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Office of Surveillance and Epidemiology**

**Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review**

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**Product Name(s):** Aciphex Sprinkle (rabeprazole sodium)  
Delayed Release Capsules

**Pediatric Labeling Approval Date:** March 26, 2013

**Application Type/Number:** NDA 204736

**Applicant/Sponsor:** EISAI Inc

**OSE RCM #:** 2015-1954

**\*\*This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information in this document has been cleared for public release.\*\***

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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 Aciphex (rabeprazole sodium) Delayed-Release Sprinkle Capsules in pediatric patients. This review was triggered by the pediatric indication for the Aciphex Delayed-Release Sprinkle Capsule formulation.

For the purpose of this review, we searched the FDA Adverse Event Reporting System (FAERS) for all the reports with the product active ingredient rabeprazole sodium, which may include reports for Aciphex Delayed-Release Tablets.

Aciphex Delayed-Release Tablet was first approved in 1999 and is indicated for the treatment of GERD in patients aged 12 years and older for up to 8 weeks. Aciphex Delayed-Release Sprinkle Capsule was first approved in 2013 and is indicated for the treatment of Gastroesophageal Reflux Disease (GERD) in patients aged 1 year and older. The safety and efficacy of Aciphex Sprinkle in children less than 1 year of age have not been established.

In order 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 Aciphex Sprinkle as well as rabeprazole tablets were assessed. For the 12-month period ending in August 2015, pediatric patients aged 0-16 years accounted for 89% (3,104 patients) of total patients with a dispensed prescription for Aciphex Sprinkle. For the same period, pediatric patients aged 0-16 years accounted for approximately 1% (2,390 patients) of total patients with a dispensed prescription for rabeprazole tablets. Off-label use in children younger than one year of age accounted for 25% of pediatric patients with a dispensed prescription for Aciphex Sprinkle and less than 1% of pediatric patients with a dispensed prescription for rabeprazole tablets. Pediatrics and Gastroenterology were the top prescribing specialties for Aciphex Sprinkle. Internal Medicine followed by Family Practice and Gastroenterology were the top prescribing specialties for rabeprazole tablets. “Esophageal Disorder NEC” (ICD-9 Code 530.8) was the most common diagnosis associated with pediatric use of Aciphex Sprinkle and rabeprazole tablets during the review period.

We evaluated all FAERS reports of adverse events in the pediatric population for rabeprazole sodium since the previous pediatric postmarketing safety review in 2009. The review of FAERS pediatric cases resulted in the identification of nine serious cases and no deaths. The majority of the pediatric cases reported labeled events or events determined to be unlikely associated with rabeprazole use. There were no apparent reporting trends suggesting increased severity or frequency of known, labeled events.

Overall, the pediatric safety profile described in these reports is consistent with the known safety profile of the current rabeprazole sodium label. We identified one case of vertigo and blurred vision with a temporal association and a positive dechallenge associated with rabeprazole sodium use. Of note, vertigo and blurred vision are labeled events in the Adverse Reactions section (6.1 or 6.2) of other marketed proton pump inhibitors (PPIs).

The Division of Pharmacovigilance-I (DPV-I) recommends adding vertigo and blurred vision to the Adverse Reactions-Postmarketing Experience section of the rabeprazole sodium label. DPV plans to continue postmarketing surveillance of all adverse events with the use of rabeprazole sodium in pediatric patients.

## **1 INTRODUCTION**

### **1.1 PRODUCT FORMULATIONS AND INDICATIONS<sup>1</sup>**

Rabeprazole sodium, a proton pump inhibitor (PPI), is available as a delayed release tablet (Aciphex) or a delayed release capsule (Aciphex Sprinkle).

Aciphex Sprinkle is available as a 5 mg and 10 mg delayed release capsule and Aciphex is available as a 20 mg delayed release tablet.

The recommended dosage of Aciphex Delayed-Release Sprinkle Capsule for pediatric patients 1 to 11 years of age by body weight is:

- less than 15 kg, 5 mg once daily for up to 12 weeks with the option to increase to 10 mg if inadequate response.
- 15 kg or more: 10 mg once daily for up to 12 weeks.

The recommended dosage of Aciphex Delayed -Release Tablet for adolescent patients 12 years of age and older is 20 mg once daily for up to 8 weeks.

### **1.2 PEDIATRIC REGULATORY HISTORY**

Rabeprazole sodium (Aciphex Sprinkle) delayed release capsule was approved on March 26, 2013 to expand the indication in pediatric patients down to 1 year of age for the treatment of Gastroesophageal Reflux Disease (GERD). Rabeprazole sodium (Aciphex) delayed release tablet was approved on June 30, 2008 for use in adolescent patients 12 years and older for the treatment of GERD for up to 8 weeks.

### **Clinical Studies<sup>2</sup>**

On September 27, 2012, the sponsor submitted NDA 204376 for Aciphex Delayed-Release Sprinkle Capsules to support an indication for healing and maintenance of healing of GERD and the improvement of GERD symptoms in children 1 to 11 years of age. The NDA was submitted in response to a Written Request and Pediatric Research Equity Act (PREA) postmarketing requirement.

