Health Canada Santé Canada

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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 July 2015 by Health Canada.

Acetaminophen Information Update Summary Safety Review	This in-depth safety review evaluated the risk of acetaminophen-related liver injury in Canada. Health Canada concluded that although acetaminophen remains a safe and effective medicine, there are risks of serious liver injury when it is not used as directed. Several options that may reduce the occurrence of acetaminophen-related liver injury, particularly in the context of unintentional overdoses, were proposed for consideration. Health Canada has worked collaboratively with stakeholders to develop an education approach to promote the safe use of acetaminophen, and continues to assess the feasibility and anticipated effectiveness of other risk minimization options. Health Canada has also communicated on the safe use of acetaminophen to Canadians.
Combined Hormonal Birth Control Products Summary Safety Review	This safety review evaluated the potential for decreased effectiveness of combined hormonal birth control products when used by obese women. Health Canada found no conclusive evidence showing a higher risk of pregnancy in obese women compared to non-obese women when using combined hormonal birth control products. Health Canada will continue to monitor this issue.
Feraheme (ferumoxytol) Summary Safety Review	This safety review evaluated the potential for hypersensitivity reactions associated with the use of Feraheme (ferumoxytol). Health Canada concluded that although the Canadian prescribing information for Feraheme contained warnings about the serious risk of hypersensitivity reactions, an update to the prescribing information was necessary in light of the totality of the evidence. Health Canada has also communicated this information to Canadians.
Foreign Health Products Foreign Product Alert	These foreign health products have been found by regulators in other countries to contain undeclared drug ingredients. These 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.

Gluconorm (repaglinide) Health Product Risk Communication	Co-administration of repaglinide and clopidogrel (a CYP2C8 inhibitor) may lead to a significant decrease in blood glucose levels due to a drug-drug interaction. The concomitant use of repaglinide and clopidogrel is now contraindicated.
NaturaLyte Sodium Bicarbonate Liquid Concentrate Health Product Risk Communication	Specific lots of NaturaLyte Sodium Bicarbonate Liquid Concentrate in 6.4 L volumes that may contain higher bacterial levels than acceptable have been recalled by Fresenius Medical Care.
Nosodes and Children's Cough, Cold and Flu Homeopathic Products Information Update	Health Canada has advised consumers that it is introducing label changes for certain homeopathic products that fall under the Natural Health Product Regulations (NHPR). More particularly, to improve the safe use of these products, Health Canada is requesting the addition of statements on homeopathic nosode products to make it clear that they are not vaccines or alternatives to vaccines.
Unauthorized Eye Drops Advisory	Health Canada is informing Canadians that five brands of unauthorized eye drops labelled to contain a prescription drug (neostigmine methylsulfate) have been seized from two retailers, Cube Inc. and Magic Queen Cosmetics in Richmond, B.C. These products may pose serious risks to the health of Canadians.
Unauthorized Natural Health Product - Remogen Information Update	Health Canada advised Canadians that it has received a serious domestic adverse reaction report of abnormal heart rhythms associated with the ingestion of "Remogen" (containing ibogaine), an unauthorized natural health product in Canada that may pose serious health risks.
Vancomycin Hydrochloride Injection (USP 1 g/vial) Health Product Risk Communication	A typographical error was identified on one lot (lot BK112A14) of SteriMax Vancomycin Hydrochloride for Injection USP 1 g/vial. The error was only found on the French text of the secondary (outer) carton's reconstitution instructions of the product. The information found on the vial label and package insert correctly indicated the dosing 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

Rivaroxaban and liver injury

Key points

- Cases of liver injury associated with rivaroxaban use have been identified in the literature.
- Cases of liver-related adverse reactions involving rivaroxaban have been reported to Health Canada; however, most reports did not contain sufficient detail to permit the exclusion of alternate causes of liver injury.
- Healthcare professionals are encouraged to report to Health Canada any cases of liver injury suspected of being associated with rivaroxaban and to provide detailed information when describing cases.

Rivaroxaban (Xarelto) is an oral anticoagulant. It acts by directly inhibiting factor Xa which occupies a central role in the blood coagulation cascade.[1] Like other direct-acting oral anticoagulants, rivaroxaban has a relatively rapid onset of action, a short half-life and is given as a fixed daily dose requiring no routine coagulation monitoring.[1,2] It has been marketed in Canada since September 2008 and is indicated for the prevention and treatment of venous thrombotic events and the prevention of stroke and systemic embolism in select patients with atrial fibrillation.[1] Rivaroxaban is contraindicated in patients with liver disease associated with coagulopathy, and having clinically relevant bleeding risk.

