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Health Product InfoWatch

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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

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 2016 by Health Canada.

Atypical antipsychotics Summary Safety Review	This safety review evaluated the risk of urinary retention associated with atypical antipsychotics. Health Canada's review found evidence supporting a potential link. The Canadian product monograph for olanzapine will be updated to highlight what is currently known about the risk of urinary retention. The update will be consistent with the safety information provided for the other products, which is considered at this time to be sufficient to remind about the risk of urinary retention.
Cervarix (human papillomavirus vaccine types 16 and 18 [recombinant, AS04 adjuvanted]) Summary Safety Review	This safety review evaluated the risk of Guillain-Barré Syndrome (GBS) associated with Cervarix (human papillomavirus vaccine types 16 and 18 [recombinant, AS04 adjuvanted]). Health Canada's review of the available information did not find an increased risk of GBS following vaccination with Cervarix. Health Canada will continue to monitor this issue.
Faslodex (fulvestrant) Health Product Risk Communication	Faslodex (fulvestrant) can interfere with antibody based estradiol measurement by immunoassay due to structural similarity of fulvestrant and estradiol. This can result in falsely elevated estradiol levels. False estradiol positive assays may lead to misinterpretation of the menopausal status of women which can put patients at risk for unnecessary surgery or endocrine therapy modification. New warnings have been added to the Canadian product monograph for Faslodex advising of this safety risk.
Fluorouracil Injection, BP (5-fluorouracil) 5 g/100 mL Health Product Risk Communication	Accord Healthcare Canada Inc. and Health Canada have identified broken or leaking vials of Fluorouracil Injection, BP 5 g/100 mL. Sterility of contents of the cracked or leaking vials could be compromised. Inadvertent exposure of healthcare professionals to 5-fluorouracil from leaking vials may lead to serious adverse reactions. Vials that show cracks, leakage, or white powder on the outside of the vial should not be used.
Foreign health products Foreign Product Alert	These foreign health products have been found by regulators in other countries to contain undeclared drug ingredients. 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.

Formula kidney dialysis machines Advisory	Health Canada advised Canadians that Formula kidney dialysis machines manufactured by Bellco may pose a potential fire hazard. According to the company, the chance of a fire occurring is low and patients should continue using their machines for dialysis treatment until service technicians can take the appropriate safety precautions.
Gilenya (fingolimod) Summary Safety Review	This safety review evaluated the risk of cancer associated with Gilenya (fingolimod). The Canadian product monograph for Gilenya includes information about the risk of cancer, especially skin cancers. Health Canada's review concluded that previous actions including labelling changes and annual assessments of information pertaining to cancer associated with the use of Gilenya remain appropriate given the information reviewed. Health Canada will continue to monitor this issue.
Havrix (hepatitis A vaccine, inactivated) Summary Safety Review	This safety review evaluated the risk of thrombocytopenia associated with Havrix (hepatitis A vaccine, inactivated). Health Canada's review of the available data did not identify a link between vaccination with Havrix and thrombocytopenia. Health Canada will continue to monitor this issue.
Heater-cooler devices Health Product Risk Communication	There have been international reports of nontuberculous mycobacteria (NTM) infections associated with heater-cooler devices used in cardiothoracic surgery; a small number of possible Canadian cases are under investigation. Healthcare professionals should consider testing for NTM in ill patients with signs of infection who have a history of cardiothoracic surgery. Health Canada reminded healthcare facilities to strictly follow the cleaning and disinfection procedures recommended by the manufacturers of the devices. Health Canada is working with heater-cooler device manufacturers to determine additional measures to further mitigate the risk of NTM infections.
Homeopathic teething products Information Update	Health Canada followed up with Canadians concerning a recent warning issued by the U.S. Food and Drug Administration regarding possible safety issues involving homeopathic teething products in the United States. At this time, there is no indication of a similar safety concern in Canada. Health Canada will continue to monitor this issue.
Incretin-based therapies Summary Safety Review	This safety review evaluated the risk of pancreatic cancer associated with incretin-based therapies: alogliptin, linagliptin, saxagliptin, sitagliptin (alone or in combination with metformin), and exenatide. Health Canada's review concluded that there is not enough evidence at this time to confirm a link. Health Canada will continue to monitor this issue.

