Evaluation of the Efficacy and Safety of Esomeprazole in Indian Patients with Gastrooesophageal Reflux Disease (GORD) - A Post Marketing Study

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ABSTRACT

Objective: In patients with gastrooesophageal reflux disease (GORD), Esomeprazole, the S-isomer of omeprazole, has demonstrated pharmacological and clinical benefits beyond those seen with the racemic parent compound. This post marketing study was conducted to confirm the efficacy and safety of Esomeprazole 40 mg once daily in adult Indian patients with GORD.

Methods: The efficacy and safety of Esomeprazole 40 mg once daily was evaluated in 309 patients with GORD in a 4-week, multicentre, open-label, non-comparative, phase IV study at 5 centres in India. The primary efficacy endpoint was complete healing of oesophageal erosions on endoscopy (oesophagoscopy) at week 4 or end of study period. The secondary efficacy endpoint was degree of symptom (heartburn, regurgitation, retrosternal pain and dysphagia) relief at the end of study. Adverse events were monitored throughout the study period.

Results: At the end of week 4, 81.1% of the patients showed complete healing of the oesophageal lesions on oesophagoscopy. There was a statistically significant decrease (89-91%) in the mean scores of the GORD symptoms (heartburn, regurgitation, and retrosternal pain) at the end of 4 weeks of therapy. Of the 85.3% of patients who reported presence of dysphagia at baseline, only 15.2% complained of it by the end of study period. As per the patient's and physician's global assessment of overall symptoms, 74.8% and 76.5% of the total subjects demonstrated complete resolution of symptoms at the end of week 4 of treatment. The most common adverse events reported were diarrhoea, headache, nausea and dizziness.

Conclusions: The findings of this study further confirm the efficacy and tolerability of Esomeprazole 40 mg/day in patients with GORD. *(The Ind. Pract. 2003; 56(9):593-600)*

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KEY WORDS

Esomeprazole omeprazole proton pump inhibitors PPIs, gastro-oesophageal reflux disease GORD acid-related disorders

INTRODUCTION

Gastrooesophageal reflux disease (GORD) is a common condition with a broad spectrum of symptoms that vary in severity and frequency. The burden of GORD results from its widespread prevalence and the unfavourable impact of its symptoms on well-being and quality of life.[1] The disease has an estimated incidence of 10-40% in the general population; however, the true incidence of GORD may be considerably higher since many patients self-medicate with over-the-counter antacids and never seek medical advice.[2] Further, 40-60% of the patients presenting with symptoms of GORD have erosive oesophagitis.[3] Erosive oesophagitis has been associated with complications such as oesophageal stricture, ulceration and bleeding, and Barrett's oesophagus, which in turn is a risk factor for adenocarcinoma.

Whereas abnormalities of the antireflux barrier (lower oesophageal sphincter) are important in the pathophysiology of GORD, pharmacologic therapy for GORD is based on suppression of acid, which is responsible for a majority of the symptoms and for epithelial damage. The primary goal in the management of GORD is suppression of basal and stimulated gastric acid secretion to alleviate symptoms, and to allow healing and prevent the recurrence of erosions.[4] Resolution of symptoms, in turn, is pivotal to improving the patient's quality of life and reducing costs associated with acid-related disorders. Furthermore, reducing acid-induced damage to the oesophagus and other gastrointestinal structures may reduce the risk of progression to adenocarcinoma and other late complications. Proton pump inhibitors (PPIs) are the agents of choice for achieving the goals of medical therapy in GORD.[5] Since the introduction of omeprazole in 1989, PPIs have consistently been shown to be far more effective than histamine-2 receptor antagonists (H_2RA_s, e.g. ranitidine, cimetidine) in terms of healing of oesophagitis and resolution of GORD symptoms. As a class, these drugs are extremely safe.

Esomeprazole, the S-isomer of omeprazole, is the first PPI to be developed as a single optical isomer. It provides better acid control than current PPIs and has a favourable pharmacokinetic profile relative to omeprazole.[2] Esomeprazole brings a statistically significant increase in healing of mucosal injury and symptom relief in patients with erosive oesophagitis, compared with omeprazole and lansoprazole. It is currently indicated in a dosage of 20 or 40 mg/day in the treatment of symptomatic gastro-oesophageal reflux disease (GORD) with on-demand symptomatic treatment, healing erosive oesophagitis, maintenance therapy in healed erosive oesophagitis, and Helicobacter pylori-positive active duodenal ulcer combined with appropriate antibiotics.[6] Esomeprazole is generally well tolerated, both as monotherapy and in combination with antimicrobial agents with a tolerability profile similar to that of other PPIs.