Drug-induced liver injury (DILI) is a relatively rare adverse drug reaction.[3] It refers to any injury to the liver by a drug manifesting as a spectrum from asymptomatic liver test elevations to acute liver failure.[4] Given the wide range of clinical presentations and potential causative factors, and a lack of an objective diagnostic test, diagnosing DILI generally relies on the systematic exclusion of alternate causes.[5] DILI is often classified as intrinsic (predictable) or idiosyncratic (unpredictable).[4,5] Intrinsic DILI (e.g., acetaminophen toxicity) has a short latency, is dose-dependent and is the most common form of DILI. Idiosyncratic DILI is less common, has a less consistent relationship to dose and has a longer latency (usually within the first 6 months after starting a new medication). DILI may also be categorized according to varying pathological patterns of liver injury including cholestatic, hepatocellular or mixed types. Distinguishing between these patterns can be accomplished by using liver biochemical parameters, primarily the ratio of the alanine aminotransferase (ALT) to alkaline phosphatase (ALP) relative to their respective upper limits of normal. The pattern of liver injury can be used to guide the diagnostic approach.[5]

Health Canada's review of rivaroxaban and liver injury identified 16 published cases of liver injury suspected of being associated with rivaroxaban use.[6,7] Patients were 41 to 91 years of age and received daily doses of rivaroxaban between 10 to 20 mg. Most patients were being treated for knee or leg surgery. Latency time from exposure to the first signs or symptoms of liver injury ranged from 3 days to 2 months. In addition, varying degrees of transaminase elevations suggest the occurrence of cholestatic, hepatocellular and mixed patterns of liver injury. Given the varied dose, latency period and pattern of liver injury, these cases may be idiosyncratic. All but one patient recovered.

In contrast, a systematic review and meta-analysis of phase III randomized controlled trials examining the risk of DILI among new oral anticoagulants (NOACs), including rivaroxaban, determined that NOACs were not associated with an increased risk of DILI compared to respective comparators.[8]

A variety of patient and medication-specific risk factors for DILI have been cited in the literature. The evidence supporting the role of patient-related risk factors (e.g., gender, age and concomitant disease) is limited.[4,5,9] For specific drugs, genetic predisposition may be influential. Progress has been made in identifying medication-specific risk factors. These include drug dose, drug lipophilicity and the degree of hepatic metabolism.[4,9] The current scientific literature indicates that rivaroxaban exhibits moderate lipophilicity and approximately two-thirds of the administered dose is metabolized by the liver via cytochrome P450 (CYP) enzymes and CYP-independent mechanisms.[1,10]

As of Sept. 30, 2014, Health Canada received 61 reports* of liver-related adverse reactions (ARs) involving rivaroxaban. However, the majority of reports lacked important information such as dosing information, duration of exposure, liver biochemistries, comorbidities and concomitant medications. In particular, most reports did not contain sufficient detail to permit the exclusion of alternate causes of liver injury (e.g., viral or autoimmune hepatitis, hepatic ischemia, etc.[5]). In several cases (including cases reported in the literature[6]), the recent or concomitant use of acetaminophen represents a potential contributory factor for liver injury. Consequently, a causal relationship between rivaroxaban and liver injury could not be established in most Canadian cases.

Healthcare professionals are encouraged to report any suspected cases to Health Canada. When reporting liver-related ARs, the following information is important to include:

- Drug dose
- Duration of treatment
- Relevant patient medical conditions (including any underlying liver disease)
- Concomitant medications and dosages
- Liver biochemistry
- Exclusion of other potential causes of liver injury (e.g., viral or autoimmune hepatitis, hepatic ischemia, etc.)
- Response to drug discontinuation
- Patient outcomes

The inclusion of such information will help in evaluating the causal relationship between rivaroxaban and liver injury. Health Canada continues to monitor the potential risk of liver injury with rivaroxaban use.

References

1. *Xarelto (rivaroxaban)* [product monograph]. Mississauga (ON): Bayer Inc.; 2015.
2. Bauer KA. Recent progress in anticoagulant therapy: oral direct inhibitors of thrombin and factor Xa. *J Thromb Haemost* 2011;9 Suppl 1:12-9.
3. Björnsson ES. Incidence and outcomes of DILI in western patients. *Clin Liver Dis* 2014;4(1):9-11.
4. Leise MD, Poterucha JJ, Talwalkar JA. Drug-induced liver injury. *Mayo Clin Proc* 2014; 89(1):95-106.
5. Chalasani NP, Hayashi PH, Bonkovsky HL, et al. ACG Clinical Guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. *Am J Gastroenterol* 2014;109(7):950-66.
6. Russmann S, Niedrig DF, Budmiger M, et al. Rivaroxaban postmarketing risk of liver injury. *J Hepatol* 2014;61(2):293-300.
7. Liakoni E, Rätz Bravo AE, Terracciano L, et al. Symptomatic hepatocellular liver injury with hyperbilirubinemia in two patients treated with rivaroxaban. *JAMA Intern Med* 2014;174(10):1683-6.
8. Caldeira D, Barra M, Santos AT, et al. Risk of drug-induced liver injury with the new oral anticoagulants: systematic review and meta-analysis. *Heart* 2014;100(7):550-6.
9. Lammert C, Bjornsson E, Niklasson A, et al. Oral medications with significant hepatic metabolism at higher risk for hepatic adverse events. *Hepatology* 2010;51(2):615-20.
10. Mueck W, Stampfuss J, Kubitza D, et al. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. *Clin Pharmacokinet* 2014;53(1):1-16.

* The sum of all reports may differ from the total number of individual patient cases, as one case may be reported from more than one source.

HELPFUL LINKS

- MedEffect™ Canada
- Recalls and Safety Alerts Database
- Summary Safety Reviews
- New Safety Reviews
- Canada Vigilance Adverse Reaction Online Database
- Drug Product Database
- Canadian Drug Shortage Database
- The Drug and Health Product Register

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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