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 and Drug Utilization Review

Date:	August 9, 2016
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Product Name(s):	Asacol (mesalamine 400 mg delayed-release tablets) Asacol HD (mesalamine 800 mg delayed-release tablets) Delzicol (mesalamine 400 mg delayed-release capsules)
Pediatric Labeling Approval Date:	Asacol (October 18, 2013) Delzicol (April 28, 2014)
Application Type/Number:	Asacol NDA 19651, Asacol HD NDA 21830, Delzicol NDA 204412
Applicant/Sponsor:	Warner Chilcott
OSE RCM #:	2016-356

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome and drug utilization data for Asacol, Asacol HD, and Delzicol in pediatric patients. This review was triggered by the pediatric indication for Delzicol (mesalamine 400 mg delayed-release capsules).

For the purpose of this review, we searched the FDA Adverse Event Reporting System (FAERS) database for all the reports with the product active ingredient *mesalamine*, which included reports for all mesalamine tradename products.

Asacol was approved on October 18, 2013 to expand the indication of treatment of mildly to moderately active ulcerative colitis (UC) to patients 5 years of age and older. (b) (4)

After bioequivalence of Delzicol to Asacol was demonstrated in adults, Delzicol was approved on April 28, 2014, for the treatment of mildly to moderately active UC in patients 12 years of age and older. The capsule size of Delzicol was larger than Asacol and may be difficult for pediatric patients to swallow, thus was not approved for ages less than 12 years at the time. On September 9, 2015, the pediatric indication for Delzicol was expanded to 5 years of age and older because of a new pediatric age-appropriate formulation.

To characterize utilization in the pediatric population and to provide context for the adverse event reports submitted to the FAERS database, drug utilization patterns for Asacol, Asacol HD, and Delzicol were assessed. From October 2013 through February 2016, pediatric patients aged 0-17 years accounted for 3% (5,607 patients) of total patients with a dispensed prescription for Asacol HD and 3% (120 patients) of total patients with a dispensed prescription for Asacol from outpatient retail pharmacies. From April 2014 through February 2016, pediatric patients aged 0-17 years accounted for 4% (6,903 patients) of total patients with a dispensed prescription for Delzicol. For Asacol, Asacol HD, and Delzicol, the proportion of use was higher among pediatric patients aged 5-17 years than compared to pediatric patients under 5 years of age. Although the data suggest that there may be some off-label use of Asacol and Delzicol in patients under 5 years of age, this use cannot be validated due to the lack of access to patient medical records.

We evaluated all FAERS reports of adverse events in the pediatric population for mesalamine from the initial approval of the mesalamine rectal enema on December 24, 1987, until February 23, 2016. The review of FAERS pediatric cases resulted in identification of four non-fatal serious cases containing unlabeled adverse events. The four cases reported the unlabeled events of benign intracranial hypertension (n=2) and nephrogenic diabetes insipidus (n=2). Three of four cases were associated with the product Pentasa and one case was associated with an unknown mesalamine product. DPV-I consulted the Division of Neurology Products (DNP) and the Division of Cardiovascular and Renal Products (DCRP) to review the cases of benign intracranial hypertension and nephrogenic diabetes insipidus, respectively. DNP determined that insufficient imaging was performed in each case to differentiate the event described from benign intracranial hypertension or cerebral venous thrombosis, thus recommended no change to

product labeling for any mesalamine product. DCRP concluded that the cases included in the consult were suspected to be drug-related and recommended adding nephrogenic diabetes insipidus to the Adverse Reactions Section 6.2 Postmarketing Experience for all mesalamine products that contain the adverse reaction of tubulointerstitial nephritis in the respective product labeling.

DPV-I concurs with DCRP's recommendation of adding nephrogenic diabetes insipidus to the Adverse Reactions Section 6.2 Postmarketing Experience for all mesalamine products. DPV-I plans to continue postmarketing surveillance of all adverse events with the use of mesalamine in pediatric patients.

1 INTRODUCTION

This review evaluated postmarketing adverse event reports with a serious outcome and drug utilization data for three mesalamine drug products, Asacol, Asacol HD, and Delzicol, in pediatric patients. This review was triggered by the pediatric indication for Delzicol (mesalamine 400 mg delayed-release capsules).

1.1 PRODUCT FORMULATIONS AND INDICATIONS

Mesalamine is an aminosalicylate that is used for the treatment and maintenance of remission in patients with ulcerative colitis (UC). Mesalamine is available in oral capsule, oral tablet, rectal suppository, and rectal enema formulations; its initial approval on December 24, 1987, was for the rectal enema. There currently are eight FDA-approved mesalamine products marketed in the United States that can be differentiated by formulation or delivery mechanism, route of administration, approved indications, and approved population for use (see Table 1).

