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**Pediatric Postmarketing Pharmacovigilance**

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## TABLE OF CONTENTS

Executive Summary .....	3
1 Introduction.....	5
1.1 Product Formulations and Indications.....	5
1.2 Pediatric Regulatory History .....	6
1.3 Highlights of Labeled Safety Issues.....	8
2 Postmarket adverse event Reports .....	8
2.1 Methods and Materials .....	9
2.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy.....	9
2.2 Results .....	9
2.2.1 Total number of FAERS reports by Age .....	9
2.2.2 Selection of Serious Pediatric Cases in FAERS .....	9
2.2.3 Characteristics of Pediatric Case Series.....	11
2.3 Summary of Non-Fatal Pediatric Serious Adverse Event Cases (N=5).....	11
2.3.1 Nervous System Disorders (n=3).....	12
2.3.2 Psychiatric Disorders (n=1) .....	14
2.3.3 Renal and Urinary Disorders (n=1) .....	15
3 Discussion .....	15
4 Conclusion .....	16
5 Recommendations.....	16
6 Appendices.....	16
6.1 Appendix A FDA Adverse Event Reporting System (FAERS).....	16
6.2 Appendix B. FAERS Case Numbers, FAERS Version Numbers And Manufacturer Control Numbers For The Pediatric Case Series With Drug (N=5).....	18
7 References.....	19

## EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA), the Division of Pharmacovigilance-I (DPV-I) evaluated postmarketing adverse event reports with a serious outcome for Prilosec (omeprazole magnesium; NDA 022056) delayed-release oral suspension and Prilosec (omeprazole; NDA 19810) delayed-release pellets capsule in pediatric patients. This review was triggered by the pediatric indication for Prilosec (omeprazole magnesium) delayed-release oral suspension.

Prilosec (omeprazole) delayed-release pellets capsule was first approved in 1989 and is indicated for the treatment of active duodenal and gastric ulcer, eradication of *Helicobacter pylori* to reduce the risk of duodenal ulcer recurrence, treatment of symptomatic gastroesophageal reflux disease (GERD), treatment of erosive esophagitis (EE) due to acid-mediated GERD, maintenance healing of EE due to acid-mediated GERD, and for the treatment of hypersecretory conditions. Pediatric labeling for the delayed-release pellets capsule was approved for patients 2 to 16 years of age for the treatment of GERD, healing of erosive esophagitis (EE), and maintenance of healing of EE on July 12, 2002. On March 20, 2008, Prilosec (omeprazole magnesium; NDA 022056) delayed-release oral suspension was approved for the short-term treatment of symptomatic GERD and healing of EE in pediatric patients 1 to 2 years old. On February 3, 2016, the indication for NDA 022056 was expanded for the treatment of EE due to acid-mediated GERD in pediatric patients aged 1 month to less than 1 year.

We evaluated all pediatric postmarketing adverse event reports with a serious outcome (n=281) for omeprazole in the FAERS database from October 16, 2013 through November 2, 2017. The start date of October 16, 2013 was chosen to capture all reports from the data lock date of a previous Division of Gastroenterology and Inborn Errors Products review for NDA 22056/S-018, which reviewed all pediatric postmarketing adverse events with omeprazole from February 1989 (U.S. approval date) through October 15, 2013. Of the 281 serious pediatric reports, 276 were not included in the pediatric case series. Reasons for exclusion of the 276 reports, including 17 deaths, were duplicate reports (n=133), contained strong alternative causes for the reported adverse events (n=49), reported a labeled event for a concomitant medication (n=40), described transplacental exposures (n=24), contained limited information for assessment (n=23), did not report an adverse event (n=6), and was an adult case coded with the wrong age (n=1).

Specifically, of the 17 death reports, seven were duplicates, three described transplacental exposure, two had insufficient information to assess the cause of death, and one described a labeled adverse event (Steven-Johnson syndrome and toxic epidermal necrolysis after receiving antibiotics and omeprazole). The remaining four reports described patients who died because of a strong alternative cause: cardiac failure in patients with multiple co-morbidities (n=2), cardiorespiratory arrest and aspiration after choking on an omeprazole tablet (n=1), and multi-organ failure in a patient receiving multiple immunosuppressant medications (n=1).

The remaining five non-fatal pediatric cases described unlabeled adverse events (seizures n=2, dystonia n=1, chromaturia n=1, autism spectrum disorder n=1, antisocial disorder n=1, speech disorder n=1, and communication disorder n=1). In three of the five cases, patients were receiving higher than recommended doses of omeprazole which may have contributed to the adverse events. In addition, all five cases either had other plausible explanations to account for the adverse event or lacked sufficient information to assess causality.

