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Health Product InfoWatch

November 2018

HEALTH PRODUCTS MENTIONED IN THIS ISSUE

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REPORTING ADVERSE REACTIONS

Canada Vigilance Program
 Online: [Adverse Reaction and Medical Device Problem Reporting](#)
 Telephone: 1-866-234-2345
 Fax or mail: Form available online

SUBSCRIBE

To receive the Health Product InfoWatch and notifications of health product advisories electronically, subscribe to [MedEffect™ e-Notice](#) or to [MedEffect™ Canada RSS feeds](#).

Pharmaceuticals and Biologics

Active pharmaceutical ingredients from Zhejiang Huahai Pharmaceuticals
 Folotyn (pralatrexate injection)
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Medical Devices

Decorative contact lenses

Other

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 October 2018 by Health Canada.

<p>Active pharmaceutical ingredients from Zhejiang Huahai Pharmaceuticals</p> <p>Information Update</p>	<p>Health Canada has found the Chuannan manufacturing site of Zhejiang Huahai Pharmaceuticals located in China to be non-compliant with requirements for Good Manufacturing Practices for the manufacturing of active pharmaceutical ingredients (APIs). A non-compliant rating means that Canadian companies can no longer import drugs that contain APIs from this site. A list of APIs manufactured at this site is provided in the information update. Zhejiang Huahai Pharmaceuticals is the manufacturer of the valsartan API found to contain the impurities N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA). All drugs containing valsartan manufactured at this site have already been recalled in Canada.</p>
<p>Decorative contact lenses</p> <p>Information Update</p>	<p>Health Canada informed consumers that decorative contact lenses pose health risks. To help make decorative contact lenses safer, Health Canada began regulating these products as medical devices in 2016. This means that they must be licensed by Health Canada before they can be sold. Consumers can search the online Medical Devices Active Licence Listing database to verify whether their decorative contact lenses are licensed by using the product or company name.</p>
<p>Jakavi (ruxolitinib)</p> <p>Summary Safety Review</p>	<p>This safety review evaluated the risk of drug interactions between Jakavi (ruxolitinib) and P-glycoprotein substrates (e.g., rosuvastatin, digoxin and dabigatran). Health Canada's review of the available information did not establish a link. Health Canada will continue to monitor the safety of ruxolitinib.</p>
<p>Unauthorized health products</p> <p>Advisory - "Surfaz-SN Triple Action Cream"</p> <p>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

Lamotrigine and international reports of hemophagocytic lymphohistiocytosis (HLH)

Lamotrigine (Lamictal and generics) is a phenyltriazine anticonvulsant agent.¹ It is thought to stabilize neuronal membranes by blocking voltage-sensitive sodium channels, which inhibits the release of excitatory amino acid neurotransmitters (e.g., glutamate, aspartate) that are thought to play a role in the generation and spread of epileptic seizures. Lamotrigine is indicated for use as monotherapy following withdrawal of concomitant antiepileptic drugs and as adjunctive therapy for the management of epilepsy in patients who are not satisfactorily controlled by conventional therapy. It is also indicated as adjunctive therapy for the management of seizures associated with Lennox-Gastaut syndrome. Lamotrigine has been on the Canadian market since December 31, 1995. There have been approximately one million prescriptions for lamotrigine in Canada each year for the past 5 years.²

Hemophagocytic lymphohistiocytosis (HLH)

Health Canada has identified international cases of hemophagocytic lymphohistiocytosis (HLH) suspected of being associated with lamotrigine.

