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Health Product InfoWatch

July 2019

HEALTH PRODUCTS MENTIONED IN THIS ISSUE

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REPORTING ADVERSE REACTIONS

Canada Vigilance Program
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 Device Problem Reporting](#)
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 advisories electronically, subscribe to
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Pharmaceuticals and Biologics

Alertec (modafinil)
 Avelox and Avelox I.V.
 (moxifloxacin)
 Brilinta (ticagrelor)
 Cipro and Cipro Oral Suspension
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 non-prescription
 Levofloxacin in 5% Dextrose
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Medical Devices

Gentian violet-containing,
 medical device
 Medtronic MiniMed insulin pumps

Natural Health Products

Aloe vera-containing health
 products

Other

Foreign health products
 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.

MONTHLY RECAP OF HEALTH PRODUCT SAFETY INFORMATION

The following is a list of [health product advisories](#), [type I recalls](#) as well as [summaries of completed safety reviews](#) published in June 2019 by Health Canada.

<p>Alertec (modafinil) Health Professional Risk Communication</p>	<p>When used during pregnancy, Alertec (modafinil) has been associated with cases of major fetal congenital malformations, including congenital cardiac anomalies. Alertec is now contraindicated in women who are pregnant or may become pregnant. Healthcare professionals are advised to discuss the following with all female patients of reproductive potential treated with, or to be treated with, Alertec: the potential risks to the fetus; the need for a negative pregnancy test within a week before starting treatment; the possible reduced effectiveness of steroidal contraceptives and the need to use alternative or additional methods of contraception during treatment and for two months after stopping treatment. The Canadian product monograph for Alertec has been updated to reflect this new safety information.</p>
<p>Fluoroquinolones, systemic Summary Safety Review</p>	<p>Health Canada's safety review evaluated the risk of aortic aneurysm and aortic dissection associated with systemic fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin). Health Canada's review concluded that there may be a link. Health Canada is working with the manufacturers to update the Canadian product monographs for systemic fluoroquinolones to include information about this potential risk (see Product Monograph updates).</p>
<p>Foreign health products Foreign Product Alert (9 products) Foreign Product Alert (5 products)</p>	<p>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.</p>
<p>Gentian violet Information Update Summary Safety Review</p>	<p>Health Canada's health risk assessments evaluated the risk of cancer associated with Gentiane Violet Liquid Topical (gentian violet) and Hydrofera Antibacterial Foam Dressings. Health Canada's risk assessment of medical devices containing gentian violet (Hydrofera antibacterial foam dressings), based on the limited exposure to gentian violet, did not find a risk of cancer. However, no evidence to support the safety of the devices for pregnant and nursing women has been provided, and as a precaution, Health Canada worked with the manufacturers and updated the Instructions for Use. Health Canada's risk assessment of the non-prescription drug product (Gentiane Violet Liquid Topical) concluded that there is evidence based on animal studies in the scientific literature of a potential for a link between gentian violet and cancer. The manufacturer of Gentiane Violet Liquid Topical voluntarily discontinued marketing of their product in Canada and their health product drug licence has been cancelled. Health Canada has also communicated this information to healthcare professionals and Canadians.</p>

<p>Linessa (21 and 28) Advisory</p>	<p>Health Canada advised Canadians of a labelling error affecting one lot of Linessa 28 birth control pills on the Canadian market (lot 190056, expiry 06/2021). The English side of Linessa 28 boxes is incorrectly labelled with the eight-digit DIN for Linessa 21 (02272903) instead of the correct Linessa 28 DIN (02257238). The French side of Linessa 28 boxes has the correct DIN. The labelling error could result in a patient using Linessa 21 inadvertently receiving Linessa 28 instead. The labelling issue does not affect the safety or quality of Linessa pills. Aspen Pharmacare Canada Inc. has asked that pharmacies contact patients prescribed Linessa 21 to confirm that they received the correct product.</p>
<p>Medtronic MiniMed insulin pumps Advisory</p>	<p>Health Canada advised patients and healthcare professionals that certain older Medtronic MiniMed 508 and MiniMed Paradigm insulin pumps distributed before 2015 may be vulnerable to cybersecurity risks (not just devices distributed between 2010 and 2015). The risk is not with the normal functioning of the device, but with the remote possibility of a cyberattack. The potential cybersecurity vulnerability could result in changes to pump settings by an unauthorized person, which could lead to hypoglycemia or hyperglycemia. Diabetic patients using an affected model are advised to identify if they have an affected device and to take the precautions listed in the advisory.</p>
<p>Opdivo (nivolumab) and Yervoy (ipilimumab) Summary Safety Review</p>	<p>Health Canada’s safety review evaluated the risk of hemophagocytic lymphohistiocytosis (HLH) associated with Opdivo (nivolumab) and Yervoy (ipilimumab) used alone, or in combination. Health Canada’s review concluded that there may be a link between the use of these products and the development of HLH. Health Canada will work with the manufacturer of Opdivo and Yervoy to determine appropriate changes to the Canadian product monographs.</p>
<p>Unauthorized health products Counterfeit Viagra Update: Multiple unauthorized health products</p>	<p>Health Canada advised Canadians about various unauthorized health products being sold at retail locations across Canada or online that may pose serious health risks.</p>

