Pediatric Focused Safety Review Aciphex® Sprinkle™ (rabeprazole) Pediatric Advisory Committee Meeting April 12, 2016

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Outline

- Background Information
- Pediatric Studies
- Labeling Changes
- Drug Use Trends
- Safety
- Summary

Background Drug Information
Aciphex® Sprinkle™ (rabeprazole)

- **Drug: Aciphex® Sprinkle™ (rabeprazole)**
- **Formulation:** delayed-release capsule for oral use
- **Sponsor:** Eisai, Inc.
- **Original Market Approval:** March 26, 2013
- **Therapeutic Category:** proton pump inhibitor (PPI)

- **Related product:** Aciphex® (rabeprazole) Delayed-Release Tablets for oral use. Originally approved August 19, 1999.

Background Drug Information, continued
Aciphex® Sprinkle™ (rabeprazole)

Pediatric Indications:

- Adolescent patients 12 years of age and older:
  - Short-term Treatment of Symptomatic GERD* (approved June 30, 2008)
- Pediatric patients 1 to 11 years of age:
  - Treatment of GERD (approved March 26, 2013, initiated safety review)

Adult Indications:

- Healing of Erosive or Ulcerative GERD
- Maintenance of Healing of Erosive or Ulcerative GERD
- Treatment of Symptomatic GERD
- Healing of Duodenal Ulcers
- *Helicobacter pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence
- Treatment of Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome

*Gastroesophageal Reflux Disease

Background Drug Information, continued

Aciphex® Sprinkle™ (rabeprazole)

Contraindications (Section 4)

Aciphex® is contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles or to any component of the formulation. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, and urticaria

Warnings and Precautions (Section 5)

- Presence of Gastric Malignancy: Symptomatic response to therapy with rabeprazole does not preclude the presence of gastric malignancy
- Concomitant Use with Warfarin: Monitor for increases in INR and prothrombin time
- Acute Interstitial Nephritis: Observed in patients taking PPIs

Background Drug Information, continued

Aciphex® Sprinkle™ (rabeprazole)

Warnings and Precautions (Section 5 continue)

- Vitamin B-12 Deficiency: Daily long-term use (e.g., longer than 3 years) may lead to malabsorption or a deficiency of vitamin B-12
- *Clostridium difficile* Associated Diarrhea: PPI therapy may be associated with increased risk of *Clostridium difficile* associated diarrhea
- 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
- *Hypomagnesemia*: Reported rarely with prolonged treatment with PPIs
- Concomitant Use with Methotrexate: Concomitant use of PPIs may elevate and prolong serum levels of methotrexate and/or its metabolite

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Pediatric Studies
Aciphex® Sprinkle™ (rabeprazole)

GERD in Pediatric Patients 1 to 11 Years of Age

- A randomized, double-blind clinical trial in 127 pediatric patients aged 1 to 11 years with endoscopic and histologic evidence of GERD
- 81% of patients demonstrated esophageal mucosal healing on endoscopic assessment after 12 weeks
- 90% retained healing at 36 weeks . (Patients could elect to continue treatment for 24 more weeks)
- There were no adverse reactions reported that were not previously observed in adolescents or adults.

Pediatric Studies continue Aciphex® Sprinkle™ (rabeprazole)

Symptomatic GERD in Infants 1 to 11 months of age

- Studies conducted do not support the use of Aciphex® Sprinkle™ for the treatment of GERD in pediatric patients younger than 1 year of age.
- A randomized, placebo-controlled withdrawal trial in 344 infants 1 to 11 months of age with a clinical diagnosis of symptomatic GERD, or suspected or endoscopically proven GERD
- Patients treated up to 3 weeks
- Infants with a clinical response (n=268) were then randomized to receive either placebo or 5 mg or 10 mg Aciphex® Sprinkle™.
- Study did not demonstrate efficacy based on assessment of frequency of regurgitation and weight-for-age Z-score.
  - Result as would be expected since GERD in infants in not acid mediated

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Pediatric Labeling Changes
Aciphex® Sprinkle™ (rabeprazole)

1 INDICATION AND USAGE
1.8 Treatment of GERD in Pediatric Patients 1 to 11 Years of Age

2 DOSAGE AND ADMINISTRATION
2.8 Treatment of GERD in Pediatric Patients 1 to 11 Years of Age
Recommended dosage:

- 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

6 Adverse reactions
6.1 Clinical Studies Experience
Pediatrics - Adverse reactions that occurred in ≥5% of patients included abdominal pain (5%), diarrhea (5%), and headache (5%). There were no adverse reactions reported in this study that were not previously observed in trials of adolescents and adults.

