# An open-label, non-comparative, non‑interventional, multi-centre, post‑authorisation safety study on the administration of rabeprazole to adults with gastro‑oesophageal reflux disease

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### Running title

Rabeprazole post-authorisation study

## Abstract

### Background

Rabeprazole produces a profound and long lasting inhibition of gastric acid secretion.

### Aim

To monitor the safety and efficacy of rabeprazole administered to patients with erosive gastro-oesophageal reflux disease (ERD), or with symptomatic GERD (non-erosive GERD - NERD), in real-life healthcare settings.

### Methods

Male and female patients, aged ≥ 18 years, with endoscopy diagnosed GERD were included; patients received at least 8 weeks treatment with rabeprazole. Changes in severity of symptoms recorded on the Likert scale were analysed using marginal homogeneity tests.

### Results

186 patients were enrolled across 17 study sites; 127 patients (68.3%) completed the study. Almost 75% of patients had an initial diagnosis of GERD with Grade A or B esophagitis.

The most commonly reported adverse events (AEs) were diarrhoea, flatulence, dizziness, cough, abdominal pain, upper abdominal pain and somnolence. Over half of AEs were unrelated to study drug; 1 severe AE of diarrhoea was possibly related to study drug. No new AEs were reported not included in the current version of Summary of Product Characteristics (SmPC).

Rabeprazole was effective in reducing the symptoms of GERD; the Likert scale scores of symptoms decreased significantly for all patients from 0–4 weeks and 4–8 weeks.

### Conclusions

In our study, rabeprazole was safe and effective in reducing the symptoms of GERD.

### Keywords

Rabeprazole, post-authorisation safety study, gastro-oesophageal reflux disease (GERD), real life clinical practice

## Introduction

Rabeprazole sodium belongs to the substituted benzimidazole group of anti‑secretory agents that inhibit gastric acid secretion by the specific inhibition of the H+/K+-ATPase enzyme (proton pump) of gastric parietal cells; rabeprazole produces a profound and long lasting inhibition of gastric acid secretion [1, 2].

Rabeprazole is indicated for the treatment of active duodenal ulcer, active benign gastric ulcer, symptomatic erosive gastro-oesophageal reflux disease (ERD), GERD long-term management (GERD maintenance treatment), symptomatic treatment of moderate to very severe GERD (NERD), Zollinger-Ellison Syndrome, and in combination with appropriate antibacterial therapeutic regimens for the eradication of Helicobacter pylori (H. pylori) in patients with peptic ulcer disease [3].

This post-authorisation safety study (PASS) was undertaken in accordance with European and International Pharmacovigilance Guidelines, which require that the safety and efficacy of drugs should be continuously monitored even after receiving marketing approval. The objective of the study was to collect data regarding the safety and efficacy of rabeprazole administered to adult patients with erosive GERD or with symptomatic GERD (non-erosive GERD), in the real life clinical practice. The effectiveness of rabeprazole was assessed with endoscopy assessments and by monitoring symptoms.

## Patients and methods

### Study design, population, and treatments

This was an open-label, non‑comparative, multi-centre study undertaken in primary healthcare settings in Greece between 12 March 2003 and 25 November 2005. The study design followed the applicable requirements of the European guidelines on clinical studies (2001/20/EC) and specifically on non-interventional studies, as well as the applicable requirements of the European pharmacovigilance guidelines CPMP/PhVWP/108/99 regarding observational safety studies. All patients gave written informed consent.

