

CLINICAL REVIEW

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Division / Office	CDER/ODE III/DGIEP
Reviewer Name(s)	Marjorie F. Dannis, MD, through Anil Rajpal, MD
Review Completion Date	December 23, 2015
Established Name	Omeprazole Magnesium
(Proposed) Trade Name	Prilosec
Therapeutic Class	Proton Pump Inhibitor (PPI)
Applicant	AstraZeneca
Formulation(s)	Delayed-Release Oral Suspension
Dosing Regimen	Once daily
Indication(s)	Treatment of erosive esophagitis (EE) due to acid- mediated gastroesophageal reflux disease (GERD)
Intended Population(s)	1-11 month olds, inclusive

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of Prilosec (omeprazole magnesium) delayed-release oral suspension for the treatment of erosive esophagitis (EE) due to acid-mediated gastroesophageal reflux disease (GERD) in pediatric patients aged 1 month to less than 1 year. This reviewer agrees with the conclusions of the committee members from the November 5, 2010 Gastrointestinal Drug Advisory Committee (GIDAC) meeting, that the course of the disease and the effects of the drug are sufficiently similar in adult and pediatric patients for acid-mediated erosive esophagitis to allow extrapolation of efficacy from adults. A Pediatric and Maternal Health Staff (PMHS) consultant also agreed that extrapolation from adults to this age group was appropriate for acid-mediated erosive esophagitis.

Although long-term safety data from the omeprazole clinical trials are limited in this age group, Prilosec has been used widely in clinical practice and has been relatively well-tolerated. Therefore, this reviewer considers existing safety information adequate for labeling.

1.2 Risk Benefit Assessment

As discussed during the GIDAC meeting on November 5, 2010, infants (less than one year of age) likely have a unique pathophysiology responsible for infantile GERD due to the differences in symptoms, duration, and prognosis from adults and older children. Symptoms commonly associated with infantile GERD (e.g., vomiting, crying, irritability related to food intake, and failure to thrive) are not specific to acid-mediated injury and may be indistinguishable from other conditions, such as food allergy.¹ However, acid-mediated erosive esophagitis, in both adults and children, is defined as the presence of endoscopically visible breaks in the esophageal mucosa at or immediately above the gastroesophageal junction.^{2,3} Therefore, as long as the indication is restricted to infants with acid-mediated erosive esophagitis, as opposed to symptomatic or suspected GERD, this reviewer believes that the relative benefit vs. risk is favorable for short-term therapy with Prilosec.

¹ Sherman PM, Hassall E, Fagundes-Neto U, et al. A global, evidence-based consensus on the definition of gastroesophageal reflux disease in the pediatric population. *Am J Gastroenterol* 2009;104:1278-95.

² Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999;45:172-80.

³ Vandenplas Y, Rudolph CD, Di Lorenzo C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr* 2009;49:498-547.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

The clinical manifestations of gastroesophageal reflux disease (GERD) range from minor symptoms, such as heartburn or regurgitation, to more complicated disease, such as erosive esophagitis, esophageal stricture, or Barrett's esophagus.⁴ Erosive esophagitis (EE) is defined as the presence of endoscopically visible esophageal injury.⁵ Although exact prevalence is unknown, a retrospective cross-sectional study of 12 children's hospitals in the U.S. using the Pediatric Endoscopy Database System-Clinical Outcomes Research Initiative (PEDS-CORI) determined that 29 of 531 (5.5%) children ages 0 to 1 year who underwent endoscopy had erosive esophagitis.⁶

2.1 Product Information

Prilosec is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H⁺/K⁺-ATPase in the gastric parietal cell. Prilosec is currently available in delayed-release capsules (10 mg, 20 mg and 40 mg) and in a delayed-release oral suspension (2.5 mg and 10 mg).

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, Nexium (esomeprazole magnesium) is approved for the treatment of EE due to acid-mediated GERD in pediatric patients one month to less than one year of age. In addition, two histamine-2 receptor antagonists (H₂RA), Zantac (ranitidine) and Pepcid (famotidine) are approved in this age group for the proposed indication.

