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Health Product InfoWatch

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REPORTING ADVERSE REACTIONS

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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 May 2016 by Health Canada.

BCR-ABL tyrosine kinase inhibitors Health Product Risk Communication	Cases of reactivation of hepatitis B virus (HBV) have occurred in patients who are chronic carriers of HBV, after they received BCR-ABL tyrosine kinase inhibitors (TKIs) [Gleevec (imatinib mesylate), Tasigna (nilotinib), Bosulif (bosutinib), Sprycel (dasatinib), Iclusig (ponatinib hydrochloride) and generics]. Patients should be tested for HBV infection status before initiating treatment with BCR-ABL TKIs and those who are carriers of HBV should be monitored for signs and symptoms of active HBV infection throughout BCR-ABL TKI therapy and for several months following termination of therapy.
Bicillin L-A injection (penicillin G benzathine) 2mL single use syringe Health Product Risk Communication	Pfizer Canada is experiencing a supply disruption of Bicillin L-A (penicillin G benzathine) sterile injection. To alleviate the temporary shortage, Health Canada has facilitated the importation of Pfizer Australian labelled Bicillin L-A, lot 72453. The Australian Bicillin L-A is the same as the Canadian product with respect to composition, packaging, specification and expiry period. However, dosage conversions may be necessary when administering Australian Bicillin L-A due to the difference in the expression of product strength as well as differences in the labelling of the syringe.
Chlorhexidine (topical antiseptic non-prescription products) Summary Safety Review	This safety review evaluated the potential risk of serious hypersensitivity reactions associated with the use of non-prescription topical antiseptic chlorhexidine products. Health Canada's review concluded that topical antiseptic chlorhexidine products may cause serious hypersensitivity reactions. Health Canada will work to update the product information with these new findings.
Essure (permanent birth control system) Summary Safety Review Health Product Risk Communication	This safety review evaluated the potential risk of complications such as changes in menstrual bleeding, unintended pregnancy, chronic pain, perforation and migration of device, allergy and sensitivity or immune-type reactions with the use of Essure. Health Canada's review concluded that there are risks associated with the use of Essure that need to be better communicated and further monitored. Health Canada will work with the manufacturer to strengthen the product labelling regarding these safety concerns and to develop a Patient Information Sheet and Checklist intended to be reviewed and signed prior to the use of the device. Health Canada has also communicated this information to healthcare professionals.

Eylea (aflibercept) Summary Safety Review	This safety review evaluated the potential risk of systemic toxicity associated with the use of Eylea. Health Canada's review found that there was not enough evidence to conclude that Eylea is associated with a greater risk of systemic adverse reactions than a similar product used for the same purpose. The potential for experiencing systemic adverse reactions is already mentioned in the Canadian prescribing information for Eylea. Health Canada will continue to monitor this issue.
Methylisothiazolinone and methylchloroiso-thiazolinone Information Update	Health Canada informed consumers of potential risks related to the combination of methylisothiazolinone and methylchloroisothiazolinone (MI/MCI) used as a preservative in certain leave-on cosmetic, non-prescription and natural health products. Use of these substances can lead to symptoms including a red rash or bumps, itching, swelling, burning, or tenderness of the skin, dry, cracked or scaly skin and blisters.
Proton pump inhibitors Summary Safety Review	This safety review evaluated the potential risk of *Clostridium difficile* infection associated with the use of proton pump inhibitors [Losec (omeprazole), Nexium (esomeprazole), Prevacid (lansoprazole), Pantoloc (pantoprazole), Pariet (rabeprazole), Dexilant (dexlansoprazole) and generics]. Health Canada's review concluded that the evidence was too limited to establish a link. However, since the potential link has not been ruled out, the prescribing information will be updated to provide more information on various risk factors as well as remind healthcare professionals and patients that these drugs should be used at the lowest dose and for the shortest duration appropriate to the condition being treated.
SGLT2 inhibitors Summary Safety Review Health Product Risk Communication	This safety review evaluated the potential risk of diabetic ketoacidosis associated with the use of sodium-glucose cotransporter-2 (SGLT2) inhibitors [Invokana (canagliflozin), Forxiga (dapagliflozin), Jardiance (empagliflozin) and Xigduo (dapagliflozin/metformin)]. Health Canada's review concluded that the evidence supports this link. Health Canada will work with the manufacturers to update the prescribing information to better explain the symptoms of diabetic ketoacidosis. Health Canada has also communicated this information to healthcare professionals.
Unauthorized health product (Animal Test) Advisory	Health Canada seized an unauthorized product being promoted as a dietary supplement, Animal Test, from Supplement King, in Burlington, Ontario. The product is labelled to contain yohimbine, a prescription drug ingredient.

