

29 April 2004



000001

Dr Sam Sample
99 Sample Street
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Dear Dr Sample

Proton pump inhibitors (PPIs) are very effective and well tolerated drugs for common symptoms and this is reflected in the high usage of this class. PPI prescribing increased rapidly following the removal of the PBS authority restriction in 2001, and continues to rise. The growing cost of use—over the 12 months to June 2003, we spent \$320 million on PPIs, 20% more than the preceding year¹—highlights the need for us to consider whether our increasing prescribing of these drugs translates into greater benefits for patients.

In this *Prescribing Practice Review (PPR)*, we look at the evidence for the benefits of PPIs in the initial and ongoing management of gastro-oesophageal reflux disease (GORD) and dyspepsia. The focus is on tailoring maintenance therapy to clinical needs, selecting a PPI and judicious use of *Helicobacter pylori* eradication therapy.

Establish the need for ongoing PPI therapy in each patient

Once the goals of initial therapy are achieved (for example, symptom resolution or *H. pylori* eradication and ulcer healing), many people can either cease or reduce their use of PPIs.

Decrease PPI use to low doses or intermittent, symptom-driven therapy once GORD symptoms are controlled

Symptom control can often be maintained with less intensive therapy.

All PPIs are very effective in controlling GORD symptoms and are clinically equivalent in most patients

Differences in efficacy between the PPIs are small and of debatable clinical significance.

Consider testing for and treating *H. pylori* in people with uninvestigated dyspepsia or who are using PPIs long term

Several guidelines now suggest *H. pylori* eradication for these groups, although further evidence is needed to confirm benefits.

For more information, see *NPS News 33*. You may also like to participate in the clinical audit, *Review of proton pump inhibitor prescribing*; see inside for enrolment details.

Yours sincerely,

Dr Stephen Phillips
Chair, NPS Board

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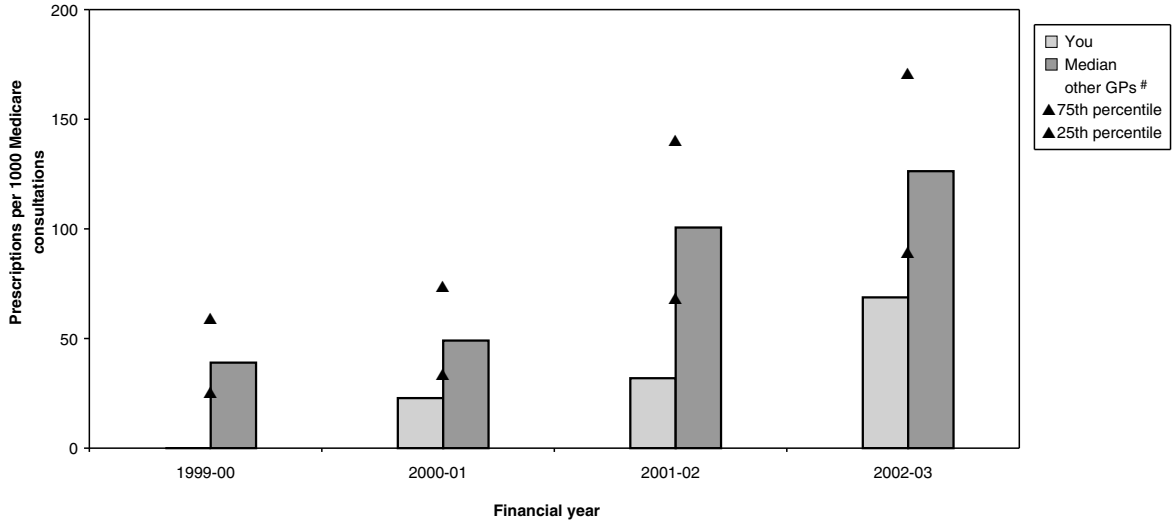
1. Source: Health Insurance Commission dispensing data.

**No. 25
Proton pump
inhibitors: too
much of a good
thing?**

Your confidential prescribing data

These data have been extracted from the Health Insurance Commission PBS claims database and are provided confidentially for your own personal review. All proton pump inhibitors (PPIs) are over the patient co-payment, therefore the data shown includes all prescriptions dispensed on the PBS for your patients.