No new safety signals were identified after review of the pediatric postmarketing cases with omeprazole. DPV-I plans to continue postmarketing surveillance of all adverse events with omeprazole.

# 1 INTRODUCTION

This review evaluated postmarketing adverse event reports with a serious outcome for two omeprazole drug products, Prilosec (omeprazole magnesium; NDA 022056) delayed-release oral suspension and Prilosec (omeprazole; NDA 19810) delayed-release pellets capsule, in pediatric patients. This review was triggered by the pediatric indication for Prilosec (omeprazole magnesium) delayed-release oral suspension.

## 1.1 PRODUCT FORMULATIONS AND INDICATIONS

Omeprazole is a proton pump inhibitor (PPI) approved in the United States (U.S.) on September 14, 1989 and is available as a prescription and over-the-counter (OTC) product (see Table 1.1.1 for omeprazole formulations and U.S. approval information).

<b>Formulations</b>	<b>Prescription or OTC Status</b>	<b>NDA/ANDA</b>	<b>Initial U.S. Approval Dates</b>	<b>Approved Indications</b>	<b>Approved Population for Use</b>
Delayed-release oral suspension	Prescription	NDA 022056	3/20/2008	Treatment of active duodenal ulcer	Adults
				Eradication of <i>Helicobacter pylori</i> to reduce the risk of duodenal ulcer recurrence	Adults
				Treatment of active benign gastric ulcer	Adults
				Treatment of symptomatic gastroesophageal reflux disease (GERD)	Children 1 year of age and older
				Treatment of erosive esophagitis (EE) due to acid-mediated GERD	Children 1 month of age and older
				Maintenance of healing of EE due to acid-mediated GERD	Children 1 year of age and older
				Pathologic hypersensitivity conditions	Adults
Delayed-release pellets capsule	Prescription	NDA 019810 (discontinued) ANDA 075347, 075576, 075757,	9/14/1989	Treatment of active duodenal ulcer	Adults

		075785, 075876, 076048, 076515, 078490, 091352, 091672, 202384, 203270, 203481, 204661		Eradication of <i>Helicobacter pylori</i> to reduce the risk of duodenal ulcer recurrence  Treatment of active benign gastric ulcer  Treatment of symptomatic GERD  Treatment of EE due to acid-mediated GERD  Maintenance of healing of EE due to acid-mediated GERD  Pathologic hypersensitivity conditions	Adults  Adults  Children 1 year of age and older  Children 1 month of age and older  Children 1 year of age and older  Adults
Delayed-release oral disintegrating tablet	OTC	NDA 209400	7/5/2017	Treatment of frequent heartburn (occurs 2 or more days a week) for 14 days	Adults
Delayed-release tablet	OTC	NDA 021229 NDA 022032 ANDA 204152	6/20/2003	Treatment of frequent heartburn (occurs 2 or more days a week) for 14 days	Adults
Delayed-release capsule	OTC	ANDA 078878	6/5/2009	Treatment of frequent heartburn (occurs 2 or more days a week) for 14 days	Adults

## 1.2 PEDIATRIC REGULATORY HISTORY<sup>1,3</sup>

Prilosec (omeprazole; NDA 19810) delayed-release pellets capsule was originally approved as a delayed-release oral capsule on September 14, 1989. Pediatric labeling for the delayed-release pellets capsule was approved for patients 2 to 16 years of age for the treatment of symptomatic gastroesophageal reflux disease (GERD), healing of erosive esophagitis (EE), and maintenance of healing of EE on July 12, 2002.

On March 20, 2008, Prilosec (omeprazole magnesium; NDA 022056) delayed-release oral suspension was approved for the short-term treatment of symptomatic GERD and healing of EE in pediatric patients 1 to 2 years old. NDA 022056 was submitted to fulfill the Phase IV commitment made upon approval of NDA 19810 to develop an age appropriate formulation for young children. A postmarketing requirement (PMR) under the Pediatric Research Equity Act

(PREA) was issued to the Sponsor, AstraZeneca, to conduct a pediatric study in pediatric patients 1 month to < 1 year of age for the treatment of GERD.

