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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

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Oral fluoroquinolones and retinal detachment

Key points

- According to a pharmacoepidemiological study, current use of oral fluoroquinolones was associated with an increased risk of developing retinal detachment.
- Health Canada received one report of retinal detachment suspected of being associated with an oral fluoroquinolone.
- Health care professionals are encouraged to report to Health Canada any adverse reactions suspected of being associated with oral fluoroquinolones, and related to the development of retinal detachment.

Oral fluoroquinolones are broad-spectrum antibacterial drugs indicated for the treatment of infections caused by susceptible strains of microorganisms.[1-5] In Canada, there are 5 marketed oral fluoroquinolones: ciprofloxacin (first marketed in 1996), levofloxacin (1997), moxifloxacin (2000), norfloxacin (1986), and ofloxacin (1990). The risk of retinal detachment is not described in any of the oral fluoroquinolone Canadian product monographs.

Retinal detachment is characterized by a separation of the retina from the underlying tissue in the eye.[6] Among the different types of retinal detachment, rhegmatogenous retinal detachment (RRD) is the most common. RRD results from retinal breaks caused by vitreoretinal traction. Risk factors commonly associated with retinal detachment include advancing age, previous cataract surgery, myopia and trauma. Patients generally present with symptoms such as light flashes, floaters, peripheral visual field loss and blurred vision. Retinal detachment is a serious medical emergency that generally requires prompt surgical intervention.[6,7]

According to a pharmacoepidemiological study, current use of oral fluoroquinolones was associated with an increased risk of developing retinal detachment.[7] Ophthalmic fluoroquinolones were excluded from the study to avoid reverse causality bias. The study identified 445 cases of retinal detachment involving oral fluoroquinolone use in a cohort of 989 591 patients from British Columbia who visited an ophthalmologist between January 2000 and December 2007. Further research is needed to confirm whether there is a potential association between retinal detachment and fluoroquinolones as well as to clarify the mechanism of action.

As of Dec. 31, 2012, Health Canada received one report of retinal detachment suspected of being

associated with the use of an oral fluoroquinolone. The report described a 52-year-old woman who experienced retinal detachment after a course of ciprofloxacin prescribed to treat a bladder infection. Limited evidence linking retinal detachment to oral fluoroquinolones may explain the low level of reporting to Health Canada.

Health care professionals are encouraged to report to Health Canada any adverse reactions (ARs) suspected of being associated with oral fluoroquinolones, and related to the development of retinal detachment. Information such as treatment duration, dosage, current or previous exposure to oral fluoroquinolones, as well as symptoms related to retinal detachment such as light flashes, floaters and peripheral visual field loss are important to include when reporting ARs. This information may help to further evaluate AR reports related to retinal detachment suspected of being associated with oral fluoroquinolone use.

Alain Beliveau, PhD, Health Canada

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Adverse reaction and incident reporting—2012

Canada Vigilance Program

The Canada Vigilance Program collects reports of suspected adverse reactions (ARs) to health products (pharmaceuticals, biotechnology products, blood products and biologics, natural health products, radiopharmaceuticals, and cells, tissues and organs). Further information about the program and its database can be found at www.health.gc.ca/medeffect.

Domestic and foreign AR reports

In 2012, Health Canada received 53 109 domestic AR reports,* of which 79% were considered to be serious.† Domestic AR reports received by product type are provided in Table 1. The 53 109 reports represent 36 101 AR cases. A case consists of all information describing the AR(s) experienced by one patient at one time and suspected of being related to the use of one or more health products; thus, an AR case will include an initial AR report as well as any subsequent additional information received as follow-up report(s).

Table 1: Number of domestic reports* of adverse reactions by product type in 2012

Product type	No. (%) of reports	
Pharmaceuticals	30 634	(57.7)
Biotechnology products	20 146	(37.9)
Blood products and biologics	1 157	(2.2)
Natural health products	683	(1.3)
Radiopharmaceuticals	440	(0.8)
Cells, tissues and organs	49	(0.1)
Total	53 109	(100.0)

* Canada Vigilance receives reports for both initial and follow-up information concerning suspected adverse reactions.

*This excludes AR reports received for product types that do not fall under the review of the Canada Vigilance Program. These reports were redirected to the appropriate AR reporting program.

†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".