Levetiracetam and methotrexate Summary Safety Review	This safety review evaluated the risk of an interaction between levetiracetam and methotrexate. Health Canada's review concluded that there is a potentially greater risk of adverse reactions when levetiracetam and methotrexate are taken together. The assessment recommended that the Canadian product monographs for levetiracetam and methotrexate products be updated to inform about this drug interaction.
Soliris (eculizumab) Health Product Risk Communication	An increased risk of hemolysis or low hemoglobin has been observed when patients already being treated with Soliris (eculizumab) were vaccinated against serogroup B meningococcal infection with Bexsero. To minimize the risk of hemolysis when patients who are being treated with Soliris are vaccinated, it is recommended that these patients be vaccinated only after their disease has been controlled and within one week following Soliris infusion, when the Soliris concentration in the blood is considered to be relatively high. The Canadian product monograph has been updated to include this new safety information.
St. Jude Medical implantable defibrillators Information Update	Health Canada informed Canadians that some batteries in implantable cardioverter defibrillators and cardiac resynchronization therapy devices manufactured by St. Jude Medical may deplete earlier than expected. Early battery depletion may occur suddenly, anywhere between hours and days, and without warning.
SurThrival colostrum products Advisory	Health Canada has requested that SurThrival voluntarily recall all lots of its colostrum products because they contain undeclared milk allergens. These authorized natural health products are marketed to strengthen the immune system, and can be found online and at various retailers across Canada.
Tumour necrosis factor (TNF) alpha blockers Summary Safety Review	This safety review evaluated the risk of autoimmune hepatitis associated with tumour necrosis factor (TNF) alpha blockers. Health Canada's review concluded that there is a possible link between the risk of autoimmune hepatitis and the use of TNF alpha blockers. The Canadian product monographs for Humira, Remicade and Enbrel already stated liver inflammation as a very rare event that may lead to liver failure. The manufacturers of Cimzia and Simponi have updated their Canadian product monographs to include this risk.
Unauthorized health product Advisory	Health Canada informed Canadians that an unauthorized health product, "Nature's Power Solutions Acidophilus Blend" contains undeclared milk allergens. The product is marketed to help the colon and digestive system and was sold at Joy in Health & Nutrition Inc., in Red Deer, Alberta.

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

Phenylephrine and acetaminophen drug interaction

Key points

- A pharmacokinetic interaction between oral phenylephrine and acetaminophen, leading to an increase in the relative bioavailability of phenylephrine was identified through information shared by the European Medicines Agency.
- It has been suggested that the combination of phenylephrine and acetaminophen has the potential to increase blood pressure more than phenylephrine alone; however, the clinical evidence to support this is insufficient.
- Healthcare professionals are encouraged to report to Health Canada any cases of hypertension or any other serious adverse reaction suspected of being associated with the use of a phenylephrine-acetaminophen combination product.

Phenylephrine is a sympathomimetic drug that acts predominantly as a selective α_1-adrenergic receptor agonist.[1] In Canada, it is frequently included in non-prescription oral health products intended for the temporary relief of cold and allergy symptoms. Many of these health products also contain acetaminophen. There are currently numerous non-prescription products on the Canadian market that combine phenylephrine and acetaminophen.

A pharmacokinetic interaction between oral phenylephrine and acetaminophen was identified through information shared by the European Medicines Agency, and recent published studies that have investigated this issue.[2-4] In one study discussing a series of 4 randomized, open-label, crossover studies, a pharmacokinetic interaction between phenylephrine and acetaminophen was identified.[3] This data from 90 healthy male volunteers, showed that the administration of phenylephrine 10 mg and acetaminophen 1000 mg resulted in nearly a quadrupling in the maximum plasma concentration (C_{max}) and a doubling in phenylephrine plasma exposure, or area under the curve (AUC). Halving the dose of phenylephrine to 5 mg, combined with acetaminophen 1000 mg, produced a phenylephrine plasma time-concentration profile similar to that for 10 mg of phenylephrine administered alone. However, the study was unable to show any changes in mean arterial blood pressure (MAP) in the healthy volunteers.

