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Health Product InfoWatch

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CONTENTS

REPORTING ADVERSE REACTIONS

Canada Vigilance Program
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HEALTH PRODUCTS MENTIONED IN THIS ISSUE

Pharmaceuticals and Biologics

- Alesse 21 (levonorgestrel and ethinyl estradiol)
- Amiodarone
- Cefoxitin for Injection (1 g/vial and 10 g/vial)
- Clavulin-400 Oral Suspension (amoxicillin-clavulanic acid)
- Harvoni (ledipasvir and sofosbuvir)
- Ibuprofen
- Methylphenidate Products
- Nexavar (sorafenib)
- Ortho-Cept (desogestrel and ethinyl estradiol)
- Primene 10% Amino Acid Injection
- RAN-Gabapentin (gabapentin)
- Sovaldi (sofosbuvir)
- Uloric (febuxostat)

Natural Health Products

- All Seasons Detox Kit
- Bulklax V
- Filix Mas
- Goldenseal
- Paranil
- W.-W.

Other

- Enhance
- Natural-Power

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

MONTHLY RECAP OF HEALTH PRODUCT SAFETY INFORMATION

The following is a list of health product advisories as well as summaries of completed safety reviews published in April 2015 by Health Canada.

Alesse 21 (levonorgestrel and ethinyl estradiol) Advisory	Health Canada advised consumers that Shoppers Drug Mart has recalled one lot of Alesse 21 (lot number G73720), an oral contraceptive that was provided to consumers in Western Canada after the expiry date (September 2014). Efforts have been made by pharmacies to contact affected patients.
Amiodarone Health Product Risk Communication	Post-marketing cases of symptomatic bradycardia have been reported in patients taking amiodarone with either Harvoni or Sovaldi in combination with another direct acting antiviral. Health Canada is working with Gilead Sciences Canada to update the Sovaldi and Harvoni prescribing information to reflect this potential risk.
Bulklax V and All Seasons Detox Kit Advisory	St. Francis Herb Farm Inc., in consultation with Health Canada, voluntarily recalled two products, “Bulklax V” and “All Seasons Detox Kit,” after they were found to contain unacceptably high levels of lead and/or arsenic.
Cefoxitin for Injection (1 g/vial and 10 g/vial) Health Product Risk Communication	Teva Canada Limited, in consultation with Health Canada, initiated a voluntary recall for one lot of Cefoxitin 1 g/vial (DIN 02128187) and one lot of Cefoxitin 10 g/vial (DIN 02240773) for Injection due to the presence of dark active pharmaceutical ingredient particles in the vials, observed only upon reconstitution.
Clavulin-400 Oral Suspension (amoxicillin-clavulanic acid) Advisory	GlaxoSmithKline Inc. (GSK), in consultation with Health Canada, voluntarily recalled one lot (lot 710535) of Clavulin-400 (70 mL) after receiving a complaint from a pharmacy that two glass pieces had been found in one bottle of the product.
Enhance and Natural-Power Information Update	Further to a recent Advisory, Health Canada testing has found that two unauthorized health products, “Enhance” and “Natural-Power,” contain undeclared sildenafil. The two products, promoted as natural sex-enhancement products, were removed from sale from Nature’s Source, in Vaughan, Ontario.

Filix Mas, Paranil and W.-W. Advisory (homeopathic product) Advisory (natural health products)	Health Canada has suspended the licence of Filix Mas, a homeopathic product, because it contains the ingredient male fern (Dryopteris filix-mas). Health Canada has also suspended the licences of two natural health products containing this ingredient, “Paranil” and “W.-W”. Safety information has raised potential concerns regarding effects of the specific ingredient at higher doses. Using the affected products may pose a serious health risk.
Goldenseal Summary Safety Review	This safety review evaluated the potential risk of herb-drug interactions associated with the herbal ingredient goldenseal. The current available evidence suggests that use of oral goldenseal may contribute to herb-drug interactions, but the data is limited and no domestic or international cases of goldenseal-drug interactions are known to Health Canada. Health Canada will continue to monitor adverse reaction information for oral goldenseal-containing health products, as it does for all health products, to identify and assess potential harms.
Ibuprofen, oral prescription-strength Information Update Summary Safety Review	This safety review evaluated the potential risk of heart and stroke related adverse events and the use of ibuprofen, especially at high doses. Health Canada concluded that there was evidence of an association between oral ibuprofen at a daily dose of 2400 mg or more and an increased risk of heart attack and stroke related adverse events. However, the overall benefits of ibuprofen continue to outweigh the risks when used as recommended. The Canadian prescribing information for ibuprofen-containing products will be updated to reflect this new information. Health Canada has also communicated this risk to Canadians.
Methylphenidate Products Health Product Risk Communication Summary Safety Review	This safety review evaluated the potential risk of priapism associated with methylphenidate products in the treatment of attention-deficit hyperactivity disorder. There is limited but good quality evidence of a possible association between priapism and the use of methylphenidate products. The Canadian prescribing information for all brand name and generic methylphenidate products have been updated to include the very rare risk of priapism. Health Canada also communicated this risk to Canadians.
Ortho-Cept (desogestrel and ethinyl estradiol) Advisory	Health Canada has advised consumers that Janssen Inc. recalled one lot of Ortho-Cept tablets (28 day), an oral contraceptive, due to the potential low potency of the two active ingredients. This may result in reduced effectiveness of the product and in some cases, a possible risk of unplanned pregnancy.

