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Health Product InfoWatch

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REPORTING ADVERSE REACTIONS

Canada Vigilance Program
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HEALTH PRODUCTS MENTIONED IN THIS ISSUE

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- Fibristal (ulipristal acetate)
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Natural and Non-prescription Health Products

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Other

- Cannabis
- 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**, 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.

Health Product InfoWatch 2015 - 2020 5 years

Canada

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 September 2020 by Health Canada.

Certain hand sanitizers that may pose health risks Advisory	Health Canada advised Canadians that certain hand sanitizers were recalled because they either contain ingredients that are not permitted by Health Canada or are not properly labelled and are missing important information.
Esbriet (pirfenidone) Health Professional Risk Communication	Drug-induced liver injury (DILI) in the form of transient and clinically silent elevations in transaminases has been commonly reported in patients treated with Esbriet. In rare cases, DILI has been associated with serious clinical consequences including isolated cases with fatal outcome. The Canadian product monograph for Esbriet has been updated to include this new safety information.
Fibristal (ulipristal acetate) Health Professional Risk Communication Advisory Drug recall	Following rare international cases of severe liver injury requiring liver transplantation, the manufacturer of Fibristal has voluntarily withdrawn the product from the Canadian market. The product was also recalled from pharmacies across Canada. Health Canada has also communicated this information to Canadians.
Hand sanitizers in non-traditional packaging Advisory	Health Canada warned Canadians, particularly parents and guardians, about the risks of accidental ingestion among children from hand sanitizers packaged in formats, including squeeze pouches, that could appeal to children and be mistaken for food or beverages.
Hydromorphone controlled release capsules Summary Safety Review	This safety review evaluated the potential increased risk of infections, such as infective endocarditis (IE) and bloodborne infections caused by human immunodeficiency virus (HIV) or hepatitis C virus (HCV), associated with the problematic use of oral hydromorphone controlled release capsules injected into the veins. Health Canada's review of the available evidence did not find a direct link. More epidemiological information is needed to understand how oral prescription opioids are prescribed as well as how they are problematically used by injection in Canada. The Department will work with the Drug Safety and Effectiveness Network to gather additional information on this topic. Health Canada will also inform manufacturers of controlled release opioid formulations that they should be monitoring the risk of increased IE and bloodborne infections caused by HIV or HCV with improper use of these formulations as part of their risk management plans and report the results to Health Canada.

Imbruvica (ibrutinib) Summary Safety Review	This safety review evaluated the risk of hemophagocytic lymphohistiocytosis associated with Imbruvica (ibrutinib) use. Health Canada's review of the available information did not establish a link. Health Canada encourages consumers and healthcare professionals to report any side effects related to the use of this product.
MAR-Diltiazem CD Advisory Drug Recall	Marcan Pharmaceuticals recalled all lots of all MAR-Diltiazem CD products in response to data integrity concerns that could lead to incorrect dosing. Marcan is not allowed to make any further sales of the product until the company can provide additional information to demonstrate that it is safe and effective.
Mesalazine-containing products Summary Safety Review	This safety review evaluated the potential risk of birth defects associated with mesalazine-containing products. Health Canada's safety review of the available information could not confirm a link between the risk of birth defects in babies and the use of mesalazine-containing products during pregnancy. Health Canada encourages consumers and healthcare professionals to report any side effects related to the use of mesalazine-containing products.
Remdesivir for Injection, US Clinical Trial-Labelled Health Professional Risk Communication	In July 2020, Health Canada authorized Veklury (remdesivir) with conditions to treat COVID-19 in adults and adolescents with pneumonia requiring supplemental oxygen. The product has not yet been marketed in Canada. Given the medical necessity of this product in Canada, Health Canada has added Remdesivir from the US intended for clinical trials with English-only labelling to the List of Drugs for Exceptional Importation and Sale. The importation of this product poses a risk for medication errors due to significant labelling deficiencies, the absence of a package insert, and label references to the drug being used as part of clinical trials.
Single incision mini-sling made from non-absorbable synthetic material (polypropylene) Summary Safety Review	This safety review evaluated the long-term (beyond 3 years) safety and effectiveness of single incision mini-slings (SIMS) used to treat stress urinary incontinence. Health Canada's review could not make conclusions due to lack of high quality post-market information. Health Canada has asked for additional long-term post-market safety and effectiveness information, including clinical data from the literature and ongoing clinical studies, from the manufacturers of SIMS. Health Canada plans to review SIMS within one year, taking into account the new and additional information provided by the manufacturers.

