AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

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

Study No: NCT00612027
TransGERD; German PMS trial no. 9

Developmental phase: Phase IV, German PMS trial (AWB)
Date of Report: 07 March 2008

OBJECTIVES:

This PMS study had the objective to evaluate under ordinary medical care conditions the efficacy and tolerability of esomeprazole in patients who were treated by general practitioners and internists. In detail, this PMS study had the following objectives:

1. Efficacy:

- to gain further insight into the efficacy of esomeprazole under ordinary medical care conditions in consideration of gastroenterological diagnoses and presence of specific acid-associated symptoms at baseline;
- by estimating the proportion of treated subjects without any specific acid-associated symptoms at the end of the observational period;
- by assessing the change in intensity of specific acid-associated symptoms.

2. Tolerability (adverse events):

- to gain further insight into the occurrence of unknown, unexpected and/or rarely occurring adverse events (AE) by estimating the incidence under ordinary medical care conditions.

3. Evaluation of a diagnosis tool:

- to evaluate the predictive value of a two items questionnaire on acid-associated symptoms.

In addition, this study had the objective to get further insight into the details of the use, dosage scheme and duration of treatment with esomeprazole in this population.

SUBJECT SELECTION CRITERIA

General practitioners and internists were asked to document relevant information for this PMS study for those subjects for whom they wanted to use esomeprazole to treat acid-associated gastrointestinal symptoms. However, the participating physicians had to be aware of and take into account limitations, possible risks, warnings, contraindications, etc. mentioned in the SPC.

METHODS:

This PMS study was a non-interventional, multi-centre, prospective observational study with 5946 centres in Germany. Each centre could document its experience with esomeprazole for a maximum of 5 subjects. It was planned to document approximately 30000 subjects in this PMS study.
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 has been performed.
Study population: Subjects fulfilling at least one of the criteria below were considered as non-evaluable:

1. missing CRF page 1;
2. date of Visit 1 is missing;
3. date of Visit 1 is before start date of the PMS study (13-Jan-2006);
4. no data after Visit 1, i.e. at Visits 2 and 3;
5. dates of consecutive visits are not in a consecutive order;
6. date of termination is before date of Visit 1;
7. no information, that the subject has been treated with esomeprazole (i.e. all information on the start date and daily dose of esomeprazole is missing)

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

RESULTS:

Patient population

Overall, 29586 subjects were documented in this PMS study by the participating investigators. In total, 1991 of 29586 subjects (6.7%) were excluded from the statistical analysis because the subjects fulfilled at least one of the criteria for non-evaluability (see above). Overall, 27595 of 29586 documented subjects (93.3%) were considered as evaluable.
The gender distribution was approximately even, 14061/27595 evaluable subjects (51.0%) were male and 13281/27595 subjects (48.1%) were female. No information on gender was available for 253/27595 subjects (0.9%). Average age amounted to 55.4 ± 15.0 [55.0] (mean ± SD [median]) years.
Most frequent underlying diagnosis was reflux oesophagitis in 11897/27595 patients (43.1%). Table S 1 summarises the most frequent underlying diagnoses recorded at Visit 1. Only terms applying to at least 1% of evaluable subjects were considered. In the majority of subjects, the underlying diagnosis was confirmed at Visit 1 (21087/27595 subjects, 76.4%).

Table S 1 Underlying disease recorded at Visit 1 (only terms applying to more than 1%) - Evaluable subjects -

SOC/ Preferred term	Evaluable subjects, n=27595	
	n	%
Subjects with specified diagnosis	25254	91.517
GASTROINTESTINAL DISORDERS	24729	89.614
REFLUX OESOPHAGITIS	11897	43.113
GASTRITIS	7948	28.802
GASTROOESOPHAGEAL REFLUX DISEASE	1665	6.034
HIATUS HERNIA	1642	5.950
GASTRIC ULCER	1393	5.048
DUODENAL ULCER	1255	4.548
REFLUX	1047	3.794
GASTRITIS EROSIVE	788	2.856
OESOPHAGITIS	730	2.645
DYSPEPSIA	501	1.816
BARRETT'S OESOPHAGUS	353	1.279
GASTROOESOPHAGEAL SPHINCTER INSUFFICIENCY	287	1.040
GASTRODUODENITIS	278	1.007
SURGICAL AND MEDICAL PROCEDURES	1082	3.921
ANALGESIC INTERVENTION SUPPORTIVE THERAPY	651	2.359
INFECTIONS AND INFESTATIONS	733	2.656
HELICOBACTER GASTRITIS	427	1.547

Multiple entries per subject possible.

In 4004/27595 subjects (14.5%) the helicobacter pylori status was positive. A considerable proportion of 12147/27595 subjects (44.0%) reported pre-trial medication of with PPI, H2-antagonists or antacids.

Efficacy results

Dosing and duration of esomeprazole therapy

The average dose prescribed amounted to 31.0 ± 10.0 [40.0] mg per day at Visit 1, 26.5 ± 9.4 [20.0] mg per day at Visit 2 and 24.4 ± 8.3 [20.0] mg per day at Visit 3. Most frequently planned duration of medical therapy with esomeprazole was 4 weeks (9717/27595 subjects (35.2%). In approximately 23.2% the planned duration was even longer.