Table 1.1.1 **Mesalamine Product Formulations and Indications**

Trade Name	Initial Approval	Formulation*	Indication	Population†
Apriso	2008	Capsule, ER	Maintenance of remission of UC	Adults
Asacol‡	1992	Tablet, DR	Treatment of mildly to moderately active UC Maintenance of remission of mildly to moderately active UC	Age ≥ 5 years (treatment) Adults (maintenance)
Asacol HD	2008	Tablet, DR	Treatment of moderately active UC	Adults
Canasa	2001	Suppository	Treatment of active ulcerative proctitis (UP)	Adults
Delzicol	2013	Capsule, DR	Treatment of mildly to moderately active UC Maintenance of remission of UC	Age ≥ 5 years (treatment) Adults (maintenance)

Lialda	2007	Tablet, DR	Induction of remission in active, mild to moderate UC Maintenance of remission of UC	Adults
Mesalamine	2015	Suppository	Treatment of mild to moderately active UP	Adults
Pentasa	1993	Capsule, ER	Induction of remission and for the treatment of patient with mildly to moderately active UC	Adults
sfRowasa	1987	Enema	Treatment of active mild to moderate distal UC, proctosigmoiditis, or proctitis	Adults

[*] Definitions: ER = extended-release, DR = delayed-release
[†] Asacol and Delzicol are the only mesalamine products indicated for the treatment of mildly to moderately active UC in patients five years of age and older
[‡] Withdrawn by the sponsor, Warner Chilcott, from the US market March 2013

1.2 REGULATORY HISTORY

January 31, 1992: Asacol 400 mg delayed-release tablet was approved for the treatment of mildly to moderately active UC in adult patients.

August 18, 1997: Asacol 400 mg delayed-release tablet was approved for the maintenance of remission of mildly to moderately active UC in adult patients.

November 15, 2001: A written request (WR) for pediatric studies with Asacol 400 mg delayed-release tablet was issued.

May 9, 2008: Asacol HD 800 mg delayed-release tablet was approved for the treatment of moderately active UC in adult patients. Pediatric Research Equity Act (PREA) postmarketing requirement (PMR) 319-1 was issued with the approval of Asacol HD requiring the sponsor to conduct a study to evaluate pharmacokinetic (PK) data, safety, and clinical response in pediatric patients aged 5 to 17 years old with UC undergoing 6 weeks of oral mesalamine therapy using an age-appropriate formulation.

2010: The enteric coating of Asacol 400 mg delayed-release tablet and Asacol HD 800 mg delayed-release tablet were found to contain the inactive ingredient dibutyl phthalate (DBP). Because of concerns of potential teratogenicity, the FDA asked the sponsor to develop new formulations without DBP.

January 20, 2011: In response to the WR for Asacol 400 mg delayed-release tablet, the sponsor notified the Agency that the study being conducted was terminated because of enrollment challenges and the WR was no longer being pursued. The sponsor planned to complete the PREA PMR for Asacol HD.

December 21, 2012: The efficacy supplement for addition of pediatric use and dosing information was submitted under Asacol HD (NDA 21830/6) which was cross referenced to Asacol (NDA 19651/24). Based upon discussion between the Agency and the sponsor, the Asacol 400 mg tablet was the age-appropriate formulation tested as part of the PREA requirement for Asacol HD. The submission included three study reports: (1) a PK study, (2) an induction of remission study which fulfilled PREA PMR 319-1, and (3) a maintenance of remission study (terminated early for lack of enrollment). The PK study showed that the average mesalamine concentrations in pediatric UC patients were comparable to those observed in healthy adults. The PMR study was a phase 3, randomized, double-blind, parallel-group, 6 week treatment study of low-dose (1.2, 2.0, or 2.4 g daily) and high-dose (2.0, 3.6, or 4.8 g daily) Asacol in 82 pediatric patients aged 5 to17 years with mildly to moderately active UC. The study was conducted to evaluate the short-term efficacy of two different doses of Asacol in three different weight cohorts (17 to less than 33 kg, 33 to less than 54 kg, 54 to 90 kg) of children. The sponsor also assessed the efficacy and safety of Asacol in patients who maintained remission of UC for one month prior to study start over a 26 week study duration. The study was terminated early because of lack of enrollment.

July 31, 2012: NDA 204412 was submitted for Delzicol which contained dibutyl sebecate instead of DBP. The submission contained a relative bioavailability study and dissolution studies which demonstrated bioequivalence to Asacol 400 mg tablets.

