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

Pediatric Postmarketing Pharmacovigilance Review

Date:	July 22, 2020
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Product Names:	Canasa (mesalamine suppositories for rectal use)
Pediatric Labeling Approval Date:	September 2, 2016
Application Type/Number:	NDA 021252
Applicant/Sponsor:	Allergan Sales, LLC
OSE RCM #:	2018-2579

TABLE OF CONTENTS

EXECUTIVE SUMMARY

The Division of Pharmacovigilance (DPV) conducted this review of FDA Adverse Event Reporting System (FAERS) reports for Canasa (mesalamine suppositories for rectal use) or other mesalamine formulations in pediatric patients younger than 17 years of age in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with mesalamine (including any mesalamine formulation, for completeness) in pediatric patients.

On January 5, 2001, FDA approved Canasa for the treatment of active ulcerative proctitis. On September 2, 2016, FDA approved a labeling change for Canasa (mesalamine suppositories) describing a study of Canasa for the treatment of ulcerative proctitis in a 6-week, open-label, single-arm study in 49 patients 5 to 17 years of age (of note, only 14 patients had histologically confirmed ulcerative proctitis); this study did not demonstrate efficacy, and adverse reactions seen in pediatric patients in the trial (e.g., abdominal pain, headache, pyrexia, pharyngolaryngeal pain, diarrhea, vomiting) were similar to those seen in adult patients. There is no approved pediatric indication for Canasa.

DPV conducted hands-on review of 100 adverse event reports in pediatric patients with mesalamine products received by FDA to the FAERS database from February 24, 2016 (data lock date of prior Office of Surveillance and Epidemiology pediatric review of mesalamine products), to November 30, 2019, and identified no new safety signals. Furthermore, DPV identified no increased severity or frequency of any labeled adverse events and identified no cases of death associated with mesalamine product use in pediatric patients.

Canasa is not indicated for use in pediatric patients. DPV recommends no regulatory action at this time based on this review. DPV will continue to monitor all adverse events associated with the use of mesalamine products.

1 INTRODUCTION

The Division of Pharmacovigilance (DPV) conducted this review of FDA Adverse Event Reporting System (FAERS) reports for Canasa (mesalamine suppositories for rectal use) or other mesalamine formulations in pediatric patients younger than 17 years of age in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with mesalamine (including any mesalamine formulation, for completeness) in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

On January 5, 2001, FDA approved Canasa for the treatment of active ulcerative proctitis. At the time of approval, the sponsor agreed to a postmarketing study commitment to conduct a clinical efficacy trial in pediatric patients with ulcerative proctitis.

On August 9, 2016, the Office of Surveillance and Epidemiology (OSE) completed an evaluation of postmarketing adverse event reports with a serious outcome and drug utilization data for mesalamine products (i.e., Apriso, Asacol, Asacol HD, Canasa, Delzicol, Lialda, Pentasa, sfRowasa) in pediatric patients. OSE's evaluation was prompted by the approval of Delzicol (mesalamine 400 milligram (mg) delayed-release capsule) on April 28, 2014, for the treatment of mildly to moderately active ulcerative colitis (UC) in patients 12 years of age and older; on September 9, 2015, following approval of a new pediatric-age-appropriate formulation, the pediatric indication for Delzicol was expanded to 5 years of age and older.

On September 2, 2016, FDA approved a labeling change for Canasa (mesalamine suppositories) describing a study of Canasa for the treatment of ulcerative proctitis in a 6-week, open-label, single-arm study in 49 patients 5 to 17 years of age (of note, only 14 patients had histologically confirmed ulcerative proctitis); this study did not demonstrate efficacy, and adverse reactions seen in pediatric patients in the trial (e.g., abdominal pain, headache, pyrexia, pharyngolaryngeal pain, diarrhea, vomiting) were similar to those seen in adult patients. The 2016 labeling change for Canasa stimulated this pediatric postmarketing pharmacovigilance review.

