Medicines Management Programme
Preferred Drugs

Proton pump inhibitors for the treatment of gastro-oesophageal reflux disease.

<table>
<thead>
<tr>
<th>Approved by:</th>
<th>Prof. Michael Barry, Clinical Lead, Medicines Management Programme (MMP).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date approved:</td>
<td>10th July 2019</td>
</tr>
<tr>
<td>Version:</td>
<td>1.0</td>
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<th>Full Form</th>
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<tr>
<td>ADR</td>
<td>Adverse drug reaction</td>
</tr>
<tr>
<td>AGAI</td>
<td>American Gastroenterological Association Institute</td>
</tr>
<tr>
<td>CADTH</td>
<td>Canadian Agency for Drugs and Technologies in Health</td>
</tr>
<tr>
<td>CDS</td>
<td>Community drugs schemes</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>COMPUS</td>
<td>Canadian Optimal Medication Prescribing and Utilisation Service</td>
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<tr>
<td>CYP</td>
<td>Cytochrome P450</td>
</tr>
<tr>
<td>DDD</td>
<td>Defined daily dose</td>
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<tr>
<td>DPS</td>
<td>Drugs Payment Scheme</td>
</tr>
<tr>
<td>EAES</td>
<td>European Association of Endoscopic Surgery</td>
</tr>
<tr>
<td>ENRD</td>
<td>Endoscopy-negative reflux disease</td>
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<tr>
<td>GDG</td>
<td>Guideline Development Group</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>GMS</td>
<td>General Medical Services</td>
</tr>
<tr>
<td>GORD</td>
<td>Gastro-oesophageal reflux disease</td>
</tr>
<tr>
<td>H. pylori</td>
<td>Helicobacter pylori</td>
</tr>
<tr>
<td>H2RA</td>
<td>Histamine-2 receptor antagonist</td>
</tr>
<tr>
<td>HPRA</td>
<td>Health Products Regulatory Authority</td>
</tr>
<tr>
<td>HSE</td>
<td>Health Service Executive</td>
</tr>
<tr>
<td>MMP</td>
<td>Medicines Management Programme</td>
</tr>
<tr>
<td>NERD</td>
<td>Non-erosive reflux disease</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
</tr>
<tr>
<td>NNT</td>
<td>Number needed to treat</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>PCRS</td>
<td>Primary Care Reimbursement Service</td>
</tr>
<tr>
<td>PPI</td>
<td>Proton pump inhibitor</td>
</tr>
<tr>
<td>PUD</td>
<td>Peptic ulcer disease</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
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</table>
Acknowledgements

The MMP wishes to acknowledge the staff of the National Medicines Information Centre (NMIC) and the National Centre for Pharmacoeconomics (NCPE) for their input and contributions to this document.
1. Purpose

Lansoprazole has been the Health Service Executive’s Medicines Management Programme (HSE-MMP) preferred proton pump inhibitor (PPI) since April 2013. The purpose of this report is to review the choice of preferred PPI in light of the current available evidence.

The MMP aims to promote safe, effective and cost-effective prescribing. The Preferred Drugs Initiative identifies a single ‘preferred drug’ within a therapeutic drug class, and offers prescribers useful guidance on selecting, prescribing and monitoring this drug for a particular condition. In this case the use of PPIs for the treatment of gastro-oesophageal reflux disease (GORD) in adults is reviewed.

Prescribers are encouraged to make the preferred drug their drug of first choice, when initiating a PPI and when there is a need to change from one PPI to another in the treatment of GORD.

This report should be used in conjunction with clinical judgement and decision making appropriate to the individual patient. Prescribers should refer to sources such as the Summary of Product Characteristics (SmPC) to inform decisions made concerning individual patients.

2. Definitions

For the purpose of this report, the associated ingredient cost refers to the reimbursed cost of the named PPIs as listed on the HSE Primary Care Reimbursement Service (PCRS) website. Reimbursed PPIs licensed for the treatment of GORD are included in this review.

When two or more preparations of the same drug are listed, (e.g. where there are different manufacturers/suppliers), the least expensive preparation with all the relevant indications has been selected for the evaluation. Costs are correct as of 19th June 2019.
3. Proton pump inhibitors

PPIs inhibit gastric acid secretion by blocking the hydrogen-potassium adenosine triphosphatase enzyme system (“proton pump”) of the gastric parietal cell.\(^2\) All PPIs have a similar mechanism of action.\(^3,4\)

There are five licensed PPIs reimbursed in Ireland; esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole.\(^5,6\) Total annual expenditure (inclusive of ingredient cost and pharmacy dispensing fees) in 2017 on PPIs under the Community Drugs Schemes (CDS) was €44.93 million.\(^7\)

Expenditure on PPIs has decreased in recent years due to the introduction of generic substitution and reference pricing. However, PPIs were the second most expensive class of medicines on the General Medical Services (GMS) scheme in 2017, with esomeprazole the fifth most commonly prescribed drug (the number of prescriptions was 1,317,708 and total annual expenditure of €16.53 million).\(^7\)

![Figure 1: Combined total number of prescriptions for PPIs on the GMS scheme 2007-2017](image)

Figure 1 illustrates there has been an increase in the number of prescriptions for PPIs under the GMS scheme from 2007 to 2017.\(^7\)
4. Preferred proton pump inhibitor

Based on the current evidence pantoprazole is the MMP’s preferred PPI for the treatment of GORD.

5. Consultation for proton pump inhibitors in the treatment of gastro-oesophageal reflux disease
A period of consultation was undertaken in which submissions from relevant stakeholders, including the pharmaceutical industry and professional bodies representing clinicians and healthcare professionals, were invited. This consultation period closed on 14th September 2018.

6. Selection criteria
A number of key criteria were considered in the MMP preferred PPI selection process:

- Licensed indications
- Clinical outcome data
- International clinical guidelines
- Adverse drug reactions
- Contraindications and cautions
- Drug interactions
- Patient factors
- Cost
- National prescribing trends
6.1 Licensed therapeutic indications

The focus of this guidance is the use of PPIs in GORD; all PPIs considered in this review are licensed to treat symptomatic GORD and in the treatment and prevention of reflux oesophagitis. The licensed indications for PPIs are summarised in Table 1.

