

# A review of esomeprazole in the treatment of gastroesophageal reflux disease (GERD)

Evangelos Kalaitzakis  
Einar Björnsson

Department of Internal Medicine,  
Section of Gastroenterology and  
Hepatology, Sahlgrenska University  
Hospital, Gothenburg, Sweden

**Abstract:** Proton-pump inhibitors (PPIs) are the drugs of choice for the treatment of gastroesophageal reflux disease (GERD). Esomeprazole is the latest PPI and was developed as the S-isomer of omeprazole as an attempt to improve its pharmacokinetic properties. Esomeprazole has been reported to have a somewhat higher potency in acid inhibition than other PPIs. Despite some controversy, data from clinical trials and meta-analyses indicate that esomeprazole 40 mg od for up to 8 weeks provided higher rates of healing of erosive GERD and a greater proportion of patients with sustained resolution of heartburn, than omeprazole 20 mg, lansoprazole 30 mg, or pantoprazole 40 mg od. Esomeprazole 20 mg od has also been shown to be more effective in maintaining healing of erosive GERD compared with lansoprazole 15 mg od or pantoprazole 20 mg od. However, it is not clear whether these statistically significant differences are of major clinical importance. Esomeprazole 20 mg od is superior to placebo for treatment of non-erosive reflux disease (NERD) but clinical trials have not shown any significant differences in efficacy between esomeprazole 20 mg and omeprazole 20 mg or pantoprazole 20 mg od. Lastly, although esomeprazole treatment in GERD has been reported to result in improvement of health-related quality of life (QoL) indices, no clinical trials have evaluated the possible differential effects of different PPIs on QoL in GERD.

**Keywords:** esomeprazole, gastro-esophageal reflux disease (GERD), esophagitis, proton pump inhibitors

## Introduction

Gastro-esophageal reflux (GERD) is defined as the reflux of gastric contents into the esophagus leading to reflux symptoms sufficient to affect patient well-being and/or cause complications (Vakil et al 2006). Population-based studies suggest that heartburn is a very common symptom in the general population with a prevalence of 10%–20% in the Western world but far from all are consulters. However, in Asia the prevalence of GERD-like symptoms is lower and has been reported to be less than 5% (Dent et al 2005; Moayyedi and Talley 2006). When traditional endoscopy is used, GERD can be subdivided into reflux esophagitis (or erosive GERD) and endoscopy-negative reflux disease (or non-erosive reflux disease, NERD) (Moayyedi and Talley 2006; Vakil et al 2006). About 50% of patients with the disease have a normal endoscopy in referral centers (Johansson et al 1986; Johnsson et al 1987), but in primary care the occurrence of esophagitis is lower (Vakil et al 2006). Erosive GERD has been associated with complications such as esophageal strictures and Barrett's esophagus (Vakil et al 2006).

The proton pump inhibitors (PPIs) are substituted benzimidazoles administered as enteric-coated tablets or capsules that pass through the stomach and are absorbed in the duodenum. They act on the proton pump molecule on the luminal surface of gastric parietal cells, resulting in inhibition of acid secretion (Hatlebakk 2003). Esomeprazole is the latest PPI and was developed as the S-isomer of omeprazole as an improvement

Correspondence: Evangelos Kalaitzakis  
Department of Internal Medicine, Section  
of Gastroenterology and Hepatology,  
Sahlgrenska University Hospital,  
413 45 Gothenburg, Sweden  
Tel +46 31 34 21000  
Fax + 46 31 82 21 52  
Email evangelos.kalaitzakis@vgregion.se

in its pharmacokinetic properties (Hatlebakk 2003; Kendall 2003). PPIs are the drugs of choice in the treatment of GERD (Moayyedi and Talley 2006).

Esomeprazole is considered to have a somewhat higher potency in acid inhibition than other PPIs (Hatlebakk 2003; Kendall 2003; Hellstrom and Vitols 2004). However, previous reports have reported variable results in comparing its efficacy in healing erosive GERD, in maintenance therapy of healed erosive GERD, and in therapy of NERD compared with other PPIs. Some systematic reviews and meta-analyses have been published on the efficacy of esomeprazole in the therapy of erosive GERD (Klok et al 2003; Vakil and Fennerty 2003; Edwards et al 2006; Gralnek et al 2006). The aim of the current systematic review was to provide an update on the efficacy of esomeprazole in acid suppression, in the acute and maintenance therapy of erosive GERD and NERD as well as in improving health-related quality of life (QoL) in GERD. Comparison with other PPIs in this context was also undertaken.

## Data selection

We performed a structured electronic search of PubMed to identify English-language, randomized clinical trials from 2000 to 2006 comparing esomeprazole vs alternative PPIs in the treatment of GERD. The bibliography of systematic reviews and meta-analyses performed comparing the efficacy of esomeprazole vs other PPIs in GERD was searched manually for references not found by the strategy described above. Abstracts from presentations at conferences, animal studies, or data from the manufacturers not published as full-text articles were not included. A review of the literature on esomeprazole and Barrett's esophagus or extraesophageal manifestations of GERD was beyond the scope of this article.

## Acid suppression

Although investigators agree that GERD is associated with dysmotility and results from an imbalance between normal defensive factors such as esophageal clearance, lower esophageal sphincter tone, and aggressive factors such as acid and pepsin, it has become increasingly clear that the key to controlling symptoms and to healing esophagitis is decreasing the duration of exposure to the acidic refluxate (Hunt 1999). The duration of esophageal exposure to a refluxate with a pH of 4.0 or less has been shown to be correlated to mucosal injury and to a reduced ability of the injured mucosa to proliferate and heal (Bell et al 1992; Hunt 1999). Controlling GERD symptoms and healing erosive GERD can be best

achieved by increasing the gastric pH to 4.0 or above for as long a duration as possible (Bell et al 1992; Hunt 1999). Furthermore, it has been suggested that in patients with more severe grades of esophagitis, there are abnormally high levels of nocturnal acid exposure (Bell et al 1992). Also, ulcerative esophagitis, esophageal strictures, and Barrett's esophagus are characterized by high levels of supine nocturnal percentage acid reflux time (Frazzoni et al 2003), indicating that control of nocturnal acid secretion is important.

PPIs reduce gastric acid secretion by inhibiting activity of the gastric  $H^+/K^+$ -ATPase. They are protonated in the acidic gastric environment to active forms, which irreversibly bind to the  $H^+/K^+$ -ATPase and inactivate it (Hunt 1999; Hatlebakk 2003; Hellstrom and Vitols 2004). As PPIs block the last step in the pathway to gastric acid secretion, they are effective in both basal and stimulated acid secretion (Hunt 1999; Hellstrom and Vitols 2004).

