Health Canada Santé Canada

Canada

Canadian Adverse Reaction Newsletter

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www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/publicat.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/hpb-dgps/therapeut/zfiles/english/forms/adverse_e.pdf

Pure red cell aplasia: suspected association with epoetin alfa (Eprex)

Eprex, a recombinant human erythropoietin (rHuEPO), is indicated for "the treatment of anaemia associated with chronic renal failure (CRF), cancer or concomitantly administered cancer chemotherapy, zidovudine-treated/HIV-infected patients, for use in patients undergoing autologous donation, and to reduce allogenic blood exposure for patients undergoing elective surgery."[1] The "primary adverse effect of erythropoietin has been an excessive increase in the hematocrit following over-treatment with the hormone in patients undergoing hemodialysis, leading to the aggravation of hypertension or thrombotic complications."[2] Recently, however, pure red-cell aplasia (PRCA), a selective failure of the erythroid elements in bone marrow resulting in a normochromic, normocytic anemia, has been reported to be associated with the use of rHuEPO.[3–5] On Nov. 26, 2001, following discussion with Health Canada, the sponsor issued a Dear Healthcare Professional Letter informing physicians of the occurrence of PRCA associated with the use of Eprex.[6] Since then, there has been a marked increase in the number of PRCA cases reported to Health Canada: 21 of the 28 cases reported as of Apr. 10, 2002, were received after the letter was issued.

The mechanism underlying PRCA is not well understood. Autoantibodies against erythropoietin have been shown to inhibit the formation of erythroid colonies by normal bone marrow cells.[5] PRCA has been demonstrated to be induced by drugs and chemicals (e.g., phenytoin, chlorpropamide).[2,5,7] It has also been associated with a variety of conditions including thymomas, lymphoproliferative disorders and viral infections such as hepatitis B and parvovirus infection.[2,7] Although rare, PRCA can occur during the course of renal failure.[2,7] The anemia in patients with rHuEPO-induced PRCA is much more severe than the anemia in patients with renal failure that prompted the rHuEPO therapy.[2] In addition, most patients with rHuEPO-induced PRCA become permanently transfusion dependent and may be resistant to other rHuEPO products.[2,5,6]

Health Canada is closely monitoring the issue and has requested that the manufacturer conduct, and submit the results of, further investigations to determine the factors that may have contributed to the increased number of PRCA cases in Canada. More data from ongoing investigations are still required to assess the risks associated with rHuEPO use. Until then, patients receiving rHuEPO should be advised to promptly report to their physician any symptoms associated with worsening anemia (e.g., excessive fatigue, pallor, syncope). Physicians should consult

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the product monograph for hematology monitoring requirements. Health professionals are encouraged to continue to report to Health Canada any suspected or confirmed cases of PRCA in patients using rHuEPO.

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Rosiglitazone (Avandia) and pioglitazone (Actos): update on cardiovascular and hepatic adverse reactions

Rosiglitazone (Avandia) and pioglitazone (Actos), members of the thiazolidinedione oral antidiabetic class of drugs, were marketed in Canada in March and August 2000, respectively. In Canada, Avandia is indicated for use as an adjunct to diet and exercise as monotherapy or in combination with metformin or a sulfonylurea in patients with type 2 diabetes mellitus.[1] Actos is indicated as monotherapy for type 2 diabetes not controlled by diet and exercise.[2]

Health Canada continues to monitor cardiac disorders and hepatic reactions with these drugs. Table 1 summarizes reports of suspected adverse reactions (ARs) associated with rosiglitazone and pioglitazone received since the date they were marketed in Canada to Mar. 1, 2002. Spontaneous reporting systems are suitable to detect signals of potential drug safety issues; however, quantitative comparisons of drug safety cannot be made from these data.

Thirty-six of the 282 reports received for rosiglitazone and 4 of the 29 received for pioglitazone were of heart failure or congestive heart failure. Cases of edema were also reported without heart failure.

