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Health Product InfoWatch

December 2023

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REPORTING ADVERSE REACTIONS

Canada Vigilance Program
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This monthly publication is intended primarily for healthcare professionals and includes information on pharmaceuticals, biologics, medical devices and natural health products. It provides a summary of key health product safety information published in the previous month by Health Canada, as well as a selection of new health product safety information meant to raise awareness. New information contained in this issue is not comprehensive but rather represents a selection of clinically relevant items warranting enhanced dissemination.

ANNOUNCEMENT

Handbook for healthcare professionals on biosimilar biologic drugs

The Handbook for healthcare professionals on biosimilar biologic drugs is now available on Health Canada's website. This handbook was developed, in consultation with a working group composed of subject matter experts from Health Canada and health professional associations, to inform healthcare professionals in Canada, including doctors, nurses and pharmacists, on biosimilar biologic drugs (biosimilars). The handbook provides objective, evidence-based information on the regulation and scientific basis for the authorization of biosimilars by Health Canada.

Visit the web page to learn more about the distinct nature of biosimilars as compared to generic drugs ("About"), data requirements for the authorization of biosimilars ("Data requirements"), and immunogenicity among other related topics.

MONTHLY RECAP OF HEALTH PRODUCT SAFETY INFORMATION

The following is a list of health product advisories, type I drug recalls and summaries of completed safety reviews published in November 2023 by Health Canada.

Baxter intravenous solution bags **Type 1 drug recalls:** 0.4% Lidocaine Hydrochloride & 5% Dextrose Injection 0.9% Sodium Chloride Injection, USP Lactated Ringer's Injection Metronidazole Injection, USP	Baxter Corporation recalled additional affected lots of: 0.4% Lidocaine Hydrochloride and 5% Dextrose Injection; 0.9% Sodium Chloride Injection, USP; Lactated Ringer's Injection; and Metronidazole Injection, USP; as the solution bags may be leaking.
Cord Blood Advisory	A site visit by Health Canada to the Canadian Cord Blood bioRepository, located in Edmonton, Alberta, has identified significant issues that may pose serious health risks. The issues identified at the site could lead to the possibility of contamination and/or the transmission of infectious diseases and could negatively impact the cord blood stored.
Donepezil Advisory	Pro Doc Limitée recalled one lot of Donepezil (donepezil hydrochloride) 10 mg tablets due to the possibility that some bottles might contain oversized tablets. Health Canada is warning patients and their caregivers that an oversized tablet could have up to 3 times the intended dose.

Herbaland brand gummy vitamins and supplements Advisory	Herbaland Naturals Inc. recalled all Herbaland gummy vitamins and supplements sold in bulk as they may pose serious health risks if misused, particularly for children and pregnant people. The products were sold at various bulk, low- or zero-waste refillery stores in Canada. Because the products are sold with little to none of the required labelling, consumers do not have the information they need to take the gummies safely, including dosing instructions, ingredients and safety warnings.
Nitroglycerin Sprays Advisory	Mylan reported ongoing supply issues with an unknown resolution date for its shortage of nitroglycerin 0.4 MG/ACT spray. To help mitigate this shortage, Health Canada authorized the importation and sale of UK-authorized nitroglycerin spray from Juno Pharmaceuticals Canada. The company is working to bring supply into Canada and to make it available as soon as possible.
Sabril (vigabatrin) Advisory	Lundbeck Canada Inc. released one lot of Sabril (vigabatrin) 500 mg tablets on the Canadian market found to contain trace amounts of another prescription drug, tiapride. The tablets were released given the current shortage and no immediate available alternative supply. Unless patients have a severe allergy to tiapride, the benefits of this drug are expected to continue to outweigh its potential risks despite the presence of trace amounts of tiapride. Patients are advised to not stop taking Sabril without consulting their healthcare professional. Health Canada has permitted the importation of foreign-authorized tablets and is working with the importer to determine when they will be available at pharmacies.
Unauthorized health products Advisory: Unauthorized blood glucose-reading smartwatches Unauthorized sexual enhancement products Unauthorized skin lightening and skin treatment products	Health Canada advised Canadians about various unauthorized health products being sold at retail locations across Canada or online that may pose serious health risks.

NEW HEALTH PRODUCT SAFETY INFORMATION

The following topics have been selected to raise awareness and encourage reporting of adverse reactions.

