Health Canada Santé Canada

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Health Product InfoWatch

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REPORTING ADVERSE REACTIONS

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HEALTH PRODUCTS MENTIONED IN THIS ISSUE

Pharmaceuticals and Biologics

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Other

Sage brand disposable skin cloths
Unauthorized health product "Black Orange"
Unauthorized 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.

Canada

ANNOUNCEMENT

New requirements for over-the-counter acetaminophen product labels

Health Canada has recently revised the Guidance Document - Acetaminophen Labelling Standard to ensure that the labels include:

- clearer instructions on packages highlighting the importance of:
  - using the lowest effective dose
  - not exceeding the recommended daily maximum (4,000 mg for adults) in a 24-hour period
  - using these products for no more than 5 days for pain or 3 days for fever
  - not mixing them with alcohol if drinking 3 or more drinks in a day
- the statement "**contains acetaminophen**" in bold, red text in the top right corner on the front of the package to make it easier for consumers to know that a product contains this drug
- a new Drug Facts table for packages to provide more uniform, easier to find, read and understand product instructions, warnings and other safety information

The revised acetaminophen labelling standard also recommends that all children's liquid products include a calibrated dosing device.

The label changes apply immediately to new products that will be introduced into the Canadian market. The labels of the products already on the market are expected to be updated within 18 months.

Health Canada also issued a Notice to industry advising of a policy to limit the amount of acetaminophen in prescription combination products to no more than 325 mg.

If you are looking for consumer resources, Health Canada has prepared the following:

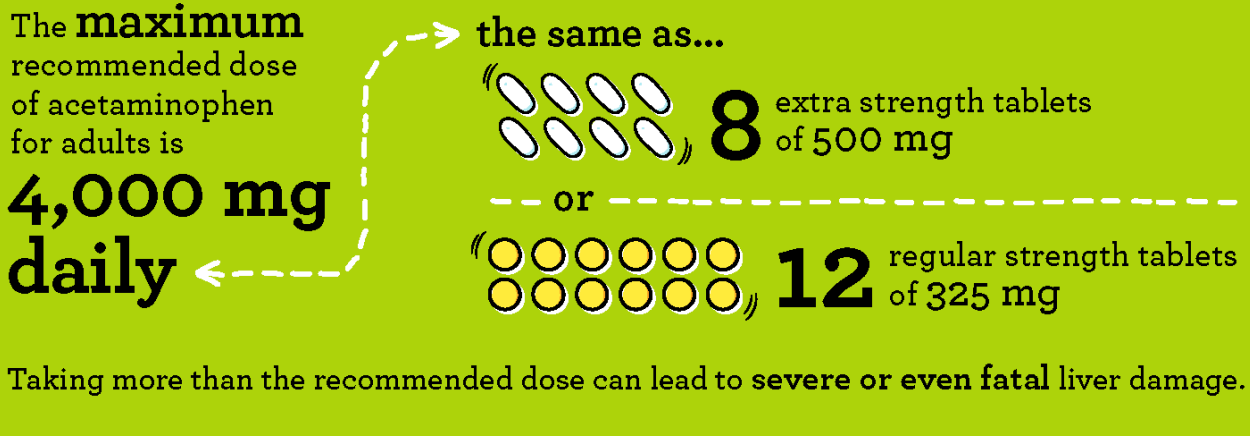
Let's talk about acetaminophen - Fact sheet

Acetaminophen: Know your dose - Poster

Using acetaminophen safely - Web banners

Acetaminophen and Acetaminophen and children

Know your dose



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 September 2016 by Health Canada.

