CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-689

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

06/18/04

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-689

Generic Name: Esomeprazole Sodium

Sponsor: AstraZeneca Pharmaceuticals

Reviewer: Suliman I. Al-Fayoumi, Ph.D.

Type of Submission: Original NDA (3S)

Proposed Indications(s): Short-term treatment (up to 10 days) of (GERD) alternative to oral therapy in patients when therapy with NEXIUM Delayed Release Capsules is not possible or appropriate

Proposed Dosage Regimen: 20/40 mg QD for up

Submission Date: 9/10/03

ORM Division: GI & Coagulation Drug Products

OCPB Division: DPE II

Team Leader: Suresh Doddapaneni, Ph.D.

I. Executive Summary

Esomeprazole (Nexium®), the S-enantiomer of omeprazole, is an inhibitor of gastric acid secretion. It is currently indicated for the treatment and maintenance therapy of a variety of acid-related GI conditions. The recommended adult dose is 20-40 mg QD for The approved dosage forms of Nexium are 20 and 40 mg Delayed Release Capsules.

In the current application, the sponsor has developed an I.V. formulation of Nexium to be used as an alternative to Nexium Capsules. The I.V. formulation is intended for short-term (10 days) treatment of GERD patients oral in not possible or not appropriate. The submission consists of fourteen studies; thirteen clinical pharmacology studies evaluating the PK and PD aspects of I.V. esomeprazole and a single clinical study evaluating the safety and efficacy of I.V. esomeprazole.

The findings of the completed clinical pharmacology studies indicate that while substantial PK differences are observed with I.V. administration of esomeprazole relative to P.O. administration on Cmax and AUC values, smaller differences are observed between the PD profiles of the two drug products. The clinical relevance of such PD differences is unknown. Moreover, administration of esomeprazole I.V. doses of 20 and 40 mg over an infusion period of 30 min results in a similar PD profile as that of the a comparable esomeprazole I.V. dose infused over 3 min.

Overall, the sponsor has adequately characterized the clinical pharmacology and biopharmaceutics-related aspects of the drug product.

A. Recommendations

From the view point of Office of Clinical Pharmacology and Biopharmaceutics, NDA 21-689 is **acceptable** provided that a satisfactory agreement is reached between the Agency and the sponsor with respect to proposed language in the package insert. See Appendix 1 for the Agency proposed package insert.

B. Phase IV Commitments

None.

II. Table of Contents

C. Summary of CPB Findings

NDA 21-689 consists of fourteen studies; thirteen clinical pharmacology studies evaluating the PK and PD aspects and a single clinical study evaluating the safety and efficacy of I.V. esomeprazole.

The results of three clinical pharmacology studies (SH-QBE-0006, SH-QBE-0045 & SHQBE-0061) are not addressed in the current review as they were originally submitted and reviewed under NDA 21-153 (Nexium® Delayed Release Capsule). In addition, the findings of those studies are duplicated by other studies in the current submission.

Administration of esomeprazole I.V. at doses of 20 and 40 mg QD results in markedly higher Cmax and AUC values relative to comparable P.O. doses. However, consistent PD differences of a smaller magnitude are observed between I.V. and P.O. esomeprazole following multiple dose administration. In addition, administration of esomeprazole I.V. infusions ranging in duration from 3 to 30 min results in similar PD profiles.

II. Question-Based Review

A. General Attributes

Esomeprazole is the single S-enantiomer of the proton pump inhibitor (PPI) omeprazole, and acts through inhibition of the proton pump enzyme H^+/K^+-ATPase located in the parietal cells of the gastric mucosa.

Esomeprazole (Nexium®) Delayed Release Capsule (20 and 40 mg) was approved in the US in February 2001. The recommended dosages are: 20 mg or 40 mg once daily for the treatment of erosive esophagitis (EE), 20 mg once daily for the maintenance of healed EE to prevent relapse, and 20 mg once daily for the short-term treatment of symptomatic GERD. [redacted]

B. General Clinical Pharmacology

1. Is esomeprazole I.V. comparable to esomeprazole P.O. on PK/PD profiles?

A total of thirteen PK/PD studies were conducted assessing the comparability of esomeprazole P.O. and I.V. using 24-hr intragastric pH in healthy subjects and pentagastrin-stimulated gastric acid output in GERD patients.

Studies SH-NEP-0002 and SH-NEP-0008 evaluated the comparative PK and PD aspects of esomeprazole following P.O. and I.V. administration based on 24-hr intragastric pH in healthy subjects. Identical study designs were employed in the two studies. Healthy male and female subjects received esomeprazole (20 mg dose in study SH-NEP-0008 and 40 mg in study SH-NEP-0002) as a 30 min I.V. infusion or an oral capsule QD for 5 days in a randomized, double blind, two-way crossover design separated by a washout period of at least 13 days. In each treatment period, blood samples were drawn for determination of esomeprazole PK for up to 24 hrs post-dose and 24-hr intragastric pH monitoring was conducted on days 1 and 5 of each treatment using a [redacted] microelectrode.

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Table 1. Estimates of geometric means of the primary PK parameters after I.V. and P.O. administration of 20 mg multiple doses of esomeprazole

Variable	Study Day	n	Treatment	Estimate	95% CI	
					Lower	Upper
AUC	1	23	20mg iv	3.40	2.69	4.29
		23	20mg po	1.86	1.48	2.36
	5	22	20mg iv	5.11	3.96	6.61
		22	20mg po	3.92	3.03	5.06
AUC_t	1	24	20mg iv	3.35	2.63	4.26
		24	20mg po	1.69	1.33	2.15
	5	23	20mg iv	5.11	4.00	6.53
		23	20mg po	3.81	2.98	4.86
C_{max}	1	24	20mg iv	3.32	2.72	4.06
		24	20mg po	0.78	0.64	0.96
	5	23	20mg iv	3.86	3.16	4.72
		23	20mg po	1.57	1.28	1.92
$t_{½}$	1	23	20mg iv	0.79	0.67	0.94
		23	20mg po	0.95	0.80	1.13
	5	22	20mg iv	1.05	0.90	1.22
		22	20mg po	1.12	0.95	1.30
CL	1	24	20mg iv	17.07	13.96	20.88
	5	23	20mg iv	11.25	9.03	14.01
V_{SS}	1	24	20mg iv	16.45	15.10	17.92
	5	23	20mg iv	15.13	13.68	16.73
F	1	23	20mg po	0.55	0.48	0.63
	5	22	20mg po	0.77	0.67	0.88

Table 2. Estimates of geometric means of the % time pH > 4 after I.V. and oral administration of 20 mg multiple doses of esomeprazole

Study day	Treatment	Estimate	95% CI	
			Lower	Upper
1	20mg iv	30.4	24.6	36.2
	20mg po	27.5	21.7	33.3
	20mg iv- 20mg po	2.9	-1.0	6.9
5	20mg iv	49.5	41.9	57.2
	20mg po	51.1	43.5	58.7
	20mg iv - 20mg po	-1.5	-7.8	4.7

Table 3. Estimates of geometric means of the primary PK parameters after I.V. and oral administration of 40 mg multiple doses of esomeprazole

