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**UK Medicines Information Pharmacists Group**

**NEW MEDICINES ON THE MARKET**

**Evaluated information for the NHS**

**ESOMEPRAZOLE**

**Summary**

- Esomeprazole is the S-isomer of omeprazole. The range of licensed indications for esomeprazole is more limited than that for omeprazole and excludes prevention and treatment of NSAID-associated gastric and duodenal ulceration, healing of gastric/duodenal ulcers other than duodenal ulcers associated with *H. pylori*, and Zollinger-Ellison syndrome.
- European patent protection for omeprazole expires in 2002 when cheaper, generic versions are likely to be made available. At current prices, esomeprazole at a dose of 40mg daily and omeprazole at a dose of 20 mg daily are cost equivalent for 28 days' treatment.
- Evaluation of esomeprazole studies is complicated both by the fact that, currently, many are published in abstract form only, and by the issue of the doses chosen in the comparative studies.
- Unlike omeprazole and other PPIs on the market, esomeprazole is licensed for 'on-demand' symptomatic control of gastro-oesophageal reflux disease (GORD) in patients without oesophagitis. Only placebo-controlled studies support the use of esomeprazole in this way. 'On-demand' use of esomeprazole will necessitate determining the patients for whom such use of a PPI is appropriate, i.e. those without oesophagitis. Although cost benefits may be derived from the use of esomeprazole on an 'on-demand' basis in patients with mild GORD, NICE guidance recommends other treatments first in such patients.
- At a dose of 40mg daily, esomeprazole has been found to be statistically significantly more effective than omeprazole 20mg daily at healing erosive oesophagitis in patients with GORD. There are no published studies comparing esomeprazole with PPIs other than omeprazole in this indication, but healing and maintenance rates are broadly similar to other PPIs.

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## ESOMEPRAZOLE

<b>APPROVED NAME:</b>	Esomeprazole
<b>BRAND NAME (MANUFACTURER):</b>	Nexium
<b>SYNONYMS</b>	H 19918, perprazole, S-omeprazole magnesium
<b>PRESENTATION:</b>	Gastro-resistant tablets containing either 20mg or 40mg of esomeprazole.
<b>BNF THERAPEUTIC CLASS</b>	Proton pump inhibitor (BNF 1.3.5)
<b>LICENSED INDICATIONS</b>	In patients with Gastro-oesophageal Reflux Disease (GORD): treatment of erosive reflux oesophagitis, long-term management of patients with healed oesophagitis to prevent relapse and symptomatic treatment [1]. Healing of <i>Helicobacter pylori</i> -associated duodenal ulcer and prevention of relapse of peptic ulcers in patients with <i>H. pylori</i> -associated ulcers (with appropriate antibacterial regimen) [1].
<b>DOSAGE AND ADMINISTRATION</b>	GORD: Treatment of erosive reflux oesophagitis: 40 mg od for 4 weeks or 8 weeks. Prevention of relapse in patients with healed oesophagitis: 20 mg od. Symptomatic treatment: 20 mg once daily (patients without oesophagitis). Once symptoms resolved: 20 mg once daily on demand [1]. <i>H. pylori</i> -associated ulcers: 20 mg esomeprazole with 1g amoxicillin and 500 mg clarithromycin, all twice daily for 7 days [1].
<b>THERAPEUTIC COMMENT</b>	Esomeprazole is the fifth proton pump inhibitor (PPI) on the UK market, but the first to be licensed for the symptomatic treatment of GORD, without oesophagitis, on an 'on-demand' basis. On-demand use could offer cost benefits, but consideration should be given to drug interactions in patients taking esomeprazole in this way as they will not have become stabilised on the drug. Esomeprazole is the only single isomer PPI and appears to possess more pronounced and sustained acid suppressing effects than omeprazole [2,3,4], which loses its European patent protection in 2002 [5]. Unlike lansoprazole and omeprazole, esomeprazole is not licensed for the treatment and prevention of NSAID-associated ulcers.
<b>SECTOR OF USE</b>	Hospital [Y] Primary Care [Y]
<b>COST AND COURSE DETAILS</b>	28 days' treatment: £18.50 (20 mg), £28.56 (40 mg)*
<b>TREATMENT ALTERNATIVES</b>	

Drug	Dose	Cost (£, 28 days) *
Lansoprazole	30 mg/day	23.75
Omeprazole	20 mg/day	28.56
Pantoprazole	40 mg/day	23.65
Rabeprazole	20 mg/day	22.75

\* Prices from MIMS February 2001

# ESOMEPRAZOLE

## INTRODUCTION

Patients experiencing acid-related gastrointestinal disorders invariably initially present with dyspepsia.