Safety brief

Bag-valve masks and the risk of hypoxemia in spontaneously breathing patients

A bag-valve mask (BVM), also known as a manual resuscitator or self-inflating bag, is a device commonly used to provide oxygen to patients who are not breathing or not breathing effectively (Figure 1). It is also used in spontaneously breathing patients, such as for preoxygenation before anesthesia induction and intubation.[1]

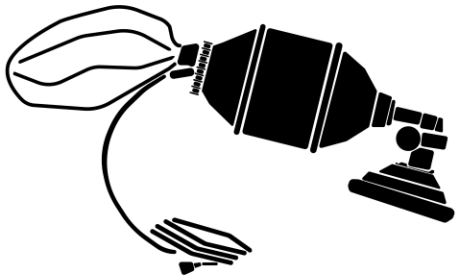


Figure 1: Sample image of a bag-valve mask (hand breathing bag)

Health Canada recently reviewed several studies comparing inspired oxygen concentrations of BVMs with different valve designs under conditions mimicking spontaneously breathing patients (i.e., without manual assistance). Evidence shows that some BVM designs, particularly those lacking a valve or disk at the expiratory port, may not perform adequately when used during spontaneous ventilation.[1-10]

Bag-valve masks with a single valve design and without a unidirectional valve or disk present at the expiratory port can cause significant incorporation of room air during spontaneous respiration. They may also limit a patient's ability to generate enough negative pressure within the mask during spontaneous breathing to fully open the inspiratory valve.[3] These factors can reduce the inspired oxygen concentrations to as low as 40%.[1-4,9] Based on clinical recommendations, optimal preoxygenation is achieved when end-tidal oxygen concentration is at least 85%. Using a BVM in spontaneously breathing patients may result in hypoxemia if there is suboptimal oxygen delivery.[1,9]

A positive end-expiratory pressure (PEEP) valve may be used with a BVM to improve oxygenation and reduce incorporation of room air during spontaneous ventilation.[1] Studies have also shown, however, that the addition of a PEEP valve may cause increased inspiratory resistance in spontaneously breathing patients. Monitoring inspiratory resistance, where possible, and manual assistance of ventilation may help reduce the risk of suboptimal ventilation in these situations.[4,9,10]

Key messages for healthcare professionals:

- BVMs can be used safely to supplement oxygen to patients, regardless of valve design, when used for positive pressure ventilation.[11]

- There are reports that some BVM devices fail to deliver adequate inspired oxygen when used in spontaneously breathing patients due to variability in design. In particular, BVMs without an additional valve or disk at the expiratory port may deliver low oxygen concentrations.[1-10]
- Consider using other devices (such as high-flow nasal cannulas) or assisting in positive pressure ventilation with a BVM for the purpose of supplementing oxygen to spontaneously breathing patients.[1,3,4,8,11]
- Consider contacting the manufacturer directly about the suitability of the device for various negative pressure applications, such as for spontaneous ventilation and/or preoxygenation.

Healthcare professionals are encouraged to report medical device incidents and adverse events suspected of being associated with the use of a BVM, including, but not limited to, its use in a spontaneous ventilation and/or preoxygenation setting. Health Canada will continue to monitor the safety of BVMs and will take appropriate action should new health risks be identified.

