AstraZeneca

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SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Nexium™
ACTIVE INGREDIENT: Esomeprazole

Trial title (number): A study to assess the effectiveness of maintenance treatment with esomeprazole 20mg od in patients with reflux disease previously maintained with lansoprazole 30mg od - A 3 month, randomised, double blind, double dummy, multicentre study- (30/20 Study)

Developmental phase: IV
First subject recruited: 10 September 2003
Last subject completed: 01 October 2004
Approval date: 21 July 2003

Primary objective

The primary objective of this study was to assess the proportion of patients requiring maintenance treatment for reflux oesophagitis (RO) who are willing to continue onesomeprazole20mg od or lansoprazole 30mg od at 3 months (13 weeks +/- 7 days).

Secondary objectives

Secondary objectives of the study were

- to assess the severity and frequency of RO symptoms (e.g. heartburn, regurgitationand dysphagia) at entry and after 3 months.
- to assess the severity and frequency of other GI symptoms (e.g. epigastric pain,nausea, diarrhoea) at entry and after 3 months.
- to assess Patient Reported Outcomes (e.g. Health related Quality of Life, OverallTreatment Evaluation and Patient Satisfaction).
- to assess safety.
- to compare the utilisation of healthcare resources from the perspective of the NHS.

Design:

This is a randomised, double-blind, double dummy, parallel-group, multicentre study to assess the effectiveness of esomeprazole 20mg od with lansoprazole 30mg od in patients with previously maintained reflux disease.
The study consisted of a 3 month (13 weeks +/- 1 week) treatment period. It aimed to recruit a total of 284 randomised patients at approximately 36 primary health care centres across the UK.
The study was comprised of 2 visits, and the total treatment time being 12-14 weeks.
Visit 1: start of treatment period, enrolment and randomisation visit, Day 0
Visit 2: final visit, occured 13 weeks (+/- 1 week) after Visit 1

Population:

Eligible patients had a documented history of RO (of any grade) verified by endoscopy, previously maintained on lansoprazole 30mg od for a minimum of 3 months. Patients were due for a review of their current maintenance PPI treatment. Patients must have experienced no more than 1 day of mild heartburn during the previous week (7 days) and must be satisfied with their current treatment (i.e. they would be willing to continue on maintenance treatmentwith lansoprazole 30mg od).

Main inclusion criteria

Patients with a documented history of endoscopically verified reflux oesophagitis (of any grade).

Patients who are currently maintained on lansoprazole 30mg capsules od and have been on this dose continuously for a minimum of 3 months. Continuous is defined as: a minimum of 84 lansoprazole 30mg capsules prescribed over the last 3 months **AND** confirmation by the patient that they have taken the medication as directed by their primary care physician i.e. one capsule per day.
Patients who have experienced no more than 1 day of mild heartburn during the previous week AND are satisfied with their current treatment (i.e. they would be willing to continue on maintenance treatment with lansoprazole 30mg od).

Main Exclusion criteria

Complications related to GORD such as oesophageal stricture, Barrett.s Oesophagus of any length or confirmed low/high grade dysplasia of the oesophagus in Barrett.s Oesophagus (refer to List of Abbreviations and Definitions for definition of Barrett.s Oesophagus).

Patients using an H2RA (either prescribed or OTC) or a PPI other than lansoprazole 30mg capsules od for maintenance of their reflux disease. Patients currently being maintained on lansoprazole 30mg Fastabs are not eligible for entry in the study.

Investigational Product (Formulation and batch numbers were as follows)

Esomeprazole (NEXIUM®) 20 mg tablet, or lansoprazole (ZOTON®, Wyeth Laboratories) 30 mg capsule were administered orally once daily before breakfast. Matching placebos to esomeprazole 20 mg and lansoprazole 30 mg were used. Batch numbers were: esomeprazole 20 mg H 1370-01-01-07 (expiry date 31 March 2005), H 1370-01-01-08 (expiry date 31 October 2005); lansoprazole 30 mg H 0995-06-01-06 (expiry date 31 March 2005), H 0995-06-01-07 (expiry date 30 November 2005); placebo to match esomeprazole 20 mg H 1482-01-01-02 (expiry date 31 March 2005) and placebo to match lansoprazole 30 mg H 14812-01-01-01 (expiry date 31 March 2005, H 1481-01-01-02 (expiry date 31 October 2005).

