MEMORANDUM

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

DATE: 3/19/08

FROM: Joyce A Korvick, MD, MPH

DGP/ODE III

SUBJECT: Deputy Division Director Approval Memo
NDA 22-056 (resubmission)

APPLICANT: AstraZeneca LLP

DRUG: Prilosec ® (omeprazole magnesium) for Delayed-Release Oral Suspension (2.5 mg, 10 mg packet)
(Proton Pump Inhibitor)

DIVISON RECOMMENDATION:
I recommend approval of this product for use in adults and pediatric patients ($\geq$ 1 year of age). For pediatric patients the indications include Gastroesophageal Reflux Disease and Erosive Esophagitis. This was discussed with the PERC committee and the Medical Review team after completion of their reviews. This recommendation was agreed on by all internal parties.

Background:
Outstanding issues regarding this NDA at the time of the original review cycle include finalization of package insert and package labeling. Since the omeprazole label is a unified label including adult indications and higher dosing, it was deemed important to finalize the review of the final report of cardiac safety data submitted July 25, 2007. It would be difficult at that time to recommend labeling in pediatric patients 0 to 2 years of age given this potential serious risk. At that time it was thought that, if the review of these studies determined that the risk is low or non-existent, additional labeling negotiations will proceed due to the fact that labeling negotiations at that time were fairly mature but not complete. This could be a two-month resubmission. Labeling recommendations were sent to the sponsor on Oct 17, 2007. These will be addressed in this current cycle.

The final review of cardiac safety was completed and a public announcement was made regarding the findings.

The following is a summary of the activity regarding cardiac safety:

"On December 10, 2007, FDA announced the completion of its review of the submitted adult safety data for the drugs Prilosec (omeprazole) and Nexium (esomeprazole). FDA stated that we continue to believe that long-term use of omeprazole or esomeprazole is not likely to be associated with an increased risk of heart problems and recommends that healthcare providers continue to prescribe and patients continue to use these products in the manner described in the labeling for the two products. Previously, on May 29, 2007, AstraZeneca, the manufacturer of Prilosec (omeprazole) and Nexium (esomeprazole), sent FDA and other regulatory authorities world-wide their preliminary review of new data from two small long-term clinical studies in patients with severe gastroesophageal reflux disease (GERD). The results from the study of Prilosec and analyses from an ongoing study of Nexium raised concerns that long-term use of Prilosec or Nexium may have increased the risk of heart attacks, heart failure, and heart-related sudden death in those patients taking either one of the drugs compared to patients who received surgery. On August 9, 2007 FDA released an "Early Communication of an Ongoing Safety Review" of both Nexium and Prilosec. The agency's initial review determined that there was no increased risk of heart problems associated with long-term use of these two products."

This current submission:
In response to the Agency's Pediatric Written Request of July-1-1999, NDA 19-810/S-74 (Prilosec® capsules) was submitted for treating GERD in patients aged 0-16 years. As a result of a positive review, pediatric exclusivity was granted to the sponsor. In addition, this product was approved only for patients aged 2-16 years due to the concern that the granules of Prilosec® delayed release capsules were too large for children aged 0-2 years.

The current NDA (22-056) was submitted to fulfill the Phase IV commitment made upon the approval of NDA (b) (4), in which the sponsor committed to develop an appropriate formulation for children aged 0-2 years. The granules of the to-be-marketed formulation are the same as those used in manufacturing the Prilosec® OTC tablets (NDA 21-229, oral delayed release tablet, 20 mg base), and are smaller than those in Prilosec® capsules (NDA 19-810).

The studies conducted in children aged 0-2 years (Study 251, Study 292, and Study 250) and Study I-678 in children aged 1-16 years submitted to NDA 19-810 (Prilosec® capsules) are referenced in the current NDA. In the efficacy (Study 251) and pharmacokinetics/ pharmacodynamics (Study 250) studies, patients aged 0-2 years were dosed with a suspension of omeprazole granules of Prilosec® capsule in 8.4% $NaHCO_3$ (2mg omeprazole/ml). A relative bioavailability study (Study D9586C00002) was submitted to bridge the clinical and to-be-marketed formulations, in the current NDA.

