**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology**
**Office of Pharmacovigilance and Epidemiology**

# Pediatric Postmarketing Pharmacovigilance Review

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|---|---|
| **Date:** | March 17, 2025 |
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| **Product Name:** | Linzess (linaclotide) capsules |
| **Pediatric Labeling Approval Date:** | June 12, 2023 |
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| **Applicant:** | Abbvie, Inc. |
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## EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Linzess (linaclotide) capsules in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with linaclotide in pediatric patients.

Linzess (linaclotide) capsule is a guanylate cyclase-C agonist initially approved in the U.S. on August 30, 2012, for the treatment of irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) in adults only. Linaclotide is currently indicated for the treatment of:

- IBS-C in adults
- CIC in adults
- Functional constipation (FC) in pediatric patients 6 to 17 years of age

On June 12, 2023, the Linzess labeling was updated to expand the indication for use to include treatment of FC in patients 6 – 17 years of age.

This pediatric postmarketing safety review was prompted by pediatric labeling on June 12, 2023. DPV has not previously performed a pediatric postmarketing pharmacovigilance review for linaclotide for the Pediatric Advisory Committee.

DPV reviewed all U.S. serious FAERS reports with linaclotide in pediatric patients less than 18 years of age from August 30, 2012 – January 29, 2025, and identified 10 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with linaclotide in pediatric patients less than 18 years of age.

DPV did not identify any new pediatric safety concerns for linaclotide at this time and will continue routine pharmacovigilance monitoring for linaclotide.

# 1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Linzess (linaclotide) capsules in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with linaclotide in pediatric patients.

## 1.1 PEDIATRIC REGULATORY HISTORY

Linzess (linaclotide) capsule is a guanylate cyclase-C agonist initially approved in the U.S. on August 30, 2012, for the treatment of irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) in adults only.[1] Linaclotide is currently indicated for the treatment of:[2]

- IBS-C in adults
- CIC in adults
- Functional constipation (FC) in pediatric patients 6 to 17 years of age

On June 12, 2023, the Linzess labeling was updated to expand the indication for use to include treatment of FC in patients 6 – 17 years of age.[2]

This pediatric postmarketing safety review was prompted by pediatric labeling on June 12, 2023. DPV has not previously performed a pediatric postmarketing pharmacovigilance review for linaclotide for the Pediatric Advisory Committee.

## 1.2 RELEVANT LABELED SAFETY INFORMATION

The Linzess labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional Linzess labeling information, please refer to the full prescribing information.[2]

**WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS LESS THAN 2 YEARS OF AGE**
***See full prescribing information for complete boxed warning.***

- **LINZESS is contraindicated in patients less than 2 years of age; in neonatal mice, linaclotide caused deaths due to dehydration. (4, 5.1, 8.4)**

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

- Patients less than 2 years of age. (4, 5.1, 8.4)
- Patients with known or suspected mechanical gastrointestinal obstruction. (4)

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

Diarrhea: Patients may experience severe diarrhea. If severe diarrhea occurs, suspend dosing and rehydrate the patient. (5.2)

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

- Most common adverse reactions (≥2%) reported in adult patients with IBS-C or CIC are: diarrhea, abdominal pain, flatulence and abdominal distension. (6.1)
- Most common adverse reaction (≥2%) reported in pediatric patients 6 to 17 years of age with FC is diarrhea. (6.1)

**8.4 Pediatric Use**

LINZESS is contraindicated in patients less than 2 years of age. In nonclinical studies, deaths occurred within 24 hours in neonatal mice (human age equivalent of approximately 0 to 28 days) following oral administration of linaclotide which increased fluid secretion as a consequence of age-dependent elevated GC-C agonism resulting in rapid and severe dehydration (see Juvenile Animal Toxicity Data).

A clinical GC-C ontogeny study in children 6 months to less than 18 years of age (N=99) was conducted to measure GC-C mRNA expression levels in duodenal and colonic samples to evaluate the risk of diarrhea and severe dehydration due to GC-C agonism. The results showed no age dependent trend in GC-C intestinal expression in children 2 to less than 18 years of age. There was insufficient data on GC-C intestinal expression to assess the risk of developing diarrhea and its potentially serious consequences in children less than 2 years of age [see Warnings and Precautions (5.1)].

The safety and effectiveness of LINZESS for the treatment of FC in pediatric patients 6 to 17 years of age have been established. Use of LINZESS for this indication is supported by evidence from adequate and well-controlled studies in adults and pediatric patients 6 years of age and older. The safety of LINZESS in adult and pediatric patients 6 to 17 years of age in clinical studies was similar [see Adverse Reactions (6.1) and Clinical Studies (14.3)].

The safety and effectiveness of LINZESS in patients with FC less than 6 years of age or in patients with IBS-C less than 18 years of age have not been established.

Juvenile Animal Toxicity Data

In toxicology studies in neonatal mice, oral administration of linaclotide at 10 mcg/kg/day caused deaths on post-natal day 7 (human age equivalent of approximately 0 to 28 days). These deaths were due to rapid and severe dehydration produced by significant fluid shifts into the intestinal lumen resulting from GC-C agonism in neonatal mice [see Contraindications (4) and Warnings and Precautions (5.1)].

