

Drugs for Dyspepsia

Dyspepsia is a complex of symptoms of the upper gastrointestinal (GI) tract. The NICE Clinical Guideline published in August 2004 defined dyspepsia as any symptom of the upper GI tract, present for 4 weeks or more, including upper abdominal pain or discomfort, heartburn, acid reflux, nausea or vomiting. Annually, dyspepsia occurs in 40% of the population, leads to GP consultation in 5% and referral for endoscopy in 1%.¹ In patients with symptoms severe enough to merit endoscopy, 40% will have non-ulcer dyspepsia (NUD), 40% will have gastro-oesophageal reflux disease (GORD) and 13% will have some form of ulcer detected.¹ Gastric and oesophageal cancers are seen in less than 3% of patients who have endoscopy and many of these cases are found during investigation for other symptoms rather than following primary care referral for dyspepsia.¹

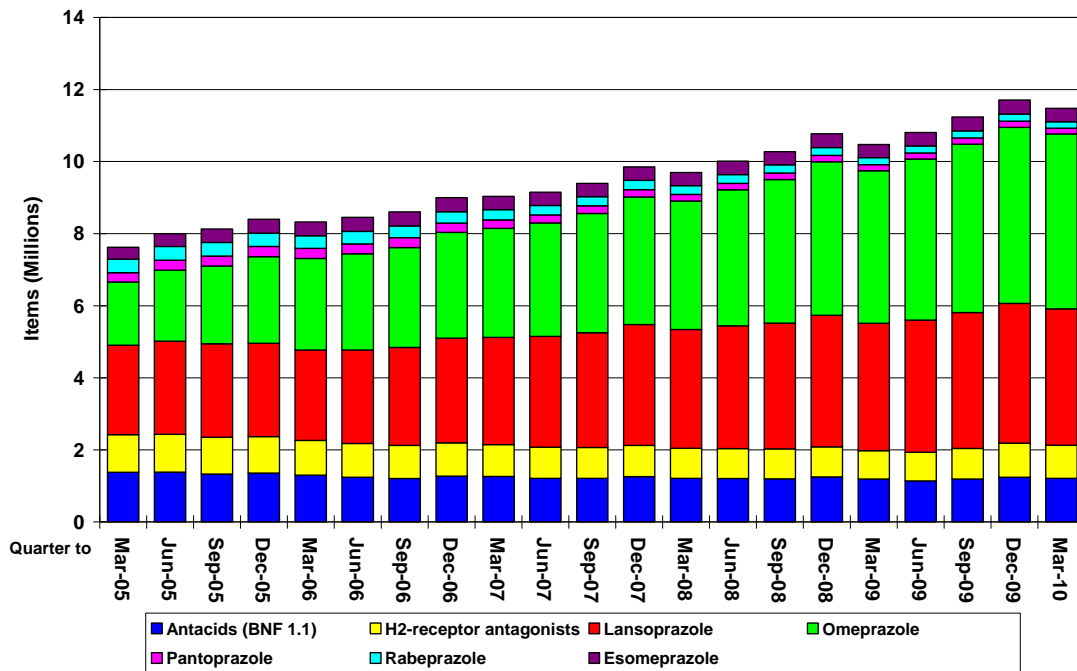
NICE referral guidance for endoscopy¹

- Same day specialist referral is indicated for patients presenting with dyspepsia with significant acute GI bleeding.
- The patient's medication should be reviewed for possible causes of dyspepsia. Drugs known to cause dyspepsia include corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), bisphosphonates, calcium antagonists, nitrates and theophyllines. In patients requiring referral, use of any NSAID should be suspended.
- Urgent specialist referral, to be seen within 2 weeks, is indicated for patients of any age with dyspepsia when presenting with any of the following alarm symptoms: chronic GI bleeding; progressive unintentional weight loss; progressive difficulty swallowing; persistent vomiting; iron-deficiency anaemia; epigastric mass; suspicious barium meal.
- Routine endoscopic investigation of patients of any age, presenting with dyspepsia and without alarm signs, is not necessary. However an urgent referral for endoscopy should be made in patients aged 55 years and older with unexplained and persistent recent-onset dyspepsia alone.

