



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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Intraocular lenses and the development of glistenings

Key points

- Health Canada received 69 reports of glistenings suspected of being associated with intraocular lenses (IOLs).
- In 67 cases, the development of glistenings was associated with visual impairment.
- Health care professionals are encouraged to report to Health Canada any adverse incidents suspected of being associated with IOLs and the development of glistenings.

An intraocular lens (IOL) is an artificial lens implanted in the eye to replace a cloudy crystalline lens in cataract patients.¹ It can also be used to correct different types of eye conditions such as myopia.² These class III medical devices (IV being the highest risk class) can be made of several types of material such as poly(methyl methacrylate) (PMMA), silicone and hydrophobic or hydrophilic acrylic.^{1,3} Different adverse incidents have been associated with IOLs including the development of glistenings.³ Glistenings are fluid-filled microvacuoles that form when the IOL is in an aqueous environment.⁴ They can range from 1 to 20 µm in size. Glistenings are usually distributed throughout the thickness of the IOL

and are visible by slitlamp due to the difference in refractive indices between the fluid and the IOL material. Light is refracted and scattered at the fluid-IOL material interface, leading to a sparkling or glistening-like appearance.

As of Mar. 19, 2013, Health Canada received 69 reports of glistenings suspected of being associated with IOLs. In 67 cases, the development of glistenings was reported to have affected the quality or amount of vision. In one case, a patient had a lens replaced due to decreased vision associated with the development of glistenings.

The incidence of glistenings in IOLs varies in the literature with results ranging from a relatively low incidence of glistenings to an incidence of 100%.⁵ The development of glistenings has been observed with different IOL materials.⁴ The current available literature often describes this phenomenon in association with hydrophobic acrylic IOLs. In a study comparing the degree of glistenings in three IOLs made of different materials (PMMA, silicone and hydrophobic acrylic), it was found that at approximately 12 years post-implantation there was a significantly higher degree of glistenings in patients with hydrophobic acrylic lenses compared to the two other lenses.⁶

Several factors that may influence the development of glistenings in IOLs have been reported in the literature. These factors include, but are not limited to, the type of IOL material, manufacturing techniques, IOL packaging and changes in temperature.⁶ Further investigation is required in order to confirm the root cause of the development of glistenings and factors influencing this phenomenon.

There is no clear consensus whether the development of glistenings in IOLs can impact visual function. Some studies found that some degree of visual impairment was associated with the development of glistenings. The impairment included decreased contrast sensitivity and decreased visual acuity.⁷⁻¹⁰ Other studies did not observe any impact of glistenings on vision.¹¹⁻¹³ These discrepancies may be attributed to the numerous differences in study designs and methods.

Health care professionals are encouraged to report to Health Canada any adverse incidents suspected of being associated with IOLs and the development of glistenings

(www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php). Information including patient symptoms, clinical test results including visual acuity and contrast sensitivity, type of IOL and concomitant visual impairment is important to include when reporting adverse incidents.

Mélanie Bousquet, PhD, Health Canada

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Exenatide: international reports of pancreatic cancer

Key points

- Glucagon-like peptide-1 (GLP-1) receptor agonists, such as exenatide, are new therapies for the management of type 2 diabetes mellitus.
- Scientific literature raises concerns that exenatide may be associated with an increased risk of pancreatic cancer, but there is limited evidence to date.
- Health care professionals are encouraged to report to Health Canada any adverse reactions suspected of being associated with the use of GLP-1 receptor agonists.

Exenatide (Byetta) is a synthetic peptide that mimics the biological properties of the incretin glucagon-like peptide-1 (GLP-1), a hormone that possesses several glucoregulatory functions.¹⁻³ Exenatide was marketed in Canada on May 31, 2011. It is indicated for the management of type 2 diabetes mellitus (T2DM) in combination with other antidiabetic therapies when these therapies, in addition to diet and

exercise, do not provide adequate glycemic control.¹ Exenatide requires subcutaneous administration.

In normal glucose homeostasis, GLP-1 is released from endocrine cells in the small intestine in response to food ingestion, activating insulin secretion among other actions.^{2,4} However, in patients with T2DM or in patients with impaired glucose tolerance, plasma levels of GLP-1 are reduced.³ Exenatide has been shown to bind to and activate the human GLP-1 receptor *in vitro*.¹ This stimulates *in vivo* secretion of insulin from pancreatic β -cells, enhancing glucose-dependent insulin secretion and restoring first-phase insulin secretion. It also suppresses glucagon secretion during periods of hyperglycemia in patients with T2DM. These actions work together to reduce fasting and postprandial glucose concentrations by modulating both glucose release and glucose disposal.

