AstraZeneca

Drug product	NEXIUM	**SYNOPSIS**	
Drug substance(s)	Esomeprazole		
Document No.	GI.000-000-643		
Edition No.	Final		
Study code	D9615C00014		
Date	9 July 2003		

An Open, Randomized, Two-Way Crossover Study Comparing the Effect of 20 mg Esomeprazole Administered Orally and Intravenously as a 3-minute Injection on Basal and Pentagastrin-Stimulated Acid Output in Patients with Symptoms of Gastroesophageal Reflux Disease (GERD)

Study centers: The study was conducted at 3 study sites in the US.

Publications: None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	26 July 2002	Therapeutic confirmatory (III)
Last patient completed	10 October 2002	

Objectives: Primary objective: To compare the maximal acid output (MAO) during pentagastrin stimulation after 10 days of oral dosing with esomeprazole to the MAO after 10 days of intravenous dosing as a 3-minute injection. Both time points represent pharmacodynamic steady state.

Secondary objectives:

- To compare the basal acid output (BAO) at steady state and when switching (after Day 2 in the second treatment period versus after Day 10 in the first treatment period) from oral to intravenous dosing and from intravenous to oral dosing.
- To compare MAO when switching (after Day 2 in the second treatment period versus after Day 10 in the first treatment period) from oral to intravenous dosing and from intravenous to oral dosing.
- To evaluate the safety of intravenous esomeprazole in patients with symptoms of gastroesophageal reflux disease (GERD).

Study design: This was an open-label, randomized, multicenter, two-way crossover study. During each treatment period, patients with symptoms of GERD were administered a once-daily dose of esomeprazole 20 mg by study personnel either orally or intravenously as a 3-minute injection for 10 days (Days 1 to 10 and Days 11 to 20). There was no washout period between treatment periods. BAO and pentagastrin-stimulated MAO were measured on Days 11 and 13, prior to administration of study drug, and on Day 21.

Target patient population and sample size: Male and female patients aged 18 (or the legal age of consent) to 75 years who had heartburn on at least 2 of the 7 days prior to screening, with or without a history of erosive esophagitis (EE), or who had a documented diagnosis of GERD within 6 months prior to screening, with or without a history of EE were eligible. If the patient had a history of EE, it was to be documented by a previous endoscopy (either an endoscopy at any time in the past or the screening endoscopy). However, patients with Los Angeles Classification Grade (LA Grade) C or D esophageal erosions (ie, moderate to severe EE) confirmed on endoscopy during screening were not eligible for enrollment.

Up to a total of 60 patients were to be enrolled to ensure at least 40 patients were evaluable. A sample size of 38 patients would provide 90% power to reject the null hypothesis that the intravenous formulation was inferior to the oral formulation.

To ensure adequate representation of patients with and without a history of EE, the following targets were set: at least 25% of the randomized patients were to have active EE (LA Grades A or B) or a history of EE; and at least 25% were to have no history of EE and no active EE. Additionally, the randomized population was to be at least 25% male and at least 25% female.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

-Esomeprazole powder for solution for injection, 20 mg, dissolved in sodium chloride solution (9 mg/mL) administered intravenously as a 3-minute injection, once daily. Batch number H 1545-01-01-02.
-Esomeprazole 20 mg delayed-release capsules administered orally, once daily. Batch number H 1189-04-01-06.
-Pentagastrin solution for injection, 0.025% w/v, administered subcutaneously on Days 11, 13, and 21 at a dose of 6 μg/kg. Batch number H 1580-01-01-01 (Manufacturer's lot number 3HH).

Additionally, the investigator supplied GELUSIL® tablets from commercial supplies at the site as rescue medication.

Duration of treatment: Each patient was administered 20 days of once-daily treatment by study personnel in this 2-way crossover study; 10 days of esomeprazole 20 mg orally and 10 days of esomeprazole 20 mg intravenously as a 3-minute injection. There was no washout period between treatment periods.

Criteria for evaluation (main variables)

Pharmacodynamics: Primary variable: The MAO during pentagastrin stimulation 23 to 24 hours after 10 days of administration of 20 mg esomeprazole for both treatment periods.

Secondary variables: BAO 22-23 hours after 10 days of administration of 20 mg esomeprazole for both treatment periods. BAO and MAO 22-24 hours after 2 days of administration of 20 mg esomeprazole in the second treatment period. This gave information on any initial changes in BAO and MAO when switching from oral to intravenous (iv) esomeprazole and vice versa.

