Health Canada Santé Canada

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Health Product InfoWatch

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REPORTING ADVERSE REACTIONS

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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

ANNOUNCEMENT

New regulations to provide better information for patients on the safe use of opioid medications

Health Canada has published new regulations in Canada Gazette, Part II that will now make warning stickers and patient information handouts mandatory with prescription opioids dispensed at pharmacies or in doctor's offices across Canada.

The warning sticker will be applied to the container being dispensed to the patient.

The patient handout will include important information about the signs of opioid overdose, safe storage and other warnings.

The mandatory warning sticker and the patient handout will begin to be distributed in October 2018.

The new regulations will also require pharmaceutical companies to develop and implement mandatory risk management plans to help characterize, monitor, prevent and manage risks associated with the use of their opioid products.

News Release
Regulations Amending the Food and Drug Regulations (Opioids)

Figure 1: warning sticker

MONTHLY RECAP OF HEALTH PRODUCT SAFETY INFORMATION

The following is a list of health product advisories, type I recalls as well as summaries of completed safety reviews published in April 2018 by Health Canada.

Atypical antipsychotics Summary Safety Review	This safety review evaluated the risk of drug reaction with eosinophilia and systemic symptoms (DRESS) associated with atypical antipsychotics. Health Canada's review followed the manufacturers' voluntary update of the product safety information for Zyprexa (olanzapine) and Zeldox (ziprasidone) to include the risk of DRESS. Health Canada's review of the available information concluded that there may be a link between the risk of DRESS and the use of 6 other atypical antipsychotics including aripiprazole, clozapine, lurasidone, paliperidone, quetiapine and risperidone. Health Canada will work with the manufacturers to update the Canadian product monographs for these atypical antipsychotics to include the risk of DRESS.

Bortezomib for Injection Drug Recall	Teva Canada Inc. has recalled Bortezomib for Injection 3.5 mg/vial, lot 9501016, due to the potential for the presence of particulate matter (glass).
EpiPen and EpiPen Jr (epinephrine) Information Update	Following Health Canada's previous communication regarding a shortage of EpiPen (0.3 mg) auto-injectors, this update provides further information on the EpiPen and EpiPen Jr (0.15 mg) shortages.
Erfa-Tranexamic 100 mg/mL Drug Recall	ERFA Canada 2012 Inc. has recalled Erfa-Tranexamic 100 mg/mL (50 mL), lot P146A, due to the presence of particulate matter.
Foreign health products Foreign Product Alert	These foreign health products have been found by regulators in other countries to contain undeclared drug ingredients. The products are not authorized for sale in Canada and have not been found in the Canadian marketplace, but it is possible they may have been brought into the country by travellers or purchased over the Internet.
Oral contraceptives Advisory	Health Canada recently communicated about instances of quality concerns involving Alesse and Alysena oral contraceptives. Health Canada continues to receive complaints of quality issues and reminds women to always check their pills before taking them. If anything unusual is noticed, such as missing or damaged pills, the package should be returned to the pharmacy for replacement as soon as possible.
"Organic Traditions Shatavari Powder" Advisory	One lot of "Organic Traditions Shatavari Powder" is being recalled by Advantage Health Matters Inc. Company testing found Salmonella bacteria contamination. The product is promoted as an Ayurvedic herbal tonic to support general health.
Percutaneous Radiofrequency Ablation Catheters Summary Safety Review Health Professional Risk Communication	This safety review evaluated the risk of atrioesophageal fistula associated with percutaneous radiofrequency ablation catheters. Health Canada's review concluded that there is a potential link. This risk is not specific to any one device or manufacturer. Health Canada will work with the manufacturers of these catheters to update the Instructions for Use to include this safety information. Health Canada has also communicated this information to healthcare professionals.
Primidone Advisory Drug Recall	AA Pharma Inc. recalled 2 lots of Primidone tablets because they contain high levels of lead. The company has indicated that only the lots identified in the advisory (lot number MT4040 and MM3274) are affected by this issue.

Sevoflurane Summary Safety Review	This safety review evaluated the risk of bradycardia associated with sevoflurane, in children with Down syndrome. Health Canada's review concluded that there is a link. Health Canada has recommended that the manufacturers of sevoflurane products strengthen the existing Canadian product monographs to include the data reported in published studies about this risk in children with Down syndrome.
"Throat Coat Lemon Echinacea" herbal tea Advisory	One lot of "Throat Coat Lemon Echinacea" herbal tea was recalled by Traditional Medicinals after a company supplier found Salmonella contamination in a tea ingredient (lemon myrtle leaf). The recalled product was sold at stores across Canada and online, including Amazon Canada, Bulk Barn, Loblaws, London Drugs and Walmart.
Unauthorized health products Update - Multiple unauthorized products	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.