The study included male and female patients aged ≥ 18 years with endoscopy diagnosed erosive or non-erosive GERD and with no Barrett type metaplasia,. Patients should have experienced symptoms of their disease for at least 3 months before entering the study, including experiencing symptoms for at least 3 days per week within the 2 weeks before entering the study; symptoms could include heartburn, retrosternal pain, acid reflux and dysphagia which is an indication of complicated disease. A patient could only be considered for participation in the study after a gastroenterologist had diagnosed GERD and prescribed treatment with rabeprazole. Upper endoscopic evaluation was, also, required for documenting the presence or absence of esophagitis. Patients were excluded for any of the following reasons: any type of oesophageal narrowing or esophagitis of secondary systemic causes; active gastro-duodenal ulcer; infections other than H. pylori gastritis; inflammatory conditions of small or large intestine; malabsorption syndromes; previous surgeries in stomach or intestine, including vagotomy (patients with history of ulcer, appendectomy or cholecystectomy could participate in the study); a recorded history of primary kinetic disorders of oesophagus other than GERD, or oesophageal or stomach varices; treatment with proton pump inhibitors within the 2 weeks before entering the study; co-existing severe systemic disease, including renal, hepatic and heart failure; receiving cancer treatment within the previous year (patients with successfully treated superficial basal cell carcinoma were allowed to participate); Zollinger-Ellison syndrome; endoscopic evidence of active, haemodynamically significant, gastro‑oesophageal haemorrhage; frequent use of aspirin, except in cases of prophylactic cardiovascular use at doses lower than 300 mg daily, or daily use of non-steroid anti-inflammatory drugs (NSAIDs).

The study comprised 4 clinic visits at week 0, week 4, week 8 and month 4 (visits 1–4) and telephone contact at 6 and 12 months (visits 5 and 6). Patients were monitored for 12 months after entering the study.

Patients received rabeprazole treatment for 8 weeks starting with a single 20 mg tablet before breakfast. The dose could be adjusted according to investigators assessment for the management of patients’ disease. Dosing could continue after the 8-week study treatment period. During the study, drugs that are absorbed in a gastric pH dependent manner, such as ketoconazole, esters of ampicillin and iron salts were not allowed.

### Safety assessments

Adverse events (AEs) were monitored from completion of 4 weeks of treatment until the end of the study. Clinical and physical examinations (including vital signs) and laboratory analyses were undertaken throughout the trial.

### Effectiveness assessments

The degree of esophagitis was determined by endoscopy according to the Los Angeles classification [4] (Grade A: one [or more] mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds; Grade B: one [or more] mucosal break more than 5 mm, that does not extend between the tops of two mucosal folds; Grade C: one [or more] mucosal break that is continuous between the tops of two or more folds but which involves less than 75% of the circumference; Grade D: one [or more] mucosal break which involves at least 75% of the oesophageal circumference).

The symptoms of erosive GERD and the relationship between severity and the degree of esophagitis were recorded before entering the study, on the first day of treatment and after 7 days of treatment; patients were interviewed using telephone questionnaires on days 1 and 7.

Symptom severity was further assessed at 4 weeks, 8 weeks, 4 months, 6 months and 12 months after the start of treatment. Recurrence was evaluated at 4, 6 and 12 months after the start of treatment.

Endoscopy assessments were undertaken at 8 weeks and 4 months after the start of treatment, if required according to the clinical practice of the study centre.

### Severity of symptoms and recurrence

Severity was determined for the symptoms of heartburn, retrosternal pain, regurgitation and dysphagia using the 5-point Likert Scale: 1, no problem; 2, mild problem, can be ignored with effort; 3, moderately severe problem, cannot be ignored but does not influences daily activities; 4, severe problem, cannot be ignored and often limits my concentration on daily activities; 5, very severe problem, cannot be ignored and markedly limits my daily activities and often requires rest [5].

Recurrence was defined as at least 2 weekly episodes of heartburn of at least severity 3 after improvement in symptoms (heartburn severity ≤ 2) had been achieved during the previous treatment period.

### Statistical methods

It was planned to recruit 300 patients in the study. This allowed for up to 15 patients to be recruited at each of the 17–21 potential study sites. The intent-to-treat (ITT) population included all patients enrolled in the study; this population was used for all the analyses. All patients included in the ITT population received at least 1 dose of rabeprazole. One patient was enrolled but did not provide any data so was excluded from the analysis.

All data were summarised descriptively. To test if there was a correlation between the different baseline characteristics, t tests were used. Categorical values were compared using a chi-square test [6]. Logistic regression analysis was performed to determine the effects of factors or covariates on binary variables [6]. McNemar tests were used to determine if 2 probabilities of success were equal at 2 time points or experimental conditions [6].