On April 29, 2010, the Office of Surveillance and Epidemiology (OSE) completed a review of pediatric postmarketing adverse events for all PPIs, including omeprazole delayed-release oral suspension, in preparation for a June 2010 Pediatric Advisory Committee (PAC) meeting.<sup>2</sup> Postmarketing pediatric adverse events in the Adverse Event Reporting System (AERS) database were reviewed for omeprazole from approval date (March 20, 2008) through April 20, 2009. No safety concerns were identified from the OSE review. The Committee recommended to return to standard safety monitoring for all adverse events. The Committee also discussed the need for additional data to evaluate efficacy, dosing regimens, and bone fractures related to PPI use. Additional data on pediatric PPI use was presented at the May 7, 2012 PAC meeting, which did not identify any PPI-related safety signals.

On October 10, 2013, FDA released AstraZeneca from part of the above mentioned PMR and replaced it with a new PMR to evaluate the pharmacokinetics, pharmacodynamics, and safety of omeprazole in patients 1 month to 11 months with EE. On June 20, 2013, based on a feasibility analysis, additional concerns were raised by the Sponsor about completing the revised PMR and proposed to use available pharmacokinetic, pharmacodynamic, and safety data from previous omeprazole studies in children to fulfil the PMR. In February 2014, FDA agreed to the Sponsor's proposal.

The following regulatory history was reproduced from Dr. Marjorie Dannis (Medical Officer in the Division of Gastroenterology and Inborn Errors Products (DGIEP)) clinical review of the pediatric supplement to extend the indication to patients 1 month to less than 1 year of age with EE due to acid-mediated GERD.<sup>3</sup>

There were no new efficacy data submitted with this sNDA (NDA 022056/S-018) submission. Acid-mediated GERD with EE has the same disease definition and similar endoscopic presentation in adults, older children, and infants. In all age groups, the treatment is targeted to reduce pH and heal acid-injury. Therefore, extrapolation of efficacy based on well-controlled adult trials is appropriate for pediatric patients 1-11 months of age. Based on the Clinical Pharmacology and Pharmacometrics review, the pharmacokinetic and pharmacodynamic data appear to support the proposed weight-based doses for infants aged 1 to 11 months.

The safety assessment was obtained from two previous clinical trials (Studies 251 and 250) as well as from post-marketing data. Overall, no major safety concerns were identified. The reviewer concluded that the reported adverse events during the clinical studies were mostly related to the natural history and/or disease-related events in this patient population. The Sponsor submitted post-marketing experience adverse event data up until October 15, 2013. The clinical reviewer concluded that with the exception of "off label use", most of the adverse events were likely related to the natural history and/or disease-related events. From February 1989 to October 2013, there were five cases with a fatal outcome in infants less than 1 year of age. A review of the case narratives failed to provide evidence that these outcomes could be treatment related.

Overall, no new safety concerns were observed during the review of the post-marketing safety data.

On February 3, 2016, Prilosec (omeprazole magnesium; NDA 022056) delayed-release oral suspension was approved for the treatment of EE due to acid-mediated GERD in pediatric patients aged 1 month to less than 1 year.

### 1.3 HIGHLIGHTS OF LABELED SAFETY ISSUES

#### -----CONTRAINDICATIONS-----

- Patients with known hypersensitivity to substituted benzimidazoles or any component of the formulation. (4)
- Patients receiving rilpivirine-containing products. (4,7)
- Refer to the Contraindications section of the prescribing information for clarithromycin and amoxicillin, when administered in combination with Prilosec. (4)

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

- Gastric Malignancy: In adult patients, symptomatic response does not preclude the presence of gastric malignancy. (5.1)
- Acute Interstitial Nephritis: Observed in patients taking PPIs. (5.2)
- Clostridium difficile-Associated Diarrhea: PPI therapy may be associated with increased risk. (5.3)
- Bone Fracture: Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. (5.4)
- Cutaneous and Systemic Lupus Erythematosus: Mostly cutaneous; new onset or exacerbation of existing disease; discontinue PRILOSEC and refer to specialist for evaluation. (5.5)
- Interaction with Clopidogrel: Avoid concomitant use of PRILOSEC. (5.6,7)
- Cyanocobalamin (Vitamin B-12) Deficiency: Daily long-term use (e.g., longer than 3 years) may lead to malabsorption or a deficiency of cyanocobalamin. (5.7)
- Hypomagnesemia: Reported rarely with prolonged treatment with PPIs. (5.8)
- Interaction with St. John's Wort or Rifampin: Avoid concomitant use of PRILOSEC. (5.9, 7)
- Interactions with Diagnostic Investigations for Neuroendocrine Tumors: Increased Chromogranin A (CgA) levels may interfere with diagnostic investigations for neuroendocrine tumors; temporarily stop PRILOSEC at least 14 days before assessing CgA levels. (5.10, 7)
- Interaction with Methotrexate: Concomitant use with PPIs may elevate and/or prolong serum concentrations of methotrexate and/or its metabolite, possibly leading to toxicity. With high dose methotrexate administration, consider a temporary withdrawal of PRILOSEC. (5.11, 7)