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 brand name pharmaceutical drugs is available on Health Canada's Web site.

Dipeptidylpeptidase-4 (DPP-4) Inhibitors

The risk of **bullous pemphigoid** has been included in the *Warnings and Precautions* and *Post-Market Adverse Drug Reactions* sections of the Canadian product monographs for DPP-4 inhibitors.*

Key messages for healthcare professionals:[1-8]

- Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with the use of DPP-4 inhibitors.
- In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor.
- Healthcare professionals should tell their patients to immediately report development of blisters or erosions while receiving a product containing a DPP-4 inhibitor. If bullous pemphigoid is suspected, this product should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

References on page 5

References

1. *Glyxambi (empagliflozin and linagliptin)* [product monograph]. Burlington (ON): Boehringer Ingelheim (Canada) Ltd.; 2017.
2. *Janumet, Janumet XR (sitagliptin and metformin)* [product monograph]. Kirkland (QC): Merck Canada Inc.; 2017.
3. *Januvia (sitagliptin)* [product monograph]. Kirkland (QC): Merck Canada Inc.; 2017.
4. *Kazano (alogliptin and metformin)* [product monograph]. Oakville (ON): Takeda Canada Inc.; 2018.
5. *Komboglyze (saxagliptin and metformin)* [product monograph]. Mississauga (ON): AstraZeneca Canada Inc.; 2018.
6. *Nesina (alogliptin)* [product monograph]. Oakville (ON): Takeda Canada Inc.; 2018.
7. *Onglyza (saxagliptin)* [product monograph]. Mississauga (ON): AstraZeneca Canada Inc.; 2018.
8. *Qtern (saxagliptin and dapagliflozin)* [product monograph]. Mississauga (ON): AstraZeneca Canada Inc.; 2018.

* The Canadian product monographs for Jentadueto (linagliptin and metformin) and Trajenta (linagliptin) already contained information on the risk of bullous pemphigoid.

Elavil (amitriptyline hydrochloride)

New information regarding the risk of **prolongation of the QT interval** has been added to the *Warnings, Precautions* and *Adverse Reactions* sections of the Canadian product monograph for Elavil.

Key messages for healthcare professionals:[1]

- Cases of QT interval prolongation and arrhythmia have been reported with the use of amitriptyline during the post-marketing period.
- Amitriptyline should be used with caution in patients with significant bradycardia, in patients with uncompensated heart failure, or in patients concurrently taking QT-prolonging drugs, methadone, or diuretics inducing hypokalemia.
- Electrolyte disturbances (hypokalemia, hyperkalemia, hypomagnesaemia) are also known to increase the proarrythmic risk in patients taking amitriptyline.
- Concurrent administration of amitriptyline and electroconvulsive therapy may increase the hazards of therapy.

Reference

1. *Elavil (amitriptyline hydrochloride)* [product monograph]. Vaughan (ON): AAPharma Inc.; 2018

Gadolinium-Based Contrast Agents (GBCAs)

Additional information related to the potential risk of **gadolinium deposition in the brain** associated with the use of Gadolinium-Based Contrast Agents (GBCAs) has been included in the *Indications and Clinical Use, Warnings and Precautions*, and *Dosage and Administration* sections of the Canadian product monographs for 6 GBCAs.

Key messages for healthcare professionals:[1-6]

- Use of macrocyclic agents may be preferable in certain patients such as those for whom repeated GBCA doses may need to be considered due to individual clinical circumstances and in other potentially vulnerable patients such as children and pregnant women.

References on page 6

References

1. *Dotarem (gadoterate meglumine)* [product monograph]. Roissy-en-France (France): Guerbet; 2018.
2. *Gadovist (gadobutrol)* [product monograph]. Mississauga (ON): Bayer Inc.; 2018.
3. *Magnevist (gadopentetate dimeglumine)* [product monograph]. Mississauga (ON): Bayer Inc.; 2018.
4. *Multihance (gadobenate dimeglumine)* [product monograph]. Montréal (QC): Bracco Imaging Canada; 2018.
5. *Omniscan (gadodiamide)* [product monograph]. Mississauga (ON): GE Healthcare Canada Inc.; 2018.
6. *Prohance (gadoteridol)* [product monograph]. Montréal (QC): Bracco Imaging Canada; 2018.

Imitrex injection (sumatriptan succinate)

The risk of **allergic reactions in latex sensitive individuals** has been included in the *Warnings and Precautions* and *Consumer Information* sections of the Canadian product monograph for Imitrex.