Proton pump inhibitors 1999-00 to 2002-03



Number and cost of proton pump inhibitors 2000-01 to 2002-03

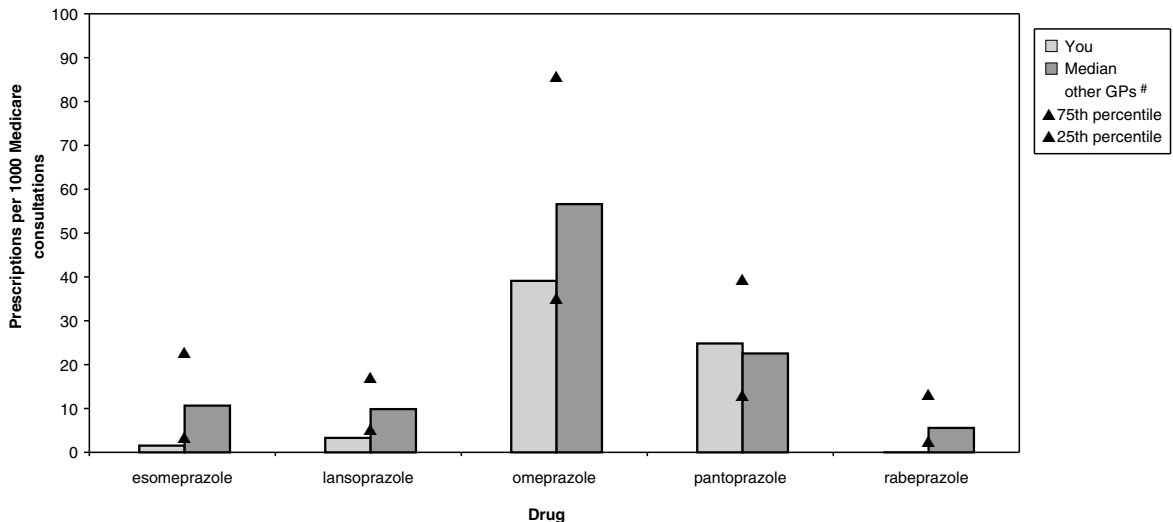
PPIs account for 9% of the total cost of all medicines prescribed by GPs on the PBS. The majority of PPI prescriptions are written by GPs; other medical specialists prescribe only 6% of PPIs.

Year	You			All GPs nationally		
	Percentage of your PBS cost	Cost	Number of prescriptions	Percentage of PBS cost	Cost	Number of prescriptions
2000-01	5%	\$4 518	73	6%	\$223 019 030	3 346 143
2001-02	5%	\$9 347	180	8%	\$329 542 997	6 380 158
2002-03	9%	\$15 244	313	9%	\$399 038 646	7 687 676

Practice Point

- Is it reasonable that 9% of our national PBS budget is spent on PPIs? Could these resources be used elsewhere more valuably to improve health?

Proton pump inhibitor selection 2002-03



Practice Point

- All PPIs are very effective in controlling GORD symptoms and are clinically equivalent in most patients.

Proton pump inhibitor prescriptions by strength 2002-03

		You		Median other GPs [#]	
		Percentage of PPI prescriptions	Number of PPI prescriptions	Percentage of PPI prescriptions	Number of PPI prescriptions
Higher strength products	esomeprazole 40mg	98%	306	89%	554
	lansoprazole 30mg				
	omeprazole 20mg				
	pantoprazole 40mg				
	rabeprazole 20mg				
Lower strength products	esomeprazole 20mg	2%	7	11%	65
	lansoprazole 15mg				
	omeprazole 10mg				
	pantoprazole 20mg				
	rabeprazole 10mg				

Practice Points

- Lower dose PPIs or intermittent symptom driven therapy control GORD symptoms effectively for many patients. (See table 1 in the accompanying PPR for dosing regimes)
- Could you use a lower dose in any of your patients?

