Health Canada Santé Canada

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Health Product InfoWatch

June 2021

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REPORTING ADVERSE REACTIONS

Canada Vigilance Program
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CORONAVIRUS DISEASE (COVID-19)

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

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

The COVID-19 vaccines and treatments portal provides information for consumers, healthcare professionals and researchers on vaccines and treatments authorized for COVID-19, as well as those currently under review.

For information about adverse events following immunization that individuals have reported after receiving a COVID-19 vaccine in Canada, please see visit the Reported side effects following COVID-19 vaccination in Canada webpage. This page is updated weekly.

DRUG AND VACCINE AUTHORIZATIONS AND COMMUNICATIONS FOR COVID-19

Recent communications related to authorized COVID-19 vaccines and treatments are highlighted in this section.

AstraZeneca COVID-19 Vaccine

Health Canada approved an extension to the expiry dates of 2 lots (MT0055 and MT0056) of the AstraZeneca COVID-19 vaccine by 30 days, from May 31, 2021, to July 1, 2021. The approval to extend the shelf life was supported by scientific evidence.

Statement

COVID-19 vaccines and reports of myocarditis and/or pericarditis

Key Messages:

• Cases of myocarditis and/or pericarditis following immunization with COVID-19 vaccines have been reported in Canada and internationally.

• These reports are rare and the relationship between COVID-19 vaccines and these events is not clear.

• International reports show that most cases involved COVID-19 mRNA vaccines (Pfizer BioNTech and Moderna), occurred more often after the second dose and in younger male adults and adolescents, and were mild and treatable.

• Healthcare professionals should consider the possibility of myocarditis and/or pericarditis when individuals present with chest pain, shortness of breath, palpitations or other signs and symptoms of myocarditis and/or pericarditis following immunization with a COVID-19 vaccine.

• Health Canada and the Public Health Agency of Canada will continue to monitor this situation and assess any new information. Appropriate action will be taken if any new safety issues are identified.

Health Canada and the Public Health Agency of Canada (PHAC) share the responsibility for monitoring the safety of vaccines in Canada. In the last few months, cases of myocarditis and/or pericarditis following immunization with COVID-19 vaccines have been reported in Canada and internationally. To date, the number of cases reported in Canada is small and not greater than the expected cases in the population. Most cases occurred with mRNA vaccines Pfizer BioNTech and Moderna.

Cases of myocarditis and/or pericarditis were first reported internationally following immunization with mRNA vaccines, Pfizer BioNTech and Moderna, and seem to:

- be rare, given the number of vaccine doses administered;
- be mild and resolve within days to a week or 2 weeks with rest and medicine;
- occur more frequently in younger male adults and adolescents, but have been reported in all age groups and in both females and males; and
- occur, in most cases, within several days after the second dose of a COVID-19 mRNA vaccine.

Since these initial reports, cases of myocarditis and/or pericarditis have also been reported in Canada following immunization with all COVID-19 vaccines. As of June 11, 2021, there have been 53 cases* reported in Canada. Of these, 40 cases were reported for the Pfizer-BioNTech vaccine, 8 cases for the Moderna vaccine, and 4 cases for the COVISHIELD/AstraZeneca vaccines. Twenty-eight of these cases were reported in females (age range: 20-78) and 25 in males (age range: 17-76). Reported side effects following COVID-19 immunization in Canada are updated weekly.

Myocarditis is an inflammation of the heart muscle, while pericarditis is an inflammation of the lining around the heart. Both conditions can occur either acutely or chronically, and can result from an infection (including COVID-19), other health event or exposure to a toxic substance or radiation. Symptoms can include lethargy, shortness of breath, chest pain, or palpitations. In many cases, these conditions are mild and require little to no treatment. However, more severe cases can lead to heart muscle damage.

Healthcare professionals are advised to consider the possibility of myocarditis and/or pericarditis in their differential diagnosis when individuals present with chest pain, shortness of breath, palpitations or other signs and symptoms of myocarditis and/or pericarditis following immunization with a COVID-19 vaccine. This could allow for early recognition and treatment. Consideration could also be given to consulting with a cardiologist for evaluation, management and follow-up.

