Health Canada Santé Canada

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

Hylan G-F 20 (Synvisc): reported incidents of joint inflammation and pain

Hylan G-F 20 (Synvisc) is an elasto-viscous fluid containing hylan polymers, which are derivatives of hyaluronan (sodium hyaluronate). It is indicated for the treatment of pain caused by osteo-arthritis of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy and simple analgesics. A treatment course involves intra-articular injection once a week for 3 weeks. Aspiration of synovial fluid or effusion should be performed before each injection. The most commonly reported adverse incidents have been pain, swelling and effusion in the injected knee.[1]

From Mar. 22, 1996, to Jan. 15, 2005, Health Canada received 31 reports of suspected incidents associated with Synvisc; 23 were received in 2003–2004. In 9 cases the synovial fluid was not removed before each injection, and in 5 the course of injection was continued after the occurrence of adverse symptoms. Six of the 23 recent reports described patients who had pain, walking disability and knee swelling with or without effusion after the third injection of the first course. Two of these 23 patients were admitted to hospital.

The occurrence of post-injection effusion may be associated with the number of injections.[1] There have been reports in the literature of pseudosepsis (severe inflammation of the joint occurring 24 to 72 hours after intra-articular injection of hylan).[2] In affected patients, pseudosepsis typically occurs after more than 1 injection. Sepsis or pseudogout should be ruled out. Mononuclear cells are present in the synovial fluid.[2] Although the cause of pseudosepsis is not fully understood, there is increasing evidence to suggest an immunologic mechanism.[2]

Health care professionals should be aware of these possible adverse incidents and encouraged to follow the labelled procedure, including aspiration of synovial fluid before each injection.[1] Patients should be alerted of the occurrence of such events, and those who have severe inflammation of the joint after an injection should be fully evaluated.[3]

Health Canada will continue to monitor incident reports associated with hylan G-F 20. Any serious or unexpected adverse incidents associated with medical devices should be reported to Health Canada at the following address:

Health Products and Food Branch Inspectorate
Health Canada
AL 3002C
Ottawa ON K1A 0K9
Inspectorate Hotline: 800 267-9675

Momir Nesic, MD, PhD; Barbara Harrison, RN; Philippe Haziza, MD, MBA, Health Canada

References

1. *Synvisc Hylan G-F 20* [prescribing information]. Ridgefield (NJ): Genzyme Biosurgery. Revised 2004 Nov 15.
2. Goldberg VM, Coutts RD. Pseudoseptic reactions to hylan viscosupplementation: diagnosis and treatment. *Clin Orthop* 2004;(419):130-7.
3. Bernardeau C, Bucki B, Liote F. Acute arthritis after intra-articular hyaluronate injection: onset of effusions without crystal. *Ann Rheum Dis* 2001;60(5):518-20.

Adverse reaction reporting — 2004

Health Canada received 10 238 new domestic reports of suspected adverse reactions (ARs) in 2004. The ARs were reported for the most part by health professionals (pharmacists, physicians, nurses, dentists, coroners and others), either directly to Health Canada or indirectly through another source (Table 1). A further analysis of the total number of reports by reporter type (originator) is outlined in Table 2.

Of the AR reports received, 7000 (68.4%) were classified as serious. A serious AR is defined in the Food and Drugs Act and Regulations as "a noxious and unintended response to a drug which occurs at any dose and requires inpatient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death."

There has been a steady increase in the reporting of ARs in Canada over the past 6 years, with 11.2% more reports in 2004 than in 2003 (Fig. 1).

Health Canada would like to thank all who have contributed to the program and encourages the continued support of post-marketing surveillance through AR reporting. ARs may be reported by using the toll-free telephone (866 234-2345) and fax (866 678-6789) lines.

Bill Wilson, BSc, BA, Health Canada

Table 1: Source of reports of adverse reactions (ARs) received by Health Canada in 2003 and 2004

	No. (and %) of reports received			
Source	2003		2004	
Manufacturer	6 125	(66.5)	6 114	(59.7)
Regional AR centre	2 671	(29.0)	3 617	(35.3)
Other*	413	(4.5)	507	(5.0)
Total	9 209	(100.0)	10 238	(100.0)

*Includes, but not limited to, professional associations, nursing homes, hospitals, physicians, pharmacists, Health Canada regional inspectors, coroners, dentists and patients.

Table 2: Number of AR reports by type of reporter (originator)

	No. (and %) of reports			
Reporter	2003		2004	
Pharmacist	2 369	(25.7)	3 011	(29.4)
Physician	2 176	(23.6)	2 667	(26.2)
Health professional*	1 974	(21.4)	1 499	(14.6)
Consumer/ patient	1 628	(17.7)	1 928	(18.8)
Nurse	689	(7.5)	873	(8.5)
Other	373	(4.1)	260	(2.5)
Total	9 209	(100.0)	10 238	(100.0)

*Type not specified in report.

