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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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Incretin-based therapies and the risk of pancreatic cancer

Key points

- Incretin-based drug products are new therapies indicated for the management of type 2 diabetes mellitus.
- Scientific studies have suggested that incretin-based therapies could possibly be associated with an increased risk of developing pancreatic cancer. In addition, cases of pancreatic cancer with the use of incretin-based therapies have been reported in Canada and internationally.
- A causal relationship between incretin-based therapies and the development of pancreatic cancer has not been established and investigations are ongoing.
- Health care professionals are encouraged to document and report to Health Canada any adverse reactions suspected of being associated with incretin-based therapies.

Incretins (glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic polypeptide [GIP]), are hormones secreted from the gastrointestinal tract into the blood stream in response to food ingestion.[1,2] They participate in the physiologic regulation of glucose metabolism by enhancing insulin production and secretion from the pancreas, among other functions. Incretins are rapidly inactivated by the enzymatic action of dipeptidyl peptidase-4 (DPP-4).

Incretin-based therapies either prolong the half-life of endogenous circulating incretins through the inhibition of DPP-4 activity or function as a GLP-1 receptor agonist resistant to DPP-4 degradation.[1,2] In Canada, incretin-based therapies used for the management of type 2 diabetes mellitus (T2DM) include 4 DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin and sitagliptin) and 2 GLP-1 receptor agonists (exenatide and liraglutide). These drugs were introduced on the Canadian market between January 2008 and April 2014.

Non-clinical studies have suggested that incretin-based therapies can lead to increased pancreatic cell proliferation.[3-5] These findings, along with international reports of pancreatic cancer in patients using incretin-based therapies, raised concerns over the potential risk of developing pancreatic cancer with the use of these drugs.

Pancreatic cancer is the fourth leading cause of cancer death in Canada with a 5 year relative survival ratio of 8%.[6] Risk factors for pancreatic cancer include, but are not limited to, smoking, obesity, a family history of pancreatic cancer, chronic pancreatitis and diabetes.[7]

In 2013, Health Canada informed health care professionals that cases of pancreatic cancer had been reported internationally with the use of exenatide; no Canadian cases were reported at the time.[8] As of July 31, 2014, Health Canada received 13 reports of pancreatic cancer suspected of being associated with all incretin-based therapies. Health Canada has not established a causal relationship between incretin-based therapies and the development of pancreatic cancer from the data currently available.

Presently, the potential risk of pancreatic cancer is labelled in the Canadian product monograph for 2 incretin-based therapies.[9,10] Health Canada has initiated an epidemiological study through the Drug Safety and Effectiveness Network (DSEN) to assess the potential association between pancreatic cancer and incretin-based therapies and will continue its ongoing monitoring of this potential safety issue.

Other regulatory agencies have also reviewed the evidence regarding the pancreatic safety of incretin-based therapies and concluded that a causal association could not be established.[11] This potential safety issue continues to be investigated internationally.

Health care professionals are encouraged to document and report to Health Canada any adverse reactions (ARs) suspected of being associated with incretin-based therapies. Information such as treatment duration or exposure to incretin-based therapies, 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 incretin-based therapies.

Alain Beliveau, PhD, Health Canada

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Intravenous methylprednisolone and liver injury

Key points

- Drug-induced liver injury such as acute hepatitis has been observed in association with intravenous methylprednisolone pulsed therapy.
- The time to onset of drug-induced liver injury, including acute hepatitis, can be several weeks or longer.
- Health care professionals are encouraged to report to Health Canada any cases of liver injury suspected of being associated with methylprednisolone.

Methylprednisolone is a potent anti-inflammatory steroid available in several dosage forms. Intravenous (IV) methylprednisolone (Solu-Medrol) is indicated in situations for which a rapid and intense hormonal effect is required.[1] These include, but are not limited to, hypersensitivity and

anaphylactic reactions, dermatologic conditions, ulcerative colitis, shock, organ transplants, cerebral edema of non-traumatic origin and as adjunctive therapy in several other conditions.

Drug-induced liver injury has been defined as a liver injury induced by a drug leading to liver test abnormalities or liver dysfunction with reasonable exclusion of other etiologies.[2] The Solu-Medrol Canadian product monograph lists the occurrence of hepatomegaly and an elevation of liver enzyme levels as potential adverse reactions (ARs).[1]

As of June 30, 2014, Health Canada received 4 reports of liver injury during patient exposure to IV methylprednisolone. It was determined that one case could possibly be linked to IV methylprednisolone therapy.

