



# Health Product InfoWatch

May 2021

## HEALTH PRODUCTS MENTIONED IN THIS ISSUE

### CONTENTS

<b>Coronavirus Disease (COVID-19)</b>	1
• <b>Drug and vaccine authorizations and communications for COVID-19</b>	
Janssen COVID-19 Vaccine	2
Pfizer-BioNTech COVID-19 vaccine	2
Veklury (remdesivir)	2
<b>Monthly Recap</b>	3
<b>New Information</b>	
• <b>Review Article</b>	
Systemic corticosteroids (including dexamethasone) and pheochromocytoma crisis when administered to patients with identified, suspected or unsuspected pheochromocytoma	4
• <b>Product monograph updates</b>	
Voluven and Volulyte	6
<b>Did you know</b>	7

### 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](#).

#### Pharmaceuticals and Biologics

APO-Amitriptyline  
 Dexamethasone  
 Janssen COVID-19 Vaccine  
 OrfenAce  
 Pfizer-BioNTech COVID-19 vaccine  
 Systemic corticosteroids  
 Veklury (remdesivir)  
 Volulyte (hydroxyethyl starch)  
 Voluven (hydroxyethyl starch)  
 Xeljanz and Xeljanz XR (tofacitinib)

#### Medical Devices

Face masks that contain graphene

#### Natural and Non-prescription Health Products

Hand sanitizers that may pose health risks  
 L'il Critters Gummy Vites  
 Vitafusion Fibre Well  
 Vitafusion MultiVites

#### Other

Unauthorized health products

### 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](https://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.

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 [COVID-19 vaccine safety 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.

### Janssen COVID-19 Vaccine

This safety review evaluated the risk of thrombosis in combination with thrombocytopenia associated with Janssen COVID-19 Vaccine. Health Canada's review of the available information concluded that a link is possible. The risk of thrombosis in combination with thrombocytopenia is very rare and the overall benefits of the vaccine in protecting Canadians from COVID-19 outweigh the risk. Health Canada worked with the manufacturer to update the Canadian product monograph for Janssen COVID-19 Vaccine to reflect current knowledge of this safety issue. Health Canada also [communicated](#) to vaccine recipients and healthcare professionals about this risk.

[Summary Safety Review – Janssen COVID-19 Vaccine](#)

[COVID-19 vaccines and treatments portal – Janssen COVID-19 Vaccine](#)

### Pfizer-BioNTech COVID-19 vaccine

Health Canada authorized the use of the Pfizer-BioNTech COVID-19 vaccine in children 12 to 15 years of age.

[Statement](#)

Health Canada authorized more flexible storage conditions for Pfizer-BioNTech COVID-19 Vaccine. Pfizer-BioNTech COVID-19 Vaccine can now be stored at regular refrigerated temperatures (2-8°C) at the point of use for up to one month.

[Statement](#)

[COVID-19 vaccines and treatments portal – Pfizer-BioNTech](#)

### Veklury (remdesivir)

This safety review evaluated the risk of acute kidney injury or acute renal failure associated with Veklury (remdesivir). Health Canada's review could not establish a direct link. The Canadian product monograph for Veklury includes information on kidney toxicity and recommendations on usage. Therefore, the safety information for Veklury is appropriate at this time.

[Summary Safety Review – Veklury \(remdesivir\)](#)