Long term therapy

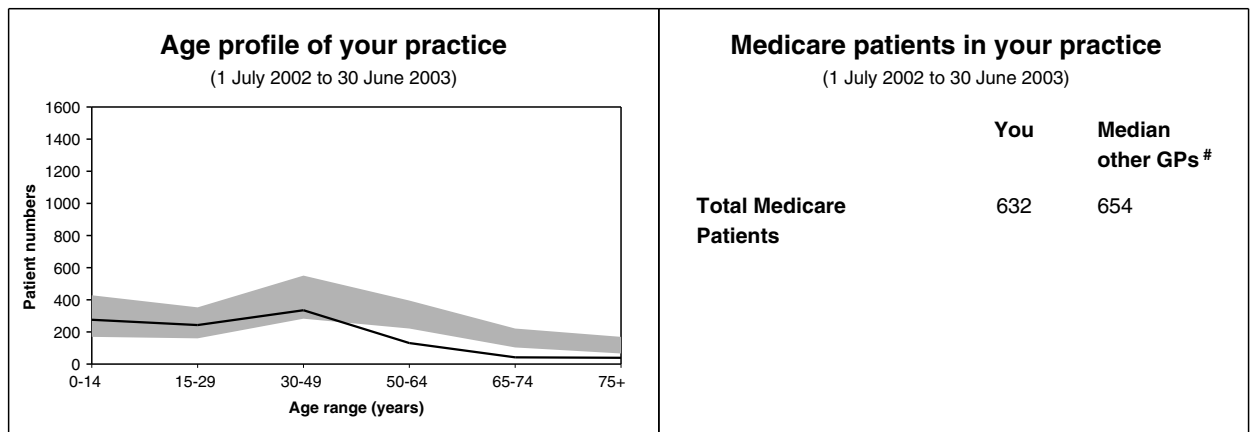
	You	Median other GPs [#]
Percentage of patients prescribed a PPI who have had more than 6 PPI prescriptions dispensed in 2002-03.	42%	52%
Total number of patients dispensed a PPI in 2002-03.	53	112

Practice Points

- How regularly do you review PPI prescriptions?
- Consider testing for and treating *H. pylori* in long-term PPI users.

Practice profile

The data below, based on Medicare claims, are provided to help you review your prescribing data within the profile of your practice.



The black line represents the age profile of patients in your practice. 25% to 75% of other GPs[#] fall within the shaded area.

Notes:

@ Data shown are an aggregate for all your provider locations.

The comparator group "other GPs" includes all prescribers who are currently located in a similar geographical region ie capital city, other metropolitan area, large rural centre, other rural area, remote centre and other remote area.

▲ 25% to 75% of all doctors in the comparator group fall in the range shown by the triangular symbols.

Proton pump inhibitors: too much of a good thing?

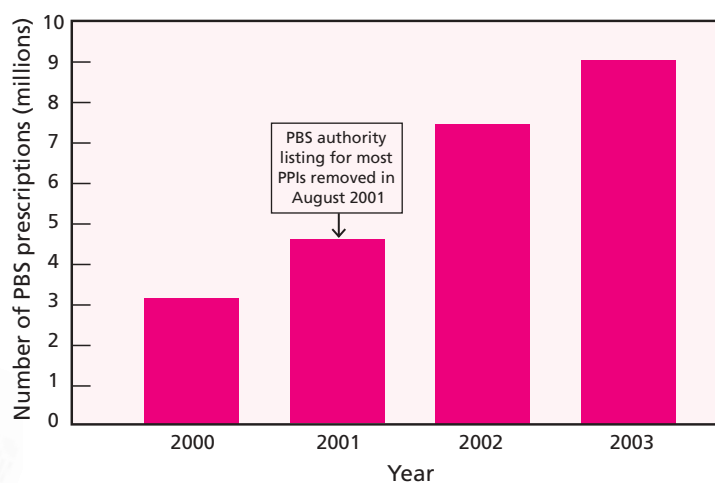
Key messages

- Establish whether ongoing proton pump inhibitor (PPI) therapy is necessary in each patient.
- Decrease PPI use to low doses or intermittent, symptom-driven therapy once symptoms of gastro-oesophageal reflux disease (GORD) are controlled.
- All PPIs are very effective in controlling GORD symptoms and are clinically equivalent in most patients.
- Consider testing for and treating *Helicobacter pylori* (*H. pylori*) in people with uninvestigated dyspepsia or who are using PPIs long term.

PPI prescribing is growing

PPIs are effective, well tolerated drugs for relieving symptoms that can be debilitating and concerning for patients. A marked increase in PPI prescribing followed the removal of the PBS authority listing in 2001 and the number of PPI prescriptions written continues to grow (Figure 1).¹ Is the growth in PPI prescribing justified by improved outcomes for patients?