On September 14, 2016, FDA presented OSE's evaluation of Delzicol safety in pediatric patients to the Pediatric Advisory Committee (PAC).[a] OSE's safety review identified benign intracranial hypertension as a safety signal, but imaging was insufficient to distinguish the events from cerebral venous thrombosis. The PAC voted against (Yes – 0; No – 15) FDA's recommendation to not change the mesalamine labeling for benign intracranial hypertension and requested that FDA further review the possible association between mesalamine and the event. OSE's safety review also identified nephrogenic diabetes insipidus as a drug-related safety signal; the PAC concurred (Yes – 15; No – 0) with FDA's recommendation to add nephrogenic diabetes insipidus to the *Postmarketing Experience* section of the labeling for mesalamine products.

On June 6, 2017, FDA issued a Safety Labeling Change Notification Letter to the sponsors for mesalamine products recommending the addition of intracranial hypertension and nephrogenic diabetes insipidus to the labeling for mesalamine products. On July 27, 2017, FDA approved

[a] Meeting minutes for the September 14, 2016, PAC are available at https://www.fda.gov/media/100628/download.

updated labeling for mesalamine products adding the events intracranial hypertension and nephrogenic diabetes insipidus to *Postmarketing Experience.*

1.2 RELEVANT LABELED SAFETY INFORMATION

The most recent mesalamine rectal suppository labeling, which was updated on July 27, 2017, contains the following safety highlights:

4 CONTRAINDICATIONS

CANASA is contraindicated in patients with known or suspected hypersensitivity to salicylates or aminosalicylates or to any ingredients in the suppository vehicle.

5 WARNINGS AND PRECAUTIONS

5.1 Renal Impairment
Renal impairment, including minimal change nephropathy, acute and chronic interstitial nephritis, and renal failure, has been reported in patients given products such as CANASA that contain mesalamine or are converted to mesalamine. Evaluate renal function prior to initiation of CANASA therapy and periodically while on therapy. Evaluate the risks and benefits of using CANASA in patients with known renal impairment or a history of renal disease or taking concomitant nephrotoxic drugs. In animal studies, the kidney was the principal organ for toxicity.

5.2 Mesalamine-Induced Acute Intolerance Syndrome
Mesalamine has been associated with an acute intolerance syndrome that may be difficult to distinguish from an exacerbation of ulcerative colitis. Although the exact frequency of occurrence has not been determined, it has occurred in 3% of patients in controlled clinical trials of mesalamine or sulfasalazine. Symptoms include cramping, acute abdominal pain and bloody diarrhea, and sometimes fever, headache, and rash. Monitor patients for worsening of these symptoms while on treatment. If acute intolerance syndrome is suspected, promptly discontinue treatment with CANASA.

5.3 Hypersensitivity Reactions
Hypersensitivity reactions have been reported in patients taking sulfasalazine. Some patients may have a similar reaction to CANASA or to other compounds that contain or are converted to mesalamine. As with sulfasalazine, mesalamine-induced hypersensitivity reactions may present as internal organ involvement, including myocarditis, pericarditis, nephritis, hepatitis, pneumonitis and hematologic abnormalities. Evaluate patients immediately if signs or symptoms of a hypersensitivity reaction are present. Discontinue CANASA if an alternative etiology for the signs and symptoms cannot be established.

5.4 Hepatic Failure
There have been reports of hepatic failure in patients with pre-existing liver disease who have been administered other products containing mesalamine. Evaluate the risks and benefits of using CANASA in patients with known liver impairment.

5.5 Interaction with Laboratory Test for Urinary Normetanephrine
Use of mesalamine may lead to spuriously elevated test results when measuring urinary normetanephrine by liquid chromatography with electrochemical detection, because of the

similarity in the chromatograms of normetanephrine and mesalamine's main metabolite, N-acetylaminosalicylic acid. Consider an alternative, selective assay for normetanephrine.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of CANASA in pediatric patients for the treatment of mildly to moderately active ulcerative proctitis have not been established. CANASA was evaluated for the treatment of ulcerative proctitis in a 6-week, open-label, single-arm study in 49 patients 5 to 17 years of age, which only included 14 patients with histologically-confirmed cases of ulcerative proctitis. However, efficacy was not demonstrated. Adverse reactions seen in pediatric patients in this trial (abdominal pain, headache, pyrexia, pharyngolaryngeal pain, diarrhea and vomiting) were similar to those seen in adult patients.

