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Esomeprazole

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Abstract

▲ Esomeprazole, a new proton pump inhibitor, is the *S*-isomer of omeprazole and is the first such inhibitor to be developed as a single isomer.

▲ Esomeprazole provided better control of intragastric pH than omeprazole, lansoprazole and pantoprazole in trials conducted in patients with gastro-oesophageal reflux disease (GORD) or healthy volunteers (n = 20 to 115).

▲ In 2 large randomised, double-blind multicentre trials esomeprazole 20 and/or 40mg for 8 weeks produced higher healing rates of erosive oesophagitis and better symptom control than omeprazole 20mg in patients with GORD.

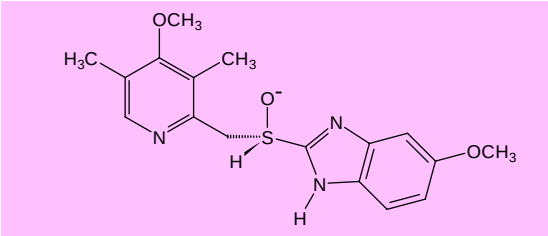
▲ Esomeprazole 10, 20 or 40mg once daily for 6 months maintained healing versus placebo ($p < 0.001$) in patients with endoscopically confirmed healed erosive oesophagitis in 2 large randomised, double-blind multicentre trials.

▲ Similarly, symptom-driven on-demand use of esomeprazole effectively controlled symptoms of GORD (heartburn) for 6 months in 2 large placebo-controlled trials.

▲ Esomeprazole-based triple therapy for 7 days was as effective for eradication of *Helicobacter pylori* as longer omeprazole-based therapy in 2 randomised double-blind trials including about 450 patients each. Endoscopically confirmed ulcer healing 4 weeks after treatment initiation was reported in about 90% of patients with active duodenal ulcer in both treatment groups.

▲ Esomeprazole-based triple therapy for 10 days was more effective than esomeprazole plus clarithromycin for eradication of *H. pylori* in 233 patients.

Features and properties of Esomeprazole (H199/18)	
Indications	
Treatment of symptomatic gastro-oesophageal reflux disease Healing and maintenance of healed erosive oesophagitis Eradication of *Helicobacter pylori* in combination with appropriate antibacterial regimens in patients with duodenal ulcer	
Mechanism of action	
Inhibits gastric acid secretion	Proton pump inhibitor
Dosage and administration	
Recommended dosage	20 or 40mg
Route of administration	Oral
Frequency of administration	Once daily (or on demand)
Pharmacokinetic profile (after multiple doses)	
Area under the plasma concentration-time curve	20mg: 2.55 μmol/L • h 40mg: 11.21 μmol/L • h
Bioavailability	20mg: 68% 40mg: 89%
Clearance	20mg: 16 L/h 40mg: 9 L/h
Elimination half-life	1.2 hours
Adverse events	
Most frequent	Headache, abdominal pain, nausea, diarrhoea, flatulence



Esomeprazole

Proton pump inhibitors are commonly used in the treatment of patients with gastro-oesophageal reflux disease (GORD) or peptic ulcer. Indeed, these agents provide the most rapid symptomatic control and best healing of oesophagitis of available agents.[1,2] Proton pump inhibitors are also associated with a higher level of patient satisfaction than treatment with histamine H_2-antagonists, although only two thirds of patients with heartburn in 1 survey were totally satisfied with the available proton pump inhibitors (omeprazole and lansoprazole were specified).[3]

Esomeprazole, the *S*-isomer of omeprazole (a racemic mixture of *S*- and *R*- optical isomers), is the first proton pump inhibitor to be developed as a single optical isomer. It has a better pharmacokinetic profile and provides greater acid suppression than omeprazole (sections 1 and 2).[4] A small study in healthy volunteers demonstrated that esomeprazole is optically stable.[5]

With 1 exception[4] all data specific to esomeprazole included in this review have been obtained from abstracts.