Table 1: Licensed therapeutic indications for PPIs*

<table>
<thead>
<tr>
<th>Indication</th>
<th>Esomeprazole 8,9</th>
<th>Lansoprazole 10,11</th>
<th>Omeprazole 12-14</th>
<th>Pantoprazole 15,16</th>
<th>Rabeprazole 17,18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic GORD</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Treatment of reflux oesophagitis</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓**</td>
</tr>
<tr>
<td>Prophylaxis of reflux oesophagitis</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓**</td>
</tr>
<tr>
<td>Treatment of duodenal ulcers</td>
<td>✓†</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Prevention of relapse of duodenal ulcers</td>
<td>✓†</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Treatment of gastric ulcers</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Prevention of relapse of gastric ulcers</td>
<td>✓†</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>H. pylori eradication Ω</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Treatment of NSAID associated ulcers (gastric &amp; duodenal)</td>
<td>✓ (gastric)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Prophylaxis of NSAID associated ulcers (gastric &amp; duodenal) in patients at risk</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Prolonged treatment after intravenous induced prevention of rebleeding peptic ulcers</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Zollinger-Ellison Syndrome</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

* Certain indications refer to specific dosages that are not detailed in this table.
** Referred to in SmPC as symptomatic erosive or ulcerative GORD and GORD long-term management (GORD maintenance).
† Associated with H. pylori in combination with appropriate antibiotics.
‡ Associated with H. pylori.
Ω In combination with appropriate antibiotics.
6.1.1 Gastro-oesophageal reflux disease

GORD is defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications.\textsuperscript{19} The characteristic symptoms of GORD are retrosternal burning (heartburn) and regurgitation. According to the definition, “troublesome” symptoms are those that adversely affect an individual’s well-being.\textsuperscript{19}

The main complications of GORD are reflux oesophagitis, the development of strictures, Barrett’s oesophagus and oesophageal adenocarcinoma. However, despite the possible serious consequences, GORD usually presents as a relatively benign condition.\textsuperscript{20}

An approximate prevalence for GORD ranges from 10-20\% in the Western world defined by at least weekly heartburn and/or acid regurgitation.\textsuperscript{21}

GORD can be subdivided based on endoscopic findings into erosive disease (reflux oesophagitis) and non-erosive reflux disease.\textsuperscript{20}

Reflux oesophagitis (also called erosive oesophagitis) is defined endoscopically by visible breaks of the distal oesophageal mucosa.\textsuperscript{19} The severity of reflux oesophagitis is usually graded according to the Los Angeles classification, from grades A to D denoting increasing severity and extension of inflammation (see Appendix A).\textsuperscript{20,22}

Non-erosive reflux disease (NERD) [also called endoscopy-negative reflux disease (ENRD)] is defined by the presence of troublesome reflux-associated symptoms and the absence of mucosal breaks at endoscopy.\textsuperscript{19}

6.2 Meta-analyses and systematic reviews in the treatment of gastro-oesophageal reflux disease

Systematic reviews and meta-analyses which utilise pooled data from clinical trials, provide a means of assessing the general and comparative efficacy of PPIs, and were considered as part of the review process.
<table>
<thead>
<tr>
<th>Review</th>
<th>Author</th>
<th>Year</th>
<th>Number of patients</th>
<th>Drugs</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparative effectiveness and acceptability of the FDA-licensed proton pump inhibitors for erosive oesophagitis-A PRISMA compliant network meta-analysis</td>
<td>Li et al.</td>
<td>2017</td>
<td>25,088</td>
<td>Esomeprazole 20 &amp; 40 mg, lansoprazole 30 mg, pantoprazole 40 mg, omeprazole 20 mg, rabeprazole 20 mg, dexamethasone 60 mg*</td>
<td>Esomeprazole 20-40 mg, pantoprazole 40 mg, lansoprazole 30 mg, showed more benefits in effectiveness and acceptability than other interventions.</td>
</tr>
<tr>
<td>A systematic review of proton pump inhibitors for the treatment of adult patients with symptomatic GORD or PUD</td>
<td>Drug Assessment Working Group of the Therapeutics Initiative</td>
<td>2016</td>
<td></td>
<td>Varying doses of esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole.</td>
<td>Esomeprazole and lansoprazole were not significantly different to other PPIs for most outcome measures.</td>
</tr>
<tr>
<td>Cochrane review: Medical treatments in the short-term management of reflux oesophagitis</td>
<td>Moayyedi et al.</td>
<td>2007</td>
<td>35,978</td>
<td>PPIs, H2RAs, prokinetics, sucralfate.</td>
<td>Standard doses of individual PPIs did not show statistically significant different effects on healing of oesophagitis.</td>
</tr>
<tr>
<td>Evidence for PPI use in GORD, dyspepsia and PUD</td>
<td>Canadian Optimal Medication Prescribing and Utilisation Service</td>
<td>2007</td>
<td></td>
<td>Varying doses of esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole.</td>
<td>No clinically important differences among PPIs in the treatment of symptomatic GORD, ENRD, erosive oesophagitis.</td>
</tr>
<tr>
<td>Esomeprazole versus other PPIs in erosive oesophagitis: a meta-analysis of randomised clinical trials</td>
<td>Gralnek et al.</td>
<td>2006</td>
<td>15,316</td>
<td>Esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg &amp; 40 mg, pantoprazole 40 mg.</td>
<td>Choice of PPI used in the treatment of GORD should be based on a number of factors: patient’s disease presentation, drug cost, formulary availability, patient tolerability of the drug.</td>
</tr>
<tr>
<td>Review</td>
<td>Author</td>
<td>Year</td>
<td>Number of patients</td>
<td>Drugs</td>
<td>Conclusion</td>
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<td>----------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Systematic review: proton pump inhibitors (PPIs) for the healing of reflux oesophagitis - a comparison of esomeprazole with other PPIs</td>
<td>Edwards et al.</td>
<td>2006</td>
<td>13,572</td>
<td>Esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg.</td>
<td>Healing benefit in terms of esomeprazole 40mg was found. Significant levels of unexplained statistical heterogeneity was detected in the primary analysis.</td>
</tr>
<tr>
<td>Systematic review: direct comparative trials of the efficacy of PPIs in the management of GORD and PUD</td>
<td>Vakil et al.</td>
<td>2003</td>
<td>Data not reported</td>
<td>Varying doses of esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole.</td>
<td>Insufficient data to establish the superiority of any one PPI over another across all disease states treated.</td>
</tr>
</tbody>
</table>
Direct comparison of the efficacy of different PPIs is difficult as different dosing regimens were used in individual studies. In terms of the National Institute for Health and Care Excellence (NICE) guidance, which contains dosage information on PPIs for the treatment of GORD and dyspepsia in adults (Table 4, page 15), esomeprazole 40 mg is considered a double dose PPI, in comparison to lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg, which are considered full (standard) dose PPIs.\textsuperscript{31}

When undertaking meta-analysis of dose related effects, NICE classed esomeprazole 20 mg as a full dose equivalent to lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg.\textsuperscript{31} In light of this guidance, some trials compared non-equivalent doses of PPIs.

