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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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LigaSure vessel sealing system and torn vessels

Key points

- Health Canada has received reports of incidents in which LigaSure instruments were sticking to tissue or clamping onto tissue and not releasing.
- Excessive sticking can lead to tearing of tissue after sealing and can interfere with the proper functioning of the instrument.
- Health care professionals should be aware of this limitation of LigaSure vessel sealing systems and are encouraged to report adverse incidents to Health Canada.

The LigaSure Dolphin Tip (formally called LigaSure V) laparoscopic vessel sealer/divider (LS1500) is a single-use class II medical device (IV being the highest risk class). The device is intended for use with a manufacturer-approved power source to seal vessels 7 mm in diameter or smaller, and to produce hemostasis in arteries, veins and tissue bundles.[1,2] The instrument can also be used to seal pulmonary vasculature but only when used with the ForceTriad Energy Platform generator.[1] The LS1500 model (first marketed on Dec. 4, 2003) is one of 6 LigaSure laparoscopic instruments marketed in Canada by Covidien.

As of March 2012, Health Canada received 24 reports of incidents suspected of being associated with the use of the LigaSure V instrument. Incidents described in the reports included stripped insulation, malfunction of the device, pieces of the device falling into the body cavity requiring retrieval, and inadequate sealing by the device. Nine of the reports described a problem of the tip of the instrument sticking to tissue or the instrument jaws clamping on tissue and not releasing, which often required physical manipulation or cutting the device off the tissue to release it. One of the 9 cases was included in the 2011 annual report of the Paediatric Death Review Committee and Deaths Under Five Committee published by the Office of the Chief Coroner, Province of Ontario.[3] The reported incident described the death of a 7-month-old infant who underwent surgical correction of a cystic lesion in his lung (intralobular sequestration of the left lower lobe) using the LigaSure V instrument and the LigaSure vessel-sealing generator. The patient's death from hemorrhagic shock was related to tearing of the pulmonary vein because of tissue sticking on the jaws of the device despite cleaning efforts.[3] In another reported incident, the device's propensity to stick to tissue led to blood loss but was described as insignificant and resulted in no further complication to the patient. The remaining 7 reports

mentioned no injuries or ill effects to the patient.

The issue of increased stickiness and difficulty in releasing the jaws of the device from tissue extends to other LigaSure devices as well. For example, as of March 2012, Health Canada received 18 reports of incidents suspected of being associated with the use of the LigaSure ATLAS instrument. Although some of the reports described incidents involving device damage or malfunction, 10 of the 18 reports were related to the stickiness of the tip or difficulty in releasing the jaws of the device. In one case, the device stuck to the tissue, resulting in a torn vessel, a blood transfusion and admission of the patient to the critical care unit. Another 3 reports described minimal bleeding because of the tip sticking, but no patient harm was reported. The remaining 6 cases reported no patient injury or serious deterioration in health.

There is evidence in the literature of the successful use of the LigaSure vessel sealing system during pediatric thoracoscopic procedures involving pulmonary vasculature.[4–6] However, one published study, involving sheep, noted a tendency of the jaws of the device to stick to tissue.[7] Irrigation and careful manipulation were required to release the sealed area unharmed.[7]

Many factors can contribute to increased charring and sticking of the tip to tissue. These factors include, but are not limited to, eschar in between the jaws due to a build-up of blood between the jaws, not using the device as per the instructions, using the device on a high-power setting or a large-power surge, and using the device beyond its intended use.[3,7]

There is a need to minimize the risk of tissue sticking to the instrument jaws, because excessive sticking can lead to tearing of tissue after sealing and can interfere with the proper functioning of the instrument.[3] Methods to minimize sticking include (a) keeping the jaws clean at all times; (b) cleaning the instrument more frequently when working in a bloody field; (c) decreasing the bar setting of the power source if consistent sticking is encountered;[3] and (d) having the sensor system calibrated at least once a year. In addition, experience with endoscopic manoeuvres within a small operative field, especially during thoracoscopic lobectomy in a small child, is recommended.[8]

Health care professionals are encouraged to report adverse incidents suspected of being associated with the use of the LigaSure vessel sealing system to the Health Products and Food Branch Inspectorate through the toll free hotline (1-800-267-9675).

Rana Filfil, PhD, Health Canada

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CARN is "going green"

Starting with the October 2012 issue, the *Canadian Adverse Reaction Newsletter* (*CARN*) will be made available exclusively in an electronic format on the MedEffect™ Canada Web site. The paper format will no longer be available. As a result, *CARN* will significantly reduce its carbon footprint in an effort to be more environmentally friendly. The electronic version of the Newsletter will continue to feature topics related to serious or unexpected adverse reactions suspected of being associated with drugs, natural health products and medical devices marketed in Canada.