1. Pharmacodynamic Profile

• Although esomeprazole is an optical isomer of omeprazole, it has a different pharmacodynamic and pharmacokinetic profile. However, esomeprazole,[6] like omeprazole,[7] acts by inhibiting the H^+/K^+-ATPase enzyme responsible for the secretion of acid by gastric parietal cells. It therefore inhibits basal and stimulated gastric acid secretion.

• Esomeprazole 20 and 40mg once daily for 5 days maintained intragastric pH >4 for longer than omeprazole 20mg once daily in 36 evaluable patients with symptoms of GORD in a randomised double-blind crossover trial (fig. 1). On day 5, the mean 24-hour median intragastric pH was also higher with both dosages of esomeprazole than with omeprazole (4.1 and 4.9 *vs* 3.6; $p < 0.01$ and $p < 0.001$, respectively) and more patients receiving either dosage of esomeprazole (20 or 40 mg/day) had a pH >4 for >12 (54 and 92% *vs* 44% of omeprazole recipients) and >16 hours (24 and 56% *vs* 14% of patients given omeprazole; $p < 0.0001$[11])[4] The proportion of the 24-hour day that an intragastric pH >4 is achieved is directly correlated with mucosal healing.[12]

• Once daily administration of esomeprazole 40mg also increased intragastric pH to >4 for a longer period than omeprazole 40mg once daily in 115 patients with GORD.[8] The percentage of the 24-hour period with pH >4 on day 1 was 48.6 and 40.6% ($p < 0.001$) for esomeprazole and omeprazole, respectively, and on day 5 values were 68.4 and 62.0% (fig. 1). On day 5 88% of esomeprazole and 77% of omeprazole recipients had pH >4 for >12 hours (no statistics presented).

• Esomeprazole 40mg once daily provided greater control of 24-hour intragastric pH than lansoprazole 30mg once daily in 20 healthy volunteers who received each drug for 5 days in a randomised nonblind crossover trial. On day 5 of each treatment period, 38 and 90% of esomeprazole recipients had an intragastric pH >4 for >16 and >12 hours, respectively; corresponding percentages of lansoprazole recipients were 5 and 57% ($p < 0.01$ and $p < 0.05$, respectively). The 24-hour median pH was 4.8 in esomeprazole and 4.2 in lansoprazole recipients ($p < 0.001$) and esomeprazole recipients spent a greater percentage of the day with a pH >3 or >4 (fig. 1) than did volunteers given lansoprazole ($p < 0.001$ for both).[10]

• Esomeprazole 40mg once daily was also more effective for control of acid secretion than pantoprazole 40mg once daily in another 5-day nonblind randomised crossover trial in 31 patients with symptoms of GORD.[9] On day 5, esomeprazole recipients had a greater percentage of the 24-hour

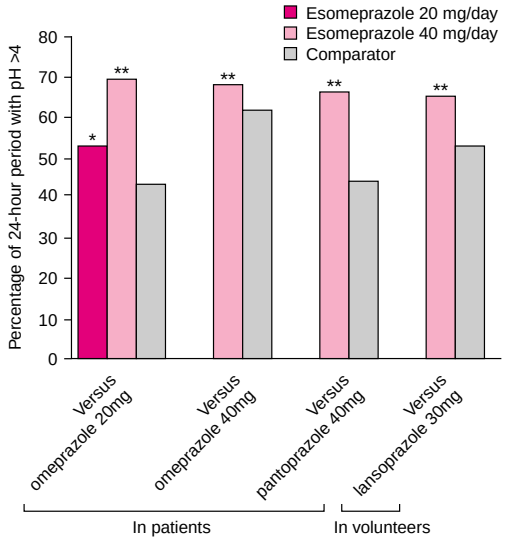


Fig. 1. Control of acid secretion with esomeprazole 20 and 40mg once daily in comparison with omeprazole 20mg or 40mg, lansoprazole 30mg or pantoprazole 40mg once daily. In randomised crossover trials patients with symptoms of gastro-oesophageal reflux disease received esomeprazole and omeprazole 20mg (n = 36; double-blind)[4] or omeprazole 40mg (n = 114; nonblind)[8] or esomeprazole and pantoprazole (n = 31; nonblind)[9] for 5 days with ≥14 day washout periods between treatments. In the other trial, 20 healthy volunteers were randomised to receive esomeprazole or lansoprazole for 5 days (with a ≥14 day washout period) in a nonblind crossover manner.[10] 24-Hour intragastric pH was monitored on day 5 of each study. * $p < 0.01$, ** $p < 0.001$ *vs* omeprazole, lansoprazole or pantoprazole.

