



Health Product InfoWatch

November 2015

HEALTH PRODUCTS MENTIONED IN THIS ISSUE

Pharmaceuticals and Biologics

- Allerject (epinephrine)
- Bexsero (multicomponent meningococcal B vaccine [recombinant, adsorbed])
- Bravelle (75 IU urofollitropin for injection, purified)
- Forxiga (dapagliflozin)
- Invokana (canagliflozin)
- Jaydess (levonorgestrel-releasing intrauterine system)
- Mirena (levonorgestrel-releasing intrauterine system)
- SGLT2 inhibitors
- Tramadol products
- Tridural (tramadol HCl extended release tablets)
- Vaccines (influenza)
- Vincristine Sulfate Injection USP 1 mg/mL
- Zostavax (zoster vaccine live, attenuated [Oka/Merck])

Medical Devices

- Flexi-T(+) 300 and 380
- Liberté TT 380
- Liberté UT 380
- Mona Lisa 5 (NT Cu380)
- Mona Lisa 10 (CuT 380A QL)
- Mona Lisa N (ST Cu300)
- Nova-T (Cu 200 Ag)

Natural Health Products

- Bio K 20 Potassium
- Bio-K Plus
- Strontium-containing natural health products

Other

- Foreign 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.

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REPORTING ADVERSE REACTIONS

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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 October 2015 by Health Canada.

Allerject (epinephrine)

Advisory

All lots of Allerject (0.15 mg/0.15 mL and 0.3 mg/0.3 mL strengths of epinephrine auto-injectors) were recalled by Sanofi-aventis Canada Inc. due to issues that may potentially affect the delivery of the required amount of epinephrine.

Bravelle (75 IU urofollitropin for injection, purified)

Health Product Risk
Communication

Four lots of Bravelle (75 IU urofollitropin for injection, purified) were recalled by Ferring Inc. Canada due to decreased follicle stimulating hormone (FSH) potency which could result in a reduced therapeutic effect.

Foreign health products

Foreign Product Alert

These foreign health products have been found by regulators in other countries to contain undeclared drug ingredients. These products are not authorized for sale in Canada and have not been found on the Canadian marketplace, but it is possible they may have been brought into the country by travellers or purchased over the Internet.

SGLT2 inhibitors (Invokana and Forxiga)

Summary Safety Review

This safety review evaluated the potential risk of acute kidney injury associated with the use of Invokana (canagliflozin) and Forxiga (dapagliflozin). Health Canada found a link between events of acute kidney injury and the use of Invokana and Forxiga. Health Canada is working with the manufacturers to update the Canadian prescribing information for these products to reflect this information and will continue to monitor this issue.

Strontium

Summary Safety Review
Information Update

This safety review evaluated the potential risk of cardiovascular side effects associated with the use of strontium. Health Canada did not find information linking strontium with cardiovascular risks at doses less than 680mg per day. While uncertainties remain, Health Canada is taking a precautionary approach by recommending updates to the labels of products containing strontium and by informing consumers not to use these products if they have pre-existing cardiovascular problems.

Tridural (tramadol HCl extended release tablets)

Health Product Risk
Communication

The tablet markings ("LP 100", "LP 200" and "LP 300") that help differentiate the 3 strengths of Tridural (tramadol HCl extended release tablets) tablets have been removed on certain lots. The lack of tablet markings may cause confusion to patients and increase the risk for medication errors.

Vincristine Sulfate Injection USP 1 mg/mL

Health Product Risk Communication

Certain lots of Vincristine Sulfate Injection USP 1 mg/mL have incorrect or outdated safety information on the inner/outer labels and package insert. Healthcare professionals are requested to consult the approved Canadian product monograph for Vincristine Sulfate Injection USP 1 mg/mL which has the most updated information.

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.

International case of respiratory depression in a child with ultrarapid CYP2D6 metabolism after tramadol use

A recently published case report described a 5-year-old child from France who underwent ambulatory adenotonsillectomy under general anesthesia for obstructive sleep apnea syndrome (OSAS).¹ The patient was discharged from the hospital after an uneventful postoperative stay of 6 hours. Eight hours after being discharged (at 11 PM), he complained of increasing pain and was given a single 20 mg dose of tramadol oral solution. The next morning, his parents found him lethargic and brought him to the hospital. He was comatose on arrival with constricted pupils, minimal respiratory effort, frequent episodes of apnea and an oxygen saturation of 48% in room air. The patient improved dramatically with non-invasive ventilation and naloxone administration. Measurements of urinary concentrations of tramadol and its active metabolite O-desmethyltramadol revealed high levels of the metabolite (relative to the parent compound). Cytochrome P450 2D6 (CYP2D6) genotyping results were consistent with ultrarapid CYP2D6 metabolism. It was also noted in the assessment of the case that the presence of OSAS may have contributed to the severity of the respiratory depression.

