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

Suspected hepatobiliary adverse reactions to the newer antidepressants that affect serotonin neurotransmission

Health Canada continues to monitor suspected hepatobiliary adverse reactions (ARs) associated with the newer antidepressants that exert an effect on serotonin neurotransmission. These include citalopram (Celexa), fluoxetine (Prozac), fluvoxamine (Luvox), mirtazapine (Remeron), nefazodone (Serzone-5HT$_2$), paroxetine (Paxil), sertraline (Zoloft), trazodone (Desyrel) and venlafaxine (Effexor). Tables 1 and 2 summarize the reports of suspected hepatobiliary ARs associated with these antidepressants that were submitted to Health Canada from the time of marketing to July 24, 2002. Spontaneous reporting systems are suitable for detecting signals of potential drug safety issues; however, these data cannot be used to determine the incidence of ARs, because ARs remain underreported and total patient exposure is unknown. From the data available, no fatal outcomes were reported for hepatobiliary ARs associated with these antidepressants. In 2 reports involving nefazodone, liver transplantation was required. In 3 other reports involving nefazodone liver transplantation was considered, but the patients' conditions eventually improved after prolonged hospital care. The time of onset of liver injury ranged from 1 to 4 months. None of these 5 patients had a prior history of liver disease.

Health Canada has been monitoring the safety profile of nefazodone since it was marketed in Canada in 1994. The following actions have been taken to inform health care professionals and the public about the safety issues with nefazodone.

- A summary of reported reactions associated with nefazodone was profiled in the April 1996 issue of this newsletter.[1]
- A summary of 9 Canadian case reports of suspected symptomatic hepatic dysfunction associated with nefazodone was outlined in the July 1999 issue of this newsletter.[2]
- In consultation with Health Canada, 2 Dear Healthcare Professional Letters were issued by the manufacturers of Serzone-5HT$_2$ and Lin-Nefazodone[3] and of Apo-Nefazodone[4] recommending that patients be counselled about the risk of hepatotoxic effects before the initiation of nefazodone therapy and that close monitoring is required should signs of hepatotoxicity or abnormal liver aminotransferase or bilirubin levels develop during treatment.
- Health Canada issued a public advisory on the safety profile of nefazodone on July 9, 2001, related to the risk of severe liver injury

Newsletter and Advisories by email

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associated with the use of nefazodone.[5]

The current literature documents several cases of severe hepatic failure associated with nefazodone.[6–8] The US Food and Drug Administration (FDA) recently included a black-box warning in Serzone's package insert, stating that the reported rate in the United States of liver failure resulting in death or liver transplantation is about 1 case per 250 000–300 000 patient-years of Serzone treatment. This rate is about 3–4 times the estimated background rate of liver failure. It is possibly an underestimate of true risk because of underreporting.[9]

At present, there is no way to predict in which patient liver failure is likely to develop.[9] Ordinarily, treatment with nefazodone should not be initiated in patients with active liver disease or with an elevated baseline serum transaminase level.[9] Although it is unclear whether periodic liver function tests can help prevent serious liver injury, it is generally believed that early detection of drug-induced hepatic injury along with immediate discontinuation of the suspected drug enhances the likelihood of recovery.[9] Patients should be advised to be alert for signs and symptoms of liver dysfunction (e.g., dark urine, jaundice [yellow discoloration of the skin or the eyes], loss of appetite and discoloured stools) and to report them to their physician immediately.[9,10]

Mano Murty, MD, CCFP, FCFP;
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References

1. Nefazodone: adverse drug reaction profile. *Can Adverse Drug Reaction Newsl* 1996;6(2):2.
2. Nefazodone (Serzone) and hepatotoxicity. *Can Adverse Drug Reaction Newsl* 1999;9(3):2-3.
3. *Important safety information on nefazodone HCl: severe and serious hepatic events* [Dear Healthcare Professional Letter]. Montreal: Bristol-Myers Squibb Canada Inc and Linson Pharma Inc; 2001 June 20. Available: www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles

Table 1: Reports submitted to Health Canada of suspected adverse reactions (ARs) associated with antidepressants exerting an effect on serotonergic neurotransmission from date marketed to July 24, 2002*

Variable	Citalopram	Fluoxetine	Fluvoxamine	Mirtazapine	Nefazodone	Paroxetine	Sertraline	Trazodone	Venlafaxine
Date marketed in Canada	Mar 1999	Dec 1989	Dec 1991	May 2001	Apr 1994	Dec 1993	Dec 1992	Dec 1983	Dec 1994
Total no. of AR reports	151	1238	184	77	213	844	445	142	314
No. of reports with suspected liver and biliary reactions	1	29	9	4	35	21	17	5	8
No. of liver transplantations	0	0	0	0	2	0	0	0	0