The key findings from the meta-analyses and systematic reviews in Table 2 were as follows:

- A network meta-analysis by Li et al. (2017) involved 25 randomised controlled trials (RCTs) and 25,088 patients with erosive oesophagitis.\textsuperscript{23} Patients were randomised to esomeprazole 20-40 mg, pantoprazole 40 mg, lansoprazole 30 mg, rabeprazole 20 mg, omeprazole 20 mg, dexlansoprazole 60 mg (no marketing authorisation in Ireland). The primary outcome was the endoscopic healing rates of erosive oesophagitis at four and eight weeks, heartburn relief rate was a secondary efficacy outcome. Acceptability of treatment was also determined based on the proportion of patients who withdrew from a study for any reason. After a clustering analysis of two outcomes (endoscopic healing rates at four weeks and acceptability of treatment with PPIs), esomeprazole 20-40 mg, pantoprazole 40 mg and lansoprazole 30 mg showed more benefits in terms of effectiveness than the other interventions. This network meta-analysis found that esomeprazole 40 mg improved the healing rate of erosive oesophagitis to a greater extent than omeprazole 20 mg at four and eight weeks, lansoprazole 30 mg at four and eight weeks, rabeprazole 20 mg at up to eight weeks, and pantoprazole 40 mg at four weeks only. Esomeprazole 40 mg improved symptoms of heartburn to a greater extent than omeprazole 20 mg and lansoprazole 30 mg, but not pantoprazole 40 mg or rabeprazole 20 mg.\textsuperscript{23} It should be noted this network meta-analysis included comparisons between non-equivalent doses of PPIs. For example, NICE dosage guidance for the treatment of GORD and dyspepsia in adults
considers esomeprazole 40 mg once a day as a double dose PPI, which in this study was compared to standard dose PPIs (lansoprazole 30 mg once a day, omeprazole 20 mg once a day, pantoprazole 40 mg once a day, rabeprazole 20 mg once a day).\textsuperscript{31}

- The Drug Assessment Working Group of the Therapeutics Initiative, Canada (2016) conducted systematic reviews to compare the efficacy and safety of different PPIs, in patients with symptomatic GORD and in patients with peptic ulcer disease (PUD).\textsuperscript{24} The first systematic review of adult patients with symptomatic GORD involved ten RCTs which compared esomeprazole to omeprazole; twelve RCTs which compared esomeprazole to pantoprazole; five RCTs which compared esomeprazole to rabeprazole. One RCT had multiple treatment arms. Patients were randomised to receive esomeprazole 20-40 mg daily, omeprazole 20 mg daily, pantoprazole 20-40 mg daily, rabeprazole 10-50 mg daily (a novel rabeprazole extended release 50 mg formulation was included, it is not currently available). Esomeprazole was not significantly different to other PPIs for most outcome measures; time to first resolution of symptoms, mortality, serious adverse events, withdrawal due to adverse events and patients with at least one adverse event. Although a few significant differences in outcome measures were noted, they were based on low to very low quality evidence.\textsuperscript{24} Therefore, they were not judged clinically relevant.

The second systematic review of adult patients with symptomatic GORD involved twelve RCTs which compared lansoprazole to omeprazole; five RCTs which compared lansoprazole to pantoprazole; two RCTs which compared lansoprazole to rabeprazole. Five trials had multiple treatment arms. Patients were randomised to receive lansoprazole 30-60 mg daily, omeprazole 20-40 mg daily, pantoprazole 40-80 mg daily, rabeprazole 20 mg daily. Lansoprazole was not significantly different to other PPIs for most outcome measures; total relief of symptoms, relief of retrosternal pain, relief of dysphagia, time to first resolution of symptoms, endoscopic healing of oesophagitis, recurrence or relapse of symptoms, mortality, serious adverse events, withdrawal due to adverse events and patients with at least one adverse event. While a few significant differences in outcome measures were noted, the differences were based on low to very low quality evidence.\textsuperscript{24} Therefore, they were not judged clinically relevant.
A Cochrane review by Moayyedi et al. (2007) involved 134 RCTs and 35,978 patients with erosive oesophagitis.\(^{25}\) The review assessed the effectiveness of PPIs, H-2 receptor antagonists (H2RAs) [cimetidine, famotidine, nizatidine, ranitidine], prokinetic therapy [cisapride, domperidone, metoclopramide], sucralfate and placebo in healing oesophagitis or curing reflux symptoms or both. The review demonstrated that PPIs had clear superiority in healing oesophagitis over all other therapies. The standard doses of individual PPIs did not show statistically significant different effects on healing of oesophagitis. This review was later divided into smaller reviews.\(^{25}\)

The Canadian Optimal Medication Prescribing and Utilisation Service (COMPUS), a service of the Canadian Agency for Drugs and Technologies in Health (CADTH), prepared a scientific report (2007), entitled “Evidence for PPI use in GORD, dyspepsia and PUD”.\(^ {26}\)

The authors of this report assessed the quality of the included evidence (consequently six good quality systematic reviews, three poor quality systematic reviews, one good quality RCT and seven poor quality RCTs were included). Patients were randomised to esomeprazole 20-40 mg, lansoprazole 15-30 mg, omeprazole 20 mg, pantoprazole 20-40 mg, rabeprazole 10-20 mg. The results of this review indicated that PPIs are equally efficacious in the initial treatment of various gastrointestinal conditions. The review found in the treatment of symptomatic GORD, including both ENRD and erosive oesophagitis, there were no clinically important differences among standard doses of PPIs (esomeprazole 20 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg).\(^ {26}\)

These are the same standard doses as the standard doses in NICE guidance for the treatment of GORD and dyspepsia in adults.\(^ {31}\)

A meta-analysis by Gralnek et al. (2006) involved ten studies (eight RCTs, one published abstract, and one unpublished trial reported in the manufacturer’s package insert) and 15,316 patients.\(^ {27}\) The study examined the efficacy of esomeprazole 40 mg, omeprazole 20-40 mg, lansoprazole 30 mg and pantoprazole 40 mg in the healing of erosive oesophagitis and GORD symptom relief. The authors concluded that the choice of PPI used in the treatment of GORD should be based on a number of factors
including the patient’s disease presentation, drug cost, formulary availability and patient tolerability of the drug. At eight weeks there was a 5% relative increase in the probability of healing of erosive oesophagitis with esomeprazole 40 mg versus other PPIs (relative risk (RR) 1.05; 95% confidence interval (CI): 1.02-1.08), the number needed to treat (NNT) for patients with Los Angeles grade A oesophagitis was 50. Esomeprazole 40 mg conferred an 8% relative increase in the probability of GORD symptom relief at four weeks (RR 1.08; 95% CI: 1.05-1.11), the NNT was 25. While the authors found that esomeprazole provided a statistically significant improvement, only a modest degree of improved effectiveness in the healing of erosive oesophagitis was found, which appeared to be limited to patients with more severe disease. Furthermore, the authors found no evidence of a clinically meaningful improvement in symptom relief with esomeprazole 40 mg compared to the other PPIs.\textsuperscript{27} Moreover, this trial did not compare equivalent doses of PPIs in nine of the included studies, which involved 14,996 patients. NICE dosage guidance for the treatment of GORD and dyspepsia in adults considers esomeprazole 40 mg once a day as a double dose PPI, which in this study was compared to standard dose PPIs (lansoprazole 30 mg once a day, omeprazole 20 mg once a day, pantoprazole 40 mg once a day).\textsuperscript{31}