## The effects of esomeprazole on gastric acidity

Recently, acid control with esomeprazole has been compared with that of other PPIs in several cross-over studies in either patients with GERD or in healthy individuals. As shown in Table 1, all studies showed that esomeprazole 40 mg od was more effective in maintaining intragastric pH at 4.0 or lower compared with all other PPIs given at standard doses. The same studies demonstrated that esomeprazole 40 mg od is superior to all other PPIs at standard doses in terms of achieving higher 24-hour median intragastric pH and in terms of the number of patients achieving intragastric pH  $\geq 4.0$  for at least 12 hours per day. Nocturnal pH was measured in one of these studies, comparing esomeprazole 40 mg with pantoprazole 40 mg bd (Miehlke et al 2005). During night-time the proportion of time with intragastric pH  $> 4.0$  was 85.4% with esomeprazole and 63.6% with pantoprazole ( $p = 0.0001$ ). Nocturnal acid breakthrough, defined as intragastric pH  $< 4.0$  for at least one consecutive hour between 10 pm and 6 am, was observed in 26.7% of subjects receiving esomeprazole and in 73.3% of those receiving pantoprazole ( $p = 0.009$ ) (Miehlke et al 2005). Data on the effect of esomeprazole on nocturnal pH in comparison with other PPIs are otherwise largely lacking.

In certain situations, it is reasonable to use higher than approved doses of PPIs, often divided in two doses. These include a diagnostic trial for noncardiac chest pain, empiric treatment trial for supraesophageal symptoms of GERD, cases of partial response to standard dose therapy, cases with breakthrough symptoms, GERD patients with severe

**Table 1** Gastric acidity, expressed as the percentage of time with intragastric pH >4.0 on day 5 in individuals treated with esomeprazole, omeprazole, pantoprazole, and rabeprazole in cross-over randomized pharmacodynamic studies

Reference	Study design	Patient/individual selection	PPIs compared	Number of individuals	Percentage of time with intragastric pH >4.0
Lind et al 2000	Double-blind, randomized, cross-over	GERD symptoms	Eso40 vs eso20 vs ome 20 od	38	69.8% vs 53.0 vs 43.7% p < 0.01
Rohss et al 2002	Open-label, randomized, cross-over	GERD symptoms	Eso40 vs ome 40 od	130	68.4% vs 62.0%, p < 0.001
Wilder-Smith et al 2003	Open-label, randomized, cross-over	Healthy volunteers	Eso40 vs lan30 od	24	65% vs 53%, p < 0.001
Wilder-Smith et al 2003	Open-label, randomized, cross-over	Healthy volunteers	Eso40 vs rabe20 od	23	61% vs 45.1%, p = 0.005
Miner et al 2003	Open-label, randomized, cross-over	GERD symptoms	Eso40 vs lan30 vs ome20 vs panto40 vs rabe20 od	34	58.4% vs 47% vs 49.1 vs 50.5%, p < 0.001
Rohss et al 2004	Open-label, randomized cross-over	GERD symptoms	Eso40 vs lan30 od	36	57.5% vs 44.6%, p < 0.0001
Rohss et al 2004	Open-label, randomized, cross-over	GERD symptoms	Eso40 vs ome20 od	38	70% vs 43.8%, p < 0.0001
Rohss et al 2004	Open-label, randomized, cross-over	GERD symptoms	Eso40 vs panto40 od	32	67.1% vs 45%, p < 0.001
Rohss et al 2004	Open-label, randomized, cross-over	GERD symptoms	Eso40 vs rabe20 od	35	59.6% vs 44.6%, p < 0.0001
Miehlke et al 2005	Single-blind, randomized, cross-over	Healthy volunteers	Eso40 vs panto bd	30	85.4% vs 63.6%, p = 0.0001
Johnson et al 2005	Open-label, randomized, cross-over	GERD symptoms	Eso40 bd vs lan30 bd vs eso40 od vs lan30 od	45	81.3% vs 65.4% vs 60.1% vs 51.3% p < 0.05

**Abbreviations:** Eso, esomeprazole; GERD, gastroesophageal reflux disease; lan, lansoprazole; ome, omeprazole; PPI, proton-pump inhibitor; panto, pantoprazole; rabe, rabeprazole.

esophageal dysmotility, and Barrett's esophagus (DeVault and Castell 2005). A recent double-blind, randomized, cross-over study investigated the 24-hour intragastric pH profile of esomeprazole 40 mg bd vs 20 mg bd vs 40 mg od in 25 healthy volunteers (Katz et al 2004). Esomeprazole 40 mg bd provided a mean time of 19.2 hours with intragastric pH >4.0 (80.1% of a 24-hour time period, 95% confidence interval (CI) 74.5%–85.7%) vs 14.2 hours with 40 mg od (59.2%, 95% CI 53.7%–64.7%) and 17.5 hours with 20 mg bd (73.0%, 95% CI 67.4%–78.5%). The percentage of time of a 24-hour period that pH remained >4.0 was significantly higher with the esomeprazole bd dosing regimens compared to the 40 mg od regimen during the supine (sleeping) portion of the monitoring period (83.7% (95% CI 74.9%–92.4%) for esomeprazole 40 mg bd vs

79.2% (95% CI 70.5%–87.9%) for esomeprazole 20 mg bd vs 57.9% (95% CI 49.0%–66.9%) for esomeprazole 40 mg od (Katz et al 2004). Esomeprazole 40 mg bd has also been shown to be superior to pantoprazole 40 mg bd and lansoprazole 30 mg bd in maintaining intragastric pH at 4.0 or lower (Table 1). These data indicate that twice-daily dosing of omeprazole provides significantly greater acid suppression than once-daily dosing and may, therefore, be a reasonable consideration for patients requiring greater acid-suppression for GERD.

### The effects of esomeprazole on esophageal acidity

Two studies have assessed the effect of esomeprazole on intraesophageal pH profiles compared to other PPIs.

In a double-blind, randomized, cross-over study in 35 patients with GERD symptoms, esomeprazole 40 mg od was compared with pantoprazole 40 mg od as to their effects on intraesophageal pH (Simon et al 2003). At baseline the median percentage of total time with pH <4.0 was 20.1% in the esomeprazole and 21.3% in the pantoprazole group. After 7 days of repeated administration, this time was reduced to 0.9% and 2.6% respectively, and the mean within-subject differences in mean 24-hour pH values between pre- and post-treatment values were 19.2% and 18.7% respectively. The Hodges-Lehmann estimate for the mean within-subjects differences in mean 24-hour pH between pre- and post-treatment values for the two PPIs was 2.86% and the corresponding 90% CI was within the equivalence range set at  $\pm 10\%$  (90% CI -2.27; 7.07) (Simon et al 2003). In another open-label randomized study, esomeprazole 40 mg od was compared with lansoprazole 30 mg od in 30 patients with complicated GERD (Frazzoni et al 2006). Normalization of total and supine nocturnal esophageal acid exposure was achieved in 75% vs 28% ( $p = 0.026$ ) and 93% vs 50% ( $p = 0.012$ ) of patients in the esomeprazole and the lansoprazole group, respectively (Frazzoni et al 2006).

## Erosive GERD

Randomized trials evaluating the role of esomeprazole in healing of erosive GERD or maintenance therapy of healed erosive GERD were reviewed.

