PROPOSAL FOR THE INCLUSION OF A PROTON PUMP INHIBITOR FOR THE TREATMENT OF DYSPEPSIA IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES

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1. **Summary statement of the proposal for inclusion, change or deletion**

This is a proposal to add omeprazole with a square box as the prototype proton pump inhibitor for gastric acid suppression. Proton pump inhibitors are the recommended drugs in all the regimens for H. pylori eradication to cure peptic ulcer disease. The proton pump inhibitors are as or more effective than the H2 blockers and aluminum hydroxide gel for all uses in which control of gastric acid secretion is desired. Because this class of drugs is needed for H. pylori eradication, drugs in this class are essential. The H2 blockers, ranitidine being the prototype, are no longer essential if omeprazole with square box is added to the Model List of Essential Medicines.

Aluminum hydroxide gel is an older and less effective drug for controlling gastric acid. It is no longer essential for control of gastric acid. It was used in the past for decreasing the absorption of phosphate. Some patients needing phosphate binders would absorb some of the aluminum causing encephalopathy or bone disease. Calcium carbonate, other calcium salts, and other medicines are safer phosphate binders than aluminum hydroxide gel. Thus, even for this indication, aluminum hydroxide gel is no longer essential.

2. **Name of the focal point in WHO submitting or supporting the application**

Not known

3. **Name of the organization(s) consulted and/or supporting the application**

Clinton Foundation

4. **International Nonproprietary Name (INN, generic name) of the medicine**

Omeprazole. The inclusion of omeprazole in the Model List of Essential Medicines is recommended in the category antacids and other antiulcer medicines, in place of ranitidine and aluminum hydroxide/

5. **Formulation proposed for inclusion; including adult and paediatric (if appropriate)**

Omeprazole delayed release capsules: 10, 20, 40mg
Omeprazole oral suspension: 20, 40 mg
6. International availability

As an example, a comprehensive listing for one proton pump inhibitor, generic omeprazole, is appended to this submission (Appendix 1), considering its worldwide availability, its evidence base (number of studies and their sample size), the easier access to provisional prices and the interest of several generic firms in producing it.

Patent expiries for omeprazole more than five years ago in developed-country markets led to the registration and production of generic omeprazole by numerous global manufacturers. Other generic proton pump inhibitors are similarly available worldwide, though documenting all available sources would have been needlessly work-intensive. For simplification, we reference omeprazole as an example of a proton pump inhibitor (e.g. national registry text for formulary) but different nations will have varying access and production capabilities of all generic proton pump inhibitors.

For other generic proton pump inhibitors, their choice will depend on their prices and availability at local (national) level.

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Listing is requested on the Model List of Essential Medicines as an example of a therapeutic group, proton pump inhibitors.

8. Information supporting the public health relevance

Proton pump inhibitors are used in the treatment of a number of conditions. They are therapeutic mainstays in the treatment of gastro-esophageal reflux disorder (GERD), peptic ulcer disease (PUD), dyspepsia, and mucosa-associated lymphoid tissue (MALT) lymphomas. As a component of first-line triple therapy for the eradication of Helicobacter pylori infection, they may also prevent gastric adenocarcinomas. The global significance of each of these clinical entities will be discussed here.

GERD:

Assessment of the global prevalence is complicated by the lack of a standard clinical definition for GERD and significant variation in symptom severity among patients with reflux. GERD is a common target for PPI therapy in developed nations, with a prevalence of approximately 10-20%, according to a 2005 systematic review of epidemiological data (Dent et al., 2005). In the same review, prevalence in Asia was observed to be 3-5%. According to 2004 review, there are no reliable data regarding prevalence in African or South American nations (Kang, 2004).
**H. pylori Infection and Sequelae (Dyspepsia, Peptic Ulcer Disease, Gastric Adenocarcinoma and MALT Lymphoma):**

**H. pylori infection**

*H. pylori* is exceedingly common throughout the world, but shows significant geographic differences in prevalence. As estimated by seroprevalence of antibodies to *H. pylori*, prevalence ranges from 13% in Russia to 52.5% in Japan to more than 80% in many African mainland populations (Bruce and Maaroos, 2008). Prevalence tends to be higher in developing nations. In industrialized nations the number is lower but still significant, with 20-50% of individuals infected (Makola et al., 2007). Infection is thought to be acquired orally, during childhood. While children may clear the bacteria spontaneously, *H. pylori* usually persists as a chronic infection (Suerbaum and Michetti, 2002).

Sanitation plays an important role in *H. pylori* infection. It has been shown that areas with cleaner water have lower incidence of *H. pylori* infection, though water purification cannot eliminate the bacteria (Bruce and Maaroos, 2008). In the United States, despite an increasing prevalence of *H. pylori*, incidence is declining substantially. Studies using mathematical modeling have attributed this decline in incidence to improved sanitation (Rupnow et al., 2000).

*H. pylori* infection may have numerous manifestations and sequelae. These are discussed below.