In Canada, Market Authorization Holders (MAHs) are required to submit AR reports received in accordance with the requirements of the *Food and Drugs Act* and Regulations. MAHs are required to send, within 15 days, all reports of serious ARs that have occurred in Canada (domestic) and all reports of serious unexpected ARs‡ that have occurred outside Canada (foreign) to the Canada Vigilance Program. In 2012, MAHs submitted 84.4% of all the domestic reports received. The remaining reports were received directly from the community and hospitals (Table 2).

The number of domestic AR reports was 26.7% higher in 2012 than in 2011 (Fig. 1). Most of the domestic reports received by both MAHs and Health Canada originated from health care professionals (Table 3).

In 2012, the number of foreign AR reports received from MAHs was 542 052 (Fig. 2). These reports are not included in the Canada Vigilance database.

Table 2: Number of domestic reports* of adverse reactions by source in 2012

Source	No. (%) of reports
MAH	44 810 (84.4)
Community†	6 994 (13.2)
Hospital	1 256 (2.4)
Other	49 (0.1)
Total	53 109 (100.0)

Note: MAH = Market Authorization Holder.
* Canada Vigilance receives reports for both initial and follow-up information concerning suspected adverse reactions.
†Consumer, patient and non-hospital–based health care professionals.

Table 3: Number of domestic reports* of adverse reactions by type of originating reporter in 2012

Reporter type	No. (%) of reports
Health professional†	17 947 (33.8)
Consumer or other non-health professional	16 205 (30.5)
Physician	13 344 (25.1)
Pharmacist	5 544 (10.4)
Lawyer	69 (0.1)
Total	53 109 (100.0)

* Canada Vigilance receives reports for both initial and follow-up information concerning suspected adverse reactions.
†Other health professional or type not specified.

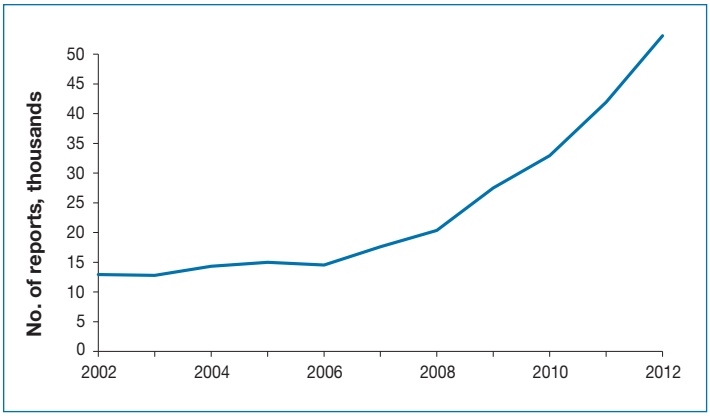

Fig. 1: Number of domestic reports of adverse reactions received by Health Canada from 2002 to 2012

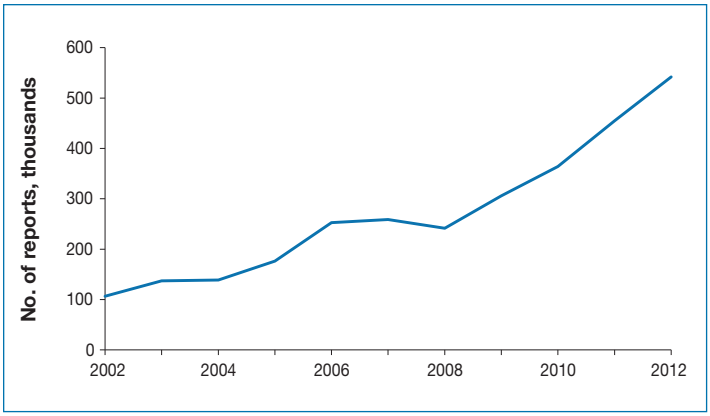

Fig. 2: Number of foreign reports of adverse reactions received by Health Canada from Market Authorization Holders from 2002 to 2012

‡In the *Food and Drugs Act* and Regulations, a serious unexpected AR is defined as "a serious adverse drug reaction that is not identified in nature, severity or frequency in the risk information set out on the label of the drug".

Sex and age

The distribution for the 36 101 cases by sex was 58% female, 36% male and 6% sex unknown. The distribution by age group was 5% pediatric (< 19 years), 52% adult (19–64 years), 26% elderly (≥ 65 years) and 17% age unknown.