Unauthorized health products

Unauthorized health products sold on Steroid Hub Canada website

Various unauthorized health products (part 1)

Various unauthorized health products (part 2)

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

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

Cannabis and warfarin – Potential drug interaction

Key messages

- Cases of increased international normalized ratio (INR) have been reported in Canada and internationally in patients taking warfarin who were also using cannabis.
- Health Canada received 2 adverse reaction reports of increased INR suspected of being associated with the concurrent use of warfarin and cannabis.
- Healthcare professionals are reminded to ask patients taking warfarin about their use of cannabis.
- Healthcare professionals are encouraged to report adverse reactions (including increased INR) to Health Canada as well as to the licence holder of the cannabis product.

In Canada, products containing cannabis fall into one of 3 categories: 1) cannabis for non-medical purposes, with no health claims or pre-market review for safety and efficacy; and 2) cannabis for medical purposes, obtained via a healthcare professional authorization, with no health claims or premarket review for safety and efficacy, both of which are regulated under the *Cannabis Act* and its Regulations; and 3) health products containing cannabis (or for use with cannabis), such as prescription drugs and medical devices, that are marketed with health claims and subject to premarket authorization by Health Canada under the *Food and Drugs Act* and its Regulations.[1]

Cannabis contains hundreds of chemical substances, including over 100 different cannabinoids.[2] Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most well known cannabinoids. Cannabinoids interact with the endocannabinoid system that is composed of an array of receptors. These receptors are distributed extensively throughout the cells and organs of the body. Currently, there are knowledge gaps regarding drug interactions involving cannabis.[3-6]

Warfarin is a prescription anticoagulant drug that acts by inhibiting the synthesis of vitamin K dependent clotting factors.[7] Many drugs, natural health products, foods and concurrent disease states are known to interact with warfarin and therefore, can affect the international normalized ratio (INR).

Cases of increased INR associated with the use of cannabis in patients taking warfarin have been reported both in Canada and internationally.

Canadian context

As of September 30, 2020, Health Canada received 2 adverse reaction reports of increased INR suspected of being associated with the use of warfarin and orally ingested or sublingually administered CBD oil or CBD-dominant cannabis oil products.

The first case involved a 76-year-old woman who experienced an increase in INR (4.8) less than one week after starting CBD oil (exact brand and concentration of cannabinoids unknown). The reporter suspected that the spike in the INR in an otherwise stable patient could be due to the initiation of the CBD oil. The second case was reported in an 83-year-old man who experienced an increase in INR (6.2) approximately 3 months after starting a CBD-dominant cannabis oil (1 mg/mL THC and 20 mg/mL CBD). There were no other changes to his medications. In both cases, the cannabis product was discontinued, warfarin dose was adjusted and the INR went back within therapeutic range.

Literature case reports

Five international case reports of increased INR in patients on warfarin who were also using cannabis have been described in the literature (Table 1).[4-6,8,9]

Table 1: Summary of literature case reports of increased INR in patients treated with warfarin who were also using cannabis

Case report	Age/ sex	Suspect product details	Adverse reaction	Outcome and additional information
1[8]	56/M	Unknown dried cannabis (smoked) Warfarin (oral) 5 mg/d	Increase of INR on 2 occasions to 10.41 and 11.55 with bleeding complications	The patient stopped cannabis and during the following 9 months, his INR values ranged from 1.08 to 4.40 with no significant bleeding complications.
2[6]	44/M	Epidiolex (cannabidiol oral solution) 265 mg twice daily Warfarin (oral) 7.5 mg/d	Non-linear increase in INR values as CBD dose increased	Warfarin and cannabis continued concomitantly. Warfarin dose reduced by approximately 30% in an effort to maintain INR within therapeutic range.
3[4]	35/M	Occasional use of unknown dried cannabis (smoked) Daily use of unknown edible cannabis Warfarin (oral) 10 mg/d	Increase of INR to 7.2	The INR dropped below 4 upon discontinuation of cannabis with dose adjustments to warfarin.
4[5]	27/M	Unknown dried cannabis (smoked) Warfarin (oral)	Increase of INR to 4.6	NA
5[9]	67/M	Two medical cannabis products: a) 0:1 THC: CBD SL oil, 5 mg/mL, 1 mL twice daily. b) 50:1 THC: CBD SL oil, 4.9 mg THC and 0.1 mg CBD per mL, recently increased from 0.5 to 1 mL 3 times per day. Warfarin (oral) 6 mg and 7.5 mg taken on alternate days	Increase of INR to 5.2	Warfarin and cannabis continued concomitantly. Increased INR values observed approximately once per month, usually after more of the 50:1 THC: CBD oil is used. The elevation resolves after holding the warfarin dose for 1-2 days.

