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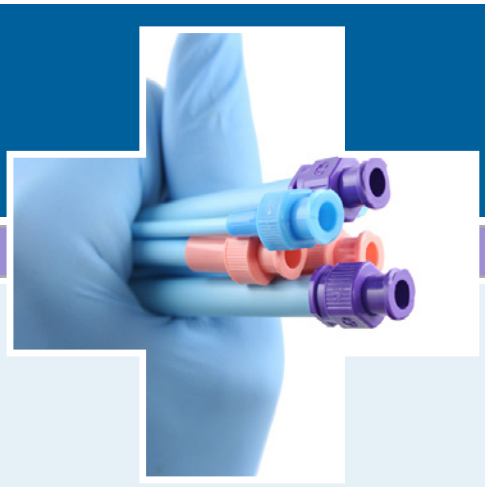

Health Product InfoWatch

March 2017

CONTENTS

REPORTING ADVERSE REACTIONS

Canada Vigilance Program
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HEALTH PRODUCTS MENTIONED IN THIS ISSUE

Pharmaceuticals and Biologics

- Avastin (bevacizumab)
- Bisphosphonates
- Capsaicin topical
- Cophylac Drops (normethadone and *p*-hydroxyephedrine)
- Erwinase (Erwinia L-asparaginase)
- Low molecular weight heparins
- Menthol topical
- Methyl salicylate topical
- PMS-Propofol
- Topical pain relievers
- Tramadol-containing products

Medical Devices

- Colorectal stents
- Esophageal stents
- Essure Permanent Birth Control System
- LivaNova Stöckert 3T Heater-Cooler Device

Other

- Unauthorized health products

ANNOUNCEMENT

Public reporting of drug shortages now mandatory

Regulations came into force this month requiring drug companies experiencing shortages and discontinuances to publicly report them.

Continued on page 5

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 150

Canada

MONTHLY RECAP OF HEALTH PRODUCT SAFETY INFORMATION

The following is a list of health product advisories as well as summaries of completed safety reviews published in February 2017 by Health Canada.

Bisphosphonates Summary Safety Review	This safety review evaluated the risk of osteonecrosis beyond the area of the jawbone associated with bisphosphonates [alendronate (Fosamax and Fosavance), clodronate (Clasteon and Bonefos), etidronate (Didronel and Didrocal) and risedronate (Actonel, Actonel DR and Actonel Plus Calcium)]. The Canadian product monographs for some of the bisphosphonate-containing products already include warnings about the risk of bone damage in the outer ear canal and/or other bones of the body. Health Canada's review of the available information did not establish a link between the use of the other bisphosphonates and the risk of osteonecrosis of the external ear canal or other parts of the body other than the jaw. Health Canada will continue to monitor the safety of bisphosphonates.
Colorectal stents and Avastin (bevacizumab) Summary Safety Review Health Product InfoWatch	This safety review evaluated the increased risk of intestinal perforation associated with the concurrent use of colorectal stents and bevacizumab. Health Canada's review concluded that there is limited evidence at this time suggesting an increased risk of intestinal perforation when colorectal stents and bevacizumab are used together. Health Canada has also communicated this information to healthcare professionals.
Erwinase (Erwinia L-asparaginase) Health Product Risk Communication	Small amounts of particulate matter have been observed bound to the stopper and/or present on the lyophilized cake of some vials of Erwinase from BATCH 180G. Vials of Erwinase with visible particulate matter must not be administered. To avoid potential shortage, Health Canada has facilitated the temporary importation of UK-labelled product from Batch CAMR-180G. If there is no visible particulate matter after reconstitution, a standard 5-micron filter needle should be used to withdraw the reconstituted product from the vial prior to administration as an additional precaution. Healthcare professionals should refer to the Erwinase Canadian product monograph for prescribing information.
LivaNova Stöckert 3T Heater-Cooler Device Health Product Risk Communication	Stöckert 3T heater-cooler devices manufactured by LivaNova prior to September 2014 are at an increased risk of contamination with *Mycobacterium chimaera*, a type of nontuberculous mycobacterium, and should be removed from service. If it is not possible to remove these devices from service, facilities should consider interim risk mitigation measures.