Suspect products

The top 10 groups of suspect products most commonly identified in AR reports are listed in Table 4. Anatomical Therapeutic Chemical (ATC) groups are classified according to the World Health Organization's ATC classification system (www.whocc.no/atc_ddd_index). Several factors may influence the number of ARs reported for a specific health product or product type, such as length of time a product is on the market, volume of use, publicity of an AR, regulatory actions, method of data collection (reports submitted voluntarily versus organized data-collection systems). For example, ARs may be reported more frequently in organized data-collection systems (e.g., patient registries, surveys, patient support and disease management programs) and may affect the pattern of reporting. It is not possible to compare the risk of health products based solely on numbers of AR reports. In addition, rare and serious reactions may not necessarily represent a large number of reported ARs.

Table 4: Top 10 groups of suspect health products most commonly reported in 2012, by Anatomical Therapeutic Chemical (ATC) group*

Health product (ATC group)	No. (%) of times reported†
Immunosuppressants (L04)	12 155 (28.5)
Antineoplastic agents (L01)	3 755 (8.8)
Analgesics (N02)	1 790 (4.2)
Drugs for treatment of bone diseases (M05)	1 764 (4.1)
Psycholeptics‡ (N05)	1 716 (4.0)
Psychoanaleptics‡ (N06)	1 588 (3.7)
Antithrombotic agents (B01)	1 493 (3.5)
Agents acting on the renin–angiotensin system (C09)	1 341 (3.1)
Antibacterials for systemic use (J01)	1 138 (2.7)
Drugs for obstructive airway diseases (R03)	1 030 (2.4)

* Solicited reports or organized data-collection systems (e.g., patient registries, surveys, patient support and disease management programs) may affect the total number of ARs reported for specific products or product types.

†One case may contain one or more suspect product(s). The total number of suspect health products reported was 42 669 in a total of 36 101 cases.

‡N05 psycholeptics: antipsychotics, anxiolytics, hypnotics and sedatives; N06 psychoanaleptics: antidepressants, psychostimulants, psycholeptics and psychoanaleptics in combination, anti-dementia drugs.

Adverse reactions

Table 5 displays the top 10 ARs reported to the Canada Vigilance Program, based on System Organ Class.§ The most commonly reported ARs were general disorders and administration site conditions, which include disorders that affect several body systems or sites (e.g., drug ineffective, fatigue, fever, edema, pain, reactions at the administration site). The next most common ARs were gastrointestinal disorders.

Conclusion

Health Canada would like to thank all who have contributed to the Canada Vigilance Program and encourages the continued support of postmarketing surveillance through AR reporting. The purpose of postmarket spontaneous reporting systems is the identification and analysis of new safety information for health products. Any ARs suspected of being associated with the use of health products can be reported to the Canada Vigilance Program (www.health.gc.ca/medeffect).

§Adverse reactions are coded using the *Medical Dictionary for Regulatory Activities* (MedDRA) Terminology. The terminology is organized in a hierarchical structure where the System Organ Class is the highest level of the hierarchy and represents the broadest concept of groupings. Further information about the MedDRA Terminology can be found at www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/meddra-eng.php.

Table 5: Top 10 adverse reactions reported in 2012, by System Organ Class*		
System Organ Class	No. (%) of times reported†	
General disorders and administration site conditions	22 617	(22.4)
Gastrointestinal disorders	11 183	(11.1)
Nervous system disorders	9 015	(8.9)
Investigations	6 397	(6.3)
Infections and infestations	6 075	(6.0)
Musculoskeletal and connective tissue disorders	5 735	(5.7)
Skin and subcutaneous tissue disorders	5 589	(5.5)
Psychiatric disorders	5 468	(5.4)
Respiratory, thoracic and mediastinal disorders	5 253	(5.2)
Injury, poisoning and procedural complications	5 169	(5.1)

* *Medical Dictionary for Regulatory Activities* (MedDRA) Terminology, version 15.1; reactions at preferred term level. Further information about the MedDRA terminology can be found at www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/meddra-eng.php.
†One case may contain one or more reaction(s). The total number of ARs reported was 101 205 in a total of 36 101 cases.