The sponsor conducted a multicenter, randomized, two parallel-group, non-placebo-controlled trial of low-dose and high-dose rabeprazole sodium delayed-release pediatric bead formulation in patients 1 to 11 years of age with endoscopically proven GERD. The study was conducted to evaluate the short-term safety and efficacy of two different doses of rabeprazole in in two different weight cohorts of children 1 to 11 years of age. The sponsor also assessed the efficacy and safety of long-term maintenance treatment. The study consisted of two parts: a double-blind, 12-week treatment phase (Part 1), followed by a double-blind 24-week maintenance phase (Part

2). The completed study reports were submitted on September 27, 2012 for review, and the study results fulfilled the sponsor's PREA obligation.

Based on the submitted data, Aciphex Delayed-Release Sprinkle Capsule was approved for the treatment of GERD for up to 12 weeks in children 1 to 11 years of age. Maintenance of healing of GERD was not approved as an indication because of the lack of data to support it.

### **1.3 SUMMARY OF RELEVANT PREVIOUS DPV SAFETY REVIEWS<sup>3,4</sup>**

The Division of Pharmacovigilance I (DPV-I) performed reviews evaluating postmarketing reports of cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) associated with the use of PPIs. An association between PPI use and the development of CLE and SLE was identified. DPV-I recommended adding class labeling to include the potential risk of lupus erythematosus, both cutaneous and systemic lupus erythematosus, to occur in association with PPI use. The recommendation was to include CLE and SLE in the Warnings and Precautions section of all PPI labels.

### **1.4 HIGHLIGHTS OF LABELED SAFETY ISSUES<sup>1</sup>**

#### **-----CONTRAINDICATIONS-----**

- History of hypersensitivity to rabeprazole (4)

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

- Symptomatic response to therapy with rabeprazole does not preclude the presence of gastric malignancy (5.1).
- Use with warfarin: Monitor for increases in INR and prothrombin time (5.2).
- Acute interstitial nephritis has been observed in patients taking PPIs (5.3).
- Cyanocobalamin (vitamin B-12) Deficiency. Daily long-term use (e.g. longer than 3 years) may lead to malabsorption or a deficiency of cyanocobalamin (5.4).
- PPI therapy may be associated with an increased risk of *Clostridium difficile* associated diarrhea (5.5).
- 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 (5.6).
- Hypomagnesemia has been reported rarely with prolonged treatment with PPIs (5.7).

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

- In the adult studies (4 to 8 weeks), adverse reactions that occurred at a rate greater than 2 % and greater than placebo included pain, pharyngitis, flatulence, infection, and constipation (6.1).
- In studies of pediatric and adolescent patients (ages 1 to 16 years, and up to 36 weeks exposure) adverse reactions that occurred at a rate of  $\geq 5$  % of patients included abdominal pain, diarrhea, and headache (6.1).

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

- Increased INR and prothrombin times have been reported with concomitant use with warfarin. Patients need to be monitored (7.2).
- Rabeprazole has been shown to inhibit cyclosporine metabolism in vitro (7.3).
- Rabeprazole inhibits gastric acid secretion and may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, iron salts, digoxin, and mycophenolate mofetil) (7.4).
- Rabeprazole may reduce the plasma levels of atazanavir (7.4).
- Methotrexate: Rabeprazole may increase serum level of methotrexate (7.7).

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

- Pregnancy: Based on animal data, may cause fetal harm (8.1).
- Studies conducted do not support the use of rabeprazole or the treatment of GERD in pediatric patients younger than 1 year of age (8.4).
- The safety and efficacy of rabeprazole for the other adult indications have not been established for pediatric patients (8.4).

## 2 DRUG UTILIZATION DATA

### 2.1 METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct this analysis. Detailed descriptions and limitations of the databases are included in *Appendix A*.

#### 2.1.1 Determining Settings of Care

IMS Health, IMS National Sales Perspectives™ database was used to determine the various retail and non-retail channels of distribution for rabeprazole. Sales data for the 12-month period ending in August 2015 indicated that approximately 84% of bottles were distributed to outpatient retail pharmacy settings, 11% to mail-order/specialty pharmacies, and 5% to non-retail pharmacies.<sup>a</sup> As a result, outpatient retail pharmacy utilization patterns were examined. Non-retail pharmacies were not included in this analysis.

#### 2.1.2 Data Sources Used

IMS Health, Vector One®: Total Patient Tracker database was used to provide the nationally estimated number of unique patients who received a dispensed prescription for rabeprazole tablets and Aciphex Sprinkle from U.S. outpatient retail pharmacies, stratified by patient age (<1, 1-11, 12-16, and 17+ years) from September 1, 2011 through August 31, 2015.

IMS Health, National Prescription Audit (NPA™) database was used to obtain the nationally estimated number of dispensed prescriptions for rabeprazole tablets and Aciphex Sprinkle by top prescribing specialty from U.S. outpatient retail pharmacies from March 1, 2013 to August 31, 2015, cumulative.

Encuity Research, LLC, TreatmentAnswers™, a U.S. office-based physician surveys database was used to obtain diagnoses associated with the use of rabeprazole tablets and Aciphex Sprinkle, stratified by patient age (<1, 1-11, 12-16, and 17+ years), from March 1, 2013 to August 31, 2015, cumulative.

### 2.2 RESULTS

#### 2.2.1 National Estimate of Patients in U.S. Outpatient Retail Pharmacies

**Table 2.2.1** shows the nationally estimated number of patients who received a dispensed prescription for rabeprazole tablets and Aciphex Sprinkle, from U.S. outpatient retail pharmacies, stratified by patient age, from September 1, 2011 through August 31, 2015. In the 12-month period ending in August 2015, approximately 1% (3,486 patients) of total patients received a dispensed prescription for Aciphex Sprinkle, compared to 99% (273,500 patients) with a dispensed prescription for rabeprazole tablets.