Figure 1: Prescribing of PPIs*



*Source: HIC PBS item reports.¹ Number of prescriptions refers to the volume of services processed by HIC. Year refers to year that service was processed by HIC, not the date of prescribing or the date of supply.



Before starting a PPI...

Is investigation needed?	<p>Anyone with alarm symptoms (such as difficulty or pain on swallowing, unexplained weight loss, evidence of GI bleeding, recurrent vomiting or upper abdominal mass) should be referred for investigation.²</p> <p>There is currently debate over the appropriate age threshold for early endoscopy in people with dyspepsia, with investigation variously advised for people aged over 45 or 55 years.^{3,4} The Gastroenterological Society of Australia (GESA) suggests that people with mild, typical reflux symptoms and no alarm symptoms be given a trial of therapy without investigation.²</p>
Are drugs causing or exacerbating symptoms?	<p>Where appropriate, stop, replace or adjust drug regimens that may be causing symptoms, such as nonsteroidal anti-inflammatory drugs (NSAIDs), calcium channel blockers, bisphosphonates, nitrates and theophylline.³</p>
Suggest lifestyle changes	<p>Before seeking treatment, people will often have identified foods or activities that exacerbate their symptoms. Reinforce that continuing to avoid these while taking a PPI will help to prevent breakthrough symptoms.</p> <p>Losing weight, stopping smoking, healthy eating and moderating alcohol intake can also be suggested; although evidence for these measures in improving symptoms is lacking, all have general health benefits and may be effective in individual patients.</p>
Establish a treatment plan	<p>Initiate treatment with a PPI based on an explicit goal, such as control of reflux symptoms or ulcer healing.</p>

Review the need for ongoing therapy in every patient

Plan to review the success of initial treatment with a view to reducing or ceasing PPIs as appropriate	<p>The fact that approximately twice as many prescriptions are written for continuation than for initiation of PPIs⁵ underlines the importance of establishing the need for ongoing therapy.</p> <p>In any patient presenting for a repeat prescription, consider whether ongoing treatment with a PPI is warranted. If a PPI has been initiated during hospitalisation, review the need for it after discharge.</p>
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Managing GORD

Use a step-down approach	<p>The step-down approach has gained popularity because it rapidly achieves the goals of initial therapy and minimises the need for repeat consultations.² For long-term management, reduce or cease use of PPIs where possible; ongoing daily standard-dose PPIs are often unnecessary.</p>
Initiate with a PPI to² <ul style="list-style-type: none">● aid diagnosis● control symptoms● reassure patients● heal oesophagitis	<p>Diagnosis of GORD is usually based on the presence of heartburn or acid regurgitation as the predominant symptom. Patient understanding of the term 'heartburn' is variable; asking about 'a burning feeling rising up from the stomach or lower chest towards the neck' may identify GORD more accurately.²</p> <p>A clear response to PPI therapy supplements a symptom-based diagnosis and can help to reassure patients that their symptoms are not the result of serious underlying disease. Endoscopy has a limited role in routine diagnosis of GORD but is indicated if the diagnosis is unclear, symptoms are suggestive of severe or complicated oesophagitis, or alarm symptoms are present.²</p>

Initiate with a trial of a PPI at a standard dose for 4 weeks. Those with insufficient response should receive a further 4 weeks' treatment.⁶ If this fails to control symptoms, doubling the PPI dose may be effective; consider seeking specialist advice.²

Following PPI therapy, the absence of symptoms is related to healing of oesophagitis; endoscopy to confirm healing is usually unnecessary in uncomplicated GORD.³

Decrease PPI use once GORD symptoms are controlled

The goals of long-term treatment for GORD are to maintain symptom control and prevent complications, while minimising costs.² After a successful initial course of treatment, try reducing PPI use while monitoring symptoms. Needs for ongoing maintenance therapy vary widely; aim for the lowest dose that maintains symptom control.

