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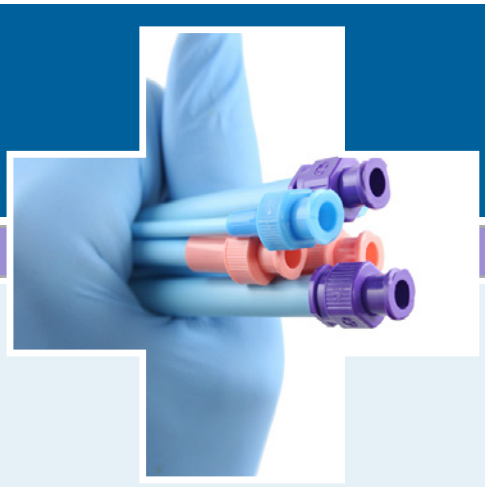

Health Product InfoWatch

February 2017

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REPORTING ADVERSE REACTIONS

Canada Vigilance Program
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HEALTH PRODUCTS MENTIONED IN THIS ISSUE

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- Unauthorized health products (poppers and sexual enhancement 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 150

Canada

ANNOUNCEMENT

Misleading advertising of human chorionic gonadotropin (hCG) products for weight loss

Health Canada has become aware that the Web sites of several weight loss clinics promote specific hCG prescription products for weight loss. Advertising of hCG prescription products for weight loss contravenes the Federal *Food and Drugs Act* and *Regulations* and may contravene provincial/territorial laws in some jurisdictions.

Health Canada would like to remind healthcare professionals of the following information:

- There are no hCG prescription products authorized by Health Canada for weight loss treatment.
- The promotion of such an unauthorized claim/benefit is considered to be off-label promotion, which is in contravention of the *Food and Drugs Act*.
- Health Canada is not aware of any substantial scientific evidence that hCG is effective for weight loss, that it redistributes fat, or that it reduces appetite or the hunger and discomfort associated with calorie-restricted diets.*

Within the past month, Health Canada has identified more than 20 clinics across the country engaging in misleading advertising. Please report complaints about hCG products being promoted for weight loss to Health Canada at mhpd_dpsc@hc-sc.gc.ca or 613-793-6922, or visit the Regulatory Advertising Web site for more information.

Health Canada assesses all advertising complaints it receives to confirm whether the advertising materials comply with the applicable legislation and regulations, and takes appropriate action to address complaints where non-compliance is found. These advertising complaints are published on the Health Canada Web site in a summary table.

* http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2017/61896a-eng.php

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 January 2017 by Health Canada.

Amiodarone (intravenous) Summary Safety Review	This safety review evaluated the risk of adverse reactions in fetuses and newborns associated with the use of amiodarone. Health Canada's review concluded that there may be a link between amiodarone use during pregnancy or in newborns and the risk of cardiac adverse reactions. Health Canada has requested that manufacturers update the Canadian product monographs for intravenous amiodarone products to include this risk.
Charac and Charac-Tol activated charcoal products Advisory	Health Canada advised Canadians that 4 lots of activated charcoal products were recalled by the company Omega Laboratories Ltd. because they may pose health risks. The company has confirmed that 2 lots have microbial contamination and is recalling the other 2 lots as a precaution.

