AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Nexium® mups 40 mg / 20 mg
ACTIVE INGREDIENT: Esomeprazole magnesium

Study No: NCT00612404
German PMS trial (AWB) to evaluate the relationship between subjective gastrointestinal symptoms and findings of a laryngopharyngeal-esophagogastric endoscopy with respect to the medicinal pre-therapy

Developmental phase: Phase IV, PMS (AWB)
Study Completion Date: 21-Dec-2006
Date of Report: 31-Jan-2008

OBJECTIVES:

This epidemiological PMS study had the following objectives:

- to gain insight into the relationship between subjective gastrointestinal symptoms and findings of a laryngopharyngeal-esophagogastric endoscopy with respect to the medicinal pretreatment;
- to gain insight into the currently used treatment strategies with esomeprazole as related to endoscopic findings.

SUBJECT SELECTION CRITERIA

Gastroenterologists were asked to document relevant information for this PMS study for those subjects for whom an endoscopy was performed and esomeprazole was prescribed as subsequent medicinal therapy. The participating physicians had to be aware of and take into account limitations, possible risks, warnings, contraindications, etc. mentioned in the SmPC of esomeprazole.

METHODS:

This PMS study was a non-interventional, multi-centre, prospective epidemiological observational study with 822 centres in Germany. It was planned that each centre had to document endoscopy findings and experiences with esomeprazole for a maximum of 20 subjects. The selection of the centres was made by the sponsor out of a pool about 1500 gastroenterologists in Germany.
Gastroenterologists were asked to document relevant information for this PMS study for those subjects for whom an endoscopy was performed and esomeprazole was prescribed as subsequent medicinal therapy.

Due to the non-interventional character of this PMS study, only an exploratory-descriptive statistical analysis covering all parameters (qualitative, quantitative, text fields including derived and coded variables) from the CRFs was performed.

Subjects fulfilling at least one of the criteria below:
1. missing CRF Page 1;
2. date of Visit 1 missing;
3. date of Visit 1 before start date of the PMS study (07-Sep-2005);
4. dates of consecutive visits not in a consecutive order.

were considered as non-evaluable. All other subjects were considered as evaluable for the statistical analysis.

The relationship between subjective gastrointestinal symptoms and findings of a laryngopharyngeal-esophagogastric endoscopy with respect to the medicinal pretreatment and treatment strategies with esomeprazole was investigated by assessment of:

Helicobacter pylori status (if available); presumptive diagnosis (reason for endoscopy); gastrointestinal symptoms; details about relevant medicinal pretreatment; relevant concomitant medication (incl. NSAIDs, if applicable) as well as prescribed esomeprazole regimes; endoscopy findings; physician's and subject's assessment of the efficacy and tolerability of prescribed esomeprazole regimes; adverse events.

RESULTS:

Patient population

In total, 1717 of 16255 subjects (10.6%) had to be excluded from the statistical analysis because the subjects fulfilled at least one of the criteria for non-evaluability (see above). Overall, 14538 of 16255 treated subjects (89.4%) were considered as evaluable.
The gender distribution was approximately even, 7199/14538 evaluable subjects (49.5%) were male and 7131/14538 subjects (49.1%) were female. No information on gender was available for 208/14538 subjects (1.4%). Average age amounted to 53.0 ± 15.8 [54.0] (mean ± SD [median]) years.
A positive Helicobacter pylori (H.p.) status was assessed in 1999/14538 subjects (13.75%).
Presumptive diagnosis and indication for endoscopy is summarized in Table S 1.

Table S 1 Presumptive diagnosis and indication for gastroscopy - Evaluable subjects -

	Evaluable subjects, n=14538	
	n	%
ERD	7336	50.4
Barrett esophagus	641	4.4
NSAID-related ulcer	1288	8.9
NERD	2562	17.6
H.p. related ulcer	2216	15.2
Other presumption diagnosis	1993	13.7
No presumption diagnosis documented	233	1.6

Multiple entries per patient possible.

Relevant pre-medication (medication in the context of the presumption diagnosis) was taken by 3756/14538 subjects (25.84%). 2536/14538 subjects (17.44%) took proton pump inhibitors (PPI), 607/14538 subjects (4.18%) took H2-antagonists and 738/14538 subjects (5.08%) reported the intake of other relevant pre-medication.