## Healing of erosive GERD

Several clinical trials have compared esomeprazole with other PPIs in healing of erosive GERD (Table 2). Studies reported in Table 2 had a similar double-blind, randomized design; they included intention-to-treat analyses of healing rates, and, as a secondary endpoint, evaluation of therapy effect on GERD symptoms. Also, all studies included patients who had endoscopy-confirmed erosive GERD at baseline. Follow-up endoscopy was performed at 4 weeks and at 8 weeks, except for one study in which patients underwent first follow-up endoscopy at 4 or 6 weeks and second follow-up endoscopy at 8 or 10 weeks (Gillessen et al 2004). Although at least two randomized studies comparing esomeprazole with each of the other PPIs were identified, no comparative studies of esomeprazole vs rabeprazole in erosive GERD could be found.

Five out of 8 studies showed that esomeprazole 40 mg od achieves better healing rates of erosive esophagitis after 4 and 8 weeks of treatment compared with omeprazole 20 mg,

lansoprazole 30 mg, or pantoprazole 40 mg od (Table 1). In these trials a total of 13,797 patients with erosive GERD were included. The greater efficacy of esomeprazole over omeprazole, lansoprazole, or pantoprazole was consistent when adjusted for baseline severity of esophagitis according to the Los-Angeles classification. Furthermore, all of these studies showed that esomeprazole 40 mg od is more effective than omeprazole 20 mg, lansoprazole 30 mg, or pantoprazole 40 mg od in providing resolution of GERD-associated symptoms (Kahrilas et al 2000; Richter et al 2001; Castell et al 2002; Fennerty et al 2005; Labenz et al 2005b). Interestingly, all these studies were supported by the manufacturer of esomeprazole.

However, 3/8 comparative studies, in which a total of 1659 patients were included, showed that there were no statistically significant differences in 4- or 8-week healing rates between esomeprazole 40 mg od and omeprazole 20 mg, lansoprazole 30 mg, or pantoprazole 40 mg od. One of these studies showed that healing rates with esomeprazole were significantly higher than those with omeprazole at weeks 4 (60.8% vs 47.9%,  $p = 0.02$ ) and 8 (88.4% vs 77.5%,  $p = 0.007$ ) in patients with moderate to severe (Los Angeles grade C or D) erosive esophagitis at baseline but were not significantly different for patients with mild (Los Angeles grade A or B) erosive esophagitis (Schmitt et al 2006). These studies reported similar efficacy of esomeprazole compared to omeprazole, lansoprazole, or pantoprazole in GERD-related symptoms (Howden et al 2002; Gillessen et al 2004; Schmitt et al 2006). One out of three of these studies was supported by the manufacturer of esomeprazole, showing some benefits of esomeprazole for patients with more severe esophagitis (Schmitt et al 2006). The other two were supported by the manufacturers of lansoprazole, showing no difference between lansoprazole and esomeprazole (Howden et al 2002), and by the manufacturer of pantoprazole, showing no difference between pantoprazole and esomeprazole (Gillessen et al 2004). Equivalence of esomeprazole 40 mg and pantoprazole 40 mg od in treating GERD-related symptoms in patients with erosive GERD was also reported in a double-blind randomized study in which 217 patients with esophagitis were included (Scholten et al 2003). In this trial no follow-up endoscopic evaluation was performed and, thus, no data on healing rates could be calculated (Scholten et al 2003).

*Helicobacter pylori* infection has been shown to elevate the intragastric pH achieved by PPIs (Verdu et al 1995; Labenz et al 1996). In a study with pantoprazole, it has also been proposed that this increased efficacy of PPIs in

**Table 2** Randomized trials evaluating the efficacy of esomeprazole vs other proton-pump inhibitors in healing erosive GERD

Reference	Study design	Number of patients	PPIs compared	Healing rates intention-to-treat analysis	
				4 weeks	8 weeks
Kahrilas et al 2000	Double-blind, randomized	1960	Eso40 vs eso20 vs ome20 od	75.9% vs 70.5% vs 64.7%, p < 0.05 for eso40 vs p = 0.09 for eso20 vs ome20	94.1% vs 89.9% vs 86.9%, p < 0.05 for all comparisons
Richter et al 2001	Double-blind, randomized	2425	Eso40 vs ome20 od	81.7% vs 68.7%, p < 0.001	93.7% vs 84.2%, p < 0.001
Schmitt et al 2006	Double-blind, randomized	1148	Eso40 vs ome20 od	68.2% vs 66.3%, p = 0.385	87% vs 85.8, p = 0.552
Castell et al 2002	Double-blind, randomized	5241	Eso40 vs lan30 od	79.4% vs 75.1%, p < 0.05	92.6% vs 88.8%, p < 0.0001
Howden et al 2002	Double-blind, randomized	284	Eso40 vs lan30 od	78.3% vs 77%, p > 0.05	91.4% vs 89.1, p > 0.05
Fennerty et al 2005	Double-blind, randomized	1001	Eso40 vs lan30 od	55.8% vs 47.5%, p = 0.005	82.4% vs 77.5%, p = 0.005
Gillessen et al 2004	Double-blind, randomized	227	Eso40 vs panto40 od	72% vs 74%, p > 0.05 <sup>a</sup>	92% vs 90%, p > 0.05 <sup>b</sup>
Labenz et al 2005b	Double-blind, randomized	3170	Eso40 vs panto40 od	81% vs 74.5%, p < 0.001	92% vs 95.5%, p < 0.001

<sup>a</sup>Healing rates regarding the first follow-up visit at 4 or 6 weeks in this study

<sup>b</sup>Healing rates at the second follow-up visit at 8 or 10 weeks in this study

**Notes:** No randomized studies comparing esomeprazole with rabeprazole for healing erosive GERD were found.

**Abbreviations:** Eso, esomeprazole; ome, omeprazole; lan, lansoprazole; panto, pantoprazole; PPI, proton-pump inhibitor.

*H. pylori*-infected patients may be associated with improved symptom control and more rapid healing of the esophagitis (Holtmann et al 1999). Furthermore, *H. pylori* eradication has been reported to be a predictor of failure in the treatment of GERD with omeprazole 20 mg od (Wu et al 2004) but this finding was not reproduced in another study (Kuipers et al 2004). A recent review on this topic concluded that at present it is unclear whether *H. pylori* should be eradicated in GERD patients (Delaney and McColl 2005). In all of the studies reviewed here *H. pylori* status was evaluated in the patients included. A significant effect of *H. pylori* infection was shown in one of the studies comparing esomeprazole 40 mg with pantoprazole 40 mg od with *H. pylori*-negative patients experiencing lower healing rates than in *H. pylori*-positive patients (Labenz et al 2005b). No difference was observed in the efficacy of esomeprazole between *H. pylori*-negative and *H. pylori*-positive GERD patients in the studies where this was investigated (Kahrilas et al 2000; Richter et al 2001; Castell et al 2002; Gillessen, et al 2004; Fennerty et al 2005; Labenz et al 2005b; Schmitt et al 2006). However, it should be taken into consideration that the effect of *H. pylori* status on healing of erosive esophagitis was only a secondary endpoint in these studies.