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 179G. 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-179G. 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. Healthcare professionals should refer to the Erwinase Canadian product monograph for prescribing information.
Fluoroquinolones Summary Safety Review Health Product Risk Communication Information Update	This safety review evaluated the risk of disabling and persistent serious adverse reactions including tendinopathy, peripheral neuropathy, and central nervous system disorders associated with fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin and ofloxacin). Health Canada's review concluded that some of the known adverse reactions, specifically tendonitis/tendinopathy, peripheral neuropathy and central nervous system disorders, may be persistent and/or disabling. These adverse reactions are considered rare. Health Canada is working with manufacturers to update the Canadian product monographs of all systemic fluoroquinolone products to include this risk. Health Canada is working with the Drug Safety and Effectiveness Network (DSEN) and the Canadian Agency for Drugs and Technologies in Health (CADTH) to conduct additional studies to better understand the use of fluoroquinolones in Canada. Health Canada has also communicated this information to healthcare professionals and to Canadians.
Foreign health products Foreign Product Alert	These foreign health products have been found by regulators in other countries to contain undeclared drug ingredients or heavy metals (lead). 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.
Gadolinium-based contrast agents (GBCAs) Information Update	Health Canada conducted a safety review of gadolinium-based contrast agents (GBCAs) due to growing scientific evidence that gadolinium may accumulate in the brain following multiple contrast-enhanced magnetic resonance imaging (MRI) scans. Although no health consequences have been identified with gadolinium accumulation in the brain, Health Canada will be working with Canadian manufacturers to update the Canadian product monographs of GBCAs to include this new information.
Human chorionic gonadotropin (hCG) Information Update	Health Canada informed Canadians that human chorionic gonadotropin (hCG) is not authorized as a weight loss aid, and could pose serious health risks. Health Canada has received several complaints that clinics across Canada are advertising hCG for weight loss, which is an unauthorized use.

Levetiracetam Summary Safety Review	This safety review evaluated the risk of acute kidney injury associated with levetiracetam (Keppra and generics). Health Canada's review concluded that there may be a link. The current Canadian product monograph for Keppra informs that cases of acute kidney injury have been reported in patients treated with levetiracetam. Health Canada has requested that the other manufacturers of levetiracetam-containing products also update their Canadian product monographs with the same wording.
Oral retinoid products Summary Safety Review	This safety review evaluated the risk of erectile dysfunction associated with oral retinoid products (isotretinoin, tretinoin, alitretinoin and acitretin). Health Canada's review concluded that there may be a link between the use of oral isotretinoin products and the risk of erectile dysfunction, but could not draw the same conclusion for the other drugs in the class. Health Canada recommended that the Canadian product monographs for all isotretinoin products be made consistent to include this risk.
Selective serotonin reuptake inhibitors (SSRIs) Summary Safety Review	This safety review evaluated the risk of autism spectrum disorders associated with selective serotonin reuptake inhibitors, or SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline). Health Canada's review found that the available evidence is not strong enough to conclude that SSRI use during pregnancy can cause autism in exposed children. Health Canada will continue to monitor this issue.
Unauthorized health product (Blow) Advisory	Health Canada advised Canadians that it seized the unauthorized health product "Blow," by Limitless Pharma, from Atomik Nutrition in Boucherville, Québec. "Blow" is promoted as a pre-workout supplement and is labelled to contain the unauthorized drug 1,3 Dimethylamylamine (DMAA), which may pose serious health risks such as high blood pressure and stroke.
Unauthorized health products (Animal PM, Blade, and Rich Piana 5% Nutrition – 5150) Advisory	Health Canada advised Canadians that it seized three unauthorized workout supplements from various Canadian retailers. "Animal PM" is labelled to contain L-dopa while "Blade" is labelled to contain yohimbine. "Rich Piana 5% Nutrition – 5150" is labelled to contain a combination of synephrine and caffeine.
Unauthorized health products (poppers and sexual enhancement products) Advisory	Health Canada advised Canadians that it seized unauthorized health products being sold at 24 Hour Adult Mart in Toronto, Ontario. Three of the seized products are "poppers" (Rush, Ram and The Original Jungle Juice Platinum) labelled to contain alkyl nitrites. These can be dangerous if inhaled or ingested. The other seized products are promoted for sexual enhancement and labelled to contain drugs that may pose serious health risks (DHEA, pregnenolone, and yohimbe/yohimbine).

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.

REVIEW ARTICLE

Colorectal stents and bevacizumab: increased risk of intestinal perforation

Key points

- Recent scientific publications have described an increased risk of intestinal perforation in patients receiving colorectal stents combined with bevacizumab-based chemotherapy for the treatment of colorectal cancer.
- The concurrent use of bevacizumab and colorectal stents should be considered with caution.
- Healthcare professionals are encouraged to report to Health Canada any cases of perforation suspected of being associated with the use of colorectal stents and/or bevacizumab, and to provide detailed information when describing cases.

