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Canada

Canadian Adverse Reaction Newsletter

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www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_adverse_newsletter_e.html

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

Contact Health Canada or a Regional AR Centre free of charge

Phone: 866 234-2345
Fax: 866 678-6789
Email: cadrmp@hc-sc.gc.ca

Form available at:

www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/adverse_e.pdf

Transdermal fentanyl (Duragesic): respiratory arrest in adolescents

Health Canada has received 2 case reports of death suspected by the reporters of being associated with the use of Duragesic (transdermal fentanyl system) prescribed off-label to adolescents. In one case, a 15-year-old girl was prescribed Duragesic 25 for chronic headache. She was discovered unresponsive and with respiratory depression 21 hours after the first and only application. She was resuscitated but suffered severe anoxic brain injury and died 2 days later. In the second case, a 14-year-old boy was prescribed Duragesic 25 for throat pain due to infectious mononucleosis. He was found in respiratory arrest 14 hours after the first and only patch was applied. Resuscitative efforts were unsuccessful.

Duragesic has been marketed in Canada since 1992 and is indicated for the management of chronic pain in patients requiring continuous opioid analgesia for pain that is not optimally managed with weak or short-acting opioids.[1] Duragesic is contraindicated for the management of acute or postoperative pain and mild or intermittent pain, and for use in opioid-naive patients. These contraindications and the risk of serious and life-threatening hypoventilation are well labelled in the Canadian product monograph. The use of Duragesic in children under 18 years of age is not recommended in Canada.[1]

A thorough understanding of the pharmacokinetics and delivery system of Duragesic is essential to the safe prescribing of this product. The Duragesic transdermal therapeutic system allows the continuous delivery of the opioid analgesic fentanyl for up to 72 hours.[1] It is a transparent patch comprised of a protective peel strip and 4 functional layers. The protective peel strip is removed before use, and the patch is attached to the skin via a silicone-based contact adhesive, which delivers a loading dose of drug upon application. The fentanyl drug reservoir is located behind a rate-control membrane. The drug diffuses through this membrane and the adhesive to reach the skin. A fentanyl depot accumulates in the upper skin layers, diffuses through to the dermis and is then available for uptake into systemic circulation.[2] In adults, the time from application to minimal effective serum concentrations can range from 1.2 to 40 hours, and the time to reach maximum serum concentrations can range from 12 to 48 hours. When the Duragesic patch is removed, fentanyl continues to be absorbed into the systemic circulation from the cutaneous depot.[2] The serum

Newsletter and Advisories by email

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Go to www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/subscribe_e.html.

fentanyl concentrations decline gradually to about 50% in about 17 (range 13–22) hours.[1]

In the 2 cases reported to Health Canada, these opioid-naive adolescents experienced severe respiratory depression 21 and 14 hours after application of Duragesic 25 and died. Prescribers are reminded that this dosage delivery system for fentanyl is not suitable for acute pain management or for opioid-naive patients. Patients and their caregivers must be instructed in how to recognize symptoms of serious opioid-related toxicity such as hypoventilation and cognitive impairment.[3]

Barbara Raymond, BSc, MD; Iza Morawiecka, BScPhm, Health Canada

References

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3. Kornick CA, Santiago-Palma J, Moryl N, Payne R, Obbens EA. Benefit–risk assessment of transdermal fentanyl for the treatment of chronic pain. *Drug Saf* 2003;26(13):951-73.

Infliximab (Remicade) and etanercept (Enbrel): serious infections and tuberculosis

Tumour necrosis factor-alpha (TNF-α) is a proinflammatory cytokine synthesized in response to infectious or inflammatory stimuli.[1] TNF-α antagonists have been shown to be effective in the treatment of signs and symptoms of rheumatoid arthritis and other autoimmune diseases.[1] Infliximab (Remicade) is indicated in adults for rheumatoid arthritis (in combination with methotrexate), Crohn's disease and fistulizing Crohn's disease.[2] Etanercept (Enbrel) is indicated for rheumatoid arthritis in adults and polyarticular juvenile rheumatoid arthritis in patients aged 4 to 17 years.[3]