Variable	Study Day	n	Treatment	Estimate	95% CI	
					Lower	Upper
AUC	Day 1	39	40 mg iv	9.88	8.20	11.89
		39	40 mg po	5.94	4.93	7.15
	Day 5	38	40 mg iv	16.21	14.46	18.16
		38	40 mg po	12.55	11.20	14.06
AUC_I	Day 1	39	40 mg iv	9.81	8.14	11.81
		39	40 mg po	5.86	4.87	7.06
	Day 5	38	40 mg iv	16.06	14.35	17.98
		38	40 mg po	12.38	11.06	13.86
C_{max}	Day 1	39	40 mg iv	6.77	6.04	7.58
		39	40 mg po	2.97	2.65	3.32
	Day 5	37	40 mg iv	7.51	6.93	8.13
		37	40 mg po	4.60	4.25	4.99
$t_{½}$	Day 1	39	40 mg iv	1.05	0.94	1.17
		39	40 mg po	1.01	0.90	1.13
	Day 5	38	40 mg iv	1.41	1.30	1.52
		38	40 mg po	1.38	1.28	1.49
Cl	Day 1	39	40 mg iv	11.72	10.04	13.68
	Day 5	38	40 mg iv	7.13	6.39	7.95
V_{ss}	Day 1	39	40 mg iv	15.71	14.86	16.60
	Day 5	38	40 mg iv	14.32	13.50	15.20
F	Day 1	39	40 mg po	0.60	0.55	0.65
	Day 5	38	40 mg po	0.78	0.74	0.82

Table 4. Estimates of geometric means of the % time pH > 4 after I.V. and oral administration of 40 mg multiple doses of esomeprazole

Study Day	Treatment	Estimate	95% CI	
			Lower	Upper
1	40 mg iv	42.1	35.2	49.1
	40 mg po	36.5	29.6	43.5
	40 mg iv - 40 mg po	5.6	1.2	10.0
5	40 mg iv	66.2	62.4	70.0
	40 mg po	63.6	59.7	67.4
	40 mg iv - 40 mg po	2.6	-0.5	5.8

The results of study SH-NEP-0008 indicate that administration of esomeprazole I.V. results in Cmax and AUC values on day 1 that are higher by 128% and 66%, respectively relative to the oral capsule, decreasing to 63% and 29%, respectively on day 5. The results of study SH-NEP-0002 indicate that administration of esomeprazole I.V. results in Cmax and AUC values on day 1 that are higher by 324% and 82%, respectively relative to the oral capsule, decreasing to 146% and 31%, respectively on day 5. As for the PD profiles, the results of the two studies indicated that the PD profiles following administration of similar doses of I.V. and oral esomeprazole are comparable in healthy subjects.

Four studies (SH-NEP-0011, SH-NEP-0012, D9615C00013 & D9615C00014) evaluated the comparability of esomeprazole P.O. and I.V. (3 min injection and 30-min infusion) on pentagastrin-stimulated gastric acid output in GERD patients. The four studies employed identical study designs.

Male and female GERD patients, with or without a history of EE received esomeprazole (20 mg in studies SH-NEP-0012 & D9615C00014, and 40 mg in studies SH-NEP-0011 & D9615C00013) as either an oral capsule or an I.V. infusion (3 min injection in studies D9615C00013 & D9615C00014, and 15-min infusion in studies SH-NEP-0011 & SH-NEP-0012) QD for 10 days in a randomized, open label, two-way crossover design without a washout period (total study period 20 days). Basal and maximal pentagastrin-stimulated acid outputs were measured 22-24 hours on day 10 of period 1 and on days 12 and 20 of period 2. After an overnight fast on the aforementioned days, gastric juice was aspirated over two 30-min periods for basal acid output (BAO) measurement. Thereafter, pentagastrin (6 µg/kg) S.C. was administered and four 15-min samples were collected for maximal acid output (MAO) measurement.

Table 5. Estimates of mean **MAO** values after administration of 20 mg doses as either a 15 min injection or P.O. for 10 days (study SH-QBE-0012)

	E20 oral (n=44)		E20 IV inf (n=44)		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)	3.29 (2.21 to 4.90)	5.26 (4.12)	4.11 (2.77 to 6.12)	5.95 (4.00)	1.25	1.58

Table 6. Estimates of mean **MAO** values after administration of 40 mg doses as either a 15 min injection or P.O. for 10 days (study SH-QBE-0011)

	E40 oral (n=47)		E40 IV inf (n=47)		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 [1]
MAO (mmol/h)	2.24 (1.55 to 3.25)	3.52 (2.86)	3.02 (2.08 to 4.36)	4.74 (3.65)	1.35	1.71

Table 7. Estimates of mean **MAO** values after administration of 20 mg doses as either a 3 min injection or P.O. for 10 days (study D9615C00014)

	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 [1]
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

Table 8. Estimates of mean **MAO** values after administration of 40 mg doses as either a 3 min injection or P.O. for 10 days (study D9615C00013)

	E40 oral (N=50)		E40 IV inj (N=50)[1]		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 [1]
MAO (mmol/h)	2.75 (1.97 to 3.85)	4.41 (3.11)	3.88 (2.76 to 5.47)	5.06 (3.90)	1.41	1.82

Overall, the PK/PD data indicate that there are substantial PK differences (Tables 1 and 3) as well as less pronounced PD differences (Tables 5-8) between I.V. and P.O. administered doses of esomeprazole in GERD patients. The PD profiles following administration of similar I.V. and P.O. esomeprazole doses are comparable in healthy subjects. The clinical relevance of the observed PD differences between I.V. and P.O. administered esomeprazole in GERD patients is unknown.

2. Are the PD profiles of esomeprazole comparable between I.V. infusions given over a period of 3-30 min?

Study SH-NEP-0003 evaluated the comparative PK/PD profiles of a 40 mg esomeprazole I.V. infusion administered over either a 3 min or 30 min period. Healthy male and female subjects (n = 41, age 28.5 ± 6.7 years, wt 73.2 ± 10.0 kg) received 40 mg esomeprazole as either a 3 min or 30 min I.V. infusion QD for 10 days in a randomized, double blind, two-way crossover design separated by a washout period of at least 13 days. In each treatment period, blood samples were drawn for determination of esomeprazole PK up to 24 hrs post-dose. 24-hr pH monitoring was conducted on days 1 and 5 of each treatment using a microelectrode attached to a Mark III Gastrograph data-logger.