Key assessments:

Patients were asked to complete the following questionnaires at each visit.
Overall Treatment Evaluation Questionaire
Quality of Life in Reflux and Dyspepsia (QOLRAD) Questionaire
Treatment Satisfaction Questionnaire (TSQ)

Patients were also asked by the doctor about there symptoms in the last 7 days (Heartburn, Regurgitation, Dysphagia, Epigastric pain, Nausea and Diarrohea) and the results recorded.

Safety:
Concomitant medications were collected throughout the study. Only AEs which resulted in the withdrawal of study medication and SAEs were recorded.

RESULTS

Table S1 Patient population and disposition

Demographic or baseline characteristic		Treatment group					
		Esomeprazole		Lansoprazole		Total	
Population							
N randomised (N planned)		166	142	163	142	329	284
Demographic characteristics (FAS)							
Sex (n and % of patients)	Male	89	(53.6)	74	(45.7)	163	(49.7)
	Female	77	(46.4)	88	(54.3)	165	(50.3)
Age (years)	Mean (SD)	55.9	(13.1)	56.3	(13.2)	56.1	(13.1)
	Range	18 to 85		21 to 81		18 to 85	
Race (n and % of patients)	Caucasian	166	(100)	162	(100)	328	(100)
Baseline characteristics (FAS)							
Weight (kg)	Mean (SD)	81.7	(15.6)	79.5	(15.0)	80.6	(15.3)
	Range	49 to 131		50 to 127		49 to 131	
Height (cm)	Mean (SD)	168.2	(9.7)	167.3	(9.1)	167.7	(9.4)
	Range	150 to 190		151 to 198		150 to 198	
Severity of heartburn	None	116	(69.9)	128	(79.0)	244	(74.4)
	Mild	43	(25.9)	21	(13.0)	64	(19.5)
	Moderate	6	(3.6)	12	(7.4)	18	(5.5)
	Severe	1	(0.6)	1	(0.6)	2	(0.6)
Disposition							
N (%) of patients who	completed	141	(84.9)	129	(79.1)	270	(82.1)
	discontinued	25	(15.1)	34	(20.9)	59	(17.9)
N analysed for safety[a]		166	(100)	163	(100)	329	(100)
N analysed for efficacy (FAS)		166	(100)	162	(99.4)	328	(99.7)
N analysed for efficacy (PP)		142	(85.5)	126	(77.3)	268	(81.5)

[a] Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing

FAS=Full analysis set; N=Number; PP=Per-protocol

Primary variable:

Proportion of patients willing to continue at 3 months

Approximately 92% of patients (91.6%, 152/166) taking esomeprazole were willing to continue treatment after 3 months compared with 88% of patients (88.3%, 143/162) taking lansoprazole. The estimated difference between treatments was 3.3%, with the 95% confidence intervals (-3.2, 9.8). As the lower limit of the confidence interval was higher than –10%, non-inferiority of esomeprazole to lansoprazole was established. These results therefore indicate that patients taking esomeprazole in this clinical setting

were at least as willing to continue on treatment after 3 months as patients on lansoprazole 30 mg. Results from a PP analysis fully supported those for the FAS (esomeprazole 90.8%; lansoprazole 87.3%; estimate of difference 3.5% (95% CI -4.0, 11.0).

Secondary variables

Severity and frequency of reflux and other GI symptoms

Descriptive comparison showed that the frequency and severity of RO (heartburn, regurgitation and dysphagia) and other symptoms (epigastric pain, nausea and diarrhoea) for the 2 treatment groups were generally similar at baseline and 3 months. However, there were slight trends of a greater improvement at 3 months in heartburn symptoms with esomeprazole and in regurgitation symptoms with lansoprazole. Dysphagia and diarrhoea symptoms were also reported slightly more at 3 months in patients treated with lansoprazole than in esomeprazole treated patients, although the patients numbers involved were small.

