OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-056	Submission Date(s): December, 20, 2006, March 15, 2007, May 2, 2007, Aug 29, 2007
Brand Name	Prilosec®
Generic Name	Omeprazole Magnesium
Reviewer	PeiFan Bai, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Gastroenterology Products
Sponsor	AstraZeneca LP
Submission Type; Code	Original
Formulation; Strength(s)	PRILOSEC® (omeprazole magnesium) FOR DELAYED-RELEASE ORAL SUSPENSION 2.5 mg omeprazole /packet and 10 mg omeprazole/ packet
Indication	Symptomatic and/or endoscopically proven Gastroesophageal Reflux Disease (GERD)

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1 Executive Summary

1.1 Recommendation

This submission fulfills the sponsor's Phase IV commitment to develop an appropriate formulation for patients aged 0-2 years. The application is acceptable from the clinical pharmacology perspective provided the labeling comments are adequately addressed by the sponsor.

1.2 Phase IV Commitments

This NDA was submitted to fulfill the Phase IV commitment made at the time of approval of NDA 19810/S-74.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Product: Prilosec® for delayed-release oral suspension (to-be-marketed formulation) contains omeprazole magnesium. Based on the amount of omeprazole, there are two strengths, 2.5 mg and 10 mg. Omeprazole, a racemic mixture, is a proton pump inhibitor (PPI) that suppresses gastric acid secretion by specifically inhibiting the H/K+-ATPase of gastric parietal cells. The proposed indication is symptomatic and/or endoscopically proven Gastroesophageal Reflux Disease (GERD) in patients aged 0-2 years.

Regulatory 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. Pediatric exclusivity was granted to the sponsor following the submission of NDA 19-810/S-74. NDA 19-810/S-74 was approved only for patients aged 2-16 years due to the Agency's concern that the granules of Prilosec® delayed release capsules were too large for children aged 0-2 years. The current NDA was submitted to fulfill the Phase IV commitment made upon the approval of NDA (b) (4) in which the sponsor was 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 21229, oral delayed release tablet, 20 mg base), but 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% NaHCO3 (2mg omeprazole/ml). To this NDA, a relative bioavailability study (Study D9586C00002) was submitted to bridge the clinical and to-be-marketed formulations.

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 thegeometric 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 non-competitive 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 (I): 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.

2 Question Based Review

2.1 General Attributes

2.1.1 What are the components and composition of Prilosec® Delayed-Release Granules for Oral Suspension?

Prilosec® (omeprazole magnesium) for delayed-release oral suspension was developed for children aged 0-24 months. The proposed formulation contains two types of granules, granules containing omeprazole magnesium and excipient granules. The active granules containing omeprazole magnesium are the same as those used in manufacturing the Prilosec® OTC tablets, 20 mg (NDA 21-229).

Table 3. components and composition of Prilosec® Delayed-Release Granules for Oral Suspension

Components (name according to AstraZeneca)	Quantity (mg/sachet)		Function	Standard
	2.5 mg strength	10 mg strength		
Omeprazole pellets[a]				
Omeprazole (corresponding to omeprazole magnesium[b])	2.5	10	Active substance	AstraZeneca
Glyceryl monostearate	(b) (4)			
Hydroxypropyl cellulose				
Hydroxypropyl methylcellulose	(b) (4)			
Magnesium stearate				
Methacrylic acid copolymer type C				
Polysorbate	(b) (4)			
	(b) (4)			
Sugar spheres	(b) (			
Talc				
Triethyl citrate				
	(b) (4)			
Weight of omeprazole pellets				

2.1.2 What is the proposed indication of Prilosec® Granules for Delayed-Release Oral Suspension?

(b) (4) treatment of gastroesophageal reflux disease (GERD), (b) (4) healing of erosive esophagitis. The proposed daily dose by body weight for pediatric patients (b) (4) 5 mg for 5 to <10 kg, 10 mg for 10 to <20 kg, and 20 mg for ≥ 20 kg.

2.1.3 What is the proposed mechanism of action of Prilosec?

Omeprazole inhibits gastric acid secretion via a selective and (b) (4) antagonism of the H+/K+-ATPase (proton pump) in the parietal cell secretory membrane (b) (4)

2.1.4 What is the exposure-response relationship for omeprazole?

For the response/exposure relationship of omeprazole, there are several publications suggesting that the AUC correlated with pharmacodynamic responses. The data presented in figures 1-4 were taken from Gut, 1983, 24, 270-276. The Cmax after oral administration occurred less than 1 hr (Fig 1); however, the inhibitory effect of omeprazole on intravenous pentogastrin-induced acid secretion lasted for more than 4 hrs (Fig 2).