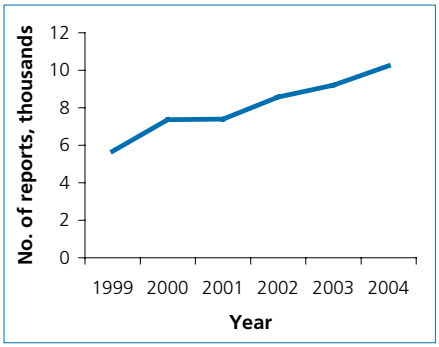

Fig. 1: Number of AR reports received annually by Health Canada from 1999 to 2004.

Products derived from bees: serious adverse reactions

Substances derived from bees include bee pollen, royal jelly and propolis. Bee pollen can come from a variety of plants and may include pollen to which people are commonly allergic (e.g., ragweed pollen). Royal jelly consists of the secretions of the hypopharyngeal and mandibular glands of worker bees. Propolis substrates are collected from poplar resin and conifer buds and are mixed with wax by bees. These substances are marketed alone or in combination products under various trade names and are indicated for multiple uses, from general health tonics to allergy and asthma treatment.[1]

From Jan. 1, 1998, to Oct. 30, 2004, Health Canada received 14 reports of suspected adverse reactions (ARs) involving bee products; 10 were considered serious. Four of the ARs were suspected allergic reactions: acute oral and laryngotracheal edema with respiratory distress; suspected autoimmune hepatitis; edema, rash and hives; and a questioned allergic reaction with chest pain. Other serious reactions were bleeding, hepatitis and seizures. Causality could not be assigned specifically to the bee product in many of the cases because of confounding factors such as pre-existing medical conditions, concomitant drug use or other suspect components of the product in question.

Allergic reactions involving products derived from bees have been documented in the literature.[2–5] The literature also suggests that there is no direct correlation between sensitivity to bee venom (stings) and sensitivity to bee products.[4]

Products containing bee pollen, royal jelly or propolis are readily available to the public; however, they often do not have a label warning of possible adverse reactions. The public and health care practitioners should be aware of the risk of allergic reactions to products derived from bees. It has been reported that atopic and asthmatic individuals may be at an increased risk of allergic reactions, possibly anaphylaxis, after ingestion of products containing royal jelly.[1,4] Individuals

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.

with seasonal allergic rhinitis (e.g., pollen allergies) may also be at an increased risk for similar serious allergic reactions to bee pollen.[1,3] With the implementation of the new Natural Health Products Regulations in January 2004, all natural health products approved for sale in Canada will eventually carry a Natural Product Number (NPN) or Drug Identification Number–Homeopathic Medicine (DIN-HM). The number will let consumers know that the product has undergone and passed a review of its quality, formulation, labelling and instructions for use. Products derived from bees are covered under the new regulations.

Chad Sheehy, BSc, ND; Trudy Hall, MSc, MD, CCFP; Karen Pilon, RN, Health Canada

References

1. Jellin JM, Gregory PJ, Batz F, Hitchens K, et al. *Pharmacist's Letter/Prescriber's Letter* Natural Medicines Comprehensive Database. 6th ed. Stockton (CA): Therapeutic Research Faculty; 2004. p. 107-8, 1053-4, 1110-1.
2. Chivato T, Juan F, Montoro A, Laguna R. Anaphylaxis induced by the ingestion of a pollen compound. *J Investig Allergol Clin Immunol* 1996;6(3):208-9.
3. Greenberger P, Flais M. Bee pollen-induced anaphylactic reaction in an unknowingly sensitized subject. *Ann Allergy Asthma Immunol* 2001;86:239-42.
4. Thien FCK, Leung R, Baldo BA, Weiner JA, Plomley R, Czarny D. Asthma and anaphylaxis induced by royal jelly. *Clin Exp Allergy* 1996;26(2):216-22.
5. Hausen BM, Wollenweber E, Senff H, Post B. Propolis allergy. (I). Origin, properties, usage and literature review. *Contact Dermatitis* 1987;17(3):163-70.

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.

Clopidogrel (Plavix): suspected drug interaction with atorvastatin (Lipitor) and cyclosporine resulting in rhabdomyolysis

A 57-year-old woman who had a heart transplant more than 10 years ago, and a myocardial infarction in 2003, was receiving cyclosporine (65 mg orally twice daily), Lipitor (80 mg orally daily), Imuran, prednisone, lisinopril, Apo-Allopurinol and furosemide. Plavix (75 mg orally daily) was added when a cardiac stent was inserted. Three weeks after starting the Plavix, the patient was admitted to hospital with muscle pain and weakness. Her creatine kinase level was 94 000 (normally ≤ 190) U/L, and rhabdomyolysis was diagnosed. The cyclosporine, Lipitor, Plavix and Apo-Allopurinol therapies were stopped. Cyclosporine was reintroduced at a lower dose 3 days later, and Lipitor was restarted following the adverse reaction without consequence. The muscle pain and weakness resolved, and the patient was discharged from hospital 11 days later.

