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Health Product InfoWatch

May 2019

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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.

Canada

ANNOUNCEMENT

Human-Use Antiseptic Drugs Guidance Document

Health Canada would like healthcare professionals and industry to be aware of the Guidance Document for Human-Use Antiseptic Drugs. The guidance applies to antiseptic skin products used in professional and commercial settings. The guidance also applies to those products used in food preparation and healthcare settings, and those products making viral, specific organisms, persistence and/or log reduction claims.

It is Health Canada's policy that antiseptic products that explicitly or implicitly claim the mitigation or prevention of disease be supported by the appropriate data, and provide the users of these products with sufficient information on the label to promote their safe use.

Please consult the guidance for further information and details regarding the current regulations and policies for human-use antiseptic drugs.

If you have any questions regarding the regulation of human-use antiseptic drugs please contact the Natural and Non-prescription Health Products Directorate at hc.nnhpd-dpsnso.sc@canada.ca.

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 April 2019 by Health Canada.

Alaris Infusion Sets Health Professional Risk Communication	Becton Dickinson (BD) has recalled affected lots of the Alaris Pump Infusion Sets due to a manufacturing defect that can cause unintended delivery which can result in over-infusion. BD has requested Canadian facilities to remove and destroy all affected products and is investigating whether additional lots may be affected. Healthcare professionals should only use Alaris Pump Infusion Sets that have not been identified as part of the affected lots and follow the instructions provided in the communication.
Auro-Irbesartan HCT Information Update Drug recall Sartan recalls and testing	One lot of Auro-Irbesartan HCT (irbesartan/hydrochlorothiazide) tablets was recalled because of a nitrosamine impurity, N-nitrosodiethylamine (NDEA). NDEA is classified as a probable human carcinogen. The affected lot was released in August 2018 and distributed only in Ontario and Quebec.
Benlysta (belimumab) Health Professional Risk Communication	In a recent post-marketing study, depression, suicidal ideation or behaviour, and self-injury were reported more frequently in patients receiving Benlysta plus standard therapy, when compared to patients taking placebo plus standard therapy. Healthcare professionals are advised to follow the recommendations provided in the communication. Health Canada is currently working with the manufacturer to update the Canadian product monograph for Benlysta regarding this risk.

Biocell breast implants Information Update (April 4, 2019) Information Update (May 28, 2019)	Health Canada advised Allergan that the Department intends to suspend its licences for Biocell breast implants. This is being done as a precautionary measure to protect Canadian patients from the rare but serious risk of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL). Health Canada continues to monitor and review all available scientific and clinical information regarding the safety of textured breast implants. Canadians and healthcare professionals will be informed of any further decisions related to the licensing of Biocell breast implants. Since this communication, Health Canada has suspended the licences for Allergan's Biocell breast implants.
Foreign health products Foreign Product Alert (4 products)	These foreign health products have been found by regulators in the United States and Australia to contain undeclared drug ingredients which may pose serious health risks. The products are not authorized for sale in Canada and have not been found in the Canadian marketplace, but it is possible they may have been brought into the country by travellers or purchased over the Internet.
Intragastric balloons Health Professional Risk Communication Summary Safety Review	This safety review evaluated the risk of gastric and esophageal perforation, acute pancreatitis, and spontaneous balloon overinflation associated with intragastric balloons (IBs). Health Canada's review of the available information has confirmed a link between the use of fluid-filled IBs and all of the risks previously mentioned. Health Canada will work with the medical device manufacturers to strengthen the Instructions for Use for all fluid-filled IBs by including these potential risks. Health Canada has also communicated this information to healthcare professionals.
Mifegymiso (mifepristone and misoprostol) Information Update	The Canadian product monograph for Mifegymiso has been updated to reflect that an ultrasound is no longer required before the drug is prescribed. Previously, the product monograph indicated that an ultrasound was required before prescribing Mifegymiso to confirm the gestational age and to rule out an ectopic pregnancy. With the changes to the product monograph, prescribers now have the flexibility to use their medical judgement on how best to determine the gestational age and to rule out an ectopic pregnancy.
Unauthorized health products A1 Herbal Ayurvedic Clinic Ltd. Gigi's Market, Ottawa, ON Multiple unauthorized health products Sunrise Lee Chinese Herbs Centre, Calgary, AB Unauthorized eye solutions and acne gel	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.

SAFETY BRIEF

Fentora (fentanyl citrate, buccal/sublingual effervescent tablets) safety reminders

Fentora (fentanyl citrate, buccal/sublingual effervescent tablets) is indicated only for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to continuous opioid therapy for their persistent baseline cancer pain.[1] It has been available in Canada since May 2014.