**Gastritis**

According to histological evidence from gathered from asymptomatic individuals in numerous studies, *H. pylori* infection causes chronic gastritis in virtually all infected individuals (Dooley et al, 1989). 10-20% of these individuals will have symptomatic gastritis (Makola et al., 2007).

**PUD**

Approximately 10% of individuals infected with *H. pylori* worldwide will develop peptic ulcer disease. This figure, however, varies geographically; lifetime risk among *H. pylori* infected individuals is only 3% in the United States, while it is as high as 25% in Japan. This variation is thought to result from different bacterial strains’ pathogenic characteristics. *H. pylori* infection accounts for approximately 90% of all duodenal and 60% of all gastric ulcers (Delaney et al., 2005). *H. pylori* eradication with a PPI- is the first-line treatment for peptic ulcer disease, with acid suppression necessary for ulcer healing.

**Gastric Cancer**

The World Health Organization’s International Agency for Research on Cancer has classified *H. pylori* as a class I human carcinogen. Evidence from animal models supports a direct role for *H. pylori* infection in the development of gastric carcinoma (Marshall and
Winston, 2005). *H. pylori*, by inducing chronic inflammation in the gastric mucosa, may lead to intestinal metaplasia of the gastric mucosa. Metaplastic areas can become dysplastic, with dysplastic lesions progressing to malignancies over time.

Gastric cancer is the second most common cause of cancer-related death in the world, second only to lung cancer. There are approximately 800,000 gastric cancer deaths per year worldwide according to conservative estimates, with 50-75% of those deaths attributable to *H. pylori*. Gastric cancer deaths are more common among men than women, with 500,000 of these deaths occurring among men and 300,000 among women (Marshall and Winston, 2005).

The incidence of gastric cancer is decreasing slowly in developed nations. For example, over a 50-year period from 1930 to 1980, incidence in the US decreased from 50 per 100,000 per year to 7 per 100,000 per year. This decrease may be attributed to a combination of dietary changes and the decreased *H. pylori* incidence accompanying sanitation improvements. The incidence of gastric cancer in developing nations, however, is projected to rise for several decades (Makola et al., 2007). As with other sequelae of *H. pylori* infection, rates of gastric cancer vary among bacterial strains. Incidence is approximately 40 per 100,000 per year in areas with a high prevalence of *H. pylori*. Japan, Korea and Columbia have the highest rates, with an incidence of 50 to 100 per 100,000 per annum.

In Japan, one prospective study of 1246 *H. pylori*-infected patient and 280 non-infected patients showed a 2.9% rate of gastric cancer among infected individuals, compared to no cases of gastric cancer among uninfected controls or among a group of previously-infected patients who successfully received eradication therapy (Uemura et al, 2001). Numerous other studies have pointed to the ability of eradication therapy to slow the progression of dysplastic changes or reduce transformation to malignancy. Because rates of gastric cancer are particularly high in Japan, a policy of universal endoscopic screening above age 40 has been implemented. While this policy has been successful in reducing morbidity and mortality in Japan, its cost precludes its implementation elsewhere. In areas with high *H. pylori* prevalence and low resources, therefore, affording some degree of protection with pharmacotherapy is more feasible than a surveillance program.

**MALT Lymphoma**

The incidence of MALT lymphoma is significantly lower than that of gastric adenocarcinoma, at 1 per 100,000 per year worldwide. Despite the low incidence of MALT lymphoma, PPI therapy can substantially reduce the disease burden, as *H. pylori* eradication induces regression of stage I MALT lymphomas in 70-80% of cases and is a component treatment regimens for all gastrointestinal lymphomas.
9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills)

9.1 Indications for use

AHFS Drug information states that omeprazole delayed-release capsules and oral suspension are used in adults for the short term treatment of active duodenal and benign gastric ulcer. Omeprazole delayed-release capsules are also used in combination with clarithromycin (dual therapy) or with amoxicillin and clarithromycin (triple therapy) for the treatment of Helicobacter pylori infection and duodenal ulcer disease in adults. Omeprazole has also been used in other drug regimens for the treatment of H. pylori infection associated with peptic ulcer disease. Omeprazole delayed-release capsules are used in adults and children 2 years of age and older, and the oral suspension is used in adults for short-term treatment and symptomatic relief of gastroesophageal reflux disease (e.g., erosive esophagitis, heartburn) and as maintenance therapy following healing of erosive esophagitis to reduce its recurrence. Omeprazole magnesium delayed-release capsules are used as self-medication for short-term treatment and symptomatic relief of frequent heartburn in adults. Omeprazole delayed-release capsules are used for the long-term treatment of pathologic GI hypersecretory conditions in adults. Omeprazole oral suspension is used to decrease the risk of upper GI bleeding in critically ill adults.

