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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 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

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Fentanyl transdermal patch and fatal adverse reactions

The fentanyl transdermal system is indicated for the management of moderate to severe chronic pain that cannot be managed by other means such as opioid combination products or immediate-release opioids.[1] The safety of this system is contingent on its use according to the conditions recommended in the Canadian product monograph.[1] The fentanyl transdermal system has been marketed in Canada under the brandname Duragesic since 1992. In July 2006, 2 generic products were introduced: Ratio-Fentanyl and Ran-Fentanyl transdermal systems.

Health Canada continues to monitor reports of serious adverse reactions (ARs) suspected of being associated with fentanyl transdermal patches. Fatal outcomes were previously described in this newsletter involving opioid-naive adolescents and adolescents who abused this medication.[2,3] The Canadian product monograph for Duragesic was revised in 2005 to emphasize safety information following reports of death related to inappropriate use of this product. Related advisories were issued in September 2005.[4,5] Numerous publications have highlighted safety issues related to the use of fentanyl patches.[6–9]

From Jan. 1, 1992, to Dec. 31, 2007, Health Canada received 105 reports of ARs suspected of being associated with fentanyl transdermal patches wherein a fatal outcome was reported. Twenty-seven of the reports were received after the last Health Canada risk communications.[4,5] As part of the ongoing monitoring of AR reports, the data were analyzed to identify potentially preventable incidents and to increase awareness regarding the safe use of this product. In 33 of the 105 reports, the cause of death was reported to be unrelated to the fentanyl transdermal patches; in 20 cases, insufficient information was provided in the report for evaluation. The remaining 52 reports are summarized in Table 1.

Health care professionals are reminded to follow the directions in the product monographs for fentanyl transdermal patches.[1] Guidance on the safe use of this product is essential for patients, caregivers and their families, including the safe storage of fentanyl patches to prevent their accessibility for abuse and prevention of accidental overdose.

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Table 1: Summary of reports of 52 adverse reactions with a fatal outcome suspected of being associated with fentanyl transdermal patches submitted to Health Canada from Jan. 1, 1992, to Dec. 31, 2007*†

Factors related to adverse reaction (AR)	No. of AR reports	Additional information
Dose initiation and titration	6	Prescribed to opioid-naive patient (3 cases). Initiation dose high (1 case). Dose titration too quick (2 cases)
Concomitant use with other central nervous system (CNS) depressants	1	Death occurred within 24 hours after initiation of 100-µg/h fentanyl patch. Cause of death reported as probable central nervous system depression due to combination of fentanyl with other CNS depressants
Drug interaction between fentanyl and CYP3A4 inhibitor	1	Death occurred less than 4 days after initiation of lopinavir–ritonavir (Kaletra), a CYP3A4 inhibitor, during fentanyl therapy
Application of patch by patient	6	Patient applied more patches than prescribed (4 cases). Patient left old patches on when applying new patch (1 case). Patient changed patch every day instead of every 3 days (1 case)
Application of patch by caregiver	3	Health care professional folded patch in half in attempt to reduce dose (1 case). Health care professional left old patches on when applying new patch (1 case). Caregiver damaged patch by pressing on it because it would not stick; fentanyl gel leaked and patient died of accidental overdose overnight (1 case)
Use of patch prescribed for another patient	1	To treat back pain, a 64-year-old man applied a 50-µg/h fentanyl patch that had been prescribed for his spouse. The patient was found unresponsive, having vomited and aspirated, and died 5 days later from pneumonia and renal failure
Accidental overdose or overdose effect	5	Patient was elderly and had lean body weight (1 case). Patient died of cardiac arrhythmia due to accidental overdose of fentanyl and elevated levels of antidepressant (1 case). Patient found dead with toxic level of fentanyl after second dose of 25-µg/h patch (1 case). Limited information provided in 2 cases
Intentional overdose or suicide	4	
Intentional drug abuse	25	Cases described abuse of fentanyl patches

*These data cannot be used to determine the incidence of adverse reactions (ARs) because ARs are underreported and neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.
†The analysis is based on the information as reported in the cases.