Safety: Safety endpoints included adverse event (AE) reports, clinical laboratory assessments (ie, chemistry, hematology, urinalysis), clinical assessments (ie, physical examination, vital signs), and 12-lead electrocardiogram assessments (ECG).

Statistical methods: All analyses of MAO and BAO were performed on the per-protocol (PP) population. The PP population included all patients who completed both treatment periods and who had MAO available for both treatment periods, with no major protocol violation. The intent-to-treat (ITT) population included all patients who were administered at least 1 dose of study medication, and had MAO available for at least 1 treatment period.

For the primary comparison (MAO after the last iv dose versus MAO after the last oral dose), log-transformed MAO was analyzed using mixed model analyses of variance with effects for sequence, patient (sequence), period, and formulation. First, the means and their 95% confidence intervals (CIs) for each formulation and the mean differences between formulations and their 1-sided upper limit of 95% confidence were estimated. These estimates were then anti–log-transformed to obtain the least squares (LS) geometric means of MAO for each formulation and their 95% CIs as well as the LS geometric mean ratios of MAO (iv versus oral) and their 1-sided upper limit of 95% confidence.

For the remaining comparisons of MAO (ie, when switching between iv and oral esomeprazole treatment), paired t-statistics for the log-transformed MAO were used to estimate mean differences between Period 1 and Period 2 and their 95% CIs. These estimates were then anti–log-transformed to obtain the LS geometric mean ratios and their 95% CIs.

BAO was analyzed using the Hodges-Lehmann method. For comparison of BAO after the last iv dose versus BAO after the last oral dose, the difference in BAO between Period 1 and Period 2 (Period 2 minus Period 1) was calculated. The two-sample Hodges-Lehmann method was then applied to the differences to estimate the median difference between treatment sequence (oral/iv minus iv/oral) and its 1-sided 95% upper confidence limit. For the remaining comparisons of BAO (ie, when switching between iv and oral esomeprazole

treatment), the paired Hodges-Lehmann method was used to estimate median differences between Period 1 and Period 2 and their 95% CIs.

Safety analyses included patients who were administered at least 1 dose of study medication. AEs, clinical laboratory tests, vital signs, and ECG results were summarized using descriptive statistics.

Patient population: Fifty patients were randomized to treatment and 45 patients completed the study (19 in the oral/iv sequence and 26 in the iv/oral sequence). Of the 5 patients who did not complete the study (all were in the oral/iv sequence), 3 were discontinued because informed consent was withdrawn, 1 because of an AE (the patient fell and experienced sciatic pain due to local trauma, which the investigator considered unrelated to study treatment), and 1 because difficulty in placing the nasogastric tube resulted in a prolonged delay in performing the acid output procedure. The number of patients in the PP population was 42 (17 in the oral/iv sequence and 25 in the iv/oral sequence). The 3 patients who completed the study but were not included in the PP analysis (2 in the oral/iv sequence and 1 in the iv/oral sequence) were excluded because the patients may have used a restricted concomitant medication (antacid or ascorbic acid) after 0000 hours on the day of an acid output test. The number of patients in the ITT population was 46 (20 in the oral/iv sequence and 26 in the iv/oral sequence). There were a total of 50 patients in the safety population.

Table S1 Patient disposition

	E20 oral		E20 IV inj		Total	
Disposition	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Randomized	50	(100.0)	50	(100.0)	50	(100.0)
Completed study	45	(90.0)	45	(90.0)	45	(90.0)
Discontinued study	4	(8.0)	1	(2.0)	5	(10.0)
Analyzed for pharmacodynamics (ITT) [a]	46	(92.0)	46	(92.0)	46	(92.0)
Analyzed for pharmacodynamics (PP) [b]	42	(84.0)	42	(84.0)	42	(84.0)
Analyzed for safety [c]	50	(100.0)	46	(92.0)	50	(100.0)

[a] Intention-to-treat population: Patients who were administered at least 1 dose of the study medication and had MAO available for at least 1 treatment period.
[b] Per-protocol population (primary analysis population): Patients who completed both treatment periods and had MAO available for both treatment periods, with no major protocol violation.
[c] Safety population: Patients who took at least 1 dose of the study medication.
E20 oral Esomeprazole 20 mg once daily oral capsule.
E20 IV inj Esomeprazole 20 mg once daily 3-minute injection.

An evaluable population of 38 patients was necessary to give 90% power to reject the null hypothesis that the iv formulation was inferior to the oral formulation. The 42 evaluable patients in this study met this goal.

