Section 17.1: Antiulcer medicines

Review for section update

Submitted for WHO Secretariat by

**Grigoris I. Leontiadis**, MD, PhD
*Assistant Professor of Medicine, Division of Gastroenterology, McMaster University, Hamilton ON, Canada*
*Joint Coordinating Editor, Upper Gastrointestinal and Pancreatic Diseases Group, The Cochrane Collaboration*

**Yuhong Yuan** MD, PhD, MSc
*Research Associate, Division of Gastroenterology, McMaster University, Hamilton ON, Canada*

**Potential conflicts of interest**

Dr. Leontiadis has acted as consultant for and received research grants from AstraZeneca (a pharmaceutical company producing PPIs)
Dr. Yuan has no COI

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Background

The 18th Expert Committee on *The Selection and Use of Essential Medicines* requested a review for possible deletion of ranitidine class of medicines and another review to answer the question ‘should adults and children with gastro-oesophageal reflux or non-ulcer dyspepsia be treated with H₂ antagonists compared to proton pump inhibitors’

This review answers the following specific questions, in adults:

- Use of H₂ antagonists compared to proton pump inhibitors for gastro-oesophageal reflux or non-ulcer dyspepsia
- Should Ranitidine be deleted from EML
- Is there need for parenteral preparation of omeprazole

Summary of review

After reviewing the available evidence (as shown below; please note that the major body of work has been done by mid-2000 and there have been only minor updates thereafter) we concluded that:

1. Ranitidine (and other H₂RAs) should not be deleted. PPIs are more effective than H₂RAs in the management of gastro-oesophageal reflux disease (GERD) and or non-ulcer dyspepsia (NUD). However, H₂RAs have advantages (some of which are particularly important for patients in developing countries): faster onset of action, no need to time administration before meals, lower cost, no fear of interaction with clopidogrel, probably safer in pregnancy. Furthermore they can be used in patients who cannot tolerate PPIs because of side effects.

2. There is a need for parenteral (intravenous) preparation of omeprazole (or another PPI) for patients experiencing acute bleeding from a peptic ulcer or patients who need potent acid suppression treatment but are unable to take oral PPIs.
1. H$_2$ RECEPTOR ANTAGONISTS (H$_2$RAS) VERSUS PROTON PUMP INHIBITORS (PPIS) FOR GASTROESOPHAGEAL REFLUX DISEASE (GERD)$^1$

According to the most recent AGA (American Gastroenterological Association) Medical Position Statement on the management of GERD “for the treatment of patients with esophageal GERD syndromes (healing esophagitis and symptomatic relief) [...] PPIs are more effective than H$_2$RAs, which are more effective than placebo” $^1$. All other recent consensus guidelines are in agreement among them with regards to the above statement $^2,^3$.

However, consensus guidelines acknowledge that H$_2$RAs maintain a position in the treatment of GERD:

- In the most recent Asia-Pacific consensus on the management of gastroesophageal reflux disease $^2$, statement #30 reads that “H$_2$RAs and antacids are useful in treating episodic heartburn”. According to this document: “H$_2$RAs and antacids are commonly used for episodic heartburn, primarily for postprandial heartburn. The perception of heartburn serves as a trigger for medication use, and the expectation is an immediate symptom relief that PPIs are unlikely to provide. The onset of action of antacids on esophageal acid concentration is 30 min after dosing and inhibition persists for 1 h.65 However, studies reported that meaningful heartburn relief can already be achieved 19 min after consumption. In contrast, H$_2$RAs have been shown to provide symptom relief within 30 min of dosing that can last up to 12 h. When consumed 30 min prior to a meal, H$_2$RAs are effective in completely or partially preventing postprandial heartburn. There is some evidence to suggest that simultaneous consumption of both an H$_2$RA and an antacid provides better control of esophageal acid exposure and heartburn symptoms, when compared to the clinical effect of each one of these products alone. On-demand treatment with H$_2$RAs has been shown to be safe and effective in GERD patients.”$^2$

- According to the ACG (American College of Gastroenterology) Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease: “The OTC [over the counter] H$_2$RAs are particularly useful when taken prior to an activity that may potentially result in reflux symptoms (heavy meal or exercise in some patients). Many patients can predict when they are going to suffer from reflux and can premedicate with the OTC H$_2$RAs. Comparisons between OTC H$_2$RAs and antacids are limited. It has been suggested that antacids provide a more rapid

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$^1$ The acronym in UK English spelling is GORD (gastro-oesophageal reflux disease)
response, but gastric pH begins to rise less than 30 min after taking a dose of H2RA so this does not seem to be a major factor. The peak potency of OTC H2RAs and antacids are similar, but the H2RAs have a much longer duration of action (up to 10 h).”