day with a pH >4 (fig. 1) or >3 ($p < 0.001$) and a higher 24-hour median pH (4.7 *vs* 3.7 $p < 0.001$) than pantoprazole recipients. On day 5, pH was >4 for >12 hours in 90% of esomeprazole and 30% of pantoprazole recipients and at these levels for >16 hours in 50 and 10% of patients, respectively ($p < 0.0001$ and $p < 0.001$, respectively). These benefits of esomeprazole over pantoprazole, indicating higher intragastric pH levels for the former, were also seen on day 1.

• Esomeprazole 40mg once daily increased gastrin levels by a mean of 21.6 to 80.9 ng/L from baseline in a 12-month noncomparative trial. Increases plateaued after 2 to 3 months. 808 patients were enrolled in this trial and 80.9% completed at least 6 months of treatment.[13]

2. Pharmacokinetic Profile

• Esomeprazole 20mg daily for 5 days had a 70% higher area under the plasma concentration-time curve (AUC) than omeprazole 20mg daily for 5 days, at steady state in 12 healthy volunteers enrolled in a randomised crossover trial.[14] *In vitro* studies indicate that esomeprazole undergoes less hydroxylation via cytochrome P450 (CYP2C19) enzymes in human liver and has lower intrinsic clearance than the R-isomer of omeprazole.[15] Hence esomeprazole also has lower clearance than omeprazole (data on file, AstraZeneca).

• Mean AUC values over 5 days for esomeprazole 40 and 20mg once daily were 5- and 2-fold higher than values for omeprazole 20mg once daily in 36 patients evaluated in a randomised double-blind crossover trial (12.6 and 4.2 *vs* 2.3 μmol/L · h; $p < 0.0001$ for both esomeprazole dosages *vs* omeprazole).[4]

• The absolute bioavailability (F) and AUC of esomeprazole increased from day 1 to day 5 of oral administration. F values increased from 50 to 68% with a dosage of 20 mg/day and from 64 to 89% with a dosage of 40 mg/day. AUC values increased from 1.34 to 2.55 μmol/L · h and 4.32 to 11.21 μmol/L · h with each dosage, respectively. The drug was given as a solution (20mg) or capsule (40mg) for 5 days to 32 healthy volunteers enrolled in either of 2 studies.[16]

• Intravenous administration of single doses of esomeprazole 1 to 2 weeks before and the day after 5 days of oral administration showed that plasma clearance (CL) decreased and the plasma elimination half-life ($t_{1/2}$) increased after repeated use. CL decreased from 22 to 16 L/h with a 20mg dose and from 17 to 9 L/h with a 40mg dose; correspondingly, $t_{1/2}$ increased from 0.8 to 1.2 hours with both drug doses.[16]

• AUC values for esomeprazole were significantly and non-linearly related to the extent of gastric acid inhibition and percentage time spent with