As shown in Figure 3, studies of different doses of omeprazole and inhibition of acid secretion showed that the response/exposure relationship followed an Emax model of Hill function with γ~1. The exposure examined was AUC. Figure 4 showed that single dose was not enough for, but continued exposure to omeprazole from multiple doses is needed for, achieving the maximal efficacy. In another study, a sigmoid relationship was observed between the response and dose (Fig. 5). Similar observation was made for lansoprazole (Ref 4).

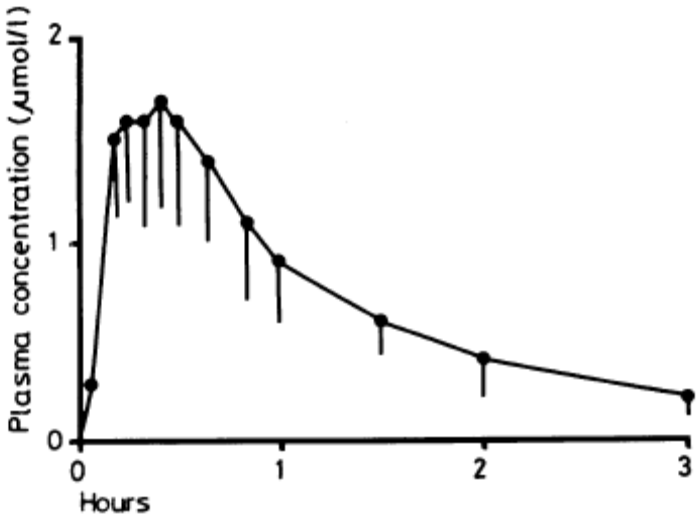


Figure 1. Plasma concentrations of omeprazole in six healthy subjects given 40 mg orally. Values are mean ± 1 SEM. During the second hour after omeprazole administration the acid response was reduced by 51±9% and 86±4% respectively, with the 20 and 40 mg doses

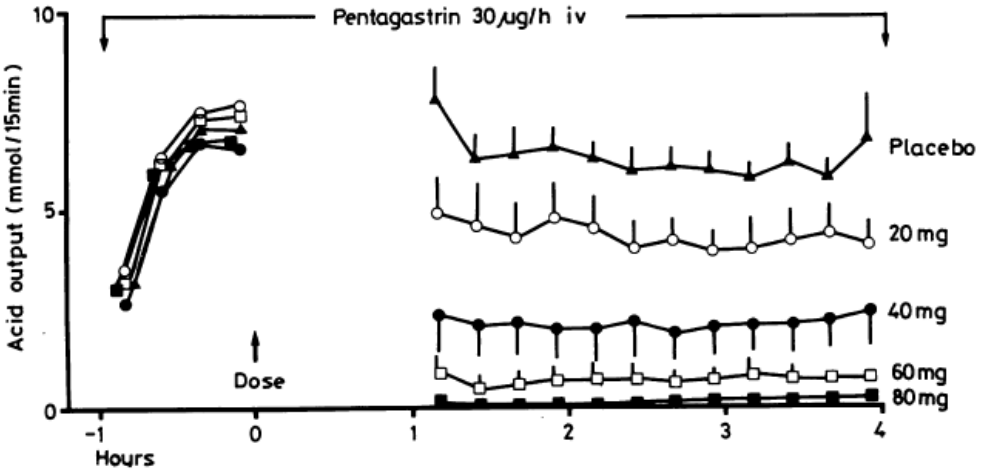


Figure 2. Effect of oral omeprazole on pentagastrin induced acid secretion in six healthy subjects. Values are mean ± 1 SEM.

