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Canadian Adverse Reaction Newsletter

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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

Form available at:

www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/form/index_e.html

Oseltamivir (Tamiflu) and warfarin: suspected increase in INR

Oseltamivir (Tamiflu), an antiviral drug marketed in Canada since 1999, is indicated for the treatment of acute illness due to influenza infection in patients 1 year and older who have been symptomatic for no more than 2 days.[1] The drug is also indicated for the prevention of influenza illness in people over 13 years of age after close contact with an infected individual.

From Jan. 1, 1999, to Oct. 31, 2005, Health Canada received 19 reports of increased international normalized ratio (INR) suspected of being associated with the use of oseltamivir. These 19 reports involved patients aged 46 to 92 years (median age 84 years), and the indication for use of oseltamivir was either treatment or prophylaxis of influenza. All of the patients were taking warfarin. The reported onset of the adverse reaction ranged from the day treatment was started to 11 days after starting oseltamivir. The increased INR ranged from 3.2 to 10.9. Eleven of the reports were submitted by the same source and described a suspected interaction between oseltamivir and warfarin. Creatinine clearances were provided in these cases; dosage adjustments of oseltamivir were necessary in 3 cases, as recommended in patients with a creatinine clearance rate of 10–30 mL/min.[1] Six patients required treatment with vitamin K. At the time of reporting, 12 patients had recovered, 2 patients had not yet recovered, and the outcome was unknown for the remaining 5 patients.

Causality assessment of these cases is difficult because some of the reports presented conflicting or insufficient clinical information, and numerous factors (e.g., diet, medical conditions, fever) are known to influence a patient's response to anticoagulants.[2] In 3 cases, the warfarin dose was increased after the introduction of oseltamivir; the increases in INR occurred following these dose changes. In 3 other cases, decreases in INR occurred during the course of oseltamivir therapy without a reported change in warfarin dose. In 2 cases, clarithromycin and levofloxacin respectively were reported as co-suspect medications; these drugs are known to interact with warfarin and may cause increases in INR.[3,4]

Available data indicate that the potential for drug interactions with oseltamivir is minimal.[5] Oseltamivir requires conversion to the active metabolite via esterases, located predominately in the liver.[1] Drug interactions involving this pathway have not been commonly documented.[1,5] The drug does not

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interact with substrates of various cytochrome P450 isoenzymes.[5] Oseltamivir is not extensively protein bound and, as a result, is not expected to contribute to drug interactions involving protein-binding displacement. In addition, clinically important drug interactions involving competition for renal tubular secretion are unlikely.[1]

As with any drug prescribed to patients taking warfarin, more frequent monitoring of INRs may be prudent when oseltamivir is prescribed concurrently with warfarin. Health Canada continues to monitor adverse reactions suspected of being associated with the use of oseltamivir. Health care professionals are encouraged to report any cases of INR fluctuation in patients receiving warfarin and oseltamivir concomitantly.

Sally Pepper, BScPhm; Hima Murty, MDCM, CCFP, Health Canada

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2. *Coumadin (warfarin)* [product monograph]. Montréal: Bristol-Myers Squibb Canada Inc.; 2002.
3. *Levaquin (levofloxacin)* [product monograph]. Toronto: Janssen-Ortho Inc.; 2005.
4. *Biaxin (clarithromycin)* [product monograph]. St-Laurent (QC): Abbott Laboratories Limited; 2003.
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Levonorgestrel-releasing intrauterine system (Mirena) and uterine perforation

The levonorgestrel-releasing system Mirena, an intrauterine device (IUD), consists of a polyethylene T-shaped frame with a reservoir containing levonorgestrel.[1] Mirena is indicated for use as a contraceptive and, after insertion into the uterus, continuously releases levonorgestrel at a low daily dose for up to 5 years. Mirena's contraceptive action is due mainly to local progestogenic effects on the uterine cavity, including a strong antiproliferative effect on the endometrium and a thickening of the cervical mucus, which prevents the passage of sperm. Ovulation is inhibited in some women. As of Nov. 28, 2005, the product monograph (PM) states that perforation or penetration of the uterus or cervix may occur during insertion but that this is very rare (less than 1 in 10 000). It also states that postpartum insertions should be postponed until 6 weeks after delivery.