9.2 Dosage regimens

Active ingredient:

Omeprazole: capsules containing 10, 20, 40mg, suspension powder, 20mg/packet, 40 mg/packet

9.3. Duration of therapy

Therapy varies from acute treatment, at approximately 2 weeks, to chronic treatment at up to 5 years.

9.4. Reference to existing WHO and other clinical guidelines

The American college of Gastroenterology Practice Guidelines for Dyspepsia recommends the use omeprazole to treat GERD.
9.5. Need for special diagnostic or treatment facilities and skills

No special diagnostic or treatment facilities are required for the treatment of patients with omeprazole.

10. Summary of comparative effectiveness in a variety of clinical settings

10.1 Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

Systematic reviews and meta-analyses relevant to the terms "omeprazole effectiveness," "omeprazole and ranitidine effectiveness" and "PPI versus H2 receptor antagonist" were searched on the Database of Abstracts of Reviews of Effectiveness (DARE: www.crd.york.ac.uk/crdweb/). Articles were limited to comparative analyses of omeprazole and ranitidine, or PPI and H2 receptor antagonist (H2RA), effectiveness in the clinical setting of acid/peptic disorders. No date restrictions were applied. Additionally, relevant reviews and clinical guidelines were retrieved through BMJ Clinical Evidence (CE: www.clinicalevidence.org).
The Cochrane Library and PubMed were searched for meta-analyses and relevant RCTs otherwise not captured. PubMed searches were language-limited to English, which necessarily limited the scope of this analysis. No date restrictions were applied. Another PubMed search was conducted for the most recent English-language practice guidelines relevant to "GERD" or "GORD." A hand search for clinical practice guidelines was done in *Gastroenterology, Gut* and through the World Gastroenterology Organisation (WGO) and National Institute for Health and Clinical Excellence (NICE) websites.

### 10.2 Summary of available estimates of comparative effectiveness (appraisal of quality, outcome measures, summary of results)

The use of PPIs over H2RAs has been thoroughly codified in the promulgated practice guidelines of national and international medical societies and panels for dyspepsia, esophagitis, GERD and peptic ulcer disease. These guidelines have been constructed after careful and ongoing review of the relevant primary and secondary data.

**Dyspepsia**

In the NICE clinical guidelines for the treatment of uninvestigated (non-endoscopic) dyspepsia, findings from three RTCs (N=1,267) comparing PPIs with H2RAs were pooled and reported. The pooled risk ratio (PPI/H2RA) for global symptoms was 0.64 (95%CI: 0.58-0.72, p<0.0001); 0.46 (95%CI: 0.38-0.60, p<0.57) for heartburn; and 0.70 (95%CI: 0.59-0.83) for epigastric pain.

NICE concluded that "PPIs are more effective in reducing dyspeptic symptoms than H2RAs."
The NICE treatment algorithm for uninvestigated dyspepsia is copied below and reflects British NHS guidelines:

**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 antiacid/antigas.
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. Detox: use carbon-13 urea breath test, stool antigen test or, when performance has been validated, laboratory-based serology.
5. Test and treat: use a PPI, amoxicillin, clarithromycin 500 mg (PACU) regimen or a PPI, metronidazole, clarithromycin 250 mg (PMC) regimen. Do not re-test even if dyspepsia remains unless there is a strong clinical need.
6. 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.
7. 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.
Short-term therapy for GERD/esophagitis

In 2005, the American College of Gastroenterology and its Practice Parameters Committee reiterated its 1995 and 1999 recommendations that PPIs should take precedence over H2RA in treating GERD: "[I]t is clear that while some patients may have relief of symptoms and improvement or healing of esophagitis on H2RAs, PPIs eliminate symptoms and heal esophagitis more frequently and more rapidly than the other agents. Both higher doses and more frequent dosing of H2RAs appear to improve results in the treatment of reflux, but are still inferior to PPIs" (DeVault and Castell, 2005).

In updating the Gstaad Treatment Guidelines for GERD, the international panel wrote in their prefatory remarks that "As reported by the experts at this consensus meeting, the generally recommended treatment in Europe for GERD symptoms at the primary care level is daily half-dose PPI, increasing to daily full dose PPI until symptoms are controlled. In those patients who prove refractory, the combination of a PPI plus antacids or alginate-antacids, histamine H2-receptor antagonists (H2RA) and lifestyle change may prove effective" (Tytgat, McColl, Jack, Holtmann, Hunt, Malfertheiner, Hungin and Batchelor, 2008).

In 2008, the American Gastroenterological Association (AGA) supported the prioritization of PPI therapy over H2RAs (and the prioritization of H2RAs over placebo) in its technical review on the management of GERD. The AGA based their recommendations, in part, on the findings from a Cochrane review of 134 RTC trials involving the short-term treatment of 35,978 patients with esophagitis (Khan, Santana, Donnellan, Preston and Moayyedi, 2007).