NA = not available, SL = sublingual

Of the 5 published international case reports, one case (case 2) involved Epidiolex, a prescription pure CBD oral solution (100 mg/mL) currently only available in the United States and Europe.[6] In another case (case 5), the patient was using 2 medical cannabis products, including a THC-dominant oil which was used with incremental doses.[9] The remaining 3 cases reported the use of smoked dried cannabis (unknown concentrations of THC and CBD), with one case also involving orally ingested edible cannabis.[4,5,8]

Adverse Reaction Mechanism

Several mechanisms have been proposed for the potential interaction between cannabinoids and warfarin.[3,5,6,8,10,11]

Cannabinoids and warfarin are metabolized by many of the same cytochrome P450 enzymes (CYP3A4, CYP2C9, CYP2C19) and therefore compete for enzymes in the same metabolic pathway.[3,5,6,10] THC, CBD and cannabinol (CBN) are thought to inhibit the activity of CYP2C9, the primary isozyme that metabolizes warfarin as a substrate, which could result in prolonged warfarin exposure and increased INR.[3,5,11]

Another hypothesis is that the cannabinoids could potentially displace warfarin, which is highly protein bound, from albumin.[8] This could lead to increased free warfarin that could potentiate the anticoagulant effect.

Information for healthcare professionals

There is limited and sometimes conflicting information about the effects of cannabis on hematological parameters in the published literature.[3,12-14] This highlights the importance of ongoing monitoring of these effects overall, especially in higher risk patients on therapeutic interventions to control bleeding or clotting events.

Healthcare professionals should be aware of the potential for increased INR values in patients on warfarin therapy who are also using cannabis. Healthcare professionals are reminded to ask patients about their use of cannabis, particularly if patients are being treated with warfarin.

Healthcare professionals are encouraged to report any cases of increased INR or any other adverse reactions suspected to be associated with cannabis to Health Canada as well as to the licence holder of the cannabis product.

Cannabis adverse reaction reporting

Adverse reaction reports for cannabis or cannabis products should be as complete as possible and should include:

- specific product information (brand name, licence holder, place of purchase, cannabinoid content/ strength, lot numbers)
- dosage
- duration of use
- other suspect products (if any)
- concomitant health products or other substances
- date of onset of the adverse reaction
- seriousness (and reason for seriousness)
- any positive dechallenge/rechallenge
- outcome

Did you know? Cannabis in Canada – Get the facts

For more information on cannabis, including educational resources, cannabis laws and medical access, as well as information for industry, please consult the Government of Canada cannabis website:

www.canada.ca/cannabis

References

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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.

Plaquenil (hydroxychloroquine sulfate)

The *Drug Interactions* and *Patient Medication Information* sections of the Canadian product monograph for Plaquenil have been updated with **new safety information concerning drug-drug interactions** with cytochrome P450 (CYP) 2C8 and 3A4 inducers and inhibitors and P-glycoprotein (P-gp) substrates.

Key messages for healthcare professionals:[1]

- **CYP2C8 and CYP3A4 inducers:** Lack of efficacy of Plaquenil was reported when rifampin, a CYP2C8 and CYP3A4 strong inducer, was concomitantly administered. Caution is advised, including monitoring for efficacy, when Plaquenil is concomitantly administered with CYP2C8 and CYP3A4 strong inducers such as rifampin, St. John's Wort, carbamazepine, or phenobarbital.
- **CYP2C8 and CYP3A4 inhibitors:** Concomitant use of cimetidine, a moderate CYP2C8 and CYP3A4 inhibitor, resulted in a 2-fold increase of chloroquine exposure. Per extrapolation, due to the similarities in structure and metabolic elimination pathways between hydroxychloroquine and chloroquine, a similar interaction could be observed for Plaquenil. Co-administration of Plaquenil with moderate and strong CYP2C8 and CYP3A4 inhibitors such as, but not limited to, cimetidine, ketoconazole, itraconazole, erythromycin, aprepitant, fluconazole, clopidogrel, teriflunomide, letermovir, gemfibrozil, ritonavir, or clarithromycin may result in increased plasma concentrations of hydroxychloroquine. Caution is advised, including monitoring for adverse reactions, when Plaquenil is concomitantly administered with moderate and strong CYP2C8 and CYP3A4 inhibitors.

Key messages for healthcare professionals (continued):[1]

- **P-glycoprotein (P-gp) substrates:** The inhibitory potential of Plaquenil on P-gp substrates has not been evaluated. *In vitro* observations show that all other aminoquinolines tested inhibit P-gp. Therefore, there is a potential for increased concentrations of P-gp substrates when Plaquenil is concomitantly administered. Increased plasma cyclosporine levels were reported when cyclosporine and Plaquenil were co-administered. Increased digoxin serum levels were reported when digoxin and Plaquenil were co-administered. Serum digoxin levels should be closely monitored in patients receiving concomitant treatment. Caution is advised, including monitoring for adverse reactions or for plasma concentrations as appropriate, when P-gp substrates with narrow therapeutic index such as digoxin, cyclosporine, or dabigatran are concomitantly administered with Plaquenil.

Reference

1. *Plaquenil (hydroxychloroquine sulfate)* [product monograph]. Laval (QC): sanofi-aventis Canada Inc.; 2020.

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

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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