Options for step-down

Low-dose PPIs

Taken daily, a low-dose PPI maintains endoscopic remission and symptom control in a substantial proportion of people with uncomplicated healed oesophagitis.⁷⁻¹¹ Currently, less than 10% of all PPI prescriptions are for lower strengths.¹

Intermittent, symptom-driven use

Patients are advised to take a PPI on days when symptoms occur. Although intermittent use allows symptoms to recur, the vast majority of patients in clinical trials have been willing to continue with this strategy after 6 months.¹²⁻¹⁴

Ceasing PPIs

Manage symptoms with lifestyle changes, antacids and histamine-2 receptor (H₂) antagonists if needed. Some patients with milder disease will not relapse when PPI treatment is withdrawn. GESA endorses a trial of treatment withdrawal to identify these patients; those who relapse can be treated with a repeat course of the initially successful therapy, then treatment stepped down to the lowest dose that maintains symptom control.²

Exceptions to step-down

People known to have severe oesophagitis will relapse unless they continue to take PPIs daily.^{2,6} Those with complications such as strictures, scleroderma or Barrett's oesophagus also require daily PPIs at standard or higher doses.⁶

Consider step-up for mild GORD symptoms

In people with mild or intermittent symptoms, consider a step-up approach: initiate with lifestyle measures and antacids, then switch to an H₂ antagonist, then a PPI, if further symptom control is required.

Managing patient expectations

Explain the treatment plan

Patients can be reluctant to reduce their PPI dose when they have experienced profound symptom relief with drug therapy. Explaining that PPI treatment is directed at controlling symptoms, rather than curing the condition, may increase acceptance of suggested changes to treatment.

Patients' concerns about the safety of long-term use of medicines may lead them to take PPIs intermittently¹⁵; reinforce that on-demand use of PPIs is appropriate for many patients.

Choosing a PPI

All PPIs are very effective and clinically equivalent in most patients

PPIs are superior to H₂ antagonists for healing oesophagitis¹⁶ and resolving symptoms in short-term empirical treatment.¹⁷

Studies have found no significant differences in clinical efficacy in oesophagitis between most PPIs.¹⁶ Some efficacy differences have been reported for esomeprazole, and there has been large uptake of this drug since its PBS-listing in August 2002.¹ Does esomeprazole provide a clinically significant benefit over other PPIs for people with GORD?

Esomeprazole is the s-enantiomer of omeprazole

Omeprazole is a racemate; that is, a mixture of equal amounts of two enantiomers, r- and s-omeprazole. Enantiomers are isomers that are mirror images of one another. Esomeprazole and r-omeprazole have the same inhibitory effect at the proton pump¹⁸, but are metabolised differently: after equal milligram doses, esomeprazole reaches much higher plasma concentrations than omeprazole.¹⁹

Clinical studies have used higher doses of esomeprazole than of comparator PPIs...

Omeprazole 20 mg has been compared to esomeprazole 20 mg or 40 mg. Thus, inequivalent doses of esomeprazole and other PPIs have been used to assess comparative clinical efficacy.

...but have found that esomeprazole provides a limited additional benefit

Although higher doses of esomeprazole have been used, studies indicate that few additional people will benefit from using it instead of another PPI.²⁰⁻²³

The clinical advantage of esomeprazole over other PPIs is limited to a relatively small benefit in people with (either active or healed) erosive oesophagitis, who make up less than half of all patients with reflux symptoms.² In comparative clinical trials in erosive oesophagitis, esomeprazole 40 mg, omeprazole 20 mg and lansoprazole 30 mg have all produced 8-week healing rates of over 80%; differences between treatment groups have ranged from 4–10%.^{*20-22} For maintenance treatment in healed oesophagitis, 11 people need to be treated for 6 months with esomeprazole 20 mg instead of lansoprazole 15 mg to prevent one additional relapse.^{*23}

*Note that standard and low doses of esomeprazole are more expensive than corresponding doses of omeprazole and lansoprazole.²⁴

Uninvestigated dyspepsia

Symptoms do not reliably predict diagnosis in uninvestigated dyspepsia

Heartburn and acid regurgitation as predominant symptoms are relatively specific indicators of the presence of GORD; however, symptoms do not reliably predict other diagnoses such as peptic ulcer disease or non-ulcer dyspepsia.

Management options in uninvestigated dyspepsia include prompt endoscopy, empirical acid suppression therapy or the *H. pylori* test-and-treat approach.

Empirical therapy or test-and-treat is generally preferred. Endoscopy is usually reserved for those at risk of serious pathology (that is, over 45 years* or with alarm symptoms) and those whose symptoms persist after initial therapy.