Pediatric Labeling Changes Aciphex® Sprinkle™ (rabeprazole)

8.4 Pediatric Use

Included information:

- A description of the clinical study in pediatric patients with GERD aged 1 to 11 years
- A description of the failed clinical study in infants 1 to 11 months with symptomatic GERD
- A statement that use of Aciphex® Sprinkle™ is strongly discouraged for the treatment of GERD in neonates based on the risk of prolonged acid suppression and lack of demonstrated safety and effectiveness
- A description of the population pharmacokinetic analysis in neonates and infants 1 to 11 months.

Pediatric Labeling Changes
Aciphex® Sprinkle™ (rabeprazole)

12 Clinical Pharmacology

12.3 Pharmacokinetics

- A description of the pharmacokinetic analysis in patients 1 to 11 years is included.
- A reference to section 8.4 Pediatric Use for patients less than 1 year is included.

14 Clinical Studies

14.7 Pediatric GERD

- A description of the clinical study in pediatric patients 1 to 11 years of age is included.

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Drug Utilization: Aciphex® Sprinkle™

Total number of patients with a dispensed prescription for Aciphex Sprinkle from U.S. outpatient retail pharmacies, stratified by patient age, September 1, 2014 – August 31, 2015

	Patients (N)	Share (%)
Total Patients	**3,486**	**100%**
0-16 years	**3,104**	**89%**
< 1 year	778	25%
1-11 years	2,133	68%
12-16 years	238	7%
17+ years	**368**	**11%**

Source: IMS, Vector One®: Total Patient Tracker. Sep 2011 - Aug 2015. Extracted October 2015.

Drug Utilization: Aciphex® Sprinkle™

Top Prescribing Specialties and Diagnosis

- **Top prescribing specialties[1]**
  (% of specialties with a dispensed prescription)
  - Pediatrics (46% of dispensed prescriptions)
  - Gastroenterology (14% of dispensed prescriptions)

- **Diagnosis[2]**
  - Esophageal Disorder Not Elsewhere Classifiable (NEC) was the only diagnosis reported among pediatric patients 0-11 years old

[1]Source: Source: IMS National Prescription Audit (NPA). Mar 2013 - Aug 2015. Extracted January 2016.

[2]Source: Encuity Research, LLC., TreatmentAnswers™ with Pain Panel, Mar 2013 - Aug 2015. Extracted October 2015.

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Number* of Adult and Pediatric FDA Adverse Event Reporting System (FAERS) Cases with Aciphex® Sprinkle™ (August 1, 2009 to August 31, 2015)

