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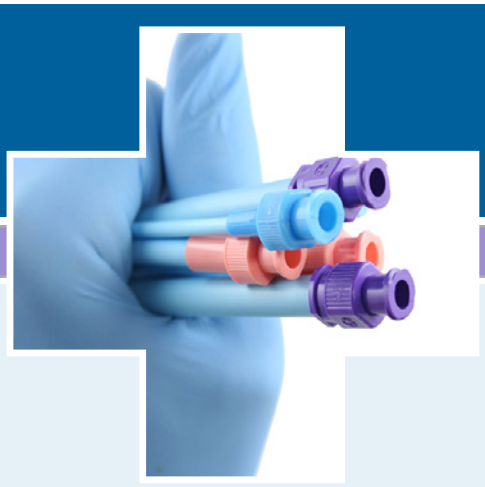

Health Product InfoWatch

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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 150

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 December 2016 by Health Canada.

Direct-acting antivirals Summary Safety Review Information Update	This safety review evaluated the risk of hepatitis B virus (HBV) reactivation associated with direct-acting antivirals (DAAs): Daklinza (daclatasvir), Epclusa (sofosbuvir, velpatasvir), Galexos (simeprevir), Harvoni (sofosbuvir, ledipasvir), Holkira Pak (dasabuvir, paritaprevir, ombitasvir, ritonavir), Sovaldi (sofosbuvir), Sunvepra (asunaprevir), Technivie (paritaprevir, ombitasvir, ritonavir), and Zepatier (grazoprevir, elbasvir). Health Canada's review concluded that there may be a link between the risk of HBV reactivation in patients infected with both HBV and hepatitis C virus that have been treated with certain DAAs. Health Canada has recommended that the Canadian product monographs for all DAAs be updated to inform about this risk, as a precaution. 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. 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.
General anesthetics and sedatives Information Update	Health Canada is reviewing the safety of certain drugs used for general anesthesia and sedation in children under the age of three, or in pregnant women during their third trimester. This follows a recent communication by the U.S. Food and Drug Administration warning the public that repeated or lengthy use of general anesthetics and sedatives in these groups may have potential negative effects on the development of children's brains. Health Canada will continue to update Canadians as the review is completed.
Unauthorized health product (Control-Max) Advisory	Health Canada advised Canadians that the unauthorized product "Control-Max" may pose serious health risks as it is labelled to contain yohimbine. The product was being sold online by the company RGR Canada Inc.
Unauthorized health products (Lithium Plus, Serotonin Support, and Brain Support) Advisory	Health Canada advised Canadians that 3 unauthorized products, "Lithium Plus, Serotonin Support, and Brain Support," may pose serious health risks because they may contain lithium orotate. The products were offered for sale online by the company Cutting Edge Naturals and were marketed to contain lithium orotate.

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.

MEDICATION ERROR ALERTS

Eligard (leuprolide acetate): Reconstitution and administration errors and risk of lack of efficacy

Key points

- Reconstitution and route of administration errors have been reported with Eligard which could compromise the clinical efficacy of the product.
- Eligard must only be administered after reconstituting the leuprolide acetate component with the Atrigel Delivery System, following proper mixing procedures, in order to provide the continued sustained release of leuprolide.
- Eligard must be administered via subcutaneous injection only.

Eligard (leuprolide acetate) is a gonadotropin-releasing hormone agonist. It is indicated for the palliative treatment of advanced prostate cancer (stage D2)[1] and has been marketed in Canada since 2003. Eligard is an extended release formulation of leuprolide acetate available as 1-month (7.5 mg), 3-month (22.5 mg), 4-month (30 mg) and 6-month (45 mg) subcutaneous injections to be administered by a healthcare professional.[1] The product is intended to provide sustained levels of leuprolide, over the respective dosing intervals, resulting in continuous testosterone suppression.

Health Canada has reviewed Canadian reports of handling errors involving incorrect reconstitution and route of administration with Eligard, which could compromise the clinical efficacy of the product.[2]

Some of the errors reported with Eligard described inadequate mixing of the product. The product consists of 2 separate prefilled syringes. One syringe contains the active ingredient, leuprolide acetate powder, and the other contains the Atrigel Delivery System to reconstitute the product. In order to thoroughly mix the product, it must first be allowed to reach room temperature by removing from the refrigerator at least 30 minutes before mixing.[1] The two syringes must then be joined together and the contents pushed back and forth between syringes for approximately 45 seconds until uniform. Shaking will not provide adequate mixing of the product. Once mixed, Eligard must be administered within 30 minutes, as the viscosity of the reconstituted product increases with time. If not used within this timeframe, the reconstituted product should be discarded.

Other medication errors involved the administration of leuprolide acetate after reconstitution with a diluent other than the supplied Atrigel Delivery System. In certain cases, the leuprolide acetate powder was mixed with saline or sterile water. As leuprolide has an elimination half-life of approximately 3.6 hours when administered subcutaneously,[3] the sustained release and intended efficacy period of Eligard is compromised if the leuprolide acetate is not reconstituted with the Atrigel Delivery System.