Key messages for healthcare professionals:[1]

- The needle shield of Imitrex pre-filled syringe contains dry natural latex rubber that has the potential to cause allergic reactions in latex sensitive individuals.

Reference

1. *Imitrex injection (sumatriptan succinate)* [product monograph]. Mississauga, (ON): GlaxoSmithKline Inc.; 2018.

Revlimid (lenalidomide)

The risk of **solid organ transplant rejection** has been included in the *Warnings and Precautions, Adverse Reactions (Post-Market Adverse Drug Reactions),* and *Consumer Information* sections of the Canadian product monograph for Revlimid.

Key messages for healthcare professionals:[1]

- Cases of solid organ transplant (SOT) rejection have been reported in the post-market setting with the use of Revlimid and, in some cases, have resulted in a fatal outcome.
- Onset of SOT rejection may be acute, occurring within 1 to 3 cycles of Revlimid treatment.
- The benefit of treatment with Revlimid versus the risk of possible SOT rejection should be considered in patients with a history of SOT before initiating Revlimid therapy.
- Clinical and laboratory signs of SOT rejection should be closely monitored such as flu-like symptoms (fever, chill, body ache, nausea, cough, shortness of breath, feeling unwell or tired), pain at the area of transplant, less urine, sudden weight gain or other possible symptoms specific to the type of transplant. Revlimid therapy should be discontinued in the event of SOT rejection.

Reference

1. *Revlimid (lenalidomide)* [product monograph]. Mississauga (ON): Celgene Inc.; 2018.

Zydelig (idelalisib)

The risk of **progressive multifocal leukoencephalopathy** has been included in the *Warnings and Precautions, Post-Market Adverse Drug Reactions* and *Consumer Information* sections of the Canadian product monograph for Zydelig (idelalisib).

Key messages for healthcare professionals:[1]

- Cases of progressive multifocal leukoencephalopathy (PML) have been reported following the use of Zydelig within the context of prior- or concomitant immunosuppressive therapies that have been associated with PML.
- Physicians should consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioural signs or symptoms. If PML is suspected then appropriate diagnostic evaluations should be undertaken and treatment suspended until PML is excluded.
- If any doubt exists, referral to a neurologist and appropriate diagnostic measures for PML including MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC viral DNA and repeat neurological assessments should be considered.
- Discontinue Zydelig permanently in patients with confirmed PML.

Reference

1. *Zydelig (idelalisib)* [product monograph]. Mississauga, (ON): Gilead Sciences Canada, Inc.; 2018.

NOTICE OF MARKET AUTHORIZATION WITH CONDITIONS

New **Notice of Market Authorization with Conditions** section will highlight Health Canada's issuance of Notices of Compliance under the Notice of Compliance with Conditions policy.

*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 on the details 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.

Bavencio (avelumab): Authorization with conditions

Health Canada has issued a Notice of Compliance, under the Notice of Compliance with Conditions policy for Bavencio* (avelumab), solution for intravenous infusion 20 mg/mL single-use vial. Bavencio is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-based chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-based chemotherapy. 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 Bavencio Canadian product monograph. The product monograph can be accessed through Health Canada's Drug Product Database, the EMD Serono Web site or by contacting EMD Serono, a Division of EMD Inc., Canada at 1-888-737-6668. Contact the company for a copy of any references, attachments or enclosures.

* Bavencio has a previous product monograph dated December 2017; the product monograph including this NOC/c indication is dated May 2018.

Imfinzi (durvalumab): Authorization with conditions

Health Canada has issued a Notice of Compliance, under the Notice of Compliance with Conditions policy for Imfinzi* (durvalumab), solution, 50 mg/mL, intravenous infusion. Imfinzi is indicated for the treatment of patients with locally advanced, unresectable non-small cell lung cancer whose disease has not progressed following platinum-based chemoradiation therapy. 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 Imfinzi Canadian product monograph. The product monograph can be accessed through: Health Canada's Drug Product Database, the AstraZeneca Web site or by contacting AstraZeneca Canada Inc., at 1-800-668-6000. Contact the company for a copy of any references, attachments or enclosures.

* Imfinzi has a previous product monograph dated November 2017; the product monograph including this NOC/c indication is dated May 2018.

HELPFUL LINKS

- MedEffect™ Canada
- Recalls and Safety Alerts Database
- Summary Safety Reviews
- New Safety 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

Suggestions?

Your comments are important to us. Let us know what you think by reaching us at HC.infowatch-infovigilance.SC@canada.ca

Health Canada
Marketed Health Products Directorate
Address Locator 1906C
Ottawa ON K1A 0K9
Telephone: 613-954-6522
Fax: 613-952-7738

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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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