

Inside ▶

[Holding the mirror up to esomeprazole](#)

[Test-and-treat gaining acceptance in dyspepsia](#)

[Case study for GPs](#)

Proton pump inhibitors: too much of a good thing?

Drugs for acid-related disorders contribute more to the cost^a of the PBS than almost any other group of drugs.¹ The cost of prescribing of this group, which consists predominantly of the proton pump inhibitors (PPIs), is rising: in 2003, it was \$534 million, an increase of 14% over the previous year. Do current levels of prescribing reflect judicious use of this class?

Step-down for gastro-oesophageal reflux disease

The 'step-down' approach is now recommended by most guidelines for people with gastro-oesophageal reflux disease (GORD).²⁻⁴ This strategy of using an initial 4–8 week course of standard-dose PPI rapidly controls symptoms and heals oesophagitis. Treatment can then be 'stepped down' to the minimum dose that maintains symptom control.

A potential problem with the step-down approach is that if the success of the initial treatment course and the need for ongoing PPI therapy are not reviewed, patients may continue to take unnecessarily high doses of PPIs.

People known to have severe or complicated oesophagitis should continue with daily PPIs. For others, options for step-down include the following.

— Low-dose maintenance therapy with PPIs

Most studies have found that a low-dose PPI prevents relapse in 70–80% of people with healed oesophagitis over 12 months.⁵⁻⁹ However, lower strength PPIs make up less than 10% of total PPI prescribing.¹⁰

— Intermittent, symptom-driven use of PPIs

Most people with endoscopy-negative GORD can satisfactorily control symptoms using this strategy¹¹⁻¹³; on average, people take tablets every 2–3 days.¹²⁻¹⁴

— Step-off PPIs

The Gastroenterological Society of Australia suggests ceasing PPIs after initial therapy except for people known to have severe oesophagitis.² Most people will relapse and require re-treatment, but some can manage their symptoms with lifestyle modifications and antacids and/or histamine-2 receptor (H₂) antagonists.

Applying the evidence for step-down strategies to practice is complicated by the fact that studies have evaluated them in people who have undergone endoscopy, whereas in clinical practice the presence of erosive oesophagitis is often unknown. Furthermore, the relative efficacy of the different strategies has not been evaluated. In practice, individual patients vary widely in their need for long-term therapy; a practical approach is to adjust therapy according to symptom control.

A 'step-up' approach is suitable for people with mild-to-moderate symptoms: initiate with lifestyle measures (such as raising the head of the bed, avoiding exacerbating foods, losing weight and stopping smoking) and antacids. If this is unsuccessful, give an H₂ antagonist, then a PPI if necessary.

Are your patients getting more than they need?

A 4–8-week course of a standard-dose PPI usually controls GORD symptoms; step-down can then be considered. However, electronically-generated prescriptions often default to the maximum number of repeats, so a patient may initially receive a script for 6-months' supply. The number of repeats can be manually changed to provide patients with the appropriate quantity for the initial course of treatment; the need for a repeat prescription is then a trigger for them to return for review.

^a Total cost over 12 months ending December 2003. Lipid-modifying medicines contribute most to the cost of the PBS.

Holding the mirror up to esomeprazole

In 2003, esomeprazole had the largest growth^b of any drug on the PBS.¹ Interestingly, the same molecule has long been available as half of the active ingredient of omeprazole.

Esomeprazole and omeprazole have the same pharmacological activity

Esomeprazole is the *s*-enantiomer of omeprazole (see *Single enantiomer drugs*, page 4). In contrast to some other isomer drugs, esomeprazole and *r*-omeprazole have the same pharmacological activity.¹⁵

The major difference between the enantiomers is in their pharmacokinetics: after equivalent doses, esomeprazole reaches higher plasma concentrations.¹⁶

The standard daily dose of esomeprazole is 40 mg, which is four times the amount of esomeprazole found in a standard daily dose of omeprazole (Table 1).

Clinical efficacy comparisons with other PPIs

Studies so far have compared esomeprazole 40 mg or 20 mg with standard or lower doses of other PPIs. However, esomeprazole 40 mg is considerably more expensive than standard doses of other PPIs (Table 2).¹⁷

There have been no clinical efficacy studies comparing esomeprazole 40 mg and omeprazole 40 mg.

Healing rates in erosive oesophagitis

In published studies in erosive oesophagitis, esomeprazole 40 mg produced small improvements in healing rates and symptom resolution over standard doses of omeprazole or lansoprazole (Figure 1).^{18–20} An unpublished study found no difference in healing rates between esomeprazole 40 mg and omeprazole 20 mg.²¹

Relapse prevention in erosive oesophagitis

Esomeprazole 20 mg offers little advantage over less expensive low-dose lansoprazole in preventing relapse in healed erosive oesophagitis; 11 people would need to be treated for 6 months with esomeprazole 20 mg instead of lansoprazole 15 mg to prevent one additional relapse.⁷

Symptom control in endoscopy-negative GORD

More than 50% of people with GORD have no evidence of erosive oesophagitis.² In this group, esomeprazole at a dose of either 40 mg or 20 mg is no more effective at controlling symptoms than omeprazole 20 mg.²¹

^b Highest volume change over 12 months ending December 2003.