Use of Omeprazole for the Treatment of GERD:
I have attached my previous review as appendix A to this review and will only address labeling issues related to: the indication, age range, safety, clinical studies and dosing and administration. As I indicated in my previous review, the language in other sections of the label was acceptable.

(b) (4)

(b) (4) recommended for 1 year and above. This integrates the availability of this formulation with the data available for the determination of efficacy for the indications. I will outline my reasoning below. In summary, there are not adequate and well controlled studies in the youngest age group and symptoms of "symptomatic GERD" (gastroesophageal reflux disease) cannot be extrapolated from the adults in this age group nor can this age group be expected to express these symptoms.

As a result of June 11, 2002, Pediatric-Gastroenterology Advisory Committee (AC) recommendations and much discussion between this division, the Pediatrics Division and various sponsors regarding Written Requests for this indication, it is the division's position that efficacy may be extrapolated to 1 year of age from adult efficacy data for the indication of GERD. Symptomatic GERD in the adult population is approved based upon symptomatic relief. This cannot be the case with the pediatric population under 1 year of age. Study 251 was the pivotal study presented by the sponsor in support of this indication. It was originally submitted and reviewed in 2001. It appeared adequate at that time to the medical reviewer, Sheldon Kress. As I mentioned the AC was convened after this date, and Written Requests have been developed for this class of drugs since that time.

Study 251 included 1 pediatric patient 0-1 month of age, 92 pediatric patients 1-11 months of age and 10 pediatric patients 1-2 years of age. It was a study in pediatric patients with reflux, no endoscopy was performed. The primary endpoint was the number of vomiting episodes in the last 2 days of the 8 week treatment period. As the pediatric division reminds us, vomiting or "spitting" is not an adequate endpoint measure, primarily because it is difficult to quantitate and also difficult for the "parent" (reporter) to accurately report. This was also an uncontrolled study.

What might have been useful to demonstrate efficacy in 2001 is not so now. (b) (4)

(b) (4)

(b) (4)

Finally, the long term safety in the youngest age group, which is most vulnerable, is unknown. Gastric acid is important to good gastrointestinal health (microbial environment) and absorption of calcium. It is important that more information in this

population is gained. As it was difficult to design efficacy studies in this age group, it was also agreed that labels should carry the warning that efficacy and safety is not demonstrated.

Pediatric labeling:

Dosing Administration Section:
Sponsor Proposal-

2.7 Pediatric Patients

For the treatment of GERD and maintenance of healing of erosive esophagitis, the recommended daily dose for pediatric patients (b) (4) 1 to 16 years of age is as follows:

Patient Weight	Omeprazole Daily Dose
(b) (4)	
5 < 10 kg	5 mg
10 < 20 kg	10 mg
≥ 20 kg	20 mg

On a per kg basis, the doses of omeprazole required to heal erosive esophagitis in pediatric patients are greater than those for adults.

FDA Recommendation:
Delete row for patient weights (b) (4) This was discussed with the PERC committee, who felt that if the initiation was for pediatric patients 1 year old and above, this weight category did not apply.

Sponsor Proposal:

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience with PRILOSEC Monotherapy

The clinical trial safety profile in pediatric patients who received PRILOSEC Delayed-Release Capsules was similar to that in adult patients. Unique to the pediatric population, however, adverse reactions of the respiratory system were most frequently reported in both the 1 to 2 and 2 to 16 year age groups (75.0% and 18.5%, respectively). Similarly, fever was frequently reported in the 1 to 2 year age group (33.0%), and accidental injuries were reported frequently in the 2 to 16 year age group (3.8%).[*See Use in Specific Populations (8.4)*]

FDA Recommendations:
It was important for the label to contain information on the population for which the drug is indicated. (b) (4)
(b) (4)
(b) (4). For these reasons the PERC recommended including only data from pediatric patients 1 year and older.