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

Hepatotoxicity associated with the use of oral *Aloe vera*-containing health products

Key messages

- Cases of hepatotoxicity suspected of being associated with the use of oral *Aloe vera*-containing products used for laxative or weight loss purposes have been reported in Canada and internationally.
- The information provided in the Canadian reported cases was not sufficient to adequately assess the causal association between the hepatotoxicity and the *Aloe vera*-containing product.
- Healthcare professionals are encouraged to report to Health Canada any adverse reactions suspected of being associated with *Aloe vera*-containing natural health products or any other health product in order to assist Health Canada in monitoring the safety of health products in Canada.

In Canada, *Aloe vera* can be used as an ingredient within a natural health product (NHP). *Aloe vera* is used as a topical healing agent for minor wounds, such as cuts and burns, minor skin irritations, and orally, as a laxative.^{1,2}

The laxative effects of *Aloe vera* are said to be attributed to its anthraquinone content.¹ In Canada, there are specified limits for anthraquinones in finished health products containing *Aloe vera*.³ The mechanism by which *Aloe vera* may cause hepatotoxicity is not confirmed.⁴ According to some studies, the anthraquinones present in *Aloe vera* may be responsible for its hepatotoxic effects.^{5,6}

Aloe vera may also be used as an ingredient in food. However, when consumed as a food, *Aloe vera* preparations are commonly made from the anthraquinone-free gel or inner pulp from the leaves of *Aloe* species.⁷ The focus of this article, keeping in line with the scope of the Health Product InfoWatch, is on the risk of hepatotoxicity with *Aloe vera*-containing health products.

Case reports

Six published studies, describing a total of 8 cases of hepatotoxicity associated with oral ingestion of *Aloe vera*-containing products, were identified in the published literature.^{4,8-12}

Ages of consumers ranged from 21 to 73 years. The majority (n=7) were female. The consumers used *Aloe vera*-containing products orally, mainly as a laxative, for weight loss or to support general health. The daily doses of *Aloe vera* varied in the different case reports and were often unclear or unavailable. Five of the consumers used capsule or tablet formulations, 2 used powder and 1 used a gel.

None of the consumers were reported to have a recent history of alcohol or illicit drug use. For most of the consumers, *Aloe vera* was the only substance declared to be used at the time of onset of hepatotoxicity. None of the consumers reported taking new concomitant medications.

Time to onset ranged from 3 weeks to several years. Laboratory abnormalities included elevated liver enzymes in all cases. Histologically, liver biopsies, which were available for 6 out of 8 patients, indicated acute hepatitis. Biopsy results generally showed portal and acinar inflammatory cell infiltration (lymphocytes, eosinophils, neutrophils and monocytes) with bridging necrosis.

In all cases, the consumers showed an improvement in their condition after discontinuation of the *Aloe vera*-containing product. In 1 case, the consumer experienced a positive rechallenge following consumption of the same *Aloe vera*-containing product one month after hospital discharge.¹¹

The causal association between the *Aloe vera*-containing products and hepatotoxicity was evaluated, by the authors of the studies, as probable in 6 cases and definite in 2 cases.⁴

Canadian context

As of December 31, 2018, Health Canada received 5 adverse reaction reports of hepatotoxicity suspected of being associated with the use of oral *Aloe vera*-containing NHPs. All 5 cases were confounded by the concomitant use of other health products with a suspect role in the reported adverse reactions. The information provided in these reports was not sufficient to adequately assess the causal association between the hepatotoxicity and the *Aloe vera*-containing NHPs.

Health Canada has authorized over 600 NHPs with *Aloe vera* as a medicinal ingredient (excluding homeopathic products and products that include *Aloe vera* as a non-medicinal ingredient) and has published 3 *Aloe vera* monographs (1 for topical use of the leaf gel; 1 for oral use of the leaf gel and 1 for oral use of the latex). The monographs do not currently include any cautionary statements regarding the potential risk of hepatotoxicity.

Conclusion

Determining causality in cases associated with NHPs is challenging, as products often contain multiple active ingredients. Previous studies have also shown that product quality (species substitution, variability in ingredient extraction and preparation methods) as well as possible herb-herb or herb-drug interactions may play a role in some of the observed cases of hepatotoxicity in association with NHPs.¹³⁻¹⁵

Healthcare professionals should be aware of the potential for some NHPs to cause hepatotoxicity and should ask patients about their use of NHPs.⁴ As such, healthcare professionals are encouraged to report to Health Canada any case of liver injury or any other adverse reaction suspected of being associated with *Aloe vera*-containing NHPs or any other health product (see “[Natural health product identification in adverse reaction reports](#)”).