February 1, 2013: Delzicol 400 mg delayed-release capsule was approved for the induction and maintenance of mildly to moderately active UC in adults. PREA PMR 2011-1 and 2011-2 were issued at the time of approval and required the sponsor to conduct a study to evaluate PK data, safety, and clinical response in pediatric patients aged 5 to 17 years old with UC undergoing 6 weeks of oral mesalamine therapy and a study to evaluate pediatric patients aged 5 to 17 years old for the maintenance of remission of UC, respectively.

March 2013: Asacol was removed from the US market because of the approval of Delzicol. The DBP-containing formulation of Asacol HD remained on the US market.

September 10, 2013: The pediatric efficacy supplement was submitted for Delzicol (NDA 204412/3) which fulfilled the obligation to PREA PMR 2011-1. This submission did not contain any new data and cross-referenced data from the efficacy supplement submitted for Asacol (NDA 19651/24) and Asacol HD (NDA 21830/6).

October 18, 2013: Asacol was approved to expand the indication of treatment of mildly to moderately active UC to patients 5 years of age and older. Because of the lack of pediatric data, [redacted] (b) (4)

April 28, 2014: Delzicol was approved for the treatment of mildly to moderately active UC in patients 12 years of age and older. The capsule size of Delzicol was larger than Asacol and may be difficult for pediatric patients to swallow, thus was not approved for ages less than 12 years.

September 9, 2015: The pediatric indication for Delzicol was expanded to 5 years of age and older because of a new pediatric age-appropriate formulation.

1.3 SUMMARY OF RELEVANT PREVIOUS DPV SAFETY REVIEWS

DPV-I performed a review evaluating postmarketing reports of difficulty swallowing and drug administration errors with Delzicol on April 8, 2014. The review identified 53 postmarketing reports of difficulty swallowing and removal of the outer capsule related to difficulty swallowing Delzicol. DPV-I recommended 1) updating the Delzicol label to inform patients not to open the capsule before swallowing and 2) asking the sponsor to monitor postmarketing serious and non-serious adverse events related to difficulty swallowing the capsules if the pediatric supplement for the treatment of mildly to moderately active UC in patients 5 years of age and older (NDA 204412/S-003) was approved. The Division of Gastroenterology and Inborn Errors Products performed a clinical review of Delzicol on July 31, 2015, and determined that because Delzicol was reformulated, the potential safety concerns related to difficulty swallowing were no longer an issue.

1.4 HIGHLIGHTS OF LABELED SAFETY ISSUES

1.4.1 Delzicol

Delzicol is the only marketed FDA approved mesalamine product indicated for use in pediatric patients.[a] The Delzicol labeling dated October 2014 contains the following safety highlights:

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

- Patient with known hypersensitivity to salicylates or aminosalicylates or to any of the ingredients of DELZICOL capsules (4, 5.3)

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

- *Renal Impairment (for example, minimal change nephropathy, acute and chronic interstitial nephritis, renal failure)* Assess renal function at beginning of treatment and periodically during treatment (5.1)
- *Mesalamine-induced Acute Intolerance Syndrome* Has been reported. Observe patients closely for worsening of these symptoms while on treatment (5.2)
- *Hypersensitivity Reactions* Use caution when treating patients who are hypersensitive to sulfasalazine. Mesalamine-induced cardiac hypersensitivity reactions (myocarditis and pericarditis) have been reported (5.3)
- *Hepatic failure* Has been reported in patients with pre-existing liver disease. Use caution when treating patients with liver disease (5.4)
- *Prolonged Gastric Retention in Patients with Upper Gastrointestinal Obstruction* May lead to a delay in onset of action (5.5)

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

- The most common adverse reactions (observed in greater than or equal to 5% of adults in clinical trials) were abdominal pain, eructation, pain, back pain, rash, dyspepsia, rhinitis, flu syndrome, asthenia, flatulence, vomiting, fever, arthralgia, constipation, and gastrointestinal bleeding (6.1)
- Adverse reactions in children were similar (6 1)

----------DRUG INTERACTIONS----------

- *Nephrotoxic Agents including NSAIDs* Renal reactions have been reported (7.1)
- *Azathioprine or 6-mercaptopurine* Blood disorders have been reported (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- *Renal Impairment* Use DELZICOL with caution in patients with a history of renal disease (5.1, 7.1, 8.6)

[a] Asacol which also has an approved pediatric indication was removed from the US market March 2013.

- *Geriatric Patients* Monitor blood cell counts in geriatric patients (8.5)

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

Proprietary databases available to the Agency were used to conduct the drug utilization analyses in this review (see Appendix A for full database descriptions and limitations).