Table I. Summary of GERD treatment data with inhibitors of gastric acid secretion

<table>
<thead>
<tr>
<th>Condition</th>
<th>Comparison</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagitis healing (all severities)</td>
<td>PPIs vs placebo: 83% vs 18% at 8wk, NNT=1.7</td>
<td>RR=0.51</td>
</tr>
<tr>
<td></td>
<td>PPIs vs H2RAs: 84% vs 52%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>H2RA vs placebo: 41% vs 20% at 6wk, NNT=5</td>
<td></td>
</tr>
<tr>
<td>Heartburn resolution (patients with esophagitis)</td>
<td>PPIs vs placebo: 56% vs 8% at 4wk, NNT=2–3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PPIs vs H2RAs: 77% vs 48% at 4–12wk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>H2RA vs placebo: 56% vs 45% at 12wk</td>
<td></td>
</tr>
<tr>
<td>Heartburn resolution (endoscopy negative or uninvestigated patients)</td>
<td>PPIs vs placebo: 36.7% vs 9.5%, NNT=3–4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PPIs vs H2RAs: 61% vs 40%, NNT=5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RR=0.66, 95% confidence interval=0.60–0.73</td>
<td></td>
</tr>
<tr>
<td></td>
<td>H2RA vs placebo: RR=0.77, 95% confidence interval=0.60–0.99</td>
<td></td>
</tr>
<tr>
<td>Maintenance of esophagitis healing or symptom control (6-12 months)</td>
<td>PPIs vs placebo for maintaining healing: 93% vs. 29%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low-dose PPI therapy is sufficient to maintain endoscopic remission in 35-95% of patients with esophagitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low-dose on-demand PPI therapy yields acceptable symptom control in 83-92% of endoscopy-negative patients</td>
<td></td>
</tr>
</tbody>
</table>

NNT, estimated number of patients needed to treat to demonstrate this benefit; RR, risk ratio, compares the probability of treatment failure in each group.
Maintenance therapy of GERD/esophagitis

GERD/esophagitis recurs in 60-80% percent of patients within 6 months to a year of successful short-term therapy. NICE pooled seven RTCs (N=941) comparing full-dose PPI with H2RA therapy, with follow-up at 6-12 months. Their results indicated that "PPIs at full dose were more effective than H2RA: the risk ratio for patients relapsing was 0.35 (95%CI: 0.26 to 0.48; Q: p=0.015, size: p=0.091). The size of effect should be treated with caution since study findings vary, although the direction of benefit is consistent. The average relapse rate in H2RA groups was 59% and full dose PPI treatment resulted in an absolute reduction of 39% (95%CI: 28% to 50%; Q: p=0.0003, size: p=0.886), a number needed to treat of 2.6 (95%CI: 2.0 to 3.6). One trial compared PPI at low dose with H2RA and found a similar benefit in favour of PPI: the risk ratio for patients relapsing was 0.43 (95%CI: 0.30 to 0.64)."

The NICE systematic review concluded that "The relapse rate without treatment is estimated to be 60-80%. The most effective therapy currently available to prevent relapse is a full dose of PPI, followed by a low dose PPI and then a[n] H2RA."

Table II. Comparison of maintenance therapies to prevent relapse of esophagitis: absolute risk reduction (and confidence interval)

<table>
<thead>
<tr>
<th>Chosen Treatment</th>
<th>PPI (full dose)</th>
<th>PPI (low dose)</th>
<th>H2RA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI</td>
<td>13% (8% to 17%)*</td>
<td>30% (19% to 41%)*</td>
<td>39% (28% to 50%)*</td>
<td>55% (49% to 63%)*</td>
</tr>
<tr>
<td>H2RA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prokinetic</td>
<td></td>
<td></td>
<td>36% (7% to 66%)*</td>
<td>15% (5% to 22%)</td>
</tr>
</tbody>
</table>

PPI low dose: omeprazole 10mg or equivalent
PPI full dose: omeprazole 20mg or equivalent
* Finding featured statistically significant heterogeneity (p<0.05)
* Finding based on one trial
The NICE treatment algorithm for GERD/GORD is copied below and reflects British NHS guidelines:

Management flowchart for patients with GORD

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1. GORD refers to endoscopically determined oesophagitis or endoscopy-negative reflux disease. Patients with uninvestigated 'reflux-like' symptoms should be managed as patients with uninvestigated dyspepsia.
   There is currently no evidence that H. pylori should be investigated in patients with GORD.

2. Offer low-dose treatment, possibly on an as-required basis, with a limited number of repeat prescriptions.

3. Review long-term patient care at least annually to discuss medication and symptoms.
   In some patients with an inadequate response to therapy or new emerging symptoms it may become appropriate to refer to a specialist for a second opinion.
   Review long-term patient care at least annually to discuss medication and symptoms.
   A minority of patients have persistent symptoms despite PPI therapy and this group remain a challenge to treat.
   Therapeutic options include doubling the dose of PPI therapy, adding an H2RA at bedtime and extending the length of treatment.
Treatment for Helicobacter pylori

The European Helicobacter Study Group (EHSG), comprising 50 participants from 26 countries, outlined their recommendations for the treatment of *H. pylori* in the Maastricht III Consensus Report. These recommendations were later reiterated in the WGO Practice Guideline for treatment of *H. pylori* in developing countries.