Ten of the 282 suspected AR reports received for rosiglitazone indicated a fatal outcome; 3 of these were described in the July 2001 issue of the newsletter.[3] Three of the remaining 7 suspected fatal cases reported heart failure or congestive heart failure, with 2 of these also indicating myocardial infarction. The other 4 fatal cases involved pulmonary edema (1), enlarged abdomen and peripheral edema (1), bone marrow depression with concomitant use of Imuran (1) and a complex case of a serum-sickness-type reaction and erythema multiforme (1), which occurred shortly after the rosiglitazone was started and which resulted in multiple organ failure. There was 1 report of a fatal outcome associated with pioglitazone in which the patient had a cardiorespiratory arrest, was found to have elevated liver enzymes and died of anoxic encephalopathy. The patient had no history of liver disease but had a history of extensive alcohol consumption and was taking other drugs. Causality assessment is difficult in most of these cases because of the lack of information or the complexity of the cases.

People with type 2 diabetes are at increased risk of diabetes-related complications such as congestive heart failure. However, results of an observational study based on analysis of insurance claims indicated that the use of glitazones was associated with a significant increase in risk of heart failure in diabetic patients treated with glitazones compared with diabetic patients who did not use glitazones.[4] However, these results were published as an abstract only, and further research is needed to confirm these findings.

To minimize the risk of hepatic and cardiovascular adverse events, physicians are advised to adhere to all recommendations and monitoring guidance listed in the product

Table 1: Reports submitted to Health Canada of suspected adverse reactions (ARs) associated with thiazolidinediones from date marketed in Canada to Mar. 1, 2002*

Variable	Rosiglitazone (Avandia)	Pioglitazone (Actos)
Date marketed in Canada	March 2000	August 2000
Total no. of AR reports	282	29
No. of serious reports	134	24
No. of reports with cardiovascular disorders†	60	8
No. of reports with liver and biliary disorders†	16	1
No. of reports with fatal outcome†	10	1

***These data cannot be used to determine the incidence of ARs or to make quantitative drug safety comparisons between the products, because neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.**
†These reports are a subset of the total AR reports and are represented only once in the most significant category.

monograph. The product monographs of Avandia[1] and Actos[2] list the following as contraindications:

- known hypersensitivity to the product or any of its components;
- serious hepatic impairment; and
- acute heart failure.

Health Canada has been continuously monitoring the safety profile of the glitazones. The following actions have been taken to inform health care professionals and the public regarding safety issues with these products:

- At product launch in Canada, Dear Healthcare Professional Letters were issued by the manufacturers of Avandia[5] and Actos[6] recommending that precautions be taken and that patients be monitored for liver and cardiac adverse reactions.
- A summary of hepatic, cardiac and hematological reactions with rosiglitazone was presented in the July 2001 issue of the newsletter.[3]
- In consultation with Health Canada a second Dear Healthcare Professional Letter was issued by the manufacturer of Actos (on Nov. 6, 2001[7]) and by the manufacturer of Avandia (on Nov. 13, 2001[8]) regarding new safety information related to fluid retention and congestive heart failure.
- Health Canada issued a public Advisory on the safety profile of the thiazolidinediones on Nov. 29, 2001,[9] related to fluid retention and congestive heart failure.

Your continued reporting of suspected ARs associated with the use of the glitazones is an important factor in evaluating their safety in the postmarketing phase.

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"It's Your Health": The Safety of Human Insulins

In the previous 2 years attention has been focused, in media reports and elsewhere, on concerns regarding the safety of recombinant human insulin and the availability of animal insulin in Canada. In an effort to clarify these issues Health Canada has posted an "It's Your Health" document on its Web site (www.hc-sc.gc.ca /english/iyh/insulins.html), with a link to it from the Canadian Diabetes Association's update on human and animal insulins (www.diabetes.ca /Section_About/bromley.asp). A distribution by fax to targeted health professionals and special interest groups was also done.

The document briefly outlines the background of the manufacture and sale of recombinant human and animal insulins in Canada, and their availability. In addition, it addresses the benefits of human insulins, how Health Canada monitors the adverse effects of insulin, and the effects of switching insulins, stressing that the choice of insulin for an individual should be made after discussion with the treating physician.

From 1983 to Mar. 31, 2002, Health Canada received about 550 reports of suspected ARs associated with recombinant human insulins. Of these suspected AR reports, 9 indicated a fatal outcome. From 1965, when Health Canada started monitoring ARs, until Mar. 31, 2002, about 250 reports of ARs associated with animal insulins were received, 20 of which

Case Presentation

Recent cases are selected based on their seriousness, frequency of occurrence or the fact that the reactions are unexpected. Please report similar reactions.

