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Canadian Adverse Reaction Newsletter

Volume 20 • Issue 2 • April 2010

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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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Leflunomide and peripheral neuropathy

Key points

- Neuropathy has been reported in association with several disease-modifying antirheumatic drugs.
- During the last 7 years, additional data regarding the suspected association between peripheral neuropathy and leflunomide have emerged in the medical literature.
- In Canada, health care professionals have reported cases of peripheral neuropathy suspected of being associated with leflunomide.

Leflunomide is a disease-modifying antirheumatic drug (DMARD) indicated for use in adults with active rheumatoid arthritis.[1] It has been marketed in Canada since 2000 under the brandname Arava and is now also available as various generic products.

Peripheral neuropathy is an impairment of the peripheral motor, sensory or autonomic nervous system.[2] Signs and symptoms include muscular weakness or flaccid paralysis and sensory disturbances, including pain.[2] Neuropathy has been reported in association with several DMARDs, including sulfasalazine, chloroquine and penicillamine.[3,4]

During the last 7 years, several cases of peripheral neuropathy suspected of being associated with leflunomide have been published.[5–15] Patients had paresthesia or weakness, or both, in the upper or lower extremities, or both. In a few cases the symptoms were severe or debilitating.[12,13,15] The incidence of peripheral neuropathy has ranged from 1.4% to 10% in open studies to assess leflunomide neurotoxicity.[5–8] In these studies, the proportion of patients for whom this adverse reaction (AR) improved after discontinuation of the drug or reduction of the dosage ranged from 37% to 100%.

From the date of marketing to Oct. 31, 2009, Health Canada received 26 AR reports of peripheral neuropathy symptoms suspected of being associated with the use of leflunomide. Peripheral neuropathy was specified in 9 of the reports; the remaining 17 reports described signs and symptoms of peripheral neuropathy such as paresthesia, hypoesthesia or burning sensation of the skin. Of the 26 cases, 23 were reported by health care professionals and 22 were reported as serious.* There were 17 women and 7 men (sex not reported in 2 cases). The greater number of women could be explained by the fact that rheumatoid arthritis is 3 times more likely in women than in men.[16] Some confounding

*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."

factors reported in the cases included concomitant diseases (e.g., rheumatoid arthritis, diabetes) and concomitant drugs (e.g., methotrexate, hydroxychloroquine).

Electrophysiologic studies had been conducted in 4 of the 9 cases reported as peripheral neuropathy, and the results were positive in 3 cases. The duration of leflunomide therapy in these 9 cases varied from 2 months to 2 years. In 9 of the 26 cases, the reaction abated after stopping the drug.

Additional data regarding the suspected association between peripheral neuropathy and leflunomide has emerged during the past 7 years. Voluntary reporting to Health Canada is an important postmarketing surveillance tool to obtain valuable information about ARs to health products. Health care professionals are encouraged to report to Health Canada any cases of peripheral neuropathy suspected of being associated with leflunomide.

Patrice Tremblay, MD, Health Canada

References

1. *Arava (leflunomide)* [product monograph]. Laval (QC): sanofi-aventis Canada Inc.; 2006.
2. Council for International Organizations of Medical Sciences. *Reporting adverse drug reactions: definitions of terms, and criteria for their use*. Geneva: The Council; 1999. Available: www.cioms.ch/publications/reporting_adverse_drug.pdf (accessed 2009 Dec. 4).
3. Parker D Jr. Peripheral neuropathy. In: Tisdale JE, Miller DA, editors. *Drug-induced diseases: prevention, detection, and management.* Bethesda (MD): American Society of Health-System Pharmacists; 2005.
4. Argov Z, Mastaglia FL. Drug-induced peripheral neuropathies. *BMJ* 1979;1:663-6.
5. Bharadwaj A, Haroon N. Peripheral neuropathy in patients on leflunomide. *Rheumatology (Oxford)* 2004;43: 934.
6. Richards BL, Spies J, McGill N, et al. Effect of leflunomide on the peripheral nerves in rheumatoid arthritis. *Intern Med J* 2007; 37:101-7.
7. Metzler C, Arlt AC, Gross WL, et al. Peripheral neuropathy in patients with systemic rheumatic diseases treated with leflunomide. *Ann Rheum Dis* 2005;64:1798-800.
8. Martin K, Bentaberry F, Dumoulin C, et al. Peripheral neuropathy associated with leflunomide: Is there a risk patient profile? *Pharmacoepidemiol Drug Saf* 2007;16:74-8.
9. Bonnel RA, Graham DJ. Peripheral neuropathy in patients treated with leflunomide. *Clin Pharmacol Ther* 2004;75:580-5.
10. Adverse Drug Reactions Advisory Committee. Leflunomide and peripheral neuropathy. *Aust Adv Drug Reactions Bull* 2006;25:18-9.
11. Martin K, Bentaberry F, Dumoulin C, et al. Neuropathy associated with leflunomide: a case series. *Ann Rheum Dis* 2005;64:649-50.
12. Gabelle A, Antoine JC, Hillaire-Buys D, et al. [Leflunomide-related severe axonal neuropathy]. *Rev Neurol (Paris)* 2005;161:1106-9.
13. Carulli MT, Davies UM. Peripheral neuropathy: An unwanted effect of leflunomide? *Rheumatology (Oxford)* 2002;41:952-3.
14. Hill CL. Leflunomide-induced peripheral neuropathy: rapid resolution with cholestyramine wash-out. *Rheumatology* 2004;43:809.
15. Lormeau C, Vandecandelaere M, Gasseu N, et al. Neuropathies périphériques au cours d'un traitement par léflunomide: deux nouvelles observations. *Revue Rhu* 2003;70:1001.
16. Lipsky PE. Rheumatoid arthritis. In: Fauci AS, Braunwald E, Hauser SL, et al, editors. *Harrison's principles of internal medicine*. 17th ed. New York (NY): McGraw-Hill; 2008. p. e2083-e2091.