Table 9. Estimates of geometric means of the primary PK parameters after administration of 40 mg doses as either a 3 min injection or 30 min infusion

Variable	Study Day	n	Treatment	Geometric Mean	95% CI Lower	95% CI Upper
AUC	Day 1	39	injection	7.10	6.08	8.29
		41	infusion	6.17	5.30	7.20
	Day 10	41	injection	12.58	11.38	13.92
		41	infusion	10.96	9.91	12.13
AUCt	Day 1	41	injection	7.16	6.15	8.35
		41	infusion	6.10	5.24	7.11
	Day 10	41	injection	12.49	11.29	13.81
		41	infusion	10.87	9.83	12.02
Cmax	Day 1	41	injection	11.87	10.62	13.28
		41	infusion	5.47	4.89	6.11
	Day 10	41	injection	13.55	12.60	14.57
		41	infusion	7.00	6.51	7.53
t½	Day 1	39	injection	0.88	0.77	1.00
		41	infusion	0.86	0.76	0.98
	Day 10	41	injection	1.23	1.14	1.34
		41	infusion	1.18	1.08	1.28
Cl	Day 1	39	injection	16.10	13.75	18.85
		41	infusion	18.69	16.02	21.79
	Day 10	41	injection	9.19	8.31	10.16
		41	infusion	10.54	9.53	11.66
Vss	Day 1	39	injection	16.85	15.68	18.11
		41	infusion	20.03	18.68	21.49
	Day 10	41	injection	15.24	14.50	16.03
		41	infusion	16.98	16.15	17.85

Table 10. Estimates of geometric means of the % time pH > 4 after I.V. administration of 40 mg single doses of esomeprazole over either 3 or 30 min

Day	Treatment	Estimate	95% CI Lower	95% CI Upper
1	injection	32.3	26.6	38.0
	infusion	33.1	27.3	38.8
	injection-infusion	-0.8	-4.0	2.4
10	injection	57.2	52.8	61.6
	infusion	55.6	51.2	60.0
	injection-infusion	1.6	-1.7	4.9

The results indicate that administration of a 40 mg dose of esomeprazole as a 3 min injection results in Cmax values that are higher by 117% and 93% on days 1 and 10, respectively relative to a 30-min infusion. The PD profiles however are similar following administration of 40 mg doses of esomeprazole as either a 3-min or 30-min infusion.

The findings of study SH-NEP-0003 suggest that I.V. infusions of esomeprazole given over a period as short as 3 min and as long as 30 min are likely to yield similar PD profiles.

E. General Biopharmaceutics

The proposed I.V. formulation for esomeprazole 20 and 40 mg contains an esomeprazole sodium salt instead of the esomeprazole magnesium salt in the oral formulation. The sodium salt was selected because the water solubility of esomeprazole magnesium was insufficient for the I.V. formulation.

Table 11. Composition of esomeprazole I.V. 20 mg

Components	Quantity (per dose)	Function	Standard
Esomeprazole sodium for injection (corresponding to esomeprazole)	21.3 mg (20 mg)	Drug substance	AstraZeneca
Edetate disodium	1.5 mg	Chelating agent	USP
Sodium hydroxide		pH adjusting agent	NF

Table 12. Composition of esomeprazole I.V. 40 mg

Components	Quantity (per dose)	Function	Standard
Esomeprazole sodium for injection (corresponding to esomeprazole)	42.5 mg (40 mg)	Drug substance	AstraZeneca
Edetate disodium	1.5 mg	Chelating agent	USP
Sodium hydroxide		pH adjusting agent	NF

F. Analytical Section

An HPLC method (BA-222) was validated for omeprazole in human heparinized plasma using a sample volume of 500 µL. Samples were extracted with dichloromethane then injected into the HPLC system.

Linear Range: 25-100,000 nmol/L

Limit of Quantitation: 25 nmol/L

Table 13. Quality Control Inter-day Variation (n = 10)

	nmol/L	nmol/L	nmol/L
Absolute Recovery	97.0	97.7	99.9
C.V.%	10.6	0.6	0.6

III. Appendices

A. **Proposed Package Insert (original and Agency proposed)**

B. **Individual Study Review**

C. **Cover Sheet and OCPB Filing/Review Form**

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Appendix A

Proposed Package Insert

13 Page(s) Withheld

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X Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-1

Appendix B

Individual Study Reviews

NDA: 21-689/ Study SH-NEP-0001 **Study Date: Jan-Mar 2001**

Type of Submission: Tolerability and PK of Esomeprazole I.V.

Study SH-QBE-0001 is entitled,

"TOLERABILITY AND PHARMACOKINETICS OF ESOMEPRAZOLE AFER INTRAVENOUS ADMINISTRATION TO HEALTHY SUBJECTS".

Objectives

To assess the safety, tolerability and PK of Esomeprazole following I.V. administration.

Study Design

Healthy male subjects (n = 12, age 26.1 ± 4.6 years, wt 76.3 ± 6.6 kg) received a maximum of two doses on different occasions in a randomized, double blind, placebo controlled, dose escalation design separated by a washout period of at least 10 days. On each dose regimen, 3 subjects received Esomeprazole I.V. while 1 subject received placebo. In each treatment period, blood samples were drawn for determination of esomeprazole before and at 5, 10, 20, 30 min and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12 and 24 hrs post-dose.

Table 1. Summary of the dose administration schedule

Dose step	Dose of esomeprazole (mg):
1	40 mg as an infusion over 20 minutes
2	80 mg as an infusion over 20 minutes
3	100 mg as an infusion over 20 minutes
4	100 mg as an infusion over 20 minutes repeated 12 hours later
5	40 mg as an injection over 3 minutes

Analytical Assay

Plasma samples were analyzed for esomeprazole according to method # BA-323 (LOQ = 25 nmol/L).

Pharmacokinetics

The following pharmacokinetic parameters were estimated for esomeprazole using non-compartmental analysis: t_{max}, C_{max}, CL, AUC_{0-t} and $AUC_{0-\infty}$.

Results

Table 2. Estimates of geometric means of the primary PK parameters after I.V. administration of escalating doses of esomeprazole

Dose (mg)	n	AUC (µmol*h/L)	C_{max} (µmol/L)	CL (L/h)	$t_{\frac{1}{2}}$ (h)	V_{ss} (L)
Injection 40	3	7.82	14.00	14.80	0.93	16.30
Infusion 40	3	4.68	5.35	24.73	0.59	18.09
Infusion 80	6	19.02	12.31	12.18	1.15	18.16
Infusion 100	3	30.08	17.48	9.62	1.37	18.11
Infusion 100+100 (1st dose)	3	34.35	16.78	8.43	1.55	17.80
Infusion 100+100 (2nd dose)	3	39.37	15.46	7.35	1.73	17.46

Intravenous administration of esomeprazole as single 20-minute infusions of 40 mg to 100 mg, two consecutive 20-minute infusions of two 100 mg separated by 12 hours and as a single 3-minute injection of 40 mg in healthy male subjects were well tolerated at all dose-levels.

Administration of escalating I.V. doses of esomeprazole resulted in greater-than-proportional increases in AUC and a decrease in total clearance (CL), which points to non-linear PK at the studied dose range.

Reviewer's Comments

- *I.V. administration of esomeprazole up to 100 mg appears to be well tolerated.*
- *As might be expected, Cmax of esomeprazole was higher when 40 mg esomeprazole was administered as a 3-min infusion relative to a 20-min infusion.*

NDA: 21-689/ Study SH-NEP-0002 **Study Date: Aug-Oct 2001**

Type of Submission: Multiple Dose PK/PD in Healthy Subjects

Study SH-QBE-0002 is entitled,

"A DOUBLE-BLIND, RANDOMISED, TWO-WAY CROSS-OVER COMPARATIVE STUDY OF 40 mg ORAL AND INTRAVENOUS ESOMEPRAZOLE REGARDING EFFECT ON 24-HOUR INTRAGASTRIC pH AND PHARMACOKINETICS DURING ONCE DAILY ADMINISTRATION FOR FIVE DAYS IN HEALTHY MALE AND FEMALE SUBJECTS".