2.3 Availability of Proposed Active Ingredient in the United States

Prilosec is available in the U.S. as a prescription drug for the treatment of several indications in adults and pediatric patients ages 1 year and older. Table 1 below outlines Prilosec's specific indications and usage at the current time.

⁴ Shepard RW, Evans JWS, Lander M, et al. Gastroesophageal reflux disease in children. *Clin Pediatr* 1987;26:55-60.

⁵ Armstrong D, Marshal JK, Chiba N, et al. Canadian Consensus Conference on the management of gastroesophageal reflux disease in adults – update 2004. *Can J Gastroenterol* 2005;19:15-35.

⁶ Gilger MA, El-Serag HB, Gold BDm et al. Prevalence of endoscopic findings of erosive esophagitis in children: a population-based study. *J Pediatr Gastroenterol Nutr* 2008;47:141-6.

Table 1: Current Prilosec Indications and Usage

Indication	Adult	Pediatric > 1yr
Treatment of Active Duodenal Ulcer	X	
<i>Helicobacter pylori</i> Eradication to Reduce the Risk of Duodenal Ulcer Recurrence	X	
Treatment of Active Benign Gastric Ulcer	X	
Treatment of Symptomatic Gastroesophageal Reflux Disease (GERD)	X	X
Treatment of Erosive Esophagitis (EE) Due to Acid-Mediated GERD	X	X
Maintenance of Healing of EE Due to Acid-Mediated GERD	X	X
Pathological Hypersecretory Conditions	X	

2.4 Important Safety Issues with Consideration to Related Drugs

PPIs have been found to be generally safe and well-tolerated. The current Prilosec labeling includes the following as **Warnings and Precautions**:

- Gastric Malignancy: Symptomatic response does not preclude the presence of gastric malignancy.
- Atrophic Gastritis: Noted with long-term therapy.
- Acute Interstitial Nephritis: observed in patients taking PPIs.
- Cyanocobalamin (vitamin B-12) Deficiency: Daily long-term use (e.g., longer than 3 years) may lead to malabsorption or a deficiency of cyanocobalamin.
- Clostridium difficile Associated Diarrhea: PPI therapy may be associated with increased risk
- Interaction with Clopidogrel: Avoid concomitant use of Prilosec
- 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.
- Interaction with St. John's Wort or Rifampin: Avoid concomitant use of Prilosec

- 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.
- 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 .

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On March 20, 2008, Prilosec (omeprazole) for Delayed-Release Oral Suspension was approved for the short term treatment of symptomatic GERD and healing of erosive esophagitis in pediatric patients 1 to 2 years old. In the approval letter, the following PREA PMR was issued:

Deferred pediatric study under PREA for the treatment of Gastrointestinal Esophageal Reflux Disease (GERD) and Erosive Esophagitis in pediatric patients ages Birth to 1 year.

On March 15, 2012, [REDACTED] ^{(b) (4)} the post marketing requirement (PMR) for Prilosec (omeprazole magnesium) for Delayed Release Oral Suspension (PMR 1396-1), a deferred pediatric study under PREA for the treatment of Gastrointestinal Esophageal Reflux Disease (GERD) and Erosive Esophagitis (EE) in pediatric patients ages birth to one year. [REDACTED] ^{(b) (4)}

On October 10, 2013, FDA released AstraZeneca from **part** of the PMR. FDA determined the partial release of the PMR was due to the following reasons:

- Studies would be impossible or highly impractical in patients aged birth to < 1 month with GERD and EE and;
- There is evidence that PPIs, like Prilosec, are not effective for the treatment of symptomatic GERD in patients < 1 year of age.

The above PREA PMR was replaced with a new PREA PMR for patients ages 1 month to 11 months with EE.⁷

⁷ as agreed upon in an email from AstraZeneca(AZ) dated June 20, 2013.

New PMR 2062-1: Deferred study under PREA to evaluate the pharmacokinetics, pharmacodynamics, and safety of omeprazole in patients 1 month to 11 months of age with EE. The new dates were as listed below:

- Final Protocol Submission: March 2014
- Study/Trial Completion: March 2016
- Final Report Submission: September 2016

The June 20, 2013 e-mail from Astra Zeneca (AZ) noted that the Sponsor still had concerns about potential recruitment difficulty for this EE study. They stated that they planned to request FDA's feedback regarding the proposed study once they had completed the feasibility analysis.