Low molecular weight heparins Summary Safety Review	This safety review evaluated the risk of spinal/epidural hematoma associated with low molecular weight heparins (LMWH). Health Canada's review concluded that the risk of bleeding may increase if the spinal procedure is carried out soon after injection of LMWH. Health Canada requested that the manufacturers of LMWH update the Canadian product monographs to include information on the recommended length of time between LMWH injection and spinal/epidural anaesthesia or spinal puncture.
Over-the-counter topical pain relievers containing menthol, methyl salicylate or capsaicin Summary Safety Review Information Update	This safety review evaluated the risk of serious skin burns associated with over-the-counter topical pain relievers containing menthol, methyl salicylate or capsaicin. Health Canada's review of the available information has established a link between the use of topical pain relievers containing menthol and the risk of rare but serious skin burns; however, there was not enough information to draw the same conclusions for the products containing methyl salicylate or capsaicin alone. Health Canada is updating the labelling standard for all topical pain relievers containing menthol alone or in combination, to inform consumers about this potential risk. Health Canada has also communicated this information to Canadians.
PMS-Propofol Drug Recall	PMS-Propofol 10 mg/mL emulsion (lots or serial numbers A051131 and A060199) has been recalled by Pharmascience Inc. due to contamination by foreign particles (type I recall). The product was distributed to wholesalers and pharmacies in Canada.
Tramadol-containing products Summary Safety Review Health Product InfoWatch	This safety review evaluated the risk of respiratory depression in children and adolescents associated with tramadol-containing products (Durela, Ralivia, Tramacet, Tridural, Ultram, and Zytram XL). Health Canada's review found evidence to show that CYP2D6 ultra-rapid metabolizers are at an increased risk of life-threatening respiratory depression. The review found limited information regarding respiratory depression with the use of tramadol in children. The Canadian product monographs for tramadol-containing products have been updated to include information on tramadol and respiratory depression in CYP2D6 ultra-rapid metabolizers. Health Canada has also communicated this information to healthcare professionals.
Unauthorized health products Advisory	Health Canada advised Canadians that it seized various unauthorized health products promoted as workout, weight loss and dietary supplements from Atomik Nutrition in Châteauguay, QC. The products are labelled to contain various drugs, including prescription and controlled drugs, which may pose serious 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.

Esophageal stents and the risk of vascular erosion

Esophageal stents are hollow tubes of varying composition implanted into the esophagus to restore structure and function, and allow for proper swallowing and passage of food and drink from the oropharynx to the stomach.[1,2] Initially used to treat malignant esophageal strictures and fistulas caused by esophageal or other nearby cancers, these devices have also been more recently used to treat benign conditions, including tracheo-esophageal fistula, esophageal perforations and leaks, and benign esophageal strictures. Currently, the most commonly used esophageal stents are self-expandable metal stents (SEMS) and self-expandable plastic stents (SEPS).[3] Some models of SEMS are partially or fully covered with a coating such as a plastic membrane or silicone.[4] In Canada, esophageal stents are typically classified as class III medical devices (IV being the highest risk class).

In October 2015, Health Canada received a report of an adverse incident associated with a fully-covered SEMS. The patient had initially been admitted to hospital with a spontaneously perforated esophagus after severe vomiting. Surgery was undertaken to drain the area and repair the esophagus. Just under 2 weeks later, the patient was diagnosed with a persistent esophageal leak. A fully covered SEMS was implanted, with correct positioning of the stent confirmed via post-operative X-ray imaging. On the 17th day after stent implantation, some blood was noted to be found draining from the left side of the patient's chest. On the 19th day after implantation, the patient experienced sudden hematemesis, became acutely unstable due to hypovolemic shock and, despite resuscitation efforts, passed away due to massive hemorrhage.

An autopsy subsequently revealed that the stent had eroded through the esophagus and into the patient's aorta. The eroded area was near the proximal end of the stent in a location distinct from the area of original esophageal perforation. The cause of death was stated as aorto-esophageal fistula (AEF).

Some case reports of AEF associated with esophageal stenting have been published in the literature.[5,6] Smaller herald bleeds may precede the massive hemorrhage seen in cases of AEF associated with esophageal stents.[5] Mediastinal contamination due to delayed stent placement or persistent esophageal leakage may lead to a local inflammatory environment that increases the risk of AEF after stenting.[5] It is recommended that healthcare professionals maintain a high index of suspicion for the possibility of this life-threatening complication when there is bleeding around the stent placement site.[6]

Health Canada encourages the reporting of vascular erosion, AEF and other adverse incidents suspected of being associated with the use of esophageal stents to the Regulatory Operations and Regions Branch through the toll free hotline (1-800-267-9675). The adverse incident reporting form and guidelines can be found on the Health Canada Web site.