Clinical Studies Section:
The sponsor proposed the Clinical Studies section be expanded to include the 1-2 year group under the symptomatic GERD indication. This was based upon studies as well as extrapolation from adult clinical trials data for efficacy. As described in section 8.4 (Pediatric Use):

> "Use of PRILOSEC in pediatric and adolescent patients 1 to 16 years of age for the treatment of GERD is supported by a) extrapolation of results, already included in the currently approved labeling, from adequate and well-controlled studies that supported the approval of PRILOSEC for adults, and b) safety and pharmacokinetic studies performed in pediatric and adolescent patients. [*See Clinical Pharmacology, Pharmacokinetics, Pediatric* for pharmacokinetic information *(12.3)* and *Dosage and Administration (2), Adverse Reactions (6.1) and Clinical Studies, (14.6)]*. The safety and effectiveness of PRILOSEC for the treatment of GERD in patients <1 year of age have not been established. The safety and effectiveness of PRILOSEC for other pediatric uses have not been established.

FDA Recommendations:
As noted before it was the strong recommendation of the PERC committee that information for patients under the age of one year not be included in this label (b) (4) (b) (4)

The sponsor was agreeable to these changes.

For final labeling refer to the approval letter with attached final label.

APPENDIX A:

MEMORANDUM

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

DATE: 10/18/07

FROM: Joyce A Korvick, MD, MPH

DGP/ODE III

SUBJECT: Deputy Division Director Approvable Comments
NDA 22-056

APPLICANT: AstraZeneca LLP

DRUG: Prilosec ® (omeprazole magnesium) for Delayed-Release Oral Suspension
(Proton Pump Inhibitor)

DIVISION RECOMMENDATION:
This application proposes the use of delayed release oral suspension of omeprazole magnesium for the short-term treatment of pediatric patients (b) (4) to 2 years old) with GERD (b) (4)

(b) (4)

The medical review team has recommended an approvable action pending resolution of the serious cardiac safety issues that have arisen external to this NDA. I am in agreement with this recommendation. (Refer to early communication posted on FDA website http://www.fda.gov/cder/drug/early_comm/omeprazole_esomeprazole.htm).

Outstanding issues regarding this NDA include finalization of package insert and package labeling. Since the omeprazole label is a unified label including adult indications and higher dosing, it will be important to finalize the review of the final report of cardiac safety data submitted July 25, 2007. It would be difficult at this time to recommend labeling in pediatric patients 0 to 2 years of age given this potential serious risk. If the review of these studies determines that the risk is low or non-existent, additional labeling negotiations will need to proceed due to the fact that labeling negotiations at this time are fairly mature but not complete. This could be a two-month resubmission. Labeling recommendations were sent to the sponsor on Oct 17, 2007. These will be addressed in the next cycle.

Background:

In response to the Agency's Pediatric Written Request of July-1-1999, NDA 19-810/S-74 (Prilosec® capsules) was submitted for treating GERD in patients aged 0-16 years. As a result of a positive review, pediatric exclusivity was granted to the sponsor. In addition, this product was approved only for patients aged 2-16 years due to the concern that the granules of Prilosec® delayed release capsules were too large for children aged 0-2 years.

The current NDA (22-056) was submitted to fulfill the Phase IV commitment made upon the approval of NDA (b) (4) in which the sponsor committed to develop an appropriate formulation for children aged 0-2 years. The granules of the to-be-marketed formulation are the same as those used in manufacturing the Prilosec® OTC tablets (NDA 21-229, oral delayed release tablet, 20 mg base), and are smaller than those in Prilosec® capsules (NDA 19-810).

The studies conducted in children aged 0-2 years (Study 251, Study 292, and Study 250) and Study I-678 in children aged 1-16 years submitted to NDA 19-810 (Prilosec® capsules) are referenced in the current NDA. In the efficacy (Study 251) and pharmacokinetics/ pharmacodynamics (Study 250) studies, patients aged 0-2 years were dosed with a suspension of omeprazole granules of Prilosec® capsule in 8.4% $NaHCO_3$ (2mg omeprazole/ml). A relative bioavailability study (Study D9586C00002) was submitted to bridge the clinical and to-be-marketed formulations, in the current NDA.

