SYNOPSIS

Name of Company: AstraZeneca LP	**Individual Study Table Referring to Item of the Submission** N/A	**(For National Authority Use only)**
Name of Finished Product: NEXIUM®	**Volume:** N/A	
Name of Active Ingredient: esomeprazole magnesium	**Page:** N/A	

Title of Study: A Randomized, Open-Label, 2-Way Crossover Study to Evaluate the Effects of Timing of Dosing in Relation to Food on the Pharmacokinetics of Esomeprazole Magnesium (NEXIUM®) in Healthy Subjects

Study Center(s): 1 investigator site initiated; 1 investigator site enrolled subjects

Publication (reference): None

Studied Period (years): < 1 year (date first drug dispensed) 26 November 2001 (date of last completed) 21 December 2001	**Phase of development:** Phase IV

Objectives:

Primary Objective

1. To measure the pharmacokinetics of esomeprazole taken 15 minutes before food and the pharmacokinetics of esomeprazole taken in a fasting condition, both on Day 1 of dosing, and to compare them.

Secondary Objectives

1. To measure the pharmacokinetics of esomeprazole taken 15 minutes before food and the pharmacokinetics of esomeprazole taken in a fasting condition, both on Day 5 of dosing (steady state), and to compare them.
2. To assess the safety and tolerability of esomeprazole.

Methodology: This was a single-center, randomized, open-label, 2-way crossover study of the pharmacokinetics of esomeprazole 40 mg in relation to ingesting food. The study enrolled healthy volunteers who were randomized to 1 of 2 dosing sequences. Each sequence consisted of two 5-day dosing periods separated by a 7- to 14-day washout period. The order in which subjects participated in the 5-day dosing periods was determined by the dosing sequence to which they were randomized.

Subjects received study drug once per day. In one of the dosing periods, subjects received study drug 15 minutes prior to a high fat, high calorie standardized meal on Days 1 and 5. In the other dosing period, they received study drug 4 hours prior to a standardized medium fat meal on Days 1 and 5. In each dosing period, subjects remained at the study center for the entire 5 days. For both study periods, the study protocol called for the subjects to receive study drug 30 minutes before breakfast on Days 2, 3, and 4; however, due to administrative errors, most subjects had their meals less than 30 minutes after receiving drug. This deviation had no effect on the primary analysis of Day 1 AUC and C_{max} comparisons as the error was made after Day 1. The variation of the time between study drug administration and mealtime was equally distributed into the 2 treatment periods, and most of the time the same subject had the same variation in the 2 treatment periods. The comparisons of the Day 5 AUC and C_{max} were not believed to be affected by this deviation.

On Days 1 and 5 of each study period, 20 blood samples for pharmacokinetic analysis were obtained, each at a time specified in relation to dosing.

Number of Subjects (Planned and Analyzed):

Number of subjects planned: 50

Number of subjects randomized: 47 (25 male/22 female)

Number of subjects analyzed: Safety population-47; Pharmacokinetic population-(Day 1) 35, (Day 5) 43

Diagnosis and Main Criteria for Inclusion: Healthy volunteer between the ages of 18 and 50 years, body weight no more than 20% above or below ideal body weight for height and frame.

Test Product, Dose and Mode of Administration, Batch or Lot Number:

Esomeprazole capsules 40 mg, oral - Lot AM-634

Duration of Treatment: Two 5-day dosing periods separated by a 7- to 14-day washout period.

Reference Therapy, Dose and Mode of Administration, Batch or Lot Number: None

Name of Company: AstraZeneca LP	**Individual Study Table Referring to Item of the Submission** N/A	**(For National Authority Use only)**
Name of Finished Product: NEXIUM®	**Volume:** N/A	
Name of Active Ingredient: esomeprazole magnesium	**Page:** N/A	

Criteria for Evaluation:

Pharmacokinetic parameters: The following pharmacokinetic parameters were estimated for each subject and were summarized for Day 1 and Day 5 of each dosing period: C_{max} (observed peak drug concentration), t_{max} (observed time to peak drug concentration), AUC_t (area under the plasma concentration-time curve from time zero to time t, where time t is the time of the last quantifiable concentration), AUC (area under the plasma concentration-time curve), and $t_{1/2}$ (terminal plasma elimination half-life of the drug).

Safety: Safety data were summarized for all dosed subjects. Adverse events were documented and vital signs were recorded daily. A physical examination and routine laboratory analyses were performed at screening and at the end of the study.

Statistical Methods:

Demographic information, and safety data were summarized.

AUC and C_{max} were log-transformed prior to analysis. They were analyzed using an analysis of variance (ANOVA) model, fitted for the effects of sequence and subject within sequence, period, and regimen. Contrasts between regimens were calculated, and the results were presented as geometric least squares means (GLS mean) of regimen effect (ratio of GLS means of food versus fasting) and its 90% confidence interval (90% CI). t_{max} was summarized using median and range; $t_{1/2}$ was summarized using mean and standard deviation.

SUMMARY

PHARMACOKINETIC RESULTS: On Day 1, esomeprazole administration 15 minutes before a high fat meal was associated with statistically significantly lower C_{max} and AUC compared to esomeprazole administration after fasting for 4 hours. This indicates that a majority of patients will have a decrease in AUC and C_{max} on Day 1 of dosing if they take esomeprazole capsules 15 minutes prior to a high fat meal.

On Day 5 of dosing, esomeprazole administration 15 minutes before a high fat meal also resulted in a statistically significantly lower C_{max} and AUC when compared to administration after fasting, but the effect of the meal timing was not as great as observed on Day 1. Both the Day 1 and Day 5 data are consistent with current labeling and previous studies, which had demonstrated that esomeprazole taken simultaneously with food leads to a reduction in both AUC and C_{max}.

Analyses of Pharmacokinetic Parameters—Evaluable Subjects

Day	Variable	Number of subjects	Ratio of 15 minute versus Fasting		
			Least squares mean	90% Confidence Interval (CI)	
				Lower CI	Upper CI
Day 1	AUC	35[a]	0.56	0.50	0.64
Day 1	C_{max}	35[a]	0.34	0.28	0.41
Day 5	AUC	43[a]	0.78	0.74	0.82
Day 5	C_{max}	43[a]	0.47	0.41	0.52

[a] Number of subjects with sufficient data to calculate both AUC and C_{max}.

SAFETY RESULTS: 40 mg esomeprazole given to healthy subjects once per day was generally well tolerated. There were no deaths, SAEs, or clinically significant laboratory abnormalities. The most frequently reported AE was headache (25/47, 53.2%). Gastrointestinal system disorders (constipation, nausea, and stomach cramps), respiratory system disorders (nasal congestion, sore throat), and skin and appendages disorders (dry lips) were all reported by between 3 (6.4%) and 7 (14.9) subjects.

Name of Company: AstraZeneca LP	**Individual Study Table Referring to Item of the Submission** N/A	**(For National Authority Use only)**
Name of Finished Product: NEXIUM®	**Volume:** N/A	
Name of Active Ingredient: esomeprazole magnesium	**Page:** N/A	
Date of the Report: February 10, 2003		