* Some guidelines suggest that a non-invasive *H. pylori* test-and-treat approach may be as appropriate as early endoscopy in patients aged over 55 years who are not taking NSAIDs and do not have alarm symptoms.⁴

Uninvestigated dyspepsia (*continued*)

Consider test-and-treat in uninvestigated dyspepsia

Test-and-treat refers to a strategy in which patients presenting with uninvestigated dyspepsia (excluding those with indications for prompt endoscopy, with suspected GORD or who are NSAID users) receive a non-invasive test for *H. pylori* (such as the urea breath test, faecal antigen test or serology). Those who test positive receive eradication therapy and those who test negative receive a short course of a PPI. People whose symptoms persist after confirmed *H. pylori* eradication or an adequate trial of a PPI can be referred to a specialist.

A recent study found that the test-and-treat approach reduced symptoms and rates of referral for endoscopy more than empirical acid suppression.²⁵ However, evidence for this approach in primary care is still limited: much of the current evidence comes from studies considering the efficacy of eradication therapy in *H. pylori*-infected subjects in secondary care settings.²⁶ Nevertheless, many guidelines now recommend this approach.^{4,27,28} GESA suggests that it is reasonable to consider eradicating *H. pylori* in dyspeptic patients younger than 50 years without further investigations if there are no alarm features.²⁹

Non-ulcer dyspepsia

What is non-ulcer dyspepsia?

Non-ulcer or functional dyspepsia describes people who have had investigations to rule out structural or biochemical causes for their dyspeptic symptoms.

Drugs are generally not effective in non-ulcer dyspepsia

PPIs, H₂ antagonists, *H. pylori* eradication and motility stimulants have all been evaluated in non-ulcer dyspepsia; each is effective only in small numbers of patients.^{30,31} Non-ulcer dyspepsia is thought to encompass a range of underlying causes, including abnormal gastrointestinal motility, acid sensitivity and *H. pylori* infection; this may explain the lack of a single effective therapy.

Explanation and reassurance are key aspects of management

Reassure patients that although symptoms are understandably troubling, they are part of a common condition and are not due to serious underlying disease. Explain that treatments are not usually very effective, although a small number of people may be helped by some medicines.

Consider test-and-treat

Eradicating *H. pylori* in infected people with non-ulcer dyspepsia improves or eliminates symptoms in a small proportion: 15 people must be treated for one to benefit.³¹ Although the effect size is small, eradication can be considered because it eliminates the need for ongoing therapy in responders. However, Australian information on the cost-effectiveness of this approach is not available.

Consider a short course of an H₂ antagonist or PPI in symptomatic patients in whom *H. pylori* has been excluded or eradicated

Short courses of H₂ antagonists or PPIs improve symptoms in 10–20% of people with non-ulcer dyspepsia.³⁰ There is currently no evidence that PPIs are more effective than H₂ antagonists in non-ulcer dyspepsia³⁰; use an H₂ antagonist for 4 weeks first because it is less expensive, but consider switching to a PPI for a further 4 weeks if the patient fails to respond.³ Encourage intermittent, short courses of treatment as needed.

Role of motility stimulants

Cisapride is the best-studied motility stimulant for non-ulcer dyspepsia³⁰ but its use has been restricted due to the potential for serious cardiac arrhythmias. Evidence for metoclopramide and domperidone is insufficient to support their use in this indication.

Eradicating *H. pylori* in long-term PPI users

Benefits are currently uncertain

It has been proposed that long-term acid suppression in the presence of *H. pylori* infection accelerates the development of atrophic gastritis, which may lead to gastric cancer. At present, evidence for PPIs accelerating *H. pylori* gastritis is conflicting.²⁸ In the absence of definitive evidence, some guidelines suggest testing for and eradicating *H. pylori* in people on long-term PPIs to reduce the potential associated risks.²⁸

Where people on long-term PPIs have underlying peptic ulcer disease, subsequent cure of the ulcer following *H. pylori* eradication should allow PPIs to be discontinued.²⁸

Table 1: Standard and low doses of PPIs⁶

PPI	Standard dose*	Low dose*
esomeprazole	40 mg daily	20 mg daily
lansoprazole	30 mg daily	15 mg daily
omeprazole	20 mg daily	10 mg daily
pantoprazole	40 mg daily	20 mg daily
rabeprazole	20 mg daily	10 mg daily

*Standard dose refers to the dose usually recommended for initial therapy in reflux oesophagitis. Low dose refers to the lower dose recommended for maintenance therapy.

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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.



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