Summary Safety Review - Methadone - Assessing the Potential Risk of Hypoglycemia

Product: Methadone

Potential Safety Issue: Low blood sugar (hypoglycemia)

Key Messages

- **Methadone is authorized in Canada for the relief of severe pain in patients who have previously used opioids, or as substitution treatment in patients with opioid dependence.**
- **Health Canada reviewed the potential risk of hypoglycemia (low blood sugar) with methadone use after becoming aware of a published case[1] in the United States (US) concerning this risk.**
- **Health Canada's review concluded that there may be a link between methadone use and the risk of hypoglycemia.**
- **Health Canada will be working with the manufacturers to update the Canadian product safety information (Canadian product monograph) for methadone to include the risk of hypoglycemia.**

Overview

Health Canada reviewed the potential risk of hypoglycemia with methadone use. This safety review was triggered by a published case in the US suggesting that patients using methadone could experience hypoglycemia.

Hypoglycemia is a condition in which your blood sugar level is lower than normal. Signs and symptoms of hypoglycemia may include shakiness, sweating and irritability. As hypoglycemia gets worse, symptoms may include confusion and loss of consciousness.

Use in Canada

- Methadone is authorized in Canada for the relief of severe pain in patients who have previously used opioids, or for use in opioid dependent patients requiring substitution treatment to prevent side effects when patients stop using other opioids (opioid withdrawal symptoms).
- Methadone has been available in Canada since the 1960s.
- Methadose (10 mg/mL oral concentrate), Metadol-D (1, 5, 10, 25 mg tablets, 1 mg/mL oral solution, and 10 mg/mL oral concentrate), Sandoz Methadone (10 mg/mL oral concentrate), Jamp Methadone Oral Concentrate (10 mg/mL oral concentrate), and Odan-Methadone (10 mg/mL oral concentrate) are authorized for sale in Canada for opioid substitution treatment in patients with opioid dependence. Methadone powder is also available to pharmacists to make methadone solutions. After being mixed with a flavoured liquid, these products are dispensed to patients and taken orally.
- Metadol (1, 5, 10, 25 mg tablets, 1 mg/mL oral solution, and 10 mg/mL oral concentrate) and pms-Methadone (1, 5, 10, 25 mg tablets) are authorized for sale in Canada for the relief of severe pain, generally in adults who have previously used opioids.
- There were about 12 million prescriptions for methadone filled in Canada in 2020.

Safety Review Findings

- Health Canada reviewed the available information from searches of the Canada Vigilance database[a], the World Health Organization's Adverse Drug Reaction Database[b], and the published literature.
- At the time of the review, Health Canada had not received any Canadian reports of hypoglycemia related to methadone use.
- This safety review looked at 19 international cases of hypoglycemia in adults after methadone use, many of which included incomplete information or described patients who were taking other medications or suffering from medical conditions (kidney disease and/or diabetes) that may contribute to hypoglycemia.
- Despite these limitations, Health Canada found sufficient evidence to determine a probable link between methadone use and the risk of hypoglycemia in 3 cases and a possible link in 9 cases. An additional 2 cases were unlikely to be linked with methadone use, while the remaining 5 cases did not have enough information to be further assessed.
    - Of the 12 cases linked to methadone use, 5 were reported in patients with kidney disease, 3 in patients with diabetes, and 1 in a patient who had received insulin for an unknown indication in the past. Resolution of hypoglycemia was reported in 11 of these 12 cases, generally following methadone discontinuation or dose reduction.
- Health Canada also assessed 6 published studies reporting cases of hypoglycemia after methadone use. These studies had weaknesses in their design, including incomplete data collection, small patient numbers, and the use of other opioids known to cause hypoglycemia at the same time as methadone. Despite these weaknesses, a possible link between the use of methadone and the risk of hypoglycemia was found, including possible biological mechanisms to explain how methadone could lead to hypoglycemia.
- Health Canada's review did not identify any trends related to risk factors, duration of use, medical conditions, dose range, or methadone formulation for the development of hypoglycemia following methadone use.

Conclusions and Actions

- Health Canada's review found a possible link between methadone use and the risk of hypoglycemia.
- Health Canada will be working with the manufacturers of methadone to update the Canadian product monographs to include the risk of hypoglycemia.
- Health Canada encourages consumers and healthcare professionals to report any side effects related to the use of methadone or other health products to the Canada Vigilance Program.
- Health Canada will continue to monitor safety information involving methadone, 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 any new health risks be identified.

Additional Information

The analysis that contributed to this safety review included scientific and medical literature, international adverse reaction reports, and what is known about the use of methadone both in Canada and internationally.

For additional information, contact the Marketed Health Products Directorate.

References

1. Otalora Y, Inkollu S, Ursu S. Methadone induced hypoglycemia, improved on dose adjustment. *J Clin Transl Endocrinol Case Rep*. 2020;18(100071):100071.

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a. Canadian reports can be accessed through the Canada Vigilance Online Database
b. World Health Organization's Adverse Drug Reaction Database