



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 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).

| 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.

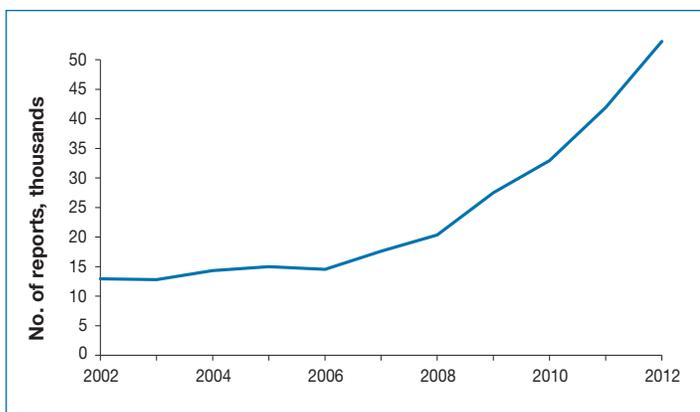


Fig. 1: Number of domestic reports of adverse reactions received by Health Canada from 2002 to 2012

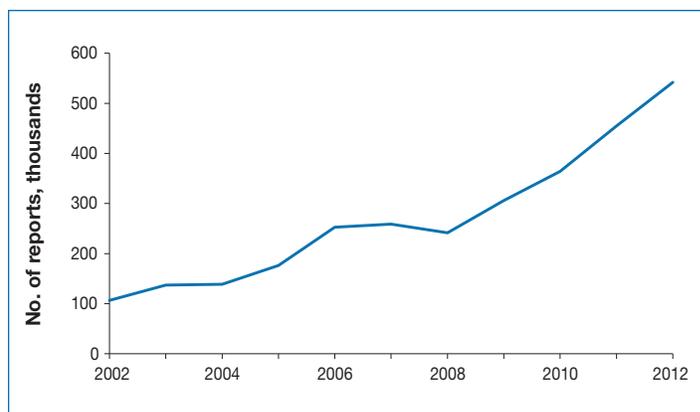


Fig. 2: Number of foreign reports of adverse reactions received by Health Canada from Market Authorization Holders from 2002 to 2012

[‡] 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.

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).

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 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.

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.

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 | Alyseno-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.

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Suggestions?

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

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