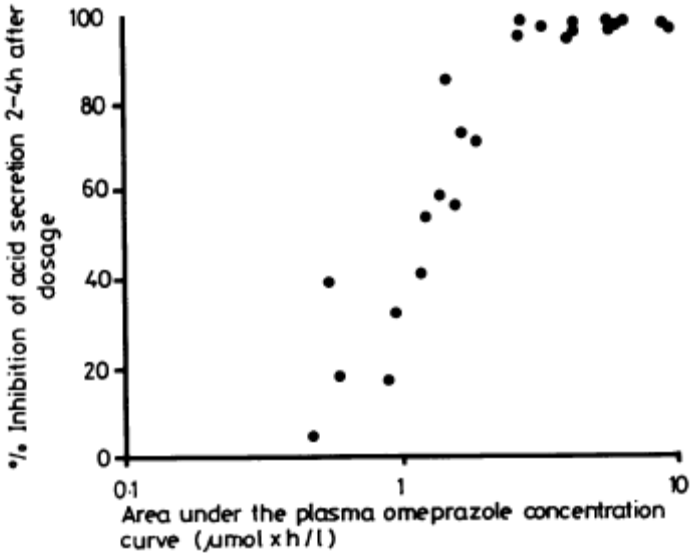


Figure 3. Relationship between percent inhibition of pentagastrin (30 µglh intravenously) induced acid secretion during the second to fourth hour after drug administration and the area under the plasma omeprazole concentration-time curve. Correlation coefficient = 0.93, p<0 001, n=24. Ref: Gut, 1983, 24, 270-276

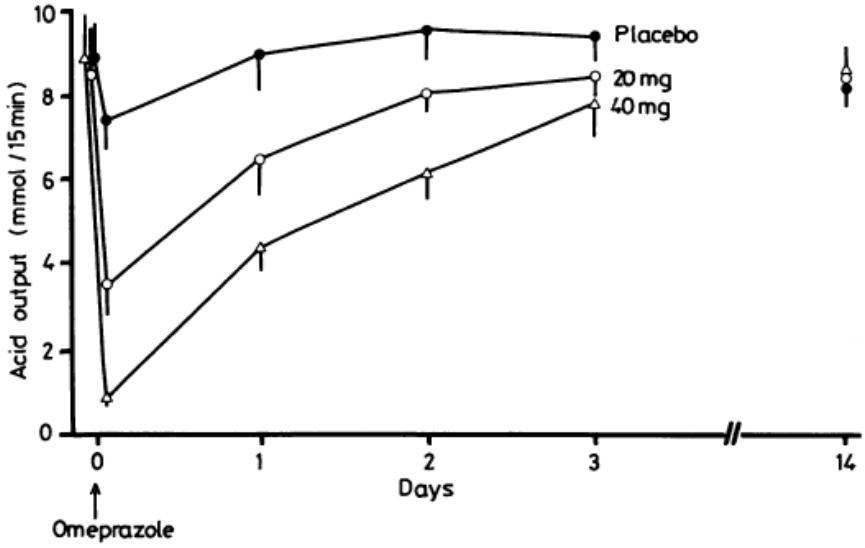


Figure 4. Duration of action of two different single oral doses of omeprazole in six healthy subjects estimated by repeated measurements of maximal responses to the one hr infusion of 91 µg pentagastrin. Values are mean ± 1 SEM.

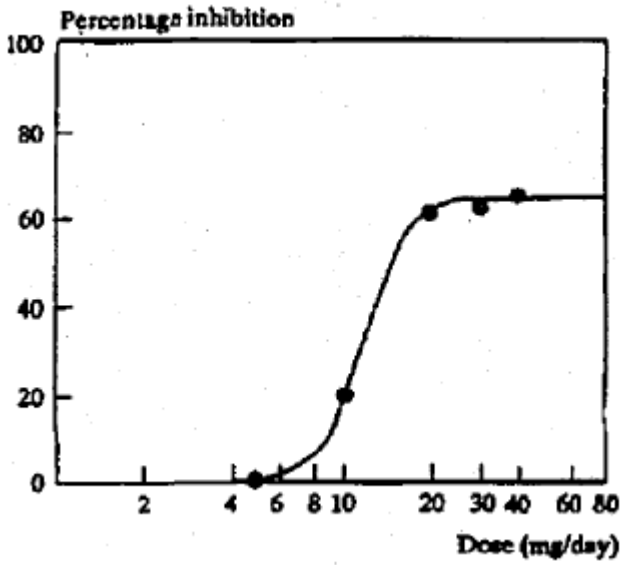


Figure 5 The dose-response curve for repeated once daily intravenous omeprazole (Lind et al. 1986). This was taken from (Clin Pharmacol Biopharm Review of 21-229 by Suliman I. Al-Fayoumi for the submissions dated 1/28/2000, 8/16/2000 and 11/1/2000) (Scand J Gastroenterol. 1986 Oct;21(8):1004-10; Scand J Gastroenterol Suppl. 1986;118:105-7.)