AEs were classified according to MedDRA version 13.0. A correlation between incidence of AEs and demographic data, clinical characteristics and concomitant medications was undertaken using a logistic regression model. Missing observational data for drug safety were not replaced. Concomitant medications were coded using the World Health Organization Drug Dictionary (WHODRUG) Q1 2008 and Anatomical-Therapeutic-Chemical (ATC) codes.

Marginal homogeneity tests were used to determine the equality of Likert scale scores between successive visits [6, 7]. All testing was 2-sided at α = 5% significance level; statistically significant differences were indicated by p values < 0.05. Missing data for effectiveness variables were not replaced.

All analyses were performed using SAS version 8.02 (SAS Institute, Cary, NC USA).

## Results

### Participants

A total of 186 patients were enrolled across the 17 study sites and were included in the ITT analysis. 127 patients (68.3%) completed the 12 month study period. 59 patients withdrew; no data were obtained from one patient, 35 patients were lost to follow-up and 11 patients withdrew their consent (Figure 1). Withdrawals most commonly occurred during the 8‑week treatment period, but there was another peak in the last 6 months of the study.

Patient demography is summarised in Table 1. There were approximately equal numbers of male and female patients and their median age (minimum–maximum) age was 55.0 (17–83) years. The most frequently reported types of gastrointestinal history were reflux esophagitis, gastritis, non-erosive GERD and previous eradication of *H. pylori*. Almost 75% of patients had an initial diagnosis of GERD with Grade A (77 patients) or Grade B (60 patients) esophagitis. Age and gender, age and smoking, age and alcohol consumption, smoking and gender, smoking and alcohol consumption and alcohol consumption and gender were all confounding factors (data not shown).

There was a statistically significant relationship between initial diagnosis and withdrawal from the study (χ2 = 13.941; p = 0.003); more patients with an initial diagnosis of non-erosive GERD or GERD with esophagitis Grade C or D withdrew from the study. There was no statistically significant relationship between withdrawals and age, gender, smoking status or alcohol consumption. Seven patients were lost to follow-up and were withdrawn from the study by the investigators after visit 2; these patients were included in the ITT population, and their inclusion did not change the results of the analysis of the relationship between withdrawals and patient demography.

As this was a non-interventional study, the length of the treatment period was at the discretion of the physician, whilst the observation period was for 1 year.

### Dose of rabeprazole

The most frequent rabeprazole dosage was 20 mg/day, followed by 40 mg/day; however, the mean daily dosage decreased from 25.0 mg during month 1 to 24.3 mg and 20.9 mg during the following two months.

### Safety and tolerability

During the study, 49 patients reported at least 1 AE (38/176 [21.6%], 16/156 [10.3%] and 11/147 [7.5%] patients during weeks 0–4, weeks 5–8 and months 3–4, respectively). At least 1 AE was reported by 39/116 (33.6%) patients with a medical history compared with 10/69 (14.5%) of patients without a medical history (χ2 = 8.130; p = 0.004); there was no statistically significant relationship between any other patient baseline demographics and the occurrence of AEs. The AEs most commonly reported during the study (reported by ≥ 5% of patients) were diarrhoea (8 patients), flatulence (8 patients), dizziness (6 patients), cough (5 patients), abdominal pain (4 patients), upper abdominal pain (4 patients) and somnolence (4 patients). Most AEs were mild (57.4%) or moderate (39.4%), and only three AEs (abdominal pain, diarrhoea and low back pain) were graded as severe. The severe case of diarrhoea was considered to be possibly related to study drug and two AEs (dry mouth and tinnitus) were considered to be at least possibly associated with study drug; more than half of AEs were unrelated to study drug. Most AEs required no intervention and the majority had resolved by the end of the study. One patient suffered a myocardial infarction, which was considered to be unrelated to the study drug.

There were no clinically significant out of range laboratory results or vital signs.