- A systematic review by Edwards et al. (2006) compared the effectiveness of esomeprazole 40 mg with lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg in the healing of reflux oesophagitis.\textsuperscript{28} No studies were identified comparing rabeprazole with esomeprazole. A meta-analysis was undertaken, which involved six trials and 13,572 patients on the healing rates of reflux oesophagitis. It showed a benefit in favour of esomeprazole 40 mg at four weeks (RR 0.92; 95% CI: 0.90-0.94; P < 0.00001) and eight weeks (RR 0.95; 95% CI: 0.94-0.97; P <0.00001). However, significant levels of unexplained statistical heterogeneity was detected at four weeks (P=0.002) and eight weeks (P=0.0009).\textsuperscript{28} Moreover, the study actually compared a double dose PPI, esomeprazole 40 mg once a day, to standard dose PPIs, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg, in terms of NICE dosage guidance for the treatment of GORD and dyspepsia in adults.\textsuperscript{31}
A systematic review by Vakil et al. (2003) involved 32 trials and was conducted to identify any consistent evidence of differences in outcomes between PPIs and doses used in the management of GORD and PUD.29 The number of participants in each study was not reported. Patients were randomised to esomeprazole 20-40 mg, lansoprazole 15-60 mg, omeprazole 20-40 mg, pantoprazole 40-80 mg, rabeprazole 10-20 mg. The review assessed healing and symptom relief in GORD, maintenance of healing of GORD and healing and maintenance of ulcers. Overall, there was insufficient data to establish the superiority of one PPI or dose over all others across all disease states treated. The results showed a higher rate of symptom relief in GORD patients treated with lansoprazole 30 mg versus omeprazole 20 mg on days one to three of treatment, and with esomeprazole 40 mg versus omeprazole 20 mg at eight weeks. The results showed that esomeprazole 40 mg was more effective than omeprazole 20 mg in the healing of oesophagitis at eight weeks, but there were no significant differences between other PPIs at standard doses in the healing of oesophagitis. While the authors made a clinical recommendation that esomeprazole is the only PPI that demonstrated superior healing in head-to-head studies with other PPIs, cost and other factors that affect clinical decisions on drug use were not considered.29 Furthermore, when the results are considered, this trial did not compare equivalent doses of PPIs. NICE dosage guidance for the treatment of GORD and dyspepsia in adults considers esomeprazole 40 mg once a day as a double dose PPI in comparison to a standard dose PPI omeprazole 20 mg once a day.31

A meta-analysis by Klok et al. (2003) involved trials where two or more PPIs were compared in the short-term management of GORD, PUD and eradication of H. pylori.30 It investigated whether clinical differences existed between PPIs. In the treatment of GORD, this study compared the efficacy of esomeprazole 20-40 mg, lansoprazole 15-30 mg, omeprazole 20-40 mg, pantoprazole 20-40 mg, rabeprazole 10-20 mg. Overall, the authors noted that all PPIs appeared to be clinically comparable, and the clinical choice of PPI may be based on other factors, such as pharmacoeconomic considerations. The authors noted that studies comparing different PPIs over a longer period, have not shown significant differences in safety and efficacy between the PPIs studied.
One statistically significant difference was found in the treatment of GORD; esomeprazole 40 mg was superior to omeprazole 20 mg (RR 1.18; 95% CI: 1.14-1.23) in endoscopic healing. The authors indicated that this difference was likely to be dose dependent and not PPI specific. No other significant differences were found. Furthermore, NICE dosage guidance for the treatment of GORD and dyspepsia in adults considers esomeprazole 40 mg once a day as a double dose PPI in comparison to omeprazole 20 mg once a day, which is considered a standard dose.

When assessing the above meta-analyses and systematic reviews, the MMP recognise the potential for bias in meta-analyses and systematic reviews carried out on behalf of a particular product or manufacturer.

Following this assessment, the MMP noted there were no significant differences in clinical efficacy among various PPIs when compared at equivalent doses.

There were no significant differences in clinical efficacy noted among various PPIs when compared at equivalent doses.
6.3 International clinical guidelines for the treatment of gastro-oesophageal reflux disease

Table 3: International clinical guidelines for the treatment of GORD

<table>
<thead>
<tr>
<th>Review body</th>
<th>Guideline</th>
<th>Year</th>
<th>Initial drug treatment options</th>
<th>Preferred PPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Institute for Health and Care Excellence (NICE) 31</td>
<td>GORD &amp; dyspepsia in adults</td>
<td>2014</td>
<td>PPI</td>
<td>None</td>
</tr>
<tr>
<td>World Gastroenterology Organisation 32</td>
<td>GORD</td>
<td>2015</td>
<td>PPI</td>
<td>None</td>
</tr>
<tr>
<td>European Association of Endoscopic Surgery (EAES) 33</td>
<td>GORD</td>
<td>2014</td>
<td>PPI</td>
<td>None</td>
</tr>
<tr>
<td>American College of Gastroenterology (ACG) 34</td>
<td>GORD</td>
<td>2013</td>
<td>PPI</td>
<td>None</td>
</tr>
<tr>
<td>American Gastroenterological Association Institute (AGAI) 35</td>
<td>GORD</td>
<td>2008</td>
<td>PPI</td>
<td>None</td>
</tr>
</tbody>
</table>

National Institute for Health and Care Excellence

National Institute for Health and Care Excellence (NICE) guidance *GORD and dyspepsia in adults: investigation and management* (2014), recommends that patients with GORD should be offered a full-dose PPI (Table 4) for four to eight weeks. If symptoms recur after initial treatment, patients should be offered a PPI at the lowest dose possible to control symptoms. “As needed” use of PPIs should also be discussed with patients. 31

Table 4: NICE dosage information on PPIs for the treatment of GORD & dyspepsia in adults