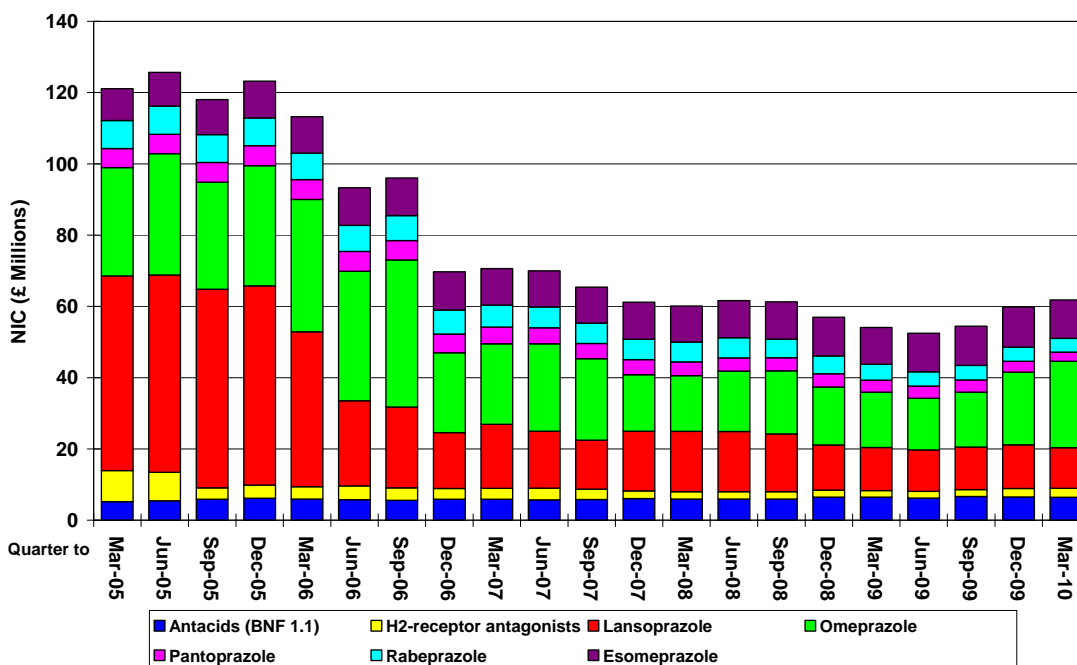
Over the last 5 years the prescribing of drugs used for dyspepsia has increased from 7.6 million items per quarter to 11.5 million items per quarter (Chart 1) whilst costs have nearly halved from £122 million to £62 million per quarter (Chart 2). The prescribing of proton pump inhibitors (PPIs) has increased by 79% over this time period and PPIs now (quarter to March 2010) account for 81% of items (9.3 million) and 86% of the cost (£52.9 million) of drugs used for dyspepsia. There are five PPIs currently approved for use within the UK for the management of dyspepsia with some formulations markedly more expensive than alternatives. There is no evidence that one PPI is more effective than another when compared at appropriate equivalent doses, and newer PPIs offer no advantage in clinical efficacy over established PPIs.² Increasing low cost PPI prescribing is one of the Better Care, Better Value indicators. This indicator measures the percentage of prescriptions written for omeprazole and lansoprazole (excluding Zoton FasTab® and Losec MUPS®) as a percentage of the total volume of PPI prescribing. If PCTs with below 92% use (achieved by the top quartile of trusts) of lower cost

PPIs increased this to over 92%, £22 million would be saved in a year (based on quarter 1 2009/10).³

Trends in Prescribing of Drugs for Dyspepsia in General Practice in England (Chart 1)



Trends in Spending on Drugs for Dyspepsia in General Practice in England (Chart 2)



NICE recommends the initial management of patients with dyspepsia to include lifestyle advice and treatment from a community pharmacist. Epidemiological studies show a weak link between obesity and GORD but no

clear association between other lifestyle factors and dyspepsia. However lifestyle advice is still important because healthy eating, weight reduction and smoking cessation offer general health benefits. Patients should be advised to avoid precipitants of dyspepsia e.g. bending, fatty or spicy foods. Obesity, smoking, alcohol, coffee and chocolate can cause reflux symptoms because they reduce lower oesophageal sphincter pressure. Raising the head of the bed may help patients who suffer reflux episodes when lying flat.^{1,2}

The interventions recommended in the NICE guideline on dyspepsia are listed below.¹ One common element of care if symptoms return is to offer PPI therapy stepped down to the lowest dose required to control symptoms and to discuss the possibility of using 'on demand' treatment with patients to manage their symptoms.