Serious infections, particularly tuberculosis (TB), are recognized risks for patients receiving TNF-α antagonists, and warnings to that effect are prominent in the product monographs.[2,3] Many serious infections have occurred in patients taking immunosupressive therapy concomitantly, which, in addition to the underlying disease, could predispose them to infections.[2,3]

Health Canada received a total of 697 reports of suspected adverse reactions (ARs) to infliximab and 536 to etanercept from Jan. 1, 2000, to May 31, 2004 (Table 1). Reports of infection were considered serious when the infection was life threatening or resulted in death, disability, hospital admission or prolonged hospital stay (as defined in the *Food and Drug Regulations*). The types of serious infections are listed in Table 2. Reports of TB comprised those of new cases (infliximab 3, etanercept 0), reactivation of latent TB (infliximab 3, etanercept 0) and cases in which the patient was prescribed antituberculous medication (infliximab 4, etanercept 2). There were 4 reports of pulmonary or pleural TB (infliximab 4, etanercept 0), 4 reports of extrapulmonary TB (infliximab 4, etanercept 0) and 4 reports in which the type of TB was not specified (infliximab 2, etanercept 2).

A number of registries have been established to assist in assessing the long-term safety and efficacy of TNF-α antagonists.[4,5] In France the program is particularly interested in infections and lymphomas.[4] In Alberta a systematic approach has been developed to collect data on effectiveness and ARs for all

Table 1: Reports submitted to Health Canada of infections suspected of being associated with infliximab and etanercept from Jan. 1, 2000, to May 31, 2004*

Variable	Infliximab	Etanercept
Total no. of AR reports	697	536
No. of AR reports with infection	188	109
No. of AR reports with serious infection (no. of deaths†)	132 (14)	82 (7)

Note: AR = adverse reaction.
***These data cannot be used to determine the incidence of ARs or to make quantitative drug safety comparisons between the products because ARs are underreported and neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.**
†Causality assessment is difficult because of multiple factors such as confounding factors, complexity of the cases as well as the quality and the completeness of the information included in the reports.

Table 2: Types of serious infections described in the reports submitted to Health Canada for infliximab and etanercept from Jan. 1, 2000, to May 31, 2004*

Type of infection†‡	Infliximab	Etanercept
Abscess	20	10
Cellulitis	11	3
Encephalitis or meningitis	2	1
Fungal infections	14	2
Pneumonia	36	30
Pyelonephritis or cystitis	7	8
Sepsis	36	15
Septic arthritis	7	4
Tuberculosis	10	2

***These data cannot be used to determine the incidence of ARs or to make quantitative drug safety comparisons between the products because ARs are underreported and neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.**
†Because of limited information in the reports, some infections could not be classified and are not included.
‡Several infection types (reaction terms) may be listed per AR report. Reaction terms are based on the *World Health Organization Adverse Reaction Dictionary* (WHOART).

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.

Alberta patients receiving these agents for the treatment of rheumatoid arthritis.[5]

Health care professionals are reminded of the following important safety information included in the Enbrel and Remicade product monographs:[2,3]

- Caution should be exercised when considering the use of TNF-α antagonists in patients with chronic infection, a history of recurrent or latent infection, including TB, or an underlying condition that may predispose them to infection.
- TNF-α therapy should not be initiated in patients with a clinically important, active infection.
- New infections should be closely monitored and therapy discontinued if the infection becomes serious.

Patients should be instructed in how to recognize early signs and symptoms of infection and be advised to seek medical attention when they occur.

Heather Dunlop, MLIS, RN, Health Canada

References

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3. *Enbrel (etanercept)* [product monograph]. Thousand Oaks (CA): Immunex Corp.; 2003. Distributed by Amgen Canada Inc., Mississauga (ON) and Wyeth Canada, Montréal (QC).
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Products containing bitter orange or synephrine: suspected cardiovascular adverse reactions

Products containing bitter orange (*Citrus aurantium*) or synephrine are used for their claims of promoting weight loss. However, these products are not authorized by Health Canada for this indication. Synephrine, the main active compound in bitter orange, is claimed to increase metabolism and promote thermogenesis.[1] Although their effectiveness remains unclear,[1] many products containing bitter orange are being promoted as "*Ephedra*/ephedrine free," since the use of *Ephedra* has been restricted in Canada[2] and prohibited in dietary supplements in the United States[3] owing to adverse cardiovascular and cerebrovascular reactions.