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<sup>a</sup> IMS Health, IMS National Sales Perspectives™. September 2014-August 2015. Extracted December 2015. File: NSP 2015-1954 Rabeprazole channels by MAT 12-28-15.xlsx

For rabeprazole tablets, pediatric patients aged 0-16 years accounted for approximately 1% (2,390 patients) of total patients in the 12-month period ending in August 2015. Adult patients aged 17 years and older accounted for 98% of total patients. Among pediatric patients, the largest proportion of use were for patients aged 12-16 years old, accounting for approximately 72% (1,734 patients) of pediatric patients; patients 1-11 years old accounted for 28% (680 patients) of pediatric patients with a dispensed prescription for rabeprazole tablets. Patients less than one year of age accounted for less than 0.3% of patients across the examined time.

For Aciphex Sprinkle, pediatric patients aged 0-16 years accounted for 89% (3,104 patients) of total patients in the 12-month period ending in August 2015; and adult patients aged 17 years and older accounted for 11% of total patients. Among pediatric patients, the largest proportion of use were for patients aged 1-11 years old, accounting for approximately 69% (2,133 patients) of pediatric patients; patients younger than 1 year old accounted for 25% (778 patients) of pediatric patients.

**Table 2.2.1**

Nationally estimated number of unique patients, stratified by patient age*, who received a prescription for rabeprazole from U.S. outpatient retail pharmacies, September 1, 2011 - August 31, 2015								
	Sep 2011 - Aug 2012		Sep 2012 - Aug 2013		Sep 2013 - Aug 2014		Sep 2014 - Aug 2015	
	Patient Count	Share	Patient Count	Share	Patient Count	Share	Patient Count	Share
	N	%	N	%	N	%	N	%
<b>Grand Total</b>	<b>507,788</b>	<b>100.0%</b>	<b>358,870</b>	<b>100.0%</b>	<b>291,437</b>	<b>100.0%</b>	<b>277,141</b>	<b>100.0%</b>
<b>rabeprazole tablets</b>	<b>507,788</b>	<b>100.0%</b>	<b>358,870</b>	<b>100.0%</b>	<b>291,261</b>	<b>99.9%</b>	<b>273,506</b>	<b>98.7%</b>
<b>Age 0 - 16 years</b>	<b>4,830</b>	<b>1.0%</b>	<b>2,453</b>	<b>0.7%</b>	<b>2,058</b>	<b>0.7%</b>	<b>2,390</b>	<b>0.9%</b>
Age < 1 year	34	0.7%	16	0.7%	21	1.0%	8	0.3%
Age 1 - 11 years	1,146	23.7%	602	24.5%	529	25.7%	680	28.5%
Age 12-16 years	3,742	77.5%	1,902	77.5%	1,538	74.7%	1,734	72.6%
Age 17 + years	503,025	99.1%	356,529	99.4%	289,250	99.3%	269,107	98.4%
Unknown Age	9	0.0%	97	0.0%	905	0.3%	3,078	1.1%
<b>Aciphex Sprinkle capsules</b>					<b>198</b>	<b>0.1%</b>	<b>3,486</b>	<b>1.3%</b>
<b>Age 0 - 16 years</b>					<b>146</b>	<b>73.6%</b>	<b>3,104</b>	<b>89.1%</b>
Age < 1 year					28	19.2%	778	25.1%
Age 1 - 11 years					108	74.0%	2,133	68.7%
Age 12-16 years					9	6.2%	238	7.7%
Age 17 + years					52	26.0%	368	10.6%
Unknown Age					0	0.0%	14	0.4%

Source: IMS, Vector One®: Total Patient Tracker. Sep 2011 - August 2015. Extracted October 2015. File:TPT 2015-1954 Aciphex by age and MAT 10-23-15.xls

\*Patient age groups are inclusive of all patients up to the day before their next birthday. For example patients aged 0-16 years include patients less than 17 years of age (16 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 in the individual categories. For this reason, summing is not advisable and will result in overestimates of patient counts.

## 2.2.2 Prescriber Specialty

Table 2.2.2 shows the top prescribing specialties for rabeprazole tablets and Aciphex Sprinkle by number of prescriptions dispensed from U.S. outpatient retail pharmacies, from March 2013 through August 2015, cumulative. During the time period examined, 3.2 million prescriptions were dispensed for rabeprazole tablets compared to 8,368 prescriptions dispensed for Aciphex Sprinkle.



For rabeprazole tablets, the top prescribing specialties were Internal Medicine at 25% of dispensed prescriptions followed by Family Practice (24% of total prescriptions) and Gastroenterology (19% of total prescriptions). All other specialties accounted for less than 10% of total prescriptions, respectively. Approximately 47% of total prescriptions for Aciphex Sprinkle were prescribed by Pediatricians followed by Gastroenterology at 14% of total prescriptions. All other specialties accounted for less than 7% of total prescriptions, respectively.

