Guidelines for the Prescribing of Proton Pump Inhibitors (PPIs) in Adults

Summary
These guidelines have been produced to promote effective use of PPIs across the Leicestershire community. It is recommended that:

- A PPI is only initiated where indicated
- Treatment is regularly reviewed and stepped down
- Lansoprazole capsules are the first line choice
- Esomeprazole should be reserved for GORD patients who have not responded to an adequate dose for an adequate time of lansoprazole (alternative omeprazole)

**Lansoprazole capsules are the recommended first line choice**
*(Alternative Omeprazole caps)*

Endorsed by the Leicestershire Medicines Strategy Group
August 2014
Original guidance November 2006
Next review due: April 2017

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**Sub-group:** See page 5
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1. Introduction

The following guidelines describe treatment pathways for dyspepsia related symptoms, including gastric ulcers and gastro-oesophageal reflux disease. The pathways are based on the clinical guidelines published by NICE in August 2004 and have been updated to reflect new guidance on endoscopy referrals. They include recommendations for monitoring and follow-up of patients diagnosed with dyspepsia.

2. Background

The guidelines have been produced in order to promote effective use of proton pump inhibitors (PPIs) and H2 Antagonists (H2As). This is particularly important against growing epidemiological evidence that PPI use is associated with an increased risk of Clostridium difficile infection, both in hospitals and in the community.

The guidelines have been produced by a sub group of the Leicestershire Medicines Strategy Group (LMSG) and are fully supported by UHL gastroenterologists and the UHL Infection Control Group.

The aims of the guidelines are to ensure PPI use is limited to situations where there is clear evidence of benefit.

3. Key points

3.1 Which PPI to use

- **Lansoprazole is the PPI of choice** and should always be considered the first line option.

- **For patients intolerant of lansoprazole, generic omeprazole** may be used as an alternative (*this guideline is for adults only but please note that lansoprazole is not licensed for use in paediatrics*)

- **For patients where gelatine content is a problem**, Pantoprazole tablets are now off-patent and are a cost-effective choice in this group of patients

- Esomeprazole is the PPI of choice in severe cases, where clinicians may consider that a PPI with greater acid suppression is required, either as a second line option or in exceptional cases, when recommended by a specialist, as first line therapy.

3.2 Indications for PPIs

- PPIs should only be prescribed as part of a treatment strategy described in the care pathways contained in this policy or as detailed below

- **Before a PPI is prescribed, clinicians should consider lifestyle changes and review medications for possible causes of dyspepsia.**

- PPI prescribing outside of these pathways is not supported unless recommended by a specialist such as a gastroenterologist, GI surgeon or ENT consultant.
Use with NSAIDS/COX-2 inhibitors

- Consider if NSAID /COX-2 inhibitor is needed at all (especially if on Aspirin)

- If needed then consider prescribing a low dose PPI when any of the following risk factors are present:

  - >65 years old.
  - Previous peptic ulcer disease (gastro or duodenal ulcers, GI bleeding or GI perforation)
  - Serious co-morbidities e.g. CVD, diabetes, renal or hepatic impairment.
  - Concomitant use of medications known to increase the likelihood of upper GI adverse events: (e.g. Anticoagulants, Aspirin [even low-dose], Corticosteroids, and Antidepressants (Selective Serotonin Reuptake inhibitors, Venlafaxine).
  - Requirement for prolonged NSAID use including (1) people with OA or RA of any age (2) Chronic low back pain and are over 45 years.

- Ensure ongoing screening of risk factors particularly where there is prolonged use of NSAID/COX-2 inhibitor.

- Ensure review and discontinue use of PPI if NSAID/COX-2 inhibitor is no longer prescribed.

- If in doubt refer to NICE guidance.

PPIs are recommended in the care pathways for patients (refer to care pathways for full details):

- as part of a H.Pylori eradication regimen
- with gastric and duodenal ulcers for 1-2 months post H.Pylori eradication regimen
- with GORD as a 6-8 week healing regimen
- with dyspepsia for 1 month duration only then review.
- with gastric and duodenal ulcers for 1-2 months duration only then review

PPIs are recommended for patients receiving aspirin who have serious gastrointestinal side effects. Although PPIs have an association with increased risk of Clostridium Difficile (odds ratio 1.9 to 3.5) the alternative option for gastroprotection, an H2 antagonist, will not reduce the risk of a gastrointestinal bleed to the same extent as a PPI when used with aspirin. Choice of gastroprotection needs to be made on an individual patient basis taking into account patient risk factors for C Diff (elderly, infirm inpatients.
and those prescribed antibiotics), risk of gastric bleeding and current incidence of C Diff in the community.