Colorectal cancer (CRC) is one of the most common cancers worldwide and remains a major health problem.[1] In Canada, CRC accounted for approximately 13% of new cases of cancer in 2012.[2] Acute malignant colorectal obstruction is a complication of primary or metastatic CRC that can occur in 7 to 29% of patients.[1-4] The optimal management of this severe clinical condition remains challenging.

Colorectal stents are a family of self-expandable metallic stents (SEMS) implanted to maintain colorectal luminal patency in the presence of colorectal obstruction. The stents are used in patients with advanced-stage cancers as an alternative to surgery for palliative care.[2] In addition, they are also used as a bridge to surgery in the management of resectable obstructions.[2,4]

One of the most important stent-related complications is intestinal perforation.[4] The incidence of perforation in patients undergoing colorectal stent placement has been reported in the literature to be between 3.8% and 6.9%, requiring a surgical intervention in 73% of cases, and leading to death in 16.3% of cases.[5]

Bevacizumab is a recombinant humanised monoclonal antibody that selectively binds to and neutralises the biologic activity of human vascular endothelial growth factor.[6] In Canada, bevacizumab in combination with fluoropyrimidine-based chemotherapy is indicated for first-line treatment of patients with metastatic CRC, among other indications. While the addition of this agent to standard fluoropyrimidine-based chemotherapy regimens has been reported to improve survival outcomes in patients with metastatic CRC, it has also been associated with a risk of intestinal perforation.[2,7] Intestinal perforations have been reported in up to 2.7% of bevacizumab-treated patients with metastatic CRC.[6]

While perforation is a known risk of both colorectal stents and bevacizumab therapy, recently, Health Canada identified several publications including a meta-analysis as well as retrospective case series indicating an increased risk of perforation in patients treated concomitantly with stents and bevacizumab-based chemotherapy, as compared to patients receiving chemotherapy without bevacizumab for the treatment of CRC.[2,5,8,9] Based on results from the meta-analysis involving 4 086 patients who underwent colorectal stent placement, the perforation rate for patients receiving bevacizumab-based chemotherapy was 12.5%, whereas the rate of perforation for patients receiving chemotherapy without bevacizumab was 7.0%.[5] A recent Canadian study of a retrospective case series reported perforation in 2 of 10 (20%) patients receiving stents combined with bevacizumab-based chemotherapy.[2] Both patients also had peritoneal disease, and it is unclear if this may have increased the risk of perforation. For patients receiving stents and chemotherapy without bevacizumab, perforation was reported in 3 of 47 (6%) patients.

The proposed mechanism for the increased risk of intestinal perforation with concurrent therapy is that the antiangiogenic effect of bevacizumab may weaken the bowel

wall and predispose the bowel to perforation by SEMS pressure.[9] Given this risk, several publications in the medical literature including the European Society of Gastrointestinal Endoscopy Clinical Guideline on SEMS have indicated that combined therapy should be carefully considered and avoided if possible.[1,2,4,5,10] Due to a similar therapeutic mechanism, other newer antiangiogenic agents may also present an increased risk of perforation when prescribed in patients with a colorectal stent implanted.[1,4,10] However, evidence to support this hypothesis is insufficient.

At the time of its assessment, Health Canada received 6 cases of perforation related to the use of stents and 83 cases of perforation related to the use of bevacizumab. Among these 83 cases, 3 cases reported the use of both bevacizumab and a stent. Two of the 3 cases were discussed in the literature.[2] In the third case, the patient experienced perforation at the level of his stent; however, no specific temporal information was provided on the stent insertion and the use of bevacizumab. Therefore, it was not possible to assess whether the stent was contributory to the perforation. None of the remaining cases reported with either bevacizumab or stents provided information on the concomitant use of both health products.

It is difficult to quantify the increased risk of perforation at this time, given the overall insufficient evidence due to limitations and confounding factors in the published studies. To reduce the potential risk of perforation associated with the use of these products, the concurrent use of bevacizumab and SEMS should be considered with caution.[1,2,4,5,10]

Healthcare professionals are encouraged to report to Health Canada any cases of perforation suspected of being associated with the use of SEMS and/or bevacizumab. When reporting cases to Health Canada, please provide detailed information to facilitate a more thorough assessment of the potential safety issue (see "Did you know?").