Adverse reaction and incident reporting — 2009

Canada Vigilance Program

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

In 2009, Health Canada received 27 496 domestic AR reports.* Of the domestic reports received, 74.9% were considered to be serious.† Domestic AR reports received by product type are provided in Table 1.

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 2009, MAHs submitted 69.4% 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 35.0% higher in 2009 than in 2008 (Fig. 1). The majority of

Table 1: Number of domestic reports of adverse reactions by product type in 2009*

Product type	No. (%) of reports
Pharmaceuticals	18 301 (70.2)
Biotechnology products	5 998 (23.0)
Biologics	833 (3.2)
Natural health products	516 (2.0)
Radiopharmaceuticals	379 (1.5)
Cells, tissues and organs	34 (0.1)
Total	26 061 (100.0)

*Canada Vigilance receives reports for both initial and follow-up information concerning suspected ARs to health products. Reports of ARs redirected to other programs are not included.

*This includes 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." 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."

domestic cases reported to both MAHs and Health Canada originated from health care professionals (Table 3).

The number of foreign AR reports received from MAHs was 305 847 (Fig. 2). At this time, foreign reports are not included in the Canada Vigilance database.

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. Any ARs suspected of being associated with the use of health products can be reported to the Canada Vigilance Program by one of the following methods:

- Call toll free at 1-866-234-2345
- Report online at www.healthcanada.gc.ca/medeffect
- Complete a Canada Vigilance Reporting Form and:
  - fax it toll free (1-866-678-6789) or
  - mail it to:
    Canada Vigilance Program
    Health Canada
    Address Locator 0701D
    Ottawa ON K1A 0K9

Postage-paid labels, the Canada Vigilance Reporting Form and the AR reporting guidelines ("Guidelines — Voluntary Reporting of Suspected Adverse Reactions to Health Products by Health Professionals and Consumers") are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca /medeffect. The reporting form is also located in the back of the *Compendium of Pharmaceuticals and Specialties* (CPS).

Table 2: Number of domestic reports of adverse reactions by source in 2009*

Source	No. (%) of reports
MAH	20 054 (77.0)
Community†	4 794 (18.4)
Hospital	1 120 (4.3)
Other	93 (0.3)
Total	26 061 (100.0)

Note: MAH = Market Authorization Holder.
*Canada Vigilance receives reports for both initial and follow-up information concerning suspected ARs to health products. Reports of ARs redirected to other programs are not included.
†Consumer, patient and non-hospital-based health care professionals.

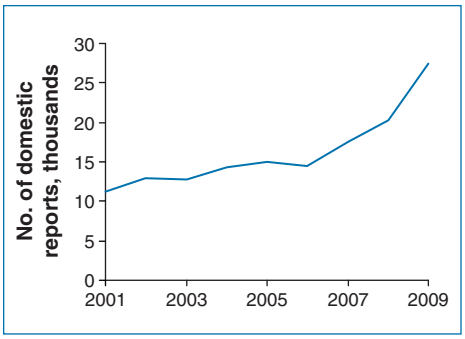

Fig. 1: Number of domestic reports of adverse reactions received by Health Canada from 2001 to 2009.

Table 3: Number of domestic reports of adverse reactions by type of originating reporter in 2009*

Reporter type	No. (%) of reports
Consumer/patient	8 428 (32.3)
Physician	6 064 (23.3)
Health professional†	4 364 (16.7)
Pharmacist	3 853 (14.8)
Nurse	2 906 (11.2)
Dentist	6 (0.02)
Naturopath	3 (0.01)
Other	437 (1.7)
Total	26 061 (100.0)

*Canada Vigilance receives reports for both initial and follow-up information concerning suspected ARs to health products. Reports of ARs redirected to other programs are not included.
†Type not specified in report.

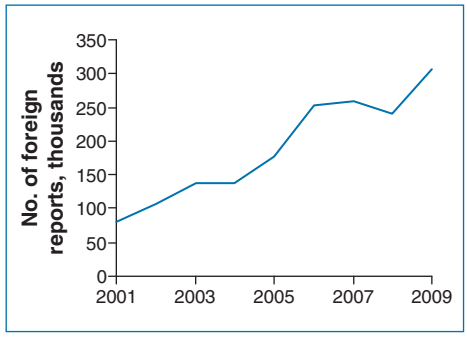

Fig. 2: Number of foreign reports of adverse reactions received by Health Canada from Market Authorization Holders from 2001 to 2009.