#### -----ADVERSE REACTIONS-----

- Adults: Most common adverse reactions in adults (incidence  $\geq 2\%$ ) are headache, abdominal pain, nausea, diarrhea, vomiting, and flatulence. (6)
- Pediatric patients (1 to 16 years of age): Safety profile similar to that in adults, except that respiratory system events and fever were the most frequently reported reactions in pediatric studies. (8.4)

#### -----DRUG INTERACTIONS-----

- Clinically relevant interactions include: antiretrovirals, warfarin, methotrexate, clopidogrel, citalopram, cilostazol, phenytoin, diazepam, digoxin, drugs dependent on gastric pH for absorption, combination therapy with clarithromycin and azithromycin, tacrolimus, St. John's Wort, rifampin, and voriconazole. (7)

## 2 POSTMARKET ADVERSE EVENT REPORTS



## 2.1 METHODS AND MATERIALS

### 2.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

The Division of Pharmacovigilance-I (DPV-I) searched the FAERS database with the strategy described in Table 2.1.1. The FAERS search strategy used *Product Active Ingredient* omeprazole and omeprazole magnesium which retrieved reports with both Prilosec delayed-release oral suspension and Prilosec delayed-release capsules to ensure all events within the same active moiety were captured. See Appendix A for a description of the FAERS database.

**Table 2.1.1 FAERS Search Strategy**

Date of Search	November 2, 2017
Time Period of Search	October 16, 2013* - November 2, 2017
Search Type	Quick Query Product-Manufacturer Reporting Summary (Profile report)
Product Name(s)	Product Active Ingredient: Omeprazole Omeprazole magnesium
Search Parameters	All ages, all outcomes, worldwide

\*This start date was chosen to capture all reports from the data lock date of a previous DGIEP Medical Officer review for NDA 22056/S-018, which reviewed all pediatric postmarketing adverse event reports with Prilosec from February 1989 (U.S. approval date for capsules) through October 15, 2013.

## 2.2 RESULTS

### 2.2.1 Total number of FAERS reports by Age

**Table 2.2.1 Total Adult and Pediatric FAERS Reports\* from October 16, 2013 to November 2, 2017 with Omeprazole**

	All reports (U.S.)	Serious <sup>†</sup> (U.S.)	Death (U.S.)
Adults (≥ 17 years)	10,033 (5,341)	7,155 (2,493)	750 (480)
Pediatrics (0 - <17 years)	334 (163)	<b>281<sup>‡</sup> (112)</b>	<b>17 (1)</b>

\* May include duplicates and transplacental exposures, and have not been assessed for causality

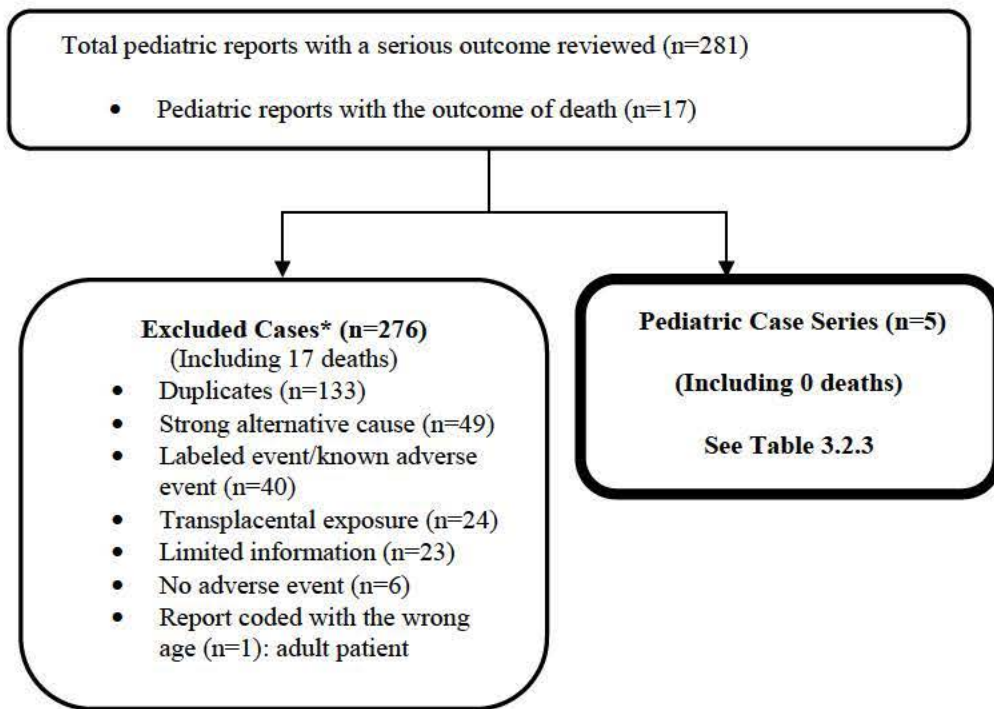
<sup>†</sup> For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