Concomitant medications were taken by 89/185 (48.1%) patients during the study (Table 2). Concomitant therapy was received by 81/116 (69.8%) patients with medical history compared with 8/69 (11.6%) patients with no medical history; χ2 = 58.771, p < 0.001. AEs were reported by 34/89 (38.2%) patients receiving concomitant therapy compared with 15/96 (15.6%) patients with no concomitant therapy (χ2 = 12.090, p = 0.001). There was a strong correlation between concomitant therapy and age; the logistic regression coefficient for age was 0.035 (standard error 0.010), p < 0.001. No other confounding factors had a significant effect.

### Effectiveness results

The number of patients reporting no or mild symptoms on the Likert scale increased throughout the study (Figure 2, all patients; Figure 3, patients with non-erosive GERD). For all patients, marginal homogeneity tests showed that the decrease of symptoms from the start of the study to the end of 4 weeks was statistically significant, as was the decrease of symptoms from the end of 4 weeks to the end of 8 weeks. For the sub-group of patients with non-erosive GERD, the decrease of symptoms from the start of the study to the end of 4 weeks was statistically significant.

Information about remission (the decrease of severity or frequency of GERD symptoms) was recorded for 171 patients. At the end of 4 and 8 weeks of treatment, 161/171 (94.2%) and 151/155 (97.4%) patients, respectively, showed remission of symptoms. Remission was observed in all 46 alcohol consumers compared with 113/123 (91.9%) alcohol non-consumers (χ2 = 4.145, p = 0.042). No other confounding factors had a significant effect.

After 4 weeks of treatment, remission was recorded in 114/123 (92.7%) patients receiving rabeprazole 20 mg/day and all patients receiving other doses (N = 168). After 8 weeks of treatment, 114/116 (98.3%) patients on rabeprazole 20 mg/day and all but one patients receiving other doses reported remission. For the sub-group of patients with non-erosive GERD who received rabeprazole 20 mg/day, remission was reported by 16/20 (80%) and 10/11 (90.9%) patients after 4 and 8 weeks of treatment, respectively. After 4 months’ treatment, relapse of symptoms was observed in only 5/136 (3.7%) of all patients and one in the sub-group of patients with non-erosive GORD.

*Heartburn*

The frequency and severity of heartburn symptoms were reduced during treatment with rabeprazole (Figure 4). 24 hours after the first dose of rabeprazole, 110/183 (60.1%) patients had no symptoms of heartburn. After 7 days of rabeprazole treatment, 92 patients experienced no heartburn and 36 patients who had experienced heartburn in the first 24 hours did not feel any heartburn. More than 80% of patients reported that the severity of their heartburn symptoms was less important after 7 days compared with 24 hours after starting treatment. The severity of symptoms continued to become less important for the majority of patients during the remainder of the study. The effect of heartburn on daily activities decreased during the study (Figure 4); heartburn had little or no effect on the daily activity of > 75% and > 90% of patients 7 days and 6 months after starting treatment, respectively. During the first 24 hours and the first 7 days after starting treatment, heartburn lasted for either < 1 hour or 1–3 hours for the majority of patients (Figure 4). At least two heartburn events per week were experienced by 10/43 (23.3%) and 10/42 (23.8%) patients at 6 months and 12 months, respectively. All other patients experienced < 2 events per week. Treatment for heartburn was received by 35/44 (79.5%) and 30/42 (71.4%) patients at 6 months and 12 months, respectively.

## Discussion

This open-label, non‑comparative, multi-centre PASS collected data regarding the safety and efficacy of rabeprazole administered to adult patients with erosive or non-erosive GERD, in the real life healthcare setting. A patient could only be enrolled in the study after a gastroenterologist had diagnosed GERD and prescribed treatment with rabeprazole and the patient had undergone upper endoscopy.

The study planned to enrol 300 patients across up to 21 study sites, but at last 186 patients were recruited across 17 study sites during the 12-month recruitment period. Considering the nature of the study (open-label, non-comparative, non-interventional) the sample size was acceptable for the main purpose of the study, that is the monitoring of rabeprazole safety.

Almost 75% of patients had an initial diagnosis of GERD with esophagitis Grade A or Grade B. Patients with an initial diagnosis of NERD or ERD with esophagitis Grade C or D were less likely to complete the one year observation period. This was not related to effectiveness however, as many patients with non-erosive GERD were prematurely withdrawn from the study despite a large improvement in symptoms, possibly because continuous treatment with rabeprazole was not necessary. As this was a non-interventional study, the physician was free to decide the adequate treatment period. However, this was a rather small group of patients so firm conclusions cannot be drawn.