In the PP population male and female patients were approximately equally distributed and the most prevalent racial group (40.5%) was “Other” (all of these patients were classified as being Hispanic by the investigator). In the PP population, more than 20% of patients had a history

of GERD of more than 5 years and nearly all (86%) had a history of GERD of more than 1 year, and approximately 36% were positive for EE. Thus, the study population met the targets established in the Clinical Study Protocol that the enrolled population should include at least: 25% males; 25% females; 25% with active EE (LA Grades A or B) or a history of EE; and 25% with no history of EE and no active EE.

Table S2 Patient demographics and baseline characteristics

Demographic or baseline characteristic		All randomized (n=50)		Per-protocol (n=42)	
Demographic characteristics					
Gender, n (%)	Male	22	(44.0)	20	(47.6)
	Female	28	(56.0)	22	(52.4)
Age (years)	Mean (SD)	39.7	(13.8)	39.2	(13.9)
	Range	18 to 70		18 to 66	
Race, n (%)	Caucasian	14	(28.0)	13	(31.0)
	Black	7	(14.0)	6	(14.3)
	Oriental	8	(16.0)	6	(14.3)
	Other [a]	21	(42.0)	17	(40.5)
BMI (kg/m^2)	Mean (SD)	27.0	(3.9)	27.0	(3.9)
	Range	19.6 to 34.0		19.6 to 34.0	
Baseline characteristics					
Erosive esophagitis status, n (%)	Positive	17	(34.0)	15	(35.7)
	Negative	33	(66.0)	27	(64.3)
GERD history, n (%)	<1 year	6	(12.0)	6	(14.3)
	1-5 years	32	(64.0)	27	(64.3)
	>5 years	12	(24.0)	9	(21.4)
Heartburn ≥2 days, n (%) [b]	Yes	50	(100.0)	42	(100.0)
H. pylori status, n (%) [c]	Positive	8	(16.0)	8	(19.0)
	Negative	42	(84.0)	34	(81.0)

[a] All of these patients were classified as Hispanic by the investigator.
[b] Patient reported heartburn symptoms on at least 2 days of the last 7 days prior to screening.
[c] The test for *H. pylori* status was performed for consistency with the methodology of prior studies.
SD=standard deviation; BMI=body mass index; GERD=gastroesophageal reflux disease

Pharmacodynamic results: Both oral and iv (3-minute injection) treatment with esomeprazole 20 mg for 10 days resulted in mean BAO values of <1 mmol/h (0.69 mmol/h and 0.71 mmol/h for oral and iv treatment, respectively) and mean MAO values of <6 mmol/h. Following treatment with iv esomeprazole, mean MAO and BAO values were numerically higher than after oral esomeprazole treatment. Although the observed differences between the arithmetic or LS geometric means of the MAO values for the 2 esomeprazole formulations were small, the LS geometric mean ratio of MAO results (iv/oral) did not meet

the statistical criterion for pharmacodynamic non-inferiority of the iv formulation (a value of <1.25 for the 1-sided 95% upper confidence limit of the LS geometric mean ratio). There was no indication of a major change in pharmacodynamic efficacy when switching between oral and iv esomeprazole. After both oral and iv treatment, the observed mean MAO and BAO values were lower in female compared to male patients, in EE-negative versus EE-positive patients, and in *H. pylori*-positive compared to *H. pylori*-negative patients.

Table S3 MAO after 10 days of esomeprazole administration (PP)

	E20 oral (n=42)		E20 IV inj (n=42)		Ratio (IV/Oral)	
Acid output	**LS geometric mean (95% CI)**	**Arith. Mean (SD)**	**LS geometric mean (95% CI)**	**Arith. Mean (SD)**	**LS geometric mean**	**1-Sided 95% upper confidence limit [a]**
MAO (mmol/h)	3.18 (2.18 to 4.65)	5.27 (5.39)	3.44 (2.36 to 5.00)	5.96 (5.41)	1.08	1.44

[a] A value <1.25 would have met the statistical criterion for pharmacodynamic non-inferiority of the IV formulation to the oral formulation.

MAO Maximal acid output (pentagastrin-stimulated) 23-24 hours after 10 days of esomeprazole 20 mg.
PP Per-protocol population.
E20 oral Esomeprazole 20 mg once daily oral capsule
E20 IV inj Esomeprazole 20 mg once daily 3-minute injection.
LS Least squares. CI Confidence interval. Arith Arithmetic.

Safety results: In this study, 50 patients were exposed to at least 1 dose of esomeprazole administered orally or intravenously as a 3-minute injection. Esomeprazole was safe and well tolerated, and the safety profiles of the 2 formulations were similar.