Health Canada will continue to work with manufacturers as well as domestic and international partners to gain a better understanding of the potential relationship between COVID-19 vaccines and these events. In addition, Health Canada and PHAC will continue to monitor Canadian and international reports of myocarditis and/or pericarditis, particularly as more adolescents and young adults are vaccinated and more second doses are administered. Appropriate action will be taken if any new safety issues are identified, which may include labelling changes or risk communications.

Healthcare professionals are encouraged to report any cases of myocarditis and/or pericarditis, or any other adverse event, suspected of being associated with COVID-19 vaccines. If a patient experiences an adverse event following immunization, please complete the Adverse Events Following Immunization (AEFI) Form for your province/territory and send it to your local Public Health Unit.

For more information on adverse events following immunization that have been reported after receiving a COVID-19 vaccine in Canada, please visit the Reported side effects following COVID-19 vaccination in Canada webpage. Information on COVID-19 vaccines can be found on the COVID-19 vaccines and treatments portal.

The benefits of COVID-19 vaccines continue to outweigh their risks in authorized populations, as they have been shown to reduce deaths and hospitalizations due to COVID-19 infections.

* The vaccine name of one was not specified.

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 May 2021 by Health Canada.

For health product advisories related to COVID-19 vaccines and treatments, please see the Drug and vaccine authorizations and communications for COVID-19 section.

Certain hand sanitizers that may pose health risks Advisory	Health Canada advised Canadians that certain hand sanitizers were recalled because they either contained ingredients that were not permitted by Health Canada, were not properly labelled, were unauthorized, or were missing important information.
Irbesartan, losartan and valsartan drugs Advisory	Several companies recalled multiple lots of irbesartan, losartan and valsartan drug products after tests found an azido impurity above the acceptable limit.
Magnesium Bis-Glycinate Powder 250 Advisory	CanPrev Natural Health Products Ltd. recalled one lot each of Magnesium Bis-Glycinate Powder 250 (Berry Hibiscus, lot MBH001) and Magnesium Bis-Glycinate Powder 250 (Rose Hip Dragonfruit, lot MRD001) because they were packaged with a scoop that is nearly twice the size it should be, which may lead users to take nearly twice the intended dose of magnesium.
Opdivo (nivolumab) Summary Safety Review	This safety review evaluated the risk of autoimmune hemolytic anemia, aplastic anemia, cytokine release syndrome and tumor lysis syndrome associated with Opdivo (nivolumab). Health Canada's review of the available information concluded that there may be a link between Opdivo, used alone or in combination with Yervoy, and the risk of autoimmune hemolytic anemia, aplastic anemia, cytokine release syndrome and tumor lysis syndrome. The Canadian product monograph for Opdivo has been updated to include these risks.
Pomalyst (pomalidomide) and Thalomid (thalidomide) Summary Safety Review	This safety review evaluated the risk of progressive multifocal leukoencephalopathy (PML) associated with Pomalyst (pomalidomide) or Thalomid (thalidomide). Health Canada's review of the available information concluded that there is a possible link. The Canadian product monograph for Pomalyst has been updated to include a warning for the risk of PML. Health Canada is working with the manufacturer to update the Canadian product monograph for Thalomid to include this rare safety issue.

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.

REVIEW ARTICLE

Dopamine agonist withdrawal syndrome

Key messages

- Dopamine agonist withdrawal syndrome (DAWS) is a collection of psychiatric and physical symptoms that have been reported in some patients who taper or discontinue their dopamine agonists (DAs).
- Health Canada completed a safety review to assess the risk of DAWS with the use of DAs and found a causal association for the dopamine agonists: pramipexole, quinagolide and ropinirole. There was limited evidence to establish a link for other DAs marketed in Canada. Therefore, a class effect could not be confirmed at this time.
- Healthcare professionals and patients should be aware of potential withdrawal symptoms and risk factors for DAWS associated with DAs.
- Healthcare professionals are encouraged to report any suspected cases of DAWS to Health Canada.