Synephrine, a sympathetic α-adrenergic agonist, is structurally related to ephedrine; thus bitter orange extract may be associated with a spectrum of adverse reactions (ARs) similar to those associated with the use of *Ephedra*/ephedrine.[4] In animals, synephrine use has been associated with dose-related cardiotoxicity, specifically ventricular arrhythmias.[5] A case of myocardial infarction in a patient with no history of heart disease has been reported in association with synephrine-containing products.[6] Health Canada issued an advisory on a natural health product containing synephrine and other stimulants, cautioning that synephrine may have cardiovascular effects similar to those of ephedrine.[4] Synephrine's cardiovascular effects may be increased when combined with other stimulants such as caffeine.[7] Previously, Health Canada warned consumers about using *Ephedra* products containing caffeine, for the same reasons,[2] and other reviews have reiterated this safety concern.[8]

From Jan. 1, 1998, to Feb. 28, 2004, Health Canada received 16 reports in which products containing bitter orange or synephrine were suspected of being associated with cardiovascular ARs, including tachycardia, cardiac arrest, ventricular fibrillation, transient collapse and blackout. All cases were considered serious. One involved a suspect product containing bitter orange but no caffeine or *Ephedra*/ephedrine. In 7 cases the suspect product also contained caffeine, and in 8 cases the suspect product also contained both *Ephedra*/ephedrine and caffeine. Two of the 16 patients died, both of whom had taken products containing *Ephedra*/ephedrine and caffeine in addition to bitter orange. Evaluation of these reports is challenging because of many factors such as the lack of information on the ingested dose of synephrine, the contributory effects of other (multiple) ingredients such as *Ephedra* and caffeine, and the ambiguity of the reported information.

Consumers need to be aware of the potential serious ARs when using these products containing bitter orange or synephrine and may wish to consult their health care providers with regard to their use. Health care professionals

New brochure on adverse reaction reporting

Health Canada has developed a new brochure on adverse reaction reporting by health care professionals and consumers. The brochure covers **what** and **when** to report, **how** to submit a report, and **how** to access safety information on marketed health products on the Internet by subscribing to Health Canada's *Health_Prod_Info* mailing list. This handy 1-page brochure can be posted in your institution for ease of reference.

You can print it from the Internet at
www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/ar_reporting_brochure_e.pdf.

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.

are encouraged to ask their patients to list the natural health products they are taking and report to Health Canada any suspected ARs related to the use of such products, including those claiming to promote weight loss.

Scott Jordan, PhD, Mano Murty, MD, CCFP, FCFP, and Karen Pilon, RN, Health Canada

References

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2. *Health Canada reminds Canadians of the dangers of Ephedra/ephedrine products*. Ottawa: Health Canada; 2003 June 9. Available: www.hc-sc.gc.ca/english/protection/warnings/2003/2003_43.htm (accessed 2004 July 5).
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Case presentations

Recent Canadian cases are selected based on their seriousness, frequency of occurrence or the fact that the reactions are unexpected. Case presentations are considered suspicions and are presented to stimulate reporting of similar suspected adverse reactions.

Ibutilide (Corvert): suspected association with torsades de pointes

A 52-year-old man with no prior history of cardiac disease presented to an emergency department with atrial fibrillation and congestive heart failure. Concomitant medications reported were metoprolol and diltiazem. The potassium level was 4 (normally 3.5–5.0) mmol/L, and the cardiac troponin level was elevated. A decision to proceed with pharmacologic cardioversion was made, and 2 doses of intravenous Corvert (ibutilide) were administered. Sustained torsades de pointes developed, and electrocardioversion was performed immediately. The patient's sinus rhythm reverted to normal, but without mechanical cardiac output. Advance cardiac life support manoeuvres were unsuccessful, and the patient died. He had no known contraindications to the use of ibutilide. The autopsy revealed coronary artery disease and aortic valvular stenosis, neither of which are noted contraindications to the use of Corvert.

