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A Post-Marketing Surveillance of the Abuse of Eluxadoline using Poison Centre Data in the United States and Canada

Version 1.0, DATE: 07 AUGUST 2018

Protocol Number:	CMO-EPI-GI-0582
Serious Adverse Event Reporting Fax Number(s):	[redacted]
Serious Adverse Event Reporting e-mail address:	[redacted]
Allergan Medical Safety Physician Contact Information:	[redacted]

PASS information

Title	A Post-Marketing Surveillance of the Abuse of Eluxadoline using Poison Centre Data in the United States and Canada
Protocol version identifier	CMO-EPI-GI-0582
Date of last version of protocol	N/A
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Medicinal product	Viberzi 75 mg film-coated tablets Viberzi 100 mg film-coated tablets
Product reference	N/A
Procedure number	N/A
Marketing authorization holder(s) (MAH)	Allergan (North America) 5 Giralda Farms Madison NJ 07940
Joint PASS	No
MAH (s) Contact	

Research question and objectives	Primary Objectives: a) To quantify the rate of abuse and serious adverse events for eluxadoline during a 3-year post approval period Secondary Objectives a) To describe characteristics in terms of exposures and patient demographics of eluxadoline exposures reported to United States and Canadian poison centres b) To describe the medical outcomes associated with eluxadoline exposures reported to United States and Canadian poison centres
Country(-ies) of study	Canada United States
Author	

Approval Page, Allergan

Project Title: A Post-Marketing Surveillance of the Abuse of Eluxadoline using Poison Centre Data in the United States and Canada

Protocol ID Number: CMO-EPI-GI-0582

Effective Date: 07 August 2018

Author:

Version: 1.0

The following people have reviewed the protocol and given their approval:

Allergan

1. Table of contents

2. List of abbreviations

Term/Abbreviation	Definition
AE	Adverse Event
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FTP	File Transfer Protocol
GPSE	Global Patient Safety & Epidemiology
IBS-D	Irritable Bowel Syndrome with Diarrhea
ISPE	International Society for Pharmacoepidemiology
MAH	Marketing Authorisation Holder
N/A	Not Applicable
NIS	Non-interventional Study
PASS	Post-Authorization Safety Study

3. Responsible Parties

Allergan Pharmaceuticals International Limited 5 Giralda Farms, Madison, NJ 07940

4. Abstract

Study Title: A Post-Marketing Surveillance of the Abuse of Eluxadoline using Poison Centre Data in the United States and Canada

Version: 1.0 Amendment: 0, Date: 07 August 2018

Rationale and background: Eluxadoline (Viberzi®) is approved for the treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults. The use of opioid agonists is associated with potential for abuse or misuse. An overdose of eluxadoline may result in symptoms resulting from an exaggeration of the known pharmacodynamic effects of the medicinal product. Health Canada has requested that Allergan monitor the drug abuse/overdose potential of eluxadoline in the post-marketing setting. Using data from calls made to poison centres in the United States and Canada, this study will describe a) the level of abuse and serious adverse events of eluxadoline since approval in the United States and Canada and b) describe the characteristics of individuals who abuse eluxadoline in the United States and Canada.

Research question and objectives:

Primary Objectives:

a) To quantify the rate of abuse and serious adverse events for eluxadoline during a 3-year post approval period

Secondary Objectives

b) To describe characteristics in terms of exposures and patient demographics of eluxadoline exposures reported to United States and Canadian poison centres
c) To describe the medical outcomes associated with eluxadoline exposures reported to United States and Canadian poison centres

Study design: Retrospective observational surveillance study using data from the United States National Poison Data System and the Canadian Poison Centre Network Program in Canada.

Population: All cases of human exposure to eluxadoline recorded in the National Poison Data System as originating in the United States during a 3-year period (January 2017 to December 2019) will be identified and included in the analysis. All cases of human exposure to eluxadoline recorded in the Canadian Poison Centre Network Program during a 2-year period (January 2018 to December 2019) will be identified and included in the analysis.

Setting: Telephone calls received from the general public and healthcare professionals to poison centres for the reporting and management of poison related exposures or injuries.