Twenty-eight additional cases of drug-induced liver injury suspected of being associated with IV methylprednisolone have been identified in the literature.[2-21] Cases were published between 1997 and 2014. With the exception of one case[10] in which the patient developed a mild elevation in liver enzymes, ARs were reported using a variety of terms including acute and severe liver damage, hepatopathy, hepatitis, hepatic necrosis and liver failure.

A significant proportion of cases (n=10) reported transaminase (ALT and AST) levels reaching greater than 1000 U/L and some were accompanied by hyperbilirubinemia and jaundice. Death was reported in 4 cases. Three patients died from liver failure[14,16], while a fourth patient underwent liver transplantation and subsequently died from kidney complications.[16]

Notably, 11 cases included a positive rechallenge (i.e., reappearance of the AR after reintroduction of IV methylprednisolone therapy), an observation which suggests a causal role for methylprednisolone. Many of these positive rechallenges were experienced several years after the last episode of liver injury.

Patients' age ranged from 11 to 71-years-old. The majority (n=17) were female. This may be related to the fact that treated conditions are more prevalent in women. Conditions included multiple sclerosis or closely related disorders such as demyelinating encephalopathy or retrobulbar optic neuritis (n=15) and thyroid-related ophthalmopathy (n=11). Other conditions included Crohn's disease and extensive alopecia areata. Additionally, the literature postulates that drug-induced liver injury is more common in women than men.[22]

IV methylprednisolone was commonly administered as high dose pulse therapy in the cases. In at least 11 cases, patients received doses of IV methylprednisolone equivalent to 1000 mg per day. The variety of dosing regimens within these cases makes it challenging to calculate treatment duration and whether the risk is dose dependent. The time to onset of liver injury, including cases of acute hepatitis, varied from several days to several months since the beginning of therapy, a timeframe compatible with drug-induced liver injury.[2]

Prompt recognition of this AR may allow for more effective management of cases of liver injury.[20] Health care professionals are encouraged to report to Health Canada any cases of liver injury suspected of being associated with methylprednisolone.

Patrice Tremblay, MD, Health Canada

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Sorafenib and osteonecrosis of the jaw

Key points

- Osteonecrosis of the jaw (ONJ), a severe bone disease of the jaw, has been reported in patients taking sorafenib. To date, no Canadian reports have been received by Health Canada.
- To decrease the risk of ONJ, patients should maintain good oral hygiene. A dental examination and appropriate preventive dental measures should be considered prior to starting treatment with drugs reported to be associated with ONJ.
- Healthcare professionals are encouraged to report all cases of ONJ suspected of being associated with the use of sorafenib to Health Canada.

Sorafenib (Nexavar), marketed in Canada since July 2006, is an oral multi-kinase inhibitor that targets tumour cell proliferation and tumour angiogenesis.[1] It is indicated for the treatment of patients with unresectable hepatocellular carcinoma, locally advanced or metastatic renal cell (clear cell) carcinoma and locally advanced or metastatic, progressive differentiated thyroid carcinoma.

Osteonecrosis of the jaw (ONJ) is a severe bone disease that affects the jaws and typically presents as infection with necrotic bone in the mandible or maxilla.[2] ONJ is characterized by the presence of exposed bone in the maxillofacial region that does not heal within 8 weeks.[2-4] Although asymptomatic at times, ONJ usually presents as pain and/or numbness in the affected area, soft-tissue swelling, drainage, and tooth mobility.[2]

Osteonecrosis is classically considered an interruption in vascular supply and therefore, the inhibition of angiogenesis is a leading hypothesis in ONJ pathophysiology.[4] There is a growing body of literature linking osteonecrosis of the jaw and other bones in patients receiving novel antiangiogenic drugs (tyrosine kinase inhibitors and monoclonal antibodies targeting vascular endothelial growth factor). Sorafenib has been listed as one of the antiangiogenic agents that have been suspected of being associated with ONJ.

The product information available in the United States for Nexavar (sorafenib) indicates that ONJ has been reported with the post-market use of sorafenib.[5,6] As of August 29, 2014, the World Health Organization (WHO) Global Individual Case Safety Reports Database System (VigiBase) contained 8 reports of ONJ suspected of being associated with sorafenib.* As of July 31, 2014, Health Canada had not received any reports of ONJ suspected of being associated with the use of sorafenib.

