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Canadian Adverse Reaction Newsletter

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In this issue

Scope

This quarterly publication alerts health professionals to potential signals detected through the review of case reports submitted to Health Canada. It is a useful mechanism to stimulate adverse reaction reporting as well as to disseminate information on suspected adverse reactions to health products occurring in humans before comprehensive risk–benefit evaluations and regulatory decisions are undertaken. The continuous evaluation of health product safety profiles depends on the quality of your reports.

Reporting Adverse Reactions

Canada Vigilance Program
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Montelukast (Singulair): suicidality and other psychiatric adverse reactions

Montelukast sodium (Singulair), a leukotriene-receptor antagonist, is indicated for the prophylaxis and chronic treatment of asthma in patients 2 years of age and older.[1] It is also indicated for the relief of symptoms of seasonal allergic rhinitis in patients 15 years of age and older when other treatments are not effective or not tolerated. Montelukast has been marketed in Canada since 1997.

Between September 2007 and July 2008, updates were made to the "Adverse drug reactions" section of the Canadian product monograph for montelukast to include depression, suicidality and anxiousness.[1] The American product monograph was similarly updated.[2] In March 2008, the US Food and Drug Administration (FDA) issued an "Early communication" stating that it was investigating further the suspected association between montelukast and suicidality.[3] Following the FDA's early communication, there was a 7-fold increase in the number of montelukast-related cases reported to the Adverse Event Reporting System database in the United States.[4]

From the date of marketing to Jan. 31, 2009, Health Canada received 13 adverse reaction (AR) reports related to suicidality or self-injury suspected of being associated with the use of montelukast (Table 1). Eight reports stated that the reaction abated after the dose was reduced or the drug was stopped. The reaction reappeared after the reintroduction of montelukast in 1 case. All but 1 of the reports were received by Health Canada after the FDA's early communication.

From the date of marketing to Jan. 31, 2009, Health Canada received 29 other AR reports relating to depression, hostility or psychosis suspected of being associated with the use of montelukast (Table 1). In 19 cases, the reaction abated after montelukast was stopped or the dose was reduced. The reaction reappeared after the reintroduction of montelukast in 4 cases. Thirteen of the 29 reports were received by Health Canada after the FDA's early communication.

If suicidal thoughts and actions occur, montelukast should be discontinued and a physician or pharmacist contacted immediately.

No deaths were reported in any of the cases discussed above. Twenty-six of the 42 reports involved patients under 18 years of age (age was not indicated in 5 reports).

Table 1: Summary of reports relating to suicidality and other psychiatric adverse reactions (ARs) suspected of being associated with montelukast received by Health Canada from date marketed in Canada (1997) to Jan. 31, 2009

Reaction*	No. of reports	Serious AR†	Positive dechallenge‡	Positive rechallenge§
Suicide attempt	2	2	NA	NA
Suicidal or self-injury ideation	11	11	8	1
Other (relating to depression, hostility or psychosis)	29	14	19	4
Total	42	27	27	5

Note: NA = not applicable.
*Terms are listed according to the *Medical Dictionary for Regulatory Activities* (MedDRA).
†In the *Food and Drugs Act* and Regulations, a serious AR is defined as "a noxious and unintended response to a drug that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death."
‡No. of reports that described abatement of reaction after montelukast was stopped or the dose was reduced.
§No. of reports that described reappearance of reaction after reintroduction of montelukast.

The consumer information section of the Canadian product monograph warns patients that, if suicidal thoughts and actions occur, montelukast should be discontinued and a physician or pharmacist contacted immediately. The product monograph also states that, if severe behaviour and mood-related changes such as agitation including aggressive behaviour (e.g., temper tantrum in children) occur, a physician or pharmacist should be consulted.[1]

Health care professionals and consumers are encouraged to consult the product monograph of montelukast, including the consumer information section, for information regarding behaviour and mood-related ARs.

Patrice Tremblay, MD, Health Canada

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Intravitreal injection of triamcinolone acetonide and serious ocular adverse reactions

Triamcinolone acetonide is a synthetic corticosteroid primarily used for its marked anti-inflammatory action.[1] It was authorized for use in Canada as a 10-mg/mL suspension (Kenalog 10) in 1966, and as a 40-mg/mL suspension (Kenalog 40) in 1973. Currently, generic products are also available. In Canada, the 40-mg/mL suspension has been authorized for intramuscular and intra-articular administration or for injection into tendon sheaths or ganglia. It is indicated for systemic corticosteroid therapy in conditions such as dermatoses, or rheumatoid arthritis and other connective tissue disorders.[1]

Intravitreal or intraocular injection of this product is not an authorized route of administration in Canada. Diabetic macular edema, cystoid macular edema and choroidal neovascularization secondary to age-related macular degeneration are among the conditions for which the use of intravitreal injection of triamcinolone has been reported.[2,3] In 2007, a safety notice was published in France regarding the occurrence of serious ocular adverse reactions (ARs) following intravitreal injections of the 40-mg/mL suspension.[4]

Topical ophthalmic, oral and intravenous corticosteroids have long been associated with ocular ARs. Local injections of steroids, even at sites far from the eye, have been associated with eye complications such as the development of cataract, glaucoma, and even retinal and choroidal emboli.[5]