Table III. Maastrict III (2005) recommendations for H. pylori treatment

<table>
<thead>
<tr>
<th>First-line options</th>
<th>Second-line options</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI + clarithromycin + amoxicillin or metronidazole</td>
<td>Bismuth-based quadruple therapies</td>
</tr>
<tr>
<td>PPI + clarithromycin + metronidazole</td>
<td>PPI + (amoxicillin or tetracycline) + metronidazole</td>
</tr>
<tr>
<td>Quadruple (PPI + bismuth + metronidazole + tetracycline) or furazolidone-based therapies</td>
<td>If bismuth available</td>
</tr>
</tbody>
</table>

Although the WGO guidelines state that the Maastricht III rubric is preferred, they report on a number of other treatment guidelines issued by consensus groups around the world. These are listed below and, without exception, prioritize the use of PPIs in the first-line treatment of *H. pylori*. Variations in recommendations, instead, reflect the local availability of antibiotics and the differential susceptibility of local *H. pylori* stains.
Table IV. International consensus group recommendations for first-line treatment of H. pylori

<table>
<thead>
<tr>
<th>Consensus Group</th>
<th>First-line recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singapore Ministry of Health</td>
<td>PPI + clarithromycin + amoxicillin</td>
</tr>
<tr>
<td></td>
<td>PPI + clarithromycin + metronidazole</td>
</tr>
<tr>
<td></td>
<td>(tinidazole as alternative)</td>
</tr>
<tr>
<td>Spanish Consensus Conference II (2005)</td>
<td>PPI + clarithromycin + amoxicillin</td>
</tr>
<tr>
<td>American College of Gastroenterology (1998)</td>
<td>PPI + amoxicillin + clarithromycin</td>
</tr>
<tr>
<td>Brazil 2004 II Consensus Conference</td>
<td>PPI + clarithromycin + amoxicillin</td>
</tr>
<tr>
<td></td>
<td>PPI/RBC + metronidazole + clarithromycin</td>
</tr>
<tr>
<td></td>
<td>PPI/RBC + amoxicillin + furazolidone</td>
</tr>
<tr>
<td></td>
<td>Bismuth + furazolidone + clarithromycin</td>
</tr>
<tr>
<td>Asian-Pacific Consensus Group (1998)</td>
<td>PPI/RBC + clarithromycin + amoxicillin</td>
</tr>
<tr>
<td></td>
<td>PPI/RBC + clarithromycin + metronidazole</td>
</tr>
<tr>
<td></td>
<td>(tinidazole as alternative)</td>
</tr>
</tbody>
</table>

11. Summary of comparative evidence on safety

11.1 Estimate of total patient exposure to date

Omeprazole first became available in 1989. Over the nearly 20 years that it has been used, several million patients have been treated with omeprazole and other proton pump inhibitors developed in subsequent years, including lansoprazole, pantoprazole, and esomeprazole. These drugs have been used safely in pregnant women and children.

11.2 Description of adverse effects/reactions

As a drug class, proton pump inhibitors have few side effects and adverse events are rare. PPIs are considered to have an excellent safety profile. The most common side effects are headache, nausea, diarrhea, rash, and constipation, which occur in 1-3% of patients. Serious adverse events are rare. Isolated case reports of toxic hepatitis and visual disturbance have been reported (Shi and Klotz, 2008). There have also been 64 case reports of acute interstitial nephritis (AIN) associated with PPI use, but a recent review of these case reports suggests that the association of the two is not predictable and is exceedingly rare. Of note, all available PPIs have been associated with AIN cases. According to the review’s authors, “While there is not sufficient evidence to establish a causal relationship with certainty, there does appear to be a low-prevalence association” (Sierra et al., 2007).
Unique safety concerns about the effects of long-term acid suppression that arise when PPI therapy is continued for a prolonged period of time.

- Long-term therapy may affect calcium absorption and indirectly increase risk for hip fracture. One large case-control study (Yang et al., 2006) showed that use of PPI for 4 years confers an odds ratio of 1.59 for hip fracture (95% CI, 1.39–1.80). Reviewing this data and smaller studies on the same topic, authors of a review of PPI safety concerns (Cote and Howden, 2007) recommend that “Patients should not be denied PPI therapy, if otherwise appropriately indicated, because of this risk. However, the judicious use of PPIs and restricting their use to only the lowest effective dose are recommended.”

- Long-term PPI therapy leads to hypergastrinemia, which in turn leads to hyperplasia of gastric enterochromaffin-like (ECL) cells (Cote and Howden, 2007). In theory, this may predispose to gastric cancers or to carcinoid tumors, although an increased incidence of gastric cancers has not been observed in long-term PPI users in numerous studies. Long-term therapy is, however, associated with a 4-fold increased incidence of fundic gland polyps.