The present post marketing study was conducted to confirm the efficacy and tolerability of a single daily dose of Esomeprazole 40 mg in patients with GORD.

MATERIAL AND METHODS

Study Design

This was an open-label, non-comparative, phase IV, prospective, multicentre study conducted to evaluate the efficacy and safety of Esomeprazole 40 mg in patients with GORD. Patients were enrolled in the study at 5 centres in India. The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The study protocol was submitted to and approved by the Ethics Committee of each participating centre.

Patients

Adult patients of either sex, aged between 18 to 75 years with a history of symptomatic GORD (heartburn, regurgitation, dysphagia and retrosternal pain) were included in the study. All patients had documented erosive

oesophagitis confirmed by oesophagoscopy, and graded according to the Hetzel-Dent classification[7] (Table 1), within 1 week before study commencement. All patients provided written informed consent during the pretreatment screening period before any study procedures were performed.

Table 1
Hetzel-Dent Classification of Oesophagitis on Oesophagoscopy[7]

Grade	Classification
Grade 0	Normal oesophageal mucosa / no mucosal abnormalities
Grade 1	No visible macroscopic erosions but erythema or hyperaemia of the oesophageal mucosa
Grade 2	Superficial ulcerations or erosions involving less than 10% of the mucosal surface of the last 5 cm of oesophageal squamous mucosa
Grade 3	Superficial ulcerations or erosions involving 10-50% of the mucosal surface of the last 5 cm of oesophageal squamous mucosa
Grade 4	Deep ulceration anywhere in the oesophagus or confluent erosions of more than 50% of the mucosal surface of the last 5 cm of oesophageal squamous mucosa

Female patients were required to be nonpregnant, nonlactating, postmenopausal, surgically sterilized, or using a medically acceptable form of birth control. Patients with any bleeding disorder or signs of gastrointestinal bleeding at the time of the baseline oesophagoscopy or within 3 days before study commencement were excluded as were those with a history of oesophageal or gastric surgery. Other exclusion criteria were: concurrent or historical evidence of gastric or duodenal ulcer or its complications, Zollinger-Ellison syndrome, primary oesophageal motility disorders, oesophageal stricture, endoscopic Barrett's oesophagus (> 3 cm), or significant dysplastic changes in the oesophagus, inflammatory bowel disease, upper gastrointestinal malignancy, unstable diabetes mellitus, or other severe concomitant disease.

Therapy with a PPI within 28 days before baseline was prohibited, as was daily therapy with an H_2RA during the 2 weeks before baseline oesophagoscopy. Patients with known hypersensitivity to any component of esomeprazole or aluminium/magnesium hydroxide (Gelusil), as well as patients previously participating in a clinical trial of esomeprazole, were excluded from the study.

Concomitant use of the following medications was not permitted during the study: anticholinergics, antineoplastic drugs, diazepam, diphenylhydantoins, H_2RAs, nonsteroidal antiinflammatory drugs (NSAIDs), PPIs (except study medication), promotility drugs, prostaglandin analogues, quinidine, salicylates (except low-dose prophylactic antithrombotic therapy), steroids, sucralfate, and warfarin.

Eligible patients took Esomeprazole 40 mg orally in the morning before breakfast for a period of 4 weeks or until study discontinuation. Aluminium/magnesium hydroxide (Gelusil) was permitted as rescue medication for breakthrough GORD symptoms, to a maximum of 6 tablets per day. Compliance with the study medication and rescue medication was calculated by counting unused tablets. Patients who discontinued from the study were asked to return for a follow-up visit at the time of, or soon after, discontinuation.

Assessment of Efficacy

Symptoms of GORD were assessed at baseline (Day 0) and at weeks 2 (Day 14), and 4 (Day 28) after initiation of treatment by the investigator by questioning in a standardized manner. Evaluated symptoms included heartburn, regurgitation, retrosternal pain and dysphagia. The severity of each symptom (except dysphagia) was graded on a 4-point scale as follows: 0 = none (no symptom); 1 = mild (symptom does not last long and is easily tolerated); 2 =

moderate (symptom causes discomfort and interrupts usual activities including sleep; 3 = severe (symptom causes great interference with usual activities and may be incapacitating [including sleep]). Dysphagia was recorded as being present or absent.