It is estimated that 40% of the adult population experience dyspepsia each year. GORD is believed to be the cause in 15-20% of these cases and gastric and duodenal ulcers in a further 15-25% [6]. Only 10% of patients who consult their GP because of dyspepsia are referred for endoscopy. For GORD to be diagnosed, it should be shown that oesophagitis or acid reflux are present and heartburn symptoms must be predominant [7].

NICE guidelines support the use of a healing dose of PPI in patients with severe GORD symptoms or a proven pathology, e.g. oesophageal ulceration. Once symptoms are controlled, it is recommended that these patients receive a lower, maintenance dose of PPI. The least expensive appropriate PPI should be used, within licensed indications [6].

## PHARMACOLOGY

Esomeprazole is a weak base, which is converted to its active form in the acidic environment of the gastric parietal cell. Like other PPIs, esomeprazole inhibits basal and stimulated acid secretion by binding to the H<sup>+</sup>/K<sup>+</sup>-ATPase enzyme in the parietal cell [1].

Esomeprazole 40 mg and 20 mg once daily maintained intragastric pH levels at above 4 for significantly longer than omeprazole 20 mg once daily (p<0.001 and p<0.01, respectively) in 36 patients with GORD symptoms [4].

Similarly designed studies found that esomeprazole 40 mg daily provided more sustained acid suppression than pantoprazole 40 mg daily (p<0.001) [8] and omeprazole 40 mg daily (p<0.001) [9] in patients with symptoms of GORD.

In healthy volunteers, acid control with esomeprazole 40 mg daily was superior to that with lansoprazole 30 mg daily (p<0.001) [10] and rabeprazole 20 mg daily (p=0.005) [11].

## PHARMACOKINETICS

**Absorption and metabolism:** Peak plasma concentrations of esomeprazole are reached 1-2 hours after oral administration and the plasma elimination half-life is 1.3 hours after repeated once daily dosing. Following 5 days' dosing with esomeprazole 20 mg daily, the area under the plasma concentration-time curve (AUC) is 80% higher than with omeprazole 20 mg [4]. Food delays and decreases absorption of esomeprazole, but does not appear to significantly alter the drug's effect on intragastric acidity [1].

Esomeprazole is metabolised by the cytochrome P450 system; the enzyme CYP2C19 is mainly responsible for its metabolism, but CYP3A4 is also involved [1].

**Elderly patients:** Metabolism was not significantly altered in 13 elderly patients (71 to 80 years) [12].

**Renal impairment:** No relevant studies have been conducted, but less than 1% of the parent drug is found in urine [1].

**Hepatic impairment:** The AUC increased by 76% and the t<sub>1/2</sub> by 29% in 12 patients with mild to severe hepatic dysfunction [13]. However, when patients were grouped according to the degree of liver function, AUC and t<sub>1/2</sub> values for patients with mild and moderate liver function were in the same range as those for GORD patients with no liver impairment. Dosage adjustment is not required in patients with mild/moderate liver impairment. However, a maximum dose of 20 mg esomeprazole should not be exceeded in patients with severe liver impairment [1].

## EFFICACY

Eight published studies covering the licensed indications of esomeprazole are discussed below (please also see Table 1). Currently, all but one of these studies are published in abstract form only, a factor that limited assessment as complete outcome details and the statistical analyses carried out are not given in all cases. Please note that unlicensed esomeprazole doses are used in some of the studies.

### Treatment of erosive reflux oesophagitis in patients with GORD

Two large, randomised, double-blind studies found that endoscopic appearance was normal in a statistically significantly greater proportion of patients receiving esomeprazole 40 mg daily than those receiving omeprazole 20 mg daily at week 4 and by week 8 [14, 15]. The percentage of patients experiencing heartburn resolution, as assessed by investigators at week 4 was also statistically significantly higher for patients receiving esomeprazole 40 mg daily than for those receiving omeprazole (68.3% vs 58.1%,  $p < 0.001$  [15]). Esomeprazole 20 mg daily did not differ significantly from omeprazole 20mg in terms of healing or investigator-assessed heartburn resolution at week four [14].

