplements.
- Health Canada's application form to obtain a NHP licence has been updated to provide directives on the format for these mineral supplement labels.

The *Natural Health Products Regulations* have been amended to include new requirements for a Product Facts Table. Any NHP authorized by Health Canada on or after June 21, 2025 must meet the new labelling requirements. Natural health products authorized by Health Canada prior to June 21, 2025 will have until June 22, 2028 to comply with the new labelling requirements. For further information on NHPs and their licence status in Canada, visit Health Canada's Licensed Natural Health Product Database. This database includes information on licensed NHPs, including a product's medicinal ingredients, its recommended use, dosage information, and any risks associated with product use.

Healthcare professionals should be aware that dosing errors have occurred with mineral supplements in practice settings due to label confusion. Healthcare professionals are encouraged to report medication errors involving these products to CMIRPS, a program in which Health Canada participates. Health Canada will continue to monitor medication errors and work with manufacturers to improve the clarity of NHP labels.

References

1. National Institute of Health. Vitamins and Minerals. National Center for Complementary and Integrative Health. https://www.nccih.nih.gov/health/vitamins-and-minerals. (accessed May 30, 2023)
2. Keshavarz P, Shafiee M, Islam N, Whiting SJ, and Vatanparast H. Prevalence of vitamin-mineral supplement use and associated factors among Canadians: results from the 2015 Canadian Community Health Survey. *Applied Physiology, Nutrition, and Metabolism* 2021;46(11): 1370-1377.
3. Institute for Safe Medication Practices Canada. Confusing Calcium Product Labels Lead to Hospitalizations. *ISMP Canada Safety Bulletin* 2021; 21(1):1-4. (accessed May 30, 2023)
4. Institute for Safe Medication Practices Canada. Opportunity for Improvement: Confusing Labels for Zinc Products. *ISMP Canada Safety Bulletin* 2021;21(11):4-5. (accessed May 30, 2023).
5. Institute for Safe Medication Practices Canada. How Much Iron Is in Here? *SafeMedicationUse.ca Newsletter* 2020;11(2):1. (accessed May 30, 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.

Third generation aromatase inhibitors: Arimidex (anastrozole), Aromasin (exemestane), and Femara (letrozole)

The *Warnings and Precautions*, *Adverse Reactions* (*Post-Market Adverse Reactions)*, and *Patient Medication Information* sections of the Canadian product monographs for Arimidex, Aromasin and Femara have been updated with the risks of **tendonitis, tenosynovitis and tendon rupture.**

Key messages for healthcare professionals:[1,2,3]

- The use of third generation aromatase inhibitors was found to be associated with tendonitis and tenosynovitis as reported in randomized controlled trials.
- Tendon rupture was found to be a potential risk.
- Tendonitis and tenosynovitis were estimated to be of uncommon occurrence, and tendon rupture of rare occurrence.
- Treating physicians should monitor patients for these adverse drug reactions.

References:

1. *Arimidex (anastrozole)* [product monograph]. Mississauga (ON): AstraZeneca Canada Inc.; 2022.
2. *Aromasin* (exemestane) [product monograph]. Kirkland (QC): Pfizer Canada ULC; 2022.
3. *Femara* (letrozole) [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2022.

Topamax (topiramate)

The *Contraindications, Warnings and Precautions,* and *Patient Medication Information* sections of the Canadian product monograph for Topamax have been updated with the risk of **neurodevelopmental disorders**.

Key messages for healthcare professionals:[1]

- Data from pregnancy registries indicate that infants exposed to topiramate in utero have an increased risk for neurodevelopmental disorders (e.g., autism spectrum disorders and intellectual disability), in addition to the previously known increased risk for congenital malformations (e.g., cleft lip and/or cleft palate [oral clefts]).
- Before initiating treatment with topiramate in a woman of childbearing potential, pregnancy testing should be performed, and a **highly** effective contraceptive method used. The patient should be fully informed of the risks related to the use of Topamax during pregnancy.
- If a woman is planning a pregnancy, a preconception visit is recommended in order to reassess the treatment of epilepsy, and to consider other therapeutic options. In case of administration during the first trimester, careful prenatal monitoring should be performed.
- Topamax for prophylaxis of migraine is contraindicated in pregnancy and in women of childbearing potential who are not using a **highly** effective method of contraception.

Reference:

1. *Topamax (topiramate)* [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.

Lynparza (olaparib): Authorization with conditions

Health Canada has issued a Notice of Compliance, under the NOC/c policy, for a new indication for Lynparza (olaparib), 100mg and 150mg tablets. Lynparza is now also indicated, in combination with abiraterone and prednisone or prednisolone, for the treatment of adult patients with deleterious or suspected deleterious *BRCA* mutated (germline and/or somatic) metastatic castration resistant prostate cancer, in whom chemotherapy is not clinically indicated. Patients must have confirmed *BRCA* mutation before Lynparza treatment is initiated. 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 Lynparza Canadian product monograph. The product monograph can be accessed through Health Canada's Drug Product Database, the AstraZeneca Canada Inc. website or by contacting AstraZeneca Canada Inc. at 1-800-668-6000. Contact the company for a copy of any references, attachments or enclosures.

*Lynparza's updated product monograph with this NOC/c indication is dated July 2023.

Tecvayli (teclistamab): Authorization with conditions

Health Canada has issued a Notice of Compliance, under the NOC/c policy, for Tecvayli (teclistamab), 153 mg / 1.7 mL (90 mg / mL) and 30 mg / 3 mL (10 mg / mL), solution for subcutaneous injection. Tecvayli is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy. 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 Tecvayli 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 or 1-800-387-8781. 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 Portal
- 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)
- Drug and vaccine authorizations for 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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