Oesophagoscopy was carried out at baseline and at the end of study period (4 weeks). The oesophageal mucosa was visualized and any abnormal findings documented. Oesophageal lesions were graded on a 5-point scale as mentioned above (Table 1).

The primary efficacy endpoint was complete healing of oesophageal erosions (grade 0 = normal mucosa) on oesophagoscopy at week 4. The secondary efficacy endpoint was degree of symptom (heartburn, regurgitation, retrosternal pain and dysphagia) relief at the end of study.

At the end of week 4, global assessment of overall symptoms by both physicians and patients was measured on a 4-point categorical scale: 0 = worsened symptoms; 1 = no change in symptoms; 2 = improvement in symptoms; 3 = complete resolution of symptoms.

The incidence of patient withdrawal and time to patient withdrawal due to lack of study drug efficacy were monitored.

Assessment of Safety and Tolerability

The safety and tolerability of study medication were assessed using physical examination at final visit (week 4), review of adverse events as reported by patients at weeks 2 and 4, and clinical laboratory evaluations at baseline and at the final visit (week 4).

Clinical laboratory tests included haematology, serum biochemistry, and urinalysis. At each follow-up visit, all adverse events reported during investigators' interviews with patients were recorded. The causal relationship of an adverse event to the study drug was classified by investigators as being probable, possible, or unlikely, and the intensity of the adverse event was rated as mild, moderate, or severe. The action taken with study drug in response to the adverse event (none, treatment temporarily stopped, treatment discontinued) was also recorded.

Statistical Analysis

Chi-square test was used to evaluate the effect of study drug on dysphagia and change in oesophagoscopy findings before and after treatment.

Changes in the other GORD symptoms (heartburn, retrosternal pain and regurgitation) and laboratory investigations following study drug treatment were analyzed using the analysis of variance (ANOVA Kruskal Wallis) test.

Significance was established at $p < 0.05$.

RESULTS

Patient Characteristics

A total of 309 patients, ranging in age from 18 to 73 (mean 43.87) years, were randomized to treatment with 40 mg Esomeprazole. 7 patients were excluded from the analyses for noncompliance with the protocol. Overall, there were slightly more male (58.6%) than female patients in the study. The patients were well balanced with respect to baseline demographic characteristics (Table 2).

Table 2
Patient Demographics

Characteristic	Esomeprazole 40 mg OD (n = 309)
Male gender	181 (58.6%)
Age	
Range (y)	18-73
Mean [y (SD)]	43.87 (1.36)
Height	
Range (cm)	153-172
Mean [cm (SD)]	163.7 (9.8)
Weight	
Range (kg)	46-81
Mean [kg (SD)]	52.84 (13.7)

oesophagitis confirmed by oesophagoscopy, and graded according to the Hetzel-Dent classification[7] (Table 1), within 1 week before study commencement. All patients provided written informed consent during the pretreatment screening period before any study procedures were performed.

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Table 3
Endoscopic oesophagitis healing rates by baseline Hetzel-Dent classification at week 4 after start of treatment with Esomeprazole 40mg once daily

Grade	Baseline No. of patients (%)	Week 4 No. of patients (%)
0	-	245* (81.1)
1	74 (24.5)	44 (14.6)
2	205 (67.9)	12 (4)
3	23 (7.6)	01 (3)
4	-	-

* P < 0.05 by Chi-square test

average score of retrosternal pain at the end of second (45.5%) and fourth (90%) week respectively. Similarly, a statistically significant decrease in mean score of regurgitation was noted both at week 2 (46.4%) and 4 (91.3%) following treatment (Table 4).

85.3% of the patients complained of dysphagia at baseline. At the end of 2 weeks of therapy, dysphagia was noted in 42.4% of patients and by the end of study period, only 15.2% of patients reported the presence of dysphagia.

Patient's and Physician's Global Assessment of Overall Symptoms

74.8% of the total subjects reported complete resolution of symptoms by the end of study period (4 weeks) (Fig. 1).