Acetaminophen Information Update	Health Canada has released an updated Labelling Standard for over-the-counter acetaminophen products to help consumers use these products more safely. Product packages will include clearer instructions and stronger warnings to help reduce the potential for liver damage. Health Canada also issued a Notice to industry advising of a policy to limit the amount of acetaminophen in prescription combination products to no more than 325 mg.
Gabapentin Summary Safety Review	This safety review evaluated the risk of respiratory depression associated with gabapentin. Health Canada's review concluded that there is evidence of a link between the use of gabapentin, in general, and the risk of respiratory depression. Health Canada will work with manufacturers to update the Canadian product monographs to further warn about this risk.
Imipenem and Cilastatin for Injection Health Product Risk Communication	The multi-vial carton of Hospira's Imipenem and Cilastatin for Injection, 500 mg/500 mg, has incorrect information regarding the final diluted concentration on the outer side panel. It indicates the diluted concentration is 2.5 mg/mL instead of 5 mg/mL (when prepared as per the instructions in the package insert). Healthcare professionals should consult the package insert for the proper reconstitution and dilution instructions.
Isotretinoin Information Update	Health Canada reminded Canadians of the serious risk of birth defects associated with taking isotretinoin while pregnant. Health professionals and women who are using, or considering using this drug are reminded of the importance of not getting pregnant while taking this treatment.
Primaxin 500 (imipenem and cilastatin sodium) Health Product Risk Communication	The label on the outer package of Primaxin 500 (imipenem and cilastatin sodium) contains incorrect information regarding the final diluted concentration after reconstitution. It indicates the diluted concentration is 2.5 mg/mL instead of 5 mg/mL (when prepared as per the instructions in the package insert). Healthcare professionals are directed to consult the package insert or the Canadian product monograph for the proper reconstitution and dilution instructions.

"Rapidcuts Shredded" capsules Advisory – expanded recall Advisory – 2 lots	All lots of Allmax-brand "Rapidcuts Shredded" capsules (NPN 80041658) were recalled by Healthy Body Services Inc., as a precaution. Two lots were found to contain an undeclared prescription drug (yohimbine hydrochloride).
Sage brand disposable skin cloths Information Update	Some lots of various Sage brand single-use, pre-moistened disposable cloths used for cleansing or protecting skin were recalled due to possible contamination with the bacteria *Burkholderia cepacia*. The affected cloths are used mainly in healthcare settings such as hospitals, but are also sold nationwide at retail pharmacies and medical supply stores.
Soliris (eculizumab) and Bexsero (multicomponent meningococcal B vaccine [recombinant, adsorbed]) Summary Safety Review	This safety review evaluated the increased risk of hemolysis and low hemoglobin when patients receiving Soliris (eculizumab) were vaccinated with Bexsero (multicomponent meningococcal B vaccine [recombinant, adsorbed]). Health Canada's review concluded that there was an increased risk of low hemoglobin or hemolysis when patients already receiving Soliris were vaccinated with Bexsero. The manufacturer has updated the Canadian product monograph for Soliris to include the risk of hemolysis with vaccines against *Neisseria meningitidis* and recommendations on timing of vaccination to minimize this risk.
Unauthorized health product "Black Orange" Advisory	Health Canada advised Canadians that an unauthorized product, "Black Orange", was seized from Keebo Sports Supplements in Regina, Saskatchewan. The product is sold as a pre-workout stimulant and is labelled to contain ingredients that can pose serious health risks (yohimbine hydrochloride, and the combination of ephedrine and caffeine).
Unauthorized health products Information Update	Health Canada advised Canadians that 5 unauthorized products promoted as workout or weight loss supplements were seized from Keebo Sports Supplements in Winnipeg, Manitoba. The products are labelled to contain various prescription and other drug substances that may pose serious risks to the health of Canadians.
Zarontin (ethosuximide) Health Product Risk Communication Information Update	Erfa Canada 2012 Inc. and Health Canada have received reports of broken or leaking Zarontin (ethosuximide) soft gel capsules, including reports of patients experiencing a higher frequency of seizures after taking capsules that appeared cloudy, broken, leaking, sticky or clumping together. Pharmacists are reminded to verify the content of each bottle to make sure that there are no defective capsules, and to store the product in a controlled temperature and humidity environment. Health Canada has also communicated this information to Canadians.

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.

Green Tea Triple Fat Burner and risk of drug-induced liver injury

Health Canada received a report of a 17-year-old woman who developed liver and kidney injury after using Green Tea Triple Fat Burner. She took the product for 5 days (1 capsule twice daily) for weight management. Initially, she presented to the emergency department (ED) with acute abdominal pain, nausea and excessive vomiting and was given intravenous rehydration and an antiemetic. She returned to the ED the following day and received additional intravenous rehydration. Following discharge from the ED, her symptoms persisted at home and her condition continued to deteriorate. Two days later, she was brought to another ED. Her blood work showed significant liver enzyme increases [e.g., alanine aminotransferase was 64 times the upper limit of normal (ULN)] and significant renal function abnormality (serum creatinine was elevated at 10 times the ULN). She was hospitalized, treated with hemodialysis and underwent additional investigations.