In December 2013, AZ completed the feasibility analysis and submitted a report to the FDA wherein they concluded that the new PMR required study would be impossible or highly impracticable to conduct. Further, they questioned whether it would be ethical to justify the risks of such an invasive study in small children as the studied therapy would not represent a meaningful benefit over already existing therapies.

On February 20, 2014, FDA stated that AZ's proposal to use available PK/PD and safety data from previous studies with Prilosec in children to fulfill a bridging strategy may be an acceptable option to fulfill the current PREA PMR.⁸

AstraZeneca had previously conducted several pediatric studies with Prilosec which included some infants aged 1-11 months.

In the current submission, AZ claims that they provided the data to support the statements below.

- PK/PD relationship is similar in children and in adults:
- PK modeling demonstrating a dose/PK relationship in small children
- Suggestion for doses in children giving an exposure in children similar to the exposure in adults given the EE dose

⁸ From February 20, 2014 written responses provided to AZ in lieu of a meeting.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The electronic application was organized and easily navigable. No new clinical efficacy data was submitted.

3.2 Compliance with Good Clinical Practices

No new clinical efficacy data was submitted; the safety data included in this submission was gathered from previously submitted safety data.

3.3 Financial Disclosures

No additional information was submitted.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No additional information was submitted. Clinical studies previously submitted in support of this application used Prilosec 2.5 mg/10 mg as Delayed-Release Oral Suspension. According to the Sponsor, this is the same formulation that is currently marketed in the U.S. As a result, AZ did not submit new CMC information.

4.2 Clinical Microbiology

No additional information was submitted.

4.3 Preclinical Pharmacology/Toxicology

No additional information was submitted.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Prilosec is a proton pump inhibitor that inhibits gastric acid secretion through irreversible inhibition of the H⁺/K⁺ ATPase in the gastric parietal cell.

4.4.2 Pharmacodynamics

Please refer to the Clinical Pharmacology and Pharmacometrics reviews by Drs. Justin Earp, Nitin Mehrotra, Dilara Jappar and Sue Chih Lee for complete details.

The Sponsor submitted results from prior PK/PD studies to describe the exposure-response relationship in patients less than 1 year of age and adults.

4.4.3 Pharmacokinetics

Please refer to the Clinical Pharmacology and Pharmacometrics reviews by Drs. Justin Earp, Nitin Mehrotra, Dilara Jappar and Sue Chih Lee for complete details.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

No new clinical data were submitted.

5.2 Review Strategy

No new clinical efficacy data were submitted during this review cycle. There have not been any clinical trials specifically designed to establish the efficacy of Prilosec in treating erosive esophagitis in children ages 1-11 months. Instead, the majority of the enrolled pediatric patients in prior clinical trials consisted of those with suspected or symptomatic GERD⁹.

Safety data from previous clinical trials which included pediatric patients ages 1-11 months was reviewed. In addition, post marketing data in this pediatric age subgroup was reviewed.

⁹ This was also the situation for the approval of Nexium for treatment of EE due to acid-mediated GERD in pediatric patients ages 1-11 months in which extrapolation and PK/PD modeling were used.

6 Review of Efficacy

The Sponsor proposes to expand the current indication of Prilosec for delayed-release oral suspension for the treatment of erosive esophagitis due to acid-mediated gastroesophageal reflux disease to include pediatric patients ages 1 month to 11 months.

As per the Code of Federal Regulations (21 CFR 314.55), where the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Agency may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, supplemented with other information obtained in pediatric patients, such as pharmacokinetics.

There were no new efficacy data submitted with this sNDA submission. However, acid-mediated GERD with erosive esophagitis has the same disease definition and has a similar endoscopic presentation in adults, older children, and infants. In all age groups, the treatment is targeted to reduce pH and heal acid-induced injury. Therefore, this reviewer considers extrapolation of efficacy based on well-controlled adult trials is appropriate for pediatric patients 1-11 months.