The risk of myopathy and rhabdomyolysis during treatment with HMG–CoA reductase inhibitors is increased with concurrent administration of cyclosporine.[1,2] Because the patient had been taking cyclosporine since the heart transplant and Lipitor for years before this reaction, the reporter suspected that the rhabdomyolysis occurred when Plavix was added. Two similar cases are described in the literature where the authors believed that clopidogrel precipitated the development of rhabdomyolysis when added to a stable regimen of cyclosporine and an HMG–CoA reductase inhibitor.[2]

References

1. *Lipitor (atorvastatin)* [product monograph]. Kirkland (QC): Pfizer Canada Inc; 2004.
2. Uber PA, Mehra MR, Park MH, Scott RL. Clopidogrel and rhabdomyolysis after heart transplantation [letter]. *J Heart Lung Transplant* 2003;22(1):107-8.

Summary of health professional and consumer advisories posted from Nov. 17, 2004, to Feb. 18, 2005
(advisories are available at www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_advisories_e.html)

Date	Product	Subject and type
Feb 10	Fortovase and Invirase	Fortovase and Invirase: hepatitis in healthy volunteers receiving rifampin in combination with ritonavir boosted saquinavir — Hoffmann-La Roche Limited — health professional communication
Feb 9	Adderall XR	Health Canada has suspended market authorization of Adderall XR — consumer information and health professional communication
Feb 2	Humira	Hematologic events associated with Humira and infections associated with the concurrent use of Humira and anakinra — Abbott Laboratories Limited — consumer information and health professional communication

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Summary of advisories continued from previous page

Date	Product	Subject and type
Feb 1	Ezetrol	Ezetrol: myalgia, rhabdomyolysis, hepatitis, pancreatitis and thrombocytopenia — Merck Frosst/Schering Pharmaceuticals — consumer information and health professional communication
Jan 31	Xigris	Xigris: mortality in patients with single organ dysfunction and recent surgery — Eli Lilly Canada Inc. — notice to hospitals
Jan 25	Apo-Mefloquine	Apo-Mefloquine: revised patient information leaflet — Apotex Inc — consumer information and health professional communication
Jan 24	Lariam	Lariam: updated patient information — Hoffmann-La Roche Limited — consumer information and health professional communication
Jan 24	Reminyl	Important safety information regarding Reminyl — Janssen Ortho Inc. — consumer information
Jan 19	Hemodialysis access devices	Inadvertent disconnection of hemodialysis access devices — notice to hospitals
Jan 12	Faaborg Lifts	Product recall: Faaborg Lifts —PL, VL and Solution/Nordic series models — notice to hospitals
Jan 12	Electric bed foot switches	Entrapment in beds due to inadvertent activation of electric foot switch — notice to hospitals
Dec 23	Artificial Tears Extra	Warning not to use lot 4G03 Artificial Tears Extra — consumer information
Dec 22	COX-2 inhibitor NSAIDs	Safety information regarding Vioxx, Celebrex, Bextra, Mobicox — consumer information
Dec 21 & 17	Reminyl and Amaryl	Medication errors involving Reminyl and Amaryl — Janssen-Ortho Inc. and Aventis Pharma Inc — consumer information and health professional communication
Dec 20 & 17	Celebrex	Celebrex: increased cardiovascular risk — Pfizer Canada Inc. — consumer information and health professional communication
Dec 14	Ultrasound and medical gels	Serious risk of infection from ultrasound and medical gels: revision — notice to hospitals
Dec 10	Bextra	Bextra: cardiovascular risks and serious skin reactions — Pfizer Canada Inc. — consumer information and health professional communication
Dec 7	LTV Series Ventilators	Safety information on LTV Series Ventilators — Pulmonetic Systems Inc. — consumer information
Dec 3	Novo-Lorazem	Certain lots of Novo-Lorazem may contain pills of a different drug — consumer information
Nov 29	Remicade	Risk of malignancies associated with Remicade — Schering — consumer information and health professional communication
Nov 26	Male Power Plus	Warning against use of Male Power Plus — consumer information
Nov 24	Crestor	Updated safety information regarding Crestor — consumer information
Nov 20	Blue Cap Shampoo and Spray	Warning against use of Blue Cap Shampoo and Spray — consumer information
Nov 18	Depo-Provera	Depo-Provera: potential effect on bone mineral density — Pfizer Canada Inc. — health professional communication
Nov 5	Aredia and Zometa	Aredia and/or Zometa: osteonecrosis of the jaw — Novartis Pharma Canada Inc. — consumer information and health professional communication
Oct 27	Oral-B toothbrushes and refills	Product removal: Oral-B Cross-Action Power and PowerMAX toothbrushes and refills — 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**.

Update

In the January 2005 issue of this newsletter (Vol. 15, Issue 1; also in *CMAJ* 2005;172[1]: 127-32) an article was published on a suspected interaction between telithromycin (Ketek) and warfarin. In consultation with Health Canada, Aventis Pharma Inc. updated the product monograph on Dec. 17, 2004, to reflect the potential interaction between Ketek and warfarin.

Canadian Adverse Reaction Newsletter

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AL 0701B
Ottawa ON K1A 0K9
Tel 613 954-6522
Fax 613 952-7738

Health professionals/consumers report toll free:

Tel 866 234-2345
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Suggestions?
Your comments are important to us.
Let us know what you think by reaching us at cadrmp@hc-sc.gc.ca

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