This young woman was previously healthy and stated that she did not consume alcohol or illicit drugs. Her past medical history, including concomitant health products did not reveal any risk factors for acute liver failure and acute kidney injury.

During her hospitalization, autoimmune and infectious causes of hepatitis were ruled out by negative laboratory testing. Her drug screens were negative. Pathology results for the renal biopsy showed acute tubular necrosis (ATN). Qualitative product testing by the manufacturer and Health Canada laboratories did not identify any known adulterants or contaminants. On discharge from the hospital, the patient's liver and kidney functions returned to baseline. She was prescribed an antihypertensive medication that had been initiated in hospital secondary to the kidney disorder.

Green Tea Triple Fat Burner is a licensed (NPN 80037935), multi-ingredient, natural health product (NHP) authorized as an antioxidant supplement and as an aid in weight management for use in adults. It contains green tea extract (*Camellia sinensis*), bitter orange (*Citrus aurantium*), 1,3,7-trimethylxanthine (caffeine) and various vitamins (vitamins B_3, B_6, B_{12}; vitamin C; vitamin E; and folic acid).

Potential drug-induced liver injury (DILI) has been described with the use of green tea extract products.[1-3] The product's label, as per Health Canada's Green Tea Extract monograph,[4] includes a cautionary statement advising consumers to consult a healthcare professional prior to use if they have a liver disorder or develop symptoms of liver trouble (such as abdominal pain, dark urine, or jaundice). None of the main medicinal ingredients in the Green Tea Triple Fat Burner are known to be nephrotoxic.[5] The acute renal injury observed in hospital and the subsequent pathologic finding of ATN was likely caused by the profound hypovolemic dehydration secondary to the DILI.

Green tea extract, bitter orange and caffeine are commonly present in NHPs promoted as weight management supplements.[6] NHP-weight management products are regulated as low risk health products and are intended to be used in conjunction with caloric reduction and physical activity. In a recent study, it was found that weight loss products available as dietary supplements in the United States were a common cause of adverse event-related ED visits.[7] Healthcare professionals are encouraged to remind patients to disclose the use of all health products, including non-prescription drugs and NHPs.

Healthcare professionals are encouraged to report to Health Canada any adverse reactions suspected of being associated with the use of NHPs used for weight management.

References

1. Sarma DN, Barrett ML, Chavez ML, et al. Safety of green tea extracts: a systematic review by the US Pharmacopeia. *Drug Saf* 2008;31(6):469-84.

2. Mazzanti G, Menniti-Ippolito F, Moro PA, et al. Hepatotoxicity from green tea: a review of the literature and two unpublished cases. *Eur J Clin Pharmacol* 2009;65(4):331-41.
3. Isomura T, Suzuki S, Origasa H, et al. Liver-related safety assessment of green tea extracts in humans: a systematic review of randomized controlled trials. *Eur J Clin Nutr* 2016. doi: 10. 1038/ejcn.2016.78.
4. *Green Tea Extracts* [monograph]. Ottawa (ON): Health Canada; 2008 April 18. (accessed 2016 June 24).
5. Nauffal M, Gabardi S. Nephrotoxicity of natural products. *Blood Purif* 2016;41(1-3):123-9.
6. Manore MM. Dietary supplements for improving body composition and reducing body weight: where is the evidence? *Int J Sport Nutr Exerc Metab* 2012; 22(2):139-54.
7. Geller AI, Shehab N, Weidle NJ, et al. Emergency department visits for adverse events related to dietary supplements. *N Engl J Med* 2015;373(16):1531-40.

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.