Health Canada will continue to monitor adverse reaction reports associated with *Aloe vera*, as it does for all health products on the Canadian market, to identify and assess potential harms.

Natural health product identification in adverse reaction reports

It is important to include as many health product identifiers as possible in the [adverse reaction reporting form](#), especially when reporting adverse reactions suspected of being associated with natural health products. This assists Health Canada in conducting accurate, thorough assessments of adverse reactions.

Consumers are also recommended to hold on to the product, as Health Canada may request a sample for further investigation.

Examples of natural health product identifiers include:

- 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, Canada vs. other countries, etc.)

See [references on the following page](#)

References

1. *Aloe, Aloe vera gel* [WHO monographs on selected medicinal plants]. Vol. 1. Geneva (Switzerland): World Health Organization; 1999. pp. 33–49. (accessed 2019 May 6)
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3. *Aloe – Aloe vera – Oral* [monograph]. Ottawa (ON): Health Canada; 2018. (accessed 2019 June 20)
4. Parlati L, Voican CS, Perlemuter K, et al. *Aloe vera-induced acute liver injury: A case report and literature review.* *Clin Res Hepatol Gastroenterol* 2017;41(4):e39-e42.
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11. Yang HN, Kim DJ, Kim YM, et al. *Aloe-induced toxic hepatitis.* *J Korean Med Sci* 2010;25(3):492-5.
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14. Teschke R, Eickhoff A. *Herbal hepatotoxicity in traditional and modern medicine: actual key issues and new encouraging steps.* *Front Pharmacol* 2015;6:72.
15. Painter D, Perwaiz S, Murty M. *Black cohosh products and liver toxicity: update.* *Can Advers Reaction News* 2010;20(1):1-2. (accessed 2019 June 20)

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 pharmaceuticals is available on Health Canada's [Product Monograph Brand Safety Updates](#). Canadian product monographs can be accessed through Health Canada's [Drug Product Database](#).

Brilinta (ticagrelor)

The risk of **thrombotic thrombocytopenic purpura (TTP)** has been included in the *Warnings and Precautions*, *Adverse Reactions (Post-Market Adverse Drug Reactions)*, and *Consumer Information* sections of the Canadian product monograph for Brilinta.

Key messages for healthcare professionals:¹

- TTP has been reported very rarely with the use of Brilinta.
- TTP is a serious, potentially fatal condition and requires prompt treatment. Plasmapheresis should be considered for the treatment of TTP.
- Healthcare professionals are advised to monitor patients for signs and symptoms of TTP, such as thrombocytopenia, microangiopathic hemolytic anemia (schistocytes seen on peripheral blood smear), neurological findings, renal dysfunction, and fever.

Reference

1. *Brilinta (ticagrelor)* [product monograph]. Mississauga (ON): AstraZeneca Canada Inc.; 2019.

Systemic fluoroquinolones and fluoroquinolone solution for inhalation: Avelox and Avelox I.V. (moxifloxacin); Cipro, Cipro Oral Suspension, Cipro XL, Ciprofloxacin Intravenous Infusion BP (ciprofloxacin); Quinsair, Levofloxacin in 5% Dextrose Injection, Teva-Levofloxacin (levofloxacin); and Norfloxacin (norfloxacin)

The risk of **aortic aneurysm and dissection** has been included in the *Warnings and Precautions* and *Patient Medication Information* sections of the Canadian product monographs (CPMs) for all respective fluoroquinolones.*

Key messages for healthcare professionals:¹⁻⁸

- Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population.
- Fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options:
 - in patients with positive family history of aneurysm disease,
 - in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or
 - in the presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g., Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).
- In case of sudden severe abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

References

1. *Avelox and Avelox I.V. (moxifloxacin)* [product monograph]. Mississauga (ON): Bayer Inc.; 2019.
2. *Cipro and Cipro Oral Suspension (ciprofloxacin)* [product monograph]. Mississauga (ON): Bayer Inc.; 2019.
3. *Cipro XL (ciprofloxacin)* [product monograph]. Mississauga (ON): Bayer Inc.; 2019.
4. *Ciprofloxacin Intravenous Infusion, BP (ciprofloxacin)* [product monograph]. Toronto (ON): Apotex Inc.; 2019.
5. *Quinsair (levofloxacin)* [product monograph]. Dublin (Ireland): Horizon Pharma Ireland Limited; 2019.
6. *Levofloxacin in 5% Dextrose Injection (levofloxacin)* [product monograph]. Kirkland (QC): Pfizer Canada ULC; 2019.
7. *Norfloxacin (norfloxacin)* [product monograph]. Vaughan (ON): AA Pharma Inc.; 2019.
8. *Teva-Levofloxacin (levofloxacin)* [product monograph]. Toronto (ON): Teva Canada Limited; 2019.