Reviewer's comments: The results published in Gut, 1983, 24, 270-276 are consistent with the report by Tolman et al (J Clin Gastroenterol 24(2): 65-70, 1997) in that the AUC of omeprazole correlated with the percent of inhibition on acid secretion and the mean 24-hr gastric pH. The maximal inhibition (66%) of gastric acid secretion occurred approximately 6 hrs after a single oral dose (30 mg) of encapsulated enteric-coated granules of omeprazole (ref 1). After one-week administration of daily 30 mg, the basal acid output was 100% inhibited. Omeprazole had a mean tmax of approximately 1.7 hrs after oral administration of omeprazole capsules, a half-life of 0.7-0.8 hrs, and AUC profiles close to completion approximately 6-7 hours after oral administration.

2.1.5 What are the proposed dosage and route of administration?

The product is available in 2 strengths of omeprazole, 2.5 mg and 10 mg, for oral suspension. The total contents of a proposed dose, is added to water to form a viscous suspension prior to use. For reconstitution of the 2.5 mg strength 5 mL of water is used and for the 10 mg strength 15 mL of water is used. The proposed daily dose by body weight is 2.5 mg for 2.5 to 5 kg, 5 mg for 5 to 10 kg, 10 mg for 10 to 20 kg, and 20 mg for > 20 kg.

2.1.6 What is the regulatory background?

A. The FDA issued a PWR for Prilosec on July 1, 1999. The key points stated in the PWR are single and multiple dose studies in the pediatric population ages 0-24 months, as listed below.

1. PK, PD and safety study in at least 80 patients of both sexes with symptomatic and/or endoscopically proven GERD.

2. Clinical outcome and safety evaluation of at least 80 patients of both sexes with symptomatic and/or endoscopically proven GERD.

B. In response to the PWR, the firm submitted NDA 19-810/S-074.

* NDA 19-810/S-74 for the pediatric labeling for the age range of 0-16 years was submitted Dec. 22, 2000 (based on the Written Request for pediatric studies issued by FDA). The 6-month exclusivity was granted in May 2001.

* The formulation submitted to NDA 19-810 was Prilosec delayed-release capsules. The clinical efficacy studies submitted to NDA 19-810/S-074 employed dosing methods of sprinkling the clinical formulation on the yogurt, or suspending clinical formulation in sodium bicarbonate or in juice.

* The supplement was found approvable on Oct 22, 2001. (b) (4)

(b) (4)

* NDA 19-810 was only approved for children aged 2-16 years. The approval of 19-810/S-74 included a Phase IV commitment. For the Phase IV Commitment, the sponsor was committed to the development of an age-appropriate formulation of Prilosec for patients 0-2 years of age. The Agency recommends that for this pediatric formulation the enteric coating of the granules remain intact before oral drug administration.

* In response to the Agency's request, the sponsor submitted a commitment statement on April 12, 2001. This formed the basis of this NDA (22-056) submission.

2.2 General Clinical Pharmacology

2.2.1 What efficacy and pharmacokinetic studies related to the pediatric population aged 0-24 months were submitted to NDA 19-810?

The pharmacokinetic, efficacy and safety studies of omeprazole magnesium for children aged 0 to 2 years, which were submitted to NDA 19810/S-074, and the administration methods used in these studies, are listed below:

1. Study 251, "A multicenter, randomized, single-blind study to evaluate omeprazole for the treatment of clinically diagnosed GERD in pediatric population aged 0 months through 24 months, inclusive." In this study, the clinical formulation was the granules of Prilosec® delayed release capsule suspended in 8.4% sodium bicarbonate solution. Three doses of 0.5 mg/kg, 1 mg/kg, and 1.5 mg/kg of omeprazole were administered in 8.4% sodium bicarbonate (2 mg/ml solution). N=79.

2. Study 292, "A multicenter, retrospective study to evaluate the effect of multiple doses of omeprazole on gastric or esophageal pH in a pediatric population (aged 0 months to 24 months)." It is not clear how omeprazole granules were administered in this study based on the previous review by Dr. Scheldon Kress. N=43.

3. Study I-678, "Omeprazole in children with reflux esophagitis-an open-dose finding study and an evaluation of the safety and efficacy during maintenance treatment (Ages 1 through 16)." There were only 2 patients younger than 2 years old. Omeprazole was given as intact capsule, or in fruit juice or yogurt (or by gastrostomy tube where necessary). The normalized median dose was 1 mg/kg (1.3 mg/kg, 1.1 mg/kg and 0.7 mg/kg) and total daily dose ranged from 7.5 mg to 80 mg.