***These data cannot be used to determine the incidence of ARs or to make quantitative drug safety comparisons between the products because ARs are underreported and neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.**

Table 2: Reports submitted to Health Canada of suspected hepatobiliary adverse reactions (ARs) associated with antidepressants exerting an effect on serotonergic neurotransmission from date marketed to July 24, 2002*

	Drug; no. of reports								
Hepatobiliary reaction	Citalopram	Fluoxetine	Fluvoxamine	Mirtazapine	Nefazodone	Paroxetine	Sertraline	Trazodone	Venlafaxine
Gallbladder disorder†	0	6	0	1	0	2	1	0	0
Hepatic function abnormal	0	3	1	2	4	2	4	2	2
Increased hepatic enzyme levels‡	1	31	16	5	69	23	18	5	14
Hepatic failure	0	0	0	0	4	0	0	0	0
Hepatitis viral	0	0	0	0	0	0	0	1	0
Hepatic necrosis	0	0	0	0	1	0	0	0	2
Hepatitis	0	1	0	2	10	1	5	0	1
Hepatitis cholestatic	0	1	1	0	2	0	0	0	0
Hepatocellular damage	0	1	0	0	1	1	1	0	1
Fatty liver	0	1	0	0	0	0	0	0	0
Bilirubinemia	0	2	3	0	15	4	2	0	4
Jaundice	0	1	3	0	15	5	2	0	3
Other§	0	1	0	0	2	1	3	0	0
Total	1	48	24	10	123	39	36	8	27

***These data cannot be used to determine the incidence of ARs or to make quantitative drug safety comparisons between the products because ARs are under reported and neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.** Several reaction terms may be listed per AR report. Reaction terms are based on the "preferred term" of the World Health Organization (WHO) *Adverse Reaction Dictionary* (WHOART).
†Includes cholecystitis and cholelithiasis.
‡Includes aspartate amino transferase, alanine aminotransferase and gamma glutamyl transferase.
§Includes hepatomegaly and porphyria.

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.

/english/advisory/industry/nefazodone_e.html (accessed 2002 Nov 18).
4. *Important safety information on nefazodone HCl: severe and serious hepatic events* [Dear Healthcare Professional Letter]. Weston (ON): Apotex Inc; 2001 June 28. Available: www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/apo-nefazodone_e.html (accessed 2002 Nov 26).
5. *Risk of severe liver injury associated with the use of the antidepressant nefazodone* [public advisory]. Ottawa: Health Canada; 2001 July 9. Available: www.hc-sc.gc.ca/english/protection/warnings/2001/2001_74e.htm (accessed 2002 Nov 18).
6. Aranda-Michel J, Koehler A, Bejarano PA, Poulos JE, Luxon BA, Khan CM, et al. Nefazodone-induced liver failure: report of three cases. *Ann Intern Med* 1999;130:285-8.
7. Schirren CA, Baretton G. Nefazodone-induced acute liver failure. *Am J Gastroenterol* 2000;95(6):1596-7.
8. Carvajal A, Garcia del Pozo J, Sanchez A, Velasco A, Rueda AM, Lucena MI. Hepatotoxicity associated with the new antidepressants. *J Clin Psychiatry* 2002;63(2):135-7.
9. *Important drug warning including black box information* [Dear Healthcare Practitioner Letter]. New York: Bristol-Myers Squibb; 2002 Jan. Available: www.fda.gov/medwatch/SAFETY/2002/serzone_deardoc.pdf (accessed 2002 Nov 18).
10. *Serzone-5HT$_2$, nefazodone hydrochloride tablets* [product monograph]. Montreal: Bristol-Myers Squibb Canada Inc.; 2001 Oct 5.

Reports of convulsions with newer-generation antihistamines

Antagonists of histamine H_1 receptors are commonly classified as first-generation or new-generation antihistamines based on their frequent sedating effect at therapeutic doses.[1] The "newer-generation" antihistamines, also known as second- or third-generation antihistamines, include astemizole, cetirizine, desloratadine, fexofenadine, loratadine and terfenadine, and were developed as nonsedating alternatives to the first-generation compounds. The sale of terfenadine and astemizole was stopped in Canada because of associated QT prolongation, which could lead to torsades de pointes or ventricular fibrillation. Loratadine, cetirizine, fexofenadine and desloratadine have been marketed in Canada since 1988, 1991, 1997 and 2002, respectively. Loratadine, fexofenadine and desloratadine are available as nonprescription drugs. Cetirizine is available as both a nonprescription (5 and 10 mg) and prescription (20 mg) drug.

