Health Canada Santé Canada

Canada

Health Product InfoWatch

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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.

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.

CORONAVIRUS DISEASE (COVID-19)

For the most up-to-date information on COVID-19, please visit the Government of Canada Coronavirus disease (COVID-19) Web site **Canada.ca/coronavirus**, which includes a dedicated section for healthcare professionals and for the health product industry.

The COVID-19 vaccines and treatments portal provides information for consumers, healthcare professionals and researchers on vaccines and treatments authorized for COVID-19.

For information about adverse events following immunization that individuals have reported after receiving a COVID-19 vaccine in Canada, new safety signals or other safety updates, please visit the COVID-19 vaccine safety in Canada webpage, which is updated weekly.

MONTHLY RECAP OF HEALTH PRODUCT SAFETY INFORMATION

The following is a list of health product advisories, type I recalls and summaries of completed safety reviews published in November 2021 by Health Canada.

Odor-Eaters Spray Powder Advisory	Blistex Corporation recalled 3 lots of Odor-Eaters Spray Powder for athlete's foot due to contamination with benzene.
TUMS Assorted Berries Extra Strength Tablets Advisory	GSK Consumer Healthcare ULC recalled 2 lots of TUMS Assorted Berries Extra Strength Tablets, sold in 750 mg bottles and packages of 3 rolls containing 8 tablets each, because the tablets may contain metal fragments.
Unauthorized health products Advisory – Ayurvedic medicinal products sold by Kerela Ayurvedic & Natural Herbal Consultation in Toronto, ON	Health Canada advised Canadians about various unauthorized health products being sold at retail locations across Canada or online that may pose serious health risks.
Verkazia (cyclosporine) Advisory	McKesson Specialized Distribution recalled 1 lot of Verkazia (cyclosporine) eye drops after certain vials from the lot were found to contain particulate matter. The manufacturer, Santen Inc., determined the particles were a crystalized form of the active drug ingredient, cyclosporine.

NEW HEALTH PRODUCT SAFETY INFORMATION

The following topics have been selected to raise awareness and encourage reporting of similar adverse reactions.

Review article

Atypical hemolytic reactions following exposure to gemtuzumab ozogamicin (Mylotarg)

Key messages

- Five international cases of atypical hemolytic reactions following exposure to gemtuzumab ozogamicin (GO) have been identified in the literature.
- These adverse reactions presented as intravascular hemolytic reactions with atypical laboratory patterns.
- Laboratory patterns in these reactions may be misinterpreted as *in vitro* hemolysis and result in delayed diagnosis and treatment.
- A proposed mechanism for the atypical laboratory findings is impaired hemoglobin-haptoglobin scavenging secondary to the effect of GO on CD33+ cells.
- Healthcare professionals are encouraged to report adverse reactions suspected of being associated with GO therapy to Health Canada to help better assess this potential risk.

Gemtuzumab ozogamicin (GO), marketed in Canada since 2020 under the brand name Mylotarg, is an antibody-drug conjugate.[1] The antibody component targets CD33, a transmembrane protein often expressed on leukemic blast cells in patients with acute myeloid leukemia (AML). The antibody component is attached to a cytotoxic calicheamicin molecule. In Canada, GO is indicated for the treatment of adult patients with previously untreated, de novo CD33-positive AML, in combination with daunorubicin and cytarabine.

Five international cases of atypical hemolytic reactions following exposure to GO have been identified in the literature (see Table 1).[2-4] These adverse reactions presented as intravascular hemolytic reactions with atypical laboratory patterns: high plasma hemoglobin, normal to high plasma haptoglobin and normal plasma bilirubin levels. Laboratory patterns in these reactions may be misinterpreted as *in vitro* hemolysis, which may delay diagnosis and treatment. The initial trigger for hemolysis in these cases was not known.

During *in vivo* hemolysis, hemoglobin is released and bound by haptoglobin. This molecular complex is cleared by CD33+ monocytes and macrophages via the CD163 scavenger receptor. In severe *in vivo* hemolysis, haptoglobin is typically undetectable.[4]

A proposed mechanism for the paradoxical accumulation of both plasma hemoglobin and haptoglobin is impaired CD163-mediated hemoglobin-haptoglobin scavenging as a result of the anti-CD33-mediated destruction of CD33+/CD163+ monocytes and macrophages.

While this mechanism is considered plausible, there is limited evidence at this time to confirm this potential adverse drug reaction. Nonetheless, healthcare professionals should be aware of the possibility of this adverse reaction and recognize that laboratory patterns may be misinterpreted.

As of July 31, 2021, no Canadian cases have been identified.

To help better assess this risk, healthcare professionals are encouraged to report adverse reactions suspected of being associated with GO therapy to Health Canada.