<sup>‡</sup>See Figure 3.2.2

### 2.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 281 pediatric reports with a serious outcome (See Table 2.2.1) for omeprazole from October 16, 2013 to November 2, 2017. See **Figure 2.2.2** below for the specific selection of cases to be summarized in **Sections 2.3**.

*Figure 2.2.2 Selection of Serious Pediatric Cases with Omeprazole*



\* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above

Of the 281 serious pediatric reports, 276 were not included in the pediatric case series. Seventeen of the 276 excluded reports had an outcome of death. Of the 17 reports with an outcome of death, seven reports were duplicates, three reports described transplacental exposure, two reports had insufficient information to assess the cause of death, and one report described a labeled adverse event (Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) after receiving antibiotics and omeprazole). The remaining four reports described patients who died because of a strong alternative cause: cardiac failure in patients with multiple co-morbidities (n=2), cardiorespiratory arrest and aspiration after choking on an omeprazole tablet<sup>a</sup> (n=1), and multi-organ failure in a patient receiving multiple immunosuppressant medications (n=1).

Forty-five reports with a non-fatal serious outcome had a strong alternative cause for the adverse events: 11 reported labeled events or known events associated with concomitant medications (psoriasis with adalimumab, anticholinergic syndrome with sertraline, drug reaction with eosinophilia and systemic symptoms (DRESS) with sulfamethoxazole/trimethoprim, elevated amylase and lipase with ceritinib), 15 reported symptoms likely attributable to an underlying disease (such as an aggravated gastrointestinal disorder, respiratory distress in a patient with pneumonia, psychiatric adverse events in a patient with a history of bipolar disorder), seven

<sup>a</sup> The parents gave their 8-month-old child a whole omeprazole dispersible tablet, which was administered inappropriately according to the Losec Mups (omeprazole) tablet product label. The administration instructions in the product label state that for patients unable to swallow whole tablets break the Mups tablet and disperse in a spoonful of water, any acidic fruit juice, or apple sauce.

reported intentional overdoses with multiple medications, seven reported adverse events related to a medication error, and five reported infections while receiving at least one concomitant immunosuppressant medication.

Thirty-nine cases with a non-fatal serious outcome reported a labeled or known adverse event associated with omeprazole. The labeled or known adverse events<sup>b</sup> included: abdominal pain (n=4), diarrhea (n=4), rash (n=4), hypersensitivity reaction (n=3), pancreatitis (n=3), drug interactions (n=3), vomiting (n=2), flatulence (n=2), melena (n=2), hepatitis (n=2), SJS (n=2), pyrexia (n=2), anxiety (n=2), constipation (n=2), neutropenia (n=1), fatigue (n=1), headache (n=1), visual impairment (n=1), malaise (n=1), *C. difficile* (n=1), confusion (n=1), dizziness (n=1), psychotic disorder (n=1), cholestasis (n=1), liver injury (n=1), hyponatremia (n=1), increased alkaline phosphatase (n=1), erythematous (n=1), sleep disturbance (n=1), anaphylaxis (n=1), interstitial nephritis (n=1), dermatitis (n=1), fracture (n=1), esophageal candidiasis (n=1), nausea (n=1), carcinoid tumor (n=1), depression (n=1), and abnormal thinking (n=1).

### 2.2.3 Characteristics of Pediatric Case Series

Appendix B lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the pediatric case series.

**Table 2.2.3 Characteristics of Pediatric Case Series with Omeprazole (N=5)**

Age	0 - < 1 month	0
	1 month - <2 years	3
	2 - < 6 years	1
	6 - <12 years	1
	12 - < 17 years	0
Sex	Female	4
	Male	1
Country	United States	3
	Foreign	2
Reported Reason for Use	GERD	5
Serious Outcome*	Hospitalized	3
	Other serious	3

\* 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.