HLH is a rare, life-threatening hematologic disorder characterized by extreme immune activation resulting in pathological inflammation.^{3,4} Defective cytotoxic cell function coupled with uncontrolled proliferation and activation of macrophages, leads to excessive production of cytokines, dysregulation of the immune system and, ultimately, tissue and organ damage. Clinically, HLH is characterized by fever, skin rash, neurological symptoms, hepatomegaly, splenomegaly, lymphadenopathy and cytopenias among others.³⁻⁵ Clinical signs and symptoms are relatively non-specific and overlap with other diseases; therefore, diagnosis is often delayed.⁴ HLH may also be confused with other serious immune-related adverse reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). HLH is generally differentiated from other intrinsic and reactive immune disorders by the severity of pathologic inflammation.³ There are two types of HLH: genetic and acquired.⁶ The genetic type is usually diagnosed in childhood, with a primary genetic cause. Acquired HLH can occur at any age secondary to infections, autoimmune diseases and malignancies.

From December 1994 through September 2017, 8 cases of confirmed or suspected HLH associated with lamotrigine use in children and adults were identified worldwide from other regulatory agencies and the scientific literature.⁷⁻¹⁰ As of June 30, 2018, no Canadian cases were identified. All international cases were found to be serious and required hospitalization. In 7 cases, patients improved following treatment of HLH and discontinuation of lamotrigine. One case had a fatal outcome. All patients had positive bone marrow biopsies consistent with hemophagocytosis and all cases had a plausible temporal relationship with the initiation of lamotrigine.

Lamotrigine-induced HLH is considered a severe adverse reaction with a delayed onset of symptoms (approximately 1 to 4 weeks).¹ The survival rate of patients was estimated to be less than 10% before immune-modulating therapy.^{3,5} Given the rapid progression and severity of HLH, early diagnosis and treatment are critical for patient survival.³⁻⁵

Although the number of cases identified to date is low, healthcare professionals should be aware of this potential risk. Accordingly, the *Warnings and Precautions*, *Adverse Reactions (Post-Market Adverse Drug Reactions)* and *Consumer Information* sections of the Canadian product monograph for Lamictal have been updated to include the risk of HLH.

Key messages for healthcare professionals from the Canadian product monograph:¹

- Hemophagocytic lymphohistiocytosis (HLH) has occurred in pediatric and adult patients taking lamotrigine for various indications, developing within approximately 1 to 4 weeks following lamotrigine initiation.
- HLH is a life-threatening disorder of pathologic immune activation characterized by clinical signs and symptoms of extreme systemic inflammation, and is associated with high mortality rates if not recognized early and treated.
- Common findings of HLH include fever, hepatosplenomegaly, rash, lymphadenopathy, neurologic symptoms, cytopenias, high serum ferritin, abnormal liver and renal function tests, and coagulation abnormalities.
- Patients who develop these signs and symptoms should be immediately evaluated and a diagnosis of HLH should be considered. Treatment with lamotrigine should be discontinued unless an alternative etiology can be established.
- The recommended initial dose and subsequent dose escalations of lamotrigine should not be exceeded.

Healthcare professionals are encouraged to report to Health Canada any case of suspected or confirmed HLH in association with lamotrigine. Information including doses, dates of treatment initiation and discontinuation, concomitant medications and date of onset of the adverse reaction will facilitate a more thorough assessment of the potential safety issue.

References

1. *Lamictal (lamotrigine)* [product monograph]. Mississauga (ON): GlaxoSmithKline Inc.; 2018.
2. IQVIA, Canadian CompuScript Audit, years 2013 to 2017. Copyright 2018, reprinted with permission. All rights reserved.
3. Allen CE, McClain KL. Pathophysiology and epidemiology of hemophagocytic lymphohistiocytosis. *Hematology Am Soc Hematol Educ Program* 2015;2015:177-82.
4. George MR. Hemophagocytic lymphohistiocytosis: review of etiologies and management. *J Blood Med* 2014;5:69-86.
5. McClain KL, Allen CE. Chapter 71. Inflammatory and malignant histiocytosis. In: Kaushansky K, Lichtman MA, Prchal JT, et al., editors. *Williams Hematology*. 9th ed. New York (NY): McGraw-Hill; 2016.
6. Malinowska I, Machaczka M, Popko K. Hemophagocytic syndrome in children and adults. *Arch Immunol Ther Exp* 2014;62(5):385-94.
7. *FDA Drug Safety Communication: FDA warns of serious immune system reaction with seizure and mental health medicine lamotrigine (Lamictal)*. Silver Spring (MD): U.S. Food and Drug Administration; 2018 April 25. (accessed 2018 October 29).
8. Gümüş H, Kumandaş S, Per H, et al. Hemophagocytic syndrome associated with high-dose lamotrigine. *Pediatr Int* 2007;49(5):672-3.
9. Yang YC, Jou ST, Chang YH, et al. Hemophagocytic syndrome associated with antiepileptic drug. *Pediatr Neurol* 2004;30(5):358-60.
10. Ignaszewski M, Ignaszewski MJ, Kohlitz P. Lamotrigine-associated hemophagocytic lymphohistiocytosis. *Am J Ther* 2017;24(4):e493.