Variables:

Data collected by the National Poison Data System and the Canadian Poison Centre Network Program will be used in the study. They include:

- Patient demographics (age, gender)
- Number of substances involved in exposure
- Reason for exposure (intentional, unintentional, intentional abuse, intentional misuse, pediatric unintentional general)
- Route of exposure (ingestion, inhalation/nasal, parenteral, other, unknown) for single substance exposures (eluxadoline exposures only)
- Major medical outcome, hospitalization, or death (serious adverse event)

- Medical outcomes (no effect/minor effect/moderate effect/major effect/death/no follow-up)

Data sources: This study includes secondary data collected from calls to the United States poison centres and the Canadian Poison Centre Network Program.

Study size: The number of cases of eluxadoline users included in the study will be dependent on market uptake of the drug, which has been commercially available in the United States since December 2015 and in Canada since May 2017. Study size will also be driven by relevant calls received at the poison centres.

Duration of Study: For the United States: January 2017 to December 2019 and for Canada: January 2018 to December 2019.

Data analysis: All cases of exposure to eluxadoline recorded in the National Poison Data System from January 2017 to December 2019 and in the Canadian Poison Centre Network Program from January 2018 to December 2019 will be identified and included in the analyses. Cases of eluxadoline exposure will be presented descriptively by patient demographics, reason and medical outcome, by quarter. Population-adjusted rates and 95% confidence intervals will be calculated using census data in order to adjust for exposure in the covered population quarterly and cumulatively. Dosage units dispensed-adjusted rates and 95% confidence intervals will be calculated using IQVIA data in order to adjust for availability of drug in the residence of the covered population quarterly and cumulatively.

A detailed Statistical Analysis Plan (SAP) will be prepared prior to data analysis.

Milestones:

Milestone	**Planned Date**
Registration in EU PASS	Upon protocol approval
Start of data collection	US: January 2017 Canada: January 2018
End of data collection	For each annual interim report and final report Report #1: US: December 2017 Canada: N/A Report #2: US: December 2018 Canada: December 2018 Final report: US: December 2019 Canada: December 2019
Interim Reports	Interim report #1: US: December 2018 Canada: N/A Interim report #2: US: July 2019 Canada: July 2019
Final report of study results	US & Canada: July 2020

5. Amendments and updates

None

6. Milestones

Milestone	**Planned Date**
Registration in EU PASS	Upon protocol approval
Start of data collection	US: January 2017 Canada: January 2018
End of data collection	For each annual interim report and final report Report #1: US: December 2017 Canada: N/A Report #2: US: December 2018 Canada: December 2018 Final report: US: December 2019 Canada: December 2019
Interim Reports	Interim report #1 US: December 2018 Canada: N/A Interim report #2 US: July 2019 Canada: July 2019
Final report of study results	US & Canada: July 2020

7. Rationale and background

Eluxadoline (Viberzi®) is an oral, peripherally acting, mixed μ-opioid receptor agonist, δ-opioid receptor antagonist, and κ-opioid receptor agonist. It is approved for the treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults. The use of opioid agonists is associated with potential for abuse or misuse. Eluxadoline has very low oral bioavailability and exerts no detectable central nervous system-mediated effects when administered orally to animals at effective doses. An overdose of eluxadoline may result in symptoms resulting from an exaggeration of the known pharmacodynamic effects of the medicinal product. In the two-human abuse potential studies, euphoria was reported to be 3- to 5-fold higher than placebo in non-dependent, recreational opioid users treated with single oral doses of 100 mg to 1000 mg; and was higher than placebo (0%) with intranasal doses of 100 mg (21.9%) and 200 mg (18.8%). In patients with IBS-D, no signal for central nervous system-mediated adverse events was identified during clinical trials. Taken together these results suggest that when using the medicinal product as directed at therapeutic doses patients will not experience significant central nervous system effects or adverse events consistent with a drug of abuse. Nevertheless, this study is proposed in response to Health Canada's request to evaluate the abuse of eluxadoline in the post-market environment.

8. Research question and objectives

This study will address the following research questions:

- What is the level of eluxadoline abuse or serious adverse events since approval in the United States and Canada
- What are the characteristics of individuals who abuse eluxadoline in the United States and Canada

The specific research objectives are:

Primary Objectives:

a) To quantify the rate of abuse and serious adverse events for eluxadoline during a 3-year post approval period

Secondary Objectives

b) To describe characteristics in terms of exposures and patient demographics of eluxadoline exposures reported to United States and Canadian poison centres
c) To describe the medical outcomes associated with eluxadoline exposures reported to United States and Canadian poison centres

9. Research methods

This study will use population based data collected from 2 countries in North America (US and Canada).