Seizures or convulsions have been reported in the literature with some first-generation antihistamines (chlorpheniramine, diphenhydramine, pheniramine and pyribenzamine) as well as with some newer-generation antihistamines (astemizole, cetirizine, fexofenadine, loratadine and terfenadine).[1–3] According to the US Food and Drug Administration Adverse Event Reporting System (July 1999), convulsions associated with cetirizine, fexofenadine and loratadine accounted for 2.5%, 3.1% and 2.1% respectively of the total adverse events reported with these drugs.[1]

From their respective dates of marketing in Canada to Sept. 19, 2002, Health Canada received 20 reports of suspected convulsive disorders associated with the use of loratadine (9), cetirizine (7) and fexofenadine (4) (Table 1). There have been no reports of suspected convulsive disorders associated with desloratadine at this time. Reports of seizures and convulsions accounted for 3.6%, 1.4% and 0.9% of the total number of ARs reported with loratadine, cetirizine and fexofenadine respectively. Fifteen of the 20 cases occurred in patients with a prior history of seizures or in those who used anticonvulsant drugs concomitantly. However, these data must be interpreted with caution, as causality has not been confirmed. It is unclear whether newer-generation antihistamines aggravate the medical condition of patients with a history of seizures or whether they interact with anticonvulsants. Further studies and continued monitoring of these agents regarding their role in causing seizures or convulsions, especially in patients predisposed to convulsive disorders, are required.

Also of note are 2 reports of patients who apparently took more than the recommended daily dose of the drug. One report involved a 27-year-old woman receiving phenytoin therapy who had been seizure free for over 2 years. She took 3 doses of cetirizine (20 mg each) in 24 hours and experienced a seizure 1½ hours after the third dose. The maximum recommended daily dose of cetirizine is 20 mg.[4] The other report was of a healthy 37-year-old man with no history of seizures who experienced 2 grand mal seizures, 3 hours apart, after 3 days of taking 25 mg of loratadine daily (in the form of 2 tablets of Claritin [each containing 10 mg loratadine] and 1 tablet of

Table 1: Reports submitted to Health Canada of suspected convulsive adverse reactions (ARs) associated with newer-generation antihistamines from date marketed in Canada to Sept. 19, 2002*

Variable	Loratadine	Cetirizine	Fexofenadine	Desloratadine
Date marketed in Canada	1988	1991	1997	2002
Total no. of AR reports	250	490	465	16
No. of reports with convulsive disorders	9†	7‡	4§	0
History of convulsive disorders	8	3	4	0
No history of convulsive disorders	1	0	0	0
History unknown	0	4	0	0

***These data cannot be used to determine the incidence of ARs or to make quantitative drug safety comparisons between products because ARs are underreported and neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.**
†Age range 17–83 years, median 46 years (age unknown in 3 cases); 4 females, 4 males (sex unknown in 1 case).
‡Age range 25–44 years, median 27 years (age unknown in 1 case); 3 females, 4 males.
§Age range 25–72 years, median 28 years; 3 females, 1 male.

Claritin Extra [containing 5 mg loratadine and 120 mg pseudoephedrine]). The patient had also ingested alcohol (½ beer) the night before the seizure. The recommended daily adult dose of loratadine is 10 mg.[5,6]

Convulsive disorders are serious ARs. Health care professionals are requested to report any suspected cases of seizures or convulsions associated with the use of newer-generation antihistamines to Health Canada. Patients should be reminded to read package labels carefully and not to exceed the recommended or maximum daily dose of any therapeutic health product, including nonprescription drugs. Patients should also be made aware that multiple products may contain the same active ingredients and to consult their health care professional for further information.

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References

1. Ten Eick AP, Blumer JL, Reed MD. Safety of antihistamines in children. *Drug Safety* 2001;24(2):119-47.
2. Blain PG, Lane RJM. Neurological disorders. In: Davies DM, Ferner RE, De Glanville H, editors. *Davies's textbook of adverse drug reactions*. 5th ed. London: Chapman and Hall Medical; 1998. p. 591-3.
3. Murphy K, Delanty N. Drug-induced seizures: general principles in assessment, management and prevention. *CNS Drugs* 2000;14(2):135-46.
4. *Reactine, cetirizine hydrochloride tablets, syrup* [product monograph]. Kirkland (QC): Pfizer Canada Inc; 2000 Sept 29.
5. *Claritin, loratadine tablets, rapid dissolve tongue tablets, syrup* [product monograph]. Pointe-Claire (QC): Schering Canada Inc; 2001 Jun 15.
6. *Claritin Extra, loratadine and pseudoephedrine repetabs tablets* [product monograph]. Pointe-Claire (QC): Schering Canada Inc; 1998 Mar 13.