Unauthorized 'LifeGive' health products Information Update	Health Canada advised Canadians not to purchase or use 'LifeGive' health products to treat diseases such as cancer and dementia. These products are not authorized for sale in Canada. Health Canada believes 'LifeGive' health products have been or will be promoted by Hippocrates Health Institute at events held in Ontario.
Zydelig (idelalisib) Health Product Risk Communication	Decreased overall survival and an increased rate of serious adverse events have been observed in patients receiving Zydelig compared to the control groups in Phase 3 studies evaluating the addition of Zydelig to standard therapies for first line treatment of chronic lymphocytic leukemia (CLL) and early lines of relapsed indolent non-Hodgkin's lymphoma (iNHL). Zydelig should not be used for first line treatment of CLL. The Canadian prescribing information will be updated to reflect this new 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.

REVIEW ARTICLE

Alpha-lipoic acid and serious hypoglycemic episodes

Key points

- Cases of insulin autoimmune syndrome (serious hypoglycemic episodes) have been reported in some individuals using products containing alpha-lipoic acid.
- For patients presenting with symptoms of hypoglycemia, obtaining a complete prescription and non-prescription medication history is important.
- Consumers who experience symptoms of hypoglycemia should be advised to discontinue use of alpha-lipoic acid-containing products and consult a healthcare professional.

Alpha-lipoic acid is a naturally occurring sulfhydryl compound synthesized enzymatically in the mitochondrion.[1] It is a necessary cofactor in mitochondrial-specific pathways that generate energy from glucose. In Canada, alpha-lipoic acid is available as a natural health product (NHP) for self-care and is used as an antioxidant for the maintenance of good health and to help promote healthy glucose metabolism.[2] Health Canada has licensed more than 800 NHPs containing alpha-lipoic acid as a medicinal ingredient for human use.

Recently, Health Canada identified several published reports of insulin autoimmune syndrome (IAS), a rare cause of serious hypoglycemia, involving patients using alpha-lipoic acid.[3-5]

IAS, also known as Hirata disease, is a relatively rare cause of spontaneous hypoglycemia characterized by serious low blood glucose, extremely high serum insulin levels, and high concentrations of autoantibodies against endogenous insulin despite no prior exposure to exogenous insulin.[6,7] The cause is unclear, but it has been shown that prior exposure to certain sulfhydryl-containing drugs such as alpha-lipoic acid can increase the risk of developing IAS in certain individuals with specific genetic predisposition.[4,6,8,9] Approximately 40 to 50% of IAS cases have been associated with prior exposure to drugs containing a sulfhydryl group (e.g., methimazole, glutathione, penicillamine, D-penicillamine and captopril).[8-11]

Key points (continued)

- Healthcare professionals are encouraged to report to Health Canada any cases of hypoglycemic episodes suspected of being associated with the use of alpha-lipoic acid-containing products, and to provide detailed information when describing cases.

What to include in your adverse reaction reports to Health Canada

In addition to the **name of the health product** and **description of the adverse reaction**, it is important to include as many as possible of the following elements:

- Patient characteristics (age, sex, height and weight)
- Dosing information and indication for use of the suspected health product
- Therapy dates: when the suspected health product was started and stopped
- Changes to therapy with the suspected health product and impact on the patient (e.g., dechallenge/ rechallenge information)
- Treatment of the adverse reaction (including date the adverse reaction occurred and was resolved, if applicable)
- Investigations to exclude alternate causes for the adverse reaction
- Relevant history and pre-existing conditions
- Relevant tests/lab data
- Other health products taken (including over-the-counter and natural health products) with therapy dates and dosing information
- Patient outcome