Presence of acid-associated symptoms from Visit 1 to Visit 3

The number of subjects with pain or a burning feeling in the upper stomach or behind the breastbone (main acid-associated symptoms, according to the 'short form questionnaire on acid-

associated symptoms') decreased from above 80 % at Visit 1 to less than 10 % at Visit 3, respectively.

Evaluation of the diagnosis tool

For this analysis, the two items 'pain behind the breastbone' and 'pain in the centre of the upper stomach' of the 'self rating questionnaire on acid associated symptoms' were summarised and correlated to the first item 'pain in the upper stomach and behind the breastbone' of the 'short form questionnaire on acid associated symptoms'. The results regarding correlation, sensitivity and specificity were independent of the gender of the subjects.

The correlation, sensitivity and specificity by diagnosis are summarised in Table S 2.

Table S 2 Predictive value of the two items of the short form questionnaire on acid-associated symptoms - Evaluable subjects -

	Pain in the upper stomach or behind the breastbone			Burning feeling in the upper stomach or behind the breastbone		
	coefficient of correlation	sensitivity [%]	specificity [%]	coefficient of correlation	sensitivity [%]	specificity [%]
ANALGESIC INTERVENTION SUPPORTIVE THERAPY	0.614	84.4	11.2	0.630	80.4	7.5
BARRETT'S OESOPHAGUS	0.633	90.0	21.3	0.528	92.1	25.9
DUODENAL ULCER	0.443	91.7	15.0	0.543	82.6	8.6
DYSPEPSIA	0.583	80.5	12.1	0.520	92.7	28.9
GASTRIC ULCER	0.381	90.7	28.3	0.553	83.9	6.6
GASTRITIS	0.487	89.0	19.1	0.565	86.5	10.0
GASTRITIS EROSIVE	0.438	89.4	15.2	0.548	85.4	9.3
GASTRODUODENITIS	0.450	93.2	27.3	0.625	89.1	12.5
GASTROOESOPHAGEAL REFLUX DISEASE	0.631	88.1	9.5	0.509	95.0	26.9
GASTROOESOPHAGEAL SPHINCTER INSUFFICIENCY	0.472	92.6	37.5	0.397	94.4	41.7
HELICOBACTER GASTRITIS	0.546	93.5	26.7	0.590	88.6	11.9
HIATUS HERNIA	0.639	91.1	14.8	0.601	95.9	20.3
OESOPHAGITIS	0.551	91.3	25.4	0.354	93.4	42.9
REFLUX	0.601	87.7	13.2	0.618	93.6	10.2
REFLUX OESOPHAGITIS	0.573	89.1	16.2	0.523	95.6	24.6

Healing rate

The analysis of the healing rate stratified according to diagnosis is presented in Table S 3.

Table S 3 Healing rate by diagnosis- Evaluable subjects

Healing rate		95%-CI limits [%]	
	[%]	lower	upper
at the end of the observational period	69.3	68.8	69.8
by diagnosis			
ANALGESIC INTERVENTION SUPPORTIVE THERAPY	66.8	63.2	70.4
BARRETT'S OESOPHAGUS	56.9	51.8	62.1
DUODENAL ULCER	75.0	72.6	77.4
DYSPEPSIA	75.2	71.5	79.0
GASTRIC ULCER	71.4	69.0	73.7
GASTRITIS	71.6	70.6	72.6
GASTRITIS EROSIVE	68.5	65.3	71.8
GASTRODUODENITIS	72.3	67.0	77.6
GASTROOESOPHAGEAL REFLUX DISEASE	68.7	66.5	70.9
GASTROOESOPHAGEAL SPHINCTER INSUFFICIENCY	64.8	59.3	70.3
HELICOBACTER GASTRITIS	71.2	66.9	75.5
HIATUS HERNIA	60.7	58.3	63.0
OESOPHAGITIS	61.2	57.7	64.8
REFLUX	67.5	64.7	70.4
REFLUX OESOPHAGITIS	69.1	68.3	70.0

Assessment of therapy at Visit 2 and 3

In most cases, the assessment of efficacy and tolerability of the therapy by patient and physician was very good at Visit 2 and Visit 3.

Safety results

Of the 27595 evaluable subjects, 87 subjects (0.32%) reported experience of at least one AE after the start of esomeprazole therapy. The primary system-organ class with the highest number of subjects experiencing AEs was 'gastrointestinal disorders' (38 subjects (0.138%)). 42 subjects (0.15%) reported AEs that were judged by the physicians to be related to esomeprazole. In 42 subjects (0.15%) AEs led to treatment discontinuation. No subject died but 6 subjects experienced serious adverse events (SAE) (including one patient each with irritability, fatigue and myalgia, acute abdomen, pneumonia aspiration, acute myocardial infarction and urticaria). Fatigue and myalgia occurring in the same patient were considered as drug related.

Inspection of comments and incomplete entries in the CRFs supplied clues to SAEs not documented on the AE page in 23 evaluable subjects (including 7 deaths) as well as 26 subjects (including 8 deaths) in the population treated with esomeprazole independent of whether they were considered as being evaluable or not. In most cases details like time of occurrence, assessment of causality and outcome, etc. were not available.