The same authors conducted a study that was a simulation model using data from ophthalmic exposure to phenylephrine to predict MAP changes, combined with pharmacokinetic data from healthy individuals given an oral combination of phenylephrine and acetaminophen.[4] This study of theoretical nature predicted a modest increase in MAP when phenylephrine 10 mg was co-administered with acetaminophen 1000 mg in comparison to phenylephrine administered alone.

According to the authors of these studies, the mechanism of the interaction is likely during the drug absorption phase. Both phenylephrine and acetaminophen undergo extensive first-pass metabolism via sulfation in the intestinal wall and liver. They suggest that the saturation of the sulfation pathways by acetaminophen results in a reduction in the amount of phenylephrine undergoing first-pass metabolism, leading to an increase in phenylephrine bioavailability. However, there is a large degree of inter-individual variability in phenylephrine pharmacokinetics.[3]

As of January 20, 2016, Health Canada received one serious Canadian report of increased blood pressure which was suspected of being associated with the use of a phenylephrine-acetaminophen combination product, and which contained enough information to be further assessed. The case report describes an increase in blood pressure associated with the use of a phenylephrine-acetaminophen combination product. However, this case is confounded by pre-existing hypertension which may have been aggravated by the suspect product. After discontinuation of the product and adjustment of the patient's antihypertensive medication, the blood pressure returned to normal. Based on the available information, Health Canada determined that the increase in the patient's blood pressure could possibly be related to an interaction between phenylephrine and acetaminophen. However, other causes such as concomitant medications and co-morbidities could not be ruled out.

Health Canada is aware of another published report in the literature of a cardiovascular adverse reaction (intracerebral hemorrhage) following the use of a cold medication containing phenylephrine and acetaminophen.[5] The patient had no significant past medical history and specifically, no hypertension. However, it could not be confirmed that this case was due to an interaction between phenylephrine and acetaminophen, given that there were multiple ingredients in the product, and the patient had used multiple cough and cold products in the previous 30 days.

Overall, there is limited evidence of a pharmacokinetic interaction between oral phenylephrine and acetaminophen leading to an increase in the relative bioavailability of phenylephrine.[4] It has been suggested that the combination of phenylephrine and acetaminophen has the potential to increase blood pressure more than phenylephrine alone. However, the clinical evidence to support this interaction is insufficient at this time.

In Canada, currently, all non-prescription, phenylephrine-containing products must include a warning statement to *"ask a doctor before use if you have heart disease, high blood pressure, thyroid disease or diabetes"*. Healthcare professionals are also reminded to ask patients about the use of any non-prescription medications. Healthcare professionals are encouraged to report to Health Canada any cases of hypertension or any other serious adverse reaction suspected of being associated with the use of a phenylephrine-acetaminophen combination product.

References

1. Brayfield A (ed). *Martindale: The complete drug reference*. [online] London (UK): Pharmaceutical Press: 2016. (accessed Oct 13, 2016)
2. Atkinson HC, Stanescu I, Anderson BJ. Increased phenylephrine plasma levels with administration of acetaminophen. *N Engl J Med* 2014;370(12):1171-2.
3. Atkinson HC, Stanescu I, Salem II, et al. Increased bioavailability of phenylephrine by co-administration of acetaminophen: results of four open-label, crossover pharmacokinetic trials in healthy volunteers. *Eur J Clin Pharmacol* 2015;71(2):151-8.
4. Atkinson HC, Potts AL, Anderson BJ. Potential cardiovascular adverse events when phenylephrine is combined with paracetamol: simulation and narrative review. *Eur J Clin Pharmacol* 2015;71(8):931-8.
5. Tark BE, Messe SR, Balucani C, et al. Intracerebral hemorrhage associated with oral phenylephrine use: a case report and review of the literature. *J Stroke Cerebrovasc Dis* 2014;23(9):2296-300.