Table 4
Mean change from baseline in GORD symptoms at weeks 2 and 4 after start of treatment with Esomeprazole 40 mg once daily

Symptoms	Mean baseline value	Mean change from baseline	
		Week 2	Week 4
Heartburn (± SD)	2.43 ± 0.98	1.71 ± 0.84*	0.27 ± 0.42*
Retrosternal pain (± SD)	1.89 ± 0.87	1.03 ± 0.68*	0.19 ± 0.38*
Regurgitation (± SD)	1.00 ± 0.73	0.74 ± 0.49*	0.12 ± 0.29*
Dysphagia			
Present (%)	85.3	42.4**	15.2**
Absent (%)	14.7	57.6**	84.8**

* P < 0.05 by ANOVA (Kruskal Wallis) test ** P < 0.05 by Chi-square test

EFFICACY

Oesophagoscopy

At baseline, endoscopy findings revealed grade 2 oesophagitis in 67.9% and grade I oesophagitis in 24.5% of the total patients respectively. At the end of study period (4 weeks). 81.1% of the total cases with abnormal baseline oesophagoscopy findings showed a normal oesophageal mucosa (grade 0) and 14.6% of patients revealed grade oesophagitis (Table 3).

GORD Symptoms

A significant reduction in the mean score of heartburn was observed at the end of second week of treatment (29.6%) which further decreased by 89% at the end of study period. There was also a significant decrease in the

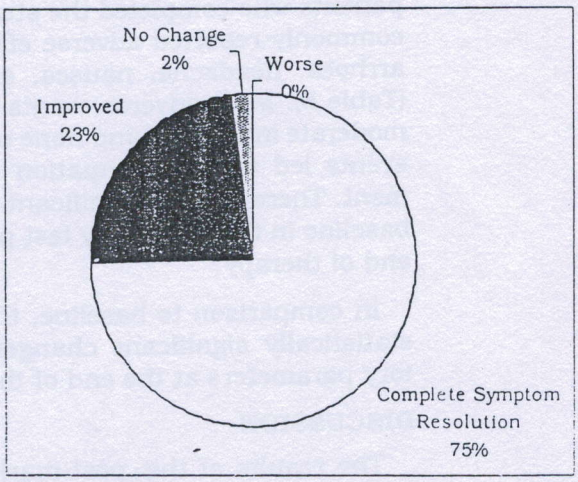

Fig. 1
Global Assessment of Overall Symptoms by Patients (End of Week 4)

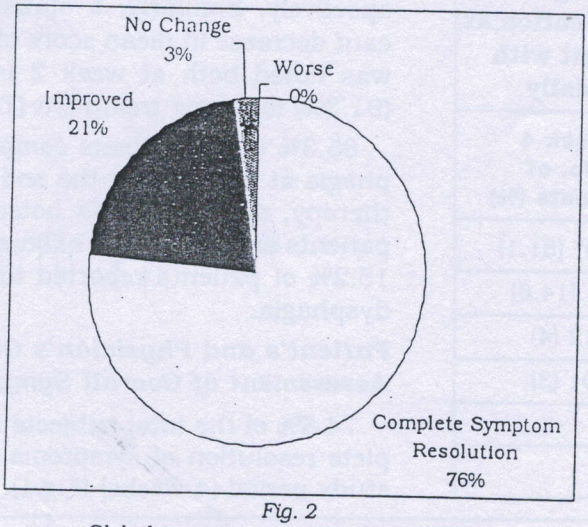

Fig. 2
Global Assessment of Overall Symptoms By Physicians (End of Week 4)

As per the physicians' assessment, 76.5% of the total cases demonstrated complete resolution of symptoms by the end of 4 weeks of treatment respectively (Fig. 2).

Approximately 3% of the patients required rescue medication with aluminium/magnesium hydroxide (Gelusil) tablets for breakthrough GORD symptoms. However, there were no discontinuations from the study due to treatment failure.

Safety and Tolerability

Adverse events were reported in 7.2% of patients who completed the study. The most commonly reported adverse effects were diarrhoea, headache, nausea, and dizziness (Table 5). Most adverse events were mild to moderate in severity and none of the adverse events led to discontinuation of the treatment. There was no significant change from baseline in the laboratory test profiles at the end of therapy.

In comparison to baseline, there were no statistically significant changes in laboratory parameters at the end of the study.

DISCUSSION

The results of this post-marketing study confirm that Esomeprazole 40 mg once daily effectively controls symptoms and also achieves significant endoscopic healing of oesophagitis in patients with GORD. Significant improvement in GORD symptoms was seen as early as 2 weeks with maximal benefit being observed by the end of 4 weeks of Esomeprazole therapy.