Aczone (dapsone) topical gel 5%

*The risk of **methemoglobinemia** associated with the use of Aczone (dapsone topical gel 5%) for the treatment of acne vulgaris has been included in the Warnings and Precautions, Post-Market Adverse Drug Reactions and Drug Interactions sections of the Canadian product monograph for Aczone.*

Key messages for healthcare professionals:[1]

- Cases of methemoglobinemia with hospitalization have been reported with dapsone gel treatment.
- Dapsone gel should be avoided in patients with glucose-6-phosphate dehydrogenase deficiency or with congenital or idiopathic methemoglobinemia. These patients are more susceptible to drug-induced methemoglobinemia.
- Initial signs and symptoms are characterized by a slate grey cyanosis seen, for example, in buccal mucous membranes, lips, and nail beds.
- Patients should discontinue dapsone gel and seek immediate medical attention in the event of cyanosis.
- Dapsone can also cause elevated methemoglobin levels when used in conjunction with methemoglobin-inducing agents such as sulfonamides or acetaminophen.

Reference

1. *Aczone (dapsone)* [product monograph]. Laval (QC): Valeant Canada LP; 2016.

Edarbyclor (azilsartan medoxomil and chlorthalidone)

*Edarbyclor (azilsartan medoxomil and chlorthalidone) is now **contraindicated** in patients with refractory hyponatremia. This information has been included in the Contraindications section of the Canadian product monograph (CPM) for Edarbyclor. Additional information on hyponatremia has also been added to the Warnings and Precautions and Dosage and Administration sections of the CPM.*

Key messages for healthcare professionals:[1]

- Edarbyclor is contraindicated in patients with refractory hyponatremia.
- Edarbyclor may cause hyponatremia. Monitor serum electrolytes periodically.
- Correct volume and/or salt depletion prior to administration.

Reference

1. *Edarbyclor (azilsartan medoxomil and chlorthalidone)* [product monograph]. Laval (QC): Valeant Canada LP; 2016.

Ferrlecit (sodium ferric gluconate complex in sucrose injection)

*The risk of **generalized seizures** has been included in the Warnings and Precautions and Adverse Reactions sections of the Canadian product monograph for Ferrlecit (sodium ferric gluconate complex in sucrose injection).*

Key messages for healthcare professionals:[1]

- There have been post-marketing reports of seizures in patients receiving Ferrlecit.
- Ferrlecit should be discontinued in patients who experience seizures suspected to be related to treatment.

Reference

1. *Ferrlecit (sodium ferric gluconate complex in sucrose injection)* [product monograph]. Laval (QC): sanofi-aventis Canada Inc.; 2016.

Intuniv XR (guanfacine)

*The risk of **hypertensive encephalopathy upon abrupt discontinuation** of Intuniv XR (guanfacine) has been included in the Warnings and Precautions section of the Canadian product monograph.*

Key messages for healthcare professionals:[1]

- Patients/caregivers should be instructed not to discontinue Intuniv XR without consulting their physician since elevations in blood pressure and heart rate above original baseline (i.e., rebound) have been reported. In very rare instances, this increase in blood pressure may result in hypertensive encephalopathy.
- To minimize the risk of an increase in blood pressure upon discontinuation, the total daily dose should be tapered by no more than 1 mg every 3 to 7 days. Monitor blood pressure and pulse when reducing the dose or discontinuing the drug.
- Patients/caregivers should be informed about the risk of persistent hypertension following discontinuation, how to identify signs and symptoms (e.g., headaches, feeling confused, nervousness, agitation, and tremors) and to seek immediate medical care.

Reference

1. *Intuniv XR (guanfacine)* [product monograph]. Saint-Laurent (QC): Shire Pharma Canada ULC; 2016.

Pomalyst (pomalidomide)

*The risk of **reactivation of hepatitis B** has been included in the Warnings and Precautions and Adverse Drug Reactions sections of the Canadian product monograph for Pomalyst (pomalidomide).*

Key messages for healthcare professionals:[1]

- Reactivation of hepatitis B, including fatal cases, has been reported rarely in patients receiving Pomalyst in combination with dexamethasone who have previously been infected with the hepatitis B virus (HBV). Some of these cases have progressed to acute hepatic failure, resulting in discontinuation of Pomalyst.
- Caution should be exercised when Pomalyst in combination with dexamethasone is used in patients previously infected with HBV. These patients should be closely monitored for signs and symptoms of active HBV infection throughout therapy.