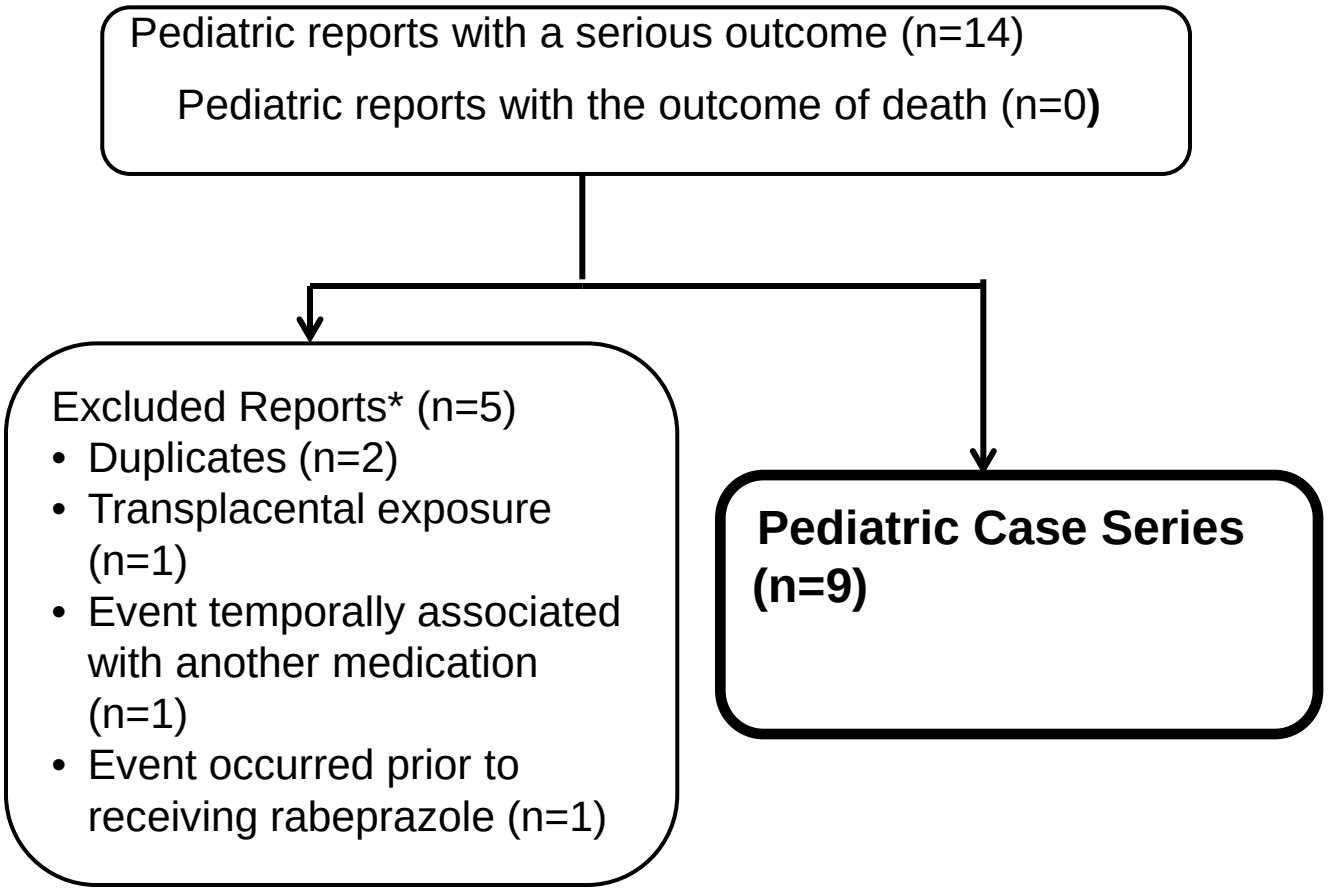
	All reports (US)	Serious† (US)	Deaths (US)
Adults (≥ 17 yrs.)	1723 (551)	836 (306)	110 (26)
Pediatrics (0- <17 yrs.)	**14 (3)**	**14 (3)**	**0§(0)**

* May include duplicates and transplacental exposures; cases have not been assessed for causality

†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

§ No additional cases of pediatric deaths were identified among cases not reporting age

Selection of Pediatric FAERS Cases



* These reports were reviewed, but they were excluded from the case series for the reasons listed above.

Characteristics of Pediatric Case Series Aciphex® Sprinkle™ (rabeprazole)

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
Reported Indication*	GERD	5
	Epigastralgia	1
	Gastritis	1
	Unknown	2
Serious Outcome†	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.

Serious Non-Fatal Unlabeled Adverse Events Aciphex® Sprinkle™ (rabeprazole) (n=4)

- Nervous System Disorders
  - Headache, vertigo and blurred vision (n=1)
    - An 11 year old male developed headache, vertigo, and blurred vision on the same day he started on rabeprazole 40 mg daily. (The recommended dose for his age is 5-10 mg daily.) He was also on sodium alginate/potassium bicarbonate. He was hospitalized and rabeprazole was discontinued two days later, and he recovered five days later.
    - Vertigo and blurred vision are unlabeled events. The temporal association and positive de-challenge suggest a relationship. Vertigo and blurred vision are labeled events for other PPIs.