## 2.3 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=5)

<sup>b</sup> Events are not mutually exclusive

## Unlabeled Events

### *2.3.1 Nervous System Disorders (n=3)*

There were two cases of the unlabeled event of seizures identified and one case of the unlabeled event of dystonia.

**Case 10667404, Hospitalization (HO), Great Britain, 2014:** A report from a parent describes a 17-month-old male (weight 12 kg) that was receiving omeprazole 15 mg orally daily for the treatment of GERD. The patient started receiving omeprazole at 8 weeks of age. On an unknown date, the dose of omeprazole was increased to 20 mg orally daily, divided in two doses, for worsening GERD. The mother reported that the patient was suffering from convulsions or what appeared to be shivering episodes for 6 weeks and was waking up 2-5 times per night. The patient was admitted to the hospital for assessment of seizures. The patient was discharged home after a negative work-up (tests and laboratory results were not provided). The patient's mother discontinued omeprazole after reading the omeprazole (Losec Mups) product label and discovered that the "shivering fits" may be due to a magnesium deficiency. The patient was given a banana daily in an attempt to increase his magnesium levels. The mother reported that the "shivering fits" appear to have gone away and the patient is having undisturbed sleep at night. Concomitant medications included ranitidine and multivitamins.

*Reviewer comment: The recommended dose for pediatric patients 1 to 16 years of age and 10 to less than 20 kg is 10 mg once daily. This patient was receiving higher than the recommended dose (15- 20 mg daily), which may have contributed to the adverse events. The patient had a negative workup for seizures; however, the "shivering fits" and sleep disturbances resolved after discontinuation of omeprazole. Seizures associated with hypomagnesemia is labeled in the Warnings and Precautions section of all PPI labels. The patient's magnesium level was not reported; however, the report states that a banana was given in an attempt to increase the patient's magnesium level. Of note, there were 10 additional unique pediatric cases of seizures and one unique pediatric case of myoclonus that were excluded from the case series. Reasons for exclusion included past medical history of seizures (n=6), labeled event associated with concomitant medication (n=2), medical history of an underlying disease that can result in seizures (n=1), intentional overdose on multiple medications (n=1), and limited clinical information to make an assessment (n=1).*

**Case 12679934, HO, Other serious (OT), U.S., 2016:** A report from a parent describes an 11-year-old female that was started on omeprazole 20.6 mg (route and frequency not reported) for the treatment of heartburn. Three days after of starting omeprazole, the patient had an extremely violent seizure type episode. The patient also had difficulty breathing, her "head turned extreme to side," right arm and leg numbness, diarrhea, and muscle spasms. Reported tests included a CT scan, vital signs, blood work (including electrolytes); however, results were not provided.

*Reviewer comment: This case reports a temporal relationship between initiation of omeprazole treatment and onset of seizures. As already mentioned, seizures associated with*

*hypomagnesemia is labeled in the Warnings and Precautions section of all PPI labels; however, typically after prolonged therapy. Diagnostic test results were not reported to confirm the patient's magnesium level or seizure cause; therefore, we are unable to determine causality in this case.*

**Case 10028445, HO, U.S., 2014:** A 19-month-old (8.2 kg) female was receiving omeprazole (2 mg/ml) 4 ml orally twice daily for the treatment of GERD for approximately 11 months. Past medical history included premature birth, chronic lung disease, oral motor issue/low muscle tone. Concomitant medications included budesonide and recent administration of respiratory syncytial virus (RSV) vaccine. According to the patient's mother, the symptoms started as a protruding tongue from the child's mouth that would come and go, often lasting for 4.5 to 5 hours; however, on the day of the report, the event lasted for only 5 to 10 minutes. The patient was hospitalized for 24 hours and underwent an electroencephalogram (EEG), which was normal. Omeprazole was discontinued at that time. Approximately five days later, the patient experienced a 30-second episode of her tongue protruding in the pediatrician's office. The patient's neurologist was unable to confirm whether the protruding tongue episode was truly characteristic of dystonia (or other types of dyskinesia) or simply typical behavior of a child sticking her tongue in and out. The neurologist also confirmed the oral motor issue was due to premature birth and in his opinion the events may not be related to omeprazole because the child still experienced episodes (lasting about 1 hour and 20 minutes) one week after discontinuation. The patient's gastroenterologist was contacted and did not feel there was a definitive link between omeprazole and dystonia; however, omeprazole was discontinued out of caution because nothing else seemed suspect. The patient was referred to a movement disorder specialist on an unknown date. The mother was contacted for follow-up and stated that her child has had no other "dystonia" episodes in the past 2-4 weeks and was still not taking any antacid medications for GERD. According to the patient's mother, the movement disorder specialist believed the child had drug-induced dystonia from omeprazole. The reporter inquired if the specialist explained why there would be a relationship to omeprazole if the child experienced a few episodes of dystonia within a week after discontinuing the product. The mother stated that she did not know, except that the specialist's opinion was that the dystonia was not primary dystonia, and that it was not a genetic issue. The patient's mother also stated that the specialist noted that the other medication the child was currently taking, budesonide, did not have a relationship to dystonia.