Patient reported outcome results

There was a consistent very minor deterioration from the high health related quality of life at baseline, as assessed by the Quality of Life in Reflux and Dyspepsia (QOLRAD) domain scores from baseline to 3 months in both treatment groups. QOLRAD point score reductions ranged from 0 to 0.36 and were not considered to be clinically relevant. There was no significant difference between esomeprazole 20 mg and lansoprazole 30 mg in the mean change in QOLRAD domains from baseline.

The patient's global evaluation of change in upper GI symptoms, as assessed in the Overall Treatment Evaluation (OTE) questionnaire at 3 months indicated that 26% of esomeprazole treated patients and 25% of lansoprazole treated patients assessed their overall treatment as better. There was no significant difference in the overall treatment evaluation between the treatment groups (p=0.622, Wilcoxon Rank Sum test).

In the treatment satisfaction questionnaire (TSQ), 48% of esomeprazole treated patients and 49% of lansoprazole treated patients were satisfied with their treatment, according to their positive response to all 7 questions. Overall, there was little difference between the treatment groups, regarding patient satisfaction with treatment.

Health economics results

The direct medical costs associated with resource use are given in Table S2. Overall, the direct medical costs from a NHS perspective were significantly lower in the esomeprazole 20 mg treatment group (mean per patient cost: £63.19) than in the lansoprazole 30 mg treatment group (mean per patient cost: £80.89) during the course of the study. Treatment with lansoprazole 30 mg was £17.70 more expensive per patient over the 12-week period. This was primarily due to the lower cost of study medication with esomeprazole 20 mg (mean £54.34) compared with lansoprazole 30 mg (mean £71.99).

Table S2 **Direct medical costs from the NHS perspective**

Cost component	Esomeprazole	Lansoprazole	Mean difference and 95% CI
Study Drug (£)			
Mean (SD)	54.34 (14.95)	71.99 (24.03)	
Concomitant medications (£)			
Mean (SD)	2.99 (10.96)	2.28 (7.65)	
GORD events [a] (£)			
Mean (SD)	5.87 (32.19)	6.62 (31.47)	
Per patient cost (£)			
Mean (SD)	63.19 (37.85)	80.89 (40.98)	-17.70
95% CI	58.11, 69.75	75.12, 87.80	-25.83, -8.67
Per patient daily cost (£)			
Mean (SD)	0.79 (1.13)	0.98 (0.41)	-0.19
95% CI	0.68, 0.99	0.92, 1.05	-0.33, 0.02

CI=Confidence intervals (derived using non-parametric bootstrapping)

[a] GORD events included RO related health care contacts and RO related tests and procedures.

Safety results

A summary of the SAEs and DAEs is presented in Table S3. Overall, esomeprazole and lansoprazole were reasonably well tolerated over the 3-month treatment period. Only one of the SAEs was reported as related to the study drug: a report of angioedema of the throat and tongue experienced by a patient after an esomeprazole 20 mg tablet became stuck in the patient's throat. The incidence of DAEs reported during the study was higher than expected, but raised no safety concerns and the nature of the DAEs was as expected given the patient population under study.

Table S3 **Number (%) of patients who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set)**

Category of adverse event	Esomeprazole (n=166)	Lansoprazole (n=163)
N (%) of patients who had an adverse event in each category[a]		
Serious adverse events leading to death	1 (0.6%)	0
Serious adverse events not leading to death	1 (0.6%)	3 (1.8%)
Discontinuations of study treatment due to adverse events	19 (11.4%)	26 (16.0%)
Adverse events causally related to study treatment	12 (7.2%)	15 (9.2%)
Total number of serious adverse events[b]	2 (1.2%)	3 (1.8%)

[a] Patients may have adverse events counted as both serious and leading to discontinuation of study treatment. 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] Events are counted by preferred term, ie, for patients with multiple events falling under the same preferred term, only 1 frequency of the event is counted.

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