CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-056

CROSS DISCIPLINE TEAM LEADER REVIEW

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DIVISION OF GASTROENTEROLOGY DRUGS

DATE: February 09, 2008

FROM: Hugo E. Gallo-Torres, MD, PhD, PNS
Division of Gastroenterology Products [HFD-180]
DGDP/ODE III

TO: DIVISION FILES, **NDA 22-056**

SUBJECT: GI Team Leader Recommendations for Regulatory Action
[Complete Response to AE letter on January 15, 2008]
PDUFA Goal date: March 15, 2008

APPLICANT: AstraZeneca LP
Wilmington DE 19803-8355
Regulatory Contact: George Kummeth
Global Director Regulatory Affairs

DRUG: Prilosec® (omeprazole magnesium) For Delayed-Release Oral Suspension

INDICATION: Short-term treatment of GERD and healing of erosive esophagitis in pediatric patients 0 to 2 years old

Documents Considered in this review:

1. **October 19, 2007 Approvable letter [Dr. Joyce Korvick]**
2. **October 18, 2007 Information request letter [Mr. Brian Strongin]**
3. **December 13, 2007 Complete Response to October 19 AE letter**
4. **January 14, 2008 4-Month Safety Update**
5. **Labeling**

I. BACKGROUND/INTRODUCTION

On 20 December 2006, the sponsor [AstraZeneca] submitted NDA 22-056 for PRILOSEC® (omeprazole magnesium) For Delayed-Release Oral Suspension. Omeprazole sachets were developed to fulfill the post-marketing commitment to develop an **age-appropriate formulation** for pediatric patients 0 to 2 years of age, issued by the Agency in the 12 July 2002 Approval letter for Supplement NDA 19-810/S-074, which was the NDA for pediatric labeling for ages 0 to 16 years for PRILOSEC.

On October 19, 2007 the sponsor was informed that the 20 December 2006 submission was **approvable**[1]. The sponsor was informed that before the application may be approved, it will be necessary for them to:

1. Submit draft labeling revised in response to our October 18, 2007 communication. This October 18, 2007 communication was an Information Request Letter that needed to be addressed as one of the components of the sponsor's Complete Response to the Approvable Letter of October 19, 2007.

The sponsor also was informed of the following:

2. "We are in receipt of your final report dated July 25, 2007 to NDA 19-810, regarding the potential imbalance of serious cardiac adverse events in two adult studies (SOPRAN and LOTUS). Upon finalizing our reviews of these data, additional changes to the professional labeling for esomeprazole magnesium may be needed".

The sponsor has now submitted a Complete Response to our Approvable Letter of October 19, 2007.

The purpose of the current MTL's review is to assess the adequacy of the information in the sponsor's Complete Response, consisting primarily of a) responses and clarifications regarding our October 18, 2007 Information Request Letter; b) a 4-Month Safety Update; and c) proposed Labeling revisions.

II. RESPONSES to the DIVISION's INFORMATION REQUEST LETTERS of October 1 and 18, 2007

As depicted in Table 1, the labeling has been revised as instructed, suggested or recommended in our October 18, 2007 letter to sponsor.

These specific labeling changes include deletions and additions, and the completion, reformatting, moving, rearranging, rewording, or simply revising the information in the various Sections/subsections of the labeling.

Based on the reviewer's evaluation [See below], the labeling has been adequately revised. The sponsor has adequately responded to our October 18 Information Request Letter.

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[1] The approvable letter acknowledged sponsor's submissions dated February 8, March 15, April 18, May 1, May 2, May 8, July 3, July 11, July 25, July 31, August 29, September 24, September 27, and October 4, 2007.

9 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__X__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

b(4)

III. REVIEW of JANUARY 14, 2008 4-Month SAFETY UPDATE REPORT for NDA 22-056

PURPOSE of this 4-MSU

The purpose of this 4-MSU is to summarize pediatric safety information for PRILOSEC received by AstraZeneca between 02 March 2007 and 31 December 2007[2].

SAFETY/EXPOSURE

Adverse events from clinical trials

[2] The previous 4-SU was submitted on 18 April 2007 for the period covering 29 August 2006 and 01 March 2007.

For **completeness**, safety information from **Study 251**, included in Dr. Gao's evaluations[3] of the initial [December 20, 2006] submission is briefly summarized in Table 2.