II. Discipline Review summary and commentary:

a. SEALD:

This label was presented in PLR format in addition to the proposed scientific changes proposed relating to the new formulation. The SEALD team had extensive revisions to this lengthy label which were sent to the sponsor on 11/18/2007. In addition, there were a few technical recommendations from the scientific reviewers. These changes will need to be and finalized and agreed upon in the resubmission of this application.

b. Chemistry:

The proposed product is a sachet of excipient granules and delayed release omeprazole pellets for oral suspension containing either 2.5 or 10 mg of omeprazole (magnesium). The chemistry division found the submission acceptable for approval, pending resolution of minor chemistry labeling issues. The EA was granted a FONSI. The inspection of the manufacturing sites was "acceptable". There are no outstanding issues.

c. Pharmacology/Toxicology:

No new information was submitted, there are no new issues. This NDA was found approvable pending labeling revisions into new PLR format.

d. Clinical Pharmacology:

The new formulation was found not to be bioequivalent by the strict definition, but comparable. The final recommendation was acceptable and the clinical pharmacology team recommended labeling.

The follow is a summary of the major points supporting the acceptability of this formulation by the clinical pharmacology reviewer.

"**Bioavailability comparison** (Study D9586C00002)**:**
A three-way cross-over study, which compared the oral bioavailabilities (BA) of three formulations, is submitted to this NDA. The three formulations compared are Prilosec® capsule (Omeprazole 20mg with 200 ml water), the clinical formulation (oral suspension of Prilosec® capsule granules containing 20 mg omeprazole in 10 ml 8.4% NaHCO3 followed by an intake of 190 ml water), and the to-be-marketed formulation containing 20mg omeprazole (in 30 ml water followed by an intake of 170 ml water). The dose regimen was 20-mg of omeprazole given once daily for 5 days. The Prilosec® capsule and clinical formulation contained omeprazole while the to-be-marketed formulation contains omeprazole magnesium. The mean PK parameters for the three formulations on Day 1 are presented in Table 1. Higher concentrations were observed on Day 5 for all formulations (see individual study review).

Table 1. Estimated geometric means and 90% CIs of AUC∞, Cmax, and AUCt from the day 1 dose in healthy adults

Variable	Treatment	N	Estimate	90% CI	
				Lower	Upper
AUC (ng·h/mL)	Sachet	19	348	266	456
	Suspension	24	388	298	506
	Capsule	20	400	305	523
C_{max} (ng/mL)	Sachet	23	190	150	240
	Suspension	24	392	310	496
	Capsule	24	215	170	271
AUC_t (ng·h/mL)	Sachet	23	323	245	425
	Suspension	24	374	285	492
	Capsule	24	359	273	472

Note: Sachet: the to-be-marketed formulation (granules from OTC tablet suspended in water); clinical formulation: capsule granules suspended in 8.4% sodium bicarbonate solution; and capsule: whole capsule (administered with water).

T1/2 was 0.71-0.84 hr for all formulations while tmax was 0.39 hr for 20 mg clinical formulation, 1.72hr for capsule, and 2.14 hr for the to-be-marketed formulation.

Comparisons (ratios) of Day-1 PK parameters between formulations are shown in Table 2. Although higher concentrations were observed on Day 5, similar trend between formulations was observed using the Day 5 data.

Table 2. Comparison of single dose PK Parameters (Day 1 data from 5 days of administration)

Parameter	to-be-marketed formulation /clinical formulation	clinical formulation/ whole capsule	to-be-marketed formulation / whole capsules
	Ratio (90% CI)	Ratio (90% CI)	Ratio (90% CI)
AUC_{∞} (ng*h/ml)	0.896 (77.9%-103.1%)	0.971 (84.6%-111.5%)	0.871 (75%-101.0%)
AUC_{0-t} (ng*h/ml)	0.863 (75.2%-99.1%)	1.043 (91.1%-119.4%)	0.901 (78.5%-103.3%)
C_{max} (ng /ml)	0.484 (39.9%-58.6%)	1.827 (151.2%-220.8%)	0.884 (72.9%-107.1%)