### Maintenance therapy in patients with GORD and healed oesophagitis

Two randomised, double-blind, six-month studies found esomeprazole 10, 20 and 40 mg daily to be statistically significantly more effective than placebo at maintaining healing in patients with endoscopically proven healed erosive oesophagitis ( $p < 0.001$ ). The percentage of patients maintaining healing at six months was markedly higher in the esomeprazole 20 and 40 mg groups [16, 17]. A statistically significant difference between each of the esomeprazole groups and the placebo group was also found at one month for the proportion of patients who had experienced seven consecutive

days without heartburn (investigator assessment,  $p < 0.001$ ). [16,17]

### Symptomatic treatment of GORD

In two double-blind, six month studies, 'endoscopically negative' patients in whom heartburn had completely resolved after four weeks of treatment with esomeprazole or omeprazole were randomised to receive esomeprazole or placebo on demand [18,19]. The time to study discontinuation because of inadequate heartburn control or for any reason was statistically significantly longer for both esomeprazole groups (20 and 40 mg daily) in the first study than for the placebo group ( $p < 0.0001$ ). Antacid usage was over two-fold greater in the esomeprazole groups, but the percentage of placebo patients who did not discontinue treatment because of inadequate heartburn control was at least 49% in both studies. In the first study, patients took a mean of 0.33 and 0.29 doses/day in the esomeprazole 20 mg and 40 mg groups, respectively.

### Healing of *H. pylori*-associated duodenal ulcer and prevention of relapse of peptic ulcer

A randomised, double-blind study found that neither healing nor *H. pylori* eradication rates differed significantly between patients receiving triple therapy with esomeprazole or omeprazole [20]. *H. pylori* eradication was determined by [<sup>13</sup>C]-urea breath test and histology at  $\geq$  four weeks after the end of therapy.

A further randomised, double-blind study comparing the effects of seven-day triple therapy with esomeprazole or omeprazole was conducted in 448 *H. pylori*-positive patients with inactive duodenal ulcer disease [21]. Eradication of *H. pylori* infection was confirmed by negative [<sup>13</sup>C]-urea breath tests at weeks four and eight. No statistically significant difference in eradication rate was noted between the groups.

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## PROMOTIONAL DATA

Esomeprazole promotional material focuses on use of the drug on an on-demand basis, its value for money, its sustained acid suppressing efficacy and there being no need for follow-up monotherapy in the healing of *H. pylori*-associated duodenal ulcer with esomeprazole.

The 'on-demand' use of esomeprazole is supported by placebo-controlled studies. There may be some cost advantages associated with the use of the drug in this way. It should be stressed, however, that on-demand therapy is only licensed in patients without oesophagitis. As with other PPIs, for patients with oesophagitis, the licensed doses are daily. There have been no studies comparing on-demand esomeprazole in GORD without oesophagitis to other PPIs or to other, less intensive treatments (antacids, histamine H<sub>2</sub>-antagonists, etc).

Randomised, cross-over studies indicate that esomeprazole 40 mg daily suppresses acidity for longer periods than omeprazole 20 or 40 mg daily [4], pantoprazole 40 mg daily [8] and lansoprazole 30 mg daily [10] and rabeprazole [11], although only one of these studies has been published in full.

Any healing advantages over existing PPIs that the sustained acid suppressing effect of esomeprazole 40 mg daily offers in erosive oesophagitis could be outweighed by the cost of the healing dose and it may be advisable to await further evidence of this advantage.

In one study, duodenal ulcer healing was achieved after seven days' triple therapy with esomeprazole, however the apparent lack of need for further PPI monotherapy in these circumstances may not be specific to esomeprazole [20]. Omeprazole and esomeprazole appear to be equally effective at eradicating *H. pylori* in patients with inactive duodenal ulceration [21].

## ADVERSE EFFECTS

The summary of product characteristics for esomeprazole lists the following adverse effects, stating that in clinical trials, none were found to be dose-related [1].

Common (>1/100, <1/10): Headache, abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation.

Uncommon (>1/1000, <1/100): Dermatitis, pruritus, urticaria, dizziness, dry mouth.

Adverse effects seen with omeprazole are also listed and may occur. Sinusitis and respiratory infection have been reported [16,17]. A twelve-month safety study in GORD patients with healed oesophagitis concluded that the adverse effect profile for esomeprazole was similar to that previously reported for other PPIs [22].

## CONTRAINDICATIONS AND PRECAUTIONS

- Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the product.
- Breast feeding.

## PRECAUTIONS AND INTERACTIONS

[1]

- Pregnancy.
- Exclude malignancy if patients present with any alarm symptom and when gastric ulcer is suspected/present.
- Keep patients on long-term treatment under surveillance.
- On-demand treatment: Instruct patients to contact doctor if symptoms change and consider drug interactions.

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- Triple therapy: Also consider drug interactions for other drugs in the therapy, e.g. clarithromycin.
- Drugs for which gastric acidity affects absorption, e.g. ketoconazole, itraconazole.
- Drugs metabolised by CYP2C19 enzyme, e.g. diazepam, citalopram, imipramine, clomipramine, phenytoin. Monitor phenytoin plasma concentrations during esomeprazole introduction or withdrawal.
- Rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency.