Table 2
Study 251
Proportion of Patients Experiencing ≥ 1 Adverse Event and the System Involved

	PRILOSEC Dose (mg/Kg)		
	0.5	1	1.5
	n= 35	n = 35	n = 36
Proportion of Patients with ≥ 1 Adverse Experience	74%	74%	86%
--- Respiratory system disorder	40%	40%	58%
--- Gastrointestinal system disorder	34%	46%	50%

Excerpted from Table 10, Study 251, Dr. Gao's review 10/15/2007.

- Although in this study, there appears to be an insinuation of dose response, no firm conclusions can be drawn because the n [35 to 36 patients per arm] is small. In addition, Study 251 did not include a negative comparator.

- Five patients enrolled in Study 251 experienced serious adverse events [005/001 = pneumonia; 006/004 = urinary tract infection; 008/007 = lymphoadenopathy; 017/001 = pertussis; and 026/008 = bronchiolitis with croup]. All five SAEs were assessed as unlikely related to test medication.

- In Study 251, there were six treatment–related dropouts [insufficient therapeutic effect resulting in exacerbation of GERD symptoms; vomiting and crying].

From his review of the data in the initial NDA 22-056 submission. [redacted]

[redacted] b(4)

Gastrointestinal disorders [likely related to the underlying disease], including vomiting and diarrhea, appeared to be the most common treatment-related AEs.

In their January 14, 2008 4-Month Safety Update, AstraZeneca notes that between the period of 02 March 2007 and 31 December 2007, there have been no clinical studies initiated or ongoing with PRILOSEC in pediatric patients; therefore, there is no new safety or exposure information for this patient population other than what has been reported through the AstraZeneca post-marketing safety database (Sponsor's Section 2.2) or identified in a literature search (Sponsor's Section 2.3).

[3] Dr. Wen-Yi Gao's review signed into DFS on October 15, 2007; co-signed by MTL on October 17, 2007.

Post-marketing safety data
According to the information submitted by the sponsor, during the period covering 02 March 2007 and 31 December 2007

- A total of **23 spontaneous reports** describing 35 AEs in pediatric patients ≤ 2 years of age exposed to oral omeprazole were identified from the AstraZeneca global safety database.

- Patients ranged in age from 6 weeks to 19 months with a median of 5 months.

- 15 of the 23 patients were male, 7 were female, and 1 did not provide information about gender.

- Daily omeprazole doses ranged from 5 mg to 12 mg

- 7 of the 23 reports provided the patient's weight ranging from 1 Kg to 9.2 Kg with a median of 6.5 Kg.

- Time to event onset, from initiation of therapy or exposure, ranged from 1 day (i.e., directly following administration) to 5 months.

- The most commonly reported indications for use were gastroesophageal reflux disease (n=12) and reflux esophagitis (n=4).

- 3 of the 23 reports (2007CG00904, 2007UW05251, and 2007UW28825) met serious criteria and described a total of 3 SAEs including hemolytic anaemia, hypoglycemia, and respiratory arrest.

- Two of these SAE reports were possibly confounded by components of extemporaneously compounded omeprazole suspensions (hypoglycemia and respiratory arrest).

- A negative de-challenge one month after omeprazole discontinuation was noted in the remaining SAE report (hemolytic anaemia).

- The remaining 20 non-serious reports described a total of 32 events. These events included the following preferred terms:

Vomiting	(7)
Drug ineffective	(3)
Regurgitation	(3)
Abnormal feces	(2)
Flatulence	(2)
Tongue discoloration	(2)
Abdominal pain upper	(1)
Anorexia	(1)
Blood CPK increased	(1)
Blood LDH increased	(1)

Choking	(1)	
Constipation	(1)	
Drug exposure via breast milk	(1)	
Epistaxis	(1),	
Feces discolored	(1),	
Nonspecific reaction	(1)	
Off-label use	(1)	
Rash macular	(1)	and
Somnolence	(1)	

- Most of these non-serious reports either involved AEs listed in the US Package Insert (USPI) or contained limited information for causality assessment.

- There were no reports of death.

- Summaries of 4 of the 23 reports, including brief narratives, company comments, and Reviewer's Comments are presented in Table 3, which is included in the current review as an Attachment. As noted above, three of these 4 cases were reported as serious. The other is an interesting case of regurgitation related to possible excretion of drug from the mother's milk to the lactating baby.

- Overall, a review of these reports did not identify any new safety concerns for omeprazole in this pediatric age group.