* At the time of this publication, several of the CPM updates have been completed for the respective fluoroquinolone products. As part of the class update, Health Canada continues to work with manufacturers to update the remaining systemic fluoroquinolone CPMs to reflect this safety information.

The listed updated fluoroquinolone CPMs provides generic drug manufacturers with the necessary information about their Canadian Reference Products' labelling to facilitate corresponding updates to generic CPMs.

Trisenox (arsenic trioxide)

The risk of **encephalopathy** has been included in the *Serious Warnings and Precautions Box* in the Canadian product monograph for Trisenox. The *Warnings and Precautions, Adverse Reactions (Post-Market Adverse Drug Reactions)*, and *Consumer Information* sections of the Canadian product monograph for Trisenox have also been updated in relation to this issue.

Key messages for healthcare professionals:¹

- Encephalopathy, including fatal outcomes, has been reported uncommonly with arsenic trioxide treatment.
- Wernicke encephalopathy after arsenic trioxide treatment was reported in patients with vitamin B₁ deficiency. Some of these patients recovered with vitamin B₁ supplementation.
- Patients at risk of vitamin B₁ deficiency should be closely monitored for signs and symptoms of encephalopathy after arsenic trioxide initiation.

Reference

1. *Trisenox (arsenic trioxide)* [product monograph]. Toronto (ON): Teva Canada Limited; 2019.

NOTICE OF MARKET AUTHORIZATION WITH CONDITIONS

A *Notice of Compliance with Conditions (NOC/c)* is a form of market authorization with conditions granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada. Communicating a *NOC/c* is intended to raise awareness on the details of the drug and the nature of authorization granted.

Healthcare professionals are encouraged to [report to Health Canada](#) any adverse reactions suspected of being associated with marketed health products, including drugs authorized under the *NOC/c* policy.

The content of these notices reflects current information at the time of publication. Conditions associated with the *NOC/c* will remain until they have been fulfilled and authorized by Health Canada, in accordance with the *NOC/c* Policy. For the most up-to-date information, consult Health Canada's [NOC database](#).

Vitrakvi (larotrectinib): Authorization with conditions

Health Canada has issued a Notice of Compliance, under the Notice of Compliance with Conditions policy for Vitrakvi (larotrectinib), 25 mg and 100 mg capsules and 20 mg/mL oral solution. Vitrakvi is indicated for the treatment of adult and pediatric patients with solid tumours that:

- have a neurotrophic tyrosine receptor kinase gene fusion without a known acquired resistance mutation;
- are metastatic or where surgical resection is likely to result in severe morbidity; and
- have no satisfactory treatment options.

Patients should be advised about the conditional market authorization for this indication.

For the complete prescribing information and information available for the patients/caregivers, please consult the Vitrakvi Canadian product monograph. The product monograph can be accessed through Health Canada's [Drug Product Database](#), the [Bayer Inc. Web site](#) or by contacting Bayer Medical Information at 1-800-265-7382 or canada.medinfo@bayer.com. Contact the company for a copy of any references, attachments or enclosures.

Did you know?

The Canadian Paediatric Surveillance Program is a joint project of the Public Health Agency of Canada and the Canadian Paediatric Society. It contributes to the improvement of the health of children and youth in Canada through national surveillance and research into childhood disorders that are high in disability, morbidity and economic costs to society. Featured in this report are studies of: serious and life-threatening adverse drug reactions; non-type 1 diabetes; neonatal abstinence syndrome; serious and life-threatening events associated with cannabis use for recreational purposes; medically serious self-harm; teething necklaces and bracelets; among others. To learn more, read the latest report: [Canadian Paediatric Surveillance Program 2018 results](#).

Health Canada News

Health Canada announces new reporting requirements for hospitals

New regulations will require hospitals to report serious adverse drug reactions and medical device incidents to Health Canada. Hospitals will be required to provide these reports within 30 days of the documentation within their institution. For more information, please consult the [Mandatory reporting requirements for hospitals Web page](#).

[News release](#)

Learn about what and how to report at: Canada.ca/drug-device-reporting

HELPFUL LINKS

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- [The Drug and Health Product Register](#)
- [Drug Shortages Canada](#)
- [Annual trends for adverse reaction case reports and medical device problem incidents](#)
- [Stop Illegal Marketing of Drugs and Devices](#)

Suggestions?

Your comments are important to us. Let us know what you think by reaching us at HC.infowatch-infovigilance.SC@canada.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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