Table 5
Profile of Adverse Events in 302 patients with GORD treated with Esomeprazole 40 mg once daily for 4 weeks

Adverse Event	Incidence No. of patients (%)
Diarrhoea	6 (1.9)
Headache	5 (1.6)
Nausea	3 (1.0)
Dizziness	2 (0.7)
Abdominal discomfort	2 (0.7)
Weakness	2 (0.7)
Vomiting	1 (0.3)
Palpitations	1 (0.3)
Total	22 (7.2)

The development of Esomeprazole, a PPI, as the first single optical isomer, confers both pharmacological and therapeutic advantages over its parent compound, omeprazole. At clinically relevant doses, Esomeprazole is appreciably better than omeprazole, lansoprazole, rabeprazole or pantoprazole in the maintenance of gastric pH at a level > 4 when given for 5 days.[2] Amongst the PPIs, Esomeprazole demonstrates the longest duration of control of intragastric pH > 4, i.e. >16 hours of the 24-hour period.[8] Further, Esomeprazole has been shown to have a faster onset of action than rabeprazole, which has been reported to have the fastest onset of action of the racemic PPIs. In addition, Esomeprazole has a more favourable pharmacokinetic profile than omeprazole, showing higher bioavailability and reduced interpatient variability.[9]

The pharmacological advantages of Esomeprazole have been translated into therapeutic benefits, with a significantly better efficacy of Esomeprazole being dem-

onstrated in comparison to other PPIs in GORD. In three large (n > 1900 in each trial), well designed, 8-week trials in patients with erosive oesophagitis, Esomeprazole recipients (4500 across all trials) achieved significantly higher rates of endoscopically confirmed healed oesophagitis than those receiving omeprazole or lansoprazole.[10-12] Esomeprazole was effective across all baseline grades of oesophagitis. In two trials, 94% of patients receiving Esomeprazole 40 mg once daily achieved healed oesophagitis versus 84-87% of omeprazole recipients (20 mg once daily). In another study in > 5000 patients, respective healed oesophagitis rates with once-daily Esomeprazole 40 mg or Lansoprazole 30 mg were 92.6 and 88.8%. Resolution of heartburn was also significantly better with Esomeprazole than with these racemic PPIs. Esomeprazole 20 or 40 mg once daily for 4 weeks effectively resolved symptoms in patients with symptomatic GORD without oesophagitis in randomised double-blind trials. 33-42% of patients achieved complete resolution of heartburn with Esomeprazole versus 12-14% of placebo recipients.[13] Further, long term (upto 12 months) therapy with Esomeprazole effectively maintained healed oesophagitis in patients with erosive oesophagitis with a good safety profile.[2,14] To date, there are no direct head-to-head comparisons of the clinical efficacy of Esomeprazole with rabeprazole or pantoprazole in patients with GORD. However, a meta-analysis of randomized comparative trials indicated Esomeprazole 40 mg once daily gave higher healing rates in the treatment of reflux oesophagitis than omeprazole after 4 or 8 weeks, whereas lansoprazole, rabeprazole, and pantoprazole showed healing rates similar to those of omeprazole at the same time points.[2]

The results of the present phase IV study are consistent with those reported in international literature earlier. The results of these clinical studies indicate that acid control with Esomeprazole is more predictable than with other PPIs, thereby providing better predictability of therapeutic response. Mucosal healing and symptom relief in GORD has been shown to correlate directly with the proportion of each 24-hour period for which the pH of the intragastric compartment is held above the level of 4.[15] The beneficial therapeutic results obtained with Esomeprazole in various clinical studies are consistent with the superior pharmacokinetic and pharmacodynamic profile of the drug and in particular, reflects the ability of this PPI to maintain the intragastric pH > 4 for >16 hours of the 24-hour period.

The clinical efficacy of Esomeprazole is further supported by the satisfaction levels of the patients as well as treating physicians. As per the patients' and physicians' ratings, 74.8 and 76.5% of the Esomeprazole-treated patients respectively, demonstrated complete resolution of symptoms by the end of study period. Only 3% of the total treated patients required rescue therapy with aluminium/magnesium hydroxide (Gelusil) tablets for breakthrough GORD symptoms.

Esomeprazole was well tolerated in the present study with 7.2% of the patients experiencing adverse events. Again, this data is consistent with the incidence of adverse events reported with Esomeprazole in international literature (10%).[6] Further, in the present study, there were no discontinuations of therapy due to adverse events.

CONCLUSION

In conclusion, the findings of this study suggest that Esomeprazole is an effective and well tolerated treatment for the management of GORD. In view of its pharmacological and clinical superiority, Esomeprazole may be an effective option for first-line therapy in the management of GORD.

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