Did you know?

Lamotrigine and hemophagocytic lymphohistiocytosis (HLH)

Cases of HLH have been reported in pediatric and adult patients using lamotrigine. HLH is a rare and life-threatening disorder. Given its rapid progression and severity, early diagnosis and treatment are critical for patient survival.

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

Kayexalate (sodium polystyrene sulfonate) and Resonium Calcium (calcium polystyrene sulfonate)

The risk of **decreased efficacy of other oral medications** has been added to the *Warnings and Precautions*, *Drug Interactions*, *Dosage and Administration (Adults, Including the Elderly)* and *Consumer Information* sections of the Canadian prescribing information for Kayexalate and Resonium Calcium.

Key messages for healthcare professionals:^{1,2}

- When administered orally, Kayexalate or Resonium Calcium may bind to other orally administered medications, which could decrease their gastrointestinal absorption and efficacy.
- Avoid co-administration of Kayexalate or Resonium Calcium with other orally administered medications.
- Administer Kayexalate or Resonium Calcium at least 3 hours before or 3 hours after administration of other oral medications. For patients with gastroparesis, a 6-hour separation should be considered.

References

1. *Kayexalate (sodium polystyrene sulfonate)* [prescribing information]. Laval (QC): sanofi-aventis Canada Inc.; 2018.
2. *Resonium Calcium (calcium polystyrene sulfonate)* [prescribing information]. Laval (QC): sanofi-aventis Canada Inc.; 2018.

Rifadin (rifampin)

The risk of **vitamin K-dependent coagulopathy** has been included in the *Precautions*, *Drug Interactions*, *Post-Market Adverse Reactions* and *Patient Medication Information* sections of the Canadian product monograph for Rifadin.

Key messages for healthcare professionals:¹

- Rifadin may cause vitamin K-dependent coagulopathy and severe bleeding. Monitoring of occurrence of coagulopathy is recommended for patients at particular bleeding risk. Supplemental vitamin K administration should be considered when appropriate (vitamin K deficiency, hypoprothrombinemia).
- The concomitant use with antibiotics causing vitamin K-dependent coagulopathy such as cefazolin or other cephalosporins with N-methyl-thiotetrazole side chains should be avoided as it may lead to severe coagulation disorders.

Reference

1. *Rifadin (rifampin)* [product monograph]. Laval (QC) sanofi-aventis Canada Inc.; 2018.

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](#).

Folotyn (pralatrexate injection): Authorization with conditions

Health Canada has issued a Notice of Compliance, under the Notice of Compliance with Conditions policy for Folotyn (pralatrexate injection), solution for intravenous use 20 mg / mL and 40 mg / 2 mL vials. Folotyn is indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma. 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 Folotyn Canadian product monograph. The product monograph can be accessed through Health Canada's [Drug Product Database](#), the [Servier Canada Web site](#) or by contacting Servier Canada Inc. at 1-888-902-9700. Contact the company for a copy of any references, attachments or enclosures.

HELPFUL LINKS

- [MedEffect™ Canada](#)
- [Recalls and Safety Alerts Database](#)
- [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](#)
- [Drug Shortages Canada](#)
- [Annual trends for adverse reaction case reports and medical device problem incidents](#)

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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