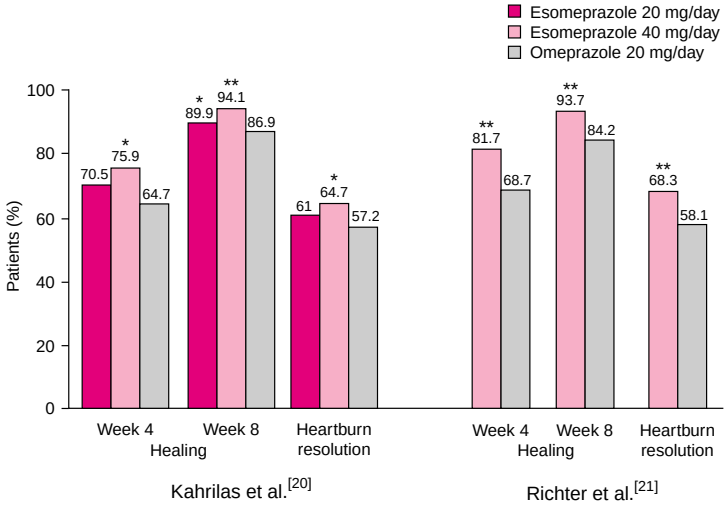


Fig. 2. Healing rates and heartburn resolution after ≤8 weeks of treatment with esomeprazole or omeprazole in patients with gastro-oesophageal reflux disease in 2 randomised double-blind multicentre trials. Heartburn resolution was defined as no episodes of heartburn at 4 weeks. *Helicobacter pylori*-negative patients with all grades of erosive oesophagitis received once daily treatment with esomeprazole 20 (n = 656) or 40mg (n = 654) or omeprazole 20mg (n = 650) in 1 trial[20] and esomeprazole 40mg (n = 1216) or omeprazole 20mg (n = 1209) in the other.[21] * $p \leq 0.05$, ** $p < 0.001$ *vs* omeprazole.

an intragastric pH >4 and proved a better predictor of these parameters than C_{max} values in healthy volunteers.[17]

In Elderly Patients

• The pharmacokinetics of esomeprazole 40mg each morning for 5 days are not significantly altered by increasing age. AUC and C_{max} values were not significantly different in 13 healthy elderly volunteers (aged 71 to 80 years) and 39 patients with symptoms of GORD (aged 29 to 58 years) enrolled in an earlier trial. On day 5 AUC and C_{max} values were 5.57 μmol/L and 15.98 μmol/L · h, respectively, in elderly volunteers.[18]

In Patients with Hepatic Dysfunction

• Mild to moderate hepatic dysfunction (Child-Pugh classification) did not affect the pharmacokinetics [AUC during the dosing interval at steady state (AUC_τ) and $t_{1/2}$] of esomeprazole 40mg once daily for 5 days. However, mean AUC_τ values were 76% higher and $t_{1/2}$ values were 29% longer in 12 patients with mild, moderate or severe hepatic dysfunction (Child-Pugh classification) when compared with values in historical controls with symptoms of GORD and normal hepatic function. These changes occurred predominantly in patients with severe hepatic dysfunction. Maximum plasma concentrations (C_{max}) and time to C_{max} (2 hours) were not significantly affected by liver dysfunction.[19]

3. Clinical Trials

Gastro-Oesophageal Reflux Disease

The efficacy of esomeprazole in patients with GORD has been evaluated in a number of randomised, double-blind multicentre trials that are summarised below.

• In 2 large trials esomeprazole 20 and/or 40mg produced higher healing rates of erosive oesophagitis than omeprazole 20mg in patients with *Helicobacter pylori*-negative GORD.[20,21] More patients were healed at week 8 [the primary effi-

cacy parameter; assessed endoscopically and using cumulative life table rates; intent-to-treat (ITT) analysis[20,21]] and at week 4 during once daily treatment with esomeprazole versus omeprazole (fig. 2). Sustained resolution of heartburn (7 consecutive days without heartburn) was also achieved by significantly more recipients of esomeprazole 40mg than omeprazole on days 1 (30 *vs* 22%) to 28 (74 *vs* 67%), as assessed using patient diary data in 1 trial of 1960 patients ($p < 0.001$).[20] Similarly, in the larger trial (n = 2425), more patients receiving esomeprazole 40 mg/day than omeprazole 20 mg/day had sustained resolution of heartburn on days 1 to 28 ($p < 0.005$).[21] Sustained resolution of heartburn was also reached faster with esomeprazole 40mg than omeprazole: after a median of 5 days with esomeprazole 40 mg/day ($p \leq 0.05$ *vs* omeprazole), 8 days with esomeprazole 20 mg/day and 9 days with omeprazole[20] and after a median of 5 and 8 days with esomeprazole 40 mg/day and omeprazole 20 mg/day ($p < 0.001$).[21] In both trials the percentage of days and nights without heartburn favoured esomeprazole over omeprazole ($p < 0.002$ and $p < 0.001$) and resolution of heartburn, as assessed by investigators, (fig. 2) was also better and occurred faster with esomeprazole.[20,21]

