AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

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

Study No: NCT00567021
German PMS trial no. 7 (AWB) to evaluate therapy in reflux disease and NSAR-symptoms

Developmental phase: Phase IV, German PMS trial (AWB)
Date of Report: 13-Feb-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 diagnosis and type of NSAID therapy (if administered)
- by estimating the proportion of treated subjects without any gastrointestinal symptoms at the end of the observational period;
- by assessing the change in intensity of gastrointestinal 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.

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 SELCTION 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 GERD or NSAID related ulcers. 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 13455 centres in Germany. Each centre could document its experience with esomeprazole for a maximum of 5 subjects. 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 GERD or NSAID-related ulcers. It was planned to document approximately 60000 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 (01-Sep-2005);
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, 67130 subjects were documented in this PMS study by the participating investigators. In total, 10497 of 67130 subjects (15.6%) were excluded from the statistical analysis because the subjects fulfilled at least one of the criteria for non-evaluability (see above). 56633 of 67130 documented subjects (84.4%) were considered as evaluable.

Visit 2 was documented in 56254/56633 evaluable subjects (99.3%). The third visit was optional and was documented in 37699/56633 evaluable subjects (66.6%). Premature study termination was documented in 1925/56633 evaluable subjects (3.4%). The most frequently documented reason was "free of discomforts" in 1982/56633 evaluable subjects (3.5%). The average duration of study participation amounted to 32.5 ± 15.0 [30.0] days (mean ± SD [median]).

The gender distribution was approximately even, 27981/56633 evaluable subjects (49.4%) were male and 27942/56633 subjects (49.3%) were female. Average age amounted to 56.1 ± 15.3 [56.0] years.

Most frequent underlying diagnosis was reflux oesophagitis in 17837/56633 patients (31.50%). 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.

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

SOC/ Preferred term	Evaluable subjects, n=56633	
	n	%
Patients with specified diagnosis	51417	90.79
GASTROINTESTINAL DISORDERS	46891	82.80
ABDOMINAL PAIN UPPER	568	1.00
DUODENAL ULCER	1950	3.44
DYSPEPSIA	998	1.76
GASTRIC ULCER	2271	4.01
GASTRITIS	16163	28.54
GASTRITIS EROSIVE	1064	1.88
GASTROOESOPHAGEAL REFLUX DISEASE	2535	4.48
HIATUS HERNIA	1538	2.72
OESOPHAGITIS	1216	2.15
REFLUX	4838	8.54
REFLUX OESOPHAGITIS	17837	31.50
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	569	1.00
INFECTIONS AND INFESTATIONS	860	1.52
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	5632	9.94
BACK PAIN	1354	2.39
OSTEOARTHRITIS	1907	3.37
NERVOUS SYSTEM DISORDERS	1081	1.91
SURGICAL AND MEDICAL PROCEDURES	3713	6.56
ANALGESIC INTERVENTION SUPPORTIVE THERAPY	2526	4.46

Multiple entries per subject possible.

For a considerable proportion of subjects (24858/56633, 43.9%) current NSAID therapy at Visit 1 was recorded.

,Subjects were asked whether they saw any coincidence or causal role of NSAID therapy to their gastrointestinal symptoms. 18841/56633 subjects (33.3%) confirmed a coincidence, whereas 9748/56633 subjects (17.2%) denied such a coincidence. Causality between symptoms and NSAID therapy was seen by 19125/56633 subjects (33.8%) and denied by 8126/56633 subjects (14.3%).
Gastrointestinal symptoms at Visit 1 were reported by 55294/56633 subjects (97.6%). Most prominent symptom was "Burning feeling in the centre of the epigastrium" (42073/56633 subjects (74.3%)).

Efficacy results

Dosing and duration of esomeprazole therapy

The average dose prescribed amounted to 26.1 ± 9.9 [20.0] mg per day at Visit 1, 23.3 ± 8.3 [20.0] mg per day at Visit 2 and 21.6 ± 7.2 [20.0] mg per day at Visit 3. Most frequently planned duration of medical therapy with esomeprazole was 4 weeks (24544/56633 subjects). The average duration of esomeprazole intake during the study was 32.1 ± 14.9 [30.0] days.

Presence of symptoms from Visit 1 to Visit 3

The number of subjects with symptoms decreased from 55294/56633 subjects (97.6%) at Visit 1 to 13766/37699 subjects (36.5%) at Visit 3. Table S 2 summarises the number of patients with each symptom at Visit 1, 2 and 3.

