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Health Product InfoWatch

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REPORTING ADVERSE REACTIONS

Canada Vigilance Program
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Natural and Non-prescription Health Products

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- Hand sanitizers labelled as "Anti-Microbe" and/or with DIN 02248351

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

DID YOU KNOW?

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.

ANNOUNCEMENT

International Coalition of Medicines Regulatory Authorities statement on the regulation of COVID-19 vaccines for safety and effectiveness

Health Canada, in collaboration with members of the International Coalition of Medicines Regulatory Authorities (ICMRA), released a statement for healthcare professionals about the role of regulators in the oversight of COVID-19 vaccines. The statement aims to inform and help healthcare professionals answer questions about COVID-19 vaccines. It explains how vaccines undergo robust scientific evaluation to determine their safety, efficacy and quality and how safety will continue to be closely monitored after approval.

ICMRA brings together the heads of 30 medicines regulatory authorities from every region in the world, including Health Canada, with the World Health Organization as an observer. Medicines regulators recognise their important role in facilitating the provision of access to safe and effective high-quality medicinal products that are essential to human health and well-being. This includes ensuring that the benefits of vaccines outweigh their risks.

DRUG AND VACCINE AUTHORIZATIONS FOR COVID-19

The Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19 (the Interim Order) allows for the issuance of an expedited authorization for the importation, sale and advertising of drugs used in relation to COVID-19; this includes both human and veterinary drugs. The Interim Order introduces expedited authorization pathways for drugs with a COVID-19 indication that are not yet authorized in Canada or other jurisdictions; as well as COVID-19 drugs that are authorized for sale by a foreign regulatory authority. In addition, the Interim Order provides a mechanism to permit the sale of a drug that is already authorized in Canada under this Interim Order or the Food and Drug Regulations, for indications related to COVID-19 that are not included in the drug's authorization.

Pfizer-BioNTech COVID-19 vaccine

Health Canada issued a label change authorization to Pfizer-BioNTech to reflect that each vial of its COVID-19 vaccine contains six doses, rather than five. The Canadian product monograph for Pfizer-BioNTech COVID-19 vaccine has also been updated with post-market adverse reaction information identified during pharmacovigilance activities. Severe allergic reactions, including anaphylaxis, have been reported during mass vaccination outside of clinical trials. This new information does not change the benefit-risk profile of this product. The updated product monograph is available on the Drug Product Database or the COVID-19 Portal at covid-vaccine.canada.ca.

Statement
Health Professional Risk Communication – Pfizer-BioNTech COVID-19 vaccine

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 January 2021 by Health Canada.

Bio Life Hand Sanitizers Information Update	Health Canada testing confirmed that Bio Life hand sanitizer by Bio Life Sciences Corp. / 10932540 Canada Inc. (Bio Life) contained methanol. Testing also showed that it did not contain enough ethanol to be an effective sanitizer. The Bio Life and Daily Shield products were sold at retail stores across Canada. Bio Life recalled all lots of Bio Life hand sanitizer in November 2020 due to suspected methanol. Bio Life recalled another hand sanitizer, Daily Shield, in October 2020 because of the presence of methanol and insufficient ethanol.
Gilenya (fingolimod) Health Professional Risk Communication	Cases of clinically significant liver injury, including acute liver failure requiring liver transplant, have been reported in patients treated with Gilenya (fingolimod). Healthcare professionals are advised to follow recommendations outlined in the health professional risk communication. The Canadian product monograph (CPM) for Gilenya has been updated to include revised guidance for monitoring liver function and criteria for treatment interruption and/or discontinuation. Health Canada will work with manufacturers of generic versions of fingolimod to update their respective CPMs.
Hand sanitizers labelled as "Anti-Microbe" and/or with DIN 02248351 Advisory	Atoms F.D. Inc. recalled various 0.3% benzalkonium chloride hand sanitizers labelled as “Anti-Microbe” and/or with the Drug Identification Number (DIN) 02248351 because they contain a higher concentration of benzalkonium chloride than permitted for personal or domestic use and may pose health risks, particularly to children up to 12 years of age. Products containing 0.3% benzalkonium chloride should be labelled for adult use in an industrial setting only. The affected products were not appropriately labelled with this information.
Hydromorphon Ethypharm Kalceks (hydromorphone hydrochloride solution for injection) with German labels Health Professional Risk Communication	There is an increased demand in Canada for hydromorphone injectable formulations as a result of the COVID-19 pandemic. Given the medical necessity of injectable hydromorphone, Health Canada has added German-labelled Hydromorphon Ethypharm Kalceks to the List of Drugs for Exceptional Importation and Sale. Healthcare professionals are advised to take additional care to help prevent serious medication errors and patient harm. TALLman lettering of the drug name, HYDROmorphone, a strategy normally used in Canada to accentuate the difference in its name from morphine, is absent from the German label. Healthcare professionals are advised to use the Canadian-labelled prescribing information as a reference.