The majority of AEs reported during the study were mild or moderate, and more than half were unrelated to study drug. The most commonly reported AEs of diarrhoea, flatulence, dizziness, abdominal pain and upper abdominal pain are all known side effects of rabeprazole; other AEs commonly associated with treatment with rabeprazole are headache, asthenia (fatigue), rash and dry mouth [4].

Rabeprazole was effective in reducing the symptoms of GERD during the study; there was a significant decrease in the Likert scale scores of symptoms for all patients from 0–4 weeks and 4–8 weeks, and for patients with non-erosive GERD from 0–4 weeks. Remission (decrease in the severity or frequency of symptoms of GERD) was observed in 94.2% patients and 97.4% patients after 4 weeks and 8 weeks, respectively. Only 3.7% patients reported relapse of symptoms after 4 months. The frequency and severity of heartburn symptoms were reduced during treatment with rabeprazole; 60.1% and 70.7% patients had no symptoms of heartburn 24 hours and 7 days after the first dose of rabeprazole, respectively, and more than 80% of patients reported their symptoms to be less important 7 days after starting treatment compared with 24 hours after starting treatment. Consistent with the reduction in the frequency and severity of heartburn symptoms, the effect of heartburn on daily activities also decreased during the study.

The effectiveness results of our study are comparable with the results of a community-based, open-label assessment of patients with erosive disease that included 2,579 patients with erosive GERD who were treated with rabeprazole 20 mg/day for 8 weeks [8]; complete relief of daytime and night-time heartburn was achieved in 64.0% and 69.2% of symptomatic patients, respectively, on day 1, and in 81.1% and 85.7% of patients, respectively, on day 7. The severity of symptoms of heartburn progressively decreased from day 1 to week 4 of treatment. The severity of symptoms of regurgitation, dysphagia and belching also decreased by day 1 and continued to improve from day 1 to week 4 of treatment. Health‑related quality of life scores were significantly improved after 8 weeks of treatment with rabeprazole.

Although patients experienced improvements in their symptoms of GERD during our study, there was no control group and therefore conclusions about the effectiveness of rabeprazole should be made with caution. The sample size of the sub-group of patients with non-erosive GERD was small, so these results should be interpreted cautiously. Similarly, the sample size included in the analyses of heartburn symptoms was low.

In conclusion, the safety of rabeprazole in this study was comparable with the previously reported rabeprazole safety profile. Rabeprazole in the everyday health care setting was effective in reducing the symptoms of GERD, complicated or not, including the frequency and severity of heartburn.

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## Tables

Table 1 Patient demography

| **Variable** |  |
| --- | --- |
| **Age, years**  N  Mean (SD)  Median (minimum–maximum) | 180  52.2 (16.6)  55.0 (17–83) |
| **Gender, n (%)**  N  Male  Female | 185  92 (49.7)  93 (50.3) |
| **1Weight, kg** N  Mean (SD) | 177  78.4 (16.5) |
| **Smoking, n (%)**  N  Smoker  Non-smoker | 185  48 (25.9)  137 (74.1) |
| **Alcohol consumption, n (%)**  N  Yes  No | 185  52 (28.1)  133 (71.9) |
| **NSAID consumption, n (%)**  N  Yes  No | 185  23 (12.4)  162 (87.6) |
| **Medical history, n (%)**  N  History in at least one system  No medical history | 185  116 (62.7)  69 (37.3) |
| **Gastrointestinal history, n**  N  Reflux oesophagitis  Gastritis  GORD without oesophagitis  Previous eradication of *H. pylori*  Duodenal ulcer  Benign gastric ulcer | 185  54  50  45  30  9  1 |
| **Initial diagnosis, n (%)**  N  GORD with Grade A oesophagitis  GORD with Grade B oesophagitis  GORD with Grade C oesophagitis  Symptomatic GORD without oesophagitis  GORD with Grade D oesophagitis | 185  77 (42.3)  60 (32.4)  22 (11.9)  21 (11.5)  2 (1.1) |