<table>
<thead>
<tr>
<th>PPI</th>
<th>Full (standard) dose</th>
<th>Low (on-demand) dose</th>
<th>Double dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole</td>
<td>20 mg once a day*</td>
<td>Not available</td>
<td>40 mg once a day†</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>30 mg once a day</td>
<td>15 mg once a day</td>
<td>30 mg twice a day**</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>20 mg once a day</td>
<td>10 mg once a day**</td>
<td>40 mg once a day</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>40 mg once a day</td>
<td>20 mg once a day</td>
<td>40 mg twice a day**</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>20 mg once a day</td>
<td>10 mg once a day</td>
<td>20 mg twice a day**</td>
</tr>
</tbody>
</table>

*When undertaking meta-analysis of dose related effects, NICE classed esomeprazole 20 mg as a full dose equivalent to omeprazole 20 mg.
** Off-label dose for GORD.
† Esomeprazole 40 mg is considered as a double dose as esomeprazole 20 mg is considered equivalent to omeprazole 20mg.
The NICE guidance provides separate information specifically for the treatment of severe oesophagitis along with separate dosage information (Table 5).

NICE guidance recommends that patients should be offered a full-dose PPI (Table 5) for eight weeks to heal severe oesophagitis (Los Angeles classification grade C/D) [see Appendix A], taking into account the patient’s preference and clinical circumstances, such as underlying health conditions and possible interactions with other medications. If initial treatment fails in the healing of severe oesophagitis, a high dose of the initial PPI should be considered, or switching to a different full-dose PPI or switching to a different high-dose PPI, taking into account the patient’s preference and clinical circumstances such as tolerability of the initial PPI, underlying health conditions and possible interactions with other drugs.  

Following completion of initial treatment, in patients with severe oesophagitis, a full-dose PPI (Table 5) should be offered as long-term maintenance treatment. In choosing a PPI, the patient’s preference, clinical circumstances and the acquisition cost of the PPI should be considered.

If the patient’s severe oesophagitis fails to respond to maintenance treatment, a clinical review should be carried out. Consideration should be given to switching to another PPI at full-dose or high dose, taking into account the patient’s preference and clinical circumstance, and/or seeking specialist advice.

Table 5: NICE dosage information on PPIs for the treatment of severe oesophagitis

<table>
<thead>
<tr>
<th>PPI</th>
<th>Full (standard) dose</th>
<th>Low (on-demand) dose</th>
<th>High (double) dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole</td>
<td>40 mg once a day*</td>
<td>20 mg once a day*</td>
<td>40 mg twice a day*</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>30 mg once a day</td>
<td>15 mg once a day</td>
<td>30 mg twice a day**</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>40 mg once a day*</td>
<td>20 mg once a day*</td>
<td>40 mg twice a day*</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>40 mg once a day</td>
<td>20 mg once a day</td>
<td>40 mg twice a day**</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>20 mg once a day</td>
<td>10 mg once a day</td>
<td>20 mg twice a day**</td>
</tr>
</tbody>
</table>

*Specifically for severe oesophagitis  
**Off-label dose for GORD

The NICE Guideline Development Group (GDG), based on the available evidence, concluded that it was not possible to determine with confidence, which PPI was the best for healing or maintenance in patients with severe erosive reflux disease. The NICE GDG agreed that a “class effect” could be assumed for all PPIs and that the choice of PPI should be based on individual
patient preferences and their clinical circumstances. The NICE GDG did not recommend a specific PPI.\textsuperscript{31}

**World Gastroenterology Organisation**

The World Gastroenterology Organisation global guideline *GORD* (2015), recommends that a formal course of PPI therapy of adequate duration (usually eight weeks), is required in order to assess the treatment response in GORD patients.\textsuperscript{32}

In order to have better symptom control, the guideline recommends that patients should be informed of appropriate use of PPI therapy; PPIs should be taken 30-60 minutes before breakfast, and in the case of twice-daily dosing, 30-60 minutes before the last meal of the day.\textsuperscript{32}

This guideline does not recommend a particular PPI to use in the treatment of GORD.

**European Association of Endoscopic Surgery**

The European Association of Endoscopic Surgery (EAES) *Recommendations for the management of GORD* (2014), recommends that PPI therapy is always the primary therapy for acute GORD. The recommendations take into account that some studies have shown a mild to moderate benefit of one PPI over another. However, standard doses of esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole for the most part have shown comparable rates of healing and remission of erosive oesophagitis.\textsuperscript{33}

**American College of Gastroenterology**

The American College of Gastroenterology (ACG) *Guidelines for the diagnosis and management of GORD* (2013), recommends that an eight-week course of a PPI is the therapy of choice for symptom relief and healing of erosive oesophagitis. Maintenance PPI therapy is recommended for GORD patients who continue to have symptoms after a PPI is discontinued and in patients with complications including erosive oesophagitis and Barrett’s oesophagus. The guidance states there are no major differences in efficacy between the different PPIs. For patients who require long-term PPI therapy, PPIs should be administered at the lowest effective dose, including on-demand or intermittent therapy.\textsuperscript{34}
The American Gastroenterological Association Institute (AGAI) *Technical review on the management of GORD* (2008), recommends antisecretory drugs for the treatment of patients with oesophageal GORD symptoms (healing oesophagitis, symptomatic relief and maintaining healing of oesophagitis). For these indications, PPIs are more effective than H2RAs.\(^{35}\)

This guideline does not recommend a particular PPI to use in the treatment of GORD. The guideline states that factors such as side-effects and onset of action will likely govern the selection of the initial therapy for most patients.\(^{35}\)
6.4 Adverse drug reactions
The common adverse drug reactions (ADRs) [incidence of ≥ 1 in 100 to < 1 in 10] for PPIs are listed in Table 6. A full list of ADRs for each drug can be found in the individual SmPC available at www.hpra.ie.

<table>
<thead>
<tr>
<th>Table 6: Common adverse drug reactions of individual PPIs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse drug reaction</strong></td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Flatulence</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Fundic gland polyps (benign)</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Stomach ache</td>
</tr>
<tr>
<td>Dry mouth or throat</td>
</tr>
<tr>
<td>Raised liver enzyme levels</td>
</tr>
<tr>
<td>Urticaria</td>
</tr>
<tr>
<td>Itching</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>Insomnia</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Pharyngitis</td>
</tr>
<tr>
<td>Rhinitis</td>
</tr>
<tr>
<td>Non-specific pain</td>
</tr>
<tr>
<td>Back pain</td>
</tr>
<tr>
<td>Asthenia</td>
</tr>
<tr>
<td>Influenza like illness</td>
</tr>
</tbody>
</table>

As seen in Table 6, rabeprazole has the greatest number of common ADRs reported in its SmPC. Conversely, pantoprazole appears to have the best safety profile based on common ADRs reported in its SmPC.