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	June 10, 2020
Time period of search	February 24, 2016,† to November 30, 2019
Search type	Quick Query
Product Active Ingredient	Mesalamine
Search parameters	All ages, all outcomes, worldwide
* See **Appendix A** for a description of the FAERS database. † Data lock date of prior pediatric postmarket pharmacovigilance review for mesalamine	

3 RESULTS

3.1 TOTAL NUMBER OF FAERS REPORTS BY AGE

Table 2 presents the number of adult and pediatric FAERS reports from February 24, 2016, to November 30, 2019, with mesalamine.

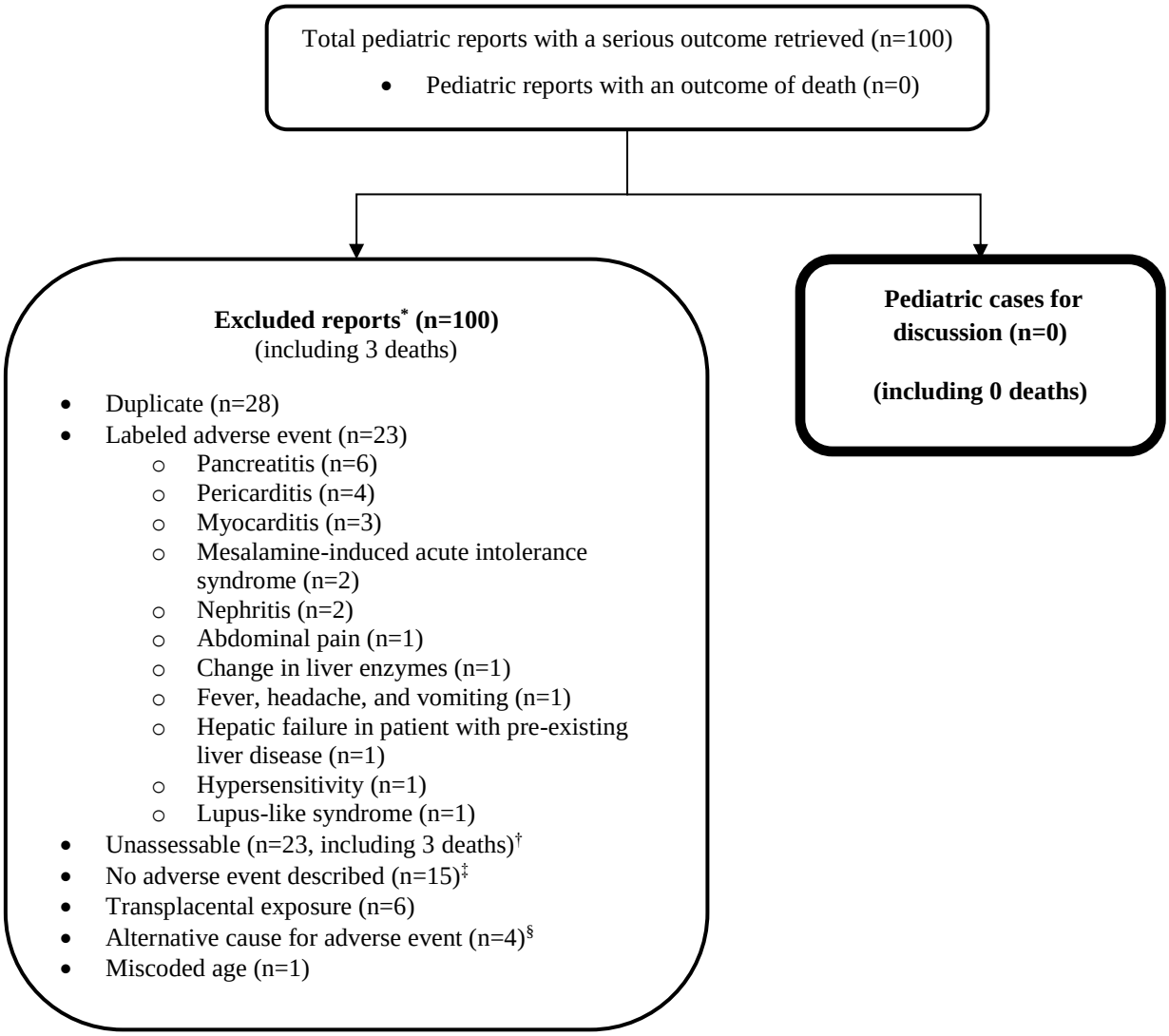
Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From February 24, 2016, to November 30, 2019, With Mesalamine			
	All Reports (United States)	**Serious† (United States)**	**Death (United States)**
Adults (≥17 years)	2,412 (1,174)	1,818 (592)	112 (26)
Pediatrics (0 to <17 years)	165 (102)	100 (38)	3 (2)
* This number may include duplicates or transplacental exposures. These reports 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, and other serious important medical events.			