Published literature

The sponsor conducted a search of the medical literature databases (including AstraZeneca's in-house Planet Database, Embase, Medline, Current Contents, IPAB and Biosis) from 02 March 2007 and 31 December 2007. The purpose of this search was to identify relevant safety information on the use of omeprazole in pediatric patients ≤ 2 years of age. The search identified no new literature articles with relevant safety information in pediatric patients ≤ 2 years of age.

4-MONTH SAFETY UPDATE: SUMMARY

Between the period of 02 March 2007 and 31 December 2007 there were no clinical studies initiated or ongoing with PRILOSEC (omeprazole) in pediatric patients 0 to ≤ 2 years of age.

During this same period, there were 23 spontaneous post-market reports describing 35AEs entered into the AstraZeneca Global Safety Database. Three of the reports were serious which included 3 SAEs The reviewer agrees with the sponsor that assessments of causality in these reports were confounded by possible components of extemporaneous compounding and a negative de-challenge.

The remaining 20 non-serious reports described a total of 32 adverse events. Most of these nonserious reports either involved AEs listed in the US Package Insert (USPI) or contained limited information for causality assessment. There were no reports of death.

Based on the information reviewed and presented for this reporting period, no new safety concerns were identified for omeprazole use in children 0 to ≤ 2 years of age.

IV. RECOMMENDATION FOR REGULATORY ACTION

Approval of NDA 22-056/000 is recommended.

Through NDA 22-056, submitted on December 26 2006, AstraZeneca [the sponsor] seeks approval of PRILOSEC® (omeprazole magnesium) For Delayed-Release Oral Suspension. The sponsor developed omeprazole sachets to fulfill the post-marketing commitment to develop an **age appropriate formulation** for pediatric patients 0 to 2 years of age, issued by the Agency in the 12 July 2002 Approval letter for Supplement NDA 19-810/S-074, which was the NDA for pediatric labeling for ages 0 to 16 years for PRILOSEC.

The indication for which approval is recommended is short-term treatment of symptomatic GERD and healing of erosive esophagitis in pediatric patients 0 to 2 years old. The initial regulatory action [October 19, 2007] was **approvable** pending satisfactory resolution of safety issues regarding serious adverse events in two adult studies (SOPRAN and LOTUS) with omeprazole and esomeprazole. These safety issues have been satisfactorily resolved.

The recommendation for approval of NDA 22-056 is based on the initial evidence resulting in an approvable regulatory action and the sponsor's Complete Response dated December 13, 2007. This CR included a) extensive labeling revisions requested in Information Request Letter of October 18, 2007; and a January 14, 2008 4-Month Safety Update. The latter included a search for Literature Publications [none found] and post-marketing safety information on the use of the drug in pediatric patients 0 to 2 years of age inclusive [the intended target population]. Evaluation of this information has not identified new safety concerns.

The MTL concludes that there no unsettled efficacy or safety issues.

Hugo E Gallo-Torres, MD, PhD, PNS
Medical Team Leader
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HFD-180

Attachment

Table 3
Summary of spontaneous pediatric (≤ 2 years of age) adverse event reports received and entered into the AstraZeneca Global Safety Database from 02 March 2007 and 31 December 2007

Report Id # / Country / Source / Age / Gender	Daily Dose / Route / Duration / Indication	AE(s) by PTs / Time to onset / Outcome	Abbreviated narrative
2007UW28825	10 mg	**Respiratory arrest***	According to the father, a compounded oral Suspension from omeprazole capsules prepared by a pharmacist was bitter and unpleasant. The first time the medication was administered; the baby choked and stopped breathing
Canada / Consumer 8 months / Male	Oral / Not provided Not provided	**Choking 1 day Not provided**	

Company comment: Events were most like the result of an aversion to the taste of the compounded suspension. Information provided is too limited for further assessment.

Reviewer's Comment
The information is too incomplete to assess this instance of respiratory arrest. The reviewer agrees with the sponsor that these AEs were more likely the result of an aversion to the taste of the drug product.

2007UW05251	10 mg	**Hypoglycaemia***	Patient had been taking a compounded omeprazole
Canada / HCP 6 months /Male	Oral / 6 months GERD	4 months & 6 months Not provided	suspension and experienced 2 episodes of hypoglycemia requiring hospitalization. Pharmacist considered the event unrelated to "therapy" and indicated that the products used to prepare the suspension were unknown.

Company comment: Hypoglycemia is listed in the USPI. Information provided is too limited for further assessment.

Reviewer's Comments
The reviewer agrees with the sponsor that the information obtained and provided on these two instances of hypoglycemia is too limited for adequate assessment. In addition, hypoglycemia is already listed in the USPI.