It is important to note that the latest major guidelines were published in 2008. The issue of publications a few years prior to the latest guidelines (since there is usually a 2-5 year lag, between the publication of evidence and the publication of guidelines) and after the latest guidelines has been dealt methodically at the end of this section. This approach was followed for the other sections as well.

Below, we examine the evidence from individual randomized controlled trials (RCTs) and systematic reviews and meta-analyses of RCTs.

1.1. SHORT TERM MANAGEMENT OF REFLUX ESOPHAGITIS

PPIs have been consistently shown to be superior to H2RAs in healing esophagitis or resolving symptoms in patients with reflux esophagitis (as defined by endoscopy).

Moayyedi et al conducted a Cochrane systematic review and meta-analysis of RCTs on short-term treatment of reflux esophagitis (one to three months) that had been published until December 2004:

The results were as follows:

- PPIs were effective in healing esophagitis compared to placebo (5 RCTs, 965 participants, relative risk, RR 0.22; 95% confidence interval, CI 0.15 to 0.31).

- H2RAs were also effective in healing esophagitis compared to placebo (10 RCTs, 1241 participants, RR 0.74, 95% CI 0.66 to 0.84).

- However, PPIs were more effective than H2RAs in healing esophagitis at 4 weeks (26 RCTs that compared PPIs vs. H2RAs or H2RAs plus prokinetics, 4032 participants, RR 0.50, 95% CI 0.45 to 0.560; PPIs were also more effective in symptom relief compared to H2RAs at 4 weeks (15 RCTs, 2941 participants, 0.57, 95% CI 0.48 to 0.68).

We conducted an updated MEDLINE literature search on December 20, 2012 for relevant RCTs that had been published after the conduction of the search by Moayyedi et al (December 2004). We identified only one relevant RCT that had compared a PPI with an H2RA in the short term management of reflux esophagitis. This RCT was a small trial (110 participants) and the results were in the same direction with the results from the Cochrane review by Moayyedi et al. Therefore we can confidently conclude
that it is very unlikely that the conclusions of the above mentioned Cochrane review would change substantially if it was updated today.

1.2. SHORT TERM MANAGEMENT OF ENDOSCOPIC NEGATIVE REFLUX DISEASE AND SHORT TERM EMPIRICAL MANAGEMENT OF GERD

PPIs are more effective than H₂RAs in symptom relief in patients with endoscopic negative reflux disease (ENRD⁵; GERD-like symptoms but no erosive esophagitis on endoscopy) and in patients receiving empirical treatment for GERD-like symptoms (no endoscopy performed or endoscopy results not used in allocating treatment).

van Pinxteren et al conducted a recent Cochrane systematic review and meta-analysis of RCTs on short-term treatment of NERD or short-term empirical treatment for GERD that had been published until November 2008 (short-term treatment was defined as treatment that lasted 1 to 12 weeks) ⁶. The results were as follows:

With regards to heartburn remission by short term management ENRD:

- PPIs were more effective than placebo (8 RCTs, RR 0.73, 95% CI 0.67 to 0.78)
- H₂RAs were also better than placebo (2 RCTs, RR 0.84, 95% CI 0.74 to 0.95)
- PPIs were more effective than H₂RAs (4 RCTs, 960 participants, RR 0.78, 95% CI 0.62 to 0.97).

With regards to empirical treatment of patients with GORD-like symptoms, the results were similar as above:

- PPIs were better than placebo (2 RCTs, RR 0.37 95% CI 0.32 to 0.44).
- H₂RAs also better than placebo (2 RCTs, RR 0.77, 95% CI 0.60 to 0.99).
- PPIs were more effective than H₂RAs (7 RCTs, 3147 participants, RR 0.66, 95% CI 0.60 to 0.73).

We conducted an updated MEDLINE literature search on December 21, 2012 for relevant RCTs that had been published after the conduct of the search by van Pinxteren et al (November 2008). We identified only one relevant RCT that had compared a PPI with an H₂RA in the short term management of NERD ⁷. This RCT was a very small trial (only 33 participants); although the difference between the two treatments was non-significant, the study was underpowered. Even if it is included in the existing meta-analysis the results of the meta-analysis are not likely to change. However, it should be noted that the

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⁵ Another acronym for ENRD is NERD (non erosive reflux disease)
results of the pooled analysis on ENRD patients had a 95% CI whose upper boundary was close to the line of no-effect 6, therefore the results could theoretically become non-significant if a large “negative” RCT appears in the future.