3.2 SELECTION OF SERIOUS PEDIATRIC CASES IN THE FAERS DATABASE

Our search of the FAERS database retrieved 100 serious pediatric reports with all mesalamine products from February 24, 2016, to November 30, 2019.

DPV performed hands-on review of all pediatric reports with mesalamine in the FAERS database with a serious outcome to identify unlabeled adverse events or intensification of labeled adverse reactions within the pediatric population and identified zero cases. We excluded reports for the reasons described in **Figure 1**.

Figure 1. Selection of Serious Pediatric Cases With Mesalamine



* DPV reviewed these reports and excluded them from further discussion for the reasons listed.
† DPV could not assess causality because the report had insufficient information (e.g., unknown time to event, concomitant medications or comorbidities, clinical course, outcome), information was contradictory, or information provided in the report cannot be supplemented or verified.
‡ Reports with no adverse event include the following: literature report describing management of

inflammatory bowel disease (IBD) or complications (n=7), IBD flare or recurrence (n=6), idiopathic disease state (n=1), and immune thrombocytopenic purpura that had negative dechallenge and negative rechallenge with mesalamine (n=1).
§ Reports with alternative causes for the event include: rectal bleeding in a patient with hemophilia following colonoscopy (n=1), retroperitoneal abscess in a patient with Crohn's disease (n=1), pseudotumor cerebri in a patient with sagittal sinus thrombosis (n=1), and drug rash with eosinophilia and systemic symptoms (DRESS) with a temporal association to piperacillin-tazobactam initiation (piperacillin-tazobactam is labeled for DRESS in WARNINGS AND PRECAUTIONS)[b] (n=1).

3.3 SUMMARY OF FATAL PEDIATRIC CASES (N=0)

We did not identify any cases of fatal pediatric adverse events with mesalamine in the FAERS database received by FDA from February 24, 2016, to November 30, 2019.

3.4 SUMMARY OF PEDIATRIC CASES WITH A SERIOUS OUTCOME (N=0)

We did not identify any pediatric cases with a serious outcome with mesalamine in the FAERS database received by FDA from February 24, 2016, to November 30, 2019.

4 DISCUSSION

DPV conducted this review of FAERS reports for Canasa (mesalamine suppositories for rectal use) or other mesalamine formulations in pediatric patients younger than 17 years of age in accordance with FDAAA PREA. This review focuses on serious unlabeled adverse events associated with mesalamine (including any mesalamine formulation, for completeness) in pediatric patients.

DPV conducted hands-on review of 100 adverse event reports in pediatric patients with mesalamine products received by FDA to the FAERS database from February 24, 2016, to November 30, 2019, and identified no new safety signals. Furthermore, DPV identified no increased severity or frequency of any labeled adverse events and identified no cases of death associated with mesalamine product use in pediatric patients.

5 CONCLUSION

DPV did not identify any pediatric safety concerns for mesalamine during this review.

6 RECOMMENDATION

Canasa is not indicated for use in pediatric patients. DPV recommends no regulatory action at this time based on this review. DPV will continue to monitor all adverse events associated with the use of mesalamine products.

[b] Zosyn (piperacillin and tazobactam) [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals; Label revised May 2020.

7 APPENDIX

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

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 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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