Risk factors for ONJ include: radiotherapy, dentoalveolar surgery, including tooth extraction and implant placement, denture use, periodontal disease, and other co-

morbid conditions such as cancer, anemia and diabetes.[4,7] Medications that have been reported as risk factors for ONJ include antiresorptive medications, such as bisphosphonates and denosumab, corticosteroids, chemotherapy, as well as antiangiogenic agents.

To help decrease the risk of ONJ, it is recommended that patients maintain good oral hygiene.[2,8] A complete dental examination and appropriate preventive dental measures prior to treatment initiation may be effective in reducing the risks of medication-related ONJ .[2,4]

In order to improve the understanding of the potential risk of ONJ in patients taking sorafenib, health care professionals are encouraged to report this adverse reaction to Health Canada.

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* World Health Organization (WHO) adverse reaction information provided by: The WHO Collaborating Centre for International Drug Monitoring. This information is not homogeneous with respect to the sources of the information or the likelihood that the health product caused the suspected adverse reaction. Also, this information does not represent the opinion of the WHO.

Quarterly summary of health professional and consumer advisories

(posted between May 27 and September 30, 2014)

Date*	Product	Subject
Sept 30	Products from 3 sites in India	Health Canada takes action to stop import of products from these sites
Sept 28	Biomedic Acetaminophen with Codeine	Recall: missing child-resistant packaging
Sept 26	Ceftriaxone for injection 10g/vial	Recall of 7 lots: presence of particulate matter
Sept 26	Cefixime	Recommended management of gonococcal infections during cefixime shortage
Sept 24	Apotex products manufactured at the Apotex Research Private Limited facility in Bangalore, India	Quarantine requested by Health Canada
Sept 21 & 22	Mylan-Nitro Sublingual Spray 0.4 mg/metered dose	Additional information on the recall
Sept 20 & 22	Baxter Calcium-45, 24 EA/CA	Recall of one lot: missing bottle labels
Sept 20	Mylan-Nitro Sublingual Spray 0.4 mg/metered dose	Recall: defective pump
Sept 19	Baxter Acid Concentrate 45X	Urgent product recall for 2 lots: presence of particulate matter
Sept 17	Products from IPCA Laboratories in India	Quarantine requested by Health Canada following falsification and manipulation of data issues
Sept 9	Dacarbazine for injection 600 mg/vial, BP	Discoloration after reconstitution of vials

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Quarterly summary of health professional and consumer advisories

(posted between May 27 and September 30, 2014)

Date*	Product	Subject
Aug 29	AMSA PD Inj 50 mg/mL (amsacrine injection)	Potential low risk of microbial contamination
Aug 18	Controlled-release opioid pain medicines	Label changes to encourage more targeted prescribing and safer use
Aug 15 & 16	Apo-Mycophenolic Acid 360 mg	Recall of one lot: French labelling error
Aug 15	White Widow marijuana for medical purposes	Recall of one lot: presence of mould
Aug 6	Arzerra (ofatumumab)	Fatal infusion reaction reported in a patient with chronic lymphocytic leukemia
Aug 1	Pre-Attached LTA Kit 4% Lidocaine Hydrochloride Topical Solution USP	Recall: cannula breakage
July 30	Nuvaring (etonogestrel / ethinyl estradiol slow release vaginal ring)	New usage restrictions
July 30	Cytarabine Injection 2g/20mL	Missing or partially detached label
July 28	Duragesic MAT (fentanyl transdermal system)	Introduction of a single ink colour (dark green) on all strengths of patches
July 25	Topical antiseptics	Risk of contamination
July 15	Testosterone products	Possible cardiovascular problems
July 11	Feraheme (ferumoxytol)	New usage restrictions due to serious allergic reactions
June 23	Cellfood	Recall of unauthorized health product: false and misleading labelling
June 12	Intravenous Zofran (ondansetron)	New dosing and administration recommendations in elderly patients
June 9	Terazol 7 Vaginal Cream and Terazol 3 Dual-Pak Vaginal Cream / Vaginal Ovules (terconazole)	Risk of anaphylaxis and toxic epidermal necrolysis
June 9	Drug products from CanadaDrugs.com LP	Wholesale no longer permitted: establishment license suspension due to significant concerns with Good Manufacturing Practices
May 29	Clinimix 5% Travasol Amino Acid Injection	Expanded recall to include 4 additional products/lots: presence of particulate matter
May 27	Vectibix (panitumumab)	Rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis
May 27 to September 30	Foreign products	26 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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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.