- Six months of treatment with esomeprazole 10, 20 or 40mg once daily maintained healing in patients with endoscopically confirmed healed erosive oesophagitis.[22,23] Maintenance of healing was dose-related, and all doses were superior to placebo in 2 trials that each included >300 patients (fig. 3). The mean number of days to recurrence of erosive oesophagitis was also greater with all doses of esomeprazole than with placebo (no statistics presented; fig. 3). However, the 10mg dose did not provide as great a benefit as the 2 higher doses. Disease symptoms were also assessed and maintenance of healing of erosive oesophagitis was highly correlated with absence of symptoms of GORD.[23]

- Healing of erosive oesophagitis was maintained during treatment with esomeprazole 40mg once daily in 93% of patients at 6 months and 89.4% of patients at 12 months, according to life-table estimates and endoscopic examination, in a noncomparative 12-month safety trial. 808 patients with endoscopically-confirmed healed erosive oesophagitis were enrolled and 80.9% continued treatment for ≥6 months.[13]

- Symptom-driven on-demand use of esomeprazole provided effective treatment of symptoms of GORD for 6 months in 2 trials that enrolled 721[24] and 342[25] patients with healed disease (as assessed endoscopically) and resolution of heartburn. Patients were allowed ≤1 dose of esomeprazole per

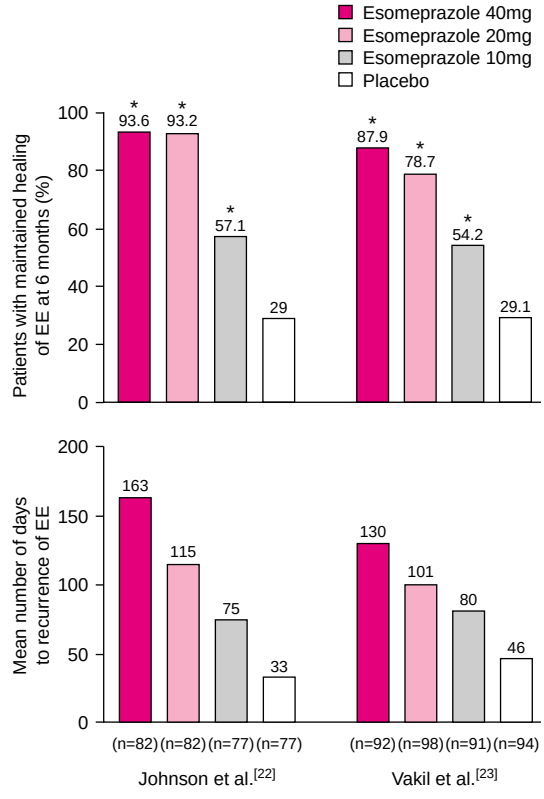


Fig. 3. Maintenance of healing of erosive oesophagitis (EE) with esomeprazole in 2 double-blind randomised placebo-controlled multicentre trials.[22,23] In each trial >300 patients with endoscopically-confirmed healed EE received one of 3 dosages of esomeprazole (10, 20 or 40mg once daily) or placebo for 6 months. Endoscopy was repeated and symptoms were evaluated at 1, 3 and 6 months. * $p < 0.001$ *vs* placebo.