Pantoprazole is the preferred PPI in terms of adverse drug reaction profiles under MMP review.
6.5 Contraindications & cautions
It is advisable to consult the SmPC of the individual PPIs for guidance on contraindications and cautions, available at www.hpra.ie.

6.5.1 Contraindications
**Hypersensitivity:** All PPIs are contraindicated where there is hypersensitivity to the active substance or any of the excipients.\(^{8-18}\)

6.5.2 Cautions
**Gastric cancer:** PPIs may mask the symptoms of gastric cancer and delay diagnosis. Particular care is needed in those presenting with alarm symptoms, e.g. recurrent vomiting, dysphagia, anaemia.\(^{8-18}\)

**Gastrointestinal infections:** PPIs may increase the risk of gastrointestinal (GI) infections caused by bacteria such as *Salmonella*, *Campylobacter* and especially in hospitalised patients, *Clostridium difficile*.\(^{8-18,36}\) Consideration should be given to stopping/reviewing the need for PPIs in patients with or at high risk of *Clostridium difficile* infection.\(^{37}\)

Patients on long-term treatment (particularly those treated for more than one year) should be kept under regular surveillance.\(^{8-18}\)

**Long-term safety concerns include the following:**

- **Bone fracture:** At high doses and for long duration (>1 year), PPIs may modestly increase the risk of hip, wrist and spine fractures, predominately in the elderly or in the presence of other recognised risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and have an adequate intake of vitamin D and calcium.\(^{8-18,38}\)

- **Vitamin B12 absorption:** With long-term treatment, PPIs may reduce absorption of vitamin B12. Particular care should be taken in treating older or malnourished patients taking PPIs for more than one year or in patients taking other drugs that can affect vitamin B12 levels e.g. metformin.\(^{8-18,36}\)

- **Hypomagnesaemia:** Prolonged use of PPIs can lead to hypomagnesaemia. Measurement of serum magnesium concentrations should be considered, before starting PPI treatment and periodically during treatment, in patients expected to be
on prolonged treatment or who take PPIs with digoxin or with drugs that may cause hypomagnesaemia e.g. diuretics.\textsuperscript{8-18,39}

Other:

- **Subacute cutaneous lupus erythematosus (SCLE):** PPIs are associated with very rare cases of SCLE, which can occur weeks, months or even years after exposure. In most cases, symptoms resolve on stopping the PPI treatment. A patient who develops SCLE with a particular PPI may be at risk of the same reaction with another PPI.\textsuperscript{8-18,40}

- **Interference with laboratory tests:** PPIs can increase Chromogranin A levels, which may interfere with investigations for neuroendocrine tumours.\textsuperscript{8-18}

> There are no significant differences between PPIs in terms of contraindications and cautions under MMP review.
6.6 Drug interactions

PPIs are metabolised through the cytochrome P450 (CYP) hepatic drug metabolising system. The isoenzymes involved are CYP2C19 and CYP3A4. Differences in metabolism among the PPIs results in differential propensities to cause interactions.\(^\text{41}\)

Lansoprazole, pantoprazole and rabeprazole appear to be associated with lower incidences of drug interactions compared to omeprazole and esomeprazole. This is resulting from either their lower affinity for specific CYP isoenzymes or the involvement of additional elimination processes.\(^\text{42}\)

An overview of potential drug-drug interactions that may occur with PPIs and commonly prescribed drugs in Ireland is summarised below. This list is not exhaustive and it is advisable to consult the SmPC of individual PPIs for a comprehensive list of drug interactions, available at www.hpra.ie.

- **Drugs known to induce or inhibit CYP2C19 or CYP3A4** may alter a PPI’s plasma concentration.\(^\text{8-18,42}\)

- **Medicinal products with pH-dependent absorption**: Gastric acid suppression during treatment with PPIs might decrease or increase the absorption of medicinal products with a gastric pH-dependent absorption e.g. ketoconazole, erlotinib, atazanavir.\(^\text{8-18}\)
  
  This type of interaction can occur with all PPIs.\(^\text{41}\)

- **Clopidogrel**: Esomeprazole and omeprazole can decrease the efficacy of clopidogrel. Therefore, concomitant use of esomeprazole or omeprazole and clopidogrel should be discouraged.\(^\text{43}\)

- **Citalopram & escitalopram**: It is predicted that esomeprazole slightly to moderately increases exposure to citalopram and escitalopram. Patients should be monitored and the dose adjusted if necessary.
  
  Omeprazole slightly to moderately increases exposure to citalopram and escitalopram. Patients should be monitored and the dose adjusted if necessary.\(^\text{2}\)

- **Methotrexate**: PPIs decrease the clearance of methotrexate.\(^\text{2}\) The risk appears to be dose dependent.\(^\text{44}\)
➢ **Tacrolimus**: Esomeprazole, lansoprazole and omeprazole have been reported to increase plasma concentrations of tacrolimus.\(^8\)-\(^{14}\) Tacrolimus concentrations and/or effects should be monitored as a matter of routine; it may be advisable to increase monitoring if a PPI is started or stopped, adjusting the tacrolimus dose if necessary.\(^{44}\)

With little difference among PPIs in terms of their clinical efficacy at equivalent doses, differences in drug interaction propensities become important factors in prescribing decisions. This is of particular importance in those receiving concomitant drugs with a narrow therapeutic window and in those patients who are taking multiple concomitant medications.\(^{42}\)

**Pantoprazole, lansoprazole and rabeprazole have favourable drug interaction profiles under MMP review.**

### 6.7 Patient factors

In the absence of clinical outcome data demonstrating superiority of one drug over another, drugs taken once daily are preferred to those requiring multiple daily doses.\(^{45}\) This is not relevant to the use of PPIs in the treatment of GORD as PPIs are usually taken once daily for this indication.\(^8\)-\(^{18}\)

PPIs when taken once daily should be administered 30-60 minutes before breakfast to ensure maximum effect.\(^{24,32,33,46,47}\)

**There are no differences between PPIs in terms of dosing and administration in the treatment of GORD under MMP review.**
6.8 Cost

Value for money is a consideration when choosing a preferred PPI. It is also a consideration for patients who pay for their medicines. A drug of lower acquisition cost is preferred unless the more expensive drug has a proven advantage in terms of either efficacy or safety.

Figure 2: PCRS reimbursed cost of 28 dosage units of each PPI.

Figure 2 illustrates the PCRS reimbursed cost comparison of 28 dosage units of each PPI. The most expensive PPIs are both esomeprazole 40 mg and rabeprazole 20 mg. The least expensive PPI is pantoprazole 20 mg. Of note is that omeprazole 10 mg is more expensive than omeprazole 20 mg (£3.36 versus £2.80).