Uninvestigated dyspepsia – There are two options, either full dose PPI therapy for one month or testing for and treating *Helicobacter pylori* where positive. There is currently insufficient evidence to support which should be offered first but a 2 week washout period following PPI use is necessary before testing for *H pylori* with a breath test or stool antigen test. For patients who test positive a 7 day, twice daily course of treatment consisting of a full-dose PPI with either metronidazole 400mg and clarithromycin 250mg or amoxicillin 1g and clarithromycin 500mg is recommended. Eradication is effective in 80-85% of patients. Retesting for *H pylori* should be performed using a carbon-13 urea breath test as there is currently insufficient evidence to recommend the stool antigen test as a test of eradication. Patients requiring long-term management of symptoms should be offered an annual review of their condition.

GORD – NICE refer to GORD as endoscopically-determined oesphagitis or endoscopy negative reflux disease and patients with uninvestigated 'reflux-like' symptoms should be managed as patients with uninvestigated dyspepsia. Patients should be offered a full dose PPI for one to two months. For recurring symptoms after initial treatment, a PPI at the lowest dose to control symptoms should be offered with a limited number of repeat prescriptions. For patients who have an inadequate response to a PPI the options include double dose PPI, H₂ receptor antagonists (H₂RA) or prokinetic therapy. Patients who have had dilatation of an oesophageal stricture should remain on long-term full dose PPI therapy.

NUD – The management of endoscopically-determined NUD involves initial treatment for *H pylori* if present, followed by symptomatic management and periodic monitoring. Patients testing positive for *H pylori* should be offered eradication therapy as described above. If *H pylori* has been excluded or treated and symptoms persist, the patient should be offered either a low dose PPI or H₂RA for one month. Antacid therapy is not effective for reducing symptoms of NUD.

Peptic Ulcer Disease – 95% of duodenal and 70% of gastric ulcers are associated with *H pylori*.⁴ NICE recommend eradication therapy to *H pylori*-positive patients who have peptic ulcer disease. Patients with a gastric ulcer and *H pylori* should receive a repeat endoscopy and retesting for *H pylori* 6-8 weeks after beginning treatment. Where possible, in patients with a diagnosed peptic ulcer and using NSAIDs, the use of NSAIDs should be stopped. Full dose PPI therapy for two months is recommended and if *H pylori* is present

subsequently offer eradication therapy. For those patients who require to take an NSAID after a peptic ulcer has healed, the continuing need for NSAID use should be reviewed at least 6 monthly and patients should be offered a trial of use on a limited, 'as required' basis. Dose reduction, substitution of the NSAID with paracetamol, an alternative analgesic or low dose ibuprofen, 1.2g daily, should also be considered. Where NSAID continuation is necessary gastric protection or substitution to a Cox-2 selective NSAID should be considered for high risk patients (previous ulceration). If there is an inadequate response to a PPI, H₂RA therapy should be offered.