Ranitidine Information Update	Pharmascience Inc. recalled additional lots of its ranitidine drugs (75 mg strength tablet) after tests found N-nitrosodimethylamine (NDMA), a nitrosamine impurity, above accepted levels. A table with detailed information on the recalled lots is provided in the information update.
Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) Summary Safety Review	This safety review evaluated the risk of persistent or worsening sexual dysfunction, as well as the appearance of new symptoms of sexual dysfunction after stopping SSRI or SNRI treatment. Health Canada's review could not confirm, nor rule out, a causal link between discontinuing SSRI or SNRI treatment and persistent sexual dysfunction. Health Canada's review could not make conclusions about worsening or new symptoms of sexual dysfunction as the studies were not designed to assess this. Health Canada will work with manufacturers to update the Canadian product monographs for all SSRIs and SNRIs to recommend that healthcare professionals inform patients about the potential risk of long lasting (possibly weeks to years) sexual symptoms persisting after discontinuing SSRI or SNRI treatment.
Sofosbuvir-containing products Summary Safety Review	This safety review evaluated the risk of severe cutaneous adverse reactions (SCAR) associated with sofosbuvir-containing products. Health Canada's review of the available information concluded that there may be a link between the use of sofosbuvir-containing products and the risk of Stevens-Johnson syndrome, but did not confirm a link with other types of SCAR. Health Canada will work with the manufacturer to update the Canadian product monographs of all sofosbuvir-containing products to include the risk of Stevens-Johnson syndrome.
Suboxone (buprenorphine and naloxone) Health Professional Risk Communication	Health Canada has authorized 2 dosage forms of Suboxone (buprenorphine and naloxone), a sublingual tablet and a soluble film, that are not bioequivalent at all doses and routes of administration. Switching between dosage forms or routes of administration could result in variations in buprenorphine or naloxone blood plasma concentrations, which could lead to inadvertent overdosing or underdosing, including opioid withdrawal. Healthcare professionals should be aware of specific recommendations for dosing and monitoring when switching between dosage forms or routes of administration.
Tamiflu (oseltamivir) Summary Safety Review	This safety review evaluated the risk of hemorrhages associated with oseltamivir. Health Canada's review of the available information was inconclusive regarding the risk of hemorrhages in general, but concluded that there may be a link between the use of oseltamivir and the risk of lower gastrointestinal hemorrhages. Given that the Canadian product monographs for oseltamivir already include information on the risk of gastrointestinal bleeding, no updates are being made at this time.

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

Ginkgo biloba-containing products and the risk of cardiac arrhythmias

Key messages

- Cases of cardiac arrhythmias suspected of being associated with the use of oral *Ginkgo biloba*-containing products have been reported in Canada and internationally.
- Healthcare professionals are reminded to ask patients about their use of natural health products, including *Ginkgo biloba.*
- Healthcare professionals are encouraged to report any case of cardiac arrhythmias suspected of being associated with *Ginkgo biloba*-containing natural health products to Health Canada for the continued monitoring and assessment of this potential risk.

Ginkgo biloba leaves have been used to help enhance cognitive function and memory in adults and to support peripheral circulation.[1,2] Ginkgo leaves and seeds are also commonly used in traditional Chinese medicines.[3,4] Licensed natural heath products (NHPs) with *Ginkgo biloba* are authorized for sale in Canada as single or multi-ingredient products.

Health Canada has authorized over 2000 NHPs containing *Ginkgo biloba* as a medicinal ingredient in a variety of dosage forms and preparations and has published 3 monographs associated with this ingredient: a *Ginkgo biloba* leaf monograph[1] as well as 2 product monographs, one for traditional Chinese medicines, and one for cognitive function products.[2,3] The monographs for *Ginkgo biloba* do not currently include any cautionary statement regarding the potential risk of cardiac arrhythmias.

As of June 30, 2020, Health Canada has received 15 domestic adverse reaction reports of cardiac arrhythmias suspected of being associated with the use of *Ginkgo biloba*-containing products in Canada. Of these 15 reports, 10 were considered serious. The information provided in these reports was insufficient to adequately assess the causal association between cardiac arrhythmias and *Ginkgo biloba*-containing products.