Extrapolation of efficacy from adults to pediatric patients does not require *stand-alone* clinical efficacy data in the indicated pediatric population, but does require that the appropriate dose and safety of the product are established in the target population.

Based on the review by the Clinical Pharmacology and Pharmacometrics team, the pharmacokinetic and pharmacodynamic data appear to support the proposed weight-based doses for infants aged 1 to 11 months. See 4.4 Clinical Pharmacology and Pharmacometrics reviews for complete details.

7 Review of Safety

Prilosec is approved for use in children in the EU, the US and many other international markets. In the US, Prilosec is approved for treatment of GERD and treatment/maintenance of healing of erosive esophagitis in children from 1 year and older. In the EU, it is approved in children over 1 year of age with a body weight of ≥ 10 kg for the indications of: reflux esophagitis, symptomatic treatment of heartburn and acid regurgitation in GERD, and for *H. pylori* eradication in combination with antibiotics in treatment of duodenal ulcer caused by *H. pylori* in children over 4 years.

In the current submission, the Sponsor resubmitted safety data for the relevant pediatric age subgroup (1-11 month) from two previous clinical studies (Studies 251 and 250 done in 2000) as well as from a compilation of post- marketing data. The safety review will focus only on the relevant population.

Study 251

Study 251 was a randomized, single-blind, 56 day, safety/efficacy study in pediatric GERD patients 0 - 24 months¹⁰. This study included patients with a 2-month history of clinically diagnosed GERD-related symptoms. Of the 115 patients randomized, 102 were < 1yr. Patients were randomized to a Prilosec dose of 0.5 mg/kg, 1.0 mg/kg, or 1.5 mg/kg. There were a total of 215 adverse events in any category and 2 serious adverse events¹¹. Table 2 below describes the particular adverse events (≥ 2 events) which occurred during the study. These events were similar to typical symptoms observed in a general population of pediatric patients.

Table 2: Study 251: Number of patients with reported adverse events ≥ 2 (preferred term) sorted by decreasing frequency in all randomized patients (safety population)

Age	< 3 months			3- <6 months			6- <12 months			0- <12 months
	0.5 mg/kg	1.0 mg/kg	1.5 mg/kg	0.5 mg/kg	1.0 mg/kg	1.5 mg/kg	0.5 mg/kg	1.0 mg/kg	1.5 mg/kg	
Omeprazole dose										Total
No of patients	(n=4)	(n=13)	(n=12)	(n=16)	(n=7)	(n=13)	(n=12)	(n=9)	(n=9)	(n=95)
Preferred term										
Otitis media	0	2	1	6	2	3	3	3	1	21
Diarrhoea	0	2	2	3	1	4	3	3	2	20

¹⁰ The primary objective was to investigate whether once-daily treatment with Prilosec safely and effectively reduced the number of regurgitation episodes

¹¹ Events are counted by preferred term, ie, for patients with multiple events falling under the same preferred term, only 1 occurrence of the event was counted

Table 2: Study 251: Number of patients with reported adverse events ≥ 2 (preferred term) sorted by decreasing frequency in all randomized patients (safety population)

Age	< 3 months			3- <6 months			6-<12 months			0-<12 months
	0.5 mg/kg (n=4)	1.0 mg/kg (n=13)	1.5 mg/kg (n=12)	0.5 mg/kg (n=16)	1.0 mg/kg (n=7)	1.5 mg/kg (n=13)	0.5 mg/kg (n=12)	1.0 mg/kg (n=9)	1.5 mg/kg (n=9)	Total (n=95)
Preferred term										
Respiratory infection	0	1	2	4	0	4	3	3	2	19
Rash	0	1	2	2	2	2	3	2	1	15
Fever	0	1	0	4	0	1	4	2	2	14
Rhinitis	0	4	1	4	1	0	1	0	1	12
Constipation	0	3	2	3	0	1	1	1	0	11
Nervousness	1	1	1	2	1	1	0	3	0	10
Vomiting	1	1	2	0	0	2	1	1	1	9
Coughing	0	1	2	1	0	1	0	1	0	6
Eczema	0	1	1	0	0	1	1	1	0	5
Flatulence	0	2	1	0	0	1	0	1	0	5