3.3. **Inappropriate uses of PPIs**

The use of PPIs for prophylaxis during steroid use is NOT recommended unless there is also concomitant use of NSAIDs or aspirin.

3.4. **Clopidogrel and PPI interaction**

The MHRA in July 2009 advised that concomitant use of a PPI with clopidogrel should be avoided unless considered essential. However, updated advice continues to support an interaction between omeprazole and possible esomeprazole, but current evidence does not support extending this advice to other PPIs.

There is a theoretical problem of potential interactions with omeprazole and clopidogrel, decreasing the effectiveness of clopidogrel, but this does not seem to translate into clinical events. Studies suggesting cardiovascular harm were all observational and retrospective, and could show bias (i.e. an increased use of PPIs in sicker patients).

The only prospective trial published in the NEJM in November 2010, was the COGENT trial, and it showed no demonstrable cardiovascular harm of omeprazole with clopidogrel and aspirin. It did show a gastrointestinal benefit.

Based on the evidence, if a patient is deemed to be at significant risk for potential GI harm, a PPI seems reasonable.

3.5 **Hypomagnesaemia with long-term use**

Prolonged use of proton pump inhibitors (PPIs) has been associated with hypomagnesaemia. Local specialist advice is that clinicians should be aware of this but there is no need for specific blood monitoring. Advice from MHRA – April 2012

Patients who will take a PPI concomitantly with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics) may be at particular risk.

3.6 **Epidemiological evidence of increased risk of fractures in long-term use**

There is recent epidemiological evidence of an increased risk of fracture with long-term use of PPIs. Patients at risk of osteoporosis should be treated according to current clinical guidelines to ensure they have an adequate intake of vitamin D and calcium. Advice from MHRA – April 2012

4. **References:**

2. Osteoarthritis – Care and management in adults NICE Feb 2014 [www.nice.org.uk/guidance/cg177](www.nice.org.uk/guidance/cg177)
3. Early management of persistent non-specific low back pain NICE May 2009
   www.nice.org.uk/guidance/cg88
4. Rheumatoid arthritis: The management of rheumatoid arthritis in adults NICE Feb 2009
   www.nice.org.uk/guidance/cg79
5. Drug Safety Update Vol 2 Issue 12 July 2009 from MHRA and CHM
6. Drug Safety Update Vol 3 Issue 9 April 2010 from MHRA and CHM

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6. Flowchart of referral criteria and subsequent management

1. Immediate referral is indicated for significant acute gastrointestinal bleeding.
   Consider the possibility of cardiac or biliary disease as part of the differential diagnosis.

   **Urgent specialist referral** for endoscopic investigation is indicated for patients of any age with dyspepsia when presenting with any of the following: chronic gastrointestinal bleeding, progressive unintentional weight loss, progressive difficulty swallowing, persistent vomiting, iron deficiency anaemia, epigastric mass or suspicious barium meal.

   Routine endoscopic investigation of patients of any age, presenting with dyspepsia and without alarm signs, is not necessary. However, in patients aged 55 years and older with unexplained** and persistent** recent-onset dyspepsia alone, an urgent referral for endoscopy should be made.

   Consider managing previously investigated patients without new alarm signs according to previous endoscopic findings.

2. Review medications for possible causes of dyspepsia, for example, calcium antagonists, nitrates, theophyllines, bisphosphonates, steroids and NSAIDs. Patients undergoing endoscopy should be free from medication with either a proton pump inhibitor (PPI) or an H\textsubscript{2} receptor (H\textsubscript{2}RA) for a minimum of 2 weeks.

   * The Guideline Development Group considered that ‘urgent’ meant being seen within 2 weeks.

   ** In the referral guidelines for suspected cancer (NICE Clinical Guideline no. 27), ‘unexplained’ is defined as ‘a symptom(s) and/or sign(s) that has not led to a diagnosis being made by the primary care professional after initial assessment of the history, examination and primary care investigations (if any)’.

   In the context of this recommendation, the primary care professional should confirm that the dyspepsia is new rather than a recurrent episode and exclude common precipitants of dyspepsia such as ingestion of NSAIDs.