Visit the MedEffect™ Canada Web site at www.health.gc.ca/medeffect to view or to subscribe to the Newsletter. The consolidation of health product safety information, including *CARN*, on the MedEffect™ Canada Web site is intended to promote centralized access to relevant and reliable information as it becomes available, in an easy to find, easy to remember location. A MedEffect™ e-Notice will be sent to all subscribers upon the release of a new electronic issue of *CARN*. Subscribers will also receive updates on health product advisories posted on Health Canada's Web site.

Adverse reaction and incident reporting — 2011

Canada Vigilance Program

The Canada Vigilance Program collects reports of suspected adverse reactions (ARs) to health products (pharmaceuticals, biotechnology products, blood products and biologics, natural health products, radiopharmaceuticals, and cells, tissues and organs). Further information about the program and its database can be found at www.health.gc.ca/medeffect.

Domestic and foreign AR reports

In 2011, Health Canada received 41 923 domestic AR reports,* of which 78% were considered to be serious.† Domestic AR reports received by product type are provided in Table 1. The 41 923 reports represent 28 675 AR cases. A case consists of all information describing the AR(s) experienced by one patient at one time and suspected of being related to the use of one or more health products; thus, an AR case will include an initial AR report as well as any subsequent additional information received as follow-up report(s).

In Canada, Market Authorization Holders (MAHs) are required to submit AR reports received in accordance with the requirements of the *Food and Drugs Act* and Regulations. MAHs are required to send, within 15 days, all reports of serious ARs that have occurred in Canada (domestic) and all reports of serious unexpected ARs‡ that have occurred outside Canada (foreign) to the Canada Vigilance Program. In 2011, MAHs submitted 81.8% of all the domestic reports received. The remaining reports were received directly from the community and hospitals (Table 2).

The number of domestic AR reports was 27.3% higher in 2011 than in 2010 (Fig. 1). Most of the domestic reports received by both MAHs and Health Canada originated from health care professionals (Table 3).

In 2011, the number of foreign AR reports received from MAHs was 454 822 (Fig. 2). At this time, foreign reports are not included in the Canada Vigilance database.

Sex and age

The distribution for the 28 675 cases by sex was 58% female, 37% male and 5% sex unknown. The distribution by age group was 6% pediatric (< 19 years), 51% adult (19–64 years), 26% elderly (≥ 65 years) and 17% age unknown.

Suspect products

The top 10 groups of suspect products most commonly identified in AR reports are listed in Table 4. Anatomical Therapeutic Chemical (ATC) groups are classified according to the World Health Organization's ATC classification system (www.whocc.no/atc_ddd_index). Several factors may influence the number of ARs reported for a specific health product or product type, such as length of time a product is on the market, volume of use, publicity of an AR, regulatory actions, method of data collection (reports submitted voluntarily v. organized data-collection systems). For example, ARs may be reported more frequently in organized data-collection systems (e.g., patient

Table 1: Number of domestic reports* of adverse reactions by product type in 2011

Product type	No. (%) of reports
Pharmaceuticals	27 602 (65.8)
Biotechnology products	12 419 (29.6)
Blood products and biologics	827 (2.0)
Natural health products	680 (1.6)
Radiopharmaceuticals	350 (0.8)
Cells, tissues and organs	45 (0.1)
Total	41 923 (100.0)

*Canada Vigilance receives reports for both initial and follow-up information concerning suspected adverse reactions.

*This excludes AR reports received for product types that do not fall under the review of the Canada Vigilance Program, as outlined above. These reports were redirected to the appropriate AR reporting program.

†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."

‡In the *Food and Drugs Act* and Regulations, a serious unexpected AR is defined as "a serious adverse drug reaction that is not identified in nature, severity or frequency in the risk information set out on the label of the drug."

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.

registries, surveys, patient support and disease management programs) and may affect the pattern of reporting. It is not possible to compare the risk of health products based solely on numbers of AR reports. In addition, rare and serious reactions may not necessarily represent a large number of reported ARs.

Adverse reactions

Table 5 displays the top 10 ARs reported to the Canada Vigilance Program, based on System Organ Class.§ 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). The next most common ARs were gastrointestinal disorders.

Conclusion

Health Canada would like to thank all who have contributed to the Canada Vigilance Program and encourages the continued support of postmarketing surveillance through AR reporting. The purpose of postmarket spontaneous reporting systems is the identification and

Table 2: Number of domestic reports* of adverse reactions by source in 2011

Source	No. (%) of reports
MAH	34 307 (81.8)
Community†	6 451 (15.4)
Hospital	1 108 (2.6)
Other	57 (0.1)
Total	41 923 (100.0)

Note: MAH = Market Authorization Holder.

*Canada Vigilance receives reports for both initial and follow-up information concerning suspected adverse reactions.

†Consumer, patient and non-hospital–based health care professionals.