Reference

1. *Pomalyst (pomalidomide)* [product monograph]. Mississauga (ON): Celgene Inc.; 2016.

Solu-Medrol (methylprednisolone sodium succinate) 40 mg and the risk of hypersensitivity in individuals with cow's milk allergy

Solu-Medrol is an intravenous steroid preparation of methylprednisolone sodium succinate.[1] Intravenous administration of Solu-Medrol is indicated in situations in which a rapid and intense hormonal effect is required. These include the treatment of various conditions such as allergic reactions or inflammation. In some conditions, it may be used as adjunctive therapy. In Canada, Solu-Medrol is available in 500 mg or 1 g Plain Vials or in 40 mg, 125 mg, 500 mg and 1 g Act-O-Vials.[1] The 40 mg Act-O-Vial formulation contains lactose hydrous as a non-medicinal ingredient (excipient). The lactose hydrous is derived from cow's milk and may contain trace amounts of protein. The other formulations of Solu-Medrol available in Canada do not contain lactose hydrous.

International cases of hypersensitivity to methylprednisolone in patients with a milk allergy have been reported to the market authorization holder,[2] including cases that have been described in the medical literature.[3-6] These published reports describe 11 cases of children with a known cow's milk allergy who were treated for asthma exacerbation or urticaria, and who experienced serious hypersensitivity reactions to intravenous methylprednisolone sodium succinate. Patients' ages ranged from 3 to 15 years, with a median age of 6.5 years.

Certain children may be highly sensitive if exposed to even very low levels of milk protein.[7] Individuals at a greater risk for severe allergic reactions include those with asthma and those with elevated levels of specific immunoglobulin E to the protein present in cow's milk.[8]

Healthcare professionals are encouraged to check for milk allergies prior to the administration of Solu-Medrol 40 mg Act-O-Vials and to report any suspected cases to Health Canada.

Solu-Medrol (methylprednisolone sodium succinate)

*Solu-Medrol Act-O-Vial 40 mg formulation is now **contraindicated** in patients with a known hypersensitivity to cow's milk or its components or other dairy products. This information has been included in the Contraindications section of the Canadian product monograph.*

Key messages for healthcare professionals:[1]

- Solu-Medrol is contraindicated in patients with known hypersensitivity to the ingredients.
- Solu-Medrol 40 mg Act-O-Vials include lactose produced from cow's milk. This dosage form is therefore contraindicated in patients with a known hypersensitivity to cow's milk or its components or other dairy products because it may contain trace amounts of milk ingredients.

References

1. *Solu-Medrol (methylprednisolone sodium succinate for injection USP)* [product monograph]. Kirkland (QC): Pfizer Canada Inc.; 2016.
2. Health Canada has the data on file, March 2016.
3. Levy Y, Segal N, Nahum A, et al. Hypersensitivity to methylprednisolone sodium succinate in children with milk allergy. *J Allergy Clin Immunol Pract* 2014;2(4):471-4.
4. Eda A, Sugai K, Shioya H, et al. Acute allergic reaction due to milk proteins contaminating lactose added to corticosteroid for injection. *Allergol Int* 2009;58(1):137-9.
5. Nahum A, Garty BZ, Marcus N, et al. Severe hypersensitivity reactions to corticosteroids in children. *Pediatr Emerg Care* 2009;25(5):339-41.
6. Savvatianos S, Giavi S, Stefanaki E, et al. Cow's milk allergy as a cause of anaphylaxis to systemic corticosteroids. *Allergy* 2011;66(7):983-5.
7. Martorell-Aragonés A, Echeverría-Zudaire L, Alonso-Lebrero E, et al. Position document: IgE-mediated cow's milk allergy. *Allergol Immunopathol (Madr)* 2015;43(5):507-26.
8. Boyano-Martínez T, García-Ara C, Pedrosa M, et al. Accidental allergic reactions in children allergic to cow's milk proteins. *J Allergy Clin Immunol* 2009;123(4):883-8.

Did you know?

Solu-Medrol Act-O-Vial consists of a two-compartment vial containing sterile powder in the lower compartment and clear diluent in the upper compartment. Pressing down on the plastic activator forces diluent into the lower compartment.

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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