The World Health Organisation (WHO) collaborating centre for drug statistics methodology lists the defined daily dose (DDD) for each PPI for the treatment of GORD (Table 7), and this is utilised to compare the reimbursed cost of each PPI.48

Table 7: The defined daily dose of each PPI for the treatment of GORD48

<table>
<thead>
<tr>
<th>PPI</th>
<th>DDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole</td>
<td>30 mg</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>30 mg</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>20 mg</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>40 mg</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>20 mg</td>
</tr>
</tbody>
</table>
The DDD can sometimes be a dose that is rarely or never prescribed because it is an average of two or more commonly used doses. For example, the DDD for esomeprazole is 30 mg.\(^4\)

The strengths of esomeprazole reimbursed by the HSE PCRS are 20 mg and 40 mg. Therefore, the reimbursed cost of one and a half times the 20 mg strength was calculated in this case.\(^5\)

Figure 3: PCRS reimbursed cost of 28 dosage units based on defined daily dose

Figure 3 illustrates a cost comparison of the PPIs’ reimbursed cost of 28 dosage units, based on the DDD. It shows that omeprazole is the least expensive PPI, while rabeprazole is the most expensive based on the DDD.

NICE have issued guidance on dosage of PPIs, shown in Table 4 (section 6.3, page 15). Based on this dosage guidance, the reimbursed cost for 28 dosage units of individual PPIs are compared below:

- The **lowest cost full (standard) dose PPI** is omeprazole 20 mg once daily (€2.80) followed by pantoprazole 40 mg once daily (€3.08).
- The **lowest cost low (on-demand) dose PPI** is pantoprazole 20 mg once daily (€2.52) followed by lansoprazole 15 mg once daily (€3.08).
- The **lowest cost double-dose PPI** is omeprazole 40 mg once daily (€5.60) followed by pantoprazole 40 mg twice daily (€6.16).
- The **lowest cost differential** between full (standard) dose and low (on-demand) dose PPI is with pantoprazole (€3.08 versus €2.52).

Pantoprazole and omeprazole are the preferred PPIs in terms of cost under MMP review. Pantoprazole has a favourable cost profile across both strengths relative to other PPIs.
6.9 National prescribing trends
The MMP recognises that clinical experience is a factor for prescribers when choosing a medication. In order to determine prescribing trends for the PPIs under review, the MMP performed analyses of the PCRS pharmacy claims.

Figure 4: Volume of claims reimbursed by the PCRS for PPIs on the GMS scheme September 2016-August 2017

Figure 4 illustrates the total volume of claims reimbursed by the PCRS for each of the PPIs on the GMS scheme from September 2016-August 2017. Esomeprazole represents 36% of the volume of claims reimbursed followed by lansoprazole, pantoprazole, omeprazole and rabeprazole.
Figure 5: Number of prescriptions for PPIs on the GMS scheme September 2016-August 2017

Figure 5 highlights that in the 12 month period from September 2016 to August 2017 inclusive, esomeprazole remained the most commonly prescribed PPI on the GMS scheme; in September 2016 there were 102,166 prescriptions for esomeprazole increasing to 110,682 prescriptions in August 2017. There was limited fluctuation in the number of prescriptions for other available PPIs.\(^9\)

Figure 6: Total expenditure for each PPI on the GMS scheme January 2015-August 2017

Figure 6 illustrates that from June 2015, total expenditure on esomeprazole started to increase following an initial reduction, while total expenditure on pantoprazole, lansoprazole and rabeprazole remained relatively static since May 2015, total expenditure on omeprazole
has decreased. Figure 6 also highlights the impact of reimbursement cost reductions that occurred in May 2015 and January 2017.

Table 8: Breakdown of total number of prescriptions for different strengths of PPIs on the GMS scheme from January 2017-September 2017

<table>
<thead>
<tr>
<th>PPI</th>
<th>Number of prescriptions*</th>
<th>Percentage of prescriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole 20 mg</td>
<td>252,044</td>
<td>26.5%</td>
</tr>
<tr>
<td>Esomeprazole 40 mg</td>
<td>699,143</td>
<td>73.5%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>951,187</strong></td>
<td></td>
</tr>
<tr>
<td>Lansoprazole 15 mg</td>
<td>81,872</td>
<td>13.1%</td>
</tr>
<tr>
<td>Lansoprazole 30 mg</td>
<td>542,671</td>
<td>86.9%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>624,543</strong></td>
<td></td>
</tr>
<tr>
<td>Omeprazole 10 mg</td>
<td>19,606</td>
<td>4.3%</td>
</tr>
<tr>
<td>Omeprazole 20 mg</td>
<td>285,148</td>
<td>62.4%</td>
</tr>
<tr>
<td>Omeprazole 40 mg</td>
<td>152,370</td>
<td>33.3%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>457,124</strong></td>
<td></td>
</tr>
<tr>
<td>Pantoprazole 20 mg</td>
<td>125,679</td>
<td>23.6%</td>
</tr>
<tr>
<td>Pantoprazole 40 mg</td>
<td>407,549</td>
<td>76.4%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>533,228</strong></td>
<td></td>
</tr>
<tr>
<td>Rabeprazole 10 mg</td>
<td>8,068</td>
<td>17.8%</td>
</tr>
<tr>
<td>Rabeprazole 20 mg</td>
<td>37,294</td>
<td>82.2%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>45,362</strong></td>
<td></td>
</tr>
</tbody>
</table>

*Cumulative number of prescriptions over the nine-month period.

Table 8 shows that the majority of prescriptions dispensed for esomeprazole, lansoprazole, pantoprazole and rabeprazole in the period from January 2017 to September 2017 were for the higher strength preparation. The majority of prescriptions dispensed for omeprazole were for the 20 mg strength.

The British National Formulary (2018) states that PPIs should be prescribed for appropriate indications at the lowest effective dose for the shortest period; the need for long-term treatment should be reviewed periodically.
7. Conclusion
Following a review of the available evidence and taking into account the following criteria: licensed therapeutic indications, clinical outcome data, international clinical guidelines, adverse drug reaction profiles, cautions and contraindications, drug interaction profiles, patient factors, cost and national prescribing trends, pantoprazole is recommended by the MMP as the preferred PPI for the treatment of GORD.

Based on the current evidence pantoprazole is the MMP’s preferred PPI for the treatment of GORD.