Five meta-analyses on the effect of different PPIs were identified (Edwards et al 2001, 2006; Klok et al 2003; Vakil and Fennerty 2003; Gralnek et al 2006), three of

which focused on the effect of different PPIs (including esomeprazole) in healing erosive esophagitis (Edwards et al 2001, 2006; Gralnek, et al 2006). In a recent meta-analysis comparing the efficacy of PPIs in short-term use (Klok et al 2003), two studies evaluating healing rates with esomeprazole 40 mg vs omeprazole 20 mg od were included (Kahrilas et al 2000; Richter et al 2001). The authors concluded that esomeprazole was superior to omeprazole (relative risk, 1.18; 95% CI 1.14–1.23) (Klok et al 2003). Another meta-analysis comparing the efficacy of PPIs in the management of GERD and peptic ulcer disease (Vakil and Fennerty 2003) included three studies comparing esomeprazole 40 mg od with either omeprazole 20 mg od (Kahrilas et al 2000; Richter et al 2001) or lansoprazole 30 mg od (Castell et al 2002). The authors concluded that esomeprazole was superior to both the PPIs with which it was compared in healing of erosive esophagitis and in speed of symptom relief (Vakil and Fennerty 2003). In a meta-analysis of the efficacy of PPIs in acute treatment of reflux esophagitis (Edwards et al 2001), three studies comparing esomeprazole 40 mg with omeprazole 20 mg od were included. Two of these were taken into consideration in the current review as well (Kahrilas et al 2000; Richter et al 2001) but Edwards et al (2001) also used data on file from the manufacturer of esomeprazole. They concluded that esomeprazole demonstrated higher healing rates

than omeprazole at 4 weeks (relative risk 1.14; 95% CI 1.10–1.18) and 8 weeks (relative risk 1.08; 95% CI 1.05, 1.10) (Edwards et al 2001). Another meta-analysis by the same investigators comparing esomeprazole with other PPIs for the healing of erosive esophagitis (Edwards et al 2006) included all the randomized trials summarized in Table 2. The authors concluded that esomeprazole demonstrated higher healing rates compared with standard dose PPIs at 4 weeks (relative risk 0.92; 95% CI 0.90,0.94;  $p < 0.00001$ ) and at 8 weeks (relative risk 0.95; 95% CI 0.94,0.97;  $p < 0.00001$ ) (Edwards et al 2006). Lastly, a meta-analysis of randomized clinical trials comparing esomeprazole with other PPIs in healing erosive esophagitis (Gralnek et al 2006), included 7 out of the 8 randomized studies summarized in Table 2 (Kahrilas et al 2000; Richter et al 2001; Castell et al 2002; Howden et al 2002; Gillessen et al 2004; Fennerty et al 2005; Labenz et al 2005b) as well as data from the manufacturer of esomeprazole included in the product information (esomeprazole vs omeprazole 20 mg od) and a study published in abstract form (esomeprazole 40 mg vs omeprazole 40 mg od). The last two mentioned studies have not been published and could therefore potentially create a bias in this context. In comparing healing rates of erosive esophagitis at 4 and 8 weeks, the authors found a 10% (relative risk 1.10; 95% CI 1.05–1.15) and 5% (relative risk 1.05; 95% CI 1.02–1.08) relative increase in the probability of healing, respectively, with esomeprazole vs alternative PPIs. Also, the authors found that esomeprazole conferred an 8% (relative risk 1.08; 95% CI 1.05–1.11) relative increase in the probability of GERD symptom relief at 4 weeks (Gralnek et al 2006). In this meta-analysis, the calculated numbers needed to treat (NNT) by Los Angeles grade of erosive esophagitis (grades A–D) were 50, 33, 14, and 8 (Gralnek et al 2006). This suggests that the benefit of esomeprazole might be important in more severe erosive disease as indicated by the decreasing NNTs with increasing Los Angeles grade (Gralnek et al 2006). It is at the present time not entirely clear if these statistically significant differences are clinically significant.

## Maintenance therapy of healed erosive GERD

GERD usually relapses once drug therapy is discontinued, with about 80% having erosive GERD relapse after 6–12 months (DeVault and Castell 2005; Moayyedi and Talley 2006). Thus, many patients with GERD require long-term, possibly life-long, PPI therapy (Moayyedi and Talley 2006). However, a recent

study on discontinuation of PPIs in long-term users found that 20% of GERD patients were able to discontinue their PPIs without development of symptoms (Björnsson et al 2006).

Two double-blind, randomized studies have shown superiority of esomeprazole 40 mg, 20 mg, or 10 mg od to placebo in maintenance therapy of healed erosive GERD (Johnson et al 2001; Vakil et al 2001). The primary endpoint of both studies was endoscopically maintained healing 6 months after inclusion. In one of these, 375 patients with endoscopically healed esophagitis were randomized to receive esomeprazole 40 mg, 20 mg, 10 mg, or placebo od (Vakil et al 2001). After 6 months, significantly ( $p < 0.001$ ) more patients remained healed with esomeprazole 40 mg (87.9%), 20 mg (78.7%), or 10 mg (54.2%) than with placebo (29.1%) at endoscopy (Vakil et al 2001). In the other placebo-controlled study, 318 patients with endoscopically confirmed healing of erosive GERD were randomized to receive esomeprazole 40 mg, 20 mg, 10 mg, or placebo od (Johnson et al 2001). After 6 months, healing was maintained in 93.6% of patients treated with esomeprazole 40 mg, 93.2% treated with esomeprazole 20 mg, and 57.1% treated with esomeprazole 10 mg;  $p < 0.001$  vs 29.1% treated with placebo (Johnson et al 2001). Both of these studies reported that patients treated with esomeprazole had less severe heartburn than those treated with placebo. However, symptom maintenance data from these studies should be interpreted with caution as only those patients who maintained healing at the previous visit continued to the subsequent visits during the 6-month study period (Johnson et al 2001; Vakil et al 2001).

Three clinical trials have compared esomeprazole with other PPIs as a maintenance therapy in GERD patients with healed erosive esophagitis (Table 3). Studies reported in Table 3 had a similar double-blind, randomized design and they included intention-to-treat analyses of endoscopy and symptom maintenance rates. Also, all three studies included patients who had endoscopy-confirmed healing of their erosive GERD at baseline and follow-up endoscopy was performed at 3 and 6 months. The primary endpoint was endoscopic and symptom maintenance at 6 months. Secondary endpoints were separate endoscopic and symptom maintenance rates at 6 months (Lauritsen et al 2003; Labenz et al 2005a; Devault et al 2006). No comparative studies of esomeprazole vs omeprazole or rabeprazole in maintenance therapy of healed erosive GERD could be found.