Table 1: Comparison of standard daily doses* of esomeprazole and omeprazole

	Dose of <i>s</i> -omeprazole	Dose of <i>r</i> -omeprazole
Esomeprazole 40 mg	40 mg	0 mg
Omeprazole 20 mg	10 mg	10 mg

* Approved doses for initiation of treatment of erosive oesophagitis.

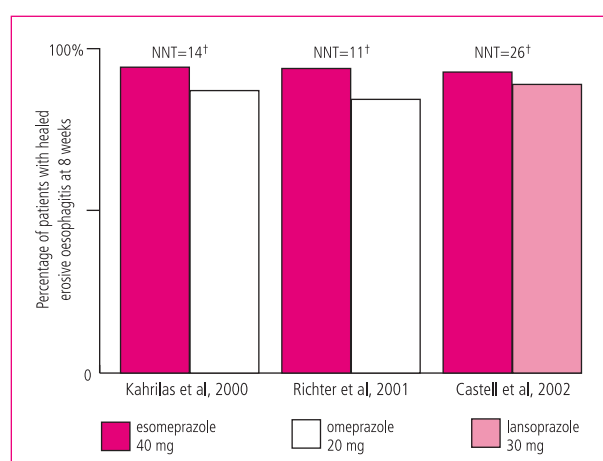
Table 2: Price[†] of one month's supply of esomeprazole and omeprazole at doses approved for initial therapy and maintenance therapy in erosive oesophagitis¹⁷

	Esomeprazole	Omeprazole
Initial therapy	\$75.26 (40 mg)	\$46.19 (20 mg)
Maintenance therapy	\$46.19 (20 mg)	\$29.55–\$46.19 [‡] (10–20 mg)

[†] PBS dispensed price. Based on 30 days of continuous therapy.

[‡] A brand price premium of \$1.50 applies to Losec 20 mg tablets.

Figure 1: Healing rate and number-needed-to-treat (NNT)^{*} with esomeprazole 40 mg compared to standard doses of omeprazole or lansoprazole in erosive oesophagitis



* NNT refers to the number of people with erosive oesophagitis who need to be treated for 8 weeks with esomeprazole 40 mg instead of omeprazole 20 mg or lansoprazole 30 mg to achieve one additional treatment success.

[†] $p < 0.05$ versus comparator PPI.

Does esomeprazole offer users any significant benefit over existing PPIs?

Differences in clinical efficacy between esomeprazole and other PPIs have not been demonstrated at equivalent doses.

Advantages for esomeprazole 40 mg over other PPIs have been small and have only been seen in people with erosive oesophagitis. This indicates that few people will benefit from using esomeprazole instead of other PPIs.

There is no evidence that esomeprazole is more effective than other PPIs for people with GORD who do not have erosive oesophagitis.

Test-and-treat gaining acceptance in dyspepsia

Most people with GORD can be identified by the presence of heartburn or acid regurgitation as their predominant symptom. However, for people with other causes of dyspepsia^c, symptoms do not reliably predict diagnosis. Empirical therapy is used as a more cost-effective method of guiding dyspepsia management than endoscopy, but the choice of empirical therapy is a matter of debate. Previously, a trial with a PPI or H₂ antagonist has been recommended. Evidence for the test-and-treat approach has emerged more recently.

In the test-and-treat approach, people who present with dyspepsia (excluding those with suspected GORD, NSAID users and people with indications for immediate endoscopy, see Figure 2) are given a non-invasive test^d for *Helicobacter pylori*: those who test positive receive eradication treatment while uninfected people receive a trial of a standard-dose PPI or H₂ antagonist. People whose symptoms persist can then be referred for specialist management.

The test-and-treat approach appears to be as effective as early endoscopy for determining management of dyspepsia²² and may improve symptoms and reduce rates of referral for endoscopy more than empiric PPI therapy.²³

This approach means that people with underlying peptic ulcer disease receive appropriate therapy without the need for endoscopy. However, people without peptic ulcer disease, in whom the benefits are less certain,

will also receive eradication therapy. Possible advantages of this include²⁴:

- achieving symptom resolution in a small proportion of people with non-ulcer dyspepsia²⁵
- removing a risk factor for future peptic ulcer disease and gastric cancer
- preventing gastric mucosal changes that may predispose to cancer in long-term PPI users infected with *H. pylori*. (Some guidelines suggest that eradication therapy be considered for long-term PPI users^{2,26}, although evidence for a benefit is currently lacking.)