Serious Non-Fatal Unlabeled Adverse Events Aciphex® Sprinkle™ (rabeprazole) (n=4)

- Blood and Lymphatic System Disorders
  - Lymphadenitis (n=1)
    - A 1 year old female started on rabeprazole as part of a study for GERD. Three months later, she developed a significantly elevated alkaline phosphatase (2316 U/L). She also developed a swollen lymph gland in the neck. Ultrasound of the lymph node showed no evidence of malignancy. Ultrasound of the abdomen revealed a hyperechoic liver without tumors. Alkaline phosphatase increased to 4757 U/L. Other liver functions were normal. She was diagnosed with lymphadenitis. Rabeprazole was continued and she recovered three months later.
    - Lymphadenitis is unlabeled, but the event resolved despite continued rabeprazole treatment.

Serious Non-Fatal Unlabeled Adverse Events Aciphex® Sprinkle™ (rabeprazole) (n=4)

- Investigations
  - Beta 2 microglobulin increased (n=1)
    - An 11 month old male developed increased beta 2 microglobulin (B2MG) levels while receiving rabeprazole as part of a study for the treatment of GERD. Baseline beta 2 microglobulin, BUN, and serum creatinine were normal prior to receiving rabeprazole. Rabeprazole was discontinued and the patient was placed on omeprazole. Ten days later, repeat beta 2 microglobulin levels normalized despite being on omeprazole.
    - Beta 2 microglobulin levels normalized despite continued PPI therapy. It is unlikely that the event is associated with rabeprazole treatment.

Serious Non-Fatal Unlabeled Adverse Events Aciphex® Sprinkle™ (rabeprazole) (n=4)

- Vascular Disorders
  - Hematoma (n=1)
    - An 11 year old male developed several hematomas 40 days after starting rabeprazole for gastritis. The hematomas were on his arm, stomach, back, and gluteal areas. He had an increase eosinophil count, increased immunoglobulin E levels and decreased antineutrophil cytoplasmic antibody titers. Rabeprazole was discontinued 2 months later. He continued to develop hematomas.
    - It is unlikely that the event was associated with rabeprazole use.

Serious Non-Fatal labeled Adverse Events Aciphex® Sprinkle™ (rabeprazole) (n=5)

- Musculoskeletal and Connective Tissue Disorders
  - Upper limb fracture (n=1)
- Infections and Infestations
  - Viral infection (n=1)
  - Bronchiolitis and dehydration (n=1)
    - A 6-month old developed worsening bronchiolitis and dehydration while receiving rabeprazole as part of a study for GERD. The patient has a history of rhinorrhea, cough, fever, allergies, eczema, and wheezing with respiratory tract infections. Thirty-eight days after starting rabeprazole, the patient was hospitalized with worsening bronchiolitis, fever and dehydration. The patient was treated with antibiotics, albuterol and prednisone. The patient was continued on rabeprazole and recovered 10 days later.
    - Bronchiolitis and dehydration are not labeled adverse events. Infection is a labeled event. The patient recovered despite continuation of rabeprazole.

Serious Non-Fatal labeled Adverse Events Aciphex® Sprinkle™ (rabeprazole) (n=5)

- Respiratory, Thoracic and Mediastinal Disorders
  - Bronchopneumonia (n-=1)
- Renal and Urinary Disorders
  - Intentional overdose and renal impairment (n=1)
    - A 13 year old female with a history of mental illness developed impairment of renal function after taking an overdose of rabeprazole along with multiple other medications including acetaminophen. She was found with a depressed level of consciousness, increase heart rate and decrease body temperature. She received N-acetylcysteine and hemodialysis. Her renal function recovered after 9 days and she was discharged from the hospital.

    - Renal impairment is not labeled. However, acute interstitial nephritis is labeled. Because the patient intentionally ingested multiple medications, the role of rabeprazole cannot be determined.

Potential Signal of Serious Risk/New Safety Information

- In September 2015, FDA reported a potential signal of a risk of systemic lupus erythematosus (SLE) in proton pump inhibitors*

- FDA is evaluating the need for regulatory action.

*http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm484294.htm

Summary of Safety Reviews
Aciphex® Sprinkle™ (rabeprazole)

- This concludes the pediatric focused safety review of FAERS reports.
- Potential safety signals of vertigo and blurred vision were identified.
- FDA recommends adding vertigo and blurred vision to prescribing information for all dosage forms of Aciphex®.
- Does the committee concur?

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