Medical device incidents

Medical device incidents are collected by the Health Products and Food Branch Inspectorate and are entered into the medical device system. The Inspectorate is responsible for compliance monitoring activities for a broad spectrum of regulated health products, including medical devices which range from adhesive bandages to pacemakers. It is also responsible for the delivery of a national compliance and enforcement program in an effort to minimize health risks to Canadians while maximizing the safety of health products. A major component of this program involves the collection, review and follow-up of incidents related to medical devices, which are reported to the Inspectorate via the submission of mandatory and voluntary problem reports. Manufacturers and importers are required to submit mandatory reports as per section 59–61 in the Medical Device Regulations. Voluntary reports are submitted mostly by health care professionals and patients/users. In 2009, a total of 5269 incidents were entered into the medical device system. Of these reports, 4839 (91.8%) were mandatory and 430 (8.2%) voluntary.

Information on mandatory and voluntary reporting of medical device incidents can be found on the Health Canada Web site (www.hc-sc.gc.ca /dhp-mps/compli-conform/info-prod /md-im/index-eng.php).

Completed Medical Devices Problem Report forms can be submitted by email as attachments to: mdpr@hc-sc.gc.ca. Please include the acronym MDPR in the subject line of the email in order to generate an automated confirmation of receipt by the Inspectorate.

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Quarterly summary of health professional and consumer advisories

(posted on Health Canada's Web site: Nov. 11, 2009 – Feb. 19, 2010)

Date*	Product	Subject
Feb 11 & 16	Accutane	Severe skin reactions
Feb 9	Complete 7-Day Cleanse	Recall – possible serious health risks
Feb 4	Surgical mesh	Complications associated with transvaginal implantation
Feb 2	NeXus I, II and III Rollators	Association with falls and serious injury
Jan 29	Nipro GlucoPro insulin syringes	Recall – needles may detach during use
Jan 29	Products containing glucomannan	Risk of choking if used with insufficient fluid
Jan 29	Natural Choice products	Unauthorized health products
Jan 27	Medication for Parkinson disease	Update – availability of some medication
Jan 16	Rolaids tablets	Recall – possible health risks
Jan 14	The Slimming Coffee	Unauthorized weight loss product
Jan 8 & 12	Optimark	Association with nephrogenic systemic fibrosis
Jan 8	Stiff Nights	Unauthorized health product
Jan 6	Foreign products	Alerts – Ku Xiu Ba Xiang Jian Fei Wan, Super Slim (Yani), SHoufsy, MIGAC (sic) FAT BURMING (sic) FACTOR, RockHard Weekend, Pai You Guo, M-Action and Full Contact Max Potency
Dec 31	Foreign product	Alert – Tylenol Arthritis Pain Caplet: recall in the United States
Dec 29	BiCNU	Type I product recall – risk of infection
Dec 24	RevolutionDS Weight Loss	Unauthorized weight loss product
Dec 22	Foreign products	Alerts – Power-Plus P, Show Party and Zeng Da Yan Shi Wan
Dec 21 & 23	Myfortic	Reports of pure red cell aplasia
Dec 21	Cerezyme	Supply and recommendations for restarting Cerezyme
Dec 10	Foreign products	Alerts – S-DROL and Bodybuilding products
Dec 8	Acai Berry products	Update – adulterated products
Dec 8	Opioid pain medications	It's Your Health: Opioid pain medications
Dec 4	Zaditen tablets	Recall of lot #440494 – decreased effectiveness
Nov 30 & Dec 3	Exjade	Proposed changes to the Canadian product monograph
Nov 26	Rapamune	Blood level measurement changes
Nov 26	Vaccines	It's Your Health: Misconceptions about vaccine safety
Nov 25 & 26	Heparin	Information on changes to potency
Nov 25	Once More	Unauthorized health product
Nov 24	Drugs on the Internet	It's Your Health: Buying drugs over the Internet
Nov 19–25	Thyrogen and certain Genzyme products	Foreign particles detected in certain products
Nov 12	Arepanrix H1N1 Vaccine	Authorization for sale and postmarketing activities

Advisories are available at www.healthcanada.gc.ca/medeffect.
*Date of issuance. This date may differ from the posting date on Health Canada's Web site.

Canadian Adverse Reaction Newsletter

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Acknowledgement

We thank the following members of the Expert Advisory Committee on the Vigilance of Health Products for their review of material for this issue: Colleen J. Metge, BSc(Pharm), PhD; Dugald Seely, ND, MSc; and Sylvia Hyland, RPh, BScPhm, MHSc. We also thank Kaitlyn Proulx and Darija Muharemagic, students in Biopharmaceutical Science, for their participation in the production of the newsletter.

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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ISSN 1499-9447, Cat no H42-4/1-20-2E

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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.