## 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 April 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.

<b>APO-Amitriptyline</b> <a href="#">Advisory</a>	Apotex Inc. recalled 2 lots (lot PY1831, expiry 12/2023 and lot RF0410, expiry 05/2024) of APO-Amitriptyline 10 mg tablets (DIN 02403137), after testing identified NDMA, a nitrosamine impurity, above the acceptable limit. The majority of lots tested by Apotex Inc. to date are within the acceptable limit; therefore, patients are not expected to be exposed to levels of NDMA that exceed safe levels for an extended period of time. Patients can continue to take their medication as prescribed by their healthcare provider and do not need to return their medication to their pharmacy.
<b>Certain hand sanitizers that may pose health risks</b> <a href="#">Advisory</a>	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.
<b>Face masks that contain graphene</b> <a href="#">Advisory</a>	Health Canada advised Canadians not to use face masks that contain graphene due to the potential risk of inhaling graphene particles. Graphene is a novel nanomaterial reported to have antiviral and antibacterial properties. Health Canada's preliminary assessment of available research identified that inhaled graphene particles had some potential to cause early lung toxicity in animals. Until the Department completes a thorough scientific assessment, it is taking the precautionary approach of removing graphene-containing face masks from the market while continuing to gather and assess information.
<b>L'il Critters Gummy Vites, vitafusion Fibre Well, and vitafusion MultiVites</b> <a href="#">Advisory</a>	Church & Dwight Canada Corp. recalled certain lots of L'il Critters Gummy Vites children's vitamins, as well as vitafusion Fibre Well and vitafusion MultiVites vitamins for adults, because certain lots may contain metal wire fragments. The affected lots were manufactured within a specific four-day period between October 29 and November 3, 2020. The products were distributed nationally.
<b>OrfenAce</b> <a href="#">Advisory</a>	SteriMax Inc. recalled OrfenAce 100 mg tablets (DIN 02047535) after testing identified a nitrosamine impurity above what is considered acceptable if the drug were to be taken over a lifetime. Health Canada is advising that there is no immediate risk to patients taking this medication since the potential risk of cancer is with long-term (every day for 70 years) exposure to nitrosamine impurities that exceeds safe levels, which is not what is expected to occur with patients taking the affected medication for a short period of time.

## Unauthorized health products

Advisory

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

## Xeljanz and Xeljanz XR (tofacitinib)

Advisory

Health Canada is conducting a safety review of Xeljanz and Xeljanz XR (tofacitinib) after a clinical trial identified an increased risk of serious heart-related issues and cancer in trial participants. The clinical trial investigated the long-term safety of Xeljanz and Xeljanz XR at 2 doses (5 mg twice a day and 10 mg twice a day) in patients with rheumatoid arthritis, who were at least 50 years of age and had at least one cardiovascular risk factor. Health Canada is working with the manufacturer to evaluate the available safety information and will inform the public of any new safety findings once the review is completed.

## 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

#### ***Systemic corticosteroids (including dexamethasone) and pheochromocytoma crisis when administered to patients with identified, suspected or unsuspected pheochromocytoma***

#### **Key messages for healthcare professionals**

- Systemic corticosteroids, such as dexamethasone, when administered to patients with an identified, suspected or unsuspected pheochromocytoma, have been reported in the medical literature to be associated with pheochromocytoma crisis, a rare and life-threatening emergency.
- Patients with identified or suspected pheochromocytoma should be carefully evaluated for risks and benefits before being administered systemic corticosteroids.
- In view of the current use of systemic dexamethasone in the treatment of COVID-19, patients receiving dexamethasone should be closely monitored for potential adverse reactions, including pheochromocytoma crisis.
- Healthcare professionals are encouraged to report related adverse reactions to Health Canada for the continued monitoring and assessment of this potential risk.

Dexamethasone is a corticosteroid product with glucocorticoid effects used to treat a wide variety of conditions associated with inflammation.<sup>1,2</sup> This includes, but is not limited to, severe allergies, rheumatoid arthritis, various skin and eye conditions, endocrine disorders, respiratory diseases, blood disorders, ulcerative colitis, and some types of blood cancers.

Recently, the Public Health Agency of Canada released a [statement](#) from the Clinical Pharmacology Task Group recommending that systemic dexamethasone, at a dose of 6 mg IV for 10 days, should strongly be considered in the treatment of hospitalized patients with COVID-19 who require supplemental oxygen or mechanical ventilation.