2.1.1 Determining Settings of Care

IMS Health, IMS National Sales Perspectives™ was used to determine the various retail and non-retail channels of distribution for Asacol, Asacol HD and Delzicol. Of note, sales of Asacol were discontinued in March 2013. Due to the residual sales volume of Asacol, sales of Asacol and Asacol HD were combined and analyzed by setting of care. Sales data for the period of October 2013 through February 2016 indicated that approximately 70% of packages for Asacol and Asacol HD were distributed to outpatient retail pharmacies; 23% were to mail-order/specialty pharmacies; and 7% were to non-retail settings.[b] For Delzicol, sales data for the period of April 2014 through February 2016 indicated that approximately 60% of packages were distributed to outpatient retail pharmacies; 26% were to mail-order/specialty pharmacies; and 14% were to non-retail settings. As a result, outpatient retail utilization patterns were examined. Neither mail-order/specialty nor non-retail settings data were included in this analysis.

2.1.2 Data Sources Used

The IMS Health, Vector One®: Total Patient Tracker (TPT) database was used to provide national estimates of patients who received an Asacol/Asacol HD prescription dispensed from U.S. outpatient retail pharmacies from October 2013 through February 2016, cumulative. We also examined national estimates of patients who received a Delzicol prescription dispensed from U.S. outpatient retail pharmacies from April 2014 through February 2016, cumulative. These data were stratified by patient age (0-4, 5-17, and 18+ years).

[b] IMS Health, IMS National Sales Perspectives™. October 2013-February 2016. Extracted March 2016. NSP 2016-356 Asacol and Asacol HD channels combined 3-29-16.xlsx; NSP 2016-356 Delzicol channels 3-29-16.xlsx

2.2 RESULTS

2.2.1 Number of Patients

Table 1. Nationally estimated number of patients who received a dispensed prescription for Asacol and Asacol HD from U.S. outpatient retail pharmacies, stratified by patient age* (0-4, 5-17, 18+ yrs), Oct 2013 - Feb 2016

	Oct 2013 - Feb 2016	
	Patient Count	*Share*
	N	%
Grand Total	**199,758**	***100.0%***
Asacol HD	**197,338**	***98.8%***
Age 0 - 17 yrs	**5,607**	***2.8%***
Age 0 - 4 yrs	44	*0.8%*
Age 5 - 17 yrs	5,570	*99.3%*
Age 18+	192,023	*97.3%*
Unknown Age	2,064	*1.0%*
Asacol	**3,732**	***1.9%***
Age 0 - 17 yrs	**120**	***3.2%***
Age 0 - 4 yrs	10	*8.2%*
Age 5 - 17 yrs	110	*91.6%*
Age 18+	3,611	*96.7%*
Unknown Age	6	*0.2%*

Source: IMS, Vector One®: Total Patient Tracker. Oct 2013 - Feb 2016. Extracted March 2016. File:TPT 2016-356 Asacol and Asacol HD by age 3-23-16.xls

**Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients 0-17 years of age include patients less than 18 years of age (17 years and 11 months).*

***Subtotals may not sum exactly, due to rounding. Patients may have received multiple administrations of drug during the study period and due to aging of patients during the study period, patients may be counted more than once across age groups. For this reason, summing is not advisable and will result in overestimates of patient counts.*

Table 2. Nationally estimated number of patients who received a dispensed prescription for Delzicol from U.S. outpatient retail pharmacies, stratified by patient age* (0-4, 5-17, 18+ yrs), Apr 2014 - Feb 2016

	Apr 2014 - Feb 2016	
	Patient Count	*Share*
	N	%
Delzicol	**188,466**	***100.0%***
Age 0 - 17 yrs	**6,903**	***3.7%***
Age 0 - 4 yrs	156	*2.3%*
Age 5 - 17 yrs	6,774	*98.1%*
Age 18+	181,491	*96.3%*
Unknown Age	1,899	*1.0%*

Source: IMS, Vector One®: Total Patient Tracker. Apr 2014 - Feb 2016. Extracted March 2016. File:TPT 2016-356 Delzicol by age 3-23-16.xls

**Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients 0-17 years of age include patients less than 18 years of age (17 years and 11 months).*

***Subtotals may not sum exactly, due to rounding. Patients may have received multiple administrations of drug during the study period and due to aging of patients during the study period, patients may be counted more than once across age groups. For this reason, summing is not advisable and will result in overestimates of patient counts.*

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV-I searched the FAERS database with the strategy described in Table 3.1.1. The FAERS search strategy used *Product Active Ingredient* mesalamine which retrieved reports with other mesalamine products (such as Apriso, Lialda, Pentasa, sfRowasa) in addition to the products of interest (Asacol, Asacol HD, and Delzicol) to ensure all events with the same active moiety were captured. The approval date of the first marketed mesalamine product (sfRowasa rectal enema), December 24, 1987, was used as the initial search date to capture all reports of off-label use of mesalamine in pediatric patients. See Appendix B for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy

Date of Search	May 26, 2016
Time Period of Search	December 24, 1987[*] - February 23, 2016
Search Type	Quick Query Product-Manufacturer Reporting Summary
Product Active Ingredient	Mesalamine
Search Parameters	All ages, all outcomes, worldwide

[*]Approval date of first marketed mesalamine product, sfRowasa

3.2 RESULTS

3.2.1 Total Number of FAERS Reports by Age

Table 3.2.1 Number of adult and pediatric FAERS reports[*] from December 24, 1987 to February 23, 2016 with mesalamine

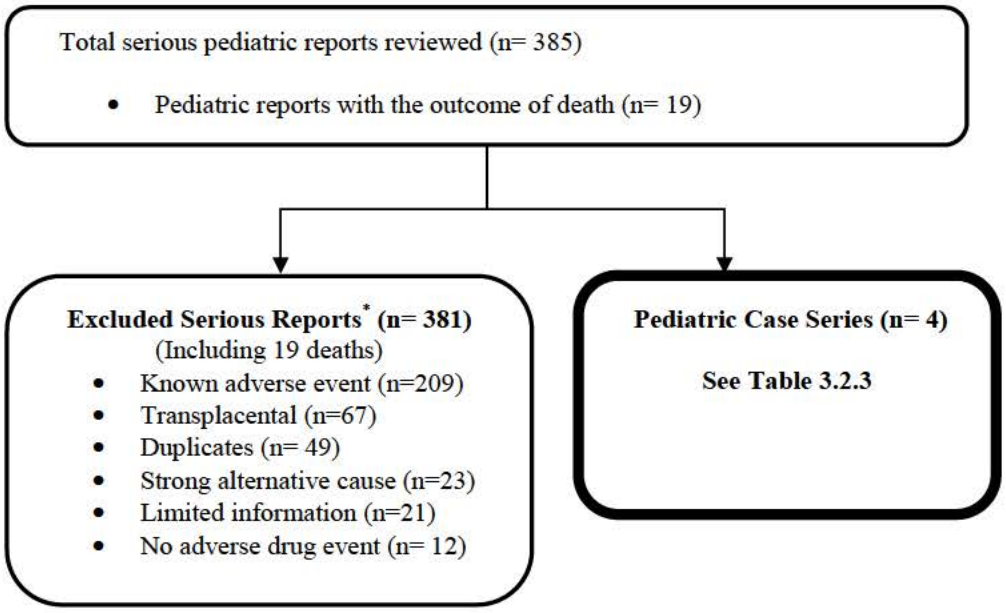
	All reports (US)	Serious[†] (US)	Death (US)
Adults (≥ 17 years)	5127(3315)	3598(1817)	214 (107)
Pediatrics (0 to <17 years)	535(302)	385(155)	19(2)[‡]

[*] May include duplicate reports and transplacental exposures; 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.
[‡] Does not include null age death reports

3.2.2 Selection of Pediatric Cases in FAERS

We identified 385 serious pediatric adverse event reports out of 5127 total adverse event reports (See Table 3.2.1) for mesalamine from December 24, 1987 to February 23, 2016. A high level review of all serious pediatric postmarketing reports (n=385) was completed. See **Figure 3.2.2** below for the specific selection of cases to be summarized in **Section 3.3.**

Figure 3.2.2 Selection of Serious Pediatric Cases with Mesalamine



*DPV-I reviewed these reports, but they were excluded from the case series for the reasons below

Of the 385 serious pediatric reports, 381 were not included in the pediatric case series. Two hundred and nine reports described a "known adverse event." An adverse event or Preferred Term that was labeled for the respective mesalamine product involved in the report was considered a "known adverse event" across all mesalamine drug products.

Nineteen of 381 excluded reports had an outcome of death. Of the 19 reports with an outcome of death, seven reports were duplicates, six reports described transplacental exposures, and one report had insufficient information to assess the cause of death. The remaining five reports described patients who died as a result of a strong alternative cause: hepatosplenic T-cell lymphoma (n=1), hemophagocytic syndrome (n=1), disseminated intravascular coagulation secondary to bacteremia (n=1), and Epstein-Barr virus-associated lymphoproliferative disorder (n=2) in patients receiving multiple immunosuppressant medications.