**Table 2.2.2**

Nationally estimated number of dispensed prescriptions for rabeprazole tablets by prescribing specialties, from U.S. outpatient retail pharmacies, March 2013 through August 2015			Nationally estimated number of dispensed prescriptions for Aciphex Sprinkle by prescribing specialties, from U.S. outpatient retail pharmacies, March 2013 through August 2015		
	Mar 2013 - Aug 2015			Mar 2013 - Aug 2015	
	TRx	Share		TRx	Share
	N	%	N	%	
<b>RABEPRAZOLE TABLETS</b>	<b>3,171,490</b>	<b>100.0%</b>	<b>ACIPIHEX SPRINKLE</b>	<b>8,368</b>	<b>100.0%</b>
INTERNAL MEDICINE	783,174	24.7%	PEDIATRICS	3,901	46.6%
FAMILY PRACTICE	771,356	24.3%	GASTROENTEROLOGY	1,147	13.7%
GASTROENTEROLOGY	602,294	19.0%	NURSE PRACTITIONER	581	6.9%
OSTEOPATHIC MEDICINE	302,426	9.5%	OSTEOPATHIC MEDICINE	476	5.7%
NURSE PRACTITIONER	197,575	6.2%	OTOLARYNGOLOGY	414	5.0%
PHYSICIAN ASSISTANT	162,445	5.1%	PHYSICIAN ASSISTANT	344	4.1%
OTOLARYNGOLOGY	45,783	1.4%	FAMILY PRACTICE	313	3.7%
CARDIOLOGY	36,329	1.2%	ALLERGY	215	2.6%
GENERAL PRACTICE	23,118	0.7%	PULMONARY DISEASES	178	2.1%
SPECIALTY UNSPECIFIED	21,205	0.7%	INTERNAL MEDICINE	137	1.6%
ALL OTHERS (< 1% each respectively)	225,785	7.1%	ALL OTHERS (< 1% each respectively)	396	4.73%

Source: IMS National Prescription Audit (NPA), Mar 2013 - Aug 2015. Extracted February 2016. File: NPA 2015-1954 Rabeprazole by MD 2-4-16.xlsx

Source: IMS National Prescription Audit (NPA), Mar 2013 - Aug 2015. Extracted February 2016. File: NPA 2015-1954 Aciphex Sprinkle by MD 2-4-16.xlsx

### 2.2.3 Diagnoses Associated with Use

**Table 2.2.3** shows diagnoses associated with the use of rabeprazole tablets and Aciphex Sprinkle by the number of drug use mentions<sup>b</sup> as reported by U.S. office-based physician surveys, stratified by patient age from March 1, 2013 through August 31, 2015, cumulative. Drug use mentions were coded according to the International Classification of Diseases (ICD-9-CM) and 95% confidence intervals were applied to the estimates.

Esophageal Disorder NEC (ICD-9 Code 530.8) was the most common diagnosis associated with the use of rabeprazole tablets among the pediatric population (age 12-16 years) during the examined period. However, the number of drug use mentions among the pediatric population was below the acceptable count allowable to provide a reliable estimate of national use, therefore the results should be interpreted with caution. No drug use mentions were reported for pediatric patients under the age of 12 years.

<sup>b</sup> The term "drug uses" refer to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

Esophageal Disorder NEC (ICD-9 Code 530.8) was also the most common diagnosis associated with the use of Aciphex Sprinkle among the pediatric population (age <1 year and 1-11 years) No drug use mentions were reported for in pediatric patients 12-16 years and adult patients aged 17 years and older.

**Table 2.2.3**

**Diagnoses associated with the use\* of rabeprazole tablets as reported by U.S. office-based physician surveys, March 1, 2013 - August 31, 2015**

	3/2013 - 8/2015		
	Uses	Share	95% Confidence Interval
	(000)	%	(000)
rabeprazole tablets	1,642	100.0%	1433-1851
Age < 1 yr		no data return	
Age 1-11 years		no data return	
Age 12-16 years	22	1.3%	<0.5-46
5308 ESOPHAGEAL DISORDER NEC	13	59.4%	<0.5-32
5368 STOMACH FUNCTION DIS NEC	9	40.6%	<0.5-24
Age 17+ years	1,574	95.9%	1370-1779
5308 ESOPHAGEAL DISORDER NEC	1,226	77.9%	1046-1407
5339 PEPTIC ULCER NOS	147	9.3%	84-210
5301 ESOPHAGITIS	51	3.3%	14-88
7872 DYSPHAGIA	38	2.4%	6-70
5354 GASTRITIS NEC	29	1.8%	1-57
5355 GASTRITIS/DUODENITIS NOS	13	0.9%	<0.5-32
5368 STOMACH FUNCTION DIS NEC	13	0.8%	<0.5-32
5770 ACUTE PANCREATITIS	9	0.6%	<0.5-24
5569 ULCERATIVE COLITIS NOS	9	0.6%	<0.5-24
7865 CHEST PAIN	9	0.6%	<0.5-24
7871 HEARTBURN	8	0.5%	<0.5-22
7862 COUGH	8	0.5%	<0.5-22
7873 FLATUL/ERUCTA/GAS PAIN	7	0.5%	<0.5-21
7870 NAUSEA AND VOMITING	7	0.5%	<0.5-21
UNSPEC	45	2.8%	11-80
5308 ESOPHAGEAL DISORDER NEC	45	100.0%	11-80

Source: Encuity Research, LLC., TreatmentAnswers™ with Pain Panel, Mar 2013- Aug 2015. Extracted February 2016. File: PDDA 2015-1954 Rabeprazole by AgeDx4 2-4-16.xls

\*Use – this term refers to the number of times a product linked to a diagnosis was captured for treatment of a particular disease.