4. Study 250, "Pharmacokinetic and pH assessment study to evaluate single and multiple doses of omeprazole in a pediatric population ages 0-24 months, inclusive." Three doses of 0.5 mg/kg, 1 mg/kg, and 1.5 mg/kg of omeprazole were administered by suspending the granules of Prilosec delayed release capsule in 8.4% sodium bicarbonate solution (clinical formulation). Twenty five subjects participated in the study.

2.2.2 What are the design features of the submitted study used to support the fulfillment of Phase IV commitments?

The Phase IV commitment states that "Commitment to the development of an age-appropriate formulation of Prilosec for pediatric patients 0-2 years of age." The Agency recommended that this pediatric formulation be one in which the enteric coating of the granules remains intact before oral drug administration.

Based on the fact that the Phase IV commitment did not require a bioequivalence study, a relative bioavailability study is deemed acceptable.

The design features of the submitted study are described below.

In the bridging study, there were two differences between the clinical and to-be-marketed formulations: the media used in omeprazole administration and the salt form of omeprazole. The clinical formulation of omeprazole 20 mg was administered in 10 ml 8.4% NaHCO3 followed by an intake of 190 ml water while the to-be-marketed formulation of omeprazole 20 mg was administered in 30 ml water followed by an intake of 170 ml water. Note that in the pivotal clinical study in patients aged 0-2 years (Study 251), the clinical formulation was administered by suspending Prilosec capsule granules in 10 ml 8.4% NaHCO3 (2 mg/ml) .The other difference was that the to-be-marketed formulation contained omeprazole magnesium while the clinical formulation contained omeprazole.

The submitted study is an open-label, randomized, three-way crossover bioavailability study in which healthy male and female subjects under fasting conditions received 5 days of repeated doses of omeprazole 20mg, either in to-be-marketed formulation, clinical formulation or approved Prilosec delayed release capsule (NDA 19-810/S-74).

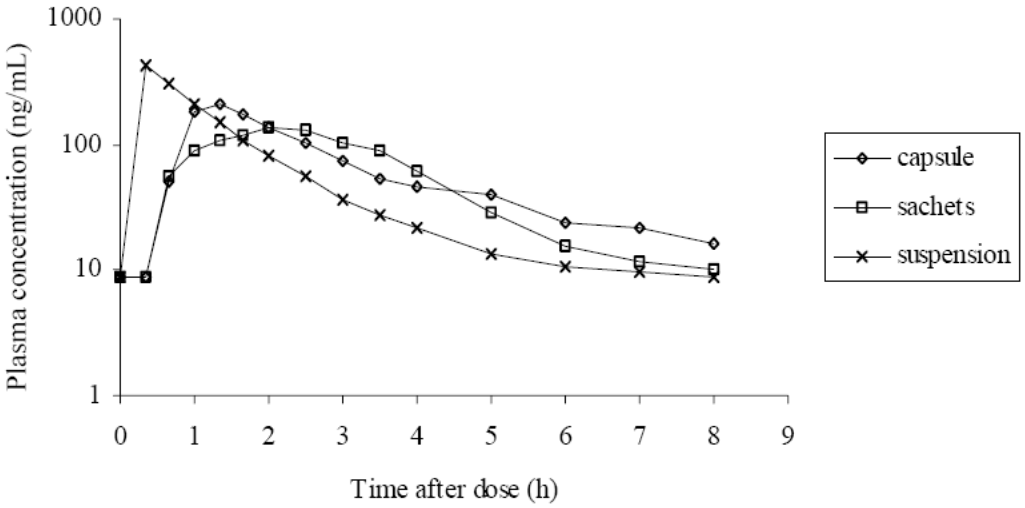
Days 1 and 5: The subjects arrived at the study site in the morning of study days 1 and 5 in each treatment period. They were instructed to abstain from all food and liquid from 22:00 pm on the evening before. On study days 1 and 5, blood samples for pharmacokinetic assessment were collected before and at selected intervals over 8 hours after intake of the investigational products.

Days 2, 3, and 4: The subjects arrived fasting at the study site in the morning of study days 2, 3, and 4 in each treatment period. They were instructed to abstain from all food and liquid during 4 hours before administration of the investigational product on study days 2, 3, and 4. The washout period between each treatment period was 13 days.