There were no serious adverse events (SAEs) or other significant adverse events (OAEs). One patient discontinued study treatment due to an AE that was considered by the investigator to be unrelated to study treatment: the patient fell and experienced sciatic pain due to local trauma. The AEs in the safety population, including the treatment-related ("attributable") events, were mostly gastrointestinal in nature; such AEs were not unexpected with this class of drug in the patient population under study. The most commonly reported AEs were those that the investigators considered to be related to the acid output procedure; the majority of these AEs were considered by the investigators to be pentagastrin-related, with the remainder being primarily related to placement of the nasogastric tube. The pentagastrin-related AEs are not a safety issue because this agent is used as part of research investigations and patients would not be administered pentagastrin as part of any accepted treatment intervention for GERD.

For most laboratory variables, isolated changes both within and outside the reference range occurred during the study. There were no clear upward or downward trends for any of the variables. One patient experienced changes in laboratory variables (increased alkaline phosphatase, bilirubin, and AST) that were classified by the investigator as AEs and not related to esomeprazole. Blood pressure changes in 3 patients and physical examination findings in 7 patients were classified by the investigators as AEs but not related to treatment

with esomeprazole. There were no other hematology, clinical chemistry, urinalysis, vital sign, ECG, or physical finding abnormalities reported as AEs by the investigators.

Table S4 Number (%) of patients who had an adverse event and total number of adverse events in any category (safety population)

	E20 oral (N=50)		E20 IV inj (N=46)		E20 total[a] (N=50)	
Category of adverse events	**n (%) of patients who had an AE in each category[b]**					
Any adverse events	46	(92.0)	40	(87.0)	49	(98.0)
Serious adverse events	0		0		0	
Discontinuations of study treatment due to adverse events	1	(2.0)	0		1	(2.0)
Other significant adverse event	0		0		0	
Attributable adverse events [c]	26	(52.0)	22	(47.8)	33	(66.0)
Severe adverse events	1	(2.0)	0		1	(2.0)
	Total number of adverse events[d]					
Any adverse events	104		87		135	
Discontinuations adverse events	1		0		1	
Attributable adverse events [c]	39		32		54	
Severe adverse events	1		0		1	

[a] For each treatment group, patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[b] Patients having the same AE during both treatments (oral and IV) were counted once in each treatment period for the specific AE and only once in the Total column.

[c] Attributable AEs are those for which there was a relationship to study treatment as judged by the investigator.

[d] Events are counted by preferred term, ie, for patients with multiple events included under the same preferred term, only 1 occurrence of the event is counted.

N Total population in each group.

E20 oral Esomeprazole 20 mg once daily oral capsule

E20 IV inj Esomeprazole 20 mg once daily 3-minute injection

Table S5 Number (%) of patients with the most commonly reported adverse events, sorted by decreasing order of frequency as summarized across both treatments (safety population)

	E20 oral (N=50)		E20 IV inj (N=46)		E20 total [b] (N=50)	
Preferred term [a]	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
AE associated with test procedure	26	(52.0)	24	(52.2)	30	(60.0)
Abdominal pain	9	(18.0)	5	(10.9)	11	(22.0)
Headache	9	(18.0)	5	(10.9)	11	(22.0)
Flatulence	7	(14.0)	6	(13.0)	9	(18.0)
Dyspepsia	5	(10.0)	6	(13.0)	7	(14.0)
Mouth dry	3	(6.0)	6	(13.0)	7	(14.0)
Nausea	5	(10.0)	2	(4.3)	6	(12.0)
Earache	3	(6.0)	3	(6.5)	4	(8.0)
Gastrointestinal symptoms NOS	4	(8.0)	1	(2.2)	4	(8.0)
Anorexia	3	(6.0)	2	(4.3)	3	(6.0)
Change in bowel habits	3	(6.0)	1	(2.2)	3	(6.0)
Constipation	3	(6.0)	1	(2.2)	3	(6.0)
Dizziness	1	(2.0)	2	(4.3)	3	(6.0)
Hypertension	2	(4.0)	1	(2.2)	2	(4.0)
Nasal irritation	2	(4.0)	1	(2.2)	2	(4.0)
Skin discolouration	2	(4.0)	2	(4.3)	2	(4.0)

[a] This table uses a cut-off of at least 2 patients in any treatment group.

[b] Patients having the same AE during both treatments (oral and IV) were counted once in each treatment period for the specific AE and only once in the Total column.

E20 oral Esomeprazole 20 mg once daily oral capsule.
E20 IV inj Esomeprazole 20 mg once daily 3-minute injection.
N Total population in each group.
n Number of patients with a specific AE.
NOS Not otherwise specified

- Date of the report 9 July 2003