Health Canada Santé Canada

Your health and safety… our priority. *Votre santé et votre sécurité… notre priorité.*

Health Product InfoWatch

October 2019

CONTENTS

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

SUBSCRIBE

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

HEALTH PRODUCTS MENTIONED IN THIS ISSUE

Pharmaceuticals and Biologics
Elmiron (pentosan polysulfate sodium)
Estradiol
Gabapentin
Keytruda (pembrolizumab)
Lenvima (lenvatinib)
Methimazole
Opioids
Pregabalin
Ranitidine

Natural Health Products
Gripe Water

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.

Canada

MONTHLY RECAP OF HEALTH PRODUCT SAFETY INFORMATION

The following is a list of health product advisories, type I recalls as well as summaries of completed safety reviews published in September 2019 by Health Canada.

Gabapentin, pregabalin Information Update	When used with opioids, gabapentinoids increase the risk of opioid overdose. Serious side effects of using gabapentinoids and opioids at the same time include respiratory depression, increased sedation, dizziness, fainting, and death.
Gripe Water Information Update	RW Consumer Products Ltd. recalled all lots of the product "Gripe Water – Alcohol And Preservative Free" (Natural Product Number [NPN] 80080669), sold under various brand names, because company testing showed microbial contamination. These products have been sold at retailers across Canada.
Methimazole Summary Safety Review	This safety review evaluated the risk of acute pancreatitis associated with methimazole. Health Canada's review of the available information found that there is a link. Health Canada is working with the manufacturers to update the Canadian product monographs of methimazole products to inform about this risk.
Ranitidine Information Update	Health Canada is assessing the issue of an impurity, N-nitrosodimethylamine (NDMA), detected in some ranitidine drugs. Current evidence suggests that NDMA may be present in ranitidine, regardless of the manufacturer. At Health Canada's request, companies marketing ranitidine products in Canada have stopped any further distribution until evidence is provided to demonstrate that they do not contain NDMA above acceptable levels. A table with detailed information on the recalled lots is provided in the information update.
Unauthorized health products Bielenda Dr. Medica anti-acne products Needle-free dermal filler devices Unauthorized Nabota botulinum toxin Update - Multiple 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.

NEW HEALTH PRODUCT SAFETY INFORMATION

The following topics have been selected to raise awareness and, in some cases, to stimulate reporting of similar adverse reactions.

CASE REPORT

Recent Canadian or international cases are selected based on their seriousness, frequency of occurrence or the fact that the reactions are unexpected. Case reports are considered suspicions and are presented to stimulate reporting of similar suspected adverse events.

Estradiol and testicular cancer

Health Canada received a report of testicular cancer in a previously healthy 38-year-old male-to-female transgender patient undergoing estrogen therapy.

The patient presented to the emergency department with abdominal and back pain, weight loss of 7 kg and swelling of the scrotum. She had been on male-to-female transgender hormonal therapy consisting of estradiol and spironolactone for 15 months. She was not taking any other medications and had no medical history or family history of testicular cancer. She was an ex-smoker, had never consumed recreational drugs, and alcohol intake was infrequent.

Clinical examination revealed a testicular mass on the right side. A right groin lesion and a retroperitoneal mass with right-sided hydronephrosis were visible on a computed tomography (CT) scan. The patient also presented with an iliofemoral deep vein thrombosis, as well as enlarged abdominal lymph nodes. Tumour marker levels were alpha-fetoprotein (AFP) < 2.5 µg/L, beta-human chorionic gonadotrophin (β-hCG) 2526 IU/L and lactate dehydrogenase (LDH) 5294 U/L. The tumour was classified as a stage IIIC germ cell tumour (Tx,N3,M1a,S3).

Anticoagulation was initiated with dalteparin, followed by chemotherapy with bleomycin, etoposide, and cisplatin. Hormonal therapy was discontinued. After 4 cycles of chemotherapy, the patient underwent right orchiectomy. Subsequent CT scans revealed a residual retroperitoneal mass. Because of the location of the mass and risks associated with surgery, excision of the mass was not recommended. The mass was instead followed by positron emission tomography and CT scans every 3 months.

Following completion of chemotherapy, the patient resumed hormonal therapy to continue with the transition from male to female. She was informed about the risks of thrombosis with estrogen therapy, as well as its possible association with testicular cancer. Anticoagulation therapy was changed from dalteparin to rivaroxaban. Two years after diagnosis, tumour markers remained within normal limits.

A detailed description of this case has been published.[1] Two similar reports were identified in the literature.[2,3] Both cases were serious and involved male to female transgender patients.

Healthcare professionals are encouraged to report similar cases to Health Canada for the continued monitoring and assessment of the risk of testicular cancer with the exogenous use of estrogens.

