Health Canada | Santé Canada

Health Products and Food Branch | Direction générale des produits de santé et des aliments

Marketed Health Products Directorate
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OTTAWA, Ontario
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June 07, 2021

21-105219-529

To whom it may concern,

Re: Health Canada will publish a summary safety review regarding dopamine agonists

As an ongoing commitment to openness and transparency, Health Canada would like to notify you that a summary safety review (SSR) regarding dopamine agonists and the potential risk of dopamine agonist withdrawal syndrome (DAWS) will be published (see attached document). The SSR is intended to provide Canadians with a sufficient understanding of the safety review conducted by Health Canada, specifically what was assessed, what was found and what action was taken. The SSR will be posted in subsequent days. [1]

This advance notification is being sent for your information only. A broader dissemination to your members would be greatly appreciated.

Any question related to the SSR process or requests for further information on the safety review should be directed to the Marketed Health Products Directorate; e-mail: hc.mhpdssrcoordinator-dpscreicoordinateur.sc@canada.ca

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[1] http://www.hc-sc.gc.ca/dhp-mps/medeff/reviews-examens/index-eng.php

Please feel free to contact us, should you require further information.

Sincerely,

E-signed by

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Attachment:

Summary Safety Review – Dopamine Agonists – Assessing the potential risk of Dopamine Agonist Withdrawal Syndrome (DAWS)

Summary Safety Review - Dopamine Agonists - Assessing the Potential Risk of Dopamine Agonist Withdrawal Syndrome

Product: Dopamine agonists (apomorphine-, bromocriptine-, cabergoline-, pergolide-, pramipexole-, quinagolide-, ropinirole-, rotigotine-containing products)

Potential Safety Issue: Dopamine agonist withdrawal syndrome (DAWS), a group of mental and physical symptoms occurring after stopping or reducing the dose of dopamine agonists

Key Messages

- **Dopamine agonists are authorized for sale in Canada to treat Parkinson's disease, restless leg syndrome, and conditions that occur when the body produces too much prolactin hormone (prolactin secretion disorders), or when the body makes too much growth hormone during adulthood (acromegaly).**
- **Health Canada has been monitoring the potential risk of dopamine agonist withdrawal syndrome (DAWS) with the use of dopamine agonists since 2019, following updates made by the Japanese Pharmaceuticals and Medical Devices Agency to the product safety information for dopamine agonists related to this risk. In 2020, the manufacturer of Mirapex (pramipexole) voluntarily updated the Canadian product information (Canadian Product Monograph) to include a warning about DAWS, which triggered Health Canada's safety review for the whole class of dopamine agonists marketed in Canada.**
- **Health Canada's review of the available information has established a link between use of the dopamine agonists pramipexole, quinagolide, or ropinirole and the risk of DAWS. The Canadian Product Monograph (CPM) for pramipexole has been updated to include a warning on the risk of DAWS. Health Canada will work with the manufacturers of quinagolide and ropinirole to update their CPMs to also include a warning about this safety issue.**
- **At this time, there is not enough information to establish a link between other dopamine agonists that were assessed as part of this safety review - apomorphine, bromocriptine, cabergoline, pergolide, or rotigotine and DAWS. However, as a precaution, Health Canada will work with the manufacturers of these dopamine agonists to include the potential risk of DAWS in their CPMs to raise awareness among healthcare professionals that DAWS has been observed for other members of the dopamine agonist drug class, and encourage reporting of this potential safety issue.**

Overview

Health Canada reviewed the potential risk of DAWS with the use of the dopamine agonists apomorphine, bromocriptine, cabergoline, pergolide, pramipexole, quinagolide, ropinirole, and rotigotine following a manufacturer-initiated CPM update to include DAWS under the Warnings and Precautions section for Mirapex (pramipexole).

DAWS may occur after reducing the dose of or stopping some dopamine agonists, and includes symptoms such as apathy, anxiety, depression, fatigue, sweating, panic attacks, insomnia, irritability and pain.

Use in Canada

- Dopamine agonists are prescription drugs authorized for sale in Canada to treat Parkinson's disease, restless-leg syndrome, prolactin secretion disorders, and acromegaly.
- Dopamine agonists have been marketed in Canada under various brand names including Kynmobi and Movapo (apomorphine), Parlodel (bromocriptine), Dostinex (cabergoline), Permax (pergolide), Mirapex (pramipexole), Norprolac (quinagolide), Requip (ropinirole), and Neupro (rotigotine). Generic versions of some dopamine agonists are also available. Dopamine agonists are available in various dosage forms including oral tablets, transdermal patches, sublingual film, and solutions for injection under the skin (subcutaneous).
- The most frequently prescribed dopamine agonists in Canada in 2019 were pramipexole and ropinirole (more than 100,000 prescriptions each); followed by bromocriptine, cabergoline, and rotigotine (more than 10,000 prescriptions each); quinagolide (more than 1,000 prescriptions), and apomorphine (more than 100 prescriptions). Pergolide is no longer marketed in Canada.

Safety Review Findings

- Health Canada reviewed information from Canadian[a] and international databases of reported adverse reactions, as well as from the scientific literature.
- Health Canada reviewed 23 case reports (2 Canadian and 21 international) of DAWS in patients treated with dopamine agonists. The 21 international cases included 5 cases reported to the Canada Vigilance database, and 16 that were only available through the scientific literature.
    - Three cases of DAWS were found to be probably linked to the use of pramipexole, 5 cases were possibly linked, and 2 cases (1 Canadian) could not be further assessed due to insufficient information. One case was found to be probably linked with the use of quinagolide. Five cases were found to be possibly linked with the use of ropirinole, and 2 cases could not be further assessed due to insufficient information.
    - One case of DAWS was found to be possibly linked to the use of bromocriptine and pramipexole taken together. Two cases, 1 with cabergolide and pergolide taken together and the other with pramipexole and ropirinole taken together, could not be further assessed due to lack of information.
    - In 2 cases (1 Canadian), patients were taking pramipexole, ropinirole and rotigotine separately at different times. For these cases, a probable link was found with the use of pramipexole and a possible link was found with the use of ropirinole. The use of rotigotine and the risk of DAWS could not be further assessed due to missing information.

Conclusions and Actions

- Health Canada's review of the available information has established a link between the use of pramipexole, quinagolide, or ropinirole and the risk of DAWS. The Canadian Product Monograph (CPM) for pramipexole has been updated to include a warning on the risk of DAWS. Health Canada will work with the manufacturers of quinagolide and ropinirole to update their CPMs to also include a warning about this safety issue.
- At this time, there is not enough information to establish a link between apomorphine, bromocriptine, cabergoline, pergolide, or rotigotine and DAWS. As a precaution, Health Canada will work with the manufacturers of these products to include the potential risk of DAWS in their CPMs to raise awareness among healthcare professionals that DAWS has been observed for other members of the dopamine agonist drug class, and encourage reporting of this potential safety issue.
- Health Canada encourages consumers and healthcare professionals to report any side effects related to the use of dopamine agonist-containing products to the Canada Vigilance Program.
- Health Canada will continue to monitor safety information involving dopamine agonists, 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.

Additional Information

The analysis that contributed to this safety review included scientific and medical literature, Canadian and international information, and what is known about the use of dopamine agonists both in Canada and internationally.

For additional information, contact the Marketed Health Products Directorate.

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a. Canadian reports can be accessed through the Canada Vigilance Online Database.