All three studies showed superiority of esomeprazole 20 mg to lansoprazole 15 mg or pantoprazole 20 mg od in the primary endpoint (Table 3). Furthermore, these studies showed superiority of esomeprazole 20 mg to lansoprazole

**Table 3** Randomized trials evaluating the efficacy of esomeprazole vs other PPIs in combined endoscopic and symptomatic maintenance of healed erosive GERD

Reference	Study design	Number of patients	PPIs compared	Maintenance rates at 6 months
Lauritsen et al 2003	Double-blind, randomized	1224	Eso20 vs lan15 od	83 % vs 74%, $p < 0.0001$
Labenz et al 2005a	Double-blind, randomized	2766	Eso20 vs panto20 od	87% vs 74.9%, $p < 0.0001$
Devault et al 2006	Double-blind, randomized	1026	Eso20 vs lan15 od	84.5% vs 75.9%, $p < 0.0007$

**Notes:** No randomized studies comparing esomeprazole with rabeprazole or omeprazole as to healing erosive GERD were found.

**Abbreviations:** Eso, esomeprazole; lan, lansoprazole; panto, pantoprazole; PPI, proton-pump inhibitor.

15 mg (endoscopic maintenance rate: 84% vs 76%,  $p < 0.0002$  (Lauritsen et al 2003); 84.5% vs 75.9%,  $p < 0.0001$  (Devault et al 2006) or pantoprazole 20 mg (88.1% vs 76.6%,  $p < 0.0001$  (Labenz et al 2005a)) od in maintaining endoscopic remission at 6 months. As regards maintenance of symptomatic remission only, one of these studies reported that esomeprazole 20 mg was more effective than lansoprazole 15 mg od (symptomatic remission maintenance rate: 78% vs 71%,  $p < 0.001$  (Lauritsen et al 2003)) and another that esomeprazole 20 mg was more effective than pantoprazole 20 mg od (94.5% vs 90.5%,  $p < 0.0001$  (Labenz et al 2005a)). However, the third study could not show any statistically significant difference between esomeprazole and lansoprazole 15 mg od in maintaining symptomatic remission (76.4% vs 73%,  $p > 0.05$ ) (Devault et al 2006). Lastly, studies comparing esomeprazole with lansoprazole showed that esomeprazole had consistently higher remission maintenance rates when patients were stratified according to initial severity of erosive GERD (Lauritsen et al 2003; Devault et al 2006). However, the study comparing esomeprazole 20 mg with pantoprazole 20 mg od reported that although esomeprazole had higher remission maintenance rates in patients with erosive GERD Los Angeles A–C, differences were not significant in patients with Los Angeles D (Labenz et al 2005a).

Although these data indicate superiority of esomeprazole compared with lansoprazole or pantoprazole in maintenance therapy of healed erosive GERD, there is a need for new clinical trials comparing esomeprazole with omeprazole and rabeprazole before definite conclusions can be drawn.

## Non-erosive GERD

Patients with NERD may exhibit similar symptom severity to those with erosive GERD but as many as half of them may have a normal esophageal pH testing demonstrating pH values within the normal range of healthy subjects (Martinez et al 2003). Although PPIs have been shown to be effective in patients with NERD (Lind et al 1997), symptom

improvement is lower compared with patients with erosive GERD (Martinez et al 2003).

Three papers on clinical trials comparing continuous esomeprazole with other PPIs as therapy in NERD patients were identified. They all had a similar double-blind, randomized design, patients had a normal baseline endoscopy, intention-to-treat analysis of data was performed, and study duration was 4 weeks (Armstrong et al 2004; Fock et al 2005; Monnikes et al 2005). No study comparing continuous esomeprazole with lansoprazole therapy in NERD was identified.

In one of these papers (Armstrong et al 2004), three studies were reported comparing A ( $n = 1282$ ) esomeprazole 40 mg, esomeprazole 20 mg, or omeprazole 20 mg od; B ( $n = 693$ ) esomeprazole 40 mg or omeprazole 20 mg od; and C ( $n = 670$ ) esomeprazole 20 mg or omeprazole 20 mg od. Resolution of heartburn at 4 weeks (no heartburn symptoms during the last 7 days) was achieved in similar proportions of patients in each treatment arm in study A (esomeprazole 40 mg, 56.7%; esomeprazole 20 mg, 60.5%; omeprazole 20 mg, 58.1%), study B (esomeprazole 40 mg 70.3%; omeprazole 20 mg 67.9%), and study C (esomeprazole 20 mg 61.9%; omeprazole 20 mg, 59.6%). There were no significant differences between treatment groups within each study. Thus, not only were esomeprazole and omeprazole treatments comparable but also esomeprazole 40 mg and esomeprazole 20 mg od did not yield significantly different results after 4 weeks in patients with NERD (Armstrong et al 2004).

Another clinical trial performed in Asian patients ( $n = 127$ ) with NERD compared esomeprazole 20 mg with rabeprazole 10 mg od (Fock et al 2005). After 4 weeks of treatment the two PPIs were comparable for the primary endpoint of the study, ie, the time needed to achieve a 24-hour symptom-free interval for heartburn (esomeprazole 20 mg, 9 days; rabeprazole 10 mg, 8.5 days;  $p > 0.05$ ) and regurgitation (esomeprazole 20 mg, 7.5 days; rabeprazole 10 mg, 6 days;  $p > 0.05$ ). The authors reported that the two therapies

were also comparable in terms of patient's global evaluation, with 87.9% of patients on esomeprazole and 96% of patients on rabeprazole reporting that symptoms improved ( $p > 0.05$ ) (Fock et al 2005).

A third study comparing esomeprazole 20 mg with pantoprazole 20 mg od for the treatment of NERD patients ( $n = 529$ ) reported that the median time to first symptom relief was 2.0 days for both PPIs (Monnikes et al 2005). This study was designed to show non-inferiority of the pantoprazole group compared with the esomeprazole group with a significance level of 5%. The Hodges-Lehmann estimator and the one-sided 95% CI according to Moses were calculated. Non-inferiority was concluded if the lower boundary of the 95% CI was greater than  $-2$  days, as the difference of 2 days was considered clinically significant. For the primary endpoint variable (time to first symptom relief), the one-sided 95% CI was zero (0.00). Considering that the non-inferiority margin was set at  $-2$  days, the lower boundary of the 95% CI (0.00) was higher. Thus, the authors concluded that pantoprazole was as effective as esomeprazole for time to first symptom relief. Similar results were obtained for time to sustained symptom relief (Monnikes et al 2005).

Although no trial comparing continuous esomeprazole with lansoprazole therapy was identified, in a recently published single-blind study esomeprazole 20 mg on demand was compared with lansoprazole 15 mg od (Tsai et al 2004). Seven hundred and seventy-four patients with NERD who achieved complete resolution of heartburn after short term (2–4 weeks) treatment with esomeprazole 20 mg were randomized to receive either esomeprazole 20 mg on demand or lansoprazole 15 mg continuous daily treatment. Significantly more patients were willing to continue taking esomeprazole on demand than lansoprazole od after 6 months (93% vs 88%,  $p = 0.02$ ). The authors concluded that esomeprazole 20 mg on demand was more acceptable to NERD patients compared with lansoprazole 15 mg od (Tsai et al 2004). However, it should be pointed out that this was a single-blind trial (due to its nature) and that it may hardly constitute evidence of superiority of esomeprazole to lansoprazole in NERD, as the two PPIs were administered in different ways. Therefore, results of this study may merely reflect patient preference for on-demand therapy.