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Atomoxetine and suicidal behaviour: update

Atomoxetine (Strattera) is a selective norepinephrine reuptake inhibitor indicated for the treatment of attention-deficit hyperactivity disorder (ADHD) in children 6 years of age and over, adolescents and adults.[1] In September 2005, following the marketing of the drug in February 2005, a Dear Health Care Professional letter was issued regarding the potential for behavioural and emotional changes, including the risk of self-harm,[2] with the use of atomoxetine. The Warnings and Precautions section of the Canadian product monograph was updated to include the following statement: "Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type of emotional and behavioural changes, and clinical worsening."[1,2]

As of Dec. 31, 2007, Health Canada received 189 reports of adverse reactions (ARs) suspected of being associated with the use of atomoxetine. Fifty-five ARs were classified as suicide attempt. According to the World Health Organization Adverse Reaction Terminology (WHOART), the term "suicide attempt" also encompasses

"non-accidental overdose," "suicide," "suicidal tendency" and "thoughts of self-harm." Reports involved 41 children (aged 6 to 17 years) and 12 adults (aged 18 to 45); the age was not provided in 2 reports. Of the 55 patients, 29 recovered without sequelae, 3 had not yet recovered at the time of reporting, 1 patient died, and the outcome was not stated in 22 reports.

Treatment options for ADHD include the non-stimulant atomoxetine and stimulants such as methylphenidate and mixed amphetamines.[3] Suicide-related behaviours have been reported with stimulant-type treatments for ADHD.[4] Treatment is complex because patients with ADHD often have other psychiatric disorders.[5] Many studies have found that over 50% of individuals diagnosed with ADHD also meet the diagnostic criteria for one or more additional psychiatric disorders (e.g., mood, anxiety, learning or behaviour disorders).[6] When ADHD is comorbid with other psychiatric disorders, it is often the first disorder to develop, and children with severe symptoms of ADHD are at increased risk of developing other psychiatric disorders.[5] Health care professionals should remind patients, family members and caregivers to monitor moods, behaviours, thoughts and feelings when ADHD medications are used.

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Twinject auto-injector

The article is not being published on the Health Canada Web site at this time due to litigation related to the article.

Quarterly summary of health professional and consumer advisories

(posted on Health Canada's website: Feb. 15 – May 15, 2008)

Date	Product	Subject
May 15	Trophic Kelp & Glutamic Acid HCl	Warning not to use Trophic Kelp & Glutamic Acid HCl
May 14	Trasylol	Comments on the publication of the BART study
May 12	Prezista	Association of Prezista with hepatotoxicity
May 8	Ayurvedic products	Reminder that some products contain heavy metals
May 5	Foreign product	Foreign product alert: vpxl No. 1 Dietary Supplement for Men
Apr 30	Foreign products	Foreign product alert: Tian Sheng Yi Bao; Qili Brand Tongbianling Jiaonang, Sincere Brand ChuanXinLian Jiaonang, Xiangyao Brand Xiangyao Weian Jiaonang, Biflora Brand Fufang Danshen Pian (film-coated), Biflora Brand 306 Xiaoyan Jiedu capsules and Xiang Sha Liu Jun Wan
Apr 29	Foreign products	Foreign product alert: Xian Zhi Wei II; Tian Li
Apr 25	Vigoureux	Warning not to use Vigoureux or any unauthorized products
Apr 17	Foreign products	Foreign product alert: Aspire 36 and Aspire Lite
Apr 11	Foreign products	Foreign product alert: Baby Balm "Eucalyptus and Scotch Pine"; Power 1 Walnut
Apr 3	Foreign products	Foreign product alert: Tetrasil, Genisil, Aviralex, OXi-MED, Beta-mannan Micronutrient, Qina and SlicPlus
Mar 27	Heparin	Details on recall of contaminated heparin
Mar 21	PediaCol	Warning not to use a certain lot of PediaCol
Mar 20	Heparin	B. Braun recalls contaminated heparin
Mar 20	Libidus	Warning not to use Libidus or any unauthorized products
Mar 20	Carbamazepine	Serious skin reactions in patients of Asian ancestry
Mar 17	Tegretol	Safety information concerning serious dermatologic reactions — Novartis Pharmaceuticals Canada Inc.
Mar 12 & 7	Sebivo	Risk of peripheral neuropathy in patients treated with Sebivo and interferon — Novartis Pharmaceuticals Canada Inc.
Mar 11	Ephedra & ephedrine	Reminder not to use Ephedra or Ephedrine Products
Mar 10	Adam	Warning not to use Adam or any unauthorized products
Mar 7	Daylight Saving Time change	Reminder to check medical device clocks
Mar 7 & 4	Exjade	Reports of hepatic failure — Novartis Pharmaceuticals Canada Inc.
Mar 6	Icy Hot Heat Therapy	Recall of Icy Hot Heat Therapy products — Chattem Canada
Mar 3	Vaccine	Measles–mumps–rubella vaccine lots released for use
Feb 27	Losec & Nexium	Update concerning safety review
Feb 20	Botox & Botox Cosmetic	Update concerning ongoing safety review of distant toxin spread

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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.