   ‘Persistent’ as used in the recommendations in the referral guidelines refers to the continuation of specified symptoms and/or signs beyond a period that would normally be associated with self-limiting problems. The precise period will vary depending on the severity of symptoms and associated features, as assessed by the healthcare professional. In many cases, the upper limit the professional will permit symptoms and/or signs to persist before initiating referral will be 4–6 weeks.

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<th>Date</th>
<th>New version</th>
<th>Reason</th>
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<tr>
<td>Updated 2015 – 03 DSud</td>
<td>Version 1.1</td>
<td>Update to part 3.2 to include NICE guidance on the use of PPIs with NSAIDs/COX-2 inhibitors</td>
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7. **Management flowchart for patients with non-ulcer dyspepsia**

- **Non-ulcer dyspepsia**

  - **H. pylori test result**
    - Positive
    - **Eradication therapy**¹
      - No response or relapse
    - Negative
      - Lansoprazole 15mg od or ranitidine 150mg bd for 1 month, then as required²
  - Return to self care
  - **Review³**

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1. Use a lansoprazole 30mg bd, clarithromycin 500mg bd, amoxicillin 1g bd regimen or a lansoprazole 30mg bd, clarithromycin 250mg bd, metronidazole 400mg bd regimen. Do not re-test unless there is a strong clinical need.
2. Offer low-dose treatment, possibly on an as-required basis, with a limited number of repeat prescriptions.
3. In some patients with an inadequate response to therapy or new emergent symptoms it may become appropriate to refer to a specialist for a second opinion. Emphasise the benign nature of dyspepsia. Review long-term patient care at least annually to discuss medication and symptoms.
4. Domperidone should no longer be recommended (see Appendix 1)
8. Management flowchart for patients with uninvestigated dyspepsia

1) **Review medications** for possible causes of dyspepsia, for example, calcium antagonists, nitrates, theophyllines, bisphosphonates, steroids and NSAIDs.

2) **Offer lifestyle advice**, including advice on healthy eating, weight reduction and smoking cessation, promoting continued use of antacid/alginates.

3) There is currently inadequate evidence to guide whether full-dose PPI for 1 month or *H. pylori* test and treat should be offered first. Either treatment may be tried first with the other being offered if symptoms persist or return.

4) **Detection**: use carbo-13 urea breath test, stool antigen test or, when performance has been validated, laboratory-based serology. Eradication: lansoprazole 30mg bd, clarithromycin 500mg bd, amoxicillin 1g bd regimen or a lansoprazole 30mg bd, clarithromycin 250mg bd, metronidazole 400mg bd regimen. Do not re-test even if dyspepsia remains unless there is a strong clinical need.

5) Offer low-dose treatment with a limited number of repeat prescriptions. Discuss the use of treatment on an as-required basis to help patients manage their own symptoms.

6) In some patients with an inadequate response to therapy it may become appropriate to refer to a specialist for a second opinion. Emphasise the benign nature of dyspepsia. Review long-term patient care at least annually to discuss medication and symptoms.

7) Domperidone should no longer be recommended for dyspepsia (see Appendix 1).
9. Leicestershire Integrated Care Pathway GORD Process Map

Alternative Diagnosis

New dyspepsia patients from any source

>1 episodes of Heartburn/week

Diagnosis (GP)
Consider H.Pylori test

Refer to locally commissioned H Pylori testing service (if available)

GORD–Management Choice (GP)

* Alarm Symptoms

No Alarm symptoms

Uncomplicated GORD (GP)

Appropriate PPI
Healing treatment (GP)
6-8 weeks
Lansoprazole 30mg od

Primary Care Review

Referral to Hospital for appropriate Investigation
E.g. Endoscopy etc.

Consider an alginate

Reduce to maintenance dose:
Lansoprazole 15mg od prn*
(consider stopping)

Switch to Omeprazole if unable to tolerate lansoprazole

Consider
a) Esomeprazole 40mg od
b) Split dose e.g. Esomeprazole 20mg bd **
(review monthly)

For best results PPI’s should be taken 30-60 minutes before food

*See below for explanation
**Unlicensed dose

SEVERITY OF GORD
- 2-5 episodes heartburn mild/short lasting/week = MILD
- >5 episodes/week heartburn, but not every day = MODERATE
- Daily episodes heartburn (at least one of: very frequent, long lasting or very painful) = SEVERE

Alternative Diagnosis

Updated to include NICE guidance on the use of PPIs with NSAIDs/Cox-2 inhibitors

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Complicated GORD e.g., Barrett’s/ Stricture
Usually full dose
PPI or higher
**Review Options**