Communicating Drug Safety Information Workshop — summary report available

Health Canada hosted the *Communicating Drug Safety Information* workshop on Nov. 29–30, 2001, with representatives from the pharmaceutical industry, health professional associations, consumer interest groups and regulatory authorities to discuss how to enhance the reporting and distribution of information about adverse drug events. Participants identified partnership opportunities to assist them in the sharing and communication of drug safety information. A second meeting is being planned for 2003. The summary report from the workshop is available at www.hc-sc.gc.ca/english/protection/summary_report/index.html.

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.

RespirActin

An 18-year-old man used RespirActin (exact dose not indicated) 1 to 3 times per week for 1½ years for the treatment of allergies. RespirActin lists the following ingredients: water, rosemary (leaf), honey, witch hazel (leaf), fenugreek (seed), black cumin (seed), Ho Shou Wu (seed), Chinese ginseng (root), damiana (leaf), marshmallow (leaf), sage (leaf), juniper (fruit), chamomile (flower), clove (fruit), cinnamon (bark), spearmint (leaf) and thyme (leaf). Following 1 week of fatigue the patient presented to hospital and was noted to have jaundice. During the next week the jaundice progressed, with increasing liver failure. Liver biopsy showed extensive fibrosis. The patient's condition progressed to hepatic encephalopathy, which necessitated an orthotopic liver transplant. The AR report indicated that there were no concomitant medications or other medical history and that alcohol use was not a contributing factor. Another potential causal factor identified in the follow-up information for this case was the patient's previous work environment, which was a poorly ventilated area where paint or solvent fumes were present.

Comments: A number of factors must be considered when a natural health product with multiple ingredients is suspected to be associated with an adverse effect. An adulterant or misidentified ingredients could be present in the product that may be responsible for any adverse effects.[1,2] Possible toxicity due to excessive dosing or prolonged intake should also be considered.[1,2] Some herbs may contain hepatotoxins, and others may contribute to idiosyncratic hepatotoxic reactions and may involve an immunological response.[2] There are published cases of hepatic adverse effects associated with Ho Shou Wu (*Polygonum multiflorum*).[3,4] Internal consumption of witch hazel is not recommended because it contains appreciable amounts of hydrolysable tannins.[5] The toxicity of tannins is complex and not well known. Although the tannins in witch hazel are poorly absorbed following oral administration, hepatic damage may occur if they are absorbed to an appreciable extent.[5]

References

1. McMorran M. Adverse reactions to natural health products. *Can Adverse Reaction Newsl* 2002;12(4):1-2.
2. Shivakumar C, Farrell GC. Herbal hepatoxicity: an expanding but poorly defined problem. *J Gastroenterol Hepatol* 2000;15(10):1093-9.
3. But PP, Tomlinson B, Lee KL. Hepatitis related to the Chinese medicine Shou-wu-pian manufactured from Polygonum multiflorum. *Vet Human Toxicol* 1996;38(4):280-2.
4. Park GJH, Mann SP, NGU MC. Acute hepatitis induced by Shou-Wu-Pian, a herbal product derived from Polygonum multiflorum. *J Gastroenterol Hepatol* 2001;16(1):115-7.
5. Witch hazel. In: DerMarderosian A, editor. *The review of natural products*. St. Louis (MO): Facts and Comparisons Inc.; 1997.

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.

How to report adverse reactions

To report a suspected adverse reaction (AR) to therapeutic products marketed in Canada, health professionals should complete a copy of the AR Reporting Form (see page 6). Copies of this form are also available from your Regional AR Centre or the National AR Centre (see addresses below), the *Canadian Compendium of Pharmaceuticals and Specialties* (*CPS*) and the Health Canada Web site (www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/forms/adverse_e.pdf).