Objectives

To assess the comparative PK/PD profiles of 40 mg esomeprazole administered as either I.V. solution or oral capsule.

Study Design

Healthy male and female subjects (n = 39, age 25.7 ± 5.6 years, wt 72.3 ± 10.4 kg) received 40 mg esomeprazole as a 30 min I.V. infusion or an oral capsule QD for 5 days in a randomized, double blind, two-way crossover design separated by a washout period of at least 13 days. In each treatment period, blood samples were drawn for determination of esomeprazole before and at 5, 10, 20, 30, 45 min and 1, 1.5, 1.75, 2, 2.5, 3, .5, 4, 5, 6, 7, 8, 10, 12, 13 and 24 hrs post-dose. 24-hr pH monitoring was conducted on days 1 and 5 of each treatment using a [redacted] microelectrode.

Of the enrolled subjects, 37 were CYP2C19 extensive metabolizers while 3 were poor metabolizers.

Analytical Assay

Plasma samples were analyzed for esomeprazole according to method # BA-222 (LOQ = 25 nmol/L).

PK/PD assessments

The following PK parameters were estimated for esomeprazole using non-compartmental analysis: t_{max}, C_{max}, **CL**, AUC_{0-t} and $AUC_{0-\infty}$. The following PD parameters were estimated for esomeprazole: % time with intragastric pH > 4 and median pH during the 24-hour monitoring period.

Results

Table 1. Estimates of geometric means of the primary PK parameters after I.V. and oral administration of 40 mg multiple doses of esomeprazole

Variable	Study Day	n	Treatment	Estimate	95% CI	
					Lower	Upper
AUC	Day 1	39	40 mg iv	9.88	8.20	11.89
		39	40 mg po	5.94	4.93	7.15
	Day 5	38	40 mg iv	16.21	14.46	18.16
		38	40 mg po	12.55	11.20	14.06
AUC_t	Day 1	39	40 mg iv	9.81	8.14	11.81
		39	40 mg po	5.86	4.87	7.06
	Day 5	38	40 mg iv	16.06	14.35	17.98
		38	40 mg po	12.38	11.06	13.86
C_{max}	Day 1	39	40 mg iv	6.77	6.04	7.58
		39	40 mg po	2.97	2.65	3.32
	Day 5	37	40 mg iv	7.51	6.93	8.13
		37	40 mg po	4.60	4.25	4.99
$t_{½}$	Day 1	39	40 mg iv	1.05	0.94	1.17
		39	40 mg po	1.01	0.90	1.13
	Day 5	38	40 mg iv	1.41	1.30	1.52
		38	40 mg po	1.38	1.28	1.49
Cl	Day 1	39	40 mg iv	11.72	10.04	13.68
	Day 5	38	40 mg iv	7.13	6.39	7.95
V_{ss}	Day 1	39	40 mg iv	15.71	14.86	16.60
	Day 5	38	40 mg iv	14.32	13.50	15.20
F	Day 1	39	40 mg po	0.60	0.55	0.65
	Day 5	38	40 mg po	0.78	0.74	0.82

Table 2. Estimates of geometric means of the % time pH > 4 after I.V. and oral administration of 40 mg multiple doses of esomeprazole

Study Day	Treatment	Estimate	95% CI	
			Lower	Upper
1	40 mg iv	42.1	35.2	49.1
	40 mg po	36.5	29.6	43.5
	40 mg iv - 40 mg po	5.6	1.2	10.0
5	40 mg iv	66.2	62.4	70.0
	40 mg po	63.6	59.7	67.4
	40 mg iv - 40 mg po	2.6	-0.5	5.8

The results indicate that administration of esomeprazole I.V. results in Cmax and AUC values on day 1 that are higher by 128% and 66%, respectively relative to the oral capsule, decreasing to 63% and 29%, respectively on day 5. The absolute bioavailability of the oral capsule increased from 60% on day 1 to 78% on day 5 (Table 1).

The PD data indicate that the PD profiles following administration of similar doses of I.V. and oral esomeprazole are comparable in healthy subjects (Table 2).

Reviewer's Comments

- *Administration of multiple doses of esomeprazole resulted in greater-than-proportional increases in Cmax and AUC and a decrease in total clearance (CL), which points to non-linear PK. This was more prominent for the oral route than the I.V. route likely due to involvement of saturable first-pass metabolism.*
- *Despite the large PK differences observed with I.V. and oral dosing, no substantial PD differences were observed, particularly on day 5. This is consistent with the 40 mg dose of esomeprazole being at the plateau phase of the dose-response curve.*

NDA: 21-689/ Study SH-NEP-0003 **Study Date: Jan-Apr 2002**

Type of Submission: Multiple Dose PK/PD in Healthy Subjects

Study SH-QBE-0003 is entitled,

"A DOUBLE-BLIND, RANDOMISED, TWO-WAY CROSS-OVER COMPARATIVE STUDY OF 40 mg ESOMEPRAZOLE GIVEN INTRAVENOUSLY OVER A PERIOD OF 3 OR 30 MINUTES REGARDING EFFECT ON 24-HOUR INTRAGASTRIC pH AND PHARMACOKINETICS DURING ONCE DAILY ADMINISTRATION FOR 10 DAYS IN HEALTHY MALE AND FEMALE SUBJECTS".

Objectives

To assess the comparative PK/PD profiles of 40 mg esomeprazole I.V. infusion administered over either a 3 min or 30 min period.

Study Design

Healthy male and female subjects (n = 41, age 28.5 ± 6.7 years, wt 73.2 ± 10.0 kg) received 40 mg esomeprazole as either a 3 min or 30 min I.V. infusion QD for 10 days in a randomized, double blind, two-way crossover design separated by a washout period of at least 13 days. In each treatment period, blood samples were drawn for determination of esomeprazole before and at 5, 10, 20, 30, 45 min and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 13 and 24 hrs post-dose. 24-hr pH monitoring was conducted on days 1 and 5 of each treatment using a microelectrode attached to a Mark III Gastrograph data-logger.

Analytical Assay

Plasma samples were analyzed for esomeprazole according to method # BA-222 (LOQ = 25 nmol/L).

PK/PD Assessments

The following PK parameters were estimated for esomeprazole using non-compartmental analysis: t_{max}, C_{max}, **CL**, AUC_{0-t} and $AUC_{0-\infty}$. The following PD parameters were estimated for esomeprazole: % time with intragastric pH > 4 and median pH during the 24-hour monitoring period.