Long-term (6 month) on-demand esomeprazole treatment has been reported to be superior to placebo in the therapy of patients with NERD as assessed in two double-blind, randomized clinical trials in which NERD patients were included after achieving complete resolution of heartburn after short-term esomeprazole or omeprazole treatment (Talley

et al 2001, 2002). In one of these, 342 patients with NERD were randomized to receive either esomeprazole 20 mg or placebo on demand for 6 months (Talley et al 2001). The proportion of patients who discontinued treatment due to insufficient control of heartburn was significantly higher among placebo compared to esomeprazole recipients (51% vs 14%,  $p < 0.0001$ ). In the second study, 721 patients were randomized to esomeprazole 20 mg, 40 mg, or placebo on demand for 6 months (Talley et al 2002). During this period, 42% of placebo recipients discontinued treatment due to unwillingness to continue, compared with 8% and 11% of esomeprazole 20 mg and 40 mg recipients, respectively. Although a  $p < 0.0001$  was calculated for comparisons between either esomeprazole group and placebo, no significant difference was observed between the esomeprazole treatment groups ( $p = 0.15$ ). Thus the authors concluded that esomeprazole 20 mg is superior to placebo for on-demand treatment of NERD and that a higher esomeprazole dose does not confer additional clinical benefit. However, it should be pointed out that almost 60% (58%) of patients who were randomized to placebo were willing to continue treatment (Talley et al 2002). These results clearly indicate that not all patients who have had resolution of symptoms after 4 weeks of PPI therapy will need continuous treatment in the future.

## **Esomeprazole in the treatment of GERD and health-related quality of life**

There has been increasing interest in evaluating patient-reported outcomes such as health-related QoL. It is widely accepted that patients with GERD experience decrements in health-related QoL compared with the general population (Revicki et al 1998; Prasad et al 2003; Pace et al 2005), similar to those seen in patients with other chronic diseases (Kulig et al 2003). Patients with non-erosive GERD, erosive GERD, and Barrett's esophagus have been reported to have similar impairment in health-related QoL (Kulig et al 2003). Successful treatment of GERD with symptom resolution results in improvements in health-related QoL (Revicki et al 1998; Prasad et al 2003).

In a recent large uncontrolled study assessing the impact of GERD on QoL as well as the effect of acute esomeprazole treatment on QoL, indices were evaluated (Kulig et al 2003). A total of 6215 patients prospectively diagnosed with GERD underwent endoscopy and received treatment with esomeprazole 20 mg od (patients with NERD) or 40 mg od (erosive GERD). Symptoms and health-related QoL were evaluated at baseline and after 2 weeks of treatment by means of validated

questionnaires (Kulig et al 2003). At baseline, QoL in GERD patients was lower than in the general population but within 2 weeks, after treatment with esomeprazole, both symptoms and QoL improved in all subscales (Kulig et al 2003).

Recently a large randomized study evaluated the long-term effect of two maintenance treatment modalities with esomeprazole in non-erosive and mild erosive GERD (Pace et al 2005). Altogether, 6017 patients with GERD symptoms (max grade I esophagitis according to Savary-Miller's classification at baseline endoscopy) received acute treatment with esomeprazole 40 mg od for 4 weeks. If successfully treated, they were randomized to either esomeprazole 20 mg od or esomeprazole 20 mg on demand for 6 months. Health-related QoL was measured with validated questionnaires at baseline as well as at the start and conclusion of the maintenance period. At baseline, GERD patients had profound reductions in QoL indices but after acute esomeprazole treatment for 4 weeks all QoL dimensions showed statistically significant ( $p < 0.0001$ ) improvements. A statistically significant difference in QoL scores was registered at the end of the maintenance phase in favor of the continuous regimen (Pace et al 2005).

Lastly, a study from Norway assessed the efficacy of three treatment regimens in improving health-related QoL in patients with GERD symptoms (Hansen et al 2006). Following a 4-week symptom-control phase (esomeprazole 40 mg od), patients were randomized to 6 months' esomeprazole 20 mg od continuously ( $n = 658$ ), esomeprazole 20 mg od on-demand ( $n = 634$ ), or ranitidine 150 mg bd continuously ( $n = 610$ ). Health-related QoL was assessed by means of validated questionnaires at baseline as well as at the start and conclusion of the maintenance period. Esomeprazole 40 mg od improved QoL during the acute symptom-control phase. At 6 months, both esomeprazole regimens were more effective than ranitidine in all dimensions of QoL ( $p < 0.0001$ ). However, esomeprazole 20 mg od continuously maintained QoL better than esomeprazole on demand and was associated with greater patient satisfaction (Hansen et al 2006).

Thus, there are data to support that esomeprazole treatment is associated with improvement in health-related QoL indices in patients with GERD, at least compared with ranitidine. However, double-blind, randomized studies comparing the effect of esomeprazole with that of other PPIs on QoL indices at GERD treatment are lacking.

## Conclusion

In patients with gastroesophageal reflux disease, standard doses of esomeprazole maintain intragastric pH above 4

for significantly longer periods compared with standard doses of other PPIs after 5 days of treatment. Despite some controversy, data from clinical trials and meta-analyses indicate that esomeprazole 40 mg od for up to 8 weeks provides higher rates of healing of erosive GERD and a greater proportion of patients with sustained resolution of heartburn, than omeprazole 20 mg, lansoprazole 30 mg, or pantoprazole 40 mg od. Esomeprazole 20 mg od has also been shown to be more effective in maintaining healing of erosive GERD compared to lansoprazole 15 mg od or pantoprazole 20 mg od. However, it is not clear whether these statistically significant differences are of major clinical importance. Comparative efficacy studies are also lacking between esomeprazole and rabeprazole in healing and maintenance of healed erosive GERD as well as between esomeprazole and omeprazole or rabeprazole in maintenance of healed erosive GERD. Esomeprazole 20 mg od is superior to placebo for treatment of NERD but clinical trials have not shown any significant differences in efficacy between esomeprazole 20 mg and omeprazole 20 mg or pantoprazole 20 mg od in this group of patients. No comparative data between esomeprazole and lansoprazole or rabeprazole in NERD could be identified. Lastly, although esomeprazole treatment in GERD has been reported to result in improvement of health-related QoL indices, no clinical trials have evaluated the possible differential effects of different PPIs on QoL in patients treated for GERD.

## Abbreviations

GERD, Gastro-esophageal reflux disease; NERD, non-erosive reflux disease; PPIs, proton pump inhibitors; QoL, quality of life; CI, confidence interval.