Table 1: Summary of 5 international case reports of atypical hemolytic reactions following GO exposure

Case report	Age (years) / sex	Diagnosis	Chemotherapy prior to hemolysis	Time from last GO therapy to hemolysis	Laboratory pattern	Outcome
1[2]	21/F	AML, relapsed	Cytarabine, idarubicin and GO	19 days	• High plasma lactate dehydrogenase • High plasma hemoglobin • Normal to high plasma haptoglobin • Normal plasma bilirubin	Recovered after > 10 TPE
2[2]	24/F	AML, no previous therapy	Cytarabine, idarubicin and GO	14 days		Recovered after 3 TPE
3[3]	2/M	AML, relapsed	FLAG and GO	3 weeks		Recovered but died later from progressive disease
4[3]	1/F	AML, relapsed	FLAG-Daunorubicin, GO and NOPHO-AML 2004 induction	5 weeks		Did not recover, died from progressive disease
5[4]	12/M	AML, refractory	GO	5 days		Did not recover, died from progressive disease

AML: acute myeloid leukemia; FLAG: fludarabine, high-dose cytarabine and granulocyte colony-stimulating factor; GO: gemtuzumab ozogamicin; NOPHO: Nordic Society for Pediatric Hematology and Oncology; TPE: therapeutic plasma exchange

References

1. *Mylotarg (gemtuzumab ozogamicin)* [Product Monograph]. Kirkland (QC): Pfizer Canada ULC; 2021.
2. Rajala HLM, Anttila V-J, Haapio M, et al. Gemtuzumab-ozogamicin-related impaired hemoglobin-haptoglobin scavenging as on-target/off-tumor toxicity of anti-CD33 AML therapy: A report of two cases. Case Rep Hematol 2021;6641349.
3. Maniecki MB, Hasle H, Friis-Hansen L, et al. Impaired CD163-mediated hemoglobin-scavenging and severe toxic symptoms in patients treated with gemtuzumab ozogamicin. Blood 2008;112(4):1510-4.
4. Tesfazghi MT, Farnsworth CW, Roper SM, et al. Confounding case of hemolysis in a patient with acute leukemia. Clin Chem 2018;64(12):1690-4.

Product monograph updates

The following safety labelling updates, which were recently made to the Canadian product monographs, 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 page. Canadian product monographs can be accessed through Health Canada's Drug Product Database.

Lupron and Lupron Depot (leuprolide acetate)

The *Warnings and Precautions*, *Adverse Reactions (Post-market Adverse Drug Reactions)*, and *Patient Medication Information* sections of the Canadian product monograph for Lupron and Lupron Depot have been updated with the **risk of pseudotumor cerebri/idiopathic intracranial hypertension in pediatric patients**.

Key messages for healthcare professionals:[1]

- Pseudotumor cerebri (PTC) / idiopathic intracranial hypertension has been reported in pediatric patients receiving leuprolide acetate.
- Monitor patients for signs and symptoms of PTC, including headache, papilledema, blurred vision, diplopia, loss of vision, pain behind the eye or pain with eye movement, tinnitus, dizziness, and nausea.
- Refer the patient to an ophthalmologist to confirm the presence of papilledema. If PTC is confirmed, treat the patient in accordance with established treatment guidelines and permanently discontinue use of leuprolide acetate.

Reference

1. *Lupron and Lupron Depot (leuprolide acetate)* [product monograph]. St-Laurent (QC): AbbVie Corporation; 2021.

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs)

The *Warnings and Precautions* section of the Canadian product monographs for SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, vilazodone and vortioxetine) and SNRIs (desvenlafaxine, duloxetine, levomilnacipran and venlafaxine) has been, or will be, updated with **new safety information concerning reports of long-lasting sexual dysfunction** where the symptoms have continued despite treatment discontinuation.

Key messages for healthcare professionals:

- Health Canada reviewed the potential risk of persistent or worsening sexual dysfunction, as well as the appearance of new symptoms of sexual dysfunction after discontinuing SSRI or SNRI treatment.
- Health Canada's review could not confirm, nor rule out, a causal link between discontinuing SSRI or SNRI treatment and persistent sexual dysfunction.
- Health Canada's review could not make conclusions about worsening or new onset sexual dysfunction because of limitations in existing evidence.

- Patients should be informed that there have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs and SNRIs.

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 type 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. For the most up-to-date information, consult Health Canada's NOC database.

Lucentis (ranibizumab injection): Authorization with conditions

Health Canada has issued a Notice of Compliance, under the NOC/c policy, for a new indication for Lucentis (ranibizumab injection)[1], single use vials, 10 mg/mL solution for injection. Lucentis is now indicated in preterm infants for the treatment of retinopathy of prematurity (ROP) with zone I [stage 1 with plus disease (1+), stage 2 with plus disease (2+), or stage 3 with or without plus disease (3 or 3+)], or zone II [stage 3 with plus disease (3+)] or aggressive posterior ROP (AP-ROP) disease. Patients/caregivers should be advised of the conditional market authorization for this new indication.

For the complete prescribing information and information available for patients/caregivers, please consult the Lucentis Canadian product monograph. The product monograph can be accessed through Health Canada's Drug Product Database, the Novartis Pharmaceuticals Canada Inc. website or by contacting Novartis Pharmaceuticals Canada Inc. at 1-800-363-8883. Contact the company for a copy of any references, attachments or enclosures.

[1] Lucentis updated product monograph with this NOC/c indication is dated November 2021.

Helpful links

- MedEffect™ Canada
- Recalls and Safety Alerts Database
- New Safety and Effectiveness 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
- Stop Illegal Marketing of Drugs and Devices
- List of drugs for exceptional importation and sale
- COVID-19: List of authorized drugs, vaccines and expanded indications
- Reported side effects following COVID-19 vaccination in Canada

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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