Kava

As a result of the Public Advisory concerning kava and liver toxicity issued by Health Canada on Jan. 16, 2002, 3 case reports of suspected hepatic adverse reactions were received. One of these cases involved a 53-year-old woman who took 3 to 10 capsules of kava (dosage unspecified) daily over a 2-year period. She also took St. John's wort, vitamins and other herbs for depression and anxiety. Four years earlier the patient had developed an inflamed liver because of alcohol consumption but had stopped drinking in the last 2 years. Three weeks before medical consultation, the patient experienced fatigue, vomiting, loss of weight, jaundice and darker urine. At presentation she had an enlarged liver and elevated bilirubin, aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase levels. After the patient stopped taking the kava, her liver profile returned to normal and her symptoms resolved.

Summary of health professional and consumer advisories issued since Feb. 15, 2002

Date	Product	Subject and Web address
May 23	Celebrex (celecoxib)	Important safety information for patients taking CELEBREX® (celecoxib) — consumer Information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_40e.htm
May 16	Longdan	Warning not to consume Longdan and Lung Tan Xie Gan Products — consumer Information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_38e.htm
May 16	Plas+SD	Important Safety Information - PLAS+SD plasma (human) — Precision Pharma Services Inc. www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/plas_sd_plasma_e.html
May 14	Rapamune (sirolimus)	Important correction to drug Safety Information on Rapamune www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/rapamune_e.html
May 13	Celebrex (celecoxib)	Important drug safety information on Celebrex www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/celebrex_e.html
May 2002	Insulins	It's Your Health: The safety of human insulins — consumer information www.hc-sc.gc.ca/english/iyh/insulins.html
Apr. 29	HIV test kits	Health Canada advises Canadians about potential false results with certain rapid HIV test kits — consumer Information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_31e.htm
Apr. 19	Vioxx (rofecoxib)	Important safety information for patients taking VIOXX® (rofecoxib) — consumer Information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_29e.htm
Apr. 15	Vioxx (rofecoxib)	Important drug safety information on VIOXX® — Merck Frosst Canada Inc. www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/vioxx_e.html
Apr. 12	IGIV (Immune Globulin)	Thrombotic events and immune globulin intravenous (IGIV) — Baxter www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/igiv_e.html
Apr. 11	Tutoplast Dura	Important medical devices safety advisory — Tutoplast Dura manufactured by Tutogen Medical GmbH www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/tpd/tutogen_e.html
Apr. 5	Hua Fo	Health Canada warns public not to use Hua Fo (DIN 02243366) — consumer information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_26e.htm
Apr. 4	Phosphate Solutions	Important safety information for patients taking sodium phosphates oral solutions (Fleet® Phospho-soda® and Phosphates Solution) — consumer information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_22e.htm
Mar. 27	Meridia (sibutramine)	Health Canada investigates safety of MERIDIA® (sibutramine) — consumer information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_21e.htm
Mar. 22	Non-sterile medical devices	Non-sterile medical devices labeled as sterile manufactured by A&A Medical, Rocket USA and LifeQuest www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/tpd/rocket_e.html
Mar. 18	Sodium Phosphates Oral Solutions	Important safety information regarding Phosphates Solution (Sodium Phosphates Oral Solution DIN 02230399) — Pharmascience Inc. www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/sodium_phosphates_e.html
Mar. 15	Sodium Phosphates Oral Solutions	Important safety information regarding Fleet® Phospho-Soda® (Sodium Phosphates Oral Solution) — Johnson & Johnson • Merck www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/fleet-phospho-soda_e.html
Mar. 6	Zerit (stavudine, d4T)	Symptoms mimicking the clinical presentation of Guillain–Barré syndrome associated with ZERIT® (stavudine, d4T) — Bristol-Myers Squibb www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/zerit_stavudine_e.html

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were of a fatal outcome. Quantitative safety comparisons of these products cannot be made on the basis of spontaneous AR reports because patient exposure is unknown and underreporting exists.

Recombinant human insulins have an established safety profile, with over 200 000 Canadians using them daily to manage their diabetes. If one assumes that patients have 2 injections a day on average, about 146 million doses are administered per year. Considering the high numbers of users, the complexity of diabetes as a disease and the benefits obtained with the use of human insulins, the number of reports of suspected ARs is not believed to suggest any unusual trend in the safety profile of these products. Regulators in other international jurisdictions have confirmed similar findings.

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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.