- Long-term PPI therapy is associated with an increased risk of enteric infections. A systematic review of 27 studies on the subject (Leonard et al, 2007) found an odds ratio of 3.33 (95% CI, 1.84–6.02) for enteric infection with PPI use. Of note, risk for enteric infection was also increased, with histamine receptor antagonist use, with an odds ratio of 2.03 (95% CI, 1.05–3.92).

- Long-term PPI therapy is associated with a modestly increased risk of community acquired pneumonia (CAP). A 2004 Netherlands analysis of data from 364,683 patients found that both PPIs and H₂RAs conferred odds ratios of 1.73 (95% CI, 1.33–2.25) and 1.59 (95% CI, 1.14–2.23), respectively, with the difference between drug classes not showing statistical significance (Laheij et al, 2004).

- In 2007, concerns were raised regarding the possibility of an increased incidence of cardiac events among long-term omeprazole and esomeprazole users compared to patients not taking a PPI. The United States Food and Drug Administration performed a review of safety data at that time. The FDA found one study showing increased incidence of cardiac events among PPI users, but noted that the intervention (omeprazole) and control groups had significant differences in cardiac event history at baseline. Citing 14 other studies of omeprazole and one ongoing study of esomeprazole that did not reveal any differences in cardiac event incidence, the FDA stated: “FDA continues to believe that long-term use of omeprazole or esomeprazole is not likely to be associated with an increased risk of heart problems and recommends that healthcare providers continue to prescribe and patients continue to use these products in the manner described in the labeling for the two products” (FDA, 2007).
11.3 Identification of variation in safety due to health systems and patient factors

Omeprazole and esomeprazole are metabolized hepatically by the CYP 2C19 and CYP3A4 complexes. Variations in the genes coding for CYP 2C19 and CYP3A4 result in different patterns of drug metabolism. The most common genotypes are CYP2C19 homozygous extensive metabolizers (homEM), heterozygous extensive metabolizers (hetEM), and poor metabolizers (PM). CYP2C19 genotype is a significant predictor of *H. pylori* and PUD treatment failure, as homEM individuals achieve lesser levels of acid suppression with standard PPI doses. It does not, however, predict treatment failure when PPIs are used to treat GERD. The PM phenotype results in a 3 to 10-fold increase in drug exposure as compared to the homEM phenotype. It is most common in Asian Oceanic populations, where 23% of the population exhibits this phenotype, and is present in 1-4% of Caucasians. In addition, a distinct allele associated with very extensive metabolism of the drugs is present in 18% of Swedish individuals and 4% of the Chinese population. Individuals with this phenotype often require higher drug doses for effective therapy (Shi and Klotz, 2008).

PPIs may interfere with the absorption or elimination of drugs taken concurrently. The higher pH resulting from PPI use may decrease absorption of ketoconazole, vitamin B12, and digoxin. PPIs decrease hepatic clearance of carbamazepine, diazepam, mephenytoin, methotrexate, nifedipine, phenytoin, warfarin, mefloquine, pyrimethamine, and sulfadoxine. Omeprazole alone may induce CYP1A2; this occurs in a dose-dependent fashion, and is more common in individuals with the PM genotype. This induction, however, has not been shown to have clinical significance (Ma and Lu, 2007). Both fluconazole and fluvoxamine inhibit the metabolism of omeprazole, leading to higher drug concentrations.

11.4 Summary of comparative safety against comparators

Histamine receptor antagonists (H₂RAs) represent the main therapeutic alternative to proton pump inhibitors. Like PPIs, H₂RAs have an excellent safety profile with few side effects. As noted above, both drug classes are associated with modestly increased risk for community acquired pneumonia and enteric infections, since this risk is mediated by the suppression of gastric acid production. Given the excellent safety profiles and low incidence of adverse events for both drug classes, considerations of drug efficacy are paramount when comparing these therapeutic agents.

12. Summary of the available data on comparative cost and cost-effectiveness within the pharmacological class of therapeutic group

The median international price of omeprazole is $0.04-0.05 per 20 mg dosage form. A representative dose is 20 mg BID for a daily cost of $0.09. The median price of ranididine is $0.02-0.03 for a 150 mg dosage form. The equivalent dose is 300mg BID or 0.10 per day. Thus, the costs are equivalent.

13. Summary of regulatory status of the medicine

Generic omeprazole is registered in many countries in the developed (e.g. US, UK) and developing world (e.g. Uganda, Thailand, Malaysia). In the United States, the FDA first
approved ANDA for omeprazole in November 2001 for the production of generic omeprazole by Andrx Pharmaceuticals, Inc. and Genpharm, Inc soon thereafter. Subsequent patent litigation only allowed those products to enter the US market after November 2002, at which point KUDCo’s ANDA approval became the first generic omeprazole product to enter the US market. 10mg and 20mg formulations entered the market first, but a robust generic marketplace emerged to offer a range of additional doses as well as intravenous and time-release formulations.