In an ongoing effort to ensure the safe and effective use of medications, Health Canada has reviewed 2 surveys of Fentora prescribers in Canada, which were conducted by the manufacturer. These surveys indicated that some prescribers did not demonstrate a full understanding of the risks of respiratory depression, coma and death when Fentora is used concomitantly with central nervous depressant drugs such as benzodiazepines.

Health Canada would like to remind healthcare professionals of the following important safety and usage information related to the risks of respiratory depression, coma and death that is in the Fentora Canadian product monograph.

Safety reminders

Fentora therapy should only be initiated in patients 18 years of age and older who are opioid tolerant and should only be used for the management of breakthrough cancer pain.

Fentora must not be used in opioid non-tolerant patients including those using opioids intermittently, on an as needed basis, because life-threatening respiratory depression and death could occur at any dose in patients not on a chronic regimen of opioids.

Patients considered opioid-tolerant include those taking:

- at least 60 mg of oral morphine daily; or
- at least 25 µg/hr of transdermal fentanyl; or
- at least 30 mg of oral oxycodone daily; or
- at least 8 mg of oral hydromorphone daily; or
- at least 25 mg oral oxymorphone daily; or
- an equianalgesic dose of another opioid daily for a week or longer.

Co-administration of Fentora with central nervous system (CNS) depressants, including benzodiazepines, or with cytochrome P450 3A4 (CYP3A4) inhibitors, may result in respiratory depression, hypotension, profound sedation, coma and death.

Fentora should be used with caution and in a reduced dosage during concomitant administration with CNS depressants such as:

- Benzodiazepines, other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics, and other CNS depressants (including alcohol and illicit drugs).

Concomitant use of Fentora with CYP3A4 inhibitors may increase the plasma concentration of fentanyl, resulting in increased depressant effects. If concomitant use is necessary, consider dosage reduction of Fentora until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. CYP3A4 inhibitors may include:

- Indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, telithromycin, aprepitant, diltiazem, erythromycin, fluconazole, grapefruit juice, verapamil, or cimetidine.

It is also important to note that patients should not discontinue Fentora without first talking to their physician. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required.

Health Canada will continue to monitor safety information involving Fentora, as it does for all health products on the Canadian market, to identify and assess potential harms. Healthcare professionals should be aware that Canadian product monographs are updated periodically as required and are available from the manufacturer or on Health Canada's Drug Product Database. Healthcare professionals are also encouraged to report to Health Canada any adverse reaction suspected of being associated with the use of Fentora.

Reference

1. *Fentora (fentanyl citrate)* [product monograph]. Toronto (ON): Teva Canada Limited; 2018.

PRODUCT MONOGRAPH UPDATES

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 is available on Health Canada's Product Monograph Brand Safety Updates. Canadian product monographs can be accessed through Health Canada's Drug Product Database.

Eliquis (apixaban)

The risk of **hemorrhage** with the concomitant use of selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) has been included in the *Warnings and Precautions*, *Drug Interactions*, and *Consumer Information* sections of the Canadian product monograph for Eliquis. In addition, the *Dosage and Administration* section has been updated with tables providing dosing and administration information according to indication and renal function. New dosing recommendations for stroke prevention in patients with atrial fibrillation having severe renal impairment were also added to the *Dosage and Administration* section of the Canadian product monograph for Eliquis.

Key messages for healthcare professionals:[1]

Concomitant use of SSRIs and SNRIs

- Care should be taken of Eliquis treated patients who are treated concomitantly with medications affecting hemostasis such as SSRIs and SNRIs.

Dosing information according to renal function

- Stroke prevention in patients with atrial fibrillation: No dose adjustment is necessary in patients with mild or moderate renal impairment, or in those with estimated creatinine clearance (eCrCl) 25 - 30 mL/min, unless at least 2 of the following criteria for dose reduction are met, in which case patients should receive a reduced dose of Eliquis, 2.5 mg twice daily:
  - age ≥ 80 years,
  - body weight ≤ 60 kg, or
  - patients with serum creatinine ≥ 133 µmol/L (1.5 mg/dL).
- Summarized dosing for the use of Eliquis in the different indications in renally impaired patients are presented in Tables 1 and 2.

Table 1: Dosage and administration for patients according to indication and renal function

	Renal impairment				
eCrCl / **Indication**	Normal	Mild	Moderate	Severe	
	> 80 mL/min	> 50 - ≤ 80 mL/min	≥ 30 - ≤ 50 mL/min	≥ 15 - < 30 mL/min	< 15 mL/min or patients undergoing dialysis
Prevention of VTE in adult patients after elective knee or hip replacement surgery	2.5 mg bid			2.5 mg bid*	Eliquis is not recommended
Treatment of VTE (DVT, PE)	10 mg bid 7 days, followed by 5 mg bid			10 mg bid 7 days, followed by 5 mg bid*	
Continued prevention of recurrent DVT and PE†	2.5 mg bid			2.5 mg bid*	

Note: bid = twice daily, DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venous thromboembolic events
* Must be used with caution due to potentially higher bleeding risks.
†After a minimum of 6 months of treatment for DVT or PE.