Eighteen reports that had a non-fatal serious outcome had a strong alternative cause for the adverse events: nine indicated the patient developed an infection (such as *Clostridium difficile*, cytomegalovirus, gas gangrene of leg) while receiving at least one concomitant immunosuppressant medication labeled for the development of serious infections (such as azathioprine, cyclosporine, prednisone), six reported labeled events for concomitant medications (such as nephrolithiasis with concomitant ceftriaxone, hemolytic anemia with concomitant

azathioprine), and three reported an underlying comorbidity (such as Sweet's syndrome in a patient with Crohn's disease, epistaxis in a patient with Hermansky-Pudlak syndrome).

3.2.3 Characteristics of Pediatric Case Series

Appendix C lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the Pediatric Case Series.

Table 3.2.3 Characteristics of Pediatric Case Series with mesalamine (N=4)

Age	0 - < 1 year	0
	1 - <3 years	0
	3- < 7 years	0
	7- <17 years	4
Sex	Male	1
	Female	3
Country	United States	0
	Foreign	4
Reported Reason for Use	Ulcerative colitis	3
	Crohn's disease	1
Serious Outcome*	Death	0
	Life-threatening	0
	Hospitalized	2
	Disability	1
	Congenital anomaly	0
	Required Intervention	0
	Other serious	2
Tradename product†	Pentasa	3
	Unknown	1

* 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. Reports may have more than one outcome.

† FAERS search strategy used *Product Active Ingredient* mesalamine, which captured reports with other mesalamine products (such as Apriso, Lialda, Pentasa) in addition to the products of interest (Asacol, Asacol HD, Delzicol).

3.3 SUMMARY OF NON-FATAL PEDIATRIC ADVERSE EVENT CASES (N= 4)

3.3.1 Nervous System Disorders (n=2)

There were two cases of the unlabeled event of benign intracranial hypertension identified.

Case 3905652, outcome-disability/ hospitalization, 2003, France: A 15-year-old female patient experienced intracranial hypertension, headache, and scotoma while taking Pentasa 3 g daily for treatment of UC. Approximately 1 month after starting Pentasa, the patient experienced torticollis-like cervical pains followed by a headache. The patient was hospitalized for

neurologic workup and diagnosed with intracranial hypertension with papillary edema. Cephalic magnetic resonance imaging (MRI) and lumbar puncture were normal. Pentasa was decreased to 2 g daily and acetazolamide was initiated. The patient's headache resolved. Campimetric tests were performed for three months following the event and showed a visual disturbance with normal visual acuity and resolved papilla edema. The outcome of intracranial hypertension was not reported. Approximately 3 months later, the patient had relapsing UC and the Pentasa dose was increased. Because of lack of effect of the dose increase and risk of developing adverse effects, Pentasa was stopped and the patient was started on corticosteroids in addition to ongoing acetazolamide. After another 3 months, the patient had another neuro-ophthalmologic exam which showed persistence of scotoma.

Case #3919280, outcome- hospitalization, 2003, France: A literature report[1] described an 11-year-old female patient who developed headaches and bilateral optic disc edema while receiving mesalamine 3 g daily for treatment of CD. The patient received concomitant silicates and trimebutine as needed when diarrhea worsened.[c] Three weeks after beginning mesalamine, the patient experienced headaches that were initially treated with acetaminophen. The headaches continued to worsen in severity and three months later the patient was admitted to the hospital because of the headaches and uncontrolled IBD. The patient had no other neurologic signs, no diplopia, normal arterial pressure, and an elevated erythrocyte sedimentation rate. A complete ophthalmologic exam was completed and revealed normal visual acuity, oculopalpebral motility, and anterior segment examination. Fundus biomicroscopy revealed bilateral stage 1 optic disc edema without retinal hemorrhage. The visual field examination showed enlarged blind spots. Computed tomography scan of the head was normal and pseudotumor cerebri was diagnosed. Mesalamine was suspected as the cause and discontinued. Fundoscopic exam performed 8 days later showed decreasing edema and steroids were initiated. One week later, the headaches began to weaken and disappeared completely 1 month later. Three to four months later, fundoscopic examination showed regression of papilloedema on the left side but persistence on the right side. The patient's visual field was normal and ophthalmologic examination showed persistent minor disc edema on the right side.

Division of Neurology Products (DNP) Review

DPV-I consulted DNP on the two aforementioned pediatric cases of benign intracranial hypertension. DPV-I also sent an additional literature case report of benign intracranial hypertension in a 23-year-old female who was receiving mesalamine.[d,2] The DNP reviewer concluded that there was insufficient neuroimaging information in the cases to distinguish whether the cases were the event of benign intracranial hypertension or cerebral venous thrombosis. Both benign intracranial hypertension and cerebral venous thrombosis rarely occur in patients with inflammatory bowel disease. It is difficult to distinguish between benign intracranial hypertension from cerebral venous thrombosis based on clinical grounds because of similar presentations, therefore specific imaging techniques (MRI venography, conventional cerebral angiography with venous images) are recommended (not performed in the cases).