Ibutilide is a class III antiarrhythmic drug indicated for the conversion of atrial flutter or atrial fibrillation to sinus rhythm, to be considered as an alternative to electrocardioversion. The potential for ibutilide to induce further arrhythmia is prominently labelled in the product monograph.[1]

Reference

1. *Corvert Injection (ibutilide fumarate injection)* [product monograph]. Kirkland (QC): Pfizer Canada Inc; 2003.

Tubersol and anaphylaxis

A 36-year-old woman experienced an anaphylactic reaction following a Tubersol (Tuberculin Purified Protein Derivative [Mantoux]) skin test. The tuberculin skin test was administred at 11:15 am. By 11:18 am the injection site was red, raised and very itchy, with swelling of more than 5 cm in diameter. At 11:22 am the patient's face was flushed and red, her lips had begun to swell, and she experienced a tingling sensation around the mouth. At 11:43 am the patient was feeling lightheaded and was experiencing nausea, intermittent hoarse voice, flushed face and tingling of mouth. At 11:45 am the patient was given 0.5 mL Adrenalin, and at 12:05 pm she was transported to the hospital. All symptoms resolved. The patient was kept in the emergency department for 2 hours and then sent home. It was reported that she had no previous tuberculin skin test. She did have a history of anaphylactic reactions to seafood and strawberries, but these foods had not been consumed on the day of the reaction.

Summary of health professional and consumer advisories posted from May 18, 2004, to Aug. 31, 2004
(advisories are available at www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_advisories_e.html)

Date	Product	Subject and type
Aug 16	TracheoSoft	Mallinckrodt, a division of Nellcor/Tyco Healthcare Issues Recall of TracheoSoft XLT Extended Length Tracheostomy Tube — consumer information
Aug 9	SSRIs and other anti-depressants	Health Canada advises of potential adverse effects of SSRIs and other anti-depressants on newborns — consumer information
July 30 & 27	Rituxan	Possible association of Rituxan (rituximab) with hepatitis B reactivation — Hoffmann–La Roche Limited — consumer information and health professional communication
July 26	Aristolochic Acid	Health Canada advises consumers not to use the products containing Aristolochic Acid — consumer information
Jul 23	Sesa	Health Canada warns Canadians not to use Sesa Hair Supplement — consumer information
July 20	Taxus Express and Express	Recall Taxus Express coronary stent systems and Express coronary stent systems — Boston Scientific — health professional communication
July 8 & June 30	Desyrel	Association of Desyrel (trazodone) with drug interactions with medications that alter CYP 3A4 metabolism — Bristol-Myers Squibb Canada — consumer information and health professional communication
June 29	Star Anise	Health Canada advises consumers not to ingest teas or health products containing Star Anise unless it is identified as Chinese Star Anise — consumer information
June 23	Clozapine	Health Canada releases important information on the dispensation of clozapine products in Canada — consumer information, health professional communication and notice to hospitals
June 21	Arava	Arava (leflunomide) and lung inflammation causing difficulty breathing — Aventis Pharma Inc. — consumer information and health professional communication
June 21 & 15	Crestor	Important safety information regarding the association between Crestor (rosuvastatin) and rhabdomyolysis — AstraZeneca Canada Inc. — consumer information and health professional communication
June 18 & 1	Pre-Pen	Health Canada advises health professionals and consumers about penicillin allergy test recall on Pre-Pen (benzylpenicilloyl polylysine injection USP) — Omega Laboratories Ltd. — consumer information and health professional communication
June 10	Hemodialysis equipment	Important safety information on hemodialysis units and blood tubing sets incorporating a transducer protector — notice to hospitals
June 8	CIDEX OPA Solution	Possibility of sensitization to CIDEX OPA Solution with repeated exposure — Johnson & Johnson Inc. — health professional communication
June 4 & 1	Proglycem Suspension	Health Canada is advising health professionals and patients regarding the recall of specific batches of Proglycem Suspension — Schering Canada Inc. — consumer information and health professional communication
June & May	SSRIs and other newer anti-depressants	Important drug safety information: warning for SSRIs and other newer anti-depressants regarding the potential for behavioural and emotional changes, including risk of self-harm — consumer information and health professional communication • Wellbutrin SR and Zyban (bupropion HCl) — Biovail Pharmaceuticals Canada • Remeron and Remeron RD (mirtazapine) — Organon Canada Ltd. • Luvox (fluvoxamine maleate) — Solvay Pharma Inc. • Zoloft (sertraline hydrochloride) — Pfizer Canada Inc. • Effexor and Effexor XR (venlafaxine) — Wyeth Pharmaceuticals • Paxil (paroxetine): — GlaxoSmithKline Inc. • Prozac (fluoxetine hydrochloride) — Eli Lilly Canada Inc. • Celexa (citalopram hydrobromide) — Lundbeck Canada Inc.
May 28	Thermonex	Health Canada warns Canadians not to use Thermonex — consumer information
May 21	Bell Magnum Bullet	Health Canada warns public not to use Bell Magnum Bullet — consumer information