## References

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**Table 1**

Ref No.	Study Design	Study Population	Study Length	Treatment Regimen	Outcome (ITT analysis)	
<b>Erosive Reflux Oesophagitis and GORD</b>						
14	RA, DB, PG, C, MC	GORD, 1960 pts Endoscopically confirmed erosive oesophagitis†	8 weeks	20 mg E od (n = 656) 40 mg E od (n = 654) 20 mg O od (n = 650)	<b>Percentage of patients healed (Cumulative life table estimates)</b> <b>4 weeks      8 weeks</b>	
					70.5	89.9*
					75.9*	94.1*
					64.7	86.9 (*p≤0.05 vs 20 mg O od)
15 (abs)	RA, DB, PG, C, MC	GORD, 2425 pts Endoscopically confirmed erosive oesophagitis †	8 weeks	40 mg E od (n = 1216) 20 mg O od (n = 1209)	81.7*	93.7*
					68.7	84.2 (*p<0.001 vs 20 mg O od)
<b>Maintenance Therapy</b>						
16 (abs)	RA, DB, PG, PC, MC	GORD, 375 pts (Healed erosive oesophagitis)	6 months	10 mg E od (n = 91) 20 mg E od (n = 98) 40 mg E od (n = 92) placebo od (n = 94)	<b>Complete healing maintained at 6 months (%)</b> *p<0.001 vs placebo	
					54.2*	<b>% pts with sustained heartburn resolution (investigator assessment at 1 month)</b>
					78.7*	50.6* *p<0.001 vs placebo
					87.9*	63.7*
					29.1	71.3*
						15.5
17 (abs)	RA, DB, PG, PC, MC	GORD, 318 pts (Healed oesophagitis)	6 months	10 mg E od (n = 77) 20 mg E od (n = 82) 40 mg E od (n = 82) placebo od (n = 77)	57.1*	51.4*
					93.2*	61.3*
					93.6*	78.7*
					29.0	17.8
					*p<0.001 vs placebo	*p<0.001 vs placebo

# ESOMEPRAZOLE

**Table 1 Continued**

Ref No.	Study Design	Study Population	Study Length	Treatment Regimen	Outcome (ITT analysis)
<b>Symptomatic Treatment of GORD</b>					
18 (abs)	RA, DB, PG, PC, MC	GORD, 721 pts (Endoscopically negative)	6 months	20 mg E (n = 282) 40 mg E (n = 293) placebo (n = 146) All on-demand (max 1 dose od)	During the 6 month period, the percentage of pts discontinuing because of inadequate heartburn control was 5, 9 and 36 in the E20 mg, E40mg and placebo groups, respectively (p<0.0001, E20/40 mg vs placebo)
19 (abs)	RA, DB, PG, PC, MC	GORD, 342 pts (Endoscopically negative)	6 months	20 mg E (n=170) placebo (n=172) On demand (max 1 dose od)	During the 6 month period, the percentage of pts discontinuing treatment because of inadequate heartburn control was 14 in the E20mg group and 51 in the placebo group (p<0.0001, E vs placebo)
<b>Ulcer Healing/Prevention of relapse</b>					
20 (abs)	RA, DB, PG, C, MC	Duodenal ulcer (≥ 0.5cm diameter) and <i>H. pylori</i> -positive, 446 pts	4 weeks (1 week triple therapy plus 3 weeks monotherapy/placebo)	20 mg E bd + A and Cl, followed by 3 weeks placebo (n = 222) 20 mg O bd + A and Cl, followed by 3 weeks O 20 mg (n = 224)	Ulcer healing and <i>H. pylori</i> eradication occurred in 91% (95% CI 87-95%) and 86% (95% CI 81-90%) of pts in the E group and 92% (95% CI 88-95%) and 88% (95% CI 83-92%) of those receiving O.
21 (abs)	RA, DB, PG, C, MC	<i>H. pylori</i> -positive. History of duodenal ulcer, 448 pts	7 days triple therapy	20 mg E bd + A and Cl (n = 224)  20 mg O bd + A and Cl (n = 224)	<i>H. pylori</i> eradication rates (% pts) were 89.7% (95% CI 84.7-93.5%) and 87.8% (95% CI 82.3-92.0%) in the E and O groups, respectively.

**Key:** RA = randomised      PC = placebo controlled      † = (LA classification grades A-D)      E = esomeprazole      A = amoxicillin 1000 mg bd  
 DB = double blind      C = comparative      O = omeprazole      Cl = clarithromycin 500 mg bd  
 PG = parallel group      MC = multicentre