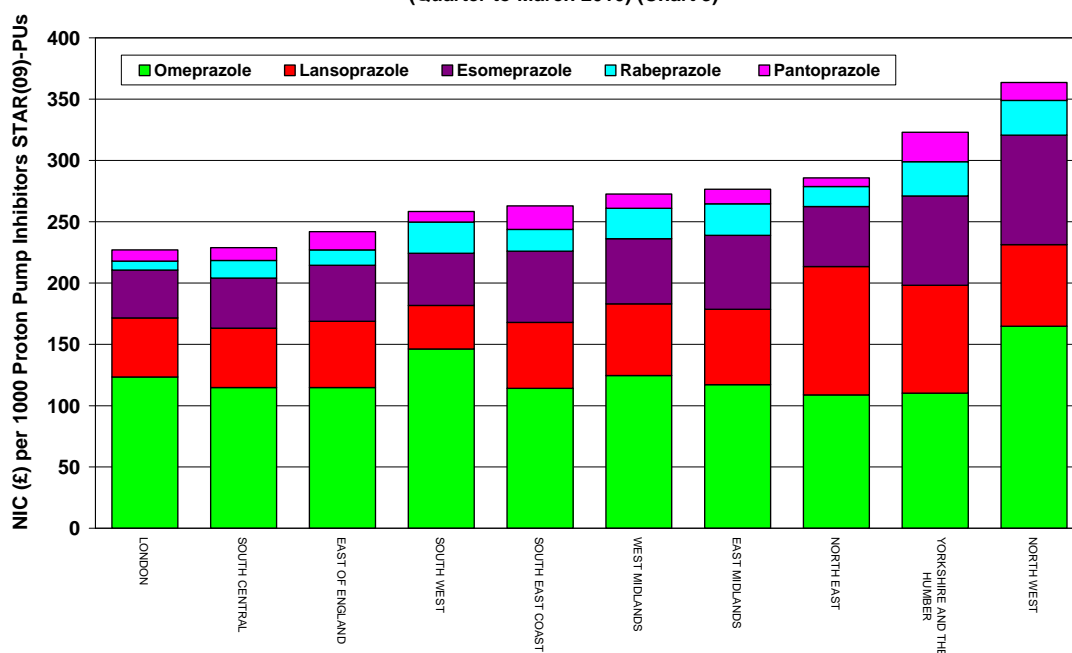
A Cochrane review looked at the effectiveness of common interventions for the prevention of NSAID-induced upper GI toxicity. The results of this meta-analysis demonstrated that misoprostol, PPIs and double dose H₂RAs are effective at reducing the risk of both gastric and duodenal NSAID-induced ulcers. In high risk patients the use of a traditional NSAID plus a PPI appears equivalent to a Cox-2 inhibitor alone whilst the most effective strategy in high risk GI patients appears to be the combination of a Cox-2 inhibitor plus PPI.⁵

Over the last 5 years prescribing and spending on NSAIDs fell by 12% and 45% respectively (to 4 million items, £22.3 million), quarter to March 2010. In this time prescribing of Cox-2 inhibitors decreased by 39% to 510,000 items, their cost falling by 56% to £7.5 million.

There has been a lot of recently published data on a possible interaction between PPIs and clopidogrel with a consequent possible loss of antiplatelet protection. The MHRA have reviewed all the available evidence and recommend that concomitant use of clopidogrel and omeprazole or esomeprazole should be avoided unless essential. The PPI of choice therefore in combination with clopidogrel is lansoprazole.⁶

A recent MeReC Rapid Review⁷ highlighted a group of US studies providing evidence around two potential harms associated with PPI use. One study found that hospital inpatients taking daily PPIs were over 70% more likely to develop *Clostridium difficile* infection than non-users and the second found that people who already had *C difficile* infection and were treated with PPIs had a more than 40% increased relative risk of recurrence of infection. The third study along with earlier evidence has prompted the FDA to update PPI product information to warn of a possible increased risk of hip, wrist and spine fractures, especially in long-term users of PPIs and when used at high doses. The widespread use of PPIs means that any potential safety issues should be evaluated in the context of the individual. Health professionals should carefully assess the necessity for continued PPI prescribing in the routine medication review and stop the PPI if at all possible. If this is not appropriate, thought should be given to reducing the dose and/or switching to 'as required' use.

Variation Between Strategic Health Authorities in Spending on Proton Pump Inhibitors
(Quarter to March 2010) (Chart 3)