To receive the Newsletter and health product Advisories free by email, join Health Canada's ***Health_Prod_Info*** mailing list.
Go to **www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/subscribe_e.html**.

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.

Reporting adverse reactions

Health professionals and consumers may report adverse reactions (ARs) to health products (pharmaceuticals, biologics, radiopharmaceuticals and natural health products) marketed in Canada toll free:

Tel: 866 234-2345 • Fax: 866 678-6789

Calls will automatically be routed to the appropriate Regional or National AR Centre. Copies of the AR Reporting Form are available from the Regional or National AR Centre (see addresses below), the *Canadian Compendium of Pharmaceuticals and Specialties* (*CPS*) and the Health Canada Web site (www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/adverse_e.pdf).

British Columbia
British Columbia Regional AR Centre
c/o BC Drug and Poison Information Centre
1081 Burrard St.
Vancouver BC V6Z 1Y6
adr@dpic.ca

Saskatchewan
Saskatchewan Regional AR Centre
c/o Saskatchewan Drug Information Service
College of Pharmacy and Nutrition
University of Saskatchewan
110 Science Place
Saskatoon SK S7N 5C9
sask.ar@usask.ca

Ontario
Ontario Regional AR Centre
c/o LonDIS Drug Information Centre
London Health Sciences Centre
339 Windermere Rd.
London ON N6A 5A5
adr@lhsc.on.ca

Québec
Québec Regional AR Centre
c/o Drug Information Centre
Hôpital du Sacré-Coeur de Montréal
5400, boul. Gouin ouest
Montréal (QC) H4J 1C5
pharmacovigilance.hsc@ssss.gouv.qc.ca

Atlantic
Atlantic Regional AR Centre
For New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland and Labrador
c/o Queen Elizabeth II Health Sciences Centre
Drug Information Centre
2421–1796 Summer St.
Halifax NS B3H 3A7
adr@cdha.nshealth.ca

All other provinces and territories
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9
Tel: (613) 957-0337; Fax: (613) 957-0335
cadrmp@hc-sc.gc.ca

Reporting adverse events associated with medical devices
Health Products and Food Branch Inspectorate
Health Canada
AL 3002C
Ottawa ON K1A 0K9
Medical Devices Hotline:
800 267-9675

Visit Health Canada's Web site to obtain copies of the Medical Devices Problem Report Form (www.hc-sc.gc.ca/hpfb/inspectorate/md_pro_rep_form_tc_e.html) and guidelines on mandatory and voluntary problem reporting for medical devices (www.hc-sc.gc.ca/hpfb/inspectorate/man_vol_pro_rep_md_entire_e.html).

Canadian Adverse Reaction Newsletter

Marketed Health Products Directorate
AL 0701B
Ottawa ON K1A 0K9
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Fax 613 952-7738

Health professionals/consumers report toll free:

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Email: cadrmp@hc-sc.gc.ca

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