1.3. MAINTENANCE THERAPY OF REFLUX ESOPHAGITIS AND ENRD

In 2005 Donnellan et al published a Cochrane systematic review and meta-analysis of RCTs that assessed treatments for the maintenance therapy of reflux esophagitis and ENRD 8. The results were as follows:

For patients with ENRD there were very limited data available, with only one RCT that showed that PPIs were superior to placebo.

For patients with healed erosive esophagitis:

- Both PPIs and H₂RAs were more effective than placebo in maintaining a remission of esophagitis and in maintaining symptom relief.
- However, PPIs were more effective than H₂RAs in maintaining a remission of esophagitis (6 RCTs, 1156 participants, RR of relapse 0.57; 95% CI 0.47 to 0.69 and in maintaining symptom relief (4 RCTs, 831 participants, RR of relapse 0.55; 95% CI 0.47 to 0.65).
- On the other hand, one RCT found a statistically significant increase in headache with PPIs compared with H₂RAs 9.

The Cochrane review concluded that “Healing doses of PPIs are more effective than all other therapies, although there is an increase in overall adverse effects compared to placebo, and headache occurrence compared to H₂RAs. H₂RAs prevent relapse more effectively than placebo, demonstrating a role for PPI-intolerant patients.” 8

We conducted an updated MEDLINE literature search on December 22, 2012 for relevant RCTs that had compared H₂RAs and PPIs and had been published after the date Donnellan et al conducted their search (2003). We identified 5 new RCTs 10,11,12,13,14. Each one of these new RCTs found that PPIs were significantly more efficacious than H₂RAs in maintenance treatment of erosive esophagitis. Therefore, it is very unlikely that the conclusions of the above mentioned Cochrane review would change substantially if it was updated today.
2. H$_2$RAS VERSUS PPIS FOR NONULCER DYSPEPSIA (NUD)

There is limited evidence on the efficacy of H$_2$RAs and PPIs in patients with non-ulcer dyspepsia iii.

In 2006 Moayyedi et al published a Cochrane systematic review and meta-analysis of RCTs on pharmacological interventions for NUD 15. Both H$_2$RAs and PPIs were more effective than placebo, and there was no evidence of a difference between H$_2$RAs and PPIs. More specifically:

- Twelve RCTs (2183 participants) compared H$_2$RAs with placebo: pooled relative risk reduction, RRR 23%, 95% CI 8% to 35%.
- Ten RCTs (3347 participants) compared PPIs with placebo: RRR 13%, 95% CI 4% to 20%.
- There was only one RCT (Blum 2000) 16 that compared H$_2$RAs with PPI therapy in 588 participants: the difference was not statistically significant (RRR 7%; 95% CI 16% to -3%).

We conducted an updated MEDLINE literature search on December 22, 2012 for relevant RCTs that had compared H$_2$RAs and PPIs and had been published after the conduction of the search by Moayyedi et al (January 2006). We found no additional RCTs.

Recent consensus guidelines on the management of NUD acknowledge the presence of the above mentioned RCTs, but note that the evidence derived from these studies (especially the ones that compared H$_2$RAs with placebo) is undermined by methodological limitations 17,18,19.

3. OTHER DIFFERENCES BETWEEN H$_2$RAS AND PPIS

3.1. H$_2$RAS VS. PPIS: SPEED OF ONSET OF ACTION

As discussed above, PPIs are superior to H$_2$RAs regarding the time required to achieve complete resolution of symptoms in GERD and NUD and regarding the time required to achieve healing of esophagitis. These time periods are in the order of days or weeks.

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iii Dyspepsia is defined as chronic or recurrent pain or discomfort centered in the upper abdomen. Non-ulcer dyspepsia (another synonym is functional dyspepsia (FD)) is diagnosed when a patient with dyspepsia has “negative or insignificant findings on their endoscopy or barium studies and have had other organic (pancreato-biliary disease, esophagitis, peptic ulcer disease and neoplastic disease) and drug-induced (non-steroidal anti-inflammatory drugs) and metabolic disorders excluded by appropriate investigations [blood tests, abdominal ultrasound or 24 hour pH studies/manometry etc]” 15.
However, H₂RAs have a faster onset of effect on the symptoms of GERD and NYD, compared to PPIs. This time period is in the order of minutes or 1-2 hours. Of note, “onset of effect” (when a patient has a noticeable improvement in his/her symptoms) is different from “complete resolution of symptoms” (when a patient is completely symptom free, even from mild, not-bothersome symptoms).