Relevant concomitant medication was summarised under two categories: Medication (3544/14538 subjects (24.38%)) and NSAR-medication (1577/14538 subjects (10.85%)).

Gastrointestinal symptoms at Visit 1 were present in 13686/14538 subjects (94.14%). Most prominent symptom was "A burning feeling behind the breastbone" (8878/14538 subjects (61.07%)).

Efficacy results

Dosing and duration of esomeprazole therapy

Based on clinical symptoms and endoscopic findings, 12978/14538 subjects (89.27%) received esomeprazole and 1560/14538 subjects (10.73%) received no esomeprazole therapy.
Esomeprazole was prescribed at a dose of 20 mg per day in 4797/14538 subjects (33.00%), at a dose of 40 mg per day in 7551/14538 subjects (51.94%) and at another dose in 443/14538 subjects (3.05%). The mean daily dose of esomeprazole amounted to 33.5 ± 12.5 [40.0] mg per day.
Planned duration of medical therapy with esomeprazole was one week in 704/14538 (4.84%), 2 weeks in 3306/14538 (22.74%) and 4 weeks in 5869/14538 (40.37%) subjects, or another duration in 2281/14538 (15.69%) subjects.

Relationship between endoscopy findings and duration of esomeprazole therapy

Presence of findings in the hypopharynx was not correlated with the planned duration of esomeprazole therapy (Kendall's τ-b = -0.013; Spearman Correlation = -0.014). However, almost half of the patients with findings in the hypopharynx (769/1558 subjects (49.4%)) were prescribed esomeprazole therapy for 4 weeks.
Presence of findings in the oesophagus was not correlated with the planned duration of esomeprazole therapy (Kendall's τ-b = 0.025; Spearman Correlation = 0.027). Again, almost half of the patients with findings in the oesophagus (4766/10450 subjects (45.6%)) were prescribed esomeprazole therapy for 4 weeks.

Presence of findings in the ventricle was not correlated with the planned duration of esomeprazole therapy (Kendall's τ-b = 0.014; Spearman Correlation = 0.015). Here, the greatest share of patients with findings in the ventricle (4671/11759 subjects (39.7%)) was prescribed esomeprazole therapy for 4 weeks.

Relationship between endoscopy findings and dose of esomeprazole therapy
Presence of findings in the hypopharynx was not correlated with the prescribed dose of esomeprazole therapy (Kendall's τ-b = -0.017; Spearman Correlation = -0.018). However, more than half of the patients with findings in the hypopharynx (948/1558 subjects (60.8%)) was prescribed esomeprazole therapy of 40 mg daily.
Presence of findings in the oesophagus was not correlated with the prescribed dose of esomeprazole therapy (Kendall's τ-b = -0.050; Spearman Correlation = -0.053). Again, more than half of the patients with findings in the oesophagus (6019/10450 subjects (57.6%)) was prescribed esomeprazole therapy of 40 mg daily.
Presence of findings in the ventricle was not correlated with the prescribed dose of esomeprazole therapy (Kendall's τ-b = 0.028; Spearman Correlation = 0.030). Again, more than half of the patients with findings in the ventricle (5992/11759 subjects (51.0%)) was prescribed esomeprazole therapy of 40 mg daily.

Relationship between gastrointestinal symptoms and findings of endoscopy
The pre-medication had no influence on the relationship between gastrointestinal symptoms and findings of endoscopy. Endoscopic findings in the oesophagus were well associated with all 7 gastrointestinal symptoms ('A burning feeling behind the breastbone', 'Pain behind the breastbone', 'A burning feeling in the centre of the epigastrium', 'Pain in the centre of the epigastrium', 'A sour taste in the mouth', 'Unpleasant upward motions of gastric contents' and 'Other symptom') inquired, whereas endoscopic findings in the hypopharynx were comparatively rare and in general not relevant for gastrointestinal complaints.

Effect of pretreatment:
Pretreatment had no influence on prevalence and relative risk for the various combinations of gastrointestinal symptoms and endoscopic findings. The results were also very similar regarding the different gastrointestinal findings.
Depending on symptom and pretreatment, the prevalence of endoscopic hypopharynx findings varied between 13.7% and 27.5% and the associated relative risk (in relation to patients without the analysed symptom) ranged between 0,69 and 4,89. For oesophagus findings, prevalence was between 72.7% and 91.5%, for ventricle findings values between 47.5% and 74.5% were calculated. The relative risk was close to 1 in all these cases.