- Pantoprazole is licensed for the treatment of GORD.
- Pantoprazole has a favourable adverse drug reaction profile.
- Pantoprazole has a favourable drug interaction profile.
- Pantoprazole has a favourable cost profile across both available strengths.
8. Prescribing recommendations and deprescribing PPIs in GORD

8.1 Prescribing recommendations for PPIs in GORD

1. Before prescribing a PPI:
   - Patients should be offered lifestyle advice including advice on healthy eating, weight reduction where appropriate and smoking cessation. Patients should be advised to avoid known precipitants associated with their dyspepsia symptoms such as smoking, alcohol, coffee, chocolate and fatty foods. Raising the head of the bed and having their main meal well before going to bed can also help some patients.\textsuperscript{31}
   - A medication review should be carried out for possible causes of dyspepsia e.g. calcium channel blockers, nitrates, bisphosphonates, corticosteroids and NSAIDs. Consider stopping or changing the drug that is causing the symptoms if possible.\textsuperscript{31,36}

2. To minimise potential side-effects from PPIs, particularly associated with long-term use, prescribers are encouraged to only use PPIs where clearly indicated, at the lowest effective dose and for the minimum period of time.\textsuperscript{2,36}

3. PPI therapy should be reviewed after the initial course of treatment (4-8 weeks), and discontinued as appropriate. For patients prescribed PPIs long-term, a review should be undertaken at least annually.\textsuperscript{36,47}

4. Patients started on a PPI while in hospital should have its use reviewed on discharge to avoid inappropriate continuation where short-term prophylactic use was intended.\textsuperscript{36}

5. The use of long-term PPI therapy should be carefully considered in older people, those who are frail and those with complex co-morbidity.\textsuperscript{36}
8.2 Deprescribing PPIs in GORD

Deprescribing is an active review process that prompts prescribers to identify medications, which are not performing effectively in the risk-benefit trade-off and may in fact be causing harm to the patient.\textsuperscript{51}

There are different approaches to deprescribing PPIs outlined in other jurisdictions.\textsuperscript{31,52,53}

In the United Kingdom, NICE guidance (CG184) \textit{GORD and dyspepsia in adults: investigation and management} (2014), recommends that patients who need long-term management of dyspepsia symptoms should be encouraged to reduce their use of prescribed medication in a stepwise manner: by using the effective lowest dose, by trying “as-needed” use when appropriate, and by returning to self-treatment with antacid and/or alginate therapy (unless there is an underlying condition or co-medication that needs continuing treatment).\textsuperscript{31}

In Canada, Farrell et al. (2017) have developed a guideline for deprescribing proton pump inhibitors.\textsuperscript{52} The deprescribing algorithm developed by Farrell et al. (2017) is available at https://deprescribing.org/.

This guideline recommends that in adults who have completed a minimum of four weeks of PPI treatment for heartburn, mild to moderate GORD, oesophagitis, and whose symptoms have resolved, the PPI dose can be reduced or used “on-demand” or stopped.\textsuperscript{52}

“On-demand” use refers to daily intake of a PPI for a period of time sufficient to achieve resolution of a patient’s reflux symptoms. Following symptom resolution, the medication is discontinued until the patient’s symptoms return, at which point medication is again taken daily until the symptoms resolve. The recommendation to lower the dose or switch to on-demand PPI use was based on factors including a lack of evidence of serious harm from deprescribing, the evidence for the benefits of reducing inappropriate PPI use in terms of pill burden and reduced side-effects and the cost of inappropriate PPI use. The authors suggest that switching to a H2RA, antacid or alginate can be considered.\textsuperscript{52}

These recommendations do not apply to patients who have or have had Barrett’s oesophagus, severe oesophagitis grade C or D, or documented history of bleeding gastrointestinal ulcers.\textsuperscript{52}

If symptoms are well controlled after the initial 4-8 week course of a PPI, NPS Medicinewise recommend that treatment is titrated down to the lowest dose and frequency that controls symptoms, or stopped. The approach to stepping down a PPI should be individualised in consultation with the patient.

NPS offer different options for stepping down a PPI. These options are:

- Taking the standard dose less often (for example, alternate-day dosing)
- Reducing the PPI dose to a lower dose
- Or only taking PPIs “on demand” when a patient experiences symptoms.

A patient can move between these options, depending on their level of symptom control. If symptoms are well controlled, an attempt can be made to step down treatment further, or to stop. In the event that symptoms return, the patient should be stepped back to the PPI dose that provided adequate symptom control.

An example of an approach which could assist in deprescribing a PPI in GORD is illustrated in Figure 7 (unless there is an underlying condition or comedication that needs continuing treatment).
A patient may move between the different step-down options, depending on their level of symptom control.

Rebound acid hypersecretion resulting in an increase in reflux and dyspepsia symptoms, may occur during deprescribing of a PPI. To help limit the occurrence of rebound acid hypersecretion:

- The dose of the PPI could be reduced gradually as above
- Patients should be counselled about the risk of an increase in symptoms and advised to manage symptoms by using an antacid and/or alginate.

Figure 7: An example of deprescribing a PPI in GORD
Based on current evidence the MMP recommends that PPI therapy for GORD should be:

- Initiated for a short duration depending on the indication and careful consideration should be given before prescribing long-term
- Prescribed at the lowest effective dose
- Reviewed regularly with the aim of reducing or stopping PPI treatment if symptoms are well controlled, unless there is a recognised indication for long-term treatment.
References


49. PCRS database-total expenditure on PPIs (GMS only January 2015-August 2017). On file.

Bibliography
- Noram A, Hawkey CJ. What you need to know when you prescribe a proton pump inhibitor. Frontline Gastroenterol 2011; 2(4): 199-205.
Appendix A

Reflux oesophagitis (also called erosive oesophagitis) is defined endoscopically by visible breaks of the distal oesophageal mucosa. The severity of reflux oesophagitis is usually graded according to the Los Angeles classification, from grades A to D denoting increasing severity and extension of inflammation. Further information on the Los Angeles classification of reflux oesophagitis is provided in Table 9.

Table 9: Los Angeles classification of reflux oesophagitis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade A</td>
<td>One (or more) mucosal break(s) no longer than 5 mm, that does not extend between the tops of two mucosal folds</td>
</tr>
<tr>
<td>Grade B</td>
<td>One (or more) mucosal break(s) more than 5 mm long, that does not extend between the tops of two mucosal folds</td>
</tr>
<tr>
<td>Grade C</td>
<td>One (or more) mucosal break(s) that is continuous between the tops of two or more mucosal folds, but which involve(s) less than 75% of the oesophageal circumference</td>
</tr>
<tr>
<td>Grade D</td>
<td>One (or more) mucosal breaks(s) which involve(s) at least 75% of the oesophageal circumference</td>
</tr>
</tbody>
</table>

Note NICE defines severe reflux oesophagitis as Los Angeles classification C or D.