Tramadol is an opioid analgesic used to manage moderate to moderately severe pain in adults.²⁻⁷ In Canada, tramadol is available as a single agent under the brand names Durela, Ralivia, Tridural, Ultram, and Zytram XL. It is also available in combination with acetaminophen under the brand name Tramacet. Generic forms are available for Ultram and Tramacet. Tramadol is not marketed as an oral solution and is not recommended for use in patients under 18 years of age in Canada.

Key points

- A case of severe respiratory depression involving a child treated with tramadol for pain, and who was found to be an ultrarapid CYP2D6 metabolizer, was published in the literature.
- In Canada, tramadol-containing products are indicated for pain management in adults and are not recommended for use in patients under 18 years of age.
- Healthcare professionals are encouraged to report to Health Canada any adverse reactions suspected of being associated with tramadol.

Did you know?

Codeine is converted into morphine in the body by CYP2D6. Ultrarapid CYP2D6 metabolizers convert codeine into morphine more rapidly, which can potentially lead to an unexpected morphine overdose. Health Canada has [previously recommended](#) that medications containing codeine should not be used in children less than 12 years of age.

Once ingested, tramadol is converted into its active metabolite O-desmethyltramadol by the liver enzyme CYP2D6. Certain individuals, known as ultrarapid metabolizers, have genetic variations of CYP2D6 that result in increased enzyme activity and cause tramadol to be converted more rapidly into O-desmethyltramadol.

O-desmethyltramadol has a 200-fold higher affinity for μ -opioid receptors compared to its parent compound and contributes to tramadol's analgesic properties. However, patients who are ultrarapid CYP2D6 metabolizers are more likely to have higher-than-normal amounts of the O-desmethyltramadol, which may result in adverse reactions (ARs). Tramadol, similar to opioid pain medications such as codeine and morphine, is known to be associated with an increased risk of central nervous system depression and respiratory depression when too much is taken. Tramadol-containing products are not labelled for risks associated with ultrarapid CYP2D6 metabolism, such as respiratory depression.

Health Canada is currently evaluating all information on this safety issue and will communicate final conclusions and actions when the review is complete. As of June 30, 2015, Health Canada has not received any reports of respiratory depression involving tramadol use in patients under 18 years of age.

Healthcare professionals are encouraged to report to Health Canada any ARs suspected of being associated with tramadol. Information such as dosage, duration of exposure to tramadol, concomitant medications, relevant patient conditions and time to onset of symptoms are important to include when reporting ARs related to this issue.

References

1. Orliaguet G, Hamza J, Couloigner V et al. A case of respiratory depression in a child with ultrarapid CYP2D6 metabolism after tramadol. *Pediatrics* 2015;135(3):e753-e5.
2. *Durela (tramadol hydrochloride)* [product monograph]. Mississauga (ON): Cipher Pharmaceuticals Inc.; 2014.
3. *Ralivia (tramadol hydrochloride)* [product monograph]. Laval (QC): Valeant Canada LP; 2014.
4. *Tramacet (acetaminophen and tramadol hydrochloride)* [product monograph]. Toronto (ON): Janssen Inc.; 2014.
5. *Tridural (tramadol hydrochloride)* [product monograph]. Saint-Laurent (QC): Paladin Labs Inc.; 2014.
6. *Ultram (tramadol hydrochloride)* [product monograph]. Toronto (ON): Janssen Inc.; 2014.
7. *Zytram XL (tramadol hydrochloride)* [product monograph]. Pickering (ON): Purdue Pharma; 2014.

PRODUCT CONFUSION ALERT

Health product name confusion: Bio-K Plus and Bio K 20 Potassium

Name confusion can occur at any step of the drug use process, including during medication reconciliation, when no physical product may be present. In cases where the name of the product is the only information available, it is important to mitigate the potential risk of error by ensuring correct identification of products.

Health Canada was recently informed of two cases of product confusion between natural health products (NHPs) containing different active ingredients but similar brand names: Bio-K Plus and Bio K 20 Potassium.

Bio-K Plus/Bio-K+ is a line of oral lactobacillus-containing probiotic supplements. Manufactured by Bio-K Plus International Inc., these products have been on the Canadian market since 1996 and licensed as NHPs since 2009.

Bio K 20 Potassium is an oral potassium supplement containing 20 mEq (780 mg) of potassium per tablet (as potassium chloride). This product has been licensed as a NHP since 2011 and is manufactured by Biomed Pharma.