Systemic dexamethasone, and other types of corticosteroids, have been reported in the medical literature to trigger pheochromocytoma crisis in patients with identified, suspected or unsuspected pheochromocytoma.<sup>3-10</sup>

Pheochromocytomas are rare, catecholamine-secreting tumours of the sympathetic nervous system originating from the chromaffin cells of the adrenal medulla.<sup>3</sup> The clinical presentation may vary, but characteristic signs and symptoms include hypertension, sweating, palpitations, and headache.<sup>3,4</sup>

Pheochromocytoma crisis is a rare, life-threatening endocrine emergency in which high levels of catecholamines are released from a pheochromocytoma.<sup>3,4</sup> This condition causes acute, severe hemodynamic instability that can lead to multi-organ dysfunction. It is often reversible with appropriate treatment, or if the crisis recedes.<sup>4,5</sup> Pheochromocytoma crisis can be difficult to diagnose if the patient is not already known to have a pheochromocytoma, as it may mimic other life-threatening conditions.<sup>3,4</sup> Prompt confirmation of the diagnosis is likely to improve survival.<sup>4</sup>

### **Evidence from literature**

Cases of pheochromocytoma crisis suspected of being induced by corticosteroids have been reported in the literature. One literature review summarized 25 cases of catecholaminergic crisis in patients with adrenal masses following corticosteroid or cosyntropin administration, 8 of which reported the use of dexamethasone.<sup>6</sup> The presenting signs and symptoms included hypertension, palpitations, arrhythmias, headache, nausea, vomiting, cardiac ischemia, pulmonary edema and shock. More than 30% of the 25 cases were fatal and most required admission to an intensive care unit. Considerable variability was noted in the type of corticosteroid, dose, route of administration, and time to onset of symptoms. In many cases, pheochromocytoma was undiagnosed prior to corticosteroid administration. Some cases of catecholaminergic crisis were reported in patients following high-dose systemic dexamethasone suppression tests (DST). For these cases, it was suggested that tumour size and the dose used for DST may have played a role in the risk of catecholaminergic crisis. The smallest documented dose of dexamethasone that is suspected of inducing a crisis was 2 mg administered orally (prescribed every 6 hours) and time to onset was 5 hours.

A Canadian case of unsuspected pheochromocytoma presenting with an adrenergic crisis following systemic dexamethasone administration was reported in the literature.<sup>7</sup> In this case, a 73-year old man with no previous relevant medical history and no regular medications presented to the emergency room with an acute onset of non-specific, mild epigastric discomfort with nausea, vomiting, orthostatic dizziness and palpitations. The patient was on his third day of treatment with amoxicillin, ibuprofen, and systemic dexamethasone (4 mg daily for 3 days) following a dental procedure. The authors indicated that the clinical course, as well as the documented transient massive release of catecholamine following administration of dexamethasone, strongly pointed to dexamethasone as the trigger for the adrenergic crisis.

As of April 21, 2021, no other suspected cases of pheochromocytoma crisis in association with systemic corticosteroids, including dexamethasone, have been reported in Canada.\*

### **Mechanism and conclusion**

Although systemic corticosteroids have been implicated in triggering pheochromocytoma crisis, the mechanism remains unclear.<sup>7,8</sup> Several mechanisms have been hypothesized including potentiation of the action of catecholamines on peripheral vessels and the heart, potentially leading to vasculopathy, tissue necrosis and hemorrhage. Another hypothesis proposes that increased corticosteroid receptor expression may mediate pheochromocytoma tumour sensitivity to corticosteroids and trigger catecholamine synthesis, production and release.

Evidence from the literature suggests that systemic dexamethasone and other corticosteroids should be avoided in patients with known pheochromocytoma, or in those with an adrenal adenoma without a negative biochemical workup for a pheochromocytoma, as it could precipitate an adrenergic crisis.<sup>6-9</sup>

Pheochromocytoma crisis should be considered as a differential diagnosis in patients who have been treated with systemic dexamethasone, or other corticosteroid products, and present with severe hemodynamic instability, shock, arrhythmia, cardiac ischemia, or other symptoms suggestive of adrenergic crisis.<sup>7,10</sup>

Healthcare professionals are encouraged to report to Health Canada any cases of pheochromocytoma crisis suspected to be associated with the use of dexamethasone or other corticosteroid products. This information will support ongoing monitoring of this safety issue.