Potential disadvantages include the development of resistance with wider use of eradication therapy and the occurrence of complications such as antibiotic-induced pseudomembranous colitis. It has also been suggested that eradication therapy exacerbates or causes reflux symptoms but it is generally accepted that this is unlikely.^{2,26}

To date, evidence for the test-and-treat strategy comes from secondary-care settings and little cost-effectiveness information is available; studies are underway to address these issues.²² Despite these limitations, several guidelines now recommend the test-and-treat approach.^{24,26-28}

Evidence for *H. pylori* eradication in gastro-intestinal disease

Indication	Evidence of benefit of <i>H. pylori</i> eradication?
Peptic ulcer disease (PUD)	Yes. Eradication therapy in infected people with PUD facilitates ulcer healing and prevents recurrence. ²⁹
GORD	No. There is no evidence that <i>H. pylori</i> eradication improves GORD symptoms. ³⁰
Uninvestigated dyspepsia	Possibly. In people in whom immediate endoscopy is not indicated, the test-and-treat approach improves dyspepsia symptoms and reduces the rate of referral for endoscopy more than empiric acid suppression. ^{22,23}
Non-ulcer dyspepsia	Yes, but only in a minority of patients. To resolve one person's symptoms, 15 people with dyspepsia who are infected with <i>H. pylori</i> must be treated. ^{30,31}
Asymptomatic patients	No. Routine testing and eradication are not indicated; however, some patients may request it. Guidelines recommend that the decision to test and eradicate be made on a case-by-case basis after discussing the risks and benefits. ²

Figure 2: Indications for immediate endoscopy for suspected upper gastro-intestinal cancers in new patients with dyspepsia^{2,24,32}

- Alarm symptoms
 - difficulty or pain on swallowing
 - recurrent vomiting
 - unexplained weight loss
 - upper abdominal mass
 - evidence of GI bleeding
- Age > 45 years[§]

§ Some guidelines give 55 years as the lower threshold for endoscopy.^{24,32} The need for endoscopy in people with dyspepsia aged 45–55 years is a matter of debate.

^c Dyspepsia refers to pain or discomfort centred in the upper abdomen. Symptoms can include bloating, early satiety, heartburn, acid regurgitation, excessive belching, nausea and vomiting. Causes of dyspepsia include GORD, peptic ulcer and, rarely, gastric or oesophageal cancer. Many people with dyspepsia have no obvious cause for their symptoms on investigation and are said to have 'non-ulcer dyspepsia' or 'functional dyspepsia'.

^d Non-invasive *H. pylori* tests available in primary care include the urea breath test (UBT), faecal antigen test (FAT) and serology.

Single enantiomer drugs

Many drugs can exist as pairs of enantiomers. Like your left and right hand, enantiomers are mirror images of identical structures and are referred to as r- (right) and s- (left) enantiomers. Hence, **e**someprazole is the **s**-enantiomer of omeprazole.

Most drugs are racemates, that is, mixtures of both enantiomers in equal amounts. However, there is a growing trend towards marketing single enantiomers of existing drugs; a recent example is escitalopram, the s-isomer of citalopram (see *NPS RADAR* at www.npsradar.org.au for more information). Enantiomers may have differing pharmacokinetic or pharmacodynamic properties, so isolating one may theoretically improve on the efficacy or safety of the racemate.

Single enantiomer drugs developed from existing drugs are attractive to the pharmaceutical industry because development costs are less and they can be used to extend the life of a drug once its patent has expired.^{33,34}

As with any new drug, the decision to use a single-enantiomer drug should be based on careful consideration of its efficacy, safety, cost and convenience in comparison to existing therapy (see *NPS News 31: New (and old) ways of looking at new drugs*).

What's what

H ₂ antagonists	
cimetidine	Cimehexal, Magicul, Tagamet
famotidine	Amfamox, Ausfam, Famohexal, Pamacid, Pepcid, Pepcidine, Pepzan
nizatidine	Tazac
ranitidine	Ausran, Rani 2, Ranihexal, Ranitic, Ranoxyl, Zantac, Zantac Relief
Proton pump inhibitors	
esomeprazole	Nexium
lansoprazole	Zoton
omeprazole	Acimax, Losec, Probor
pantoprazole	Somac
rabeprazole	Pariet

Reviewers

Dr James Best, General Practitioner
A/Prof Nick Buckley, Clinical Pharmacologist, The Canberra Hospital
Ms Jan Donovan, Consumer
Dr John Dowden, Australian Prescriber
Ms Simone Rossi, Australian Medicines Handbook
Prof John Murtagh, Dept of General Practice, Monash University, Melbourne
Ms Susan Parker, Australian Self-Medication Industry

Any correspondence regarding content should be directed to the NPS. Declarations of interest have been sought from all reviewers.