1one patient had an extreme weight value (216 kg)

N, total number of patients in data set; SD, standard deviation; n, number of patients; NSAID, nonsteriodal anti-inflammatory drug; GORD, gastro‑oesophageal reflux disease

Table 2 Summary of concomitant medications taken during the study

| **Concomitant medication** |  |
| --- | --- |
| **ATC drug class** | **Number of patients** |
| Thyroid hormones | 30 |
| HMG CoA reductase inhibitors | 24 |
| Beta blocking agents, selective | 19 |
| Dihydropyridine derivatives | 15 |
| Benzodiazepine derivatives | 13 |
| Angiotensin II antagonists, plain | 11 |
| Salicylic acid and derivatives | 11 |
| ACE inhibitors, plain | 9 |
| Penicillins with extended spectrum | 9 |
| Synthetic anticholinergics, esters with tertiary amino group | 9 |
| ACE inhibitors and diuretics | 7 |
| Macrolides | 7 |
| Propulsives | 7 |
| Sulfonamides, plain | 6 |
| Alpha-adrenoreceptor agonists | 5 |
| Anti-vertigo preparations | 5 |
| Bisphosphonates | 5 |
| Sulfonamides, urea derivatives | 5 |
| Vitamin D and analogues | 5 |
| Angiotensin II antagonists and diuretics | 4 |
| Anti-infectives | 4 |
| Calcium compounds | 4 |
| Mucolytics | 4 |
| Other cardiac preparations | 4 |
| Preparations inhibiting uric acid production | 4 |
| Scilla glycosides | 4 |
| Selective beta-2-adrenoreceptor agonists | 4 |
| Alpha and beta blocking agents | 3 |
| Analides | 3 |
| Anti-cholinergics | 3 |
| Anti-inflammatory preparations, non-steroids for topical use | 3 |
| Calcitonin preparations | 3 |
| Corticosteroids | 3 |
| Platelet aggregation inhibitors excluding heparin | 3 |
| Second generation cephalosporins | 3 |
| Selective estrogen receptor modulators | 3 |
| Selective serotonin re-uptake inhibitors | 3 |

Concomitant medications were coded using the WHODRUG Q1 2008 and further coded to the ATC code; the table shows ATC drug classes in which concomitant medications were reported by at least 3 patients

## Figures

Figure 1 Patient disposition



Figure 2 Likert scale scores during the study–all patients



Figure 3 Likert scale scores during the study–patients with non-erosive GORD



Figure 4 Heartburn symptoms 



## Figure legends

Figure 1 Patient disposition

Figure 2 Likert scale scores during the study–all patients

Likert scale scores: 1, no problem; 2, mild problem; 3, moderately severe problem; 4, severe problem; 5, very severe problem. Assessments were done before treatment and 4 weeks, 8 weeks and 4 months after starting treatment

Start, N=185 for heartburn, 184 for retrosternal pain and regurgitation, 183 for dysphagia; 4 weeks, N=171; 8 weeks, N=156; 4 months, N=145 for heartburn and 146 for retrosternal pain, regurgitation and dysphagia

Figure 3 Likert scale scores during the study–patients with non-erosive GORD

NA, not available

Likert scale scores: 1, no problem; 2, mild problem; 3, moderately severe problem; 4, severe problem; 5, very severe problem. Assessments were done before treatment and 4 weeks, 8 weeks and 4 months after starting treatment

Start, N=21; 4 weeks, N=20; 8 weeks, N=12; 4 months, N=12

Figure 4 Heartburn symptoms

h, hour; d, day; m, months

Frequency: patients were asked at each visit if they had experienced heartburn (yes) or not (no); 24h, N=183; 7d, N=181; 6m, N=144; 12m, N=127

Severity: severity at each visit was compared with the previous visit; 24h, N=72; 7d, N=52; 6m, N=45; 12m, N=42

Duration of symptoms: 24h, N=73; 7d, N=53

Effect on daily activities: 24h, N=72; 7d, N=53; 6m, N=44; 12m, N=42