[c] Silicates have adsorbent properties and have been used in the management of diarrhea. Trimebutine is an antispasmodic agent that appears to relieve spasm and restore normal colonic motility.

[d] For labeling consideration, DPV-I performed an additional FAERS search in the adult population using the search strategy described in Table 3.1.1. The medical literature was also searched for case reports of benign intracranial hypertension in all ages. One additional case was identified in the literature.

Additionally, the response to acetazolamide in the first case and corticosteroids in the second case does not help distinguish benign intracranial hypertension from cerebral venous thrombosis.

3.3.1 Renal and Urinary Disorders (n=2)

There were two cases of the unlabeled event of nephrogenic diabetes insipidus that were co-reported with a labeled event of interstitial nephritis. "Renal impairment, including minimal change nephropathy, acute and chronic interstitial nephritis, and renal failure" are labeled in the Warnings and Precautions Section 5.1 Renal Impairment. "Renal impairment, including renal failure" is labeled in Section 6 Adverse Reactions and Section 6.2 Postmarketing Experience.

Case 4088971, outcome- other serious important medical events, 2004, Japan: A physician reported that a 14-year-old female experienced interstitial nephritis and nephrogenic diabetes insipidus while receiving Pentasa 2250 mg daily for treatment of UC. The patient's baseline laboratory values prior to initiation of Pentasa were as follows: serum creatinine (SCr) 0.47 mg/dL, blood urea nitrogen (BUN) 8.5 mg/dL, and serum sodium 138 mEq/L. Approximately 5 months after starting Pentasa, the patient drank water more often, urinated more frequently at night, and experienced a 6 kg decrease in weight. The patient was hospitalized for observation and a water deprivation test and vasopressin-loaded test were performed and resulted in suspicion for nephrogenic diabetes insipidus. A renal biopsy was performed revealing interstitial nephritis. Pentasa was discontinued 5 days later and the patient's laboratory values at that time were SCr 0.72 mg/dL, BUN 10.3 mg/dL, and serum sodium 139 mEq/L. Three days after Pentasa discontinuation, the nephrogenic diabetes insipidus improved and the laboratory values were reported as SCr 0.64 mg/dL, BUN 7.9 mg/dL, and serum sodium 138 mEq/L. Prednisolone was initiated 7 days later to treat the nephritis and a drug-induced lymphocyte stimulation test was positive for mesalamine. At the time of the report (approximately 2 weeks later), the nephrogenic diabetes insipidus was reported as recovered and interstitial nephritis was improved but not completely recovered. Concomitant medications included azulene and icosapent ethyl. [e]

Case 5808701, outcome- other serious important medical events, 2005, Japan: A non-healthcare professional reported that a 9-year-old male patient developed interstitial nephritis (no histopathologic diagnosis) and nephrogenic diabetes insipidus during treatment with Pentasa 1250 mg orally daily and Pentasa rectal enema 1000 mg daily for the treatment of UC. The patient was also being treated with prednisolone and granulocytapheresis. Approximately 1 month after the most recent Pentasa oral dose increase (1000 mg daily to 1250 mg daily), the patient developed increased urine volume. Pentasa rectal enema was initiated approximately two weeks later. Approximately 2 weeks later, the patient experienced dipsesis, passed 1200 mL of urine over 8 hours, and was diagnosed with nephrogenic diabetes insipidus. Laboratory tests at that time showed a SCr of 0.49 mg/dL (normal level for this patient was reported as 0.27 – 0.35 mg/dL) and BUN of 2.9 mg/dL. Pentasa was discontinued and the dipsesis and increased urine volume resolved the next day. The patient's SCr peaked at 0.83 mg/dL approximately 7 weeks later and then returned to 0.38 mg/dL after 3.5 more weeks. The patient fully recovered. The patient had a reported allergy of "eruption" to salazosulfapyridine. Concomitant medications included prednisolone, icosapent ethyl, and famotidine.

[e] Azulene is one of the bioactive constituents from chamomile. Icosapent ethyl is an ethyl ester of eicosapentaenoic acid and is FDA-indicated as adjunct to diet to reduce triglyceride levels in adult patients with severe hypertriglyerceidemia.