Table 3: Number of domestic reports* of adverse reactions by type of originating reporter in 2011

Reporter type	No. (%) of reports
Consumer/patient	11 503 (27.4)
Physician	10 052 (24.0)
Nurse	7 319 (17.5)
Health professional†	6 674 (15.9)
Pharmacist	5 418 (12.9)
Dentist	7 (0.02)
Naturopath	2 (0.005)
Other	948 (2.3)
Total	41 923 (100.0)

*Canada Vigilance receives reports for both initial and follow-up information concerning suspected adverse reactions.

†Type not specified in report.

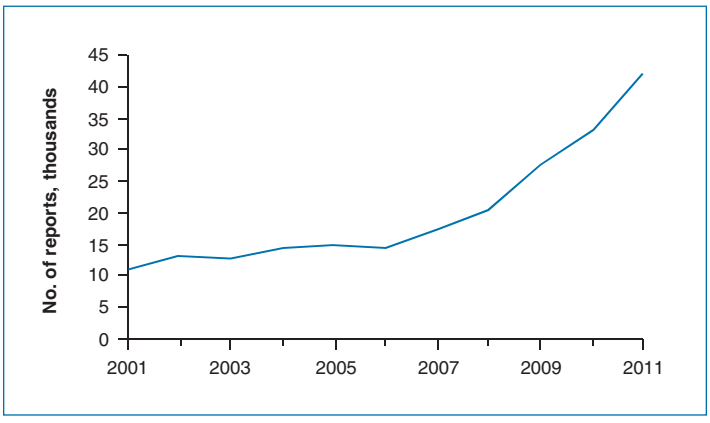

Fig. 1: Number of domestic reports of adverse reactions received by Health Canada from 2001 to 2011.

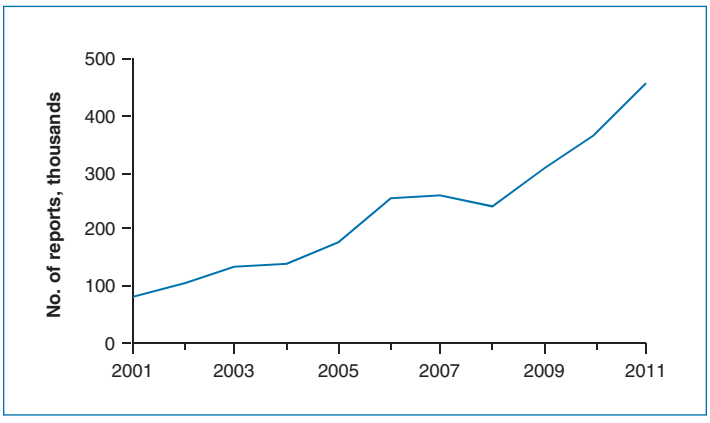

Fig. 2: Number of foreign reports of adverse reactions received by Health Canada from Market Authorization Holders from 2001 to 2011.

§Adverse reactions are coded using the Medical Dictionary for Regulatory Activities (MedDRA) Terminology. The terminology is organized in a hierarchical structure where the System Organ Class is the highest level of the hierarchy and represents the broadest concept of groupings. Further information about the MedDRA Terminology can be found at www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/meddra-eng.php.

analysis of new safety information for health products. Any ARs suspected of being associated with the use of health products can be reported to the Canada Vigilance Program (www.health.gc.ca/medeffect).

Table 4: Top 10 groups of suspect health products most commonly reported in 2011, by Anatomical Therapeutic Chemical (ATC) group*

Health product (ATC group)	No. (%) of times reported†
Immunosuppressants (L04)	7 708 (23.3)
Psycholeptics‡ (N05)	2 461 (7.4)
Drugs for treatment of bone diseases (M05)	1 872 (5.7)
Psychoanaleptics‡ (N06)	1 588 (4.8)
Antineoplastic agents (L01)	1 493 (4.5)
Analgesics (N02)	1 424 (4.3)
Agents acting on the renin–angiotensin system (C09)	1 286 (3.9)
Antithrombotic agents (B01)	1 058 (3.2)
Antibacterials for systemic use (J01)	1 045 (3.2)
Pituitary and hypothalamic hormones and analogues (H01)	825 (2.5)

*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 contain one or more suspect product(s). The total number of suspect health products reported was 33 063 in a total of 28 675 cases.

‡N05 psycholeptics: antipsychotics, anxiolytics, hypnotics and sedatives; N06 psychoanaleptics: antidepressants, psychostimulants, psycholeptics and psychoanaleptics in combination, anti-dementia drugs.