Results

Table 1. Estimates of geometric means of the primary PK parameters after administration of 40 mg doses as either a 3 min injection or 30 min infusion

Variable	Study Day	n	Treatment	Geometric Mean	95% CI Lower	95% CI Upper
AUC	Day 1	39	injection	7.10	6.08	8.29
		41	infusion	6.17	5.30	7.20
	Day 10	41	injection	12.58	11.38	13.92
		41	infusion	10.96	9.91	12.13
AUCt	Day 1	41	injection	7.16	6.15	8.35
		41	infusion	6.10	5.24	7.11
	Day 10	41	injection	12.49	11.29	13.81
		41	infusion	10.87	9.83	12.02
Cmax	Day 1	41	injection	11.87	10.62	13.28
		41	infusion	5.47	4.89	6.11
	Day 10	41	injection	13.55	12.60	14.57
		41	infusion	7.00	6.51	7.53
t½	Day 1	39	injection	0.88	0.77	1.00
		41	infusion	0.86	0.76	0.98
	Day 10	41	injection	1.23	1.14	1.34
		41	infusion	1.18	1.08	1.28
Cl	Day 1	39	injection	16.10	13.75	18.85
		41	infusion	18.60	16.02	21.79
	Day 10	41	injection	9.19	8.31	10.16
		41	infusion	10.54	9.53	11.66
Vss	Day 1	39	injection	16.85	15.68	18.11
		41	infusion	20.03	18.68	21.49
	Day 10	41	injection	15.24	14.50	16.03
		41	infusion	16.98	16.15	17.85

Table 2. Estimates of geometric means of the % time pH > 4 after I.V. administration of 40 mg single doses of esomeprazole over either 3 or 30 min

Day	Treatment	Estimate	95% CI Lower	95% CI Upper
1	injection	32.3	26.6	38.0
	infusion	33.1	27.3	38.8
	injection-infusion	-0.8	-4.0	2.4
10	injection	57.2	52.8	61.6
	infusion	55.6	51.2	60.0
	injection-infusion	1.6	-1.7	4.9

The results indicate that administration of a 40 mg dose of esomeprazole as a 3 min injection results in Cmax values that are higher by 117% and 93% on days 1 and 10, respectively relative to a 30-min infusion (Table 1).

The PD data indicate that the PD profiles are similar following administration of 40 mg doses of esomeprazole as either a 3-min or 30-min infusion (Table 2).

NDA: 21-689/ Study SH-NEP-0004 **Study Date: Mar-Apr 2001**

Type of Submission: Multiple Dose PK/PD in Healthy Subjects

Study SH-NEP-0004 is entitled,

"A PILOT STUDY TO COMPARE 40 mg ORAL AND INTRAVENOUS ESOMEPRAZOLE REGARDING EFFECT ON 24-HOUR INTRAGASTRIC pH AND PHARMACOKINETICS DURINGONCE DAILY ADMINISTRATION FOR 5 DAYS IN HEALTHY MALE AND FEMALE SUBJECTS".

Objectives

To assess the comparative PK/PD profiles of 40 mg esomeprazole I.V. infusion administered as either I.V. solution or oral capsule.

Study Design

Healthy male and female subjects (n = 12, age 24.0 ± 3.7 years, wt 74.5 ± 11.2 kg) received 40 mg esomeprazole as a 30 min I.V. infusion or an oral capsule QD for 5 days in a randomized, double blind, two-way crossover design separated by a washout period of at least 13 days. In each treatment period, blood samples were drawn for determination of esomeprazole before and at 5, 10, 20, 30, 45 min and 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 13 and 24 hrs post-dose. 24-hr pH monitoring was conducted on days 1 and 5 of each treatment using a [redacted] microelectrode.

Analytical Assay

Plasma samples were analyzed for esomeprazole according to method # BA-222 (LOQ = 25 nmol/L).

PK/PD assessments

The following PK parameters were estimated for esomeprazole using non-compartmental analysis: t_{max}, C_{max}, **CL**, AUC_{0-t} and $AUC_{0-\infty}$. The following PD parameters were estimated for esomeprazole: % time with intragastric pH > 4 and median pH during the 24-hour monitoring period.

Results

Table 1. Estimates of geometric means of the primary PK parameters after I.V. and oral administration of 40 mg multiple doses of esomeprazole

Parameter	Study Day	Treatment	Geometric Mean	95% CI Lower	95% CI Upper
AUC (umol·h/L)	1	40 mg iv	7.10	4.36	11.56
		40 mg po	3.73	2.29	6.08
	5	40 mg iv	13.09	9.10	18.82
		40 mg po	9.62	6.62	13.70
AUC_t (umol·h/L)	1	40 mg iv	7.06	4.33	11.52
		40 mg po	3.70	2.26	6.03
	5	40 mg iv	13.02	9.04	18.74
		40 mg po	9.44	6.56	13.59
C_{max} (umol/L)	1	40 mg iv	6.34	4.65	8.63
		40 mg po	2.37	1.74	3.23
	5	40 mg iv	7.78	6.14	9.85
		40 mg po	4.57	3.61	5.79
$t_{1/2}$ (h)	1	40 mg iv	0.83	0.67	1.02
		40 mg po	0.82	0.66	1.01
	5	40 mg iv	1.14	0.96	1.35
		40 mg po	1.14	0.96	1.36
CL (L/h)	1	40 mg iv	16.18	11.37	23.03
	5	40 mg iv	8.87	6.74	11.68
V_{ss} (L)	1	40 mg iv	15.10	13.55	16.82
	5	40 mg iv	13.64	12.17	15.28
F	1	40 mg po	0.53	0.42	0.66
	5	40 mg po	0.73	0.63	0.85

Table 2. Estimates of geometric means of the % time pH > 4 after I.V. and oral administration of 40 mg multiple doses of esomeprazole

Day	Treatment	Estimate	95% CI Lower	95% CI Upper
1	40 mg iv	26.1	16.9	35.3
	40 mg po	26.3	17.0	35.5
	40 mg iv – 40 mg po	-0.1	-8.2	7.9
5	40 mg iv	54.6	44.5	64.7
	40 mg po	54.1	44.0	64.3
	40 mg iv – 40 mg po	0.5	-7.4	8.4

The results indicate that administration of esomeprazole I.V. 40 mg results in Cmax and AUC values on day 1 that are higher by 167% and 90%, respectively relative to the oral capsule, decreasing to 70% and 37%, respectively on day 5. The absolute bioavailability of the oral capsule increased from 53% on day 1 to 73% on day 5 (Table 1).

The PD data indicate that the PD profiles following administration of similar doses of I.V. and oral esomeprazole are similar (Table 2).

Reviewer's Comments

- *Administration of multiple doses of esomeprazole resulted in greater-than-proportional increases in Cmax and AUC and a decrease in total clearance (CL), which points to non-linear PK. This was more prominent for the oral route than the I.V. route likely due to involvement of saturable first-pass metabolism.*
- *Despite the large PK differences observed with I.V. and oral dosing, no substantial PD differences were observed, particularly on day 5. This is consistent with the 40 mg dose of esomeprazole being at the plateau phase of the dose-response curve.*

NDA: 21-689/ Study SH-NEP-0008 Study Date: Aug-Sep 2001

Type of Submission: Multiple Dose PK/PD in Healthy Subjects

Study SH-NEP-0008 is entitled,

"AN OPEN, RANDOMISED, TWO-WAY CROSS-OVER COMPARATIVE STUDY OF 20 mg ORAL AND INTRAVENOUS ESOMEPRAZOLE REGARDING EFFECT ON 24-HOUR INTRAGASTRIC pH AND PHARMACOKINETICS DURING ONCE DAILY ADMINISTRATION FOR FIVE DAYS IN HEALTHY MALE AND FEMALE SUBJECTS".

Objectives

To assess the comparative PK/PD profiles of 20 mg esomeprazole administered as either a 30-min I.V. infusion or oral capsule.