NEC - Not Elsewhere Classifiable NOS - Not Otherwise Specified

**Diagnoses associated with the use\* of Aciphex Sprinkle as reported by U.S. office-based physician surveys, March 1, 2013 - August 31, 2015**

	3/2013 - 8/2015		
	Uses	Share	95% Confidence Interval
	(000)	%	(000)
Aciphex Sprinkle	15	100.0%	<0.5-36
Age < 1 year	8	51.8%	<0.5-22
5308 ESOPHAGEAL DISORDER NEC	8	100.0%	<0.5-22
Age 1-11 years	7	48.2%	<0.5-21
5308 ESOPHAGEAL DISORDER NEC	7	100.0%	<0.5-21
Age 12-16 years		no data return	
Age 17+ years		no data return	

Source: Encuity Research, LLC., TreatmentAnswers™ with Pain Panel, Mar 2013 - Aug 2015. Extracted January 2016. File: PDDA

2015-1954 Aciphex Sprinkle by AgeDx4 1-27-16.xls

\*Use – this term refers to the number of times a product linked to a diagnosis was captured for treatment of a particular disease.

NEC - Not Elsewhere Classifiable

### 3 POSTMARKET ADVERSE EVENT REPORTS

#### 3.1 METHODS AND MATERIALS

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

We searched the FAERS database with the strategy described in Table 3.1.1. See Appendix B for a description of the FAERS database.

Date of Search	September 1, 2015
Time Period of Search	August 1, 2009 <sup>*</sup> - August 31, 2015
Search Type	Product-Manufacturer Summary
Product Name(s)	Product Name: aciphex sprinkle Product Active Ingredient: rabeprazole sodium, rabeprazole <sup>†</sup>
Search Parameters	All ages, all outcomes, worldwide

<sup>\*</sup> End of FAERS search date used for the last Pediatric Advisory Committee (PAC) held in 2010.  
<sup>†</sup> FAERS limitation: searching by **Product Name** only retrieves reports that list suspect product by product name (i.e., Aciphex sprinkle); however, searching by **Product Active Ingredient** captures both Aciphex sprinkle capsule and Aciphex tablet reports.

#### 3.2 RESULTS

##### 3.2.1 Total number of FAERS reports by Age

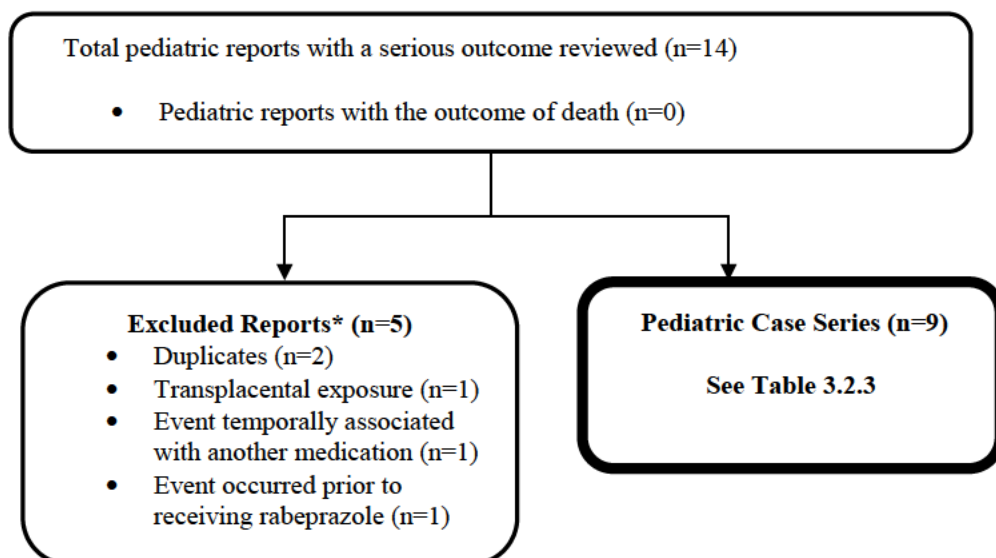
	All reports (US)	Serious <sup>†</sup> (US)	Death (US)
Adults (≥ 17 years)	1723 (551)	836 (306)	110 (26)
Pediatrics (0 - <17 years)	14 (3)	14 <sup>‡</sup> (3)	0 <sup>§</sup> (0)

<sup>\*</sup> May include duplicates and transplacental exposures, and have not been assessed for causality.  
<sup>†</sup> Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.  
<sup>‡</sup> See Figure 3.2.2  
<sup>§</sup> No additional cases of pediatric deaths were identified among cases not reporting age.

### 3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 14 pediatric reports with a serious outcome (See Table 3.2.1). See **Figure 3.2.2** below for the specific selection of cases to be summarized in **Sections 3.3 and 3.4**.

**Figure 3.2.2 Selection of Serious Pediatric Cases with Rabeprazole Sodium**



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

### 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 Rabeprazole Sodium (N=9)**

Age	0 - < 1 month	0
	1 month - <2 years	5
	2 - < 6 years	0
	6 - <12 years	3
	12 - < 17 years	1
Sex	Male	5
	Female	4
Country	United States	3
	Foreign	6
Reported Indication*	GERD	5
	Epigastralgia	1
	Gastritis	1
	Unknown	2
Serious Outcome <sup>†</sup>	Hospitalized	6
	Other serious	3

- 
- \* Reported indication- the information that was provided in the indication field of the Medwatch report.
  - † Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. Reports may have more than one outcome.
- 

### 3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=0)

There were no pediatric deaths in this case series.