Tolerability to linaclotide increases with age in juvenile mice. In 2-week-old mice, linaclotide was well tolerated at a dose of 50 mcg/kg/day, but deaths occurred after a single oral dose of 100 mcg/kg. In 3-week-old mice, linaclotide was well tolerated at 100 mcg/kg/day, but deaths occurred after a single oral dose of 600 mcg/kg.

# 2 METHODS AND MATERIALS

## 2.1 FAERS SEARCH STRATEGY

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

| **Table 1. FAERS Search Strategy**[*] | |
|---|---|
| Date of search | January 30, 2025 |
| Time period of search | August 30, 2012[†] - January 29, 2025 |
| Search type | RxLogix Pediatric Focused Review Alert – DPV |
| Product terms | Product active ingredient: Linaclotide, linaclotide acetate |
| MedDRA search terms (Version 27.1) | All Preferred Terms |
| Other search terms[‡] | Case Seriousness: Serious<br>Country Derived: USA |

| **Table 1. FAERS Search Strategy*** |
|---|
| * See Appendix A for a description of the FAERS database.<br>† Linzess U.S. approval date<br>‡ 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.<br>Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; USA=United States of America |

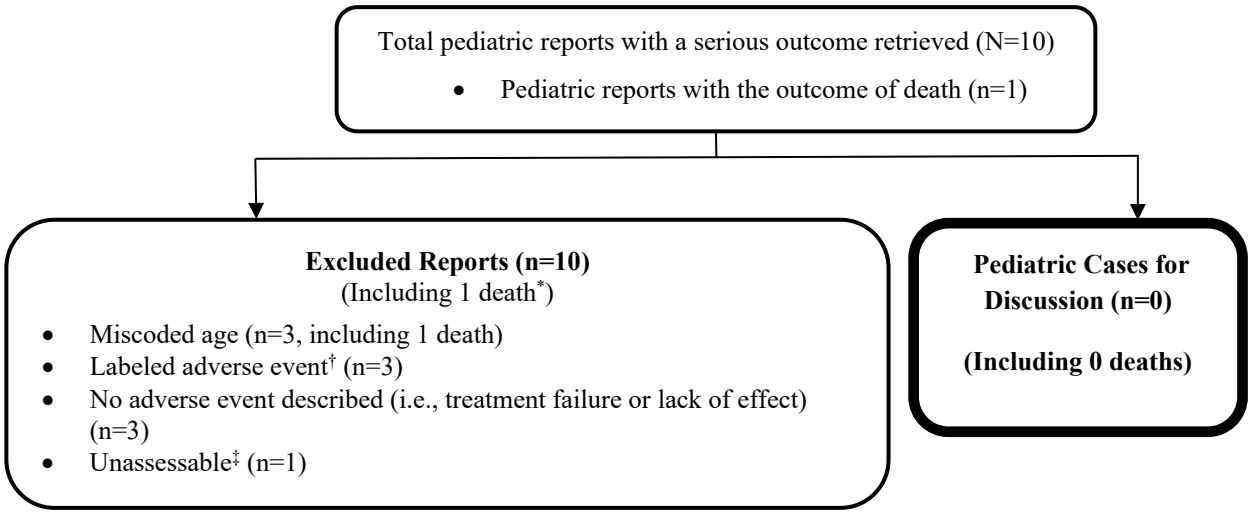
# 3 RESULTS

## 3.1 FAERS

### *3.1.1 Selection of U.S. Serious Pediatric Cases in FAERS*

Our FAERS search retrieved 10 U.S. serious pediatric reports for patients less than 18 years old from August 30, 2012 – January 29, 2025. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all 10 reports from the case series for the reasons listed in **Figure 1**. **Figure 1** presents the selection of cases for the pediatric case series.

**Figure 1. Selection of U.S. Serious Pediatric Cases With Linaclotide**




* One excluded U.S. FAERS report described a fatal outcome. The case described an adult patient that was miscoded as a pediatric patient.
† Labeled adverse event does not represent increased severity.
‡ Unassessable: The report 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.

### *3.1.2 Summary of U.S. Fatal Pediatric Cases (N=0)*

There are no fatal pediatric adverse event cases for discussion.

### *3.1.3 Summary of U.S. Serious Non-Fatal Pediatric Cases (N=0)*

There are no non-fatal pediatric adverse event cases for discussion.

# 4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with linaclotide in pediatric patients less than 18 years of age from August 30, 2012 – January 29, 2025, and identified 10 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with linaclotide in pediatric patients less than 18 years of age.

# 5 CONCLUSION

DPV did not identify any new pediatric safety concerns for linaclotide at this time and will continue routine pharmacovigilance monitoring for linaclotide.

# 6 REFERENCES


1. Linzess (lincalotide) capsules. [Prescribing information]. St Louis, MO; Ironwood Pharmaceuticals, Inc.: August 2012.
2. Linzess (linaclotide) capsules. [Prescribing information]. North Chicago; Abbvie, Inc.: June 2023.


# 7 APPENDICES

## 7.1 APPENDIX A. 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 terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

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 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.