Study Design

Healthy male and female subjects (n = 24, age 26.6 ± 7.2 years, wt 69.6 ± 8.1 kg) received 20 mg esomeprazole as either a 30 min I.V. infusion or oral capsule QD for 5 days in a randomized, open label, two-way crossover design separated by a washout period of at least 13 days. In each treatment period, blood samples were drawn for determination of esomeprazole before and at 10, 20, 30, 45 min and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 13 and 24 hrs post-dose. 24-hr pH monitoring was conducted on days 1 and 5 of each treatment using a microelectrode attached to a ——————pH-datalogger.

Analytical Assay

Plasma samples were analyzed for esomeprazole according to method # BA-222 (LOQ = 25 nmol/L).

PK/PD asessments

The following PK parameters were estimated for esomeprazole using non-compartmental analysis: t_{max}, C_{max}, **CL**, AUC_{0-t} and $AUC_{0-\infty}$. The following PD parameters were estimated for esomeprazole: % time with intragastric pH > 4 and median pH during the 24-hour monitoring period.

Results

Table 1. Estimates of geometric means of the primary PK parameters after administration of 20 mg doses as either a 30 min infusion or oral capsule

Variable	Study Day	n	Treatment	Estimate	95% CI	
					Lower	Upper
AUC	1	23	20mg iv	3.40	2.69	4.29
		23	20mg po	1.86	1.48	2.36
	5	22	20mg iv	5.11	3.96	6.61
		22	20mg po	3.92	3.03	5.06
AUC_t	1	24	20mg iv	3.35	2.63	4.26
		24	20mg po	1.69	1.33	2.15
	5	23	20mg iv	5.11	4.00	6.53
		23	20mg po	3.81	2.98	4.86
C_{max}	1	24	20mg iv	3.32	2.72	4.06
		24	20mg po	0.78	0.64	0.96
	5	23	20mg iv	3.85	3.16	4.72
		23	20mg po	1.57	1.28	1.92
$t_{½}$	1	23	20mg iv	0.79	0.67	0.94
		23	20mg po	0.95	0.80	1.13
	5	22	20mg iv	1.05	0.90	1.22
		22	20mg po	1.12	0.95	1.30
CL	1	24	20mg iv	17.07	13.96	20.88
	5	23	20mg iv	11.25	9.03	14.01
V_{SS}	1	24	20mg iv	16.45	15.10	17.92
	5	23	20mg iv	15.13	13.68	16.73
F	1	23	20mg po	0.55	0.48	0.63
	5	22	20mg po	0.77	0.67	0.88

Table 2. Estimates of geometric means of the % time pH > 4 after I.V. and oral administration of 20 mg multiple doses of esomeprazole

Study day	Treatment	Estimate	95% CI	
			Lower	Upper
1	20mg iv	30.4	24.6	36.2
	20mg po	27.5	21.7	33.3
	20mg iv- 20mg po	2.9	-1.0	6.9
5	20mg iv	49.5	41.9	57.2
	20mg po	51.1	43.5	58.7
	20mg iv - 20mg po	-1.5	-7.8	4.7

The results indicate that administration of esomeprazole I.V. 20 mg results in Cmax and AUC values on day 1 that are higher by 324% and 82%, respectively relative to the oral capsule, decreasing to 146% and 31%, respectively on day 5. The absolute bioavailability of the oral capsule increased from 55% on day 1 to 77% on day 5 (Table 1).

The PD data indicate that the PD profiles following administration of similar doses of I.V. and oral esomeprazole are comparable in healthy subjects (Table 2).

Reviewer's Comments

- *Administration of multiple doses of esomeprazole resulted in greater-than-proportional increases in Cmax and AUC and a decrease in total clearance (CL), which points to non-linear PK. This was more prominent for the oral route than the I.V. route likely due to involvement of saturable first-pass metabolism.*
- *Cmax data on day 1 for the oral treatment was not consistent with the findings of other studies, most notably study SH-QBE-0006, an identical study that was submitted under NDA 21-153. This anomaly was attributed by the sponsor to the study drug being administered under non-fasting conditions which resulted in high variability in Cmax and tmax values, especially on Day 1.*
- *Despite the large PK differences observed with I.V. and oral dosing, no substantial PD differences were observed, particularly on day 5. This is consistent with the 20 mg dose of esomeprazole being close to the plateau phase of the dose-response curve.*

NDA: 21-689/ Study SH-NEP-0009 **Study Date: Jan-Mar 2002**

Type of Submission: Single Dose PK in Healthy Subjects

Study SH-QBE-0009 is entitled,

"A SINGLE-CENTRE, OPEN, RANDOMISED, THREE-PERIOD, FIVE-TREATMENT, SIX-SEQUENCE CROSS-OVER STUDY OF PHARMACOKINETICS AFTER INTRAVENOUS SINGLE DOSE ADMINISTRATION OF 40 mg ESOMEPRAZOLE GIVEN AT DIFFERENT INFUSION RATES OR 20 mg ESOMEPRAZOLE GIVEN AS AN INJECTION IN MALE AND FEMALE SUBJECTS".

Objectives

To assess the PK profiles following single dose administration of 40 mg esomeprazole I.V. given over 10, 15, 20 or 30 min or 20 mg esomeprazole I.V given over 3 min.

Study Design

Healthy male and female subjects (n = 23, age 25.2 ± 4.5 years, wt 72.5 ± 10.4 kg) received single doses of 40 mg esomeprazole I.V. given over 10, 15, 20 or 30 min or 20 mg esomeprazole I.V given over 3 min in a randomized, open label, six-way crossover design separated by a washout period of at least 13 days. In each treatment period, blood samples were drawn for determination of esomeprazole before the start of the infusion and at the end of infusion and at 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10 and 12 hrs post-dose.

Analytical Assay

Plasma samples were analyzed for esomeprazole according to method # BA-222 (LOQ = 25 nmol/L).

PK/PD Assessments

The following PK parameters were estimated for esomeprazole using non-compartmental analysis: t_{max}, C_{max}, CL, AUC_{0-t} and $AUC_{0-\infty}$.

Results

Table 1. Estimates of geometric means of the primary PK parameters after administration of esomeprazole I.V. given over 10, 15, 20 or 30 min or 20 mg esomeprazole I.V given over 3 min

Variable	n	Treatment	Estimate	95% CI	
				Lower	Upper
AUC	23	40 mg 30 min	7.18	5.95	8.65
	11	40 mg 20 min	7.38	6.05	8.99
	12	40 mg 15 min	7.19	5.90	8.75
	11	40 mg 10 min	7.07	5.80	8.62
	12	20 mg 3 min	2.86	2.35	3.48
C_{max}	23	40 mg 30 min	5.16	4.61	5.78
	11	40 mg 20 min	6.39	5.54	7.36
	12	40 mg 15 min	6.67	5.81	7.66
	11	40 mg 10 min	7.57	6.57	8.73
	12	20 mg 3 min	3.56	3.10	4.09

Administration of 40 mg single doses of esomeprazole as I.V. infusions of varying lengths resulted in similar AUC values. However, Cmax decreased with the length of infusion.

NDA: 21-689/ Study SH-NEP-0011 **Study Date: Aug-Oct 2002**

Type of Submission: Multiple Dose PD in GERD Patients

Study SH-NEP-0011 is entitled,

"An Open, Randomized, Two-Way Crossover Study Comparing the Effect of 40 mg Esomeprazole Administered Orally and Intravenously as a 15-minute Infusion on Basal and Pentagastrin-Stimulated Acid Output in Patients with Symptoms of GERD".

