AstraZeneca

Drug product:	Esomeprazole	**SYNOPSIS**	
Drug substance(s):	esomeprazole		
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PPI Comparator Study to Compare the Efficacy of Healing and Maintenance treatment with Esomeprazole and Pantoprazole in Subjects with Reflux Oesophagitis – A Multi-Centre, Randomized, Double-Blind Study - EXPO

Study centre(s)

This study was conducted in Argentina (5 centres), Australia (11 centres), Austria (20 centres), Belgium (18 centres), Brazil (5 centres), Canada (24 centres), Denmark (9 centres), Germany (105 centres), Hungary (9 centres), The Netherlands (14 centres), Poland (9 centres), Slovakia (16 centres), South Africa (12 centres) and Switzerland (6 centres).

Publications

Labenz J, Keeling N, Eklund S. A comparison of esomeprazole 40 mg once-daily and pantoprazole 40 mg once-daily for the healing of reflux oesophagitis. Gut 2003;52 (Suppl 6):A241, Abs WED-G-317.

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Labenz J, Armstrong D, Katelaris P, Schmidt E, Naucler E, Eklund S. Analysis of healing associated with 4 weeks' esomprazole 40 mg treatment relative to lansoprazole 30 mg and pantoprazole 40 mg in patients with all grades of erosive esophagitis. Gut 2004;53 (Suppl VI) A105, Abs MON-G-164.

Labenz J, Armstrong D, Katelaris P.H., Schmidt S, Adler J, Eklund S**.** A comparison of esomeprazole and pantoprazole for maintenance treatment of healed erosive esophagitis. Gut 2004;53 (Suppl VI) A108, Abs MON-G-175.

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Schmidt S, Keeling N, Eklund S, Naucler E, Labentz J. A comparison of esomeprazole 40 mg once-daily and pantoprazole 40 mg once-daily for the healing of erosive esophagitis. SAMJ South African Medical Journal 2004;94 (8):688.

Study dates		**Phase of development**
First patient enrolled	26 September 2002	Therapeutic confirmatory (IV)
Last patient completed	14 January 2004	

Objectives

Primary:

Healing phase

- To compare the efficacy (defined as complete healing of reflux oesophagitis*) of esomeprazole 40 mg o.d. with pantoprazole 40 mg o.d. during 8 weeks of treatment

Maintenance phase

- To compare endoscopic and symptomatic remission rates during 6 months of treatment with esomeprazole 20 mg o.d. or pantoprazole 20 mg. o.d., after initial healing of reflux oesophagitis

Secondary:

Healing phase

- To compare the efficacy (defined as complete healing of reflux oesophagitis) of esomeprazole 40 mg o.d. with pantoprazole 40 mg o.d. after 4 weeks' treatment
- To assess the efficacy (defined as complete healing of reflux oesophagitis*), by LA grade (separately for each baseline LA grade), of esomeprazole 40 mg o.d. and pantoprazole 40 mg o.d. after 4 and 8 weeks of treatment
- To compare time to first resolution and time to sustained resolution of heartburn between esomeprazole 40 mg o.d. and pantoprazole 40 mg o.d
- To compare complete resolution of GORD symptoms (heartburn, acid regurgitation, dysphagia and epigastric pain) with esomeprazole 40 mg o.d. or pantoprazole 40 mg o.d. at Week 4 and Week 8 of treatment

Maintenance phase

- To compare endoscopic remission rates during 6 months of treatment with esomeprazole 20 mg o.d. or pantoprazole 20 mg o.d., after initial healing of reflux oesophagitis
- To assess safety and tolerability

* Absence of breaks in the oesophageal mucosa. Edema, erythema or friability might, however, have been present according to the LA classification.

Study design

This was a multi-centre, randomized, double blind study comparing the efficacy of the healing and maintenance treatment in two phases with eosomeprazole and pantoprazole in patients with reflux oesophagitis grade A-D according to the Los Angeles (LA) Classification .The treatment period was 7 to 8 months.

Target patient population and sample size

Male and female patients, aged 18 years or older with reflux oesophagitis documented by endoscopy within 7 days before enrolment.

The healing of reflux oesophagitis during the initial healing phase was used as the basis for sample size calculation. Assuming a healing rate of 88% for esomeprazole 40 mg and 83% for pantoprazole 40 mg after eight weeks, 1500 patients were needed in each of the two treatment groups for a two sided c 2 test with an 8% significance level and a power of 95%.This number allowed for 10% of the patients to be excluded from the PP analysis.