*Reviewer comment: The patient's neurologist was unable to confirm the adverse events as dystonia or simply typical childhood behavior. The neurologist also suggested the patient's oral motor issue was due to premature birth and may not be related to omeprazole. The case reported a positive dechallenge approximately a week after omeprazole was discontinued; however, the patient did have dystonic episodes during the first week after omeprazole was stopped. Based on the patient's age and weight, she was receiving over 3 times the*

*recommended daily dose (10 mg once daily for up to 4 weeks), which may have also contributed to the adverse events.*

*For completeness, we searched the FAERS database for additional pediatric reports (all reports prior to October 16, 2013) of dystonia with omeprazole. We retrieved two additional pediatric reports of dystonia. One case reported a dystonic reaction associated with intrathecal methotrexate toxicity. The remaining case described a 16-year-old female receiving omeprazole 20 mg twice daily for GERD (concomitant medications included domperidone and polyethylene glycol) and experienced severe chest pain, headache, dystonia, unable to speak, and gastrointestinal reflux. Domperidone is labeled for extrapyramidal adverse events, including dystonia; however, the patient recovered from the events when omeprazole was discontinued.*

*Based on the limited number of cases and plausible alternative causes (i.e., higher than recommended dose, premature birth, concomitant medications labeled for dystonia), we are unable to determine what role, if any, omeprazole contributed to the dystonic episodes. We recommended continued surveillance of this adverse event.*

### **2.3.2 Psychiatric Disorders (n=1)**

There was one case of the unlabeled events of autism spectrum disorder, antisocial behavior, speech disorder, and communication disorder.

**Case 12659748, OT, Canada, 2016:** A 34-month-old female started omeprazole 10 mg orally twice daily for the treatment of severe gastrointestinal reflux. On an unknown date, the patient developed possible autism spectrum disorder, social interaction disorder, speech disorder, and communication skills disorder. It was reported that because of recent reports about adult dementia associated with PPI use, the family opted to stop omeprazole treatment. Within a short period of time, the patient's speech, social interaction, and communication skills improved. Outcome of possible autism spectrum disorder was not reported. Past medical history and concomitant medications were not reported.

*Reviewer comment: This case reported a positive dechallenge when omeprazole was discontinued; however, based on the limited information (date of event, concomitant medication, past medical history) a causal association between omeprazole and the events of autism spectrum disorder, antisocial behavior, speech disorder, and communication disorder cannot be established. For completeness, we searched the FAERS database for additional pediatric reports (all reports prior to October 16, 2013) of autism spectrum disorder, antisocial behavior, speech disorder, and/or communication disorder with omeprazole. We retrieved four additional pediatric cases of speech disorder (n=3), autism spectrum disorder (n=1), and/or communication disorder (n=1).<sup>c</sup> Of the four cases, two lacked sufficient detail to assess causality and two had strong alternative causes (intrathecal methotrexate-induced neurologic*

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<sup>c</sup> Events are not mutually exclusive

*toxicity and concomitant administration with domperidone). These cases do not represent a new safety signal.*

### **2.3.3 Renal and Urinary Disorders (n=1)**

There was one case of the unlabeled events of chromaturia and abnormal urine odor.

**Case 10227290, OT, U.S., 2014:** One-month-old twins were started on omeprazole (2 mg/ml) compounded suspension 3.4 mg orally twice daily for acid reflux. Approximately 3 hours after the third dose, both babies developed “light pink” urine. The report stated that, “the prescribed dose by the pediatrician is 3.4 mg (1.7 ml) orally twice daily. If one is to calculate the recommended dose range (0.5 to 1.5 mg/kg/dose orally once daily) based upon current clinical literature, the dose prescribed by the pediatrician is greater than the current clinical literature recommended dose range using the patient’s weight of 7.9 lbs.” In subsequent follow-ups with the patient’s grandmother, it was reported that the color of the urine was more “orangey pink” than “light pink.” On the evening of the first episode, the patient had, “black urine with a strong odor.” After the patient’s family stopped the omeprazole treatment, the twin’s urine had cleared. Omeprazole suspension was reintroduced a few days later and the twin’s urine became “orangey-pink” after one dose of omeprazole. The omeprazole was stopped again and the urine cleared. At the twins two-month check-up, the pediatrician discontinued omeprazole and started them back on ranitidine (the patients received ranitidine prior to omeprazole). The patient’s grandmother reported that the pediatrician did not comment on what could have possibly caused the “black urine with strong odor.” The patient’s frequency of urine output has not changed during and since the reported events.