In the two instances reported to Health Canada, the patients' medication reconciliation list (a summary of medications a patient is taking that often accompanies them on admission to hospital) included "Bio-K 20 potassium". In one case, the admitting physician assumed it to be Bio-K Plus probiotic and did not prescribe the medication, as probiotics were not part of this hospital's formulary. In the second case, "Bio-K 20 1 tablet daily" was prescribed by the physician, as per the patient's list. The receiving pharmacist assumed the prescription to be for the probiotic and advised the ward that it would not be supplied since it was a non-formulary product. As a result, both patients missed an unknown number of doses of potassium.

Inadvertent substitution of one "Bio K" named product for another over a period of time may result in hyperkalemia or hypokalemia. Patients with high or low blood potassium may be asymptomatic until serious adverse effects occur.¹

Health Canada is working with Biomed Pharma on a name change for their potassium product.

Reference

1. Porter RS, Kaplan JL, et al. Chapter 97. Fluid and Electrolyte Metabolism: Disorders of Potassium Concentration. In: Porter RS, Kaplan JL, et al., editors. *The Merck Manual of Diagnosis and Therapy*. 19th ed. Whitehouse Station (NJ): Merck Sharp & Dohme Corp; 2011. (accessed 2015 Oct 1).

VACCINE SAFETY REVIEW

Report for January 1, 2015 to March 31, 2015

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 (MAHs) are required to report serious adverse events following immunization (AEFIs) to the Canada Vigilance Program in the Marketed Health Products Directorate (MHPD) 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 Review summarizes AEFI reports received by the Canada Vigilance Program between January 1, 2015 and March 31, 2015. To access reports published by CAEFISS, please visit the [CAEFISS website](#).

- From January 1, 2015 to March 31, 2015, the Canada Vigilance Program received 229 reports of adverse events for which vaccines were the suspected cause.
- There were more reports received during this period than was previously received during the same period of 2013 (125 reports) and 2014 (129 reports). This increase was because of the reports involving Bexsero (multicomponent meningococcal B vaccine [recombinant, adsorbed], 57 reports) and Zostavax (zoster vaccine live, attenuated [Oka/Merck], 51 reports).
- There were 94 (41%) serious reports. Most of these involved patients with underlying medical conditions and were unlikely related to the vaccination.
- The most frequently reported AEFIs were vaccination site erythema, pain in the extremities, fatigue, vaccination site swelling, headache, pyrexia, vaccination site pain, nausea, vomiting and erythema. The majority of these adverse events involved Bexsero, Zostavax, and influenza vaccines. These are known events following immunization and are captured 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.

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](#).

Hormonal intrauterine systems: Jaydess (levonorgestrel-releasing intrauterine system) and Mirena (levonorgestrel-releasing intrauterine system)

Non-hormonal intrauterine devices: Flexi-T(+) 300 and 380, Liberté TT 380, Liberté UT 380, Mona Lisa 5 (NT Cu380), Mona Lisa 10 (CuT 380A QL), Mona Lisa N (ST Cu300), and Nova-T (Cu 200 Ag)

The increased risk of **uterine perforation** has been included in the Warnings and Precautions and Postmarket Adverse Drug Reactions sections of the Canadian product monographs for hormonal intrauterine systems and in the medical device instructions for use for non-hormonal intrauterine devices.

Key message for healthcare professionals:

- A recent study showed that both breastfeeding at the time of device insertion and insertion up to 36 weeks postpartum were associated with an increased risk of uterine perforation (Table 1). These risk factors were independent of the type of device inserted.¹
- The risk of uterine perforation may be increased in women with abnormal uterine anatomy or who have a fixed retroverted uterus.
- Delayed detection of perforation may lead to device migration outside the uterine cavity and/or injury to other adjacent organs.

Table 1: Incidence of perforation per 1000 insertions for the entire study cohort, stratified by breastfeeding status and time since delivery at insertion (parous women)

	Breastfeeding at time of insertion	Not breastfeeding at time of insertion
Insertion ≤ 36 weeks after delivery	5.6 (95% CI 3.9-7.9; n=6 047 insertions)	1.7 (95% CI 0.8-3.1; n=5 927 insertions)
Insertion > 36 weeks after delivery	1.6 (95% CI 0.0-9.1; n=608 insertions)	0.7 (95% CI 0.5-1.1; n=41 910 insertions)

Reference

1. Heinemann K, Reed S, Moehner S et al. Risk of uterine perforation with levonorgestrel-releasing and copper intrauterine devices in the European Active Surveillance Study on Intrauterine Devices. *Contraception* 2015;91(4):274-9.

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.

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