Prescribing Data

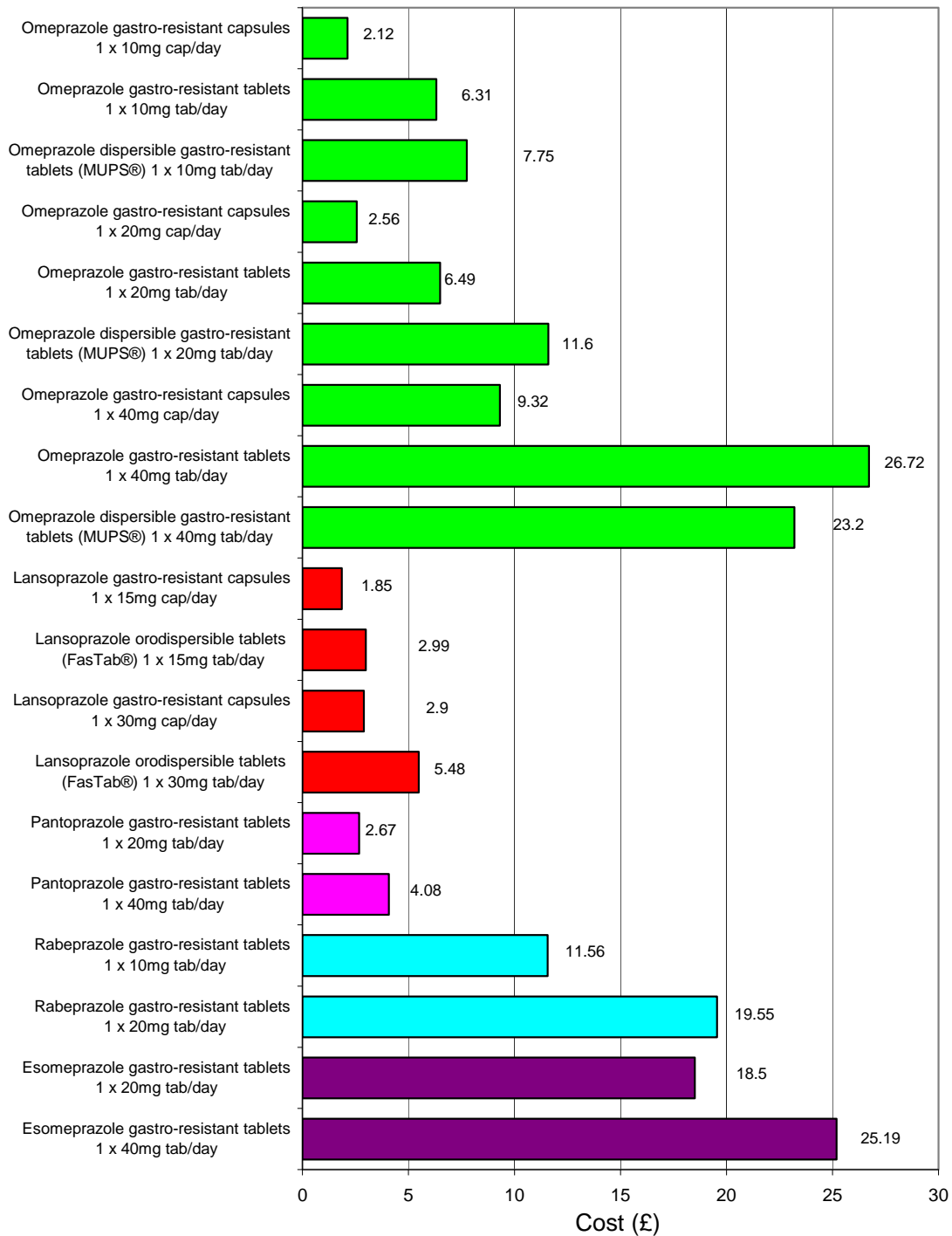
(Reporting quarter = January-March 2010, Index quarter = January-March 2005)

Omeprazole is the most commonly prescribed PPI, 4.9 million items costing £24.2million, followed by lansoprazole with 3.8 million items and a cost of £11.4 million (quarter to March 2010). Prescribing of omeprazole and lansoprazole has risen by 177% and 52% respectively, whereas cost has fallen by 20% and 79% respectively. Esomeprazole prescribing has increased (by 11%) to nearly 371,000 items per quarter with costs rising 20% to £10.7 million. Rabeprazole and pantoprazole account for 177,000 items and 164,000 items respectively, with costs of each falling by more than 50% to £3.9 million and £2.6 million per quarter. Chart 3 shows the variation in PPI spending between SHAs.

Prescribing of H₂RAs has fallen by 12% (to 917,000 items) during the last 5 years, with cost decreasing by 71% (to £2.5 million). Ranitidine is the most commonly prescribed, accounting for 92% of H₂RA items (846,000) and 71% of cost (£1.8 million), quarter to March 2010. Cimetidine accounts for 5% of H₂RA items (44,000) and 15% of the cost (£371,000).

Items for 'drugs for dyspepsia and GORD' (BNF section 1.1) have decreased by 12% over the last 5 years to 1.2 million items, with cost increasing by 23% to £6.4 million, quarter to March 2010. Compound alginates account for 93% of items (1.1 million) and 87% of cost (£5.6 million) for this group of drugs. Prescribing of antacids and simeticone has decreased by a third to 86,000 items and their cost has doubled to £823,000 in the quarter to March 2010.