From Feb. 22, 2001 (the date of marketing in Canada), to Sept. 26, 2005, Health Canada received 26 reports of uterine perforation suspected of being associated with the use of Mirena. In 8 of the cases, Mirena was inserted between 6 weeks and 6 months post partum. A long-term prospective study of Mirena found a higher uterine perforation rate (0.9 per 1000 insertions) than that described in the PM.[2] With copper IUDs, the rate of uterine perforation has been 0.6–1.6 per 1000 insertions.[3,4] In addition, evidence suggests that women who have IUDs inserted in the first 6 months post partum are at increased risk of uterine perforation.[5] This elevated risk may be due to the soft consistency of the uterus and the underestimated variability in uterine size during the first 6 months post partum.

Uterine perforation is a rare but serious complication of IUD insertion that occurs or is initiated at the time of insertion.[3] Evidence indicates that the rate of uterine perforation is lower in cases where the health care professional inserting the IUD has performed at least 10 previous insertions.[4] Currently, there is a shortage of health care providers trained in IUD insertion; access to good knowledge, proper equipment and a mentor to demonstrate and supervise several insertions are prerequisites to providing this service.[3,6]

Health care professionals inserting the levonorgestrel-releasing intrauterine system are encouraged to take this information into account. Special care should be taken with postpartum insertion, since perforations of the uterus have been reported.[7]

Andrew Gaffen, BSc, DDS; Gina Coleman, MD, Health Canada.

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Guidance document for industry: issuance of health product safety communications

Health Canada is pleased to announce the release of the final *Guidance Document for Industry — Issuance of Health Professional Communications and Public Communications by Market Authorization Holders (MAH)*. Health Professional Communications (HPCs) and Public Communications (PCs) are one of the principal means used by industry to communicate new information about safety and therapeutic effectiveness of marketed health products to health care professionals and the public in a timely manner. This guidance document clarifies the roles and responsibilities, the issuance process, the content and the timelines to assist MAHs in developing and disseminating HPCs and their accompanying PCs.

In August 2004, a draft version of this document was released for stakeholder consultation. A total of 183 comments were submitted by stakeholders, including pharmaceutical companies, pharmaceutical associations and academic centres. The comments were related to technical issues, clarifications and other issues. The final version of the guidance document has been updated in light of these comments. The Marketed Health Products Directorate would like to thank all those who participated in the consultation.

The final version of the guidance document is available on the new Health Canada website, MedEffect (www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/index_e.html).

Safe use of energy drinks

There are many "energy drink" products currently sold in Canada. They are available in corner stores, gas stations and bars, usually displayed alongside soft drinks, juices and sports drinks. Excessive intake of "energy drinks" or mixing them with alcohol can have serious health effects. Health Canada received 4 reports of adverse reactions involving "energy drinks." The reported symptoms included electrolyte disturbances, heart irregularities, nausea and vomiting. More information on this topic is available in the *It's Your Health* article at **www.hc-sc.gc.ca/iyh-vsv/prod/energy-energie_e.html**

Case presentation

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.

Rosiglitazone (Avandia): suspected association with parotid gland enlargement

Health Canada has received 5 reports of parotid enlargement suspected of being associated with the use of rosiglitazone (Avandia). The cases involved 1 man and 4 women (age range 53 to 72, age not specified in 1 case). Some reports indicated multiple concomitant medications and a complex medical history. Four of the cases involved bilateral parotid enlargement, and 1 had enlargement of the parotid gland to 5 times its normal size. In 1 of the cases, swelling of the submandibular glands occurred as well, and in another case, parotiditis was considered as a differential diagnosis. The reaction onset was reported in 4 of the cases and ranged from 6 to 11 months after the start of the rosiglitazone therapy. The reaction was reported as painless in 3 cases. Upon withdrawal of the rosiglitazone therapy, 1 case reported improvement in 1 week, and in another case, there was gradual resolution of the reaction over 4 months. The outcome was not stated in 2 reports, and in the remaining case, the patient had not yet recovered at the time of reporting.