References

1. Chandhoke G, Shayegan B, Hotte SJ. Exogenous estrogen therapy, testicular cancer, and the male to female transgender population: a case report. *J Med Case Rep* 2018;12(1):373.
2. Kobori Y, Suzuki K, Iwahata T, et al. Mature testicular teratoma with positive estrogen receptor beta expression in a transgendered individual on cross-sex hormonal therapy: a case report. *LGBT Health* 2015;2(1):81-3.
3. Hannoush ZC, Ayala A. Estrogen exposure and testicular choriocarcinoma: case report of a male to female transgender patient [ENDO meeting abstract]. *Endocrine Reviews* 2016;37(2 Supplement).

PRODUCT MONOGRAPH UPDATE

The following safety labelling updates, which were recently made to the Canadian product monograph, 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. Canadian product monographs can be accessed through Health Canada's Drug Product Database.

Elmiron (pentosan polysulfate sodium)

The risk of **pigmentary maculopathy** has been included in the *Warnings and Precautions*, *Post-Market Adverse Drug Reactions*, and *Consumer Information* sections of the Canadian product monograph for Elmiron.

Key messages for healthcare professionals:[1]

- In the post-market setting, pigmentary maculopathy has been reported with chronic use of Elmiron. Visual symptoms included difficulty reading and prolonged dark adaptation.
- Patients, particularly those with chronic use of Elmiron, should have regular ophthalmic examinations for early detection of pigmentary maculopathy.
- If pigmentary maculopathy is confirmed, Elmiron treatment discontinuation should be considered.

Reference

1. *Elmiron (pentosan polysulfate sodium)* [product monograph]. Toronto (ON): Janssen Inc.; 2019.

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 nature 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, in accordance with the NOC/c Policy. For the most up-to-date information, consult Health Canada's NOC database.

Keytruda (pembrolizumab): Authorization with conditions

Health Canada has issued a Notice of Compliance, under the Notice of Compliance with Conditions policy, for a new indication for Keytruda* (pembrolizumab), powder for solution for infusion, 50 mg vial and solution for infusion, 100 mg/4 mL vial. The new indication for Keytruda is for the treatment of adult patients, in combination with lenvatinib, with advanced endometrial carcinoma that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior platinum-based systemic therapy, and are not candidates for curative surgery or radiation. Patients should be advised about the conditional market authorization for this indication.

For the complete prescribing information and information available for the patients/caregivers, please consult the Keytruda Canadian product monograph. The product monograph can be accessed through Health Canada's Drug Product Database, the Merck Canada Web site or by contacting Merck Canada at 1-800-567-2594. Contact the company for a copy of any references, attachments or enclosures.

*Keytruda's updated product monograph with this NOC/c indication is dated September 2019.

Lenvima (lenvatinib): Authorization with conditions

Health Canada has issued a Notice of Compliance, under the Notice of Compliance with Conditions policy, for a new indication for Lenvima* (lenvatinib), available in 4mg and 10mg capsules (as lenvatinib mesylate). The new indication for Lenvima is in combination with pembrolizumab for the treatment of adult patients with advanced endometrial carcinoma that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior platinum-based systemic therapy, and are not candidates for curative surgery or radiation. Patients should be advised about the conditional market authorization for this indication.

For the complete prescribing information and information available for the patients/caregivers, please consult the Lenvima Canadian product monograph. The product monograph can be accessed through Health Canada's Drug Product Database, the Eisai Limited Web site or by contacting Eisai Limited at 1-877-873-4724. Contact the company for a copy of any references, attachments or enclosures.

*Lenvima's updated product monograph with this NOC/c indication is dated September 2019.

Did you know?

Health Canada has issued a Notice of Compliance for the combination of pembrolizumab (Keytruda) plus lenvatinib (Lenvima) for patients with certain types of endometrial carcinoma (see indications listed in the communication). This review was conducted under Project Orbis, which provides a framework for concurrent submission and review of oncology drugs among international partners. Health Canada, the US Food and Drug Administration and the Australian Therapeutic Goods Administration collaborated on this review, allowing for simultaneous decisions in all three countries.

Health Canada Tweet

US Food and Drug Administration review decision

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
- Annual trends for adverse reaction case reports and medical device problem incidents
- Stop Illegal Marketing of Drugs and Devices

Suggestions?

Your comments are important to us. Let us know what you think by reaching us at HC.infowatch-infovigilance.SC@canada.ca

Health Canada
Marketed Health Products Directorate
Address Locator 1906C
Ottawa ON K1A 0K9
Telephone: 613-954-6522
Fax: 613-952-7738

Copyright

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.: 190000