References

1. Meisner S. Stent for palliation of advanced colorectal cancer. *Tech Gastrointest Endosc* 2014;16(3):125–8.
2. Imbulgoda A, MacLean A, Heine J, et al. Colonic perforation with intraluminal stents and bevacizumab in advanced colorectal cancer: retrospective case series and literature review. *Can J Surg* 2015;58(3):167-71.
3. Han SH, Lee JH. Colonic stent-related complications and their management. *Clin Endosc* 2014; 47(5): 415–9.
4. Cetinkaya E, Dogrul AB, Tirnaksiz MB. Role of self expandable stents in management of colorectal cancers. *World J Gastrointest Oncol* 2016;8(1):113-20.
5. van Halsema EE, van Hooft JE, Small AJ, et al. Perforation in colorectal stenting: a meta-analysis and a search for risk factors. *Gastrointest Endosc* 2014;79(6):970-82.
6. *Avastin (bevacizumab)* [product monograph]. Mississauga (ON): Hoffmann-La Roche Limited; 2016.
7. Geiger-Gritsch S, Stollenwerk B, Miksad R, et al. Safety of bevacizumab in patients with advanced cancer: a meta-analysis of randomized controlled trials. *Oncologist* 2010;15(11):1179–91.
8. Manes G, de Bellis M, Fuccio L, et al. Endoscopic palliation in patients with incurable malignant colorectal obstruction by means of self-expanding metal stent: analysis of results and predictors of outcomes in a large multicenter series. *Arch Surg* 2011;146(10):1157-62.
9. Small AJ, Coelho-Prabhu N, Baron TH. Endoscopic placement of self-expandable metal stents for malignant colonic obstruction: long-term outcomes and complication factors. *Gastrointest Endosc* 2010;71(3):560-72.
10. van Hooft JE, van Halsema EE, Vanbiervliet G, et al. Self-expandable metal stents for obstructing colonic and extracolonic cancer: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2014; 46(11): 990-1053.

Did you know?

What to include in your adverse reaction or incident reports to Health Canada concerning intestinal perforation following the use of SEMS and/or bevacizumab

It is important to include as many as possible of the following elements:

- Patient characteristics (age, sex, height and weight)
- Name of suspected health product or products if concomitant therapies are administered (including device trade/brand name, model and licence number for medical devices such as stents)
- Description of the adverse reaction or incident
- Dosing information and indication for use of the suspected health product(s)
- Therapy dates: when the use of the suspected health product(s) began and ended
- Changes to therapy with the suspected health product(s) and impact on the patient (e.g., dechallenge/rechallenge information)
- Treatment of the adverse reaction or incident (including date the adverse reaction or incident occurred and was resolved, if applicable)
- Investigations to exclude alternate causes for the adverse reaction or incident
- Relevant history and pre-existing conditions
- Relevant tests/lab data
- Other health products used (including over-the-counter and natural health products) with therapy dates and dosing information

VACCINE SAFETY QUARTERLY SUMMARY

Report for April 1, 2016 to June 30, 2016

Post-market surveillance is essential to monitor the safety and effectiveness of vaccines and other health products. The monitoring of the safety of vaccines is a shared responsibility between Health Canada and the Public Health Agency of Canada (PHAC). Market authorization holders are required to report serious adverse events following immunization (AEFIs) to the Canada Vigilance Program in the Marketed Health Products Directorate at Health Canada. The Canada Vigilance Program also receives voluntary AEFI reports from healthcare professionals and consumers. Provincial and territorial public health authorities report AEFIs from publicly funded vaccine programs to the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) in PHAC to monitor the safety of immunization programs.

This Vaccine safety quarterly summary summarizes AEFI reports received by the Canada Vigilance Program between April 1, 2016 and June 30, 2016. To access reports published by CAEFISS, please visit the CAEFISS Web site.