- Khury et al showed in a RCT in healthy volunteers that postprandial oral ranitidine (75 or 150 mg) provided more rapid increase in gastric pH to > 3 and > 4 compared to postprandial oral omeprazole (10 or 20 mg) 20.
- Dettmar et al showed in a RCT studying 4-hour pH in GERD patients that oral ranitidine was superior to oral omeprazole in reducing the acidity in the stomach and the esophagus 21. Hedenstrom et al in a RCT that assessed 4-hour pH in healthy volunteers, found that oral ranitidine and famotidine resulted in a fast and significant raise in the intragastric pH while oral omeprazole had no effect in the intragastric pH during the study period (4-h) 22.
- Pipkin et al showed that, in GERD patients, oral ranitidine or famotidine had a faster onset of action compared to oral omeprazole or a lansoprazole: the H₂RAs achieved a significantly greater and more rapid rise in intragastric pH in the hour immediately after dosing and offered a faster relief of symptoms 23.

This suggests that H₂RAs may be more effective than PPIs for on-demand treatment for episodic heartburn or episodic dyspepsia.

### 3.2. H₂RAS VS. PPIS: TIMING OF ADMINISTRATION IN RELATION TO MEALS

PPIs are more effective when administered before a meal 24,25,26.

As Howden & Chey have stated “PPIs are best absorbed in the absence of food. Ingestion of food after a PPI stimulates parietal cell activity when blood levels of the PPI are increasing; this promotes uptake of the PPI by the parietal cells. Therefore, patients should be advised to take their PPI between 30 and 60 minutes before eating. For patients on a once-daily PPI, the best time to take it is about 30 to 60 minutes before breakfast.” 27

On the other hand, H₂RAs can be administered at any time in relation to the meals:

- Orr et al, in a RCT in healthy volunteers, showed that the timing of oral ranitidine administration in relation to a meal did not result in differences in pharmacokinetics (peak ranitidine concentrations, time to peak concentration, area under the serum-concentration time curve or
elimination half-life) or pharmacodynamics (median intragastric pH or mean hydrogen-ion activity over the 23-h study interval)²⁸.

- Pouder et al, in a RCT in healthy volunteers, showed the exact timing of oral cimetidine administration in relation to meals was not critical²⁹.

This difference between H₂RAs and PPIs, may offer an advantage to the H₂RAs as on-demand treatment for episodic postprandial dyspepsia or episodic postprandial heartburn (a patient who has already had a meal and developed postprandial symptoms, can only treat this episode with a medication that can be administered postprandially).

Of note, most of our knowledge on the pharmacokinetics of PPIs and H₂RAs in relation to meals is derived from trials on healthy volunteers. However, we have no reason to expect that the results will be different in ambulatory patients.

### 3.3. H₂RAS VS. PPIs: SAFETY IN PREGNANCY

An additional argument in favor of retaining H₂RAs in the WHO List of Essential Medicines, is their proven safety during pregnancy (interestingly there is an even higher need for acid suppression during pregnancy, because the prevalence of GERD is higher during pregnancy³⁰,³¹). According to the FDA labeling system for drugs in pregnancy ³² (Table 1), all H₂RAs (ranitidine, cimetidine, famotidine and nizatidine) are “relatively safe” in pregnancy and are classified as category B drugs³³. Of the PPIs, lansoprazole, rabeprazole, pantoprazole and esomeprazole are also “relatively safe” in pregnancy and are also classified as category B drugs³³. However there have been safety concerns about omeprazole in pregnancy (animal studies that showed that omeprazole in doses about 5.5 to 56 times the human dose was associated with dose-related embryo-lethality and fetal toxicity and postnatal developmental toxicity), therefore it is classified as category C drug³³. Epidemiological studies of pregnant women have revealed no evidence of adverse events of omeprazole on pregnancy or an increased risk of congenital malformations, but there these studies may have methodological limitations³⁴,³⁵.