14. Availability of pharmacopoeial standards

European Pharmacopeia: Yes (5.5)
International Pharmacopoeia: Yes (Martindale ExtraPharmacopeia)
United States Pharmacopoeia: Yes (Version 29)

15. Proposed text for the WHO Model Formulary

Description:

As an example, omeprazole will be quoted as a representative of a generic proton pump inhibitor available.

Omeprazole is a substituted benzimidazole gastric antisecretory agent useful for the treatment of duodenal ulcer, gastric ulcer, Crohn’s Disease-associated Ulcers, Gastroesophageal Reflux, Pathologic GI Hypersecretory Conditions, and Upper GI Bleeding.

How supplied:

Capsules, delayed release, 10mg, 20mg, 40mg; suspension powder, 20mg/packet, 40 mg/packet of omeprazole as active ingredient.

Uses:

Omeprazole capsules are indicated for the treatment of duodenal ulcer, gastric ulcer, Crohn’s Disease-associated Ulcers, Gastroesophageal Reflux, Pathologic GI Hypersecretory Conditions, and Upper GI Bleeding. Use with other medicines that treat H. pylori infection is recommended. Omeprazole therapy can be short term or life long, depending on the indication.

Contraindications:

Hypersensitivity to omeprazole and its products.
Warnings:

Gastric Carcinoma
Omeprazole treatment may delay gastric carcinoma diagnosis by relieving dyspeptic symptoms.

Helicobacter Infection
Proton pump inhibitor treatment may cause false-negative results in the urea breath test for H. pylori infection.

Hepatic impairment
Cirrhotic liver will lead to an increase in omeprazole bioavailability.

Precaution (summarized from MICROMEDEC ®)

Bartter’s syndrome
Hypocalcemia
Hypokalemia
Long-term administration of bicarbonate with calcium or milk can cause milk-alkali syndrome
Long-term omeprazole therapy; risk of atrophic gastritis
Metabolic alkalosis
Patients on a sodium-restricted diet
Respiratory alkalosis
Symptomatic response to omeprazole therapy does not preclude the presence of gastric malignancy

Drug Interactions

Omeprazole is metabolized by the cytochrome P450 system, primarily by CYP2C19, and may alter the metabolism of some drugs metabolized by these enzymes. Omeprazole may prolong the elimination of diazepam, phenytoin, and warfarin; can reduce the absorption of ketoconazole, and itraconazole. With voriconazole, plasma concentrations of both drugs may be increased. Use with clarithromycin may increase plasma concentrations of omeprazole.

Pediatric Use

Omeprazole delayed release capsules are used in children age 2 and older.

Geriatric Use

Dosage adjustments based on age are not necessary in geriatric patients.
Pregnancy

Metaanalyses lead to the conclusion that proton pump inhibitors don’t pose an important teratogenic risk, although they are not generally licensed for use during pregnancy. The United Kingdom has licensed omeprazole for such use.

Adverse Effects

The most frequently reported adverse effects are headache, diarrhea, and skin rashes. Other effects include pruritus, dizziness, fatigue, constipation, nausea and vomiting, flatulence, abdominal pain, atherosclerosis, and dry mouth. Effects on the central nervous system include occasional insomnia, somnolence, and vertigo. In severely ill patients, reversible confusional states, agitation, depression, and hallucinations have been reported.

Dosage and Administration

Omeprazole is given by mouth as capsules containing enteric coated-pellets at 10mg, 20, 40mg, and as suspension powder at 20mg/packet and 40mg/packet

Patient advice

Take omeprazole as your healthcare provider prescribed it. It is usually taken before meals. Contact your healthcare provider if you are not sure what to do.

Information for Patients (DRUGDEX ®)

Patients should be advised that omeprazole:
Treats heartburn, stomach ulcers, gastroesophageal reflux disease (GERD), and conditions that cause your stomach to make too much acid (such as Zollinger-Ellison syndrome, endocrine tumors, and systemic mastocytosis). It also helps heal the esophagus when the stomach makes too much acid and helps prevent bleeding in the stomach for patients with a serious illness. This medicine may be used in combination with antibiotics, such as clarithromycin and amoxicillin, to treat certain types of ulcers.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to omeprazole.

How to Use This Medicine:

Delayed Release Capsule, Powder for Suspension, Delayed Release Tablet
Your doctor will tell you how much of this medicine to use and how often. Do not use more medicine or use it more often than your doctor tells you to.
It is best to take this medicine before a meal.
Swallow the delayed-release capsule or delayed-release tablet whole. Do not crush, break, or chew it. If you cannot swallow the delayed-release capsule, you may open it and pour the...
medicine into a small amount of soft food, such as applesauce. Stir this mixture well and swallow it without chewing. Drink a full glass (8 ounces) of cool water to make sure you swallow all of the medicine.