- From April 1, 2016 to June 30, 2016, the Canada Vigilance Program received 145 reports* of adverse events following immunization (AEFIs) for which vaccines were the suspected cause.
- There were 120 (83%) serious reports. Most of these involved patients with underlying medical conditions and were unlikely related to the vaccination.
- The largest proportion of all AEFIs (serious and non-serious) received involved influenza vaccines (32%) followed by herpes zoster vaccine (25%) and pneumococcal vaccines (20%).
- The most frequently reported AEFIs (serious and non-serious) were all indicative of lack of effectiveness / vaccination failure. These cases were due to incomplete vaccination or had limited information for assessment.
- Other common AEFIs such as nausea, injection site erythema, pain and swelling, and pyrexia are included in the respective Canadian product monographs.
- No new safety signals (potential safety issues) were identified during this period.
- The benefits of vaccines authorized in Canada continue to outweigh the risks.
- Health Canada, in collaboration with PHAC, will continue to closely monitor the safety of vaccines authorized in Canada.

For additional information, contact the Marketed Health Products Directorate.

Note that because of updated information received by the Canada Vigilance Program, there may be differences in the number of AEFI reports and adverse events retrieved at different dates.

* http://www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/glossary_definition-eng.php
This summary may contain duplicate reports. Duplicate reports are reports related to the same patient and event received from more than one source (e.g., pharmacist and consumer). Therefore, the sum of all reports in the line listing may exceed the total number of individual patient cases.

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 for brand name pharmaceutical drugs is available on Health Canada's Web site.

Tramadol-containing products (Durela, Ralivia, Tramacet, Tridural, Ultram, and Zytram XL)

*Additional information concerning the risk of **respiratory depression in CYP2D6 ultra-rapid metabolizers** has been added to the Warnings and Precautions and Action and Clinical Pharmacology sections of the Canadian product monographs for tramadol-containing products: Durela, Ralivia, Tramacet, Tridural, Ultram, and Zytram XL.*

Key messages for healthcare professionals:[1-6]

- Some individuals may be CYP2D6 ultra-rapid metabolizers. These individuals convert tramadol more rapidly than other people into its more potent opioid metabolite O-desmethyltramadol (M1). This rapid conversion could result in higher than expected opioid-like side effects including life-threatening respiratory depression.
- The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese, Japanese and Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups.

References

1. *Durela (tramadol)* [product monograph]. Mississauga (ON): Cipher Pharmaceuticals Inc.; 2016.
2. *Ralivia (tramadol)* [product monograph]. Laval (QC): Valeant Canada LP.; 2016.
3. *Tramacet (tramadol and acetaminophen)* [product monograph]. Toronto (ON): Janssen Inc.; 2017.
4. *Tridural (tramadol)* [product monograph]. Saint-Laurent (QC): Paladin Labs Inc.; 2016.
5. *Ultram (tramadol)* [product monograph]. Toronto (ON): Janssen Inc.; 2017.
6. *Zytram XL (tramadol)* [product monograph]. Pickering (ON): Purdue Pharma; 2016.

Votrient (pazopanib)

*The risk of **male-mediated teratogenesis** has been included in the Warnings and Precautions section of the Canadian product monograph for Votrient (pazopanib).*

Key message for healthcare professionals:[7]

- Male patients (including those who have had vasectomies) with sexual partners who are pregnant, possibly pregnant, or who could become pregnant should use condoms during sexual intercourse while taking pazopanib and for at least 2 weeks after the last dose of drug.

Reference

7. *Votrient (pazopanib)* [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2016.

Zyprexa (olanzapine)

*The risk of **Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)** has been included in the Warnings and Precautions and Adverse Reactions sections of the Canadian product monograph for Zyprexa (olanzapine).*

Key messages for healthcare professionals:[8]

- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported with olanzapine exposure.
- DRESS consists of a combination of 3 or more of the following: cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, lymphadenopathy and one or more systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and pericarditis.
- Zyprexa should be discontinued if DRESS is suspected.

Reference

8. *Zyprexa (olanzapine)* [product monograph]. Toronto (ON): Eli Lilly Canada Inc.; 2016.

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
- Canadian Drug Shortage Database

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.

Pub.: 160256
ISSN: 2368-8025