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>DEFINITION</th>
<th>MANAGEMENT STRATEGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy.</td>
<td>Because studies are not able to rule out the possibility of harm, (name of drug) should be used during...</td>
</tr>
</tbody>
</table>

Table 1.
Definitions and management strategies from the US Food and Drug Administration categories for drugs taken during pregnancy ³²
<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>DEFINITION</th>
<th>MANAGEMENT STRATEGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Animal reproduction studies have failed to demonstrate a risk to the fetus, but there are no adequate and well-controlled studies of pregnant women. Or animal studies demonstrate a risk, and adequate and well-controlled studies in pregnant women have not been done during the first trimester.</td>
<td>Because the studies of humans cannot rule out the possibility of harm, (name of drug) should be used during pregnancy only if clearly needed.</td>
</tr>
<tr>
<td>C</td>
<td>Animal reproduction studies have shown an adverse effect on the fetus, but there are no adequate and well-controlled studies of humans. The benefits from the use of the drug in pregnant women might be acceptable despite its potential risks. Or animal studies have not been conducted and there are no adequate and well-controlled studies of humans.</td>
<td>(Name of drug) should be given to pregnant women only if clearly needed.</td>
</tr>
<tr>
<td>D</td>
<td>There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies of humans, but the potential benefits from the use of the drug in pregnant women might be acceptable despite its potential risks.</td>
<td>If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.</td>
</tr>
<tr>
<td>X</td>
<td>Studies in animals or humans have demonstrated fetal abnormalities or there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both. The risk involved in the use of the drug in pregnant women clearly outweighs any possible benefits.</td>
<td>(Name of drug) is contraindicated in women who are or might become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.</td>
</tr>
</tbody>
</table>

3.4. \textbf{H}_2\textbf{RAS VS. PPIS: COST}

\textit{H}_2\textit{RAs cost less than PPIs in North America (Table 2 and 3). Although PPIs are more effective than H2RAs, some patients can be switched to \textit{H}_2\textit{RAs are remain satisfied with their treatment} 36. This is particularly important for low and middle income countries. However, it is important to note that internationally the range of the price for omeprazole (a PPI) is much higher than for ranitidine (an \textit{H}_2\textit{RA). Therefore, it is possible that omeprazole may be purchased at a lower price than ranitidine in some countries.}

\textit{According to the International Drug Price Indicator Guide} 37 the cost of omeprazole and ranitidine is as follows:

\textbf{Ranitidine:}

- Median Price 0.0235$/tab-cap
- Lowest Price 0.0161$/tab-cap
- High/Low Ratio 3.42
- Highest Price 0.0551$/tab-cap

Omeprazole:
- Median Price 0.0255$/tab-cap
- Lowest Price 0.0114$/tab-cap
- High/Low Ratio 12.54
- Highest Price 0.1429$/tab-cap

Table 2

The Cost of Your Prescribing 2006–2010

<table>
<thead>
<tr>
<th>PPI</th>
<th>Total # of Your Patients</th>
<th>Total Cost of Your Prescriptions</th>
<th>Typical Daily Treatment Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabeprazole (Prilosec®)</td>
<td>43</td>
<td>$8,957</td>
<td>$1.43</td>
</tr>
<tr>
<td>Rabeprazole generic</td>
<td>99</td>
<td>$20,667</td>
<td>$0.97</td>
</tr>
<tr>
<td>Omeprazole (Losec®)</td>
<td>7</td>
<td>$3,030</td>
<td>$0.15</td>
</tr>
<tr>
<td>Omeprazole generic</td>
<td>20</td>
<td>$8,954</td>
<td>$0.45</td>
</tr>
<tr>
<td>Esomeprazole (Nexum®)</td>
<td>52</td>
<td>$13,081</td>
<td>$0.53</td>
</tr>
<tr>
<td>Pantoprazole (Pantoloc®)</td>
<td>18</td>
<td>$6,137</td>
<td>$0.23</td>
</tr>
<tr>
<td>Pantoprazole generic</td>
<td>25</td>
<td>$9,204</td>
<td>$0.37</td>
</tr>
<tr>
<td>Lansoprazole (Prevacid®)</td>
<td>30</td>
<td>$8,512</td>
<td>$0.23</td>
</tr>
<tr>
<td>Totals</td>
<td>280 distinct patients</td>
<td>$80,022</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>H2-Blocker</th>
<th>Total # of Your Patients</th>
<th>Total Cost of Your Prescriptions</th>
<th>Typical Daily Treatment Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine generic</td>
<td>28</td>
<td>$1,204</td>
<td>$0.36</td>
</tr>
<tr>
<td>Ranitidine (Zantac®)</td>
<td>96</td>
<td>$2,964</td>
<td>$0.37</td>
</tr>
<tr>
<td>Ranitidine generic</td>
<td>42</td>
<td>$1,700</td>
<td>$0.33</td>
</tr>
<tr>
<td>Famotidine (Pepcid®)</td>
<td>8</td>
<td>$273</td>
<td>$0.34</td>
</tr>
<tr>
<td>Famotidine generic</td>
<td>1</td>
<td>$32</td>
<td>$1.14</td>
</tr>
<tr>
<td>Nizatidine (Axid®)</td>
<td>5</td>
<td>$70</td>
<td>$1.63</td>
</tr>
<tr>
<td>Nizatidine generic</td>
<td>0</td>
<td>$0</td>
<td>$0.00</td>
</tr>
<tr>
<td>Totals</td>
<td>165 distinct patients</td>
<td>$7,231</td>
<td></td>
</tr>
</tbody>
</table>