The World Health Organization (WHO) investigated this issue and published a safety signal summary in their WHO Pharmaceuticals Newsletter.[4] As of September 11, 2019, 162 international reports of cardiac arrhythmias involving patients using *Ginkgo biloba*-containing products were identified in the WHO Global Individual Case Safety Report Database System (VigiBase).* These reports came from 18 countries. *Ginkgo biloba* was the sole suspect ingredient in 92 cases (57%). For the 162 reports, the 5 most frequently reported adverse reactions were palpitations (n=67), tachycardia (n=24), loss of consciousness (n=14), syncope (n=13), and bradycardia (n=10). Key limitations which were identified included potential confounding by indication and the contribution of possible underlying co-morbidities to the adverse reactions. The WHO's signal review concluded that the number, nature and diversity of the reports and published cases suggest a suspected association between *Ginkgo biloba* and cardiac arrhythmias.

* World Health Organization (WHO) adverse reaction information provided by: The WHO Collaborating Centre for International Drug Monitoring. This information is not homogeneous with respect to the sources of the information or the likelihood that the health product caused the suspected adverse reaction. In addition, this information does not represent the opinion of the WHO. The WHO Global Individual Case Safety Report Database System (VigiBase) was searched for reports received as of September 2019.

Cases of cardiac arrhythmias involving *Ginkgo biloba* have also been reported in the literature.[5-7] The cardiac adverse reactions described in these case reports include ventricular arrhythmia, ventricular tachycardia and paroxysmal atrial fibrillation. In all these cases, the patient's condition improved after discontinuation of the *Ginkgo biloba*-containing product.

The mechanism by which *Ginkgo biloba* could induce cardiac arrhythmias remains unclear.[4]

Healthcare professionals should be aware of the potential for cardiac adverse events in patients using *Ginkgo biloba*-containing products. Healthcare professionals are reminded to ask patients about their use of *Ginkgo biloba* and other NHPs. Healthcare professionals are encouraged to report to Health Canada any case of cardiac arrhythmias suspected of being associated with *Ginkgo biloba*-containing products for the continued monitoring and assessment of this potential risk.

Article citation: Health Canada. Ginkgo biloba-containing products and the risk of cardiac arrhythmias. Health Product InfoWatch February 2021.

References

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5. Cianfrocca C, Pelliccia F, Auriti A, et al. Ginkgo biloba-induced frequent ventricular arrhythmia. *Ital Heart J* 2002; 3(11):689-91.
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SAFETY BRIEF

Tecentriq (atezolizumab) in combination with conventional paclitaxel for the treatment of unresectable locally advanced or metastatic triple-negative breast cancer does NOT reduce the risk of cancer progression or death

- The multicenter, phase 3 study (IMpassion 131) demonstrated that treatment with Tecentriq (atezolizumab) in combination with conventional paclitaxel did **NOT** significantly reduce the risk of cancer progression or death in patients with previously untreated, unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours express Programmed Death-Ligand 1 (PD- L1).[1,2]

Healthcare professionals are advised that:

- **only** the combination of Tecentriq (atezolizumab) and **nab**-paclitaxel (nanoparticle, albumin-bound form of paclitaxel) has been authorized with conditions, pending the results of studies to verify its clinical benefit, for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumours have PD-L1 expression ≥ 1%, and who have not received prior chemotherapy for metastatic disease.[3,4]
- the combination of Tecentriq (atezolizumab) and conventional paclitaxel has **NOT** demonstrated benefit over placebo in this patient population.[1,2]
- **nab**-paclitaxel should **NOT** be substituted with conventional paclitaxel when prescribing, administering and/or dispensing the drug in combination with Tecentriq in this patient population.[2,4]
- the Canadian product monograph for Tecentriq, which is available on Health Canada's Drug Product Database, should be referred to for a complete list of authorized indications and other product information.

References

1. A Study of Atezolizumab and Paclitaxel Versus Placebo and Paclitaxel in Participants With Previously Untreated Locally Advanced or Metastatic Triple Negative Breast Cancer (TNBC) (IMpassion131). ClinicalTrials.gov identifier: NCT03125902. Updated Jan 7, 2021. (accessed 2021 January 7).
2. FDA issues alert about efficacy and potential safety concerns with atezolizumab in combination with paclitaxel for treatment of breast cancer. Silver Spring (MD): U.S. Food and Drug Administration; 2020 Sept 8. (accessed 2021 January 7).
3. *Tecentriq (atezolizumab)* [product monograph]. Mississauga (ON): Hoffmann-La Roche Limited; 2021.
4. *Abraxane (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound [nab] paclitaxel)* [product monograph]. Mississauga (ON): Celgene Inc; 2018.

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

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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