References

1. Grauman S, Johansson J, Drevhammar T. Large variations of oxygen delivery in self-inflating resuscitation bags used for preoxygenation - a mechanical simulation. *Scand J Trauma Resusc Emerg Med*. 2021;29(1):98. Published 2021 Jul 19. doi:10.1186/s13049-021-00885-3
2. Kwei P, Matzelle S, Wallman D, Ong M, Weightman W. Inadequate preoxygenation during spontaneous ventilation with single patient use self-inflating resuscitation bags. *Anaesth Intensive Care*. 2006;34(5):685-686.
3. Nimmagadda U, Salem MR, Joseph NJ, et al. Efficacy of preoxygenation with tidal volume breathing. Comparison of breathing systems. *Anesthesiology*. 2000;93(3):693-698. doi:10.1097/00000542-200009000-00018
4. Kazlovic K, Anwari V and Mashari A. Bag-Valve-Mask (BVM) Performance Evaluation Report. Published online February 22, 2021. Updated April 7, 2021. Accessed October 1, 2023.
5. Khoury A, Hugonnot S, Cossus J, et al. From mouth-to-mouth to bag-valve-mask ventilation: evolution and characteristics of actual devices--a review of the literature. *Biomed Res Int*. 2014;2014:762053. doi:10.1155/2014/762053
6. Mills PJ, Baptiste J, Preston J, Barnas GM. Manual resuscitators and spontaneous ventilation--an evaluation. *Crit Care Med*. 1991;19(11):1425-1431. doi:10.1097/00003246-199111000-00020
7. Godoy AC, Vieira RJ, Vieira Neto RJ. Oxygen outflow delivered by manually operated self-inflating resuscitation bags in patients breathing spontaneously. *J Bras Pneumol*. 2008;34(4):212-216. doi:10.1590/s1806-37132008000400005
8. Groombridge C, Chin CW, Hanrahan B, Holdgate A. Assessment of Common Preoxygenation Strategies Outside of the Operating Room Environment. *Acad Emerg Med*. 2016;23(3):342-346. doi:10.1111/acem.12889
9. Broc A, Morin F, Schmit H, et al. Performances and limits of Bag-Valve-Device for pre-oxygenation and manual ventilation: A comparative bench and cadaver study. *Resuscitation*. Published online October 12, 2023. doi:10.1016/j.resuscitation.2023.109999
10. Hess D, Hirsch C, Marquis-D'Amico C, Kacmarek RM. Imposed work and oxygen delivery during spontaneous breathing with adult disposable manual ventilators. *Anesthesiology*. 1994;81(5):1256-1263. doi:10.1097/00000542-199411000-00020
11. Becker DE, Rosenberg MB, Phero JC. Essentials of airway management, oxygenation, and ventilation: part 1: basic equipment and devices. *Anesth Prog*. 2014;61(2):78-83. doi:10.2344/0003-3006-61.2.78

Adverse reactions to health products: annual report 2022

Introduction

Post-market reporting systems help in the identification and analysis of new safety information for health products so that appropriate action can be taken to minimize risks to human health. In Canada, adverse reactions (ARs) or medical device incidents (MDIs) suspected of being associated with the use of health products can be reported to the Canada Vigilance Program (CVP). This report summarizes information about domestic AR cases reported for pharmaceuticals, natural health products, biologics, radiopharmaceuticals, disinfectants, and sanitizers with disinfectant claims received by the CVP in 2022. Although foreign AR cases are included in the internal CVP database, they are not included in this report.

Domestic adverse reaction reports and cases

In 2022, Health Canada received 207,238 domestic post-market AR reports. These reports represented 74,540 AR cases (Table 1). A case consists of all information describing the AR(s) experienced by one patient at one time, which is suspected of being related to the use of one or more health products. A case may include an initial AR report and possibly several follow-up reports that provide additional information. Duplicate cases may exist if an AR report about the same event was received from different reporters (e.g., from a healthcare professional, consumer, hospital, and/or manufacturer).

Table 1: Number of domestic AR cases reported in 2022, by product type

Product type	No. (%) of reports
Pharmaceuticals	39,641 (53.2)
Biologics*	33,457 (44.9)
Radiopharmaceuticals	511 (0.7)
Natural health products	307 (0.4)
Other†	624 (0.8)
Total	74,540 (100)

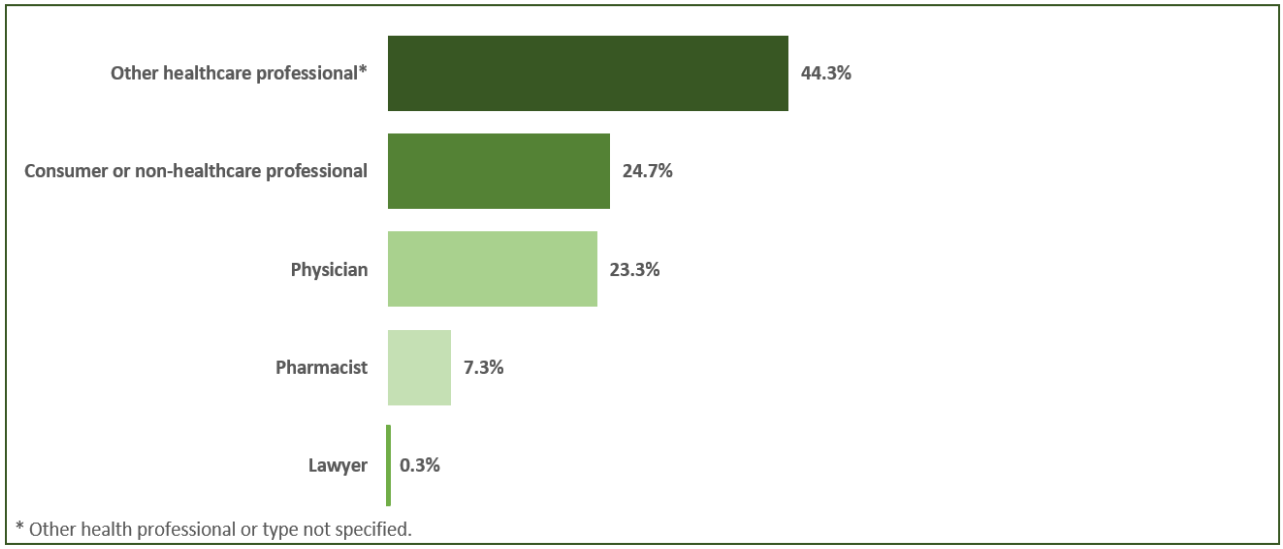
* Biologics include biotechnology products; vaccines; fractionated blood products; human blood and blood component products; human cells, tissues, and organs; and sperm and ova products.