The results showed that the to-be-marketed formulation was not bioequivalent to the clinical formulation (Table 2). The AUC∞ of the to-be-marketed formulation was lower than that of the clinical formulation, and the 90% CI of the geometric mean ratio of AUC (77.9%-103.1%) lied outside the range 80%-125% (bioequivalence acceptance criteria). The Cmax value of the to-be-marketed formulation was much lower (ratio: 0.484) than that of the clinical formulation with the 90% CI of the geometric mean ratio being 39.9%-58.6%. It should be noted that the Cmax ratio of the to-be-marketed formulation versus capsule was 0.884 with the 90% CI of the geometric mean ratio being 72.9%-107.1%.

A discussion with the clinical division revealed that dosing with sodium bicarbonate in children aged 0-2 years is undesirable because of safety concerns. Additional studies comparing the to-be-marketed and clinical formulations using sodium bicarbonate in administering omeprazole for both formulations was thus not pursued. After OCP internal discussions, the results of the bridging study are considered acceptable based on the following reasons.

- Study D9586C00002: Sodium bicarbonate was used in administering the clinical formulation while water was used in administering the to-be-marketed formulation and whole capsules. The presence of sodium bicarbonate facilitated dissolution and absorption of omeprazole, thereby causing a higher Cmax and shorter Tmax for the clinical formulation compared to the to-be-market formulation and whole capsules.

- Study I-678: The granules of approved capsule sprinkled in juice or yogurt, but not in sodium bicarbonate, was effective in treating GERD in children aged 0-16. Although there were few patients younger than 2 years old in this study, the study demonstrated that capsule granules without sodium bicarbonate was efficacious in treating children with GERD. As such, the much higher Cmax observed with the clinical formulation was not essential for the efficacy

- Literature: Omeprazole inhibits gastric acid secretion via a noncompetitive antagonism of the H+/K+-ATPase (proton pump) in the parietal cell secretory membrane through the formation of an irreversible linkage of a disulfide bond with the proton pump. Suppression of acid secretion was associated with the AUC of omeprazo1e (Clin Pharmacokinet 20 (l): 38-49. 1991), which could be described by an Emax model. There was no correlation between the temporal concentrations and pharmacodynamic effect.

- Study D9586C00002 shows the following: The mean single-dose AUC of the to-be-marketed formulation was comparable to those of the clinical formulation. The mean AUC, Cmax and tmax of the to-be-marketed formulation were comparable to those of the approved capsules.

Based on the above discussion, the results of the study submitted to this NDA are considered acceptable for the fulfillment of the Phase IV commitment.

Food effect: In the May-2-2007 amendment in response to our April-23-2007 request for the food effect pharmacokinetic data, the sponsor indicated that the to-be-marketed formulation are only to be administered before meals, which is the same as that indicated in the labeling of Prilosec® capsules. Therefore, a food effect study was not conducted. In the approved NDA 19-810 labeling, no food effect or study is mentioned. After internal discussions, it is concluded that the sponsor's response is acceptable.

DSI report: The DSI report cited several analytical deficiencies at analytical CRO site (b) (4). The majority were documentation deficiencies. There are two major issues identified: light protection during analytical procedure and no stability raw data for omeprazole including long-term, bench top, and freeze thaw stability data. Upon our request, the sponsor satisfactorily addressed the issues.

e. Efficacy/Safety:

Study 251 was a Multicenter, Randomized, Single-Blind Study to Evaluate Omeprazole for the Treatment of Clinically Diagnosed Gastroesophageal Reflux Disease (GERD) in Pediatric Patients Ages 0 months through 24 months, Inclusive.

Selection of Doses:
Previous clinical trials in a pediatric population showed that omeprazole, administered as 0.7 mg/kg through 1.4 mg/kg, was clinically effective in the majority of those patients considered to be healed. The doses selected for this study, 0.5 mg/kg, 1.0 mg/kg, and 1.5 mg/kg incorporate those doses already proven to be effective. The 20 mg capsule, which is currently approved by the Food and Drug Administration (FDA), was used to prepare a 2 mg/mL bicarbonate suspension to facilitate appropriate dosing. All patients were dosed with omeprazole suspension.