It is believed that the sulfhydryl group in these drugs may dissociate the disulfide bond of the insulin molecule, thereby modifying its form and signaling it as foreign to the immune system.[4,12,13] This triggers an immune response resulting in the production of insulin autoantibodies. Insulin autoantibodies are assumed to combine with secreted insulin as blood glucose increases after meals to inhibit insulin action and this further promotes the secretion of insulin. Excessive insulin combined with the autoantibody dissociates as blood glucose is reduced and eventually induces hypoglycemia.[4,12,13]

Genetic predisposition appears to be associated with an increased risk for IAS onset or development.[3,4,6] Individuals with certain genetic variants involving the human leucocyte antigen (HLA) DRB1 (or HLA-DRB1) gene, in particular HLA-DRB1*0406 and HLA-DRB1*0403, have been found to be at increased risk of IAS. Although the prevalence of IAS appears to be higher in Asian populations, where the DRB1*0406 genotype is relatively common,[4,6,8,14] cases have also been reported in patients of other races.[3,5,15]

At the time of its review, Health Canada identified 12 published cases of IAS in patients using alpha-lipoic acid in the scientific literature.[3-5,16-19] The cases are predominantly reported in middle-aged patients, mostly female and were found in both Asian and Caucasian populations. All the patients in the case reports were genotyped and found to have a genetic predisposition as carriers of the DRB1*0406 or *0403 genes. Doses of alpha-lipoic acid taken by the patients ranged from 200 to 600 mg/day, and the duration of use ranged from 10 days to several months. In all cases, there was a dramatic increase in serum insulin levels and a significant decrease in serum glucose levels. Furthermore, in all cases, the patients recovered after discontinuation of the alpha-lipoic acid. In one case, hypoglycemic symptoms recurred with two rechallenges of alpha-lipoic acid.

As of March 31, 2015, no reports of IAS involving Canadian consumers using alpha-lipoic acid have been received by Health Canada.

The current evidence suggests an association between the spontaneous onset of IAS and oral alpha-lipoic acid use in patients with a specific genetic predisposition, resulting in potentially serious or life-threatening low blood sugar, if not properly managed. Health Canada is updating the ingredient information for alpha-lipoic acid to inform consumers to discontinue product use and consult a healthcare professional if they experience symptoms that could suggest hypoglycemia (e.g., sweating, paleness, chills, headache, dizziness and/or confusion).

Healthcare professionals are encouraged to ask patients who present with symptoms of hypoglycemia about their use of health products containing alpha-lipoic acid, and to report any suspected cases to Health Canada.

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In addition, for natural health products (NHPs), more comprehensive information is helpful to accurately identify the product and to ensure the quality and usefulness of the report.

Information needed in a NHP adverse reaction report to accurately identify the product:

- Exact product brand name (including modifying prefix or suffix)
- Natural Product Number (NPN) or Homeopathic Medicine Number (DIN-HM)
- List of ingredients (or a copy or picture of the label or container) and their amount per serving
- Lot number
- Expiration date
- Company name
- Where the product was purchased (e.g., Internet, pharmacy, ethnic store)

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Did you know?

All natural health products (NHPs) must have a product licence before they can be sold in Canada. To get a licence, applicants must give detailed information about the product to Health Canada, including: medicinal ingredients, source, dose, potency, non-medicinal ingredients and recommended use(s).

The safety and efficacy of NHPs and their health claims must be supported by proper evidence so that consumers and Health Canada know the products are indeed safe and effective.

Once Health Canada has assessed a product and decided it is safe, effective and of high quality, it issues a product licence along with an eight-digit Natural Product Number (NPN) or Homeopathic Medicine Number (DIN-HM), which must appear on the label.

All NHPs must meet specific labelling requirements, including any cautionary statements, warnings, contra-indications and possible adverse reactions associated with the product. When Health Canada identifies a new risk, such as for alpha-lipoic acid and IAS, the corresponding pre-cleared information (PCI) is updated. Licence holders for alpha-lipoic acid-containing products identified as of potential concern are also expected to amend their product licence to add this new risk information to their product label.

Health Canada has published over 250 pre-cleared information (PCI) documents including monographs. As an example, the PCI on alpha-lipoic acid provides an established safety and efficacy profile that industry may attest to as one of the ways to acquiring market authorization.

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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