Department of Health and Human Services
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Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	April 19, 2022
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Product Name:	Amitiza (lubiprostone)
Pediatric Labeling Approval Date:	April 26, 2018
Application Type/Number:	NDA 21908
Applicant:	Sucampo Pharma Americas, LLC
OSE RCM #:	2021-1623

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports and the medical literature for Amitiza (lubiprostone) in pediatric patients through age 17 years. The Division of Pharmacovigilance-I (DPV-I) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events reported to the FAERS database associated with lubiprostone in pediatric patients.

Lubiprostone is an oral chloride channel activator, approved on January 31, 2006, indicated for the treatment of chronic idiopathic constipation (CIC) in adults, opioid-induced constipation (OIC) in adult patients with chronic, non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent opioid dosage escalation and irritable bowel syndrome with constipation (IBS-C) in women ≥18 years old. The safety and efficacy of lubiprostone has not been established in pediatric patients with IBS-C, pediatric functional constipation (PFC), and OIC.

Lubiprostone is not indicated for use in pediatric patients. DPV-I did not identify any new pediatric safety concerns for lubiprostone and recommends no regulatory action specific to pediatric patients at this time. DPV-I will continue to monitor all adverse events associated with the use of lubiprostone.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Amitiza (lubiprostone) in pediatric patients through age 17 years. The Division of Pharmacovigilance-I (DPV-I) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This PREA review was initiated by the pediatric labeling on April 26, 2018, that described failed safety and efficacy pediatric studies. This review focuses on serious unlabeled adverse events associated with lubiprostone in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY[1]

Lubiprostone is an oral chloride channel activator, approved on January 31, 2006, indicated for the treatment of:

- chronic idiopathic constipation (CIC) in adults.
- opioid-induced constipation (OIC) in adult patients with chronic, non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent opioid dosage escalation. The effectiveness of lubiprostone in the treatment of OIC in patients taking diphenylheptane opioids (e.g., methadone) has not been established.
- irritable bowel syndrome with constipation (IBS-C) in women ≥18 years old.

The safety and efficacy of lubiprostone has not been established in pediatric patients with IBS-C, pediatric functional constipation (PFC), and OIC.

Efficacy was not demonstrated for the treatment of PFC in patients 6 years of age and older in a 12 week, randomized, double-blind, placebo-controlled trial conducted in 606 patients ages 6 to 17 years with PFC comparing lubiprostone to placebo. The primary efficacy endpoint was an overall response based on spontaneous bowel movement frequency over the duration of the trial; the treatment difference from placebo was not statistically significant. In this age group, adverse reactions to lubiprostone were similar to those reported in adults.

In a 36-week, long-term safety extension trial after approximately 9 months of treatment with lubiprostone one case of reversible elevation of alanine transaminase 17 times the upper limit of normal (ULN), aspartate aminotransferase 13 times the ULN, and gamma-glutamyltransferase 9 times the ULN was observed in a child with baseline elevated values less than or equal to 2.5-times the ULN.

A pediatric safety review for lubiprostone has not previously been presented to the Pediatric Advisory Committee (PAC).

1.2 RELEVANT LABELED SAFETY INFORMATION[1]

The following provides a summary of safety information and information on use in pediatrics excerpted from the pertinent sections of the lubiprostone labeling.

----------CONTRAINDICATIONS----------

- Amitiza is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

----------WARNINGS AND PRECAUTIONS----------

- *Nausea:* Patients taking Amitiza may experience nausea. Concomitant administration of food with Amitiza may reduce symptoms of nausea
- *Diarrhea:* Avoid use of Amitiza in patients with severe diarrhea. Instruct patients to discontinue Amitiza and contact their healthcare provider if severe diarrhea occurs.
- *Syncope and Hypotension*: Syncope and hypotension resulting in hospitalization have been reported with Amitiza in the postmarketing setting. Concomitant use of medications known to lower blood pressure, diarrhea, and vomiting may increase the risk of developing syncope and or hypotension.
- *Dyspnea*: Described as a sensation of chest tightness and difficulty taking in a breath, with an acute onset within 30 to 60 minutes after taking the first dose. Instruct patients to contact their healthcare provider if dyspnea occurs.
- *Bowel Obstruction*: In patients with symptoms suggestive of mechanical gastrointestinal obstruction, perform a thorough evaluation to confirm the absence of an obstruction prior to initiating therapy with Amitiza.

----------ADVERSE REACTIONS----------

- Nausea
- Diarrhea
- Syncope and Hypotension
- Dyspnea

----------POSTMARKETING EXPERIENCE----------

- Cardiovascular: syncope and/or hypotension, tachycardia
- Gastrointestinal: ischemic colitis
- General: asthenia
- Immune System: hypersensitivity reactions including rash, swelling, and throat tightness malaise
- Muscoskeletal: muscle cramps or muscle spasms

----------USE IN SPECIAL POPULATIONS----------

Safety and effectiveness have not been established in pediatric patients with IBS-C, pediatric functional constipation (PFC), and OIC.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV-I searched the FAERS database with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of search	August 16, 2021
Time period of search	January 31, 2006† - August 15, 2021
Search type	FBIS Product-Manufacturer Reporting Summary
Product terms	Product Active Ingredient: lubiprostone
MedDRA search terms (Version 24.0)	All PTs