### 3.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=9)

Cases in this section are categorized by Preferred Terms that best represent the reported adverse event(s). Preferred Terms are then grouped by like terms and organized by System Organ Class.

#### 3.4.1 *Musculoskeletal and Connective Tissue Disorders (n=1)*

Labeled Event in Warnings and Precautions, Adverse Reactions-Postmarketing Experience, and Medication Guide sections: Bone fractures

##### **Upper limb fracture (n=1)**

A 7-year-old male with a past medical history of ear issues began treatment with rabeprazole 20 mg orally once daily for an unknown indication on an unknown date. On October 12, 2010, the patient experienced a broken right arm involving the right radius, 2 to 3 inches proximal to the wrist. On an unknown date, the patient recovered from the event. No other information was provided.

*Reviewer's comment: Of note, the patient was receiving a higher than recommended dose for his age. For pediatric patients 1 to 11 years of age, the recommended dose is 5 -10 mg orally once daily.*

#### 3.4.2 *Respiratory, Thoracic and Mediastinal Disorders (n=1)*

Labeled Event in Adverse Reactions-Postmarketing Experience section: Pneumonia

##### **Bronchopneumonia (n=1)**

A 22 month-old female with a history of eczema on both legs, a right oophorectomy, middle ear infection, grommet insertion, and pneumonia started rabeprazole, as part of a study,<sup>5</sup> for reflux. The patient started rabeprazole 0.5 mg/kg on September 20, 2009. On (b) (6), the patient was hospitalized and diagnosed with bronchopneumonia. The study medication, rabeprazole, was withdrawn. The patient received ceftriaxone, mefenamic acid, oxymetazoline, nystatin, and amoxicillin/clavulanic acid as treatment. The patient's mother withdrew her consent for the patient's participation in the study, and the patient discontinued from the study because of the adverse event. On an unknown date, the patient recovered from the event and was discharged from the hospital.

### 3.4.3 Infections and Infestations (n=2)

#### Labeled Event in Adverse Reactions section and Medication Guide: Infection

##### **Viral infection (n=1)**

A one-month-old male developed a viral infection while receiving rabeprazole, as part of a study,<sup>6</sup> for GERD. The patient was diagnosed with GERD on May 13, 2011 and started the study medication, rabeprazole, six days later. The patient developed a fever of 39.2 Celsius on (b) (6) with symptoms of lethargy, moaning, crying, diarrhea, and failure to finish his feeding bottles. The patient was hospitalized, and laboratory diagnostic tests performed suggested a viral infection of the upper respiratory tract. The patient was treated with paracetamol 60 mg per day for pain relief, and rabeprazole therapy was continued. The patient recovered from the viral infection on (b) (6) and was discharged from the hospital.

##### **Bronchiolitis and dehydration (n=1)**

A 6-month-old developed worsening bronchiolitis and dehydration while receiving rabeprazole, as part of a study,<sup>6</sup> for GERD. The patient has a history of rhinorrhea, cough, fever, allergies, eczema, and wheezing with respiratory tract infection. The patient had one previous hospitalization with bronchiolitis. Thirty-eight days after starting rabeprazole, the patient was hospitalized with worsening bronchiolitis, fever, and dehydration. The patient received antibiotics, albuterol, and prednisolone treatment. The patient recovered from worsening bronchiolitis 10 days later. Rabeprazole treatment was maintained throughout the patient's hospitalization. In the investigator's opinion, the events were unlikely related to rabeprazole, given the patient's past medical history and were more likely related to a viral infection.

*Reviewer's comment: Bronchiolitis and dehydration are unlabeled events; however, infection is a labeled event. Considering that the patient has a past medical history of respiratory tract infections and bronchiolitis is a common illness of the respiratory tract in young children, the events are unlikely associated with rabeprazole treatment.*

### 3.4.4 Renal and Urinary Disorders (n=1)

#### Labeled Event in Warnings and Precautions and Adverse Reactions-Postmarketing Experience sections: Interstitial nephritis

##### **Intentional overdose and renal impairment (n=1)**

A 13-year-old female experienced impairment of renal function after taking an overdose of rabeprazole along with multiple other medications. The patient had a history of abuse and neglect since her childhood, and she visited a psychiatric clinic on an irregular basis. The patient was found after having a fall and was taken to the emergency room. She had a depressed level of consciousness, increased heart rate, and decreased body temperature. The patient was treated with N-acetylcysteine for acetaminophen ingestion and hemodialysis for renal function impairment. After 9 days in the hospital, the patient's renal function had recovered to the normal range, and she was discharged from the hospital.

*Reviewer's comment: Although acute interstitial nephritis (AIN) is labeled, the more general term, renal impairment is not labeled. Based on the reported information and lack of renal biopsy, it is difficult to determine whether the patient's renal impairment was a result of AIN.*

*Because the patient ingested multiple medications in an intentional overdose, the role of rabeprazole in the patient's renal impairment cannot be determined.*

### **3.4.5 Nervous System Disorders (n=1)**

Labeled Event in Adverse Reactions section and Medication Guide: Headache

Unlabeled Event: Vertigo and Vision blurred

#### **Headache, vertigo, and vision blurred (n=1)**

An 11-year-old male patient experienced headache, vertigo, and blurred vision the same day he started rabeprazole 40 mg daily. Concomitant medication was sodium alginate/potassium bicarbonate. The patient was admitted to the hospital, and two days later rabeprazole was discontinued. The patient recovered from the events five days after discontinuing rabeprazole. Sodium alginate/potassium bicarbonate was discontinued on an unreported date.