Your PPI and H2RA Prescription Trends

- Indications not included. See PDR DXP for detailed treatment information.
- Patients who are prescribed more than one type of PPI/H2RA are counted more than once. Patient sales are distinct patient counts.
- Based on Prescriber allowable cost per tablet, the standard dose recommended by the USPDI Compendium of Pharmacists' Costs and Specialties (CPS).
4. PPI PARENTERAL PREPARATION

The vast majority of patients that require PPI treatment can be treated with oral PPIs. However, there are some situations were intravenous (IV) PPI treatment is either preferable or is the only possible route of administration.

The official FDA-approved indication for IV Nexium (esomeprazole) in the US, reads: “NEXIUM I.V. is a proton pump inhibitor indicated for the treatment of Gastroesophageal Reflux Disease (GERD) with erosive esophagitis (EE) in adults and pediatric patients greater than one month of age, when oral therapy is not possible or appropriate.”

The official indication for IV Nexium (esomeprazole) in the Wales, is wider: “Esomeprazole (Nexium® IV) is recommended as an option for use within NHS Wales for gastric antisecretory treatment when the oral route is not possible, such as gastro-oesophageal reflux disease (GORD) in patients with erosive reflux oesophagitis and/or severe symptoms of reflux for children and adolescents aged 1–18 years of age.”

The UK Summary of Product Characteristics for IV Nexium (esomeprazole) as provided by AstraZeneca states:

“Nexium for injection and infusion is indicated for:

**Adults**
• gastric antisecretory treatment when the oral route is not possible, such as:
  • gastro-oesophageal reflux disease (GORD) in patients with oesophagitis and/or severe symptoms of reflux
  • healing of gastric ulcers associated with NSAID therapy
  • prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk.
  • prevention of rebleeding following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.

**Children and adolescents aged 1-18 years**

• gastric antisecretory treatment when the oral route is not possible, such as:
  - gastro-oesophageal reflux disease (GORD) in patients with erosive reflux oesophagitis and/or severe symptoms of reflux.”

**IV PPIs can be used in patients who require potent acid suppression therapy but:**

• cannot swallow oral medications because of severe stricturizing GERD, or
• have gastric outlet obstruction due to peptic ulcer disease.

Less often, patients with an obstruction of the oro-pharynx or the upper GI tract (due to malignancy, or trauma) may need short-term IV PPI treatment.

However, the most important and most common indication for IV PPIs is peptic ulcer bleeding. IV esomeprazole has already approved for this indication in Europe, and a relevant application to the FDA is pending. This is based mainly on the results of a large high-quality multi-center RCT that was published in 2009 42, but even older Cochrane systematic reviews and meta-analyses of RCTs had found that there is strong evidence supporting the efficacy of high-dose IV PPI treatment in such patients (while the evidence for the efficacy of oral PPI treatment in such patients is not very strong, especially regarding the effects on mortality) 43. With the exception of the UK NICE guidelines, where the guideline development group “did not feel able to make a firm recommendation on the preferred route of administration”44, all other consensus guidelines (for example, American College of Gastroenterology guidelines45, International Consensus Guidelines46, Asia-Pacific Guidelines47) have recommended the use of high-dose IV PPIs in patients with peptic ulcer bleeding following appropriate endoscopic treatment.
REFERENCES


44 CG141 Acute upper GI bleeding: NICE guideline. 13 June 2012
http://guidance.nice.org.uk/CG141/NICEGuidance/pdf

