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

Date:	March 24, 2025
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Product Name:	Lialda (mesalamine) delayed-release tablets
Pediatric Labeling Approval Date:	June 26, 2020
Application Type/Number:	NDA 022000
Applicant:	Takeda Pharmaceuticals USA, Inc.
TTT Record ID:	2025-13181

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Lialda (mesalamine) delayed-release tablets in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with mesalamine in pediatric patients.

Lialda (mesalamine) delayed-release tablet is an aminosalicylate first approved in the U.S. on January 16, 2007, for the induction of remission in adult patients with mildly to moderately active ulcerative colitis. On June 26, 2020, FDA approved expanding the Lialda indication to include treatment of mildly to moderately active ulcerative colitis in pediatric patients weighing at least 24 kg.

This pediatric postmarketing safety review was prompted by pediatric labeling on June 26, 2020.

FDA presented a pediatric postmarketing pharmacovigilance review for mesalamine to the Pediatric Advisory Committee (PAC) on two prior occasions:

> On August 9, 2016, the Office of Surveillance and Epidemiology (OSE) completed a review of postmarketing adverse event reports with a serious outcome for mesalamine in pediatric patients. OSE's evaluation identified safety signals of benign intracranial hypertension and nephrogenic diabetes insipidus with mesalamine. OSE's evaluation was presented to the PAC on September 14, 2016.[3] FDA issued a Safety Labeling Change notification letter to the applicants for mesalamine products recommending the addition of intracranial hypertension and nephrogenic diabetes insipidus to the labeling of mesalamine products. On July 27, 2017, FDA approved updated labeling for mesalamine products adding the events intracranial hypertension and nephrogenic diabetes insipidus to *Postmarketing Experience.*
>
> On July 22, 2020, DPV completed another review of postmarketing adverse event reports with a serious outcome for mesalamine in pediatric patients. DPV's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with mesalamine. On September 1, 2020, DPV's evaluation was presented to the PAC via webposting.

DPV reviewed all U.S. serious FAERS reports with mesalamine in pediatric patients less than 18 years of age from December 1, 2019 – February 9, 2025, and identified 50 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 mesalamine in pediatric patients less than 18 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Lialda (mesalamine) delayed-release tablets in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with mesalamine in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Lialda (mesalamine) delayed-release tablet is an aminosalicylate first approved in the U.S. on January 16, 2007, for the induction of remission in adult patients with mildly to moderately active ulcerative colitis.[1] On June 26, 2020, FDA approved expanding the Lialda indication to include treatment of mildly to moderately active ulcerative colitis in pediatric patients weighing at least 24 kg.[2]

This pediatric postmarketing safety review was prompted by pediatric labeling on June 26, 2020.

FDA presented a pediatric postmarketing pharmacovigilance review for mesalamine to the Pediatric Advisory Committee (PAC) on two prior occasions:

> On August 9, 2016, the Office of Surveillance and Epidemiology (OSE) completed a review of postmarketing adverse event reports with a serious outcome for mesalamine[a] in pediatric patients. OSE's evaluation identified safety signals of benign intracranial hypertension and nephrogenic diabetes insipidus with mesalamine. OSE's evaluation was presented to the PAC on September 14, 2016.[3] FDA issued a Safety Labeling Change notification letter to the applicants for mesalamine products recommending the addition of intracranial hypertension and nephrogenic diabetes insipidus to the labeling of mesalamine products. On July 27, 2017, FDA approved updated labeling for mesalamine products adding the events intracranial hypertension and nephrogenic diabetes insipidus to *Postmarketing Experience.*[1,4-10]
>
> On July 22, 2020, DPV completed another review of postmarketing adverse event reports with a serious outcome for mesalamine[b] in pediatric patients. DPV's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with mesalamine. On September 1, 2020, DPV's evaluation was presented to the PAC via webposting.[11]

1.2 RELEVANT LABELED SAFETY INFORMATION

The Lialda labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional Lialda labeling information, please refer to the full prescribing information.[12]