Medical device incidents

Medical device incident reports are collected by Health Canada and are entered into the Medical Devices System database. A major component of Health Canada's Medical Devices Program involves the collection, review and follow-up of incidents related to medical devices, which are reported to Health Canada via the submission of mandatory and voluntary problem reports. Manufacturers and importers are required to submit mandatory reports as per sections 59 to 61 of the Medical Devices Regulations. Voluntary reports are submitted mostly by health care professionals and patients/users.

In 2012, a total of 8 976 reports were entered into the Medical Device System database. Of these reports, 8 259 (92%) were domestic mandatory reports, 313 (3.5%) were foreign mandatory reports, and 404 (4.5%) were domestic voluntary reports.

A small reduction (2%) in the total number of reports received was noted for 2012, relative to the previous year. This change is primarily due to a decrease in foreign mandatory reports received by Health Canada. The number of domestic mandatory reports was slightly higher (1%) in 2012 compared with 2011. The majority of these mandatory reports were for incidents involving class II (29%) and class III (46%) medical devices (class IV being the highest-risk devices). The device categories representing the highest proportion of mandatory reports continue to be general hospital (29%) and cardiovascular (21%) devices.

The collection and maintenance of mandatory problem reports for medical devices is the responsibility of the Canada Vigilance—Medical Device Problem Reporting Program. For information on the submission of mandatory and voluntary reports for medical device incidents, please visit the Health Canada Web site (www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php).

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Quarterly summary of health professional and consumer advisories

(posted between February 18, 2013 and May 17, 2013)

Date*	Product	Subject
May 17	Diane-35 (cyproterone acetate and ethinyl estradiol)	Safety review completed
May 16	Rochefort, Rush and Amsterdam Special	May pose serious risks to health
May 14 & 16	Zithromax and Zmax SR (azithromycin)	Risk of potentially fatal irregular heart beats
May 8	Cathflo (alteplase)	Particulate matter observed in some vials: additional instructions for use
May 3 & 7	Alenti Lift and Hygiene chair	Risk of chair tipping and patient falls
May 3 & 7	FL14E Rose Bed	Risk of bed siderail collapse
Apr 29 & May 2	Avastin (bevacizumab)	Cases of necrotizing fasciitis reported
Apr 26 & May 1	Thalomid (thalidomide)	Risk of arterial blood clots
Apr 25	Clear Care, Aosept and Oxysept contact lens solutions	Risk of eye injury with improper use
Apr 19 & 24	Flolan (epoprostenol sodium)	Potential for glass-related particles in sterile diluent
Apr 16	Dexamethasone Sodium Phosphate Injection USP (dexamethasone phosphate)	Recall: presence of visible particles in some vials
Apr 12	Alysena-28 (levonorgestrel and ethinyl estradiol)	Additional lots recalled
Apr 9 & 12	Tasigna (nilotinib)	Possible risk of developing atherosclerosis-related conditions
Apr 4	Proton pump inhibitors	Risk of bone fractures
Apr 3 & 8	HomeChoice and HomeChoice PRO automated peritoneal dialysis systems	Important safety information
Mar 20 & 25	Tykerb (lapatinib ditosylate)	Updated information on efficacy
Mar 15	Libigrow	Unauthorized health product removed from sale
Mar 15	Fibrin sealants	Instructions for safe use
Mar 14	Rifadin (rifampin)	Recall: capsules under fill weight
Mar 8 & 15	Hospira infusion pumps	Important safety information
Mar 7	Sensipar (cinacalcet)	Unapproved use in children
Feb 27 & Mar 1	Samsca (tolvaptan)	Potential risk of liver damage
Feb 27	Catena (idebenone)	Voluntary withdrawal from the market
Feb 22 & 27	Incivek (telaprevir)	Serious skin reactions reported with combination treatment
Feb 22	18 Again and Stiff 4 Hours	Unauthorized health products removed from sale
Feb 21	Vega One French Vanilla	Recall: microbial contamination
Feb 20 & 25	Rituxan (rituximab)	Association with severe skin reactions
Feb 18	Viagra (sildenafil citrate) and Cialis (tadalafil)	Counterfeit products removed from sale in Toronto
Feb 18 to May 17	Foreign products	4 Foreign Product Alerts (FPAs) were posted during this period

Advisories can be accessed at www.health.gc.ca/medeffect.
*Date of issuance. This date may differ from the posting date.

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.