There were several primary and secondary endpoints developed in this study. A key evaluation was requested by the MO during the review which was the proportion of patients who had decreased vomiting/regurgitation episodes.

The results are as follows:
1.5 mg/kg = 22/33 (67%);
1.0 mg/kg = 23/33 (70%);
0.5 mg/kg = 23/34 (68%);
Total 68/100 (68%).

Secondary endpoints included severity of overall vomiting/regurgitation of GERD, severity of overall pain-related symptoms of GERD, and Physician's Global Assessment. These were supportive of the overall demonstration of effectiveness in the pediatric population.

The medical reviewer concluded that omeprazole effectively decreased the number of vomiting/regurgitation episodes and improved the overall GERD-related symptoms.

Safety:

The patient population consisted of 106 subjects. Among them, the data of 100 (ITT)/96 (PP) were used for efficacy analysis. Seventy-nine patients completed the 8-week study. Three dose levels (0.5, 1.0, and 1.5 mg/kg, once daily for 8 weeks) were studied. The proposed market dose is 2.5 mg or 10 mg once daily for up to 8 weeks.

The profile of drug-related adverse events of omeprazole in pediatric patients 0 to 2 years old is similar to that of 12 to 18 years old and adults. Gastrointestinal disorders (vomiting and diarrhea) appeared to be the most common treatment-related adverse events.

Overall the conclusion is that omeprazole was safe and well tolerated in the pediatric GERD patients aged 0.7 to 22 months old. There was no death. There were 6 treatment-related dropouts due to adverse events (exacerbation of GERD symptoms, vomiting, and crying). The most common adverse events reported from this population were consistent with the known adverse events of omeprazole. In addition, there were no clinically important findings or trends in hematology, clinical chemistry, vital signs, or physical examination observed across treatment groups.

The medical officer concluded that based upon the comparable bioavailability studies (Study 250 and Study 9586C0002) and the safety and efficacy study (Study 251) in the pediatric patients, NDA 22,056 is recommended for Approvable action pending resolution of labeling and potential cardiac safety issues in adults currently under review.

III. Labeling:

It is important to note that this current label includes both adult and pediatric labeling and two different formulations. The Delayed-Release capsule is currently approved for use in adults and children (2-16 years).

The adult labeled indications include short-term treatment of active duodenal ulcer, *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence, gastric ulcer, GERD, and maintenance of healing of erosive esophagitis, and pathological hypersecretory conditions.

The pediatric indications which have been previously approved include Gastroesophageal reflux disease, and maintenance of healing of erosive esophagitis for children 2 years to 16 years of age.

For adult patients who could not swallow the capsule, there have been studies and it is labeled for use by opening the capsule and sprinkling it on applesauce.

This new formulation was specifically developed for pediatric use in patients aged 0-2 years. Bioequivalance studies bridging these formulations were conducted in adults. While strict bioequivalence was not demonstrated, the clinical data in children supported the clinical activity of this formulation.

It may be that adults who cannot swallow the capsule may have this new formulation administered to them for all of the indications currently approved in adults. Thus, it will be important to further explore this "sameness" issues. The clinical pharmacology team looked at this issue and comment as follows:

"The current label for Prilosec indicates that the granules in the delayed release capsule can be placed in applesauce and given this way if there is difficulty swallowing the intact capsule. No change in dosage is suggested. The clin pharm portion clearly indicates that in a study in adults the Cmax decreased by 25% when the capsule granules were given this way, and that the clinical significance of this is unknown. For AUC the label says there is not a significant difference in AUC, however, it does not say what the degree of difference is. Given the magnitude of the Cmax change it is likely that the change in AUC is on the order of 10% or so, which actually would place it closer to the new Sachet formulation. Thus it would seem to me that the interchange of the Sachet for the Delayed release capsules (that would otherwise be opened and put into applesauce) would be a wash, ie., the net pharmacologic effect would be the same."

Therefore, unintended use in adults should not present an efficacy issue for the other indications.

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/s/

Joyce Korvick
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MEDICAL OFFICER
d.dir approval letter