> **---------- WARNINGS AND PRECAUTIONS ----------**
>
> - Renal Impairment: Assess renal function at the beginning of treatment and periodically during treatment. Evaluate the risks and benefits of LIALDA in patients with known renal

[a] Prompted by pediatric labeling for Asacol on October 18, 2013, and Delzicol on April 28, 2014.
[b] Prompted by pediatric labeling for Canasa on September 2, 2016.

impairment or taking nephrotoxic drugs. Discontinue LIALDA if renal function deteriorates while on therapy. (5.1, 7.1, 8.6)

- Mesalamine-Induced Acute Intolerance Syndrome: Symptoms may be difficult to distinguish from an ulcerative colitis exacerbation. Monitor for worsening symptoms while on treatment. Discontinue treatment if acute intolerance syndrome is suspected. (5.2)
- Hypersensitivity Reactions, including myocarditis and pericarditis: Evaluate patients immediately and discontinue LIALDA if a hypersensitivity reaction is suspected. (5.3)
- Hepatic Failure: Evaluate the risks and benefits of using LIALDA in patients with known liver impairment. (5.4)
- Severe Cutaneous Adverse Reactions: Discontinue at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation. (5.5)
- Upper Gastrointestinal Tract Obstruction: Avoid in patients with pyloric stenosis or other organic or functional obstruction. (5.6)
- Photosensitivity: Advise patients with pre-existing skin conditions to avoid sun exposure, wear protective clothing, and use a broad-spectrum sunscreen when outdoors. (5.7)
- Nephrolithiasis: Cases of nephrolithiasis have been reported with the use of mesalamine. Mesalamine-containing stones are undetectable by standard radiography or computed tomography (CT). Ensure adequate hydration during treatment. (5.8)
- Interference With Laboratory Tests: Use of mesalamine may lead to spuriously elevated test results when measuring urinary normetanephrine by liquid chromatography with electrochemical detection. (5.9)

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

Most common adverse reactions in:

- adults (≥2%) are headache, flatulence, liver function test abnormal, abdominal pain, and diarrhea. (6.1)
- pediatric patients (≥5%) are abdominal pain, upper respiratory tract infection, vomiting, anemia, headache, and viral infection. (6.1)

8.4 Pediatric Use

The safety and effectiveness of LIALDA have been established for the treatment of mildly to moderately active ulcerative colitis in pediatric patients weighing at least 24 kg. Use of LIALDA in this population is supported by evidence from adequate and well-controlled trials in adults, a multicenter, randomized, double-blind, parallel group trial in 105 pediatric patients 5 to 17 years of age, and additional pharmacokinetic analyses. The safety profile in pediatric patients was similar to that observed in adults [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.2)].

The safety and effectiveness of LIALDA have not been established in patients weighing less than 24 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	February 10, 2025
Time period of search	December 1, 2019[†] - February 9, 2025
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product active ingredient: Mesalamine
MedDRA search terms (Version 27.1)	All Preferred Terms

Table 1. FAERS Search Strategy*	
Other search terms‡	Case Seriousness: Serious Country Derived: USA

* See Appendix A for a description of the FAERS database.
† Data lock date from last pediatric postmarketing pharmacovigilance review for mesalamine.
‡ 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.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; USA=United States of America