Dopamine agonists (DAs) are a class of drugs used in the treatment of conditions such as Parkinson's disease (PD), restless leg syndrome, acromegaly and prolactin secretion disorders. DAs marketed in Canada include products with the following active ingredients: apomorphine, bromocriptine, cabergoline, pramipexole, quinagolide, ropinirole and rotigotine.

Dopamine agonist withdrawal syndrome (DAWS) was initially described by Rabinak and Nirenberg as "a severe, stereotyped cluster of physical and psychological symptoms that correlate with DA withdrawal in a dose-dependent manner, cause clinically significant distress or social/occupational dysfunction, are refractory to levodopa and other PD medications, and cannot be accounted for by other clinical factors."[1]

Symptoms of DAWS include anxiety, panic attacks, depression, agitation, irritability, drug craving, insomnia, daytime fatigue, diaphoresis, nausea, vomiting, flushing, orthostasis, and generalized pain.[2] Psychiatric symptoms are the most common complaint, with agitation being the most frequent.

Some patients only present with one symptom of DAWS, while others present with 2 or more.[3] Symptoms may start at any point in the DA taper or after discontinuation and may range in severity from mild to severe.[2,4] In some patients, symptoms are self-limited with a full recovery within days or weeks, while in others, symptoms may last for months or years.

The biological mechanism connecting DAs and DAWS is unclear; therefore, it is difficult to attribute a class effect based on available evidence at this time. However, re-administration of a dopamine agonist (the original DA or another in the class) has been noted in case reports of DAWS to be effective in managing the symptoms.[2]

Risk factors for DAWS include patients with impulse control disorder (ICD) (e.g., pathological gambling, hypersexuality, compulsive buying and compulsive eating) and higher DA dose and/or cumulative exposure.[2,4] A history of deep brain stimulation may also be a risk factor.[5] The frequency of DAWS does not seem to be related to the rate of DA tapering, or to whether the medication was discontinued completely or the dose was reduced.

An assessment was conducted by Health Canada on a case series of 23 reports (2 Canadian and 21 international) of potential DAWS in patients treated with DAs. These cases included exposures to bromocriptine, cabergoline, pramipexole, quinagolide, ropinirole, or rotigotine. Causality was determined to be 'probable' or 'possible' for pramipexole, quinagolide, and ropinirole.

The following is a summary of 1 Canadian report that was evaluated by Health Canada.[6] This case illustrates a typical cluster of DAWS symptoms and the temporal relationship (onset after discontinuing a DA) is plausible.

Case report

A 64-year old man with a history of PD and no history of depression or psychiatric conditions was taking pramipexole. He experienced features of ICD (i.e., excessive spending), which led to the discontinuation of pramipexole. He did not tolerate pramipexole discontinuation and developed leg pain, marked apathy, anxiety, depression, dizziness, and generalized fatigue. Pramipexole was re-introduced and later ropinirole then rotigotine were introduced, all on separate instances, with a similar outcome. Each time a DA was introduced, he experienced symptoms of ICD and then DAWS symptoms would reappear upon withdrawal or taper. In one instance, the symptoms of DAWS lasted 7 years unchanged despite therapy with rasagiline and incremental doses of levodopa/carbidopa. Finally, he remained on rotigotine at a reduced dose and an acceptable balance between DAWS and ICD was achieved.

There were no confounding drugs or medical conditions related to this case. DAs were restarted 3 times and associated with the disappearance of DAWS symptoms while incremental levodopa/carbidopa dosing was not.

Health Canada will work with manufacturers to update the Canadian product monographs with language in line with the current level of evidence.

Healthcare professionals and patients should be aware of potential withdrawal symptoms and risk factors for DAWS associated with DAs.[2] Healthcare professionals are encouraged to report any suspected cases of DAWS to Health Canada.