2.2.3 What is the relative bioavailability of the to-be-marketed formulation compared to the approved capsule (NDA 19-810) or clinical formulation?

The clinical formulation consisted of granules of the approved capsule suspended in 8.4% sodium bicarbonate for administration. To-be-marketed formulation and capsules were administered in water. For all three formulations, the total volumes of water used were 200 ml.

Pharmacokinetic results



Note: Sachet: the to-be-marketed formulation (suspended in water), suspension: clinical formulation (suspended in a sod. bicarbonate solution), and capsule: whole capsule (administered with water).

Table 4. The relative bioavailability of the to-be-marketed formulation as compared to the clinical formulation and capsule.

	AUCt (ng *h/ml)	Bioavailability (%) relative to clinical formulation	Bioavailability (%) relative to capsule	N
to-be-marketed	323	90%	90%	19
clinical formulation	374	100%		24
Capsule	359		100%	20

Table 5. Comparison of the PK parameters between the to-be-marketed and clinical formulations.

	N	Point Estimate	90% CI
AUC∞ (ng * h/ml)	19/24	0.896	77.9%-103.1%
Cmax (ng/ml)	23/24	0.484	39.9%-58.6%
AUCt(ng * h/ml)	23/24	0.863	75.2%-99.1%

The pivotal efficacy study (study 251) was performed in the age group of 0-24 months and clinical formulations were administered in 8.4% sodium bicarbonate at the dose of 0.5 mg/kg, 1 mg/kg, or 1.5 mg/kg. Based on the 90% CI of bioequivalence (BE) acceptance criteria of 80%-125%, the to-be-marketed formulation are not bioequivalent to clinical formulation considering both Cmax and AUC.

Plasma concentrations on Day 5 were higher than those on Day 1 for all formulations. This is consistent with the findings in previous studies. The relative bioavailbility on Day 5 was similar to that observed on Day 1.

Reviewer's comments: The results demonstrated that the to-be-marketed formulation administered in water were not bioequivalent to the clinical formulation administered in sodium bicarbonate. Sodium bicarbonate likely dissolved the delayed-release coating of granules and protected omeprazole from degradation by gastric acid, resulting in much higher Cmax.

In addition, the approved capsule formulation had a comparable Cmax with the proposed granule formulation. The AUC ratio of the to-be-marketed formulation versus clinical formulation was 0.863 with the 90% CI close to the bioequivalence acceptance criteria. It is concluded that the to-be-marketed versus clinical formulations showed comparable systemic exposures of omeprazole based on the followings:

- 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 non-competitive 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.

2.2.4 What were the previous review conclusions of the pivotal efficacy studies (study 250 and study 251) for the age group submitted to this NDA?

The following comments are taken from Dr. Kress's review (Sheldon Kress is an MO).

Study 250: "An increased exposure to omeprazole for a few patients under 5 months, while patients over 5 months have exposure levels that are consistent across ages. According to Dr. Kress's review, there was 1 patient less than 5 month old. The analysis of pH indicates that a single dose of omeprazoe reduces esophageal acid exposure and increases gastric pH in pediatric patients. All doses were safely administered and well tolerated in this pediatric population."

Study 251:"It can be concluded that omeprazole administered as a bicarbonate suspension effectively reduced the number by approximately 50% and the intensity of vomiting/regurgitation episodes as well as the intensity of pain-related GERD symptoms."

2.2.5 What were the previous review conclusions of the pharmacokinetic and pharmacodynamic (study 250) for the age group submitted to this NDA?

The information below was taken from Dr. Suliman I. Al-Fayoumi's review for NDA: 19-810 / SE5-074, which was submitted Jan 15, 2002.

Table 1. Estimates of the geometric means of the primary PK parameters for omeprazole in pediatrics

Omeprazole Dose	PK Parameter	Geometric Mean (95% CI)
1.0 mg/kg	C_{max}	447.6 (253.6-789.9)
	AUC_{0-t}	658.0 (340.4-1272.1)
	$AUC_{0-\infty}$	1248.5 (569.3-2738.2)
1.5 mg/kg	C_{max}	345.6 (137.7-867.4)
	AUC_{0-t}	580.7 (274.6-1227.8)
	$AUC_{0-\infty}$	827.0 (352.3-1941.6)

Table 2. Estimates of the means of the primary PD Parameter (Mean change in %time pH < 4 after dosing) for omeprazole in pediatrics