If you are using the oral suspension, add the contents of the packet into a container with 1 teaspoonful of water (2.5 mg packet) or 3 teaspoonfuls of water (10 mg packet) and stir well. Let the mixture sit to thicken for 2 to 3 minutes. Then stir it again and drink it within 30 minutes. If any mixture is left in the container, add more water, stir, and drink the water right away.

The oral suspension may also be given through a nasogastric or gastric feeding tube. Add 1 teaspoonful of water (2.5 mg packet) or 3 teaspoonfuls of water (10 mg packet) to a catheter tipped syringe. Add the contents of the packet to the syringe and shake the mixture right away. Let the mixture sit to thicken for 2 to 3 minutes. Shake the syringe again and inject it into the nasogastric or gastric tube within 30 minutes. Put the same amount of water in the syringe again, shake it, and then flush the tube to rinse all of the medicine from the tube into the stomach.

If you are using this medicine without a prescription, follow the instructions on the medicine label.

If you are using this medicine to treat heartburn, do not take it for more than 14 days or more often than every 4 months unless directed by your doctor.

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next dose, wait until then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after you have finished your treatment. You will also need to throw away old medicine after the expiration date has passed.

Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Make sure your doctor knows if you are also using clarithromycin (Biaxin®), ampicillin, ketoconazole (Nizoral®), atazanavir (Reyataz®), tacrolimus (Prograf®), cyclosporine (Neoral®, Sandimmune®), or voriconazole (Vfend®). Tell your doctor if you are also using diazepam (Valium®), digoxin (Lanoxin®), phenytoin (Dilantin®), disulfiram (Antabuse®), an iron supplement, or a blood thinner such as warfarin (Coumadin®).
Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant or breastfeeding, or if you have liver disease or heart disease. Tell your doctor if you also have trouble breathing, nausea or vomiting, stomach pain, or unexplained weight loss.

Before using this medicine, tell your doctor if you have had heartburn for longer than 3 months. Make sure your doctor knows if you have trouble swallowing food, if you are vomiting blood, or have blood in your stools. These may be signs of a more serious stomach condition.

Heartburn pain that causes you to sweat, become lightheaded or dizzy, and chest pain that spreads to your arms or shoulders may be symptoms of a heart attack. Seek emergency medical help if you have any of these symptoms.

This medicine is sometimes given together with other medicines to treat ulcers. Be sure you understand about the risks and proper use of any other medicine your doctor gives you together with omeprazole.

If your symptoms do not improve or if they get worse, call your doctor.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.

Blistering, peeling, red skin rash.

Change in how much or how often you urinate.

Chest pain.

Confusion, agitation, or depressed mood.

Fast, slow, or uneven heartbeat.

Fever, chills, cough, sore throat, and body aches.

Lightheadedness, dizziness, or fainting.

Numbness, tingling, or burning pain in your hands, arms, legs, or feet.

Pain on urination.

Problems with your vision or hearing.

Red or dark brown urine.

Sudden and severe stomach pain, nausea, or vomiting.

Swelling in your hands, ankles, or feet.

Unusual bleeding, bruising, or weakness.

Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:

Back, joint, or leg pain.

Constipation, diarrhea, or stomach pain.

Dry skin, dry mouth, or increased sweating.

Hair loss.

Headache.

Loss of appetite.
Mild skin rash or itching.
Muscle cramps or twitching.
Nervousness or tremors.
Sores or white patches on your lips, mouth, or throat.
Trouble sleeping.
Weight gain.

If you notice other side effects that you think are caused by this medicine, tell your doctor.
References (arranged alphabetically)


Appendix 1. Global Suppliers of omeprazole (from Matt Price, The Clinton Foundation)

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<th>Name</th>
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<td>ANDRX Pharmaceuticals (now Watson)</td>
<td>311 Bonnie Circle</td>
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<td>Brantford, ON N3T 5W5, Canada</td>
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<td>Aurobindo Pharma Limited Beijing Kawin Bio-Tech Co., Ltd.</td>
<td>Plot 2, Maitri Vihar, Ameerpet No. 6 Rongjing East Street, BDA</td>
<td>Hyderabad, Andhra Pradesh 500.038, India</td>
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<td>Bridge Pharmaceuticals Pvt Ltd, Hyderabad</td>
<td>#Plot. No. 89, Prashanthi Nagar, IE, Kukatpally 203-B City Towers University Road,</td>
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<td>IDEAL PHARMACIA</td>
<td>3, Rajeshwardeep Chs, Near Nehru Maidan, 30831 Huntwood Avenue 51/57, Dattad Street, 1st Floor, Office No. 11,</td>
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<td>No. 45-58-15/7, Flat No. 14, Millinium Plaza, One Merck Drive</td>
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<td>201 &amp; 202, Bhanu Enclave, 7-1-638 to 643/1, Plot No. 5, 2nd Floor, Neelkanth Chambers - 1, Induchacha House. Opp. Chhani Octroi Naka, Chhani,</td>
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