## References

- Armstrong D, Talley NJ, Lauritsen K, et al. 2004. The role of acid suppression in patients with endoscopy-negative reflux disease: the effect of treatment with esomeprazole or omeprazole. *Aliment Pharmacol Ther*, 20:413–21.
- Bell NJ, Burget D, Howden, et al. 1992. Appropriate acid suppression for the management of gastro-oesophageal reflux disease. *Digestion*, 51(Suppl 1):59–67.
- Bjornsson E, Abrahamsson H, Simren M, et al. 2006. Discontinuation of proton pump inhibitors in patients on long-term therapy: a double-blind, placebo-controlled trial. *Aliment Pharmacol Ther*, 24:945–54.
- Castell DO, Kahrilas PJ, Richter JE, et al. 2002. Esomeprazole 40 mg, compared with lansoprazole 30 mg, in the treatment of erosive esophagitis. *Am J Gastroenterol*, 97:575–83.
- Delaney B, McColl K. 2005. Review article: Helicobacter pylori and gastro-oesophageal reflux disease. *Aliment Pharmacol Ther*, 22(Suppl 1):32–40.
- Dent J, El-Serag HB, Wallander MA, et al. 2005. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut*, 54:710–17.

- DeVault KR, Castell DO. 2005. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Am J Gastroenterol*, 100:190–200.
- Devault KR, Johanson JF, Johnson DA, et al. 2006. Maintenance of healed erosive esophagitis: a randomized six-month comparison of esomeprazole twenty milligrams with lansoprazole fifteen milligrams. *Clin Gastroenterol Hepatol*, 4:852–9.
- Edwards SJ, Lind T, Lundell L. 2001. Systematic review of proton pump inhibitors for the acute treatment of reflux oesophagitis. *Aliment Pharmacol Ther*, 15:1729–36.
- Edwards SJ, Lind T, Lundell L. 2006. Systematic review: proton pump inhibitors PPIs. for the healing of reflux oesophagitis – a comparison of esomeprazole with other PPIs. *Aliment Pharmacol Ther*, 24:743–50.
- Fennerty MB, Johanson JF, Hwang C, et al. 2005. Efficacy of esomeprazole 40 mg vs lansoprazole 30 mg for healing moderate to severe erosive oesophagitis. *Aliment Pharmacol Ther*, 21:455–63.
- Fock KM, Teo EK, Ang TL, et al. 2005. Rabeprazole vs esomeprazole in non-erosive gastro-oesophageal reflux disease: a randomized, double-blind study in urban Asia. *World J Gastroenterol*, 11:3091–8.
- Frazzoni M, De Micheli E, Savarino V. 2003. Different patterns of oesophageal acid exposure distinguish complicated reflux disease from either erosive reflux oesophagitis or non-erosive reflux disease. *Aliment Pharmacol Ther*, 18:1091–8.
- Frazzoni M, Manno M, De Micheli E, et al. 2006. Intra-oesophageal acid suppression in complicated gastro-oesophageal reflux disease: esomeprazole versus lansoprazole. *Dig Liver Dis*, 38:85–90.
- Gillesen A, Beil W, Modlin IM, et al. 2004. 40 mg pantoprazole and 40 mg esomeprazole are equivalent in the healing of esophageal lesions and relief from gastroesophageal reflux disease-related symptoms. *J Clin Gastroenterol*, 38:332–40.
- Gralnek IM, Dulai GS, Fennerty MB, et al. 2006. Esomeprazole Versus Other Proton Pump Inhibitors in Erosive Esophagitis: A Meta-Analysis of Randomized Clinical Trials. *Clin Gastroenterol Hepatol*, 4:1452–8.
- Hansen AN, Bergheim R, Fagertun H, et al. 2006. Long-term management of patients with symptoms of gastro-oesophageal reflux disease – a Norwegian randomised prospective study comparing the effects of esomeprazole and ranitidine treatment strategies on health-related quality of life in a general practitioners setting. *Int J Clin Pract*, 60:15–22.
- Hatlebakk JG. 2003. Review article: gastric acidity – comparison of esomeprazole with other proton pump inhibitors. *Aliment Pharmacol Ther*, 17(Suppl 1):10–15; discussion 16–17.
- Hellstrom PM, Vitols S. 2004. The choice of proton pump inhibitor: does it matter? *Basic Clin Pharmacol Toxicol*, 94:106–11.
- Holtmann G, Cain C, Malferteiner P. 1999. Gastric Helicobacter pylori infection accelerates healing of reflux esophagitis during treatment with the proton pump inhibitor pantoprazole. *Gastroenterology*, 117:11–16.
- Howden CW, Ballard ED II, Robieson W. 2002. Evidence for therapeutic equivalence of lansoprazole 30 mg and esomeprazole in the treatment of erosive esophagitis. *Clin Drug Investig*, 22:99–109.
- Hunt RH. 1999. Importance of pH control in the management of GERD. *Arch Intern Med*, 159, 649–57.
- Johansson KE, Ask P, Boeryd B, et al. 1986. Oesophagitis, signs of reflux, and gastric acid secretion in patients with symptoms of gastro-oesophageal reflux disease. *Scand J Gastroenterol*, 21:837–47.
- Johnson DA, Benjamin SB, Vakil NB, et al. 2001. Esomeprazole once daily for 6 months is effective therapy for maintaining healed erosive esophagitis and for controlling gastroesophageal reflux disease symptoms: a randomized, double-blind, placebo-controlled study of efficacy and safety. *Am J Gastroenterol*, 96:27–34.
- Johnson DA, Stacy T, Ryan M, et al. 2005. A comparison of esomeprazole and lansoprazole for control of intragastric pH in patients with symptoms of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther*, 22:129–34.
- Johnsson F, Joelsson B, Gudmundsson K, et al. 1987. Symptoms and endoscopic findings in the diagnosis of gastroesophageal reflux disease. *Scand J Gastroenterol*, 22:714–18.
- Kahrilas PJ, Falk GW, Johnson DA, et al. 2000. Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: a randomized controlled trial. The Esomeprazole Study Investigators. *Aliment Pharmacol Ther*, 14:1249–58.
- Katz PO, Castell DO, Chen Y, et al. 2004. Intra-gastric acid suppression and pharmacokinetics of twice-daily esomeprazole: a randomized, three-way crossover study. *Aliment Pharmacol Ther*, 20:399–406.
- Kendall MJ. 2003. Review article: Esomeprazole – the first proton pump inhibitor to be developed as an isomer. *Aliment Pharmacol Ther*, 17(Suppl 1):1–4.
- Klok RM, Postma MJ, van Hout BA, et al. 2003. Meta-analysis: comparing the efficacy of proton pump inhibitors in short-term use. *Aliment Pharmacol Ther*, 17:1237–45.
- Kuipers EJ, Nelis GF, Klinkenberg-Knol EC, et al. 2004. Cure of Helicobacter pylori infection in patients with reflux oesophagitis treated with long term omeprazole reverses gastritis without exacerbation of reflux disease: results of a randomised controlled trial. *Gut*, 53:12–20.
- Kulig M, Leodolter A, Vieth M, et al. 2003. Quality of life in relation to symptoms in patients with gastro-oesophageal reflux disease – an analysis based on the ProGERD initiative. *Aliment Pharmacol Ther*, 18:767–76.
- Labenz J, Armstrong D, Lauritsen K, et al. 2005a. Esomeprazole 20 mg vs pantoprazole 20 mg for maintenance therapy of healed erosive oesophagitis: results from the EXPO study. *Aliment Pharmacol Ther*, 22:803–11.
- Labenz J, Armstrong D, Lauritsen K, et al. 2005b. A randomized comparative study of esomeprazole 40 mg versus pantoprazole 40 mg for healing erosive oesophagitis: the EXPO study. *Aliment Pharmacol Ther*, 21:739–46.
- Labenz J, Tillenburg B, Peitz U, et al. 1996. Helicobacter pylori augments the pH-increasing effect of omeprazole in patients with duodenal ulcer. *Gastroenterology*, 110:725–32.
- Lauritsen K, Deviere J, Bigard MA, et al. 2003. Esomeprazole 20 mg and lansoprazole 15 mg in maintaining healed reflux oesophagitis: Metropole study results. *Aliment Pharmacol Ther*, 17:333–41.
- Lind T, Havelund T, Carlsson R, et al. 1997. Heartburn without oesophagitis: efficacy of omeprazole therapy and features determining therapeutic response. *Scand J Gastroenterol*, 32:974–9.
- Lind T, Rydberg L, Kyleback A, et al. 2000. Esomeprazole provides improved acid control vs omeprazole in patients with symptoms of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther*, 14:861–7.
- Martinez SD, Malagon IB, Garewal HS, et al. 2003. Non-erosive reflux disease NERD – acid reflux and symptom patterns. *Aliment Pharmacol Ther*, 17:537–45.
- Miehle S, Madisch A, Kirsch C, et al. 2005. Intra-gastric acidity during treatment with esomeprazole 40 mg twice daily or pantoprazole 40 mg twice daily – a randomized, two-way crossover study. *Aliment Pharmacol Ther*, 21:963–7.
- Miner P Jr, Katz PO, Chen Y, et al. 2003. Gastric acid control with esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole: a five-way crossover study. *Am J Gastroenterol*, 98:2616–20.
- Moayyedi P, Talley NJ. 2006. Gastro-oesophageal reflux disease. *Lancet*, 367:2086–100.
- Monnikes H, Pfaffenberger B, Gatz G, et al. 2005. Novel measurement of rapid treatment success with ReQuest: first and sustained symptom relief as outcome parameters in patients with endoscopy-negative GERD receiving 20 mg pantoprazole or 20 mg esomeprazole. *Digestion*, 71:152–8.
- Pace F, Negrini C, Wiklund I, et al. 2005. Quality of life in acute and maintenance treatment of non-erosive and mild erosive gastro-oesophageal reflux disease. *Aliment Pharmacol Ther*, 22:349–56.
- Prasad M, Rentz AM, Revicki DA. 2003. The impact of treatment for gastro-oesophageal reflux disease on health-related quality of life: a literature review. *Pharmacoeconomics*, 21:769–90.