2007CG00904	Not provided	**Haemolytic**	Shortly after birth, the infant experienced gastroesophageal
France / HCP 6	Oral / 6	**anaemia* Not**	reflux and began domperidone therapy. Esomeprazole

months / Female	weeks GERD	**provided Not recovered**	and alginic acid/sodium bicarbonate therapies were added the following month. One-month later, pneumococcal conjugate vaccine and diphtheria/tetanus/pertussis/polio/haemophilus/influenzae vaccines) were administered. The following week, domperidone, esomeprazole, alginic acid/sodium bicarbonate therapies were switched to omeprazole and cisapride. Approximately 1-month later, she presented with sudden pallor. Hemoglobin level was 3.7 g/dL. She received a transfusion, corticosteroids, and human immunoglobulin for 4 days. Additional labs showed a very low haptoglobin level and positive Coombs' test with IgG and complement. Hemolytic anemia was diagnosed. Serologies for HIV, hepatitis B and C, Epstein-Barr virus, Mycoplasma pneumoniae, rotavirus and adenovirus were negative. Serologies for cytomegalovirus and Parvovirus B19 were positive for IgG and negative for IgM. Hemoglobin electrophoresis was normal. The following week omeprazole was discontinued. The next day, her hemoglobin was at 9.7 g/dL, fluctuated then dropped down to 4.6 g/dL over 2 weeks. She was transferred the hospital. On admission, cisapride was switched to domperidone. Hemoglobin levels continued to fluctuate from 10.2 g/dL down to 5.6 g/dL over the next 3 weeks.

Company comment: Hemolytic anemia is a listed event in the USPI. Causality assessment is difficult based on information provided. Although all viral serologies were negative, hemoglobin levels continued to fluctuate post-omeprazole withdrawal; thereby bringing into question a possible drug-induced etiology due to omeprazole. Contributions of other concomitant medications, undiscovered underlying conditions, or hereditary disorders must also be considered.

Reviewer's Comments

The reviewer agrees with the sponsor that, due to the incompleteness of the information, it is difficult to make an assessment of causality in this instance of hemolytic anemia. In addition, hemolytic anemia is a listed event in the USPI.

2007SE01245 Denmark / HCP 5 months / Male	Not provided Oral via breast milk / 1- month Not applicable	**Drug exposure via breast milk** **Regurgitation 1 day Not provided**	Mother received omeprazole for hiatal hernia. Report indicates that baby was exposed to omeprazole via breast milk and developed moderate regurgitation the same day. Mother stopped treatment with omeprazole and the baby recovered. Mother restarted treatment and baby again developed regurgitation

Company comment: Acid regurgitation is a listed event in the USPI. Positive de-challenge and re-challenge strengthens a possible causal relationship; however, other maternal dietary factors need to be considered as well. In addition, breast milk only contains very minor amounts of omeprazole and it is unlikely that these would have affected the baby.

Reviewer's Comment

The reviewer believes that this AE of regurgitation was due to the drug.
On the one hand, there was a ***positive de-challenge*** *[when the mother stopped treatment with omeprazole, the baby recovered] as well as a* ***positive re-challenge*** *[when the mother restarted treatment with omeprazole the baby again developed*

regurgitation]. In their comment to this case of regurgitation in a nursing baby, the sponsor notes that breast milk only contains very minor amounts of omeprazole and it is unlikely that these would have affected the baby. This statement, however, is not entirely congruent with the following subsection of the labeling:

> *8.3 Nursing Mothers*
> ***The excretion of esomeprazole in milk has not been studied. However, omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. Because esomeprazole is likely to be excreted in human milk, because of the potential for serious adverse reactions in nursing infants from esomeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenic studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.***

Although this AE is discussed in detail in the current review, the MTL does not suggest revision to the labeling because of the following: 1. acid regurgitation is a listed event in the USPI; 2. as an event, this case of regurgitation in a nursing infant was not assessed as serious; and 3. the wording in the above cited 8.3 Nursing Mothers paragraph is adequate.

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/s/

Hugo Gallo Torres
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MEDICAL OFFICER

Medical Team Leader Recommendations for regulatory action: follow up of our Oct 19, 2007 AE Letter. Materials reviewed included Dec 13, 2007 CR to AE Letter; Jan 14, 2008 4-Month SU; and numerous Labeling revisions requested in Oct 18, 2007 IR Letter.