British Columbia
BC Regional AR Centre
c/o BC Drug and Poison Information Centre
1081 Burrard St.
Vancouver BC V6Z 1Y6
Tel: 604 806-8625; Fax: 604 806-8262
adr@dpic.bc.ca

Saskatchewan
Sask AR Regional Centre
Saskatchewan Drug Information Service
College of Pharmacy and Nutrition
University of Saskatchewan
110 Science Place
Saskatoon SK S7N 5C9
Tel: 306 966-6340 or 800 667-3425
Fax: 306 966-2286
vogt@duke.usask.ca

Ontario
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All other provinces and territories
National AR Centre
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Finance Building, Tunney's Pasture
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Tel: 613 957-0337; Fax 613 957-0335
Toll free: Tel 866 234-2345; Fax 866 678-6789

Summary of health professional and consumer advisories issued since Aug. 22, 2002
(advisories are available at www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/advhp_e.html and www.hc-sc.gc.ca/english/protection/warnings/2002.htm)

Date	Product	Subject and type
Nov 26	Tamoxifen	Tamoxifen associated with increased risk of stroke, pulmonary embolism and uterine cancer — consumer information
Nov 7	Tamoxifen	Important safety information regarding tamoxifen — health professional advisory
Oct 31	Serzone-5HT$_2$/ Seroquel	Important safety information regarding medication errors resulting from confusion between Seroquel and Serzone-5HT$_2$ — AstraZeneca and Bristol–Myers Squibb — health professional advisory and consumer information
Oct 30	Refludan	Important safety information regarding Refludan — Berlex Canada Inc. — health professional advisory
Oct 22	Menomune	Urgent vaccine recall — voluntary recall of single-dose Menomune – A/C/Y/W-135 (meningococcal polysaccharide vaccine groups A, C, Y and W-135 combined) — Aventis Pasteur — health professional advisory
Oct 17	Risperdal (risperidone)	Updated safety information for Risperdal (risperidone) in elderly dementia patients, announced in Canada by Janssen–Ortho Inc. — consumer information
Oct 11	Risperdal (risperidone)	Important drug safety information: Risperdal (risperidone) and cerebrovascular adverse events in placebo-controlled dementia trials by Janssen–Ortho Inc. — health professional advisory
Sept 20	Infant formulas	*Enterobacter sakazakii* infection and powdered infant formulas — health professional advisory
Aug 27	Cryolife tissues	Risks associated with soft tissues from Cryolife Inc. used for transplantation — notice to hospitals

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Canadian Adverse Reaction Newsletter

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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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Health Canada / Santé Canada

Canadian Adverse Drug Reaction Monitoring Program

Report of suspected adverse reaction
due to drug products marketed in Canada
(Vaccines excluded)

Health Products and Food Branch
Direction générale des produits de santé et des aliments

- See page 5 for return address.
- La version française de ce document est disponible sur demande. Voir page 5 pour connaître le centre à contacter.

PROTECTED

A. Patient Information

1. Patient identifier	2. Age at time of reaction	3. Sex	4. Height	5. Weight
	_____ or	☐ Male	_____ feet	_____ lbs
Chart Number	**Date of birth** DD MM YYYY	☐ Female	**or** _____ cm	**or** _____ kgs

B. Adverse Reaction

1. Outcome attributed to adverse reaction (check all that apply)

- ☐ Death _____ (dd / mm / yyyy)
- ☐ Disability
- ☐ Life-threatening
- ☐ Congenital malformation
- ☐ Hospitalization
- ☐ Required intervention to prevent damage / permanent impairment
- ☐ Hospitalization - prolonged
- ☐ Other: _____

2. Date and time of reaction DD MM YYYY

3. Date of this report DD MM YYYY

4. Describe reaction or problem

5. Relevant tests / laboratory data (including dates (dd / mm / yyyy)

6. Other relevant history, including preexisting medical conditions (e.g. allergies, pregnancy, smoking and alcohol use, hepatic / renal dysfunction)

C. Suspected drug product(s) (See "How to report" section on reverse)

1. Name (give labelled strength & manufacturer, if known).
#1
#2

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration)
#1	#1 From (dd / mm / yyyy) - To (dd / mm / yyyy)
#2	#2

4. Indication for use of suspected drug product	5. Reaction abated after use stopped or dose reduced
#1	#1 ☐ Yes ☐ No ☐ Doesn't apply
#2	#2 ☐ Yes ☐ No ☐ Doesn't apply

6. Lot # (if known)	7. Exp. date (if known)	8. Reaction reappeared after reintroduction
#1 _____	#1 (dd / mm / yyyy) _____	#1 ☐ Yes ☐ No ☐ Doesn't apply
#2	#2	#2 ☐ Yes ☐ No ☐ Doesn't apply

9. Concomitant drugs (name, dose, frequency and route used) and therapy dates (dd / mm / yyyy) (exclude treatment of reaction)

10. Treatment of adverse reaction (drugs and / or therapy), **including dates** (dd / mm / yyyy)

D. Reporter (See "Confidentiality" section on reverse)

1. Name, address & phone number.

2. Health professional?	3.Occupation	4. Also reported to manufacturer?
☐ Yes ☐ No		☐ Yes ☐ No

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the adverse reaction.

Canada