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
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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.

Contents

MONTHLY RECAP OF HEALTH PRODUCT SAFETY INFORMATION

The following is a list of health product advisories, type I drug recalls and summaries of completed safety reviews published in November 2024 by Health Canada.

Cyclosporine

This safety review evaluated the risk of hearing impairment associated with the use of cyclosporine-containing products. Health Canada's review of the available information did not find sufficient evidence in the post-market setting regarding the link between cyclosporine and the risk of hearing impairment to support changes to the Canadian product monograph. Health Canada will continue to monitor safety information involving cyclosporine.

Summary Safety Review: Cyclosporine

Dasatinib

This safety review evaluated the risk of delayed growth in children associated with the use of dasatinib-containing products. Health Canada's review of available information concluded that there is a possible link. Health Canada will work with the manufacturers to update the Canadian product monograph for all dasatinib-containing products to include this risk.

Summary Safety Review: Dasatinib

Ilaris (canakinumab)

This safety review evaluated the risk of drug reaction with eosinophilia and systemic symptoms (DRESS) associated with the use of Ilaris. Health Canada's review of the available information concluded that there is a possible link. Health Canada is working with the manufacturer to update the Canadian product monograph for Ilaris with a warning about reported cases of DRESS, predominantly in patients with systemic juvenile idiopathic arthritis.

Summary Safety Review: Ilaris (canakinumab)

Kit for the preparation of technetium TC 99M Sestambi Injection

One lot of the Kit for the preparation of technetium TC 99M Sestambi Injection was recalled as product sterility may be compromised in the affected lot.

Type 1 drug recall: Kit for the preparation of technetium TC 99M Sestambi Injection

Unauthorized Health Products

Health Canada advised Canadians about various unauthorized health products being sold at retail locations across Canada or online that may pose serious health risks.

Type 1 drug recall: Titanium 4000, Titanium 4000+ tablets, Titanium 4000+ capsules

NEW HEALTH PRODUCT SAFETY INFORMATION

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

Review article

Glucagon-like peptide-1 receptor agonists and the risk of suicide, self-harm, and suicidal/self-harm ideation

Key messages:

- Health Canada's review concluded that the available evidence does not support a causal link between glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and suicide, self-harm, and suicidal/self-harm ideation in the general type 2 diabetes mellitus (T2DM) population. For obese patients, regardless of underlying T2DM status, the existing evidence is inconsistent and inconclusive.
- At this time, updates to the Canadian product monograph (CPM) for GLP-1 RAs are not warranted.
- Healthcare professionals are encouraged to report any adverse reactions suspected of being associated with GLP-1 RAs to the Canada Vigilance Program.

GLP-1 RAs are a class of drugs which have been marketed in Canada since 2010.* The GLP-1 RA products currently marketed in Canada include:

- Ozempic/Rybelsus (semaglutide), Soliqua (insulin glargine and lixisenatide), Trulicity (dulaglutide), Victoza (liraglutide) , and Xultophy (insulin degludec and liraglutide), which are indicated for the management of adults with T2DM and,
- Saxenda (liraglutide) and Wegovy (semaglutide), which are indicated for chronic weight management in patients who are obese or overweight.

In recent years, the use of GLP-1 RAs has been increasing with approximately 7.1 million prescriptions dispensed in Canada in 2023.[1] International case reports[2] of suicidal thoughts and self-harm in patients being treated with GLP-1 RAs led Health Canada to conduct a safety review to evaluate the risks of suicide, self-harm and suicidal/self-harm ideation with the use of GLP-1 RAs.

Relevant data were collected from the drug manufacturers, including product specific meta-analyses of randomized clinical trials (RCT). Data were also retrieved from searches of Canadian and international databases of spontaneous adverse event reports. In addition, the Canadian Network for Observational Drug Effect Studies (CNODES) was commissioned to conduct a systematic search and appraisal of the published real-world evidence on this safety topic.[3]

Health Canada reviewed the evidence from these sources and conducted additional meta-analyses of RCTs across the various GLP-1 RAs to explore a potential class effect.

Product specific meta-analyses of RCTs conducted by drug manufacturers did not demonstrate a significantly increased risk of suicide, self-harm, suicidal/self-harm ideation or depression with GLP-1 RAs versus placebo or no active treatment.[4] Exploratory meta-analyses conducted by Health Canada across the GLP-1 RA drug products demonstrated consistent findings of no increased risk for the drug class, which were further

corroborated by a recently published meta-analysis of RCTs investigating similar outcomes in patients treated with GLP-1 RAs.[5]

Four studies with relevant real-world epidemiological evidence were identified and evaluated, including two unpublished[4] and two published cohort studies.[6,7] Important biases in the study methods and analyses were noted across the studies, lending to some uncertainty in the findings. Individually, these studies either demonstrated statistically significant risk reductions for the outcomes of suicide, self-harm, and/or suicidal/self-harm ideation, or imprecise and inconclusive estimates of effect. However, for the subgroup of patients with obesity, findings from two of the four studies were inconsistent, with one study estimating a statistically significant higher risk of suicidality and another demonstrating a statistically significant lower risk of incident and recurrent suicidal ideation with GLP-1 RAs versus alternative therapies.