Primene 10% Amino Acid Injection Health Product Risk Communication (update) Health Product Risk Communication	Baxter Corporation, in collaboration with Health Canada, communicated about the potential for discoloration and formation of a precipitate when trace elements are added to Primene 10% as a result of a suspected interaction between trace elements and cysteine. Formation of this precipitate may result in insufficient levels of cysteine and trace elements in total parenteral nutrition solutions. Deficiencies of cysteine or trace elements can lead to serious health consequences. Infusion of a precipitate may lead to serious adverse effects including phlebitis, thrombophlebitis, thrombosis and major organ dysfunction. Baxter Corporation provided an update with further instructions.
RAN-Gabapentin (gabapentin) Advisory	Ranbaxy Pharmaceuticals Canada Inc., in consultation with Health Canada, recalled one batch (number 2582026) of RAN-Gabapentin, a medication used to treat epilepsy, due to cross-contamination during the manufacturing process with etodolac, a non-steroidal anti-inflammatory drug.

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

Febuxostat and international reports of agranulocytosis and drug rash with eosinophilia and systemic symptoms (DRESS)

Key points

- Cases of agranulocytosis and drug rash with eosinophilia and systemic symptoms (DRESS) in patients using febuxostat (Uloric) have been reported internationally.
- As of Jan. 10, 2015, Health Canada received no cases of agranulocytosis and one case of suspected DRESS in association with febuxostat use.

Febuxostat (Uloric) is a non-purine selective inhibitor of xanthine oxidase indicated to lower serum uric acid levels in patients with gout.[1] It was first marketed in Canada in September 2010. It is one of two types of xanthine oxidase inhibitors currently available in Canada, along with allopurinol, which has been available for decades. As part of Health Canada's ongoing monitoring of health product related safety information, international cases of agranulocytosis and drug rash with eosinophilia and systemic symptoms (DRESS) suspected of being associated with febuxostat use were identified. Safety reviews were initiated to evaluate the currently available information on these potential risks.

Agranulocytosis

Agranulocytosis is an acute condition involving severe neutropenia associated with the sudden onset of signs and symptoms of bacterial

Key points (continued)

- Healthcare professionals are encouraged to report to Health Canada any case of agranulocytosis or DRESS suspected of being associated with febuxostat use.

infection.[2] Neutropenia is defined as an absolute neutrophil count of less than 1.5 x 10^9/L, and severe neutropenia as a count of less than 0.5 x 10^9/L.

Thirteen international reports of agranulocytosis involving patients using febuxostat were identified in the World Health Organization (WHO) Global Individual Case Safety Report Database System (VigiBase).* No cases of agranulocytosis, severe neutropenia or neutropenia involving Canadian patients treated with febuxostat were reported to Health Canada as of Jan. 10, 2015.

In 2013, 2 cases of acute neutropenia in patients treated with febuxostat were published.[3] In both cases, the neutrophil count dropped to less than 1.5 x 10^9/L during febuxostat therapy and returned to normal values within 2 weeks of the drug being discontinued. A probable relationship between neutropenia and febuxostat was reported for both cases.

Proposed mechanisms for febuxostat-induced neutropenia include: 1) antibody-mediated granulocyte destruction, 2) polymorphisms involving human leukocyte antigen (HLA) alleles which may be associated with an increased risk of neutropenia or 3) a direct toxic effect on the bone marrow microenvironment or myeloid precursors.[3]

Although the number of case reports identified to date is low, agranulocytosis is a serious clinical event. Raising awareness among healthcare professionals of this potential risk is important. The current Canadian product monograph (CPM) for febuxostat is labelled for neutropenia, but does not include the risk of agranulocytosis.[1] Allopurinol has been reported to be associated with agranulocytosis[4,5], and the CPMs for allopurinol products available on the market mention the risk of agranulocytosis.†

DRESS

DRESS is a rare and potentially life-threatening hypersensitivity reaction characterized by a variable combination of symptomatic and asymptomatic features, including severe skin rash, fever above 38°C, hematologic abnormalities (eosinophilia, atypical lymphocytosis), enlarged lymph nodes, and multi-organ involvement (liver, kidney, lung, etc.).[6,7] The onset is typically delayed, often 2 to 8 weeks after initiation of a drug therapy, and symptoms can persist or worsen despite discontinuation of the culprit drug.