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

Esomeprazole (NEXIUM™), 40 mg (2x20 mg capsules) or pantoprazole (ALTANA Pharma AG former Byk Gulden, Germany), 40 mg (2x20 mg capsules) was given orally once daily in the healing phase. In the maintenance phase esomeprazole, 20 mg and pantoprazole, 20 mg was given orally once daily. Batch numbers for esomeprazole were (1189-04-01-08, 20 mg) and for pantoprazole (1559-01-01-01,1559-01-01-02).

Duration of treatment

The first phase allowed for up to an 8-weeks-long healing treatment period followed by a maintenance treatment for up to 6 months comparing esomeprazole and pantoprazole.

Criteria for evaluation (main variables)

Efficacy

- Primary variable (Healing phase):
  - Proportion of patients healed after 8 weeks of treatment.
- Primary variable (Maintenance phase):
  - The number of days in the maintenance phase to relapse, based on endoscopy and GORD symptoms.
- Secondary variables (Healing phase):
  - Proportion of patients healed, based on endoscopy, after 4 and 8 weeks of healing treatment.

- The number of days to first resolution and sustained resolution of heartburn.
- Proportion of patients with complete resolution of GORD symptoms at Week 4 and Week 8.

- Secondary variable (Maintenance phase):
  - The number of days in the maintenance phase to relapse, based on endoscopy.

Safety

Serious adverse events and adverse events causing premature discontinuation of the investigational product.

Statistical methods

The primary endpoint was analysed using life table methods both for an intention-to-treat (ITT) population and for a per protocol (PP) population. Analyses of efficacy variables other than the primary endpoint were made according to the ITT approach. The safety population was used for evaluating the safety variables.

Patient population

See Table S 1

Table S 1 Patient population and disposition- ITT-population in the healing phase

		Esomeprazole 40 mg	Pantoprazole 40 mg	Total	
Population					
N randomized (N planned)		1574	1596	3170	(3000)
Demographic characteristics					
Gender (n and % of patients)	Male	969(62.0%)	1012(63.7%)	1981(62.9%)	
	Female	593(38.0%)	577(36.3%)	1170(37.1%)	
Age (years)	Mean	50.6	50.5	50.6	
	Range	18 to 86	18 to 85	18 to 86	
Race (n and % of patients)	Caucasian	1512(96.8%)	1549(97.5%)	3061(97.1%)	
	Black	13(0.4%)	15(0.9%)	28(0.9%)	
	Oriental	6(0.8%)	4(0.3%)	10(0.3%)	
	Other	31(2.0%)	21(1.3%)	52(1.7%)	

		Esomeprazole 40 mg	Pantoprazole 40 mg	Total
Baseline characteristics				
LA Grade	A	523(33.5%)	478(30.1%)	1001(31.8%)
	B	665(42.6%)	716(45.1%)	1381(43.8%)
	C	304(19.5%)	303(19.1%)	607(19.3%)
	D	70(4.5%)	92(5.8%)	162(5.1%)
Barrett's oesophagus [a]	No	1410(90.3%)	1443(90.8%)	2853(90.5%)
	Yes	152/9.7%)	146(9.2%)	298(9.5%)
History of GORD symptoms	<6 months	1(0.1%)	5(0.3%)	6(0.2%)
	6<12 months	185(11.8%)	208(13.1%)	393(12.5%)
	1-5 years	798(51.1%)	798(50.2%)	1596(50.7%)
	> 5 years	578(37%)	578(36.4%)	1156(36.7%)
Days with heartburn during last 7 days	0	3(0.2%)	0(0.0%)	3(0.1%)
	1	1(0.1%)	0(0.0%)	1(0.0%)
	2	1(0.1%)	2(0.1%)	3(0.1%)
	3	6(0.4%)	8(0.5%)	14(0.4%)
	4	200(12.8%)	192(12.1%)	392(12.4%)
	5	214(13.7%)	227(14.3%)	441(14.0%)
	6	122(7.8%)	129(8.1%)	251(8.0%)
	7	1015(65%)	1031(64.9%)	2046(64.9%)
Severity of heartburn	None	3(0.2%)	0(0.0%)	3(0.1%)
	Mild	8(0.5%)	7(0.4%)	15(0.5%)
	Moderate	873(55.9%)	844(53.1%)	1717(54.5%)
	Severe	678(43.4%)	738(46.4%)	1416(44.9%)
Helicobacter pylori status	Negative	1078(69.0%)	1113(70.0%)	2191(69.5%)
	Positive	429(27.5%)	412(25.9%)	841(26.7%)
	Missing	55(3.5%)	64(4.0%)	119(3.8%)

[a] Barrett's oesophagus was also assessed at visit 2 or 3 (when EE was healed in most patients) making the precision in the assessment more accurate and classified according to a new classification. The proportion of patients with grades W-Z (corresponding to at least 1 cm of Barrett's mucosa) was 8.4%.