- Revicki DA, Wood M, Maton PN, et al. 1998. The impact of gastro-oesophageal reflux disease on health-related quality of life. *Am J Med*, 104:252–8.
- Richter JE, Kahrilas PJ, Johanson J, et al. 2001. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. *Am J Gastroenterol*, 96:656–65.
- Rohss K, Hasselgren G, Hedenstrom H. 2002. Effect of esomeprazole 40 mg vs omeprazole 40 mg on 24-hour intragastric pH in patients with symptoms of gastroesophageal reflux disease. *Dig Dis Sci*, 47:954–8.
- Rohss K, Lind T, Wilder-Smith C. 2004. Esomeprazole 40 mg provides more effective intragastric acid control than lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg in patients with gastro-oesophageal reflux symptoms. *Eur J Clin Pharmacol*, 60:531–9.
- Schmitt C, Lightdale CJ, Hwang C, et al. 2006. A multicenter, randomized, double-blind, 8-week comparative trial of standard doses of esomeprazole 40 mg and omeprazole 20 mg for the treatment of erosive esophagitis. *Dig Dis Sci*, 51:844–50.
- Scholten T, Gatz G, Hole U. 2003. Once-daily pantoprazole 40 mg and esomeprazole 40 mg have equivalent overall efficacy in relieving GERD-related symptoms. *Aliment Pharmacol Ther*, 18:587–94.
- Simon B, Muller P, Pascu O, et al. 2003. Intra-oesophageal pH profiles and pharmacokinetics of pantoprazole and esomeprazole: a crossover study in patients with gastro-oesophageal reflux disease. *Eur J Gastroenterol Hepatol*, 15:791–9.
- Talley NJ, Lauritsen K, Tunturi-Hihnala H, et al. 2001. Esomeprazole 20 mg maintains symptom control in endoscopy-negative gastro-oesophageal reflux disease: a controlled trial of on-demand therapy for 6 months. *Aliment Pharmacol Ther*, 15:347–54.
- Talley NJ, Venables TL, Green JR, et al. 2002. Esomeprazole 40 mg and 20 mg is efficacious in the long-term management of patients with endoscopy-negative gastro-oesophageal reflux disease: a placebo-controlled trial of on-demand therapy for 6 months. *Eur J Gastroenterol Hepatol*, 14:857–63.
- Tsai HH, Chapman R, Shepherd A, et al. 2004. Esomeprazole 20 mg on-demand is more acceptable to patients than continuous lansoprazole 15 mg in the long-term maintenance of endoscopy-negative gastro-oesophageal reflux patients: the COMMAND Study. *Aliment Pharmacol Ther*, 20:657–65.
- Vakil N, Fennerty MB. 2003. Direct comparative trials of the efficacy of proton pump inhibitors in the management of gastro-oesophageal reflux disease and peptic ulcer disease. *Aliment Pharmacol Ther*, 18:559–68.
- Vakil NB, Shaker R, Johnson DA, et al. 2001. The new proton pump inhibitor esomeprazole is effective as a maintenance therapy in GERD patients with healed erosive oesophagitis: a 6-month, randomized, double-blind, placebo-controlled study of efficacy and safety. *Aliment Pharmacol Ther*, 15:927–35.
- Vakil N, van Zanten SV, Kahrilas P, et al. 2006. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol*, 101:1900–20; quiz 1943.
- Verdu EF, Armstrong D, Fraser R, et al. 1995. Effect of *Helicobacter pylori* status on intragastric pH during treatment with omeprazole. *Gut*, 36:539–43.
- Wilder-Smith CH, Rohss K, Nilsson-Pieschl C, et al. 2003. Esomeprazole 40 mg provides improved intragastric acid control as compared with lansoprazole 30 mg and rabeprazole 20 mg in healthy volunteers. *Digestion*, 68:184–8.
- Wu JC, Chan FK, Ching JY, et al. 2004. Effect of *Helicobacter pylori* eradication on treatment of gastro-oesophageal reflux disease: a double blind, placebo controlled, randomised trial. *Gut*, 53:174–9.