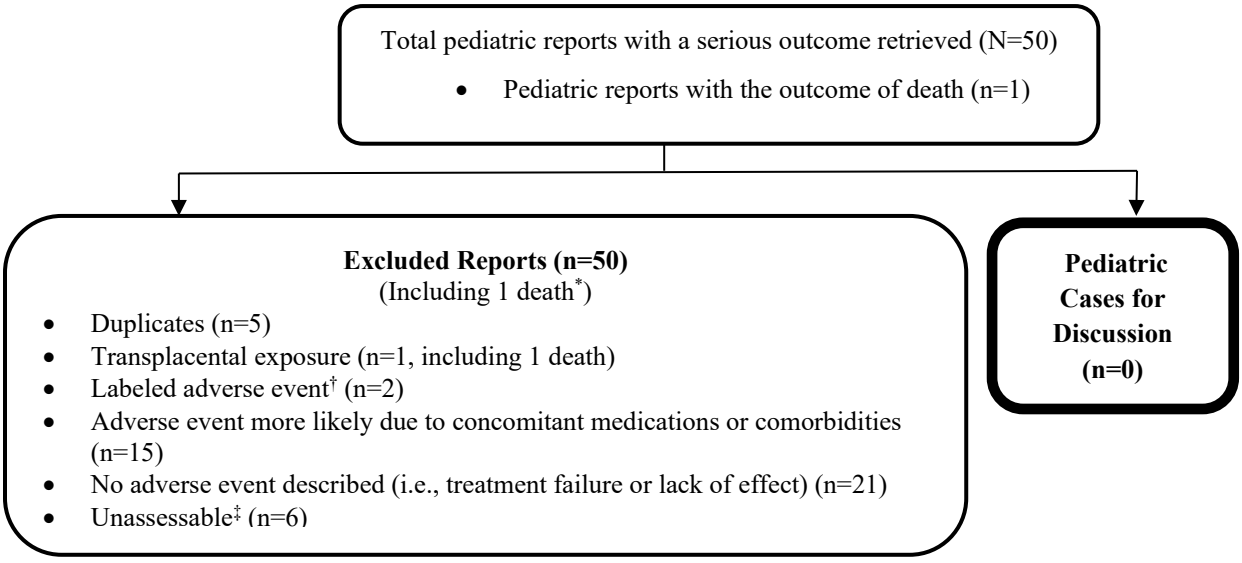
3 RESULTS

3.1 FAERS

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

Our FAERS search retrieved 50 U.S. serious pediatric reports for patients less than 18 years old from December 1, 2019 – February 9, 2025.[c] We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all 50 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 Mesalamine



* One excluded U.S. FAERS report described a fatal outcome. The case described fetal death after prenatal listeriosis infection and exposure to multiple therapeutic drug products.
† 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.

[c] Includes one pediatric report that was identified among reports not coded with an age.

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 mesalamine in pediatric patients less than 18 years of age from December 1, 2019 – February 9, 2025, and identified 50 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 mesalamine in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Lialda (mesalamine) delayed release tablets. [Prescribing information]. Wayne, PA; Shire US, Inc.: January 2017.
2. Lialda (mesalamine) delayed-release tablets. [Prescribing information]. Lexington, MA; Shire US, Inc.: June 2020.
3. Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review. NDA 19651, 21830, 204412. August 9, 2016. Available at: https://www.fda.gov/advisory-committees/pediatric-advisory-committee/asacol-asacol-hd-and-delzicol-mesalamine-briefing-materials
4. Apriso (mesalamine) extended-release capsules. [Prescribing information]. Bridgewater, NJ; Svaleant Pharmaceuticals North America, LLC: July 2017.
5. Asacol (mesalamine) delayed-release tablets. [Prescribing information]. Irvine, CA; Allergan USA, Inc.: July 2017.
6. Asacol HD (mesalamine) delayed-release tablets. [Prescribing information]. Irvine, CA; Allergan USA, Inc.: July 2017.
7. Canasa (mesalamine) suppositories. [Prescribing information]. Irvine, CA; Allergan USA, Inc.: July 2017.
8. Delzicol (mesalamine) delayed-release. [Prescribing information]. Irvine, CA; Allergan USA, Inc.: July 2017.
9. Pentasa (mesalamine) extended release capsule. [Prescribing information]. Lexington, MA; Shire US, Inc.: July 2017.
10. Rowasa (mesalamine) rectal suspension enema. [Prescribing information]. Somerset, NJ; Meda Pharmaceuticals, Inc.: June 2017.
11. Pediatric Postmarketing Pharmacovigilance Review. NDA 021252. July 22, 2020. Available at: https://www.fda.gov/media/141739/download
12. Lialda (mesalamine) delayed-release tablets. [Prescribing information]. Lexington, MA; Takeda Pharmaceuticals America, Inc.: October 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.