Objectives

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 I.V. dosing as a 15-minute infusion at a daily dose of 40 mg.

Study Design

Male and female GERD patients, with or without a history of EE (n = 53 (25 M/28 F), age 44.6 ± 12.3 years, BMI 29.1 ± 3.7 kg/m^2) received 40 mg esomeprazole as either an oral capsule or a 15 min I.V. infusion QD for 10 days in a randomized, open label, two-way crossover design without a washout period (total study period 20 days). Basal and maximal pentagastrin-stimulated acid outputs were measured 22-24 hours on day 10 of period 1 and on days 12 and 20 of period 2. After an overnight fast on the aforementioned days, gastric juice was aspirated over two 30-min periods for BAO measurement. Thereafter, pentagastrin (6 μg/kg) S.C. was administered and four 15-min samples were collected for MAO measurement.

PD Assessment

The following PD parameters were estimated for esomeprazole: BAO and MAO 22-24 hours on day 10 of period 1 and on days 12 and 20 of period 2. If the difference between the MAOs of the two treatments at pharmacodynamic steady-state (i.e., on day 10 of each treatment period) was < 20% of the P.O. MAO value, then the two dosage forms were considered therapeutically equivalent.

Results

Table 1. Estimates of mean **MAO** values after administration of 40 mg doses as either a 15 min injection or P.O. for 10 days

	E40 oral (n=47)		E40 IV inf (n=47)		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)	2.24 (1.55 to 3.25)	3.52 (2.86)	3.02 (2.08 to 4.36)	4.74 (3.65)	1.35	1.71

Table 2. Estimates of mean **BAO** values after administration of 40 mg doses as either a 15 min injection or P.O. for 10 days

	E40 oral (n=47)		E40 IV inf (n=47)		Difference (IV - oral)	
Acid output	Median (range)	Arith. Mean (SD)	Median (range)	Arith. Mean (SD)	Median	95% CI
BAO (mmol/h)	0.05 (0.00 to 1.65)	0.22 (0.39)	0.04 (0.00 to 3.65)	0.36 (0.79)	0.02	-0.04 to 0.16

Table 3. Estimates of mean **BAO** values when switching from P.O. to I.V. dosing and vice versa

	Period 1, Day 11		Period 2, Day 3		Ratio (Period 2/Period 1)	
Switch	LS geometric mean	95% CI	LS geometric mean	95% CI	LS geometric mean	95% CI
Oral to IV (n=21)	2.82	1.95 to 4.07	4.16	2.88 to 6.02	1.48	1.14 to 1.91
IV to Oral (n=26)	2.94	1.71 to 5.06	2.57	1.50 to 4.43	0.87	0.62 to 1.23

The study results indicate that administration of 40 mg esomeprazole either as a 15-min I.V. infusion or P.O. results in higher MAO and BAO values with the I.V. route of administration relative to the P.O. route (i.e., more pronounced gastric acid suppression in GERD patients is achieved with the P.O. administration relative to I.V. administration). The clinical relevance of a mean difference of 35% on MAO is unknown.

NDA: 21-689/ Study SH-NEP-0012 **Study Date: Sep-Oct 2002**

Type of Submission: Multiple Dose PD in GERD Patients

Study SH-NEP-0012 is entitled,

"An Open, Randomized, Two-Way Crossover Study Comparing the Effect of 20 mg Esomeprazole Administered Orally and Intravenously as a 15-minute Infusion on Basal and Pentagastrin-Stimulated Acid Output in Patients with Symptoms of GERD".

Objectives

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 I.V. dosing as a 15-minute infusion at a daily dose of 20 mg.

Study Design

Male and female GERD patients, with or without a history of EE (n = 50 (27 M/23 F), age 36.6 ± 13.9 years, BMI 26.4 ± 3.8 kg/m^2) received 20 mg esomeprazole as either an oral capsule or a 15 min I.V. infusion QD for 10 days in a randomized, open label, two-way crossover design without a washout period (total study period 20 days). Basal and maximal pentagastrin-stimulated acid outputs were measured 22-24 hours on day 10 of period 1 and on days 12 and 20 of period 2. After an overnight fast on the aforementioned days, gastric juice was aspirated over two 30-min periods for BAO measurement. Thereafter, pentagastrin (6 μg/kg) S.C. was administered and four 15-min samples were collected for MAO measurement.

PD Assessment

The following PD parameters were estimated for esomeprazole: BAO and MAO 22-24 hours on day 10 of period 1 and on days 12 and 20 of period 2. If the difference between the MAOs of the two treatments at pharmacodynamic steady-state (i.e., on day 10 of each treatment period) was < 20% of the P.O. MAO value, then the two dosage forms were considered therapeutically equivalent.

Results

Table 1. Estimates of mean **MAO** values after administration of 20 mg doses as either a 15 min injection or P.O. for 10 days

	E20 oral (n=44)		E20 IV inf (n=44)		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)	3.29 (2.21 to 4.90)	5.26 (4.12)	4.11 (2.77 to 6.12)	5.95 (4.00)	1.25	1.58

Table 2. Estimates of mean **BAO** values after administration of 20 mg doses as either a 15 min injection or P.O. for 10 days

	E20 oral (n=44)		E20 IV inf (n=44)		Difference (IV - oral)	
Acid output	Median (range)	Arith. Mean (SD)	Median (range)	Arith. Mean (SD)	Median	95% CI
BAO (mmol/h)	0.25 (0.00 to 6.44)	0.82 (1.34)	0.27 (0.00 to 8.20)	0.78 (1.38)	0.03	-0.17 to 0.33

Table 3. Estimates of mean **BAO** values when switching from P.O. to I.V. dosing and vice versa

	Period 1, Day 11		Period 2, Day 3		Ratio (Period 2/Period 1)	
Switch [a]	LS geometric mean	95% CI	LS geometric mean	95% CI	LS geometric mean	95% CI
Oral to IV (n=23)	3.26	1.70 to 6.24	2.61	1.38 to 4.94	0.80	0.50 to 1.29
IV to oral (n=21)	3.77	2.03 to 7.02	4.35	2.34 to 8.10	1.15	0.83 to 1.61

The study results indicate that administration of 20 mg esomeprazole either as a 15-min I.V. infusion or P.O. results in higher MAO and BAO values with the I.V. route of administration relative to the P.O. route (i.e., more pronounced gastric acid suppression in GERD patients is achieved with the P.O. administration relative to I.V. administration). The clinical relevance of a mean difference of 25% on MAO is unknown.

NDA: 21-689/ Study D9615C00013 **Study Date: Sep-Nov 2002**

Type of Submission: Multiple Dose PD in GERD Patients

Study D9615C00014 is entitled,

"An Open, Randomized, Two-Way Crossover Study Comparing the Effect of 40 mg Esomeprazole Administered Orally and Intravenously as a 3-minute Injection on Basal and Pentagastrin-Stimulated Acid Output in Patients with Symptoms of GERD".

Objectives

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 I.V. dosing as a 3-minute infusion at a daily dose of 40 mg.