- Failure of response to current PPI therapy – consider trial of **more potent PPI** eg esomeprazole and/or referral for endoscopy
- Step down therapy if symptoms are controlled

**Alarm symptoms**

- Unintentional weight loss =>3kg
- Gastrointestinal Bleeding
- Previous Gastric Surgery
- Epigastric Mass
- Previous Gastric Ulcer
- Unexplained Iron Deficiency Anaemia
- Dysphagia and Odynophagia
- Persistent continuous vomiting
- Suspicious barium meal
10. Management flowchart for patients with duodenal ulcer

[Diagram showing management flowchart for patients with duodenal ulcer]

Date
Updated 2015 – 03 DSud

New version
Version 1.1

Reason
Update to part 3.2 to include NICE guidance on the use of PPIs with NSAIDs/COX-2 inhibitors
1 If NSAID continuation is necessary, after ulcer healing offer long-term PPI. Review cardiovascular risk for individual patients carefully.
2 Use a carbon-13 urea breath test, stool antigen test or, when performance has been validated, laboratory based serology.
3 Use a lansoprazole 30mg bd, clarithromycin 500mg bd, amoxicillin 1g bd regimen or a lansoprazole 30mg bd, clarithromycin 250mg bd, metronidazole 400mg bd regimen.
4 Use a carbon-13 urea breath test.
5 Follow guidance found in the British National Formulary for selecting second-line therapies or consider specialist referral.
6 Offer low-dose treatment, possibly on an as-required basis, with a limited number of repeat prescriptions.
7 Consider: non-adherence with treatment, possible malignancy, failure to detect H. pylori infection due to recent PPI or antibiotic ingestion, inadequate testing or simple misclassification; surreptitious or inadvertent NSAID or aspirin use; ulceration due to ingestion of other drugs; Zollinger Ellison syndrome, Crohn’s disease.
8 Review care annually, to discuss symptoms, promote stepwise withdrawal of therapy when appropriate and provide lifestyle advice.
11. **Management flowchart for patients with gastric ulcer**

![Management flowchart for patients with gastric ulcer]

- **Gastric ulcer**
  - **Stop NSAIDs, if used**
    - **Eradication therapy**
      - **H. pylori positive, ulcer not associated with NSAID use**
        - **Return to self care**
      - **H. pylori negative**
        - **Ulcer not healed, H. pylori negative**
          - **Refer to specialist secondary care**
        - **Ulcer healed, H. pylori positive**
          - **Periodic Review**
            - **Lansoprazole 15mg od**
              - **Healed**
            - **Endoscopy**
              - **Refer to specialist secondary care**
        - **Ulcer healed, H. pylori negative**
          - **Lansoprazole 30mg od for 1 or 2 months**
            - **H. pylori negative**
              - **Endoscopy**
                - **Refer to specialist secondary care**
            - **H. pylori positive**
              - **Eradication therapy**
                - **H. pylori positive, ulcer not associated with NSAID use**
                  - **Endoscopy and H. pylori test**
                    - **Ulcer not healed, H. pylori negative**
                      - **Refer to specialist secondary care**
                    - **Ulcer healed, H. pylori positive**
                      - **Periodic Review**
                        - **Lansoprazole 15mg od**
                          - **Healed**
                        - **Endoscopy**
                          - **Refer to specialist secondary care**

**Date**
Updated 2015 – 03 DSud

**New version**
Version 1.1

**Reason**
Update to part 3.2 to include NICE guidance on the use of PPIs with NSAIDs/COX-2 inhibitors
## 12. Appendix 1

### Summary of Cardiac risks with Domperidone

**Domperidone: risks of cardiac side effects - indication restricted to nausea and vomiting, new contraindications, and reduced dose and duration of use: MHRA**

- Domperidone is associated with a small increased risk of serious cardiac side effects.
- Its use is now restricted to the relief of nausea and vomiting and the dosage and duration of use have been reduced to 10mg three times daily orally (30mg twice daily rectally) for one week.
- It should no longer be used for the treatment of bloating and heartburn.
- Patients should be advised to seek prompt medical attention if symptoms such as syncope or tachyarrhythmia appear during treatment.
- Domperidone should be avoided in patients who are taking concomitant medication known to cause QT prolongation (such as ketoconazole and erythromycin).
- Non-prescription domperidone products - sold under the supervision of a pharmacist (P legal status) - should not be supplied to patients with contraindications as specified by the MHRA.
13. Flowchart to Guide Pharmacist Management of Dyspepsia