9.1 Study design

This is a retrospective observational surveillance study using data from the American Association of Poison Control Centers in the United States and the Canadian Poison Centre Network Program in Canada.

9.2 Setting

The surveillance (study) population will be specific to each data source and will include the entire population enrolled by each data source, as described below.

Data Source	Surveillance (Study) Population
Canadian Poison Centre Network Program and National Poison Data System	Exposure cases recorded by regional poison centres covering people in urban, suburban, and rural regions.

Inclusion Criteria

All cases of human exposure to eluxadoline recorded in the National Poison Data System from January 2017 to December 2019 and in the Canadian Poison Centre Network Program from January 2018 to December 2019 will be identified and included in the analyses.

Exclusion Criteria

Exposures confirmed to be non-exposures and non-human exposures will be excluded.

9.3 Variables

Exposure Variables

N/A; the exposure in the evaluation is based on drug dispensing in the geographic region and is not linked to an individual

Outcome Variables

Patient Demographics:

Age

The age in years, categorized as follows, will be presented:

- National Poison Data System:
  - ≤12
  - 13-17
  - 18-64
  - ≥65
  - Unknown age
- Canadian Poison Centre Network Program:
  - <12
  - 12-15
  - 16-19
  - 20-29
  - 30-39
  - 40-49
  - 50-59
  - ≥60
  - Unknown age

Gender

The gender, categorized as follows, will be presented for both the National Poison Data System and Canadian Poison Centre Network Program:

- Male
- Female
- Unknown gender

Exposure Characteristics:

Reason for Exposure

The reason for exposure, categorized as follows, will be presented for both the National Poison Data System and Canadian Poison Centre Network Program:

- Intentional Exposures: Intentional exposures are those resulting from a purposeful action. The following four categories relate to intentional exposures: intentional suspected suicidal, intentional misuse, intentional abuse, and intentional unknown. These exposures reason definitions are available in the 2016 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 34th Annual Report.[1]
- Intentional Abuse: An intentional abuse exposure is "an exposure resulting from the intentional improper or incorrect use where the patient was likely attempting to gain a

high, euphoric effect or some other psychotropic effect, including recreational use of a substance."[1]

- Intentional Misuse: An intentional misuse exposure is "an exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of psychotropic effect."[1]
- Unintentional Exposures: Unintentional exposures are those resulting from an unforeseen or unplanned event. The following categories relate to unintentional exposures: general, environmental, occupational, therapeutic error, misuse, bite/sting, food poisoning, and unknown. These exposures reason definitions are available in the 2016 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 34th Annual Report.[1]
- Pediatric Unintentional General Exposures: Pediatric (age 0 to 5 years) are all unintentional exposures other than environmental, occupational, therapeutic error, unintentional misuse, bite/sting, food poisoning, or unintentional unknown.[1] For the purposes of standardization, unintentional general exposures within the data sources consist primarily of accidental unsupervised ingestions where the patient was 5 years or younger.[1]

Route of Exposure

The route of exposure, categorized as follows, will be presented for both the National Poison Data System and Canadian Poison Centre Network Program for single substance exposures (eluxadoline exposures only):

- Ingestion (defined as ingestion and aspiration (with ingestion))
- Inhalation/nasal
- Parenteral
- Other (defined as ocular, dermal, bite/sting, otic, rectal, vaginal, and other)
- Unknown

Outcomes:

Major Medical Outcome, Hospitalization or Death (Serious Adverse Event)

Any exposure for both the National Poison Data System and Canadian Poison Centre Network Program resulting in a major medical outcome (life-threatening or resulted in significant residual disability or disfigurement[1]), hospitalization (level of healthcare facility coded as: admitted to critical care, admitted to non-critical care, or admitted to psychiatric care facility), or death will be included in this category.[1]

Medical Outcomes

The medical outcomes associated with the exposures, categorized as follows, will be presented for both the National Poison Data System and Canadian Poison Centre Network Program:

- No effect: the patient did not develop any signs or symptoms as a result of the exposure[1]
- Minor effect: The patient developed some signs or symptoms as a result of the exposure, but they were minimally bothersome and generally resolves rapidly with no residual disability or disfigurement. A minor effect is often limited to the skin or mucus membranes.[1]

- Moderate effect: The patient exhibited signs or symptoms as a result of the exposure that were more pronounced, more prolonged or more of a systemic nature than minor symptoms. Usually some form of treatment is indicated. Symptoms were not life-threatening, and the patient had no residual disability or disfigurement.[1]
- Major effect: The patient exhibited signs or symptoms as a result of the exposure that were life-threatening or resulted in significant residual disability or disfigurement.[1]
- Death: The patient died as a result of the exposure or as a direct complication of the exposure.[1]
- No follow-up: Exposures defined as not followed, judged as nontoxic exposure; not followed, minimal clinical effects possible; unable to follow, judged as potentially toxic exposure; unrelated effect.[1]

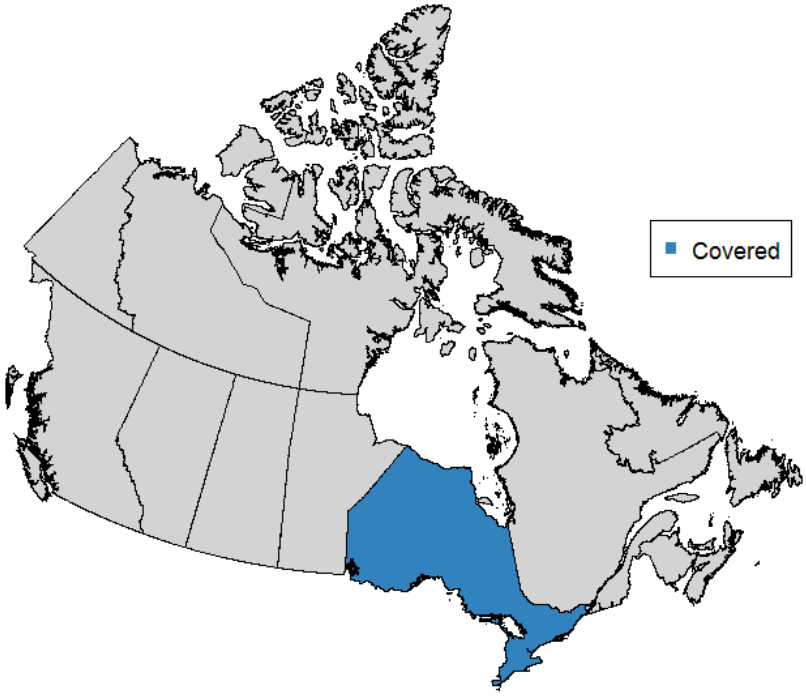
9.4 Data sources

Canadian Poison Centre Network Program

The Canadian Poison Centre Network Program is a third-party data source operated in Canada by Denver Health and Hospital Authority, a not-for-profit, political subdivision of the State of Colorado. It is a comprehensive, integrated health care system established in 1860 and is Colorado's primary safety net institution. For the purpose of this study, experience from the province of Ontario will be described.

The Canadian Poison Centre Network Program collects observational data on human exposures to pharmaceutical products as reported to poison centre sites in Canada. Data are collected as part of the poison centre's daily routine activities as they provide medical management assistance to healthcare providers and the public. Human exposures to eluxadoline will be identified. An exposure is defined as an actual or suspected contact with any substance, which has been ingested, inhaled, absorbed, applied to, or injected into the body, regardless of toxicity or clinical manifestation. All data are de-identified to protect the privacy of the patients. A computerized, standardized, relational database is used for data capture; therefore, no data collection tool is available.

Figure: Canadian Poison Centre Network Program Coverage Map, 2017



National Poison Data System

The National Poison Data System is the data repository for the regional poison centres of the American Association of Poison Control Centres in the United States. American Association of Poison Control Centers member centres offer coverage for the entire United States, providing free medical management services to both healthcare professionals and the general public. Data are collected as part of the poison centre's daily routine activities as they provide medical management assistance to healthcare providers and the public. Data from regional poison centres is uploaded in real-time to the National Poison Data System. The National Poison Data System will be searched to identify human exposures to eluxadoline. An exposure is defined as an actual or suspected contact with any substance, which has been ingested, inhaled, absorbed, applied to, or injected into the body, regardless of toxicity or clinical manifestation. All data are de-identified to protect the privacy of the patients. A computerized, standardized, relational database is used for data capture; therefore, no data collection tool is available.

Census Data

Canadian Census Data

Population-based rates provide an assessment of the number exposures within the covered population. This approach is a measure of the impact on the population in a specified area. Population-based rates are calculated using the sum of cases as the numerator and the population covered as the denominator. These rates are scaled to yield rates per 100,000 population, but this scaling factor may be adjusted to give more interpretable values. The 2011 and 2016 Canadian Censuses data are used to determine the historical population growth of Canada and to extrapolate annual population estimates used to calculate rates for 2016 and beyond.

Population rates are calculated for the census divisions within the coverage area of the Canadian Poison Centre Network Program. The coverage area is the regions served by the participating poison centres for all hours. Quarterly populations are estimated for these census divisions by extrapolating the 2011 and 2016 Canadian Censuses. The population estimates for Canada were obtained from the census site (http://www.statcan.gc.ca/start-debut-eng.html), accessed on 21 December 2016.

United States Census Data

Three-digit ZIP code population data from the United States decennial censuses will be utilized to compute rates for specific endpoints. Estimates between Census will be computed using linear extrapolation. All three-digit ZIP code tabulation areas will be used to calculate rates using National Poison Data System data given National Poison Data System coverage is national. All rates will be scaled per 100,000 person-years, but this scaling factor may be adjusted to give more interpretable values.

Drug Dispensing Data

Canadian Drug Dispensing Data

The Canadian IQVIA™ (Kirkland, Quebec) data are calculated based on Geographic Prescription Monitor (GPM) for the opioid and pain management market. GPM is a monthly service that tracks prescriptions dispensed from retail pharmacies at multiple levels of geography using a proven geospatial projection methodology to provide the most complete view of retail dispensing information. IQVIA data are provisioned at the census division level, but there are census divisions which have too few pharmacies that are required to display the data at the same level of specificity. Therefore, these areas were excluded from the dosage units dispensed analyses. The proposed study will use dosage units dispensed projections obtained at the census division level from IQVIA for eluxadoline. For a given year-quarter, the total of dosage units dispensed in the census division covered by the Canadian Poison Centre Network Program will be computed for eluxadoline, and these numbers used as the denominators in the calculation of drug dispensing rates for Canadian Poison Centre Network Program. Initially, rates will be scaled per 100,000 dosage units dispensed, but this scaling factor may be adjusted to give more interpretable numbers as needed. All analysis and interpretation of results are those of

United States Drug Dispensing Data

Dosage units dispensed data are based on projections provided by IQVIA™ (Danbury, CT). IQVIA obtains data on prescription drug dispensing at retail pharmacies. The IQVIA prescription database uses timely product and geographically-specific data obtained from approximately 3.8 billion prescription transactions covering 92% of retail pharmacy transactions in the United States. IQVIA uses a proprietary projection methodology to extrapolate from the observed data to all retail prescriptions in the United States. The proposed study will use dosage units dispensed projections obtained at the three-digit ZIP code from IQVIA for eluxadoline. For a given year-quarter, the total of dosage units dispensed in all three-digit ZIP codes, given National Poison Data System coverage is national, will be computed for eluxadoline, and these numbers used as the denominators in the calculation of drug dispensing rates for National Poison Data System. Initially, rates will be scaled per 100,000 dosage units dispensed, but this scaling factor may be adjusted to give more interpretable numbers as needed.

9.5 Study size

This evaluation is not intended to test a pre-specified statistical hypothesis; therefore, a pre-determined sample size is not calculated. The number of eluxadoline exposures included in the study will be dependent on market uptake of the drug, which has been commercially available in the United States since December 2015 and in Canada since May 2017. Study size will also be driven by relevant calls received at the poison centres in the United States and Canada.

9.6 Data management

Access to the data is restricted to qualified individuals who must complete training through standard operating procedures implemented by a quality system. The network where the data are stored is secure, accessed only via username/password, and fully encrypted. All staff members are required to openly show and wear identification while on the premises. Data are backed up daily with backups stored at an offsite facility for datasets and programs. Allergan (MAH) will not have access to the data. All data received from external sources is verified by the data management team to ensure the contents are within the parameters of interest. Internal quality procedures are used to identify quality errors in the data before analysis. Specific details on the preparation, receipt and validation are provided by program below. Data will be managed and analyzed using SAS version 9.4 or later.

Canadian Poison Centre Network Program

Participating poison centres have a standard protocol for the management of all cases. The specialists who manage the calls obtain details of the exposure from the caller and populate standardized fields in the call log database. Investigators at each participating poison centre have been trained to use a standardized pre-formatted database to extract all exposure cases regarding the drugs of interest. Each site coordinator reviews each case and removes all patient identifiers prior to electronic transfer to the coordinating centre. To ensure confidentiality, each database is encrypted before the data transfer occurs. Data matching the drugs of interest are sent to the coordinating centre on a weekly basis.

Staff at the coordinating centre review these databases for inconsistencies. Each exposure case is then reviewed by staff to determine the accuracy of the products involved, reason code, route of exposure, and medical outcome. If inconsistencies are found the site is notified in order to rectify the queries and the data are corrected in the Canadian Poison Centre Network Program database.

National Poison Data System

As previously noted, the National Poison Data System is the data repository for the regional poison centres of the American Association of Poison Control Centers. Exposure information is collected using a standardized data collection system by trained personnel. Standardized definitions and product indexing systems are used to ensure the accuracy of the substance information and all categories of data collected. Each regional poison centre manages a quality assurance process and automatic data checks are performed at the time of upload to the National Poison Data System database. Data received from the National Poison Data System are validated using standardized procedures to ensure the completeness and accuracy of the data.

Census Data

Canadian Census Data

Population data at the census division level are available from the Canadian Census Website for the 2011 and 2016 censuses. Extrapolation by linear regression is performed at the census division area level to estimate the population each quarter through the study period.

United States Census Data

Population data at the three-digit ZIP code level are available from the United States Census website for the 2000 and 2010 censuses. Extrapolation by linear regression is performed at the three-digit ZIP code tabulation area level to estimate the population each quarter through the study period.

Drug Dispensing Data

Drug dispensing data are obtained from IQVIA quarterly and are uploaded via a FTP site. The data file is transferred into a secure internal network location. Upon delivery, data are checked to ensure completeness of fields and are compared to prior data for any new products not reported in previous quarters. This later step is undertaken to ensure that new drugs are appropriately categorized by drug class, active pharmaceutical ingredient, and drug product.

9.7 Data analysis

Overall demographics and exposure characteristics will be presented using descriptive statistics for the cases included in the study period. The analysis will include age and gender, reason (intentional, unintentional, intentional abuse, intentional misuse, pediatric unintentional general), medical outcome, and number of substances involved in the exposure. Cases will be presented quarterly.

For the primary objective, rates of abuse will be calculated using the different data systems. Rates will use cases of abuse as the numerator with both population and dosage units dispensed as denominators. Population-adjusted rates and 95% confidence intervals will be calculated using census data in order to adjust for exposure to the general population in the community quarterly and cumulatively.

Dosage units dispensed-adjusted rates and 95% confidence intervals will be calculated using IQVIA data in order to adjust for availability of drug in the residence of the covered population quarterly and cumulatively.

To evaluate secondary objective, rates will be calculated by medical outcome type and reason. Additional demographics will be used in the further subgroup comparisons. Both population and drug utilization will be used as denominators for the fitting of the trend models.

As these data are collected from unsolicited calls to poison centres and represent a number of different scenarios, there are instances where information for certain variables is not collected or unavailable. These instances of missing information to the case are generally considered missing completely at random. Using the outcome variables of interest, tests of association with other covariates can be evaluated to determine if there are any patterns of missing data beyond completely at random. In the case the data have patterns of missingness, these will be accounted for in any analysis or imputation techniques applied.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary outcome definitions or their analyses would be reflected in a protocol amendment.

9.8 Quality control

To ensure quality of data used in this surveillance, each SAS program used to conduct programming and analyses will be written by a biostatistician or statistical research specialist trained in SAS programming and with training in relevant statistical analyses. Programmers will also have knowledge of the Canadian Poison Centre Network Program and National Poison Data System databases. These programs will be validated by another biostatistician or statistical research specialist with a similar level of training. Any inconsistencies will be resolved by the director of biostatistics.

9.9 Limitations of the research methods

IQVIA data are used as an indicator of quarterly drug dispensing based upon a sample of data and a proprietary projection algorithm; hence the methodology is not well understood. The Canadian Poison Centre Network Program and National Poison Data System data are based on spontaneous self-reported information which presents a potential bias of ambiguous answers or incomplete data. In addition, not all exposures are reported to poison centres; therefore, cases may underestimate the true number of exposures in the population. Finally, exposure information is specific to the exposure not necessarily substance involved in the exposure. Therefore, the motivation assigned to the exposure (e.g. abuse) may not apply to all substances involved in the exposure.

Indication for all prescription drugs cannot be obtained within the data sources; therefore, outcomes may include off-label use or prescription drugs obtained through diversion. This is a limitation common to all surveys. Medical records are not being accessed in this study.

9.10 Other aspects

N/A

10. Protection of human subjects

Canadian Poison Centre Network Program

The Colorado Multiple Institutional Review Board determined the Canadian Poison Centre Network Program to be non-human subject research on 29 April 2015. In addition, the study protocol was reviewed and approved by the ethics committee/institutional review board of participating poison centres.

National Poison Data System

In alignment with Colorado Multiple Institutional Review Board's Policies and Procedures for the Protection of Human Subjects, the Principal Investigator determined that analysis of National Poison Data System data involves non-human subjects research per 45 CFR 46.102(f)(2).

To ensure the quality and integrity of research, the conduct of this study will be governed by the Guidelines for Good Pharmacoepidemiology Practices (2015) issued by the International Society for Pharmacoepidemiology (ISPE), the Declaration of Helsinki and its amendments, and any applicable national guidelines.

The study will be conducted in accordance with the International Society for Pharmacoepidemiology's (ISPE) Guidelines for Good Pharmacoepidemiology Practices (Revision 3: June 2016) and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance's (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (ENCePP, Revision 5: July 2016).

The ENCePP Checklist for Study Protocols (ENCePP, Revision 3: July 2016) has been completed.

The study will be registered in the ENCePP Electronic Register of Studies (ENCePP, 2010) after the protocol is finalized.

The study will comply with the definition of the non-interventional (observational) study provided in Article 2(c) of Directive 2001/20/European Commission and its refinement provided in Chapter I.7 Section 1 of Volume 9A of the Rules Governing Medicinal Products in the EU: Guidelines on Pharmacovigilance for Medicinal Products for Human Use (European Commission, 2008), and referred to in the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use's Pharmacovigilance Planning (ICH, 2004) and the Guideline on Good Pharmacovigilance Practices, Module VIII—Post-Authorisation Safety Studies (European Medicines Agency [EMA], 2016).

11. Management and reporting of adverse events/adverse reactions

These data sources include data that already exist as structured data in an electronic database. In these data sources, it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an AE (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and AEs are not reportable as individual AE reports.

12. Plans for disseminating and communicating study results

Two annual interim reports and one final study report (Table 12.1) including data from the 2 annual interim reports are planned for this study.

12.1 Study Reports

Reports	Reporting Period	Data Lock Point	Planned submission date*
Interim Report #1	01 January 2017- 31 December 2017	31 August 2018	31 December 2018

Interim Report #2	01 January 2018- 31 December 2018	30 April 2019	31 July 2019
Final report of study results	01 January 2017- 31 December 2019	30 April 2020	31 July 2020

**Dates are proposed submission dates to Health Canada*

12.2 Publications of Study Results

A study abstract(s) may be submitted to a scientific conference(s), and a manuscript summarizing the study results may also be submitted to a peer-reviewed journal for publication at the discretion of MAH after providing vendor with 30 days for review. Vendor may publish or present data after providing MAH with 30 days prior notice.

13. References

1. Gummin DD, Mowry JB, Spyker DA, Brooks DE, Fraser MO, et al. 2016 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 34th Annual Report. Clin Toxicol (Phila). 2017;55(10):1072-1252.