Table 5: Top 10 adverse reactions reported in 2011, by System Organ Class*

System Organ Class	No. (%) of times reported†
General disorders and administration site conditions	16 580 (20.8)
Gastrointestinal disorders	8 539 (10.7)
Nervous system disorders	7 484 (9.4)
Investigations	5 539 (7.0)
Psychiatric disorders	4 970 (6.3)
Skin and subcutaneous tissue disorders	4 547 (5.7)
Infections and infestations	4 375 (5.5)
Musculoskeletal and connective tissue disorders	4 286 (5.4)
Injury, poisoning and procedural complications	4 045 (5.1)
Respiratory, thoracic and mediastinal disorders	3 864 (4.9)

**Medical Dictionary for Regulatory Activities* (MedDRA) Terminology, version 13.1; reactions at preferred term level. Further information about the MedDRA terminology can be found at www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/meddra-eng.php.

†One case may contain one or more reaction(s). The total number of ARs reported was 79 571 in a total of 28 675 cases.

Medical device incidents

Medical device incident reports are collected by Health Canada and are entered into the Medical Devices System database. A major component of Health Canada's Medical Devices Program involves the collection, review and follow-up of incidents related to medical devices, which are reported to Health Canada via the submission of mandatory and voluntary problem reports. Manufacturers and importers are required to submit mandatory reports as per sections 59 to 61 of the Medical Devices Regulations. Voluntary reports are submitted mostly by health care professionals and patients/users. Effective Oct. 3, 2011, the responsibility for the collection and entering of mandatory problem reports for medical devices was transferred from the Health Products and Food Branch Inspectorate to the Canada Vigilance — Medical Device Problem Reporting Program.

In 2011, a total of 9228 reports were entered into the Medical Device System database. Of these reports, 8199 (88.9%) were domestic mandatory reports, 611 (6.6%) were foreign mandatory reports, and 418 (4.5%) were domestic voluntary reports.

Information on mandatory and voluntary reporting of medical device incidents can be found on the Health Canada Web site (www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php).

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Quarterly summary of health professional and consumer advisories

(posted on Health Canada's Web site: Feb. 28, 2012 – May 20, 2012)

Date*	Product	Subject
May 18	Miracle Mineral Solution (sodium chlorite solution)	New Web site selling the nonauthorized product
May 10	Spinbrush Pro Clean SONIC Recharge Toothbrushes	Recall: may overheat and cause fire, burn or shock
May 7	Cipralex (escitalopram)	Updated information regarding dose-related heart risk
May 3 & 8	Benlysta (belimumab)	Association with hypersensitivity and infusion reactions
May 1 & 3	Revlimid (lenalidomide)	Association with increased risk of second cancers
Apr 18	Compliments Extra Strength Acetaminophen Gelcaps	Recall: labelling error — may cause serious harm to children
April 16 & 19	Actos (pioglitazone)	Potential association with bladder cancer
April 11 & May 9	Metal-on-Metal Hip Implants	Information for orthopedic surgeons regarding patient management following surgery
Apr 5	Benzocaine health products	New risk statements to be added to product labels
Mar 22 & 24	Sandoz Morphine Sulfate Injection USP 2 mg/mL (1 mL)	Urgent recall: potential presence of ampoules of Isoproterenol HCl Injection in boxes of Morphine Sulfate Injection
Mar 21	Sandoz Morphine Sulfate Injection USP 2 mg/mL (1 mL)	Some boxes may contain ampoules labelled as Isoproterenol HCl Injection
Mar 19	Apo-Ramipril 5 mg	Recall of lot JR2178: intact but empty capsules
Mar 19	Finasteride (Proscar, Propecia) and dutasteride (Avodart, Jalyn)	May increase risk of high-grade prostate cancer
Mar 16 & 21	Pradax (dabigatran)	Updated labelling regarding kidney function assessment and use in patients with certain types of heart valve disease or artificial heart valves
Mar 12	Power X	Unauthorized health product removed from sale at BC's Chong Kun Dang Health Store because of possible serious health risks
Mar 12	Rexall Extra Strength Sinus Relief Daytime and Nighttime Caplets	Recall: labelling error misidentifying daytime and nighttime medications
Mar 9 & 14	Fluoroquinolone antibiotics (Avelox, Cipro, Cipro XL and Levaquin)	Worsening of symptoms in patients with myasthenia gravis
Mar 9	GemStar Bolus Cord	Potential risk owing to device failure
Mar 6	EnTrust VR/DR/AT Implantable Cardioverter Defibrillators	Medical device correction: more rapid than expected drop in battery voltage
Mar 6	Bios Diagnostics Rollator 56001	Recall: potential manufacturing defect that could results in falls
Mar 2 & 7	Domperidone Maleate	Association with serious ventricular arrhythmias and sudden cardiac death
Mar 1	Arm and Hammer's Spinbrush Powered Toothbrush	New safety information

Advisories are available at www.health.gc.ca/medeffect.

*Date of issuance. This date may differ from the posting date on Health Canada's Web site.

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 mhpd_dpsc@hc-sc.gc.ca

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