Additional adverse reaction (AR) information is emerging subsequent to the marketing of exenatide. One study examined the US Food and Drug Administration Adverse Event Reporting System database for reported adverse events associated with the use of exenatide from 2004 to 2009.⁵ The reported event rate for pancreatic cancer was found to be 2.9 times higher for exenatide compared with control therapies. However, the study was subject to various limitations and potential confounding factors. In line with these findings, an analysis of spontaneous reports from Germany

found an unusual frequency of reports of pancreatic cancer associated with exenatide compared with other antidiabetic therapies.⁶ The scientific literature discusses various mechanisms of action that may be involved in mediating the potential association between exenatide and pancreatic cancer.^{5,7} However, due to limited evidence, there is a need for additional long-term prospective studies and continued monitoring.

There are also several known risk factors associated with pancreatic cancer. Although the relationship between diabetes and pancreatic cancer is complex, T2DM has been associated with an increased risk of pancreatic cancer.⁸

The current Canadian product monograph for exenatide includes the following AR terms in the Post-Market Adverse Drug Reactions section: adenocarcinoma pancreas, pancreatic carcinoma, pancreatic carcinoma metastatic, pancreatic carcinoma non-resectable, pancreatic carcinoma recurrent and pancreatic carcinoma stage II.¹

As of Oct. 31, 2012, Health Canada received 6 reports of ARs suspected of being associated with exenatide. None of the reports involved pancreatic cancer. Another GLP-1 receptor agonist, liraglutide (Victoza), was marketed in Canada on May 27, 2010.⁹ As of Oct. 31, 2012, there were no reports of pancreatic cancer suspected of being associated with liraglutide in Canada.

Health care professionals are encouraged to report to Health

Canada any ARs suspected of being associated with exenatide or liraglutide. Information such as treatment duration or exposure to exenatide or liraglutide, concomitant medications and date of onset of T2DM are important to include when reporting ARs. This information may help to further evaluate ARs suspected of being associated with exenatide or liraglutide.

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Quarterly summary of health professional and consumer advisories
(posted on the Healthy Canadians Web site: November 19, 2012—February 17, 2013)

Date*	Product	Subject
Feb 8	IND Diagnostic	Medical device licences suspended
Jan 31	Diane-35 (cyproterone acetate and ethinyl estradiol)	Safety being reviewed by Health Canada
Jan 31	Cough and cold products	Recall: faulty child resistant bottle cap mechanism
Jan 30	RE9 Advanced for Men Facial Moisturizer SPF 20 Sunscreen	Recall: microbial contamination
Jan 24	Infant's Little Remedies for Fevers	Recall: one lot may contain less than the claimed amount of acetaminophen
Jan 24	Statins	Labelling update regarding the risk of increased blood sugar levels and diabetes
Jan 21	Botulinum toxin products	New labelling information
Jan 3	Weight-loss health products	Important safety reminder
Jan 1	ExtenZe products	Unauthorized health products removed from sale
Dec 21	Pradaxa (dabigatran, previously called Pradax)	Contraindication in patients with artificial heart valves
Dec 21	EV Princess Express Peeling, EV Princess Extra Whitening Night Cream and Ling Zhi BB Whitening Cream	Unauthorized health products containing high levels of mercury
Dec 4	Chemi Pharmaceutical Inc.	Suspension of establishment licence due to falsified testing results
Nov 30 & Dec 20	Unauthorized health products	Removed from sale at Richmond store due to possible serious health risks
Nov 30	Man Up Now, Black Ant and Triple Power Zen Gold 1200 mg	Recall: presence of undeclared ingredients
Nov 28	Thermography machines	Unauthorized for breast cancer screening in Canada
Nov 26	Banana Boat sun care products	Additional products recalled due to fire risk
Nov 21	Prolia (denosumab)	New safety information on the risk of atypical femoral fractures
Nov 19 to Feb 17	Foreign products	6 Foreign Product Alerts (FPAs) were posted on the Healthy Canadians Web site during this period

Advisories are available at www.healthycanadians.gc.ca.

*Date of issuance. This date may differ from the posting date on the Healthy Canadians Web site.

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Suggestions?

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