† Other includes those without an Anatomical Therapeutic Chemical Classification System (ATC) code.

In Canada, Market Authorization Holders (MAHs) and hospitals are required to submit AR reports to the CVP in accordance with the requirements of the *Food and Drugs Act* and its Regulations. For serious ARs that have occurred in Canada, MAHs are required to send a report within 15 days of becoming aware of the incident. In accordance with the Protecting Canadians from Unsafe Drugs Act (Vanessa's Law), hospitals are required to send all reports of serious ARs to therapeutic products that have been documented in their facility within 30 days of documentation. Community members (consumers, patients and non-hospital-based healthcare professionals) can voluntarily submit AR reports at any time.

In 2022, MAHs submitted 88.8% of all domestic AR cases. The remaining cases were mainly submitted by hospitals (5.6%) and community members (5.3%). For most of the domestic AR cases reported to Health Canada directly or via a MAH, the originating reporter was a healthcare professional (Figure 1).

Figure 1: Number of domestic AR cases reported in 2022, by type of originating reporter



Sex and age distribution

The distribution for the 74,540 cases by sex was 58.0% female, 38.5% male and 3.5% unknown or unreported, which reflects the sex distribution of AR cases seen globally.[1] The distribution by age group was 3.8% pediatric (< 19 years), 54.3% adult (19-64 years), 28.4% elderly (≥ 65 years) and 13.5% age unknown or unreported.

Suspect products and adverse reactions

The top 10 groups of suspect products most commonly identified in domestic AR cases are listed in Table 2. The groups are classified according to the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification system.

Table 2: Top 10*† suspect health product groups most commonly identified in domestic AR cases reported in 2022, by ATC group

Health product (ATC group)	No. (%) of times reported‡
Immunosuppressants (L04)	32,866 (44.2)
Antineoplastic agents (L01)	12,857 (17.3)
Vaccines (J07)	4,025 (5.4)
Psycholeptics (N05)	3,481 (4.7)
Analgesics (N02)	2,953 (4.0)
Drugs for obstructive airway diseases (R03)	2,358 (3.2)
Antiepileptics (N03)	2,295 (3.1)
Corticosteroids for systemic use (H02)	1,867 (2.5)
Antibacterials for systemic use (J01)	1,822 (2.4)
Psychoanaleptics (N06)	1,425 (1.9)

* Solicited reports or organized data collection systems (e.g., patient registries, surveys, patient support and disease management programs) may affect the total number of ARs reported for specific products or product types.

† One case may involve one or more suspect product(s).

‡ This indicates the number of cases that had one or more occurrences of the suspect health product (ATC group).

Table 3 displays the top 10 domestic ARs reported to the CVP based on System Organ Class codes. The ARs are coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology. The most commonly reported ARs were general disorders and administration site conditions, which include disorders that affect several body systems or sites (e.g., drug ineffective, fatigue, fever, edema, pain, reactions at the administration site), followed by injury, poisoning and procedural complications.

Table 3: Top 10 domestic ARs reported in 2022, by System Organ Class*†

System Organ Class	No. (%) of times reported‡
General disorders and administration site conditions	43,236 (58.1)
Injury, poisoning and procedural complications	21,476 (28.9)
Infections and infestations	17,631 (23.7)
Gastrointestinal disorders	15,539 (20.9)
Investigations	13,999 (18.8)
Nervous system disorders	13,186 (17.7)
Musculoskeletal and connective tissue disorders	12,431 (16.7)
Skin and subcutaneous tissue disorders	9,613 (12.9)
Respiratory, thoracic and mediastinal disorders	9,593 (12.9)
Psychiatric disorders	6,520 (8.8)

* MedDRA version 26.1. Reactions are at preferred term level.