Table S 2 Presence of symptoms from Visit 1 to Visit 3 - Evaluable subjects

Evaluable subjects, n=56633	Visit 1 n=56633		Visit 2 n=56254		Visit 3 n=37699	
	n	%	n	%	n	%
Patients with gastrointestinal symptoms	55294	97.6	37028	65.8	13766	36.5
A burning feeling behind the breastbone	38737	68.4	22566	40.1	7087	18.8
Pain behind the breastbone	32844	58.0	16397	29.1	4466	11.8
A burning feeling in the centre of the epigastrium	42073	74.3	21500	38.2	5922	15.7
Pain in the centre of the epigastrium	41977	74.1	21380	38.0	6066	16.1
A acid taste in the mouth	35976	63.5	15563	27.7	5004	13.3
Unpleasant movement of material upwards from stomach	29318	51.8	11728	20.8	3557	9.4

Change in the intensity of symptoms between baseline and the end of the observational period

All symptoms decreased in intensity between baseline and the end of the observational period (Visit 3 LOCF). Table S 3 summarises the change in intensity for each symptom and for the sum of all symptoms (total symptom score).

Table S 3 Change in the intensity of symptoms between baseline and the end of the observational period - Evaluable subjects

	Absolute change					
	arith. mean	SD	95%-confidence interval lower	95%-confidence interval upper	median	n
Burning feeling behind the breastbone	-1.99	1.59	-2.00	-1.98	-2.0	52836
Pain behind the breastbone	-1.63	1.58	-1.64	-1.62	-2.0	51976
Burning feeling in the centre of the epigastrium	-2.18	1.54	-2.20	-2.17	-2.0	52413
Pain in the centre of the epigastrium	-2.21	1.57	-2.22	-2.19	-2.0	52560
Acid taste in the mouth	-1.76	1.58	-1.77	-1.75	-2.0	51987
Unpleasant movement of material upwards from stomach	-1.38	1.52	-1.39	-1.37	-1.0	51238
Total symptom score	-10.68	5.88	-10.73	-10.64	-10.0	55264

Healing rate

Overall healing rate amounted to 56.9% subjects. Analysis of healing rate was stratified according to symptom class (diagnosis) and NSAID therapy and is presented in Table S 4.

Table S 4 Healing rate by diagnosis and NSAID therapy- Evaluable subjects

Healing rate	[%]	95%-CI limits [%]	
		lower	upper
Overall	56.9	56.5	57.3
by diagnosis			
Gastrointestinal disorder	62.5	61.7	63.2
Gastrointestinal and reflux disorder	50.1	49.3	51.0
Reflux disorder	57.8	57.2	58.4
No remark	37.5	35.3	39.7
by NSAID therapy			
None	55.4	54.8	55.9
Diclofenac	60.7	59.9	61.5
Ibuprofen	57.6	56.5	58.7
Naproxen	60.3	55.8	64.8
Meloxicam	54.0	51.2	56.8
Other NSAID	52.6	50.6	54.6

Assessment of therapy at Visit 2 and 3

The number of patients with assessment of efficacy by subject and investigator declined from Visit 2 to Visit 3. However, in most cases, the assessment of efficacy by patient and investigator was satisfactory, good or very good. Similar to the assessment of efficacy, tolerability was assessed as good or very good in most cases by the subject as well as by the physician at Visit 2 and 3.

Safety results

Of the 56633 evaluable subjects, 165 subjects (0.291%) reported experience of at least one AE after the start of esomeprazole therapy. The primary system-organ classes with the highest number of subjects experiencing AEs were ‘gastrointestinal disorders’ (62 subjects (0.109%)) and ‘infections and infestations’ (32 subjects (0.057%)). In total, 72 subjects (0.127%) reported AEs that were judged by the physicians to be related to esomeprazole. In 64 subjects (0.113%) AEs led to treatment discontinuation.

In the population of evaluable subjects, 12 subjects experienced a documented SAE (including 3 patients with assessment of causal relation to the study drug) and 3 subjects died, whereas in the population of subjects treated with esomeprazole two more subjects experienced a documented SAE (including one patient with assessment of causal relation to the study drug).

In addition, inspection of comments and incomplete entries in the CRFs supplied clues to further SAEs. Including these cases, in total 53 subjects experienced a SAE and 14 subjects died in the population of evaluable subjects while 68 subjects experienced a SAE and 15 subjects died in the population treated with esomeprazole (i.e. in all subjects independent if 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.