Table S 2 Disposition

		Esomeprazole 40 mg	Pantoprazole 40 mg	Total
Healing phase				
N of patients who	completed	1411	1402	2813
	discontinued	163	194	357
N analysed for safety[a]		1562	1587	3149
N analysed for efficacy (ITT)		1562	1589	3151
N analysed for efficacy (PP)		1341	1365	2706
Maintenance phase		**Esomeprazole 20 mg**	**Pantoprazole 20 mg**	
N of patients who	completed	1208	1141	2349
	discontinued	190	274	464
N analysed for safety[a]		1383	1402	2785
N analysed for efficacy (ITT)		1377	1389	2766
N analysed for efficacy (PP)		1138	1126	2264

[a] Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing
ITT=Intention-to-treat; N=Number; PP=Per-protocol

No clinically significant differences were shown between the two treatment groups with reference to the baseline demographic and the clinical characteristics.

Efficacy results

Table S 3 Life table estimates together with 95% CI and a log-rank test for the difference between treatments in the healing of reflux oesophagitis by Week 8, ITT

Treatment	Estimate	95% CI		p-value
		lower	upper	(vs P40)
Esomeprazole 40 mg	95.51%	94.43%	96.58%	0.0006
Pantoprazole 40 mg	92.03%	90.65%	93.41%	.

For the primary variable in the healing phase of the study esomeprazole was significantly more effective than pantoprazole in the healing of erosive oesophagitis within 8 weeks of treatment (Table S 3). Esomeprazole was also significantly more effective in healing at 4 weeks of treatment and in healing at 4 and 8 weeks after making adjustments for imbalances in baseline grade of oesophagitis. Esomeprazole also achieved faster resolution of diary-

recorded heartburn and a higher proportion of investigator reported resolution of heartburn and dysphagia at 4 weeks of treatment.

Table S 4 Life table estimates of percentage in remission at 6 months together with 95% CI and a log rank test for the difference in remission rates, ITT

Treatment	Estimate	95% CI		P-value
		lower	upper	
Esomeprazole 20mg	87.0	85.1	88.9	<.0001
Pantoprazole 20mg	74.9	72.5	77.3	

For the primary variable in the maintenance phase esomeprazole was significantly more effective than pantoprazole in maintaining patients in remission (endoscopic and symptomatic) (Table S 4). Esomeprazole was also more effective in maining pure endoscopic remission.

In a management comparison between two subsets of patients, who were given the same drug in both phases of the study, an esopmeprazole regimen was shown to be significantly more effective than a pantoprazole regimen, as measured by the proportion of patients who were healed and kept in remission until the end of the maintenance phase (Table S 5).

Table S 5 Number and proportion of patients who were healed and still in remission at 6 months (comparison of management regimes). ITT population in the healing phase.

LA grade at baseline	Esomeprazole	Pantoprazole	p-value[a]
Grade A	204/267 (76.4%)	169/248 (68.1%)	
Grade B	230/316 (72.8%)	205/352 (58.2%)	
Grade C	93/151 (61.6%)	79/147 (53.7%)	
Grade D	20/38 (52.6%)	22/50 (44.0%)	
All	547/772 (70.9%)	475/797 (59.6%)	<.0001

[a] Mantel-Haenzel test stratified on baseline LA grade

Safety results

Healing phase

The number of patients with reported SAEs/DAEs was similar in the two treatment groups (3.3% in E40 , 2.7% in P40). The most common SAEs/DAEs in the E40 group were nausea, dizziness, abdominal pain NOS, abdominal pain upper, diarrhoea and headache.

Two deaths were reported, one in each treatment group. None of the SAEs were assessed as causally related to the investigational product.

DAEs belonging to gastrointestinal disorder were more commonly reported compared to the other system organ classes. No differences of clinical significance were seen between the two treatment groups.

Table S 6 Number (%) of patients who had an SAE/DAE in any category in the healing phase, safety population

	N(%) of patients[a] who had an adverse event in each category			
Drug	**Esomeprazole 40 mg**		**Pantoprazole 40 mg**	
No of patients	**(n=1562)**		**(n=1587)**	
Category of adverse events				
SAEs/DAEs	51	(3.3)	42	(2.7)
SAEs	23	(1.5)	20	(1.3)
SAEs leading to death	1	(0.1)	1	(0.1)
SAEs not leading to death	22	(1.4)	19	(1.2)
DAEs[b]	33	(2.1)	29	(1.8)
Attributable SAEs[c]	0		0	
SAE/DAE with severe intensity	19	(1.2)	18	(1.1)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

[b] The number of patients may differ from Section 6 as only AEs leading to discontinuation of investigational product are listed in the table.