References

1. Sharma P, Kozarek R. Practice Parameters Committee of American College of Gastroenterology. Role of esophageal stents in benign and malignant diseases. *Am J Gastroenterol* 2010;105(2):258-73.
2. Irani S, Kozarek R. Esophageal stents: past, present, and future. *Tech Gastrointest Endosc* 2010;12(4):178-90.
3. Didden P, Spaander MC, Bruno MJ, et al. Esophageal stents in malignant and benign disorders. *Curr Gastroenterol Rep* 2013;15(4):319.
4. Kang HW, Kim SG. Upper gastrointestinal stent insertion in malignant and benign disorders. *Clin Endosc* 2015;48(3):187-93.
5. Schweigert M, Dubecz A, Stadlhuber RJ, et al. Risk of stent-related aortic erosion after endoscopic stent insertion for intrathoracic anastomotic leaks after esophagectomy. *Ann Thorac Surg* 2011;92(2):513-8.
6. Aryaie AH, Singer JL, Fayezizadeh M, et al. Efficacy of endoscopic management of leak after foregut surgery with endoscopic covered self-expanding metal stents (SEMS). *Surg Endosc* 2017; 31(2):612-7.

ANNOUNCEMENT

Continued from page 1

Public reporting of drug shortages now mandatory

Drug manufacturers are now required to report on www.drugshortagescanada.ca:

- an anticipated drug shortage 6 months in advance
- a planned discontinuation of a drug 6 months in advance
- any unanticipated shortage or discontinuation within 5 days of learning about it, if less than 6 months in advance

As part of the regulations, a new, independent Web site, www.drugshortagescanada.ca, replaces the industry-run Web site, www.drugshortages.ca, where manufacturers have been voluntarily reporting drug shortages and discontinuances since 2012. The new Web site features enhanced notification features and a mobile application. As well, it provides updated information for healthcare providers and patients, including tools and guidance to help manage shortages.

PRODUCT MONOGRAPH AND MEDICAL DEVICE INSTRUCTIONS FOR USE UPDATES

The following safety labelling updates, which were recently made to the Canadian product monograph or medical device instructions for use, have been selected for your awareness. A complete list of safety labelling updates for brand name pharmaceutical drugs is available on Health Canada's Web site.

Cophylac Drops (normethadone and *p*-hydroxyephedrine)

Cophylac Drops should not be used in children under 6 years of age due to a risk of serious harm, including misuse, overdose, and adverse reactions. The **pediatric age restriction** has been included in the *Indications and Clinical Use, Warnings and Precautions,* and *Dosage and Administration* sections of the Canadian prescribing information for Cophylac Drops. Health Canada is working with the manufacturer to update the Cophylac Drops packaging labels in order to reflect the revised pediatric dosage recommendations.

Key messages for healthcare professionals:[1]

- The use of Cophylac Drops is not recommended in patients under 6 years of age.
- For children between 6 to 14 years of age, the recommended dosage is 5 to 10 drops twice daily.

Reference

1. *Cophylac Drops (normethadone hydrochloride and p-hydroxyephedrine hydrochloride)* [prescribing information]. Laval (QC): Valeant Canada LP; 2017.

Essure Permanent Birth Control System

The instructions for use for Essure Permanent Birth Control System have been updated, including the insertion of a **Boxed Warning**. The warning highlights the potential for various adverse events (perforation, improper device location, persistent pain, hypersensitivity reactions) that may lead to surgical removal of the device. The warning also stresses the need to use alternative contraception until an Essure Confirmation Test is performed three months after implantation to verify correct location and retention of the insert.

A Patient-Doctor Discussion Checklist has been added to the Canadian Patient Information Brochure for Essure. This checklist, to be reviewed and signed by both the patient and physician prior to device placement, outlines various risks associated with Essure (pregnancy risks, risks around the time of device insertion, long-term risks) as well as the availability of other birth control options.

Key messages for healthcare professionals:[2]

- An **Essure Confirmation Test** should be performed three months after insert placement to evaluate insert retention and location. The patient must use alternative contraception until an Essure Confirmation Test demonstrates satisfactory results.
- There have been reports of perforation of the uterus and/or fallopian tubes, inserts located in the intra-abdominal or pelvic cavity, persistent pain, and allergy or hypersensitivity reactions in some patients. Some of these reported events resulted in insert removal that required abdominal surgery.
- As with any procedure, hysteroscopic placement of Essure inserts into the fallopian tubes is NOT without risks. Essure placement is an elective procedure, and the patient must be well counseled and understand the risk/benefit relationship. The patient should read the **Patient Information Brochure**. Allow the patient adequate time after reviewing and considering this information before deciding whether to have the Essure procedure. The **Patient-Doctor Discussion Checklist** should be reviewed with the patient, and all of the patient's questions answered.

Reference

2. *Essure Permanent Birth Control* [Instructions For Use and Canadian Patient Information Brochure]. Berlin (Germany): Bayer Pharma AG; 2017. (accessed 2017 March 3)

HELPFUL LINKS

- MedEffect™ Canada
- Recalls and Safety Alerts Database
- Summary Safety Reviews
- 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

Suggestions?

Your comments are important to us. Let us know what you think by reaching us at InfoWatch_InfoVigilance@hc-sc.gc.ca

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

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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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