Age	< 3 months			3- <6 months			6-<12 months			0-<12 months
	0.5 mg/kg (n=4)	1.0 mg/kg (n=13)	1.5 mg/kg (n=12)	0.5 mg/kg (n=16)	1.0 mg/kg (n=7)	1.5 mg/kg (n=13)	0.5 mg/kg (n=12)	1.0 mg/kg (n=9)	1.5 mg/kg (n=9)	Total (n=95)
Preferred term										
Gastroenteritis	0	0	2	0	0	1	0	2	0	5
Pharyngitis	0	0	0	0	0	0	3	0	2	5
Ear infection NOS	0	1	1	0	0	1	1	0	0	4
Accident and/or injury	0	0	0	0	1	0	2	0	0	3
Anorexia	0	1	0	1	1	0	0	0	0	3
Bronchitis	0	0	1	0	0	0	0	0	2	3
Moniliasis	0	0	1	1	0	1	0	0	0	3
Rash maculo-papular	0	0	0	0	0	0	0	1	2	3
Dysphonia	0	0	0	0	0	0	1	1	0	2
Gastroesophageal reflux	0	0	0	0	1	1	0	0	0	2

Age	< 3 months			3- <6 months			6- <12 months			0- <12 months Total
	0.5 mg/kg (n=4)	1.0 mg/kg (n=13)	1.5 mg/kg (n=12)	0.5 mg/kg (n=16)	1.0 mg/kg (n=7)	1.5 mg/kg (n=13)	0.5 mg/kg (n=12)	1.0 mg/kg (n=9)	1.5 mg/kg (n=9)	
Preferred term										
Infection fungal	0	0	0	0	0	2	0	0	0	2
Infection viral	0	0	0	1	0	1	0	0	0	2
Purpura	0	1	0	0	0	0	1	0	0	2
Tooth disorder	0	0	0	1	0	1	0	0	0	2
Unusual behaviour	0	1	0	0	1	0	0	0	0	2

Adapted from AZ Response to IR dated June 9, 2015

In addition, there were two SAEs in two patients who were less than 12 months. One patient was a 1.9 month year old with a urinary tract infection and the other was a 2.1 month old patient with pertussis. Neither the Sponsor nor this reviewer believes that either of these SAEs was secondary to Prilosec.

Study 250

Study 250 was a pharmacokinetic single dose study¹². Adverse events were collected for an additional 14 days after study completion. Doses used were 0.5 mg/kg-1.5 mg/kg. Only nineteen patients were included in the safety population. During the treatment period, there was a total of 18 AEs in any category. There were no deaths, SAEs or AEs leading to discontinuation during study treatment. Table 3 below lists the number of patients with reported adverse events during study drug treatment sorted by decreasing frequency in all randomized patients (safety population)

Table 3: Study 250: Number of patients with reported adverse events (preferred term) during study drug treatment sorted by decreasing frequency in all randomized patients (safety population)

¹² Four patients had more than one dose

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Age	< 3 months			3- <6 months			6-<12 months			0-<12 months
	0.5 mg/kg	1.0 mg/kg	1.5 mg/kg	0.5 mg/kg	1.0 mg/kg	1.5 mg/kg	0.5 mg/kg	1.0 mg/kg	1.5 mg/kg	Total
No of patients	(n=1)	(n=3)	(n=3)	(n=0)	(n=3)	(n=3)	(n=0)	(n=3)	(n=3)	(n=19)
Preferred term										
Nervousness	0	0	0	0	1	0	0	1	1	3

Age	< 3 months			3- <6 months			6-<12 months			0-<12 months
	0.5 mg/kg	1.0 mg/kg	1.5 mg/kg	0.5 mg/kg	1.0 mg/kg	1.5 mg/kg	0.5 mg/kg	1.0 mg/kg	1.5 mg/kg	Total
No of patients	(n=1)	(n=3)	(n=3)	(n=0)	(n=3)	(n=3)	(n=0)	(n=3)	(n=3)	(n=19)
Preferred term										
Agitation neonatal	0	1	1	0	0	0	0	0	0	2
Bradycardia	1	0	0	0	0	1	0	0	0	2
Injection site reaction	0	0	1	0	0	0	0	0	1	2
Respiratory disorder	1	1	0	0	0	0	0	0	0	2
Anuria	1	0	0	0	0	0	0	0	0	1
Cyanosis	0	0	0	0	0	1	0	0	0	1
ECG abnormal	0	0	1	0	0	0	0	0	0	1
Sputum increased	0	0	1	0	0	0	0	0	0	1

From AZ Response to IR dated June 9, 2015

This reviewer concludes that the reported AEs during the above clinical studies were mostly related to the natural history and/or disease-related events in a neonatal patient population.