Fourteen reports of DRESS suspected of being associated with febuxostat were identified in VigiBase.* As of Jan. 10, 2015, Health Canada received one case of DRESS suspected of being associated with febuxostat. This case was published in the literature and describes a drug-induced hypersensitivity syndrome in a patient receiving a febuxostat-azathioprine (AZA) combination.[8] The patient had previously experienced a similar adverse reaction (AR) when treated with an allopurinol-AZA combination. It was not clear whether allopurinol and febuxostat or AZA were the causative

agents. Additional international cases reporting DRESS in association with febuxostat therapy have also been published in the literature.[9,10]

The current CPM warns against serious skin and hypersensitivity reactions but does not include DRESS.[1] The febuxostat CPM also mentions a potential risk in patients who have experienced prior skin reactions to allopurinol, which is also known to be associated with serious skin reactions including generalized hypersensitivity† and DRESS.[6,7]

In summary, existing evidence that febuxostat can cause these rare and serious ARs is limited. In order to better investigate this issue, healthcare professionals are encouraged to report to Health Canada any case of agranulocytosis or DRESS suspected of being associated with febuxostat. Information such as treatment duration, concomitant medications and date of onset of the AR are important to include when reporting.

References

1. *Uloric (febuxostat)* [product monograph]. Oakville (ON): Takeda Canada Inc.; 2013.
2. Bankowski Z, Bruppacher R, Crusius I, et al. Reporting adverse drug reactions: Definitions of terms and criteria for their use. Geneva (Switzerland): Council for International Organizations of Medical Sciences (CIOMS); 1999.
3. Kobayashi S, Ogura M, Hosoya T. Acute neutropenia associated with initiation of febuxostat therapy for hyperuricaemia in patients with chronic kidney disease. *J Clin Pharm Ther* 2013;38(3): 258–61.
4. Andrès E, Zimmer J, Affenberger S, et al. Idiosyncratic drug-induced agranulocytosis: Update of an old disorder. *Eur J Intern Med* 2006;17(8):529-35.
5. Mari E, Ricci F, Imberti D, et al. Agranulocytosis: an adverse effect of allopurinol treatment. *ITJM* 2011;5(2):120-3.
6. Cacoub P, Musette P, Descamps V, et al. The DRESS syndrome: a literature review. *Am J Med* 2011;124(7):588-97.
7. Kardaun SH, Sekula P, Valeyrie-Allanore L, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. *Br J Dermatol* 2013;169(5):1071-80.
8. Doré M, Frenette AJ, Mansour AM, et al. Febuxostat as a novel option to optimize thiopurines' metabolism in patients with inadequate metabolite levels. *Ann Pharmacother* 2014;48(5):648-51.
9. Mauck M, DeGueme A, Taintor A, et al. Cross-sensitivity of allopurinol and febuxostat induced drug rash with eosinophilia and systemic symptoms (DRESS) syndrome [tracking ID # 196031]. *J Gen Intern Med* 2010;25:S504-5.
10. Abeles AM. Febuxostat hypersensitivity. *J Rheumatol* 2012;39(3):659.

* 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. Also, 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 April 1, 2015.

† Current product monographs for allopurinol products available on the Canadian market can be accessed by searching Health Canada's Drug Product Database.

PRODUCT MONOGRAPH UPDATE

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.

Nexavar (sorafenib)

The risk of **thyroid dysfunction** has been included in the Warnings and Precautions section.

Key message for healthcare professionals:[1]

- Thyroid dysfunction has been reported in association with sorafenib use. Both hypothyroidism and hyperthyroidism may occur. Hypothyroidism has been observed more frequently.
- Thyroid function tests monitoring is recommended at baseline and during treatment with sorafenib.

Reference

1. *Nexavar (sorafenib)* [product monograph]. Mississauga (ON): Bayer Inc.; 2014.

HELPFUL LINKS

- MedEffect™ Canada
- Recalls and Safety Alerts Database
- Summary Safety Reviews
- New Safety Reviews
- Canada Vigilance Adverse Reaction Online Database
- Drug Product Database
- Canadian Drug Shortage Database
- The Drug and Health Product Register

Suggestions?

Your comments are important to us. Let us know what you think by reaching us at InfoWatch_InfoVigilance@hc-sc.gc.ca

Health Canada
Marketed Health Products Directorate
Address Locator 0701D
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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