Study Design

Male and female GERD patients, with or without a history of EE (n = 53 (20 M/33 F), age 41.7 ± 11.9 years, BMI 29.4 ± 4.6 kg/m^2) received 40 mg esomeprazole as either an oral capsule or a 3 min I.V. injection QD for 10 days in a randomized, open label, two-way crossover design without a washout period (total study period 20 days). Basal and maximal pentagastrin-stimulated acid outputs were measured 22-24 hours on day 10 of period 1 and on days 12 and 20 of period 2. After an overnight fast on the aforementioned days, gastric juice was aspirated over two 30-min periods for BAO measurement. Thereafter, pentagastrin (6 μg/kg) S.C. was administered and four 15-min samples were collected for MAO measurement.

PD Assessment

The following PD parameters were estimated for esomeprazole: BAO and MAO 22-24 hours on day 10 of period 1 and on days 12 and 20 of period 2. If the difference between the MAOs of the two treatments at pharmacodynamic steady-state (i.e., on day 10 of each treatment period) was < 20% of the P.O. MAO value, then the two dosage forms were considered therapeutically equivalent.

Results

Table 1. Estimates of mean **MAO** values after administration of 40 mg doses as either a 3 min injection or P.O. for 10 days

	E40 oral (N=50)		E40 IV inj (N=50)[a]		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 [b]
MAO (mmol/h)	2.75 (1.97 to 3.85)	4.41 (3.11)	3.88 (2.76 to 5.47)	5.06 (3.90)	1.41	1.82

Table 2. Estimates of mean **BAO** values after administration of 40 mg doses as either a 3 min injection or P.O. for 10 days

	E40 oral (N=50)		E40 IV inj (N=50)		Difference (IV - oral)	
Acid output	Median (range)	Arith. Mean (SD)	Median (range)	Arith. Mean (SD)	Median	95% CI
BAO (mmol/h)	0.05 (0.00 to 2.55)	0.31 (0.55)	0.07 (0.00 to 3.34)	0.36 (0.61)	0.01	-0.06 to 0.12

Table 3. Estimates of mean **BAO** values when switching from P.O. to I.V. dosing and vice versa

	Period 1, Day 11		Period 2, Day 3		Ratio (Period 2/Period 1)	
Switch [a]	LS geometric mean	95% CI	LS geometric mean	95% CI	LS geometric mean	95% CI
Oral to IV (n=25)	2.37	1.38 to 4.07	3.94	2.29 to 6.77	1.66	0.85 to 3.26
IV to Oral (n=25)	4.26	2.73 to 6.67	3.40	2.19 to 5.28	0.80	0.60 to 1.05

The study results indicate that administration of 40 mg esomeprazole either as a 3-min injection or P.O. results in higher MAO and BAO values with the I.V. route of administration relative to the P.O. route (i.e., more pronounced gastric acid suppression in GERD patients is achieved with the P.O. administration relative to I.V. administration). The clinical relevance of a mean difference of 41% on MAO is unknown.

NDA: 21-689/ Study D9615C00014 **Study Date: Sep-Nov 2002**

Type of Submission: Multiple Dose PD in GERD Patients

Study D9615C00014 is entitled,

"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 GERD".

Objectives

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 I.V. dosing as a 3-minute infusion at a daily dose of 20 mg.

Study Design

Male and female GERD patients, with or without a history of EE (n = 50 (22 M/28 F), age 39.7 ± 13.8 years, BMI 27.0 ± 3.9 kg/m^2) received 20 mg esomeprazole as either an oral capsule or a 3 min I.V. injection QD for 10 days in a randomized, open label, two-way crossover design without a washout period (total study period 20 days). Basal and maximal pentagastrin-stimulated acid outputs were measured 22-24 hours on day 10 of period 1 and on days 12 and 20 of period 2. After an overnight fast on the aforementioned days, gastric juice was aspirated over two 30-min periods for BAO measurement. Thereafter, pentagastrin (6 μg/kg) S.C. was administered and four 15-min samples were collected for MAO measurement.

PD Assessment

The following PD parameters were estimated for esomeprazole: BAO and MAO 22-24 hours on day 10 of period 1 and on days 12 and 20 of period 2. If the difference between the MAOs of the two treatments at pharmacodynamic steady-state (i.e., on day 10 of each treatment period) was < 20% of the P.O. MAO value, then the two dosage forms were considered therapeutically equivalent.

Results

Table 1. Estimates of mean **MAO** values after administration of 20 mg doses as either a 3 min injection or P.O. for 10 days

	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 (5.29)	3.44 (2.36 to 5.00)	5.96 (5.41)	1.08	1.44

Table 2. Estimates of mean **BAO** values after administration of 20 mg doses as either a 3 min injection or P.O. for 10 days

	E20 oral (n=42)		E20 IV inj (n=42)		Difference (IV - oral)	
Acid output	Median (range)	Arith. Mean (SD)	Median (range)	Arith. Mean (SD)	Median	95% CI
BAO (mmol/h)	0.09 (0.00 to 5.38)	0.69 (1.24)	0.19 (0.00 to 6.47)	0.71 (1.24)	0.00	-0.26 to 0.16

Table 3. Estimates of mean **BAO** values when switching from P.O. to I.V. dosing and vice versa

	Period 1, Day 11		Period 2, Day 3		Ratio (Period 2/Period 1)	
Switch [a]	LS geometric mean	95% CI	LS geometric mean	95% CI	LS geometric mean	95% CI
Oral to IV (n=17)	3.01	1.55 to 5.83	3.48	1.79 to 6.74	1.16	0.61 to 2.19
IV to oral (n=24)	5.40	3.89 to 7.49	3.58	2.58 to 4.97	0.66	0.45 to 0.98

The study results indicate that administration of 20 mg esomeprazole either as a 3-min I.V. injection or P.O. results in comparable MAO and BAO values. A mean difference of 8% on MAO is unlikely to be of clinical relevance.

Appendix C

Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-689	Proposed Brand Name	Nexium I.V.
OCPB Division (I, II, III)	II	Generic Name	Esomeprazole Sodium
Medical Division	GI & Coagulation	Drug Class	Proton Pump Inhibitor
OCPB Reviewer	Suliman Al-Fayoumi	Indication(s)	Acid-related conditions
OCPB Team Leader	Suresh Doddapaneni	Dosage Form	I.V. Solution
		Dosing Regimen	20/40 mg QD
Date of Submission	9/10/03	Route of Administration	Oral
Estimated Due Date of OCPB Review	5/31/04	Sponsor	AstraZeneca Pharmaceuticals
PDUFA Due Date	7/10/04	Priority Classification	Standard (3S)
Estimated Division Due Date	6/10/04		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	2	2	1	
multiple dose:	3	3	1	
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	4	4	4	
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	4	4	4	

Phase 3 clinical trial:				
Population Analyses –				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**13**	**13**	**10**	

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?	Not needed at this time	
QBR questions (key issues to be considered)	1. Are the PK/PD profiles of esomeprazole I.V. and P.O. comparable? 2. Are the PD profiles comparable for esomeprazole I.V. infusions given over a period of 3-30 min?	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Suliman Alfayoumi
6/18/04 10:14:59 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
6/18/04 10:18:22 AM
BIOPHARMACEUTICS