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# Oregon Health Resources Commission



## Proton Pump Inhibitors

### Subcommittee Report

**Update #4, JULY 2006**

This report is the fourth update of the initial Subcommittee Report of June 2002.  
All revisions are highlighted.

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## Overview

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-Managed Prescription Drug Plan (PMPDP). The statute specifically directs the Health Resources