*Reviewer's comment: Vertigo and blurred vision are unlabeled events. The temporal association and positive dechallenge between rabeprazole and the events suggest a causal relationship. Of note, the patient was receiving a higher than recommended dose for his age. For pediatric patients 1 to 11 years of age, the recommended dose is 5 -10 mg orally once daily. It is difficult to determine if the high dose contributed to the adverse events. Vertigo and blurred vision are labeled events for all other PPIs.<sup>7,8,9,10,11</sup>*

### **3.4.6 Blood and Lymphatic System Disorders (n=1)**

Unlabeled Event: Lymphadenitis

#### **Lymphadenitis (n=1)**

A 1-year-old female with a past medical history of hypertrophied lymph nodes (localized enlarged lymph nodes) started rabeprazole, as part of a study,<sup>5</sup> for GERD. Three months after starting rabeprazole, the patient's alkaline phosphatase was significantly elevated (2316 U/L). This was thought to be benign hyperphosphatasemia and was considered clinically not significant by the investigator. The parents of the child found a swollen lymph gland in the neck. An ultrasound of the lymph node indicated there was no evidence of malignancy. Ultrasound of the abdomen revealed hyper-echoic liver without tumors. Alkaline phosphatase was 4757 U/L at that time. Other parameters of liver function were normal. A slight elevation of monocytes and thrombocytes indicated a possible viral infection. The patient was diagnosed with lymphadenitis. Rabeprazole was continued and the patient recovered from the event three months later. It was reported that the lymphadenitis occurred after an episode of acute gastroenteritis and resolved despite continuation of rabeprazole.

*Reviewer's comment: Lymphadenitis is an unlabeled event; however, it occurred after an episode of gastroenteritis and resolved despite continuation of rabeprazole. Lymphadenitis often occurs in response to a bacteria or viral infection and usually resolves with antibiotics a few weeks to a few months later.*

### 3.4.7 Investigations (n=1)

#### Unlabeled Event: Beta 2 microglobulin increased

#### **Beta 2 microglobulin increased (n=1)**

An 11-month-old male experienced increased beta 2 microglobulin levels while receiving rabeprazole, as part of a study,<sup>6</sup> for the treatment of GERD. The patient had a history of constipation, eczema, respiratory syncytial virus, and otitis media. Rabeprazole treatment started on September 4, 2010. Bisacodyl was administered concomitantly. On September 29, 2010, the patient experienced mild diarrhea. On October 1, 2010, the patient visited the clinic for a scheduled procedure and found to have increased beta 2 microglobulin levels. Baseline beta 2 microglobulin, BUN, and serum creatinine levels were normal prior to receiving rabeprazole. Rabeprazole was discontinued. The patient recovered from the diarrhea. On October 10, 2010, repeat beta 2 microglobulin levels were performed and had normalized. A follow-up report from the investigator indicated that “the repeat B-2 microglobulin was done two weeks after stopping the study drug and despite being on prevacid, it was completely normal, which makes me question whether her high value could have been a lab error vs. a real event.”

*Reviewer’s comment: Increased beta 2 microglobulin level is an unlabeled event. The beta 2 microglobulin levels normalized despite continued therapy with another PPI, which makes the event unlikely associated with rabeprazole treatment.*

### 3.4.8 Vascular Disorders (n=1)

#### Unlabeled Event: Hematoma

#### **Hematoma (n=1)**

An 11-year-old male developed a hematoma while receiving rabeprazole for gastritis. The patient started rabeprazole on July 5, 2012. On August 16, 2012, the patient started to present with progressive hematoma of the arm, stomach, back, and gluteal areas. The patient’s laboratory tests revealed increased eosinophil count, increased immunoglobulin E (IgE) levels, and decreased antineutrophil cytoplasmic antibody titers in August 2012. The patient stopped rabeprazole treatment in October 2012. The frequency of the hematoma occurrence increased between October 2012 and March 2013. At the time of the report, the hematomas were ongoing.

*Reviewer’s comment: The hematomas continued and increased in frequency despite discontinuing rabeprazole treatment; therefore, it is unlikely the event was associated with rabeprazole use.*

## 4 DISCUSSION

In order to characterize utilization by the pediatric population and to provide context for the adverse event reports submitted to the FAERS database, drug utilization patterns for rabeprazole products were assessed. For the 12-month period ending in August 2015, the drug utilization data in this review indicate that the pediatric population (age 0-16 years) accounted for 89% of the 3,486 patients with a dispensed prescription for Aciphex Sprinkle in U.S. outpatient retail pharmacies. Approximately 1% of the total 273,500 patients with a dispensed prescription for rabeprazole tablets were pediatric patients for the same time period. Of these pediatric patients, the largest proportion of use was among pediatric patients 12-16 years for rabeprazole tablets and 1-11 years for Aciphex Sprinkle. There appears to be off label use in children younger than one



year of age accounting for 25% (778 patients) of pediatric patients with a dispensed prescription for Aciphex Sprinkle for the examined time, although medical chart review is not available for validation. The most common diagnosis associated with pediatric use of rabeprazole and Aciphex Sprinkle during the review period was Esophageal Disorder NEC across all age groups (ICD-9 Code 530.8).