† One case may contain one or more reaction(s).

‡ This indicates the number of cases that had one or more occurrences of the AR.

Reason for seriousness

Of the 74,540 AR cases, 73.4% were considered serious.* A case can have more than one reported reason for seriousness. In 2022, 22.8% of all AR cases indicated that hospitalization was required, 2.5% indicated a life-threatening condition, and 8.6% indicated a death had occurred.

Investigation of reported adverse reactions

As part of routine surveillance monitoring activities, an AR report submitted to the CVP is assessed for potential safety issues and signals through progressing levels of escalation. Results of concern are presented to the evaluation bureau responsible for the product for signal confirmation, prioritization, and assessment.

When a reported AR is known and included in the product monograph, it is not considered to be a new signal unless there is a change in the frequency or severity of the AR. Post-market ARs may be attributed to a variety of factors, including previously unrecognized pharmacological effects of the product, idiosyncratic effects, drug interactions (e.g., drug-drug, drug-disease, drug-natural health product interactions), individual

patient factors (e.g., pharmacogenomic factors), medication incidents, or other factors that may have been too infrequent to be identified in clinical trials.

It is difficult to compare the risk of health products based solely on submitted reports. Several factors may influence AR reporting patterns, such as the known risks associated with a product, the length of time a product has been on the market, volume of use, publicity about an AR, regulatory actions taken to minimize risks, and/or method of data collection. For example, rare and serious ARs may be reported more frequently in organized data collection systems[†] compared to voluntary reporting, which may affect the pattern of reporting. In general, there is underreporting of adverse events to spontaneous reporting programs like the CVP.

Adverse reaction reports are an important part of Health Canada's monitoring of health products. These reports, along with other sources of information from domestic and international sources, help in the identification and analysis of new safety information to support Health Canada's decisions to take action. For example, a causal association between the product and the AR may prompt an action from Health Canada. The same applies if new risks are determined from a cluster of similarly reported ARs, or from AR reports suggesting labelling gaps or product quality issues.

Drug-related information received and assessed by Health Canada may result in actions including communicating new safety information to Canadians and healthcare professionals, addressing false or misleading advertising, or other regulatory actions such as recommending label changes or removing a drug product from the market. Important new safety information for healthcare professionals and Canadians is communicated via the Recalls and Safety Alerts Database on the Healthy Canadians website. Safety information is also distributed through the MedEffect™ e-Notice email notification system. In addition, in 2022 Health Canada published 11 summaries of its safety reviews, which describe Health Canada's findings and risk management actions related to potential safety issues.

Conclusion

Each year, the CVP receives thousands of reports that contribute to a better understanding of the safety associated with the use of marketed health products. Health Canada would like to thank all who have contributed information and encourage the continued support of post-market surveillance through AR and MDI reporting. Any ARs or MDIs suspected of being associated with the use of health products should be reported to the CVP. Every report counts, and together, they tell a story.

Reference

1. Watson, S., Caster, O., Rochon, P.A. & den Ruijter, H. (2019). Reported adverse drug reactions in women and men: Aggregated evidence from globally collected individual case reports during half a century. *EClinicalMedicine,* 17*,* 100188, ISSN 2589-5370. https://doi.org/10.1016/j.eclinm.2019.10.001.

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- MedEffect™ Canada
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- Canada Vigilance Adverse Reaction Online Database
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Suggestions?

Your comments are important to us. Let us know what you think by reaching us at: infowatch-infovigilance@hc-sc.gc.ca

Health Product InfoWatch Editorial Team
Marketed Health Products Directorate, Health Canada
Address Locator 1906C, Ottawa ON K1A 0K9
Telephone: 613-954-6522 Teletypewriter: 1-800-465-7735 (Service Canada)

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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.

Due to time constraints relating to the production of this publication, information published may not reflect the most current information.

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* In the *Food and Drugs Act* and Regulations, a serious AR is defined as "a noxious and unintended response to a drug that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death". Other situations may also warrant a designation as serious, "such as medically important events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition from the Regulations".

† Organized data collection systems include patient registries, surveys, and patient support or disease management programs.