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

Table S 7 Number (%) of patients with the most commonly reported SAEs/ DAEs in the healing phase presented by preferred term, sorted by the E40 treatment group, safety population

Preferred term	**Esomeprazole 40 mg (n=1562)**		**Pantoprazole 40 mg (n=1587)**	
	n	**(%)**	**n**	**(%)**
Nausea	6	(0.4)	3	(0.2)
Dizziness	5	(0.3)	3	(0.2)
Abdominal pain NOS	3	(0.2)	2	(0.1)
Abdominal pain upper	3	(0.2)	2	(0.1)
Diarrhoea NOS	3	(0.2)	4	(0.3)
Headache	3	(0.2)	5	(0.3)
Rash NOS	3	(0.2)	1	(0.1)
Abdominal distension	2	(0.1)	0	
Epigastric discomfort	2	(0.1)	0	
Hypersensitivity NOS	2	(0.1)	0	
Myalgia	2	(0.1)	0	
Vertigo	2	(0.1)	2	(0.1)

Preferred term	Esomeprazole 40 mg (n=1562)		Pantoprazole 40 mg (n=1587)	
	n	(%)	n	(%)
Chest pain	1	(0.1)	3	(0.2)
Pruritus	0		3	(0.2)
Asthma NOS	0		2	(0.1)
Restlessness	0		2	(0.1)

SAEs/DAEs experienced by at least two patients in any treatment group are included in the table.
Data from Table 62

Maintenance phase

The number of patients with reported SAEs/DAEs was similar in the two treatment groups (4.2% in E20 , 3.2% in P20). The most common SAEs/DAEs in the E20 group were headache, intervertebral disc protrusio, myocardial infarction, asthma and cholelithiasis.

Four deaths were reported, two in each treatment group. There was no difference of clinical importance in the distribution of the SAEs in the different system organ classes. One of the SAEs, hepatocellular damage in the P20 group, was assessed as causally related to the investigational product.

DAEs belonging to gastrointestinal disorder were more commonly reported compared to the other system organ classes. No differences of clinical significance were seen between the two treatment groups.

Table S 8 Number (%) of patients who had an SAE/DAE in any category in the maintenance phase, safety population

	N(%) of subjects[a] who had an adverse event in each category			
Drug	**Esomeprazole 20 mg**		**Pantoprazole 20 mg**	
No of patients	**(n=1383)**		**(n=1402)**	
Category of adverse events				
SAEs/DAEs	58	(4.2)	45	(3.2)
SAEs	45	(3.3)	32	(2.3)
SAEs leading to death	2	(0.1)	2	(0.1)

	N(%) of subjects[a] who had an adverse event in each category			
Drug	**Esomeprazole 20 mg**		**Pantoprazole 20 mg**	
No of patients	**(n=1383)**		**(n=1402)**	
SAEs not leading to death	43	(3.1)	30	(2.1)
DAEs[b]	19	(1.4)	18	(1.3)
Attributable SAEs[c]	0		1	(0.1)
SAEs/DAEs with severe intensity	33	(2.4)	22	(1.6)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

[b] The number of patients may differ from Section 6 as only AEs leading to discontinuation of investigational product are listed in the table.

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

Table S 9 Number (%) of patients with the most commonly reported SAEs/ DAEs in the maintenance phase presented by preferred term, sorted by the E40 treatment group, safety population

Preferred term	**Esomeprazole 20 mg (n=1383)**		**Pantoprazole 20 mg (n=1402)**	
	n	**(%)**	**n**	**(%)**
Headache	3	(0.2)	3	(0.2)
Intervertebral disc protrusion	3	(0.2)	0	
Myocardial infarction	3	(0.2)	1	(0.1)
Asthma	2	(0.1)	1	(0.1)
Cholelithiasis	2	(0.1)	1	(0.1)
Depression	2	(0.1)	0	
Diverticulitis	2	(0.1)	0	
Goitre	2	(0.1)	0	
Nausea	2	(0.1)	2	(0.1)
Uterine leiomyoma	2	(0.1)	1	(0.1)
Angina pectoris	1	(0.1)	2	(0.1)
Diarrhoea	0		4	(0.3)
Constipation	0		3	(0.2)

SAEs/DAEs experienced by at least two patients in any treatment group are included in the table.
Data from Table 63

Date of the report 10 November, 2004