Intravitreal injection of triamcinolone has several reported complications. Immediate complications include retinal detachment and vitreous hemorrhage. Complications developing later include cataract progression, steroid-induced glaucoma and endophthalmitis.[2] Triamcinolone persists for long periods. Low concentrations were found in samples of aqueous humor up to 1.5 years after intravitreal injection.[6] Cases of increased intraocular pressure requiring medical intervention following intravitreal injection have

also been reported. Patients with a history of primary open-angle glaucoma are at a higher risk of increased intraocular pressure.[2]

A number of ocular ARs following intravitreal injection of triamcinolone in Canada have been reported in scientific literature.[2] They included increased intraocular pressure requiring glaucoma medication (60 cases), cataract progression requiring extraction (12), endophthalmitis (1) and temporary occlusion of the central retinal artery (1).

Local injections of steroids, even at sites far from the eye, have been associated with eye complications.

From Jan. 1, 1973, to Jan. 31, 2009, Health Canada received 1 report of serious ocular ARs suspected of being associated with combined photodynamic therapy and intravitreal injection of triamcinolone. The case involved a 13-year-old girl in whom increased intraocular pressure, retinal hemorrhage and reduced visual acuity developed following two injections of triamcinolone given about 3 months apart.

Although underreporting of ARs is well documented, voluntary reporting is one of the most common ways to monitor the safety and effectiveness of marketed health products. Health care professionals are encouraged to report to Health Canada any ocular ARs suspected of being associated with triamcinolone.

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Fentanyl transdermal patches and accidental child exposure

The fentanyl transdermal system is indicated in the management of persistent, moderate to severe chronic pain that cannot be managed by other means such as opioid combination products or immediate-release opioids.[1] The system has been marketed in Canada under the brand name Duragesic since 1992. In 2006, the generic products Ratio-Fentanyl and Ran-Fentanyl transdermal systems were introduced.

The safety of the fentanyl transdermal system is contingent on its use according to the conditions recommended in the Canadian product monographs. The "Warnings and precautions" section of the monographs were updated to include accidental exposure. Examples of accidental exposure include the transfer of a fentanyl transdermal patch while hugging, sharing a bed or moving a patient.[1–3]

Examples of accidental exposure include the transfer of a fentanyl transdermal patch while hugging, sharing a bed or moving a patient.

In December 2008, Health Canada received a report of suspected accidental fentanyl exposure in a healthy 19-month-old child. He was sleeping in the same bed as his mother, who was using a fentanyl patch for chronic pain. The patch inadvertently became attached to the child. He was taken to hospital and given naloxone 0.01mg/kg intramuscularly as required. The child was monitored overnight, and his condition improved after treatment.

Health care professionals, patients and caregivers should be aware of serious medical consequences, including death, that have occurred when people were accidentally exposed to a fentanyl transdermal patch.[1–4]

Maria Longo, RPh, BScPharm, Health Canada

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How to submit a report?

There are three easy ways to report an adverse reaction to the Canada Vigilance Program:

- by **calling toll-free** at 1-866-234-2345
- by reporting **online** at www.healthcanada.gc.ca/medeffect
- by **completing a form** that you can send by:
  - postage-paid mail or
  - fax toll-free to 1-866-678-6789

The form and postage-paid label are available at **www.healthcanada.gc.ca/medeffect** or by calling **1-866-234-2345**.

The adverse reaction reporting form is also available at the back of the *Compendium of Pharmaceuticals and Specialties* (*CPS*).

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Quarterly summary of health professional and consumer advisories

(posted on Health Canada's website: Mar. 11, 2009 – June 1, 2009)

Date	Product	Subject
May 25	Vitamin Maxum Matragen and Maxum Multi Vite Supplements	Information for pregnant and breastfeeding women
May 15	Dobutamine Hydrochloride	Recall — labelling error
May 15	Rofact	Recall — labelling error
May 8	Tarceva	Association with cases of gastrointestinal perforation, Stevens–Johnson syndrome and corneal perforation
May 3	H1N1 flu virus products	Counterfeit and unapproved products
May 1 & 3	Hydroxycut products	Unauthorized products under review and update
Apr 21	Herceptin	Association with oligohydramnios
Apr 21	Enbrel	Association with histoplasmosis and other invasive fungal infections
April 3	BHM/Medi-Man Combi Sling	Possible stitching failure
Apr 1	Mattresses	Standards for improved fire resistance
Mar 27	Prefilled saline and heparin syringes	Important safety information
Mar 27	Electronic cigarettes	Health Canada advises not to use electronic smoking products
Mar 25	Phosphocol P32	Association with acute lymphocytic leukemia
Mar 24 & 25	Blood lancing devices	Misuse of blood lancing devices
Mar 19	Silver Care toothbrushes and toothbrush refills	Recall — addition to warning label
Mar 16 & 19	EVRA transdermal contraceptive system	Drug-release information
Feb 12	AED Plus Defibrillator	Urgent medical device correction
Jan 29	COLLEAGUE infusion volumetric pumps	Urgent medical device correction

Advisories are available at www.healthcanada.gc.ca/medeffect.

Canadian Adverse Reaction Newsletter

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Suggestions?

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