References

1. Rabinak CA, Nirenberg MJ. Dopamine agonist withdrawal syndrome in Parkinson disease. *Arch Neurol* 2010;67(1):58-63.
2. Yu XX, Fernandez HH. Dopamine agonist withdrawal syndrome: A comprehensive review. *J Neurol Sci* 2017;374:53-5.
3. Patel S, Garcia X, Mohammad ME, et al. Dopamine agonist withdrawal syndrome (DAWS) in a tertiary Parkinson disease treatment center. *J Neurol Sci* 2017;379:308-11.
4. Nirenberg MJ. Dopamine agonist withdrawal syndrome: Implications for patient care. *Drugs & Aging* 2013;30(8):587-92.
5. Garcia X, Patel S, Mohammad M.E., et al. Higher doses of dopamine agonists, impulse control disorders and history of deep brain stimulation (DBS): Risk factors for dopamine agonists withdrawal syndrome (DAWS)? [abstract]. *Mov Disord* 2016; 31 (suppl 2). (accessed 2021 April 13)
6. Huynh NT, Sid-Otmane L, Panisset M, et al. A man with persistent dopamine agonist withdrawal syndrome after 7 years being off dopamine agonists. *Can J Neurol Sci* 2016;43(6):859-60.

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 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.

Ofev (nintedanib)

The *Warnings and Precautions, Adverse Reactions (Post-Market Adverse Reactions)*, and *Patient Medication Information* sections of the Canadian product monograph for Ofev have been updated with the risk of **nephrotic range proteinuria**.

Key messages for healthcare professionals:[1]

- Very few cases of nephrotic range proteinuria have been reported in the post-marketing period.
- Histological findings in individual cases were consistent with glomerular microangiopathy, with or without renal thrombi.
- Reversal of symptoms has been observed after Ofev was discontinued.
- Treatment interruption should be considered in patients who develop signs or symptoms of nephrotic syndrome.

Reference

1. *Ofev (nintedanib)* [product monograph]. Burlington (ON): Boehringer Ingelheim (Canada) Ltd.; 2021.

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 of the drug and the nature 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 in accordance with the NOC/c policy. For the most up-to-date information, consult Health Canada's NOC database.

Abecma (idecabtagene vicleucel): Authorization with conditions

Health Canada has issued a Notice of Compliance, under the Notice of Compliance with Conditions policy, for Abecma (idecabtagene vicleucel), a suspension for intravenous infusion of 275 x 10^6 to 520 x 10^6 chimeric antigen receptor (CAR)-positive T cells in one or more patient specific infusion bag(s) (target dose of 450 x 10^6 CAR-positive T cells). Abecma, a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy, is indicated for the treatment of adult patients with multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and who are refractory to their last treatment. Patients should be advised about the conditional market authorization for this indication.

For the complete prescribing information and information available for the patients/caregivers, please consult the Abecma Canadian product monograph. The product monograph can be accessed through Health Canada's Drug Product Database, the Celgene Inc. Web site or by contacting Celgene Inc., a Bristol Myers Squibb company at 1-866-463-6267. Contact the company for a copy of any references, attachments or enclosures.

Tepmetko (tepotinib): Authorization with conditions

Health Canada has issued a Notice of Compliance, under the Notice of Compliance with Conditions policy for Tepmetko (tepotinib), 225mg tablets (as tepotinib hydrochloride). Tepmetko is indicated for the treatment of adult patients with locally advanced unresectable or metastatic non-small cell lung cancer harbouring mesenchymal-epithelial transition tyrosine kinase receptor exon 14 skipping alterations. Patients should be advised about the conditional market authorization for this indication.

For the complete prescribing information and information available for the patients/caregivers, please consult the Tepmetko Canadian product monograph. The product monograph can be accessed through Health Canada's Drug Product Database, the EMD Serono website or by contacting EMD Serono at 1-888-737-6668. Contact the company for a copy of any references, attachments or enclosures.

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
- Drug and vaccine authorizations for 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 HC.infowatch-infovigilance.SC@canada.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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