*Reviewer comment: This case reports a temporal relationship between omeprazole and the adverse event of chromaturia. In addition, a positive dechallenge and rechallenge was reported in both patients. Omeprazole was used off-label for the treatment of GERD (recommended age is 1 to 16 years). According to the reporter, the twins were receiving higher than the current literature recommended dose of 0.5 to 1.5 mg/kg/dose orally once daily, which may have contributed to the adverse events. An alternative explanation for the “pink urine” may be the development of “pink diaper syndrome,” which results from the deposition of urate crystals found in the setting of concentrated urine in infants.<sup>4</sup> For completeness, we searched the FAERS database for additional pediatric reports (all reports prior to October 16, 2013) of chromaturia with omeprazole. We retrieved three additional pediatric cases of chromaturia. Of the three cases, one lacked sufficient detail to assess causality and two had strong alternative causes (hepatitis/increased bilirubin and porphyria). These cases do not represent a new safety signal.*

## **3 DISCUSSION**

We evaluated all pediatric postmarketing adverse event reports with a serious outcome for Prilosec (omeprazole) in the FAERS database from October 16, 2013 through November 2,

2017. The start date of October 16, 2013 was chosen to capture all reports from the data lock date of a previous DGIEP review for NDA 22056/S-018, which reviewed all pediatric postmarketing adverse events with Prilosec (omeprazole) from February 1989 (U.S. approval date) through October 15, 2013. Of the 281 pediatric reports, including 17 death cases, 133 were duplicates, 49 contained strong alternative causes for the reported adverse events, 40 reported a labeled event for a concomitant medication, 24 described transplacental exposures, 23 contained limited information for assessment, 6 reported no adverse event, and 1 was an adult case coded with the wrong age.

The remaining five non-fatal pediatric cases described unlabeled adverse events<sup>d</sup> (seizures n=2, dystonia n=1, chromaturia n=1, autism spectrum disorder n=1, antisocial disorder n=1, speech disorder n=1, and communication disorder n=1). In three of the five cases, patients were receiving higher than recommended doses of omeprazole which may have contributed to the adverse events. In addition, all five cases either had other plausible explanations to account for the adverse event or lacked sufficient information to assess causality. No new safety signals were identified after review of the pediatric postmarketing cases with omeprazole.

#### **4 CONCLUSION**

We did not identify any new safety signals with omeprazole in pediatric patients. There is no evidence from these data that there are pediatric safety concerns with omeprazole delayed-release oral suspension at this time.

#### **5 RECOMMENDATIONS**

OSE recommends returning to routine pharmacovigilance monitoring for all adverse events with omeprazole.

#### **6 APPENDICES**

##### **6.1 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 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

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<sup>d</sup> Events are not mutually exclusive



(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.

**6.2 APPENDIX B. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH DRUG (N=5)**

<b>FAERS Case Number</b>	<b>Version Number</b>	<b>Manufacturer Control Number</b>
10227290	1	C14 029 AE
10667404	1	Not Applicable (Direct report)
10028445	2	C14 007 AE
12659748	1	PHHY2016CA111734
12679934	1	Not Applicable (Direct report)

## 7 REFERENCES

- <sup>1</sup> Mehrotra N. Cross-Discipline Team Leader (CDTL) review of Prilosec (omeprazole magnesium) delayed-release oral suspension (NDA 22056/S-018). January 16, 2016. Available at <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=022056>
- <sup>2</sup> Summary minutes of the Pediatric Advisory Committee Meeting. June 21, 2010. Available at <https://wayback.archive-it.org/7993/20170403223515/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/ucm201871.htm>
- <sup>3</sup> Dannis, M. Medical officer review of Prilosec (omeprazole magnesium) delayed-release oral suspension (NDA 22056/S-018). December 23, 2015. Available at <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM491208.pdf>
- <sup>4</sup> Zorc JJ (2013). *Schwartz's Clinical Handbook of Pediatrics*. Philadelphia, PA: Lippincott Williams & Wilkins, a Wolters Kluwer business.