8 Postmarket Experience

A 2010 FDA review of the PPI utilization in the US showed that between 2002 -2009 more than (b) (4) Prilosec prescriptions were dispensed to children in the age group <1 year.¹³

Adverse event data were collected from Prilosec marketed use (medically confirmed reports) up to Oct 15, 2013.¹⁴ In total, since the first approval in 1987, the Sponsor received information regarding more than 800 medically confirmed case reports in the age group 0-17. Except for classically neonatal diseases, there were no major differences in AEs between pediatric age groups, also when compared with adult AEs.

In the relevant pediatric age subgroup, Table 4 below lists the most commonly reported AEs (≥ 5 patients). With the exception of “Off label Use”, this reviewer concludes that most of these common AEs would be most likely related to the natural history and/or disease-related events in a neonatal patient population.

Table 4: Post Marketing: Most frequently Reported Adverse Events in Children Age ≤ 1 year

Preferred Term	Number of patients
Vomiting	34
Off label use	25
Diarrhoea	12
Drug ineffective	12
Neutropenia	8
Regurgitation	8
Faeces discoloured	7
Wrong technique in drug usage process	7
Gastrooesophageal reflux disease	5
Rash	5

Out-of-scope AEs reported by at least 5 patients are included in this table.

Adapted from Appendix B of Population PKPD Modeling Report dated February 24, 2014

¹³ FDA briefing information for the November 5, 2010 meeting of the Gastrointestinal Drug Advisory Committee.

¹⁴ The Sponsor did not provide updated data as they stated they had no new data to report (although requested in the safety update)

From February 1989 up to October 2013, there were five infants < 1 year reported to have a fatal outcome. Two of them had been exposed to Prilosec via placenta during the pregnancy and the remaining three had been exposed after birth. Both of the two pregnant mothers had been treated with other drugs during the pregnancy. The mother of one patient had been treated with five concomitant drugs (including a fetotoxic benzodiazepine). This baby was born with esophageal, tracheal and anus atresias and died as a neonate. The other Prilosec treated pregnant mother had ureteral stenosis and recurrent urinary tract infections for which she was treated with antibiotics. The baby was born with a hypoplastic left heart and died after numerous open heart procedure.

Among the remaining three babies, one died due to sudden infant death syndrome. A second Prilosec treated baby had been born prematurely (in week 25) and had been diagnosed with congenital short bowel disease and secondary hepatic cirrhosis. He died during a combined liver and small bowel transplantation. In the third Prilosec treated baby, a follow-up report revealed that the reported cholestatic jaundice and thrombocytopenia existed before the Prilosec treatment had been started. This patient had been treated with a high dose Prilosec due to gastrointestinal bleeding.

A review of the case narratives failed to provide evidence that Prilosec could be directly attributable to the fatal outcomes reported in these 5 patients. Apart from the patient who died from sudden infant death syndrome, all patients in this age group were seriously ill and had other/alternative explanations for the fatal outcomes.

The Sponsor reported that no case reports were received for children aged 0 to 11 months during the safety update period. Overall, no new safety concerns were raised during the review of the post-marketing safety data.

9 Appendices

9.1 Literature Review/References

None

9.2 Labeling Recommendations

At the current time, labeling negotiations are taking place with the Sponsor, thus the final labeling recommendations are unavailable.

9.3 Advisory Committee Meeting

No advisory committee meeting is planned regarding this submission.

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/s/

MARJORIE F DANNIS
12/25/2015

ANIL K RAJPAL
12/26/2015
I concur with Dr. Dannis.