day; a mean of about 0.3 doses/day (about 1 dose every 3 days) was required. Fewer recipients of esomeprazole 40 or 20 mg/day than placebo discontinued treatment because of unwillingness to continue treatment for any reason or inadequate control of heartburn ($p < 0.0001$ for all comparisons *vs* placebo).[24] Inadequate control of heartburn caused 9, 5 and 36% of esomeprazole 40 and 20 mg/day and placebo recipients to withdraw from treatment in 1 study ($p < 0.0001$ *vs* placebo for both dosages),[24] and 14 and 51% of esomeprazole 20 mg/day and placebo recipients to withdraw in the other ($p < 0.001$ *vs* placebo).[25] Rescue use of antacids was >2-fold higher with placebo than esomeprazole.[24,25]

Eradication of *Helicobacter pylori* in Patients with Duodenal Ulcer

- A 7-day regimen of esomeprazole-based triple therapy was as effective as omeprazole-based therapy in 2 randomised double-blind trials each including about 450 patients with either inactive[26] or active duodenal ulcer.[27] Both proton pump inhibitors were given at a dosage of 20mg twice daily with amoxicillin 1000 mg twice daily and clarithromycin 500mg twice daily for 7 days. Patients with active duodenal ulcer then received a further 3 weeks of monotherapy with omeprazole whereas patients in the esomeprazole group received placebo during this period.[27] ^{13}C-urea breath test and histology results ≥4 weeks post-treatment indicated *H. pylori* eradication in 86% of esomeprazole and 88% of omeprazole recipients in this trial (ITT analysis). Endoscopically confirmed ulcer healing 4 weeks after treatment initiation occurred in 91% of esomeprazole and 92% of omeprazole recipients (ITT analysis).[27] 89.7% of patients with inactive disease receiving esomeprazole and 87.8% of those receiving omeprazole had negative ^{13}C-urea breath test results at both 4 and 8 weeks post-treatment in the other trial (ITT analysis).[26] No significant between treatment differences were observed in either trial[26,27] and symptom relief was similar with both regimens.[27] In these trials *H. pylori* eradication rates exceeded that recommended in the Maastricht consensus report (80%).[28]

- A 10-day regimen of esomeprazole-based triple therapy was more effective for eradication of *H. pylori* than dual therapy, but duodenal ulcer healing rates did not differ between treatments (69 *vs* 62%). *H. pylori* was eradicated at day 38 in 77% of 233 patients randomised to esomeprazole 40mg once daily plus amoxicillin 1000mg twice daily and clarithromycin 500mg twice daily for 10 days and 52% of 215 patients randomised to the same dosages of esomeprazole and clarithromycin ($p < 0.0001$; ITT analysis). When results for both regimens were pooled, duodenal ulcer healing rates were higher in patients with eradicated *H. pylori* than in patients with persistent infection (76 *vs* 57%). Per protocol results were similar with eradication rates of 84 and 55% ($p < 0.0001$) and healing rates of 75 and 66% reported.[29]

4. Tolerability

- Adverse events occurred at a similar frequency during up to 8 weeks of treatment with esomeprazole 20 or 40mg once daily or omeprazole 20mg once daily in 2 large double-blind randomised trials in patients with GORD (n = 1960 and 2425).[20,21] 15.3% of patients receiving esomeprazole 40 mg/day (n = 1216) and 15.1% of patients receiving omeprazole (n = 1209) reported adverse events in 1 trial[21] and about 2% of patients in each group withdrew from treatment because of adverse events in the other.[20] The most common adverse events were headache, abdominal pain, diarrhoea, nausea and respiratory infection.[20]

- Maintenance therapy with esomeprazole 10, 20 or 40mg once daily for up to 6 months was generally well tolerated in patients with healed GORD. The most commonly reported adverse events were headache, respiratory infection, sinusitis, flatulence and diarrhoea.[22,23] Adverse events were reported to be similar in all treatment groups in these placebo-controlled dose ranging trials including 318 and 375 patients (no further comparative data presented).[22,23]