Omeprazole Dose	PK Parameter	Mean PD (S.D.)
1.0 mg/kg	Esophageal pH	-2.1 (4.5)
	Gastric pH	-21.8 (18.8)
1.5 mg/kg	Esophageal pH	-6.4 (10.6)
	Gastric pH	-11.9 (10.5)

In study 250, higher mean PK (Cmax and AUC) and PD (mean change in % time gastric pH < 4) values were observed at the 1.0 mg/kg dose relative to the 1.5 mg/kg dose. The sponsor was requested to address the issues raised by reviewer Dr. Suliman I. Al-Fayoumi.. In Dr. Al-Fayoumi's review of the sponsor's response, it was concluded that "the sponsor's responses to Agency's Clinical Pharmacology & Biopharmaceutics-related comments to supplement SE8-074 to NDA 19-810 have been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics and have been found to be acceptable."

2.3 Intrinsic Factors

Omeprazole is extensively metabolized by CYP2C19 and CYP3A4 in the liver. The absolute bioavailability of omeprazole increases with repeated dosing in children due to a combination of decreased first-pass elimination and reduced systemic clearance (Clin Pharmacokinet 44(5):441-66, 2005). Genetic polymorphism of CYP enzymes will influence the exposure, and consequently pharmacologic response of omeprazole. For example, poor metabolizers of CYP 2C19 reportedly had several fold higher area under curve (AUC) than extensive metabolizers. Furthermore, diseases or genetic defects that affect CYP enzyme activities will likely impact the exposure and response of omeprazole.

2.4 General Biopharmaceutics

2.4.1 Is the proposed formulation identical to the one used for the pivotal efficacy study (study 251)?

No. The formulation of this NDA is different from the clinical formulation used for the pivotal efficacy study (study 251) in that the granule size of to-be-marketed formulation is smaller and that the clinical formulation contained omeprazole while the to-be-marketed formulation omeprazole magnesium. The granules of the to-be-marketed formulations are the same as those used for manufacturing the Prilosec OTC tablets.

2.5 Analytical Section

2.5.1 What analytical methods were used to assess concentrations?

Mean accuracy (Mean Dev.%) for the calibration samples was within the range of -2.6% and 2.6%, and CV% was within the range of 1.3% and 3.9%. The correlation coefficients (r2) of the standard curves were between 0.9991 and 1.0. The percent deviation from the nominal value (= mean accuracy) was determined for each quality control pool. The percent deviations were -4.4%, -1.4% and -0.7% for QC L(50 nmole/L), QC M (500 nmole/L), and QC H ($1.5E^{+3}$ nmole/L) , respectively.

2.6.2 Are the analytical assay methods adequately validated?

Yes. The linearity of the assay method was shown in the concentration range of (b) (4) Intra-assay precision was evaluated for each quality control pool. The theoretical plasma concentrations of omeprazole in the quality control pools were 50, 500 and 1500 nrnol/L and the intra-assay coefficients of variation were 2.4%, 0.71% and 0.64%, respectively. Inter-assay precision and accuracy were evaluated for each quality control pool. The theoretical plasma concentrations of omeprazole in the quality control pools were 50, 500 and 1500 nmol/L with the inter-assay coefficients of variation being 2.3%, 1.0% and 0.94%, respectively. The percent difference from theoretical value (= mean accuracy) was -5.7%, -6.7% and -6.8% for QC L(50 nmole/L), M(500 nmole/L) and H ($1.5E^{+3}$ nmole/L), respectively. In the Aug-29-2007 submission, the sponsor stated that omeprazole was stable at -18^{o}C for more than 1 year and the validated stability covers the analysis condition in study D9586C00002. Furthermore, the freeze-thaw and bench-top stability raw data demonstrated the sufficient stability of omeprazole during the analytical condition. The analytical assay method was adequately validated.

3 Detailed Labeling Recommendations

On page 25 of the annotated labeling, the pharmacokinetic data for children (b) (4) months in the table, entitled “pharmacokinetic parameters of omeprazole following single and repeated oral administration in pediatric population compared with adults,” should be removed from the table.

The following statement should be added to section 12.3 Pharmacokinetics: Based on a relative bioavailability study, the AUC and Cmax of Prilosec (omeprazole magnesium) for Delayed-Release Oral Suspension were 87% and 88% of those for Prilosec Delayed-Release Capsules, respectively.

49 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

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