Some medication errors also included cases of incorrect route of administration where the product was administered intramuscularly instead of by the intended subcutaneous route. Eligard is approved for subcutaneous administration only. The Canadian product monograph does not include information pertaining to either efficacy or clinical outcomes if administered via the intramuscular route.

The *Warnings and Precautions* and *Dosage and Administration* sections of the Canadian product monograph have recently been updated to include the risk of lack of clinical efficacy due to incorrect reconstitution or administration of Eligard. The package labels and educational materials have also been updated to highlight key information for healthcare professionals.

Healthcare professionals are reminded to consult the updated Eligard Canadian product monograph or the package insert for detailed mixing and administration procedure information. Healthcare professionals are also advised to consider additional testosterone level monitoring in cases of suspected or known handling errors with Eligard.

References

1. *Eligard (leuprolide acetate)* [product monograph]. Laval (QC) : sanofi-aventis Canada Inc.; 2016.
2. Data on file, Health Canada, December 2015.
3. Sennello LT, Finley RA, Chu S, et al. Single-dose pharmacokinetics of leuprolide in humans following intravenous and subcutaneous administration. *J Pharm Sci* 1986;75(2):158-60.

Did you know?

Other continuous sustained release leuprolide acetate injectable products authorized for sale in Canada require administration via the intramuscular route. Eligard must be administered via subcutaneous injection only.

Methotrexate: Serious dosing errors

Methotrexate is a folate antagonist used in the treatment of cancer and autoimmune diseases such as psoriasis and rheumatoid arthritis.[1] As a high-alert medication, methotrexate carries an increased risk of significant, even fatal, consequences when it is used in error.[2]

Health Canada is aware of recent serious errors reported in the media in which patients received daily instead of weekly doses of oral methotrexate. Patient safety organizations and regulators have issued a number of notices reporting similar errors in the past.[3-5]

Health Canada's recently published Good Label and Package Practices Guide for Prescription Drugs includes direction to manufacturers regarding the inclusion of prominent warning statements on labels. The guide suggests that labels for oral methotrexate should state "check dose and frequency – methotrexate is usually taken once a week." Health Canada will continue to investigate whether additional label changes could help to mitigate the potential for error.

Healthcare professionals are reminded that the risks associated with methotrexate dosing errors require vigilance at all stages of the medication use process. The importance of taking the medication as prescribed should be clearly communicated to patients and caregivers.

References

1. *Methotrexate* [product monograph]. Kirkland (QC): Pfizer Canada Inc.; 2016.
2. *ISMP List of high-alert medications in community/ambulatory healthcare*. Horsham (PA): Institute for Safe Medication Practices; 2011 January 30. (accessed 2017 January 18)
3. Severe harm and deaths associated with incidents involving low-dose methotrexate. *ISMP Canada Safety Bulletin* 2015;15(9):1-5. (accessed 2017 January 18)
4. Stewart I. Errors involving oral methotrexate. *Pharmacy Connection* 2015;22(4):54-5. (accessed 2017 January 18)
5. Incidents of inadvertent daily administration of methotrexate. *ISMP Canada Safety Bulletin* 2008;8(2):1-3. (accessed 2017 January 18)

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.

Mekinist (trametinib)

*The risk of **colitis and gastrointestinal perforation** has been added to the Warnings and Precautions and Adverse Reactions sections of the Canadian product monograph for Mekinist (trametinib).*

Key messages for healthcare professionals:[1]

- Colitis and gastrointestinal perforation, including fatal outcome, have been reported in patients taking Mekinist.
- Mekinist monotherapy or in combination with dabrafenib should be used with caution in patients with risk factors for gastrointestinal perforation, including a history of diverticulitis, metastases to the gastrointestinal tract and concomitant use of medications with a recognized risk of gastrointestinal perforation.
- Patients should be advised to seek immediate medical care if they develop symptoms of colitis and gastrointestinal perforation.

Reference

1. *Mekinist (trametinib)* [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2016.

Neurontin (gabapentin)

*Additional information concerning the risk of **respiratory depression** has been added to the Warnings and Precautions section of the Canadian product monograph (CPM) for Neurontin (gabapentin). The CPM already included information on the risk of respiratory depression when used concomitantly with opioids.*

Key messages for healthcare professionals:[2]

- Gabapentin has been associated with central nervous system (CNS) depression including sedation, somnolence, loss of consciousness as well as serious cases of respiratory depression.
- Patients with compromised respiratory function, respiratory or neurological disease, renal impairment and the elderly are at higher risk of experiencing these severe adverse effects.
- Concomitant use of CNS depressants with gabapentin is also a contributing factor.

Reference

2. *Neurontin (gabapentin)* [product monograph]. Kirkland (QC): Pfizer Canada Inc.; 2016.

Related content: Summary Safety Review - Gabapentin - Assessing the Potential Risk of Serious Breathing Problems

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

Health Canada
Marketed Health Products Directorate
Address Locator 1906C
Ottawa ON K1A 0K9
Telephone: 613-954-6522
Fax: 613-952-7738

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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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