Health Canada also reviewed 15 case reports (3 Canadian) of suicide, self-harm, and/or suicidal/self-harm ideation suspected of being associated with GLP-1 RAs.[8,9,10] Of the 15 case reports, 12 (3 Canadian) were found to be possibly linked to the use of GLP-1 RAs, and 3 could not be assessed due to missing clinical information. Overall, these case reports provided limited evidence for a link between GLP-1 RAs and suicide, self-harm, and/or suicidal/self-harm ideation, as confounders (such as pre-existing mental health problems, life stressors, family history, concomitant medications and, social and environmental factors) could not be ruled out due to the limited clinical information in these reports.

Health Canada concluded that the totality of evidence reviewed does not support an increased risk of suicide, self-harm and/or suicidal/self-harm ideation with the use of GLP-1 RAs in the general T2DM population. However, for obese patients, regardless of underlying T2DM status, the existing evidence is inconsistent and inconclusive requiring further investigation. Health Canada considers that no update to the CPM for GLP-1 RAs is warranted at this time.

Health Canada will continue to monitor the safety of GLP-1 RAs, as it does for all health products on the Canadian market, to identify and assess potential harms. Health Canada will take appropriate and timely action should new health risks be identified.

References

1. Vannabouathong C, Crotty C, Le K, Eurich D, Dyrda P. Current Utilization Patterns of Glucagon-Like Peptide-1 Receptor Agonists. Canadian Drug Expert Committee (CADTH). *Canadian Journal of Health Technologies.* 2022; 2(9). https://www.cda-amc.ca/sites/default/files/hta-he/HC0042-Utilization-of-Glucagon-Like-Peptide1-(GLP-1)-Agonists-aug26_KT-meta.pdf
2. European Medicines Agency. EMA statement on ongoing review of GLP-1 receptor agonists. Published July 11, 2023. https://www.ema.europa.eu/en/news/ema-statement-ongoing-review-glp-1-receptor-agonists
3. Canada's Drug Agency. Exploration of the Risk of Suicidality and Self-Harm With Glucagon-Like Peptide-1 Receptor Agonists. Published May 16, 2024. https://www.cda-amc.ca/exploration-risk-suicidality-and-self-harm-glucagon-peptide-1-receptor-agonists
4. Health Canada has data on file.

5. Silverii GA, Marinell, C, Mannucci E, Rotella F. (2024). Glucagon-like peptide-1 receptor agonists and mental health: A meta-analysis of randomized controlled trials. *Diabetes Obes Metab.* 2024 26(6):2505-2508. doi:10.1111/dom.15538

6. Gamble JM, Chibrikov E, Midodzi WK, Twells LK, Majumdar SR. Examining the risk of depression or self-harm associated with incretin-based therapies used to manage hyperglycaemia in patients with type 2 diabetes: a cohort study using the UK Clinical Practice Research Datalink. *BMJ Open.* 2018;8(10):e023830. Published October 8, 2018. doi:10.1136/bmjopen-2018-023830

7. Wang W, Volkow ND, Berger NA, Davis PB, Kaelber DC, Xu R. Association of semaglutide with risk of suicidal ideation in a real-world cohort. *Nat Med*. 2024;30(1):168-176. doi:10.1038/s41591-023-02672-2

8. Health Canada. Adverse Reaction Database. Accessed October 10, 2023. https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-database.html

9. Kohen I, Lester P. Exenatide-induced depression in a geriatric patient. *IntJ Geriatr Psychiatry*. 2008; 23(4), 443–444. doi:10.1002/gps.1937

10. Li J R, Cao J, Wei J, Geng W. Case Report: Semaglutide-associated depression: a report of two cases. *Front Psychiatry*, 2023; 14:1238353**.** Published August 29, 2023. doi:10.3389/fpsyt.2023.1238353

Product monograph update

The following safety labelling update, which was recently made to the Canadian product monograph, has been included 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.

Kymriah (tisagenlecleucel)

The *Warnings and Precautions, Adverse Reactions (Post-Marketing Adverse Reactions)* and *Patient Medication Information* sections of the Canadian product monograph (CPM) for Kymriah have been updated to include the risk of **secondary T-cell malignancies.**

Key messages for healthcare professionals:[1]

- T-cell malignancies, including chimeric antigen receptor (CAR)-positive tumours, have occurred following treatment of hematologic malignancies with genetically modified autologous T-cell immunotherapies, including Kymriah.
- The T-cell malignancies may present as soon as weeks following Kymriah infusion and may include fatal outcomes.
- Patients should be monitored life-long for secondary malignancies, including those of T-cell origin.

Health Canada is working with the manufacturers to include aligned information about the risk of secondary T-cell malignancy in the CPM for all chimeric antigen receptor T-cell (CAR-T) therapies.

Reference

1. *Kymriah (tisagenlecleucel)*[product monograph]. Montreal (QC): Novartis Pharmaceuticals Canada Inc.;2024.

Helpful links

- 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 Portal
- Drug Shortages Canada
- Medical device shortages
- COVID-19 vaccines and treatments portal

Contact us

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Health Product InfoWatch Editorial Team
Marketed Health Products Directorate, Health Canada
Address Locator 1906C,
Ottawa ON K1A 0K9

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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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[*] *Mounjaro (tirzepatide), a dual Glucose-Dependent Insulinotropic Polypeptide (GIP) and GLP-1 RA marketed in Canada, was not included in Health Canada's review due to its dual mechanism of action.*