References:

1. Australian Government Department of Health and Ageing. Pharmaceutical Pricing Section, Pharmaceutical Benefits Branch. Expenditure and prescriptions: twelve months to 31 December 2003.
2. Gastroenterological Society of Australia. Gastro-oesophageal reflux disease in adults: guidelines for clinicians. 3rd ed, 2001. (www.gesa.org.au/members_guidelines/goreflux/01.htm, accessed 19 February 2004.)
3. Australian Medicines Handbook 2004.
4. Therapeutic Guidelines: Gastrointestinal. Version 3, 2002.
5. Birbara C et al. Eur J Gastroenterol Hepatol 2000;12:889-97.
6. Plein K et al. Eur J Gastroenterol Hepatol 2000;12:425-32.
7. Lauritsen K et al. Aliment Pharmacol Ther 2003;17:333-41.
8. Thjodleifsson B et al. Dig Dis Sci 2000;45:845-53.
9. Robinson M et al. Ann Intern Med 1996;124:859-67.
10. Health Insurance Commission PBS Item Statistics. (www.hic.gov.au/providers/health_statistics/statistical_reporting/pbs.htm, accessed 19 February 2004.)
11. Lind T et al. Aliment Pharmacol Ther 1999;13:907-14.
12. Talley N et al. Eur J Gastroenterol Hepatol 2002;14:857-63.
13. Talley N et al. Aliment Pharmacol Ther 2001;15:347-54.
14. Johnsson F et al. Scand J Gastroenterol 2002;37:642-7.
15. Lindberg P et al. Aliment Pharmacol Ther 2003;17:481-8.
16. Andersson T et al. Aliment Pharmacol Ther 2001;15:1563-9.
17. Schedule of Pharmaceutical Benefits, 1 February 2004.
18. Castell DO et al. Am J Gastroenterol 2002;97:575-83.
19. Richter JE et al. Am J Gastroenterol 2001;96:656-65.
20. Kahrilas PJ et al. Aliment Pharmacol Ther 2000;14:1249-58.
21. United States Food and Drug Administration Centre for Drug Evaluation and Research. Approval package for Nexium (esomeprazole magnesium) Delayed-Release Capsules, AstraZeneca LP. Application No.: 21-153 and 21-154. Approval date: 20 February 2001. (www.fda.gov/cder/approval/index.htm, accessed 19 February 2004.)
22. Delaney BC et al. Initial management strategies for dyspepsia (Cochrane Review). In: The Cochrane Library, Issue 1, 2004. Chichester, UK: John Wiley and Sons Ltd.
23. Manes G et al. BMJ 2003;326:1118.
24. Scottish Collegiate Guidelines Network. Guideline 68. Dyspepsia: a national clinical guideline, March 2003. (www.sign.ac.uk/pdf/sign68.pdf, accessed 19 February 2004.)
25. Moayyedi P et al. Pharmacological interventions for non-ulcer dyspepsia (Cochrane Review). In: The Cochrane Library, Issue 1, 2004. Chichester, UK: John Wiley and Sons Ltd.
26. Malfertheiner P et al. Aliment Pharmacol Ther 2002;16:167-80.
27. PRODIGY Guidance – Dyspepsia – symptoms. Last revised April 2002. (www.prodigy.nhs.uk/guidance.asp?gt=Dyspepsia%20-%20symptoms, accessed 19 February 2004.)
28. American Gastroenterological Society. Gastroenterology 1998; 114:579-81.
29. Ford A et al. Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients (Cochrane Review). In: The Cochrane Library, Issue 1, 2004. Chichester, UK: John Wiley and Sons Ltd.
30. Clin Evid, Issue 10, 2003.
31. Malfertheiner P et al. Aliment Pharmacol Ther 2003;18:615-25.
32. National Institute for Clinical Excellence. Guidance on the use of proton pump inhibitors in the treatment of dyspepsia. June 2000. (www.nice.org.uk/article.asp?a=3587, accessed 19 February 2004.)
33. Therapeutics Initiative. Do single stereoisomer drugs provide value? June–September 2002. (www.ti.ubc.ca/pages/letter45.htm, accessed 19 February 2004.)
34. Somogyi A et al. Aust Prescr 2004;27:47-9.

The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence.

Any treatment decisions based on this information should be made in the context of the individual clinical circumstances of each patient.



National Prescribing Service Limited

Our goal To improve health outcomes for Australians through prescribing that is: ▲ safe ▲ effective ▲ cost-effective
Our programs To enable prescribers to make the best prescribing decisions for their patients, the NPS provides:
▲ information ▲ education ▲ support ▲ resources

Level 7 / 418A Elizabeth Street Surry Hills NSW 2010

Phone: 02 8217 8700 | Fax: 02 9211 7578 | email: info@nps.org.au | net: <http://www.nps.org.au>