We evaluated all FAERS reports of adverse events in the pediatric population for rabeprazole sodium since the previous pediatric postmarketing safety review in 2009. The review of FAERS pediatric cases resulted in the identification of nine serious cases and no deaths. The majority of the pediatric cases reported labeled events or events determined to be unlikely associated with rabeprazole sodium use. There were no apparent reporting trends suggesting increases in severity or frequency of known, labeled adverse events. We identified one pediatric case of vertigo and blurred vision with a temporal association and positive dechallenge associated with rabeprazole sodium treatment; however, the patient was receiving a higher than recommended dose. Of note, vertigo and blurred vision are labeled events in the Adverse Reactions sections (6.1 or 6.2) of other marketed PPIs.

## **5 CONCLUSION**

The Office of Surveillance and Epidemiology analyzed (1) pediatric drug utilization data for rabeprazole products and (2) the pediatric postmarketing safety database for rabeprazole. The Division of Pharmacovigilance analyzed the nine non-fatal serious postmarketing cases for rabeprazole sodium that were received in the FAERS database from August 1, 2009 to August 31, 2015. The majority of Aciphex Sprinkle utilization appears to be in the pediatric population with data suggestive of off-label use in patients <1 year of age. The pediatric safety profile of rabeprazole described in the majority of reports is consistent with the known safety profile described in the current rabeprazole sodium label. One safety concern identified was vertigo and blurred vision, which is a labeled event in the Adverse Reaction section (6.1 or 6.2) for all other marketed PPIs.

## **6 RECOMMENDATIONS**

DPV-I recommends adding vertigo and blurred vision to the Adverse Reactions-Postmarketing Experience section of the rabeprazole sodium label. DPV plans to continue postmarketing surveillance of all adverse events with the use of rabeprazole sodium in pediatric patients.

## **7 REFERENCES**

<sup>1</sup> Aciphex Delayed-Release Sprinkle Capsule Prescribing Information. Eisai, Inc. Woodcliff Lake, New Jersey. Revised December 2014.

<sup>2</sup> Troiani, John, MD, PhD. Medical Officer Review of Aciphex Delayed-Release Sprinkle Capsules. March 5, 2013.

<sup>3</sup> Swank, Kimberley, PharmD, La Grenade, Lois, MD. Proton Pump Inhibitors and Cutaneous Lupus Erythematosus Review. April 7, 2015.

<sup>4</sup> Swank, Kimberley, PharmD, La Grenade, Lois, MD. Proton Pump Inhibitors and Systemic Lupus Erythematosus. October 23, 2015.

<sup>5</sup> Hussain S, Kierkus J, Hu P, Hoffman D, Lekich R, Sloan S, Treem W. Safety and efficacy of delayed release rabeprazole in 1- to 11-month-old infants with symptomatic GERD. *J Pediatr Gastroenterol Nutr* 2014;58:226-236.

<sup>6</sup> Hussain S, Kierkus J, Tron E, Ulmer A, Hu P, Sloan S, Silber S, Leitz G. Efficacy and safety of rabeprazole in children (1-11 years) with gastroesophageal reflux disease. *J Pediatr Gastroenterol Nutr* 2013;57:798-807.

<sup>7</sup> Prevacid Delayed-Release Capsule Prescribing Information. Takeda Pharmaceuticals. Deerfield, Illinois. Revised December 2014.

<sup>8</sup> Prilosec Delayed-Release Capsule Prescribing Information. AstraZeneca. Wilmington, Delaware. Revised December 2014.

<sup>9</sup> Protonix Delayed-Release Tablet Prescribing Information. Wyeth Pharmaceuticals. Philadelphia, Pennsylvania. Revised December 2014.

<sup>10</sup> Nexium Delayed-Release Capsule Prescribing Information. AstraZeneca. Wilmington, Delaware. Revised December 2014.

<sup>11</sup> Dexilant Delayed-Release Capsule Prescribing Information. Takeda Pharmaceuticals. Deerfield, Illinois. Revised December 2014.

## **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<sup>®</sup> receives over 2.1 billion prescription claims per year.

### **IMS, National Prescription Audit**

The National Prescription Audit (NPA<sup>™</sup>) measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPA<sup>™</sup> receives over 2.7 billion prescription claims per year, captured from a sample of the universe of approximately 57,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 86% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 40 - 70% (varies by class and geography) of mail service pharmacies and approximately 45-55% of long-term care pharmacies. Data are available on-line for 72- rolling months with a lag of 1 month.

### **Encuity Research, LLC., TreatmentAnswers<sup>™</sup>**

Encuity Research, LLC., TreatmentAnswers<sup>™</sup> and TreatmentAnswers<sup>™</sup> with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

## **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 RABEPRAZOLE SODIUM (N=9)**

<b>FAERS CASE NUMBER</b>	<b>FAERS VERSION NUMBER</b>	<b>MANUFACTURER CONTROL NUMBER</b>
7199949	3	ZA-EISAI INC-E3810-03327-CLI-ZA
7391570	3	DK-EISAI INC-E3810-03783-CLI-DK
7638914	2	US-EISAI INC-E3810-04512-CLI-US
7675508	1	US-EISAI INC-E3810-04220-SPO-US
7955145	3	US-EISAI INC-E3810-04681-CLI-US
8020895	2	NL-EISAI INC-E3810-04770-CLI-NL
8684382	2	IT-EISAI INC-E3810-05697-SPO-IT
8762469	2	JP-EISAI INC-E3810-05825-SPO-JP
9471150	1	BR-EISAI INC-E3810-06605-SPO-BR

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