## References

1. Dexamethasone. In: Buckingham R (ed), *Martindale: The complete drug reference*. [online] London (UK): Pharmaceutical Press: 2019. (accessed 2021 March 24)
2. Corticosteroids: Systemic [CPhA monograph]. In: CPS. [online] Ottawa (ON): Canadian Pharmacists Association; updated August 2018. (accessed 2021 March 24).
3. Castellino T, Elliot M. Pheochromocytoma crisis. In: Lew JI. *Clinical management of adrenal tumors*. London (UK): IntechOpen; 2017.
4. Whitelaw BC, Prague JK, Mustafa OG, et al. [Phaeochromocytoma \[corrected\] crisis](#). *Clin Endocrinol (Oxf)* 2014; 80(1):13-22.
5. Geva GA, Gross DJ, Mazeh H, et al. [Adrenocorticotrophic hormone secreting pheochromocytoma underlying glucocorticoid induced pheochromocytoma crisis](#). *Case Rep Endocrinol* 2018; 2018:3963274.
6. Barrett C, van Uum SH, Lenders JW. [Risk of catecholaminergic crisis following glucocorticoid administration in patients with an adrenal mass: a literature review](#). *Clin Endocrinol (Oxf)* 2015; 83(5):622-8.
7. Dupont MF, Battista MC, Comeau E, et al. [Corticosteroid-induced case of a lightning pheochromocytoma crisis: Insight into glucocorticoid receptor expression](#). *Integr Cancer Sci Ther* 2016; 3(1):345-8.
8. Rosas AL, Kasperlik-Zaluska AA, Papierska L, et al. [Pheochromocytoma crisis induced by glucocorticoids: a report of four cases and review of the literature](#). *Eur J Endocrinol* 2008;158(3):423-9.
9. Eagan D, Munoz Pena J, Barb D. [SAT-214 Steroid induced pheochromocytoma crisis](#). *J Endocr Soc* 2020; 4, Issue Supplement\_1.
10. Ibrahim M, Banga S, Venkatapuram S, et al. [Transient cardiogenic shock during a crisis of pheochromocytoma triggered by high-dose exogenous corticosteroids](#). *BMJ Case Rep* 2015;2015:bcr2014208683. doi: 10.1136/bcr-2014-208683.

\* Please note that there may be reports which have been received but not yet processed and entered into the database. New and additional information may be available at a later date.

## 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](#).

## Voluven and Volulyte (hydroxyethyl starch)

The *Indications and Clinical use*, *Contraindications*, *Warnings and Precautions (Serious Warnings and Precautions Box)*, *Dosage and Administration*, and *Consumer Information* sections of the Canadian product monographs for Voluven and Volulyte, have been updated to further mitigate the **risk of renal injury and death**.

### Key messages for healthcare professionals:<sup>1,2</sup>

- Voluven and Volulyte are now indicated for the treatment of hypovolemia due to acute blood loss when crystalloids alone are not considered sufficient.
- Voluven and Volulyte are now **contraindicated** in patients with critical illness. In critically ill patients, including patients with sepsis, use of hydroxyethyl starch products, including Voluven and Volulyte, increases risk of mortality and renal replacement therapy.
- Voluven and Volulyte are not recommended for use in children due to limited data.

## References

1. *Voluven (hydroxyethyl starch 130/0.4)* [product monograph]. Toronto (ON): Fresenius Kabi Canada Ltd; 2020.
2. *Volulyte (hydroxyethyl starch 130/0.4)* [product monograph]. Toronto (ON): Fresenius Kabi Canada Ltd; 2020.

## DID YOU KNOW

The MedEffect e-Notice is a free subscription service that provides email notifications to keep subscribers up to date when Health Canada publishes new safety information, including health product risk communications, public advisories and the Health Product InfoWatch. To better serve Canadians, this system is being upgraded with a modernized new look and feel while also enabling a range of customization features giving subscribers more choice in the type of information they receive and how this information is delivered. The new system is expected to be launched in the coming weeks, with more information to follow on how current subscribers can update their preferences as well as sign up instructions for new subscribers.

## 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](mailto: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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