Table 2: Dosage and administration for patients according to indication and renal function

	Renal impairment					
eCrCl / **Indication**	Normal	Mild	Moderate	Severe		
	> 80 mL/min	> 50 - ≤ 80 mL/min	> 30 - ≤ 50 mL/min	≥ 25 - ≤ 30 mL/min	≥ 15 - ≤ 24 mL/min	< 15 mL/min or patients undergoing dialysis
Prevention of stroke and systemic embolism in patients with atrial fibrillation	5 mg bid Dose adjustment to 2.5 mg bid, if ≥ 2 of following criteria are met‡: • age ≥ 80 years • body weight ≤ 60 kg • serum creatinine ≥ 133 µmol/L (1.5 mg/dL)				No dosing recommendation due to very limited clinical data	Eliquis is not recommended

Note: bid = twice daily
‡ These patients have been determined to be at higher risk of bleeding.

Reference

1. *Eliquis (apixaban)* [product monograph]. Montreal (QC): Bristol-Myers Squibb Canada Co.; 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 Notices of Compliance, under the Notice of Compliance with Conditions policy for Keytruda* (pembrolizumab), powder for solution for infusion, 50 mg vial and solution for infusion, 100 mg/4mL vial, for the following indications:

- the treatment of patients with locally advanced unresectable or metastatic urothelial carcinoma, as monotherapy, in adults who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by a validated test, or in adults who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. An improvement in survival or disease-related symptoms has not yet been established.
- as monotherapy for the treatment of adult patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
    - colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, or
    - endometrial cancer that has progressed following prior therapy and who have no satisfactory alternative treatment options.

Patients should be advised about the conditional market authorization for these indications.

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 these NOC/c indications is dated April 2019.

ILLEGAL MARKETING OF DRUGS AND DEVICES

When making decisions about treatments for patients, healthcare providers consider many different information sources, including marketing materials. Health Canada is responsible for ensuring compliance with the legislation and regulations that apply to drug and device advertisements. To be compliant, information in health product marketing materials should not be false, misleading or deceptive, and should accurately convey the benefits and risks of a health product.

To learn more about illegal advertising and marketing in Canada, visit the Health Canada Stop Illegal Marketing of Drugs and Devices Web page.

The following cases have been selected to raise awareness and to stimulate reporting of illegal marketing. If you encounter any situations involving the dissemination of misleading or unauthorized health product claims, please report to Health Canada at: drug-device-marketing@canada.ca.

Health Canada has become aware of the dissemination of false and misleading information for the following onychomycosis treatment options:

Julia (efinaconazole topical solution)

Healthcare professionals may have received brochures containing information on Julia that is inconsistent with the Canadian product monograph, with an unauthorized use of a logo of a Health Canada recognized advertising preclearance agency, misleading healthcare professionals to believing that the brochure has been precleared and was compliant with Health Canada's requirements. In addition, the product has been illegally marketed directly to consumers through brochures, educational Web sites, and television.

Healthcare professionals are reminded that:

- Julia, a triazole antifungal agent, is indicated for the topical treatment of mild to moderate onychomycosis (*tinea unguium*) of toenails without lunula involvement due to *Trichophyton rubrum* and *Trichophyton mentagrophytes* in immunocompetent adult patients.[1]
- Direct-to-consumer advertising of prescription drugs beyond name, price and quantity is prohibited as per section C.01.044 of the *Food and Drug Regulations*.

Laser treatment for onychomycosis

Over 60 clinics and numerous vendors in Canada have been involved in the dissemination of false or misleading claims of laser-based medical devices for the treatment of onychomycosis.

Healthcare professionals are reminded that:

- Health Canada has authorized some laser-based medical devices for "temporary increase of clear nail in patients with onychomycosis." These devices are NOT authorized for claims such as "treatment of onychomycosis" or "destruction of nail fungus."
- Statements indicating or implying Health Canada's authorization may only be used for claims that are in line with the authorized indications. To confirm the authorized indications for a medical device, please contact the Medical Devices Bureau at mdb_enquiries@hc-sc.gc.ca.

Reference

1. *Julia (efinaconazole topical solution)* [product monograph]. Laval (QC): Valeant Canada LP.; 2017.

HELPFUL LINKS

- MedEffect™ Canada
- Recalls and Safety Alerts Database
- New Safety 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

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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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