Division of Cardiovascular and Renal Products (DCRP) Review
DPV-I consulted DCRP on the two aforementioned pediatric cases of nephrogenic diabetes insipidus. DPV-I also sent two additional foreign literature case reports of nephrogenic diabetes insipidus in a 36-year-old female[3] and 26-year-old-male[4] who were receiving mesalamine.[f,5] The DCRP reviewer concluded that the cases included in the consult were suspected to be drug-related because (1) mesalamine is known to cause tubulointerstitial nephritis (co-reported in all cases), (2) the reports of polyuria and polydipsia were seen in the setting of a rise in creatinine, (3) the concomitant medications that the patients were receiving were not associated with renal toxicity, and (4) the relationship between the initiation of the drug and the adverse event and the improvement in renal function and nephrogenic diabetes insipidus following drug withdrawal.

4 DISCUSSION

The drug utilization data showed that pediatric patients less than 17 years of age accounted for approximately 3% of the total patients who received dispensed prescriptions for Asacol and Asacol HD from outpatient retail pharmacies. Pediatric patients less than 17 years of age accounted for approximately 4% of the total patients who received dispensed prescriptions for Delzicol. Although the data suggest that there may be some off-label use of Asacol and Delzicol in patients under 5 years of age, this use cannot be validated due to the lack of access to patient medical records.

We evaluated all FAERS reports of adverse events in the pediatric population for mesalamine from the initial approval of the mesalamine rectal enema on December 24, 1987, until February 23, 2016. The review of FAERS pediatric cases resulted in identification of four non-fatal serious cases containing unlabeled adverse events and no fatal cases. The four cases reported the unlabeled events of benign intracranial hypertension (n=2) and nephrogenic diabetes insipidus (n=2). Three of four cases were associated with the product Pentasa and one case was associated with an unknown mesalamine product. DPV-I consulted DNP and DCRP to review the cases of benign intracranial hypertension and nephrogenic diabetes insipidus, respectively.[2,5] DNP determined that insufficient imaging was performed in each case to differentiate the event described from benign intracranial hypertension or cerebral venous thrombosis, thus recommended no change to product labeling for any mesalamine product. DCRP suspected that the cases of nephrogenic diabetes insipidus were drug-related and recommended adding nephrogenic diabetes insipidus to the Adverse Reactions Section 6.2 Postmarketing Experience for all mesalamine products that contain the adverse reaction of tubulointerstitial nephritis in the respective product labeling.

5 CONCLUSION

The Office of Surveillance and Epidemiology analyzed the following data: (1) pediatric drug utilization data for Asacol, Asacol HD, and Delzicol and (2) the pediatric postmarketing adverse event reports for all mesalamine drug products received in FAERS from December 24, 1987 to

[f] For labeling consideration, DPV-I performed an additional FAERS search in the adult population using the search strategy described in Table 3.1.1. Additionally, the medical literature was searched for cases of nephrogenic diabetes insipidus in all ages. One additional case was identified in the FAERS search and literature and one additional case was identified in the literature only.

February 23, 2016. Two safety signals (benign intracranial hypertension and nephrogenic diabetes insipidus) were identified. After review of the benign intracranial hypertension cases by DNP, it was determined that insufficient imaging was performed in each case to differentiate the event described from benign intracranial hypertension or cerebral venous thrombosis, thus recommended no change to product labeling for any mesalamine product. After review of the nephrogenic diabetes insipidus cases by DCRP, it was determined that there was sufficient evidence that the events were drug-related and recommended updates to the product labeling for all mesalamine products.

6 RECOMMENDATIONS

DPV-I concurs with DCRP's recommendation of adding nephrogenic diabetes insipidus to the Adverse Reactions Section 6.2 Postmarketing Experience for all mesalamine products. DPV-I plans to continue postmarketing surveillance of all adverse events with the use of mesalamine in pediatric patients.

7 REFERENCES

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[4] Masson EA, Rhodes JM. Mesalazine associated nephrogenic diabetes insipidus presenting as weight loss. *Gut* 1992;33:563-64.
[5] Blank MJ. Consultative review: Nephrogenic diabetes insipidus with mesalamine. *DAARTS*; July 25, 2016.

8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS, Total Patient Tracker (TPT)

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

The patient estimates focus on only outpatient retail pharmacies; therefore, they may not be representative of utilization in other settings of care such as mail-order/specialty and non-retail settings.

8.2 APPENDIX B. 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 the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference 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.

8.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH MESALAMINE (N=4)

Row	FAERS Case	FAERS Version	Manufacturer Control Number
1	4088971	2	2004-00049FE
2	5808701	2	SUS1-2005-00355
3	3905652	2	2003-00052FE
4	3919280	1	MESA 2003-009

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/s/

LISA M HARINSTEIN
08/09/2016

PATTY A GREENE
08/15/2016
drug use data cleared by database vendors 8/5/16

EILEEN WU
08/15/2016

TRAVIS W READY
08/15/2016

CINDY M KORTEPETER
08/15/2016

GRACE CHAI
08/15/2016