• A noncomparative trial in 808 patients with healed erosive oesophagitis in which esomeprazole 40mg once daily was administered for 12-months (80.9% of patients received treatment for ≥6 months), showed the drug to be generally well tolerated. Adverse events were reported by 37.4, 68.3 and 78.2% of patients at 1, 6 and 12 months, respectively, (cumulative percentages) and no patient reported a serious drug-related adverse event. Adverse events considered to be possibly or probably treatment related (figure 4 summarises the most common) were reported in 23.8% of patients; 7.5% of patients withdrew from treatment because of adverse events (usually nausea, abdominal pain and flatulence). Laboratory changes were usually small and not clinically relevant.[13]

• On-demand therapy with esomeprazole 20 or 40mg up to once daily was also well tolerated in two 6-month trials in 342 and 721 patients with healed GORD. Adverse event and laboratory data were reported to be similar in all groups.[24,25]

• In 222 and 224 patients with duodenal ulcer and *H. pylori* infection, 7-days of esomeprazole-based triple therapy (see section 3 for details) was generally well tolerated.[26,27] In these trials in 448[26] and 446[27] patients, esomeprazole-based triple therapy demonstrated a similar tolerability profile to omeprazole-based triple therapy: 58.5 and 54.5% of 224 esomeprazole and 224 omeprazole recipients experienced adverse events.[26] Adverse events were reported to be those expected of proton pump inhibitor-antibacterial combination therapies.[26,27]

• Dual- and triple-therapy 10-day regimens of esomeprazole 40 mg/day plus antibacterials were similarly tolerated with no serious drug-related adverse events reported (additional tolerability data were not reported in this abstract).[29]

• Gastric biopsy results from the above study in 808 patients indicated that few had increases in chronic inflammation, atrophy or intestinal metaplasia.[13] As is usual with proton pump inhibitor treatment, increases in gastrin levels were observed (section 1). Pooled data from this study and two 6-month randomised double-blind placebo-controlled dose ranging trials in 519 patients with healed erosive oesophagitis indicate that gastric histological scores underwent only minor fluctuations compared with that expected in untreated populations. Gastric histology scores generally improved with a similar or greater frequency than they worsened. Abnormal enterochromaffin-like (ECL) cell ratings (simple, linear or micronodular hyperplasia) were reported in 5 to 12% of patients at their final biopsy, compared with in 1 to 2.5% of patients at baseline. No ECL cell dysplasia, carcinoids or neoplasia was reported.[30]

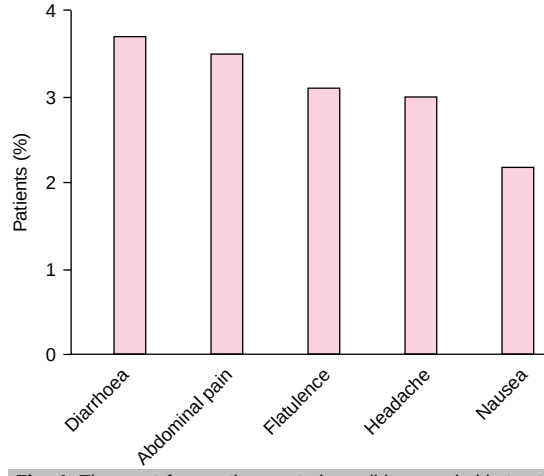


Fig. 4. The most frequently reported possibly or probably treatment-related adverse events occurring in 808 patients with healed erosive oesophagitis receiving esomeprazole 40mg once daily. 80.9% of patients received the drug for ≥6 months in this non-comparative 12-month trial.[13]

5. Esomeprazole: Current Status

Esomeprazole is a new proton pump inhibitor and is an optical isomer of omeprazole. Preliminary evidence suggests that it has significant efficacy in the treatment of patients with GORD and as maintenance treatment for patients with healed erosive oesophagitis; healing rates were higher with esomeprazole 40mg once daily than with omeprazole 20mg once daily. On-demand use of the drug provided effective control of symptoms of

GORD in 6-month trials. Esomeprazole has also demonstrated efficacy combined with appropriate antibacterial regimens for the eradication of *H. pylori* and treatment of duodenal ulcer. Esomeprazole was well tolerated in trials of up to 12 month's duration.

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