Cost for 28 Days (£)



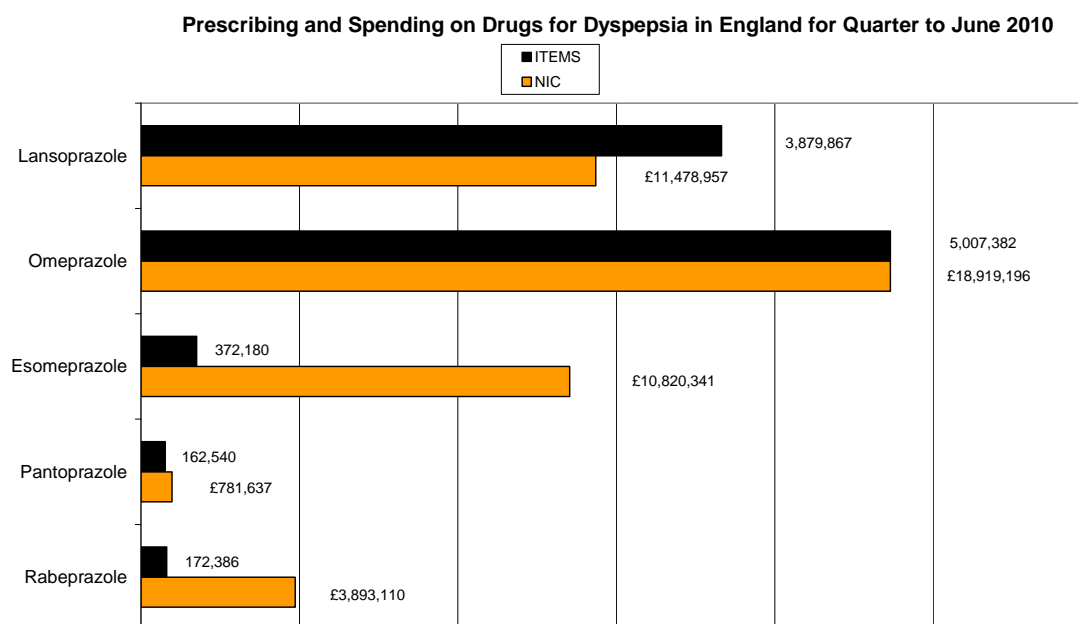
Prices based on Drug Tariff August 2010 and the NHS dictionary of medicines and devices.

1. NICE. Dyspepsia: Managing dyspepsia in adults in primary care. August 2004 (updated June 2005)
2. MeReC Bulletin Volume 16 Number 3 (March 2006)
3. NHS Better Care, Better Value Indicators. www.productivity.nhs.uk

4. Ford, A.C., Delaney, B.C., Forman, D. and Moayyedi, P. Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients. Cochrane Database of Systematic Reviews 2006 issue 2
5. Rostron A et al. Prevention of NSAID-induced gastro-duodenal ulcers. Cochrane Database of Systematic Reviews 2002 issue 4.
6. Drug Safety Update, MHRA. Volume 3, Issue 9, April 2010
7. MeReC Rapid Review, Increased risk of C difficile infections and of fractures: two more good reasons to review PPI prescribing, 3 June 2010.

Summary

- Urgent referral for endoscopic examination is indicated in all patients with alarm symptoms and those aged 55 years and older with unexplained and persistent recent-onset dyspepsia alone.
- There is no evidence that one PPI is more effective than another when compared at appropriate equivalent doses. Low cost PPI prescribing should be encouraged.
- Continued PPI prescribing should be assessed in the routine medication review and stopped if possible. If stopping is not appropriate, consider reducing the dose and/or switching to 'as required' use.



| | Quarter to June 2010 | |
|--------------------------------------|----------------------|--------------|
| | National | |
| | ITEMS/1000 PUs | NIC/1000 PUs |
| Antacids and simeticone | 1.13 | £12.46 |
| Compound alginates etc | 14.99 | £78.17 |
| H ₂ -receptor antagonists | 12.79 | £45.86 |
| Proton pump inhibitors | 131.72 | £630.11 |