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.

Summary of health professional and consumer advisories posted from Aug. 24 to Nov. 15, 2005
(advisories are available at www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/index_e.html)

Date	Product	Subject and type
Nov 10	Instant thermometers	Potential safety risk — consumer information
Nov 9	Weight loss products	Warning not to use certain weight loss products from China — consumer information
Nov 5	GenTeal Artificial Tears	Warning not to use Lot 51436 of GenTeal Artificial Tears — consumer information
Oct 31 & 5	Implantable medical devices	Interactions: active implantable medical devices and systems and other medical devices — notice to hospitals — notice to hospitals (revision)
Oct 25	Liqiang 4	Warning not to take Liqiang 4 — consumer information
Oct 25	Baxter infusion pumps	Important safety information — notice to hospitals
Oct 19	Gamunex	Hemolytic reactions — Talecris Biotherapeutics Inc. (Bayer Inc., Canadian distributor and importer) — notice to hospitals and consumer information
Oct 14	Flomax	Intraoperative floppy iris syndrome — Boehringer Ingelheim (Canada) Ltd. — health professional communication
Oct 6	Cardiac defibrillators	Safety information: implantable cardiac defibrillators — St. Jude Medical Canada, Inc. — health professional communication
Oct 6 & Sept 29	Paxil	Possible increased risk of birth defects — GlaxoSmithKline Inc. — consumer information and health professional communication
Oct 4	Long-acting β_2 agonists	Safety information about a class of asthma drugs — consumer information
Sept 29 & 28	Strattera	Potential for behavioral and emotional changes, including risk of self-harm — Eli Lilly Canada Inc. — consumer information and health professional communication
Sept 28	Kohl products	Traditional kohl products contain lead — consumer information
Sept 22	Insignia and Nexus pacemakers	Safety information: implantable pacemakers — Guidant Canada Corporation — health professional communication
Sept 21	Nimotop	Inappropriate administration of Nimotop capsules — Bayer Inc. — notice to hospitals
Sept 21	Celebrex	Important safety information — Pfizer Canada Inc. — consumer information and health professional communication
Sept 19	Linvatec surgical handpieces	Important safety information — notice to hospitals
Sept 16	Blood glucose monitors	Important safety information — Abbott Diabetes Care — consumer information
Sept 16 & 13	Duragesic	Important safety information — consumer information and health professional communication
Sept 8	Metallic airway stents	Important safety information — notice to hospitals
Sept 8 & Aug 31	Thioridazine	Important safety information — consumer information and health professional communication
Sept 7	Oxeze Turbuhaler	Important safety information — AstraZeneca Canada Inc. — health professional communication
Sept 7	Foradil	Important safety information — Novartis Pharmaceuticals Canada Inc. — health professional communication
Sept 7	Serevent	Important safety information — GlaxoSmithKline Inc. — health professional communication
Aug 31	Adderall XR	Safety information and Report of the Adderall XR New Drug Committee — Shire BioChem Inc. — health professional communication
Aug 26	Iressa 250 mg tablets	Important safety information — AstraZeneca Canada Inc. — consumer information and health professional communication
Aug 24	Adderall XR	Health Canada allows Adderall XR back on the Canadian market — consumer information

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MedEffect e-Notice

MedEffect e-Notice is the new name that replaces Health Canada's Health_Prod_Info mailing list. Subscribers will continue to receive notices of new safety advisories on health products along with the *Canadian Adverse Reaction Newsletter*. Thus, the content of the e-notices will remain the same and are now part of MedEffect, a new Health Canada Web site dedicated to adverse reaction information and reporting. MedEffect can be visited 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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