Effect of helicobacter infection:
Infection with Helicobacter pylori increased the prevalence (ca. 75%) and relative risk (ca. 1.5) of endoscopic ventricle findings, while reducing the prevalence of findings in the oesophagus, especially for those symptoms related to the epigastrium. On the other hand, negative finding of Helicobacter pylori infection led to a reduced relative risk and prevalence (ca. 50%) of endoscopic findings in the ventricle.

Effect of presumptive diagnosis:
Regardless of symptoms, the relative risk for endoscopic findings in the hypopharynx was minimal (ca. 1.5) in patients with ERD or with NERD and reached a maximum of ca. 5 in patients with presumption diagnosis of NSAID-related ulcer.
The relative risk for endoscopic findings in the oesophagus and the ventricle was between 1 and 2 for all combinations of gastrointestinal symptoms and presumption diagnoses.
Regardless of symptoms the prevalence of hypopharynx findings was minimal (ca. 13%) in patients with other presumption diagnoses and reached a maximum of ca. 39% in patients with presumption diagnosis of Barrett oesophagus.

Regardless of symptoms the prevalence of oesophagus findings was minimal (ca. 60%) in patients with Helicobacter pylori related ulcer and reached a maximum of ca. 97% in patients with presumption diagnosis of Barrett oesophagus.
Regardless of symptoms the prevalence of ventricle findings was minimal (ca. 40%) in patients with NERD and reached a maximum of ca. 93% in patients with presumption diagnosis of NSAID-related ulcer.

Effect of gender:
In comparison, males and females had a comparable prevalence of endoscopic findings in the ventricle (both ca. 55%), whereas the prevalence of endoscopic findings in the oesophagus was slightly lower for females (ca. 80% vs. ca. 85%).

Changes in endoscopic findings and gastrointestinal symptoms between Visit 1 and Visit 2
From 5595 subjects with evaluable documentation of Visit 2, only 1272 subjects (22.73%) did undergo a second endoscopy. Most patients without a second endoscopy probably did not present an indication for this examination any more. This conclusion is supported by the marked decrease in the presence of gastrointestinal symptoms from Visit 1 to Visit 2 as the rate of patients with any gastrointestinal symptoms decreased from 13686/14538 (94.14%) to 1048/5595 subjects (18.73%), respectively. New findings in hypopharynx, oesophagus and ventricle were rare (less than 1%). The prevalence of endoscopic findings in patients with two endoscopic examinations (1272 subjects) showed a marked reduction in the number of findings that was more pronounced for the hypopharynx and ventricle than for the oesophagus.

Assessment of therapy at Visit 2
5595 subjects presented evaluable data on Visit 2, including assessment of efficacy and tolerability. In most cases, the assessment of efficacy and tolerability by patient and investigator was good or very good.

Safety results

Of the 14538 evaluable subjects, 44 subjects (0.30%) reported experience of at least one AE after the start of esomeprazole therapy. In total, 15 subjects (0.10%) reported AEs that were judged by the physicians to be related to esomeprazole. The primary system-organ classes with the highest number of subjects experiencing AEs were ‘gastrointestinal disorders’ (18 subjects (0.1238%)) and ‘infections and infestations’ (11 subjects (0.0756%)).
Most reported AEs were mild or moderate in intensity, required no action and were assessed as recovered. Only 5 subjects (0.03%) reported experience of AEs of severe intensity. Dose reduction, temporary or complete stop of esomeprazole therapy was performed in 4 (0.03%), 5 (0.03%) and 5 (0.03%) subjects, respectively. In 11 subjects (0.08%) with reported AEs the outcome of at least one AE was assessed as not yet recovered.
Deaths or serious adverse events (SAE) fulfilling the predefined criteria of analysis were not recorded. Serious adverse events documented but not used for the analysis as well as serious adverse events documented in non-evaluable subjects were observed in three patients: In one evaluable patient with missing onset date of the SAE (myocardial infarction) and in two non-evaluable patients. This comprised one patient each with oesophageal candidiasis of severe intensity and with visual disturbance of mild intensity. Both SAEs were considered as related to esomeprazole.