PRODUCT CONFUSION ALERT

Posanol (posaconazole) – Oral dosage forms not interchangeable

Posanol (posaconazole) is an antifungal agent available on the Canadian market as a 40 mg/mL oral suspension (marketed in 2007), a 100 mg delayed-release tablet (marketed in 2014) and a 300 mg/vial (18 mg/mL) solution for injection (marketed in 2014).

International and Canadian medication errors have occurred with posaconazole use due to confusion related to the 2 oral formulations (wrong formulation was dispensed).[1-4] Use of the incorrect formulation may lead to overdosage or lack of therapeutic effect due to underdosing.

Posaconazole delayed-release tablets have substantially higher bioavailability than the oral suspension.[2] As a result, the dosage for a given indication is lower for the delayed-release tablets compared to the suspension. The recommended dosing frequency for Posanol (posaconazole) also varies between the 2 oral formulations.[5] In addition, the 2 formulations have different instructions regarding administration with food. The delayed-release tablets may be taken with or without food, whereas the oral suspension should only be administered with a meal or nutritional supplement.

The risk of medication error is compounded by the fact that the delayed-release tablets were introduced to the market several years after the oral suspension. Healthcare providers may not be aware that a second oral formulation is available or that their bioavailabilities are significantly different.

In order to avoid inadvertent confusion between the 2 oral formulations resulting in adverse reactions or ineffective treatment, prescribers are reminded to specify which oral formulation is intended and pharmacists are encouraged to confirm that the correct oral formulation and directions for use are being provided to the patient.

Posanol (posaconazole)

The Warnings and Precautions and Dosage and Administration sections of the Canadian product monograph have recently been updated to warn healthcare professionals that ***Posanol (posaconazole) delayed-release tablets and the oral suspension are not interchangeable*** *and to follow the specific dosage recommendations for each oral formulation. The package labels have also been updated to warn of this risk.*

Key messages for healthcare professionals:[5]

- Oral Formulations: Posanol delayed-release tablets and Posanol oral suspension are NOT interchangeable.
- Posaconazole plasma concentrations following administration of Posanol tablets are generally higher than those obtained with posaconazole oral suspension.

References

1. Martino J, Fisher BT, Bosse KR, et al. Suspected posaconazole toxicity in a pediatric oncology patient. *Pediatr Blood Cancer* 2015;62(9):1682.
2. Cohen MR, Smetzer JL. Posaconazole dose depends on dosage form; limit magnesium sulfate premix to 20 gram bags; vancomycin injection for oral use given intramuscularly; phenylephrine injection needs dilution for intravenous bolus use; similar drug names confused. *Hosp Pharm* 2014;49(9):796-9.
3. Worth repeating: Posaconazole dosage forms not interchangeable. *Acute Care ISMP Medication Safety Alert* 2014;19(25):1-2.
4. Health Canada has the data on file, January, 2016.
5. *Posanol (posaconazole)* [product monograph]. Kirkland (QC): Merck Canada Inc.; 2016.

Did you know?

In the United States and in some countries in Europe, posaconazole delayed-release tablets and oral suspension are available under the brand name Noxafil.

VACCINE SAFETY QUARTERLY SUMMARY

Report for January 1, 2016 to March 31, 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 January 1, 2016 and March 31, 2016. To access reports published by CAEFISS, please visit the CAEFISS website.

- From January 1, 2016 to March 31, 2016, the Canada Vigilance Program received 108 reports of adverse events for which vaccines were the suspected cause.
- The largest proportion of reports received were for influenza vaccines (27 reports), followed by Zostavax (zoster vaccine live, attenuated [Oka/Merck]; 24 reports) and the pneumococcal vaccines (11 reports).
- There were 90 (83%) serious reports. Most of these involved patients with underlying medical conditions and were unlikely related to the vaccination.
- The most frequently reported AEFIs from the serious reports were headache, nausea, pain in extremity, pyrexia and injection site pain. These are known events following immunization and 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.

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.

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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