* See Appendix A for a description of the FAERS database.
† U.S. Approval Date for Amitiza (lubiprostone)
Abbreviations: FBIS=FDA Business Intelligence System, MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from January 31, 2006, through August 15, 2021, with lubiprostone.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From January 31, 2006, through August 15, 2021 for Lubiprostone			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	1100 (662)	716 (372)	81 (40)
Pediatrics (0 - <18 years)	32 (24)	17‡ (10)	2‡ (2)

* May include duplicates and transplacental exposures, and have not been assessed for causality
† For the purposes of this review, the following outcomes qualify as serious: death, life- threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.
‡ See Figure 1. One additional report of pediatric death was identified among reports not reporting an age. This report is reflected in the counts of pediatric reports.

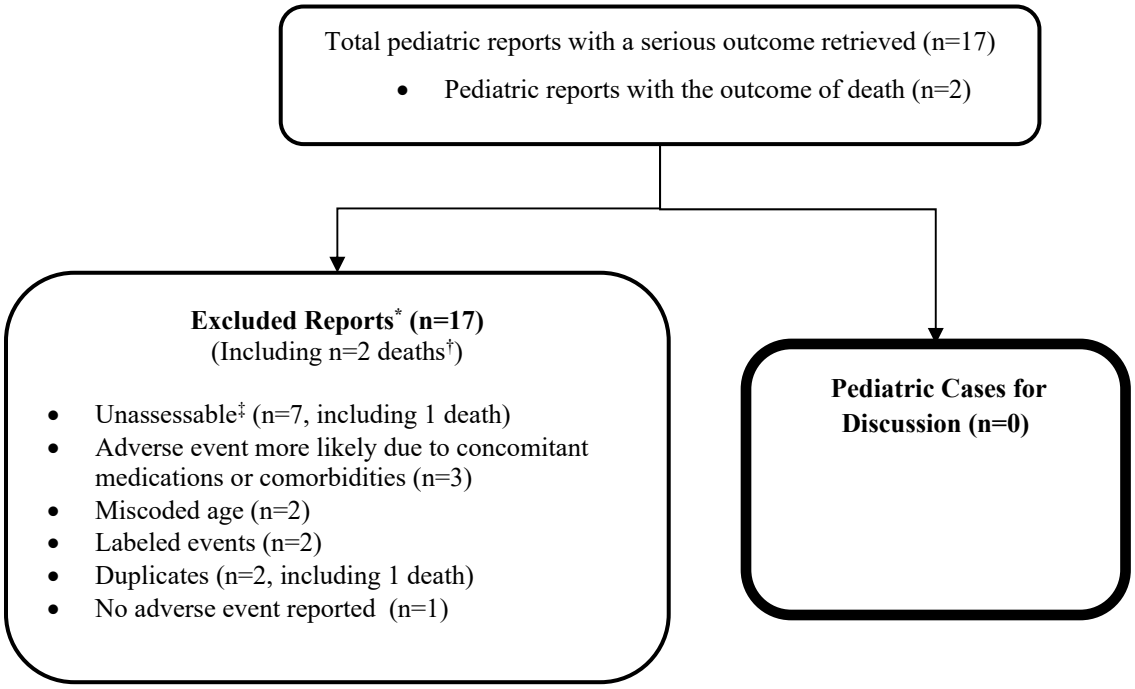
3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved 17 serious pediatric reports from January 31, 2006, through August 15, 2021, with lubiprostone.

DPV-I reviewed all FAERS pediatric reports with a serious outcome. We excluded reports from the case series for various reasons, such as unassessable reports, adverse event was more likely due to concomitant medications or comorbidities, miscoded age (i.e., not a pediatric patient), labeled adverse event, duplicate reports, or reports describing no adverse events.

Figure 1. presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious Pediatric Cases with Lubiprostone



* DPV reviewed these reports, but they were excluded from further discussion for the reasons listed above

† There is one fatal pediatric report of a patient who experienced abdominal distention, bloody diarrhea, decreased body temperature, lethargy, and death. Police investigation and autopsy were performed; however, neither result was reported. Concomitant medications included levothyroxine and guanfacine. No additional clinical details were available for review.

‡ Unassessable: Adverse event cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), the information is contradictory, or information provided in the report cannot be supplemented or verified.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for further discussion.

4 DISCUSSION

DPV-I reviewed all FAERS reports coded with a serious outcome (n=17) for lubiprostone in the pediatric population (ages 0 - < 18 years) during the period from January 31, 2006, through August 15, 2021. Of the 17 reports reviewed, DPV-I identified no cases of interest for discussion. Lubiprostone is not indicated for use in pediatric patients. There are no new safety signals, no increased severity or frequency of any labeled adverse events, and no pediatric deaths that could definitively be attributed to lubiprostone.

5 CONCLUSION

DPV-I did not identify any pediatric safety concerns for lubiprostone at this time.

6 RECOMMENDATION

Lubiprostone is not indicated for use in pediatric patients. DPV-I recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of lubiprostone.

7 REFERENCES

1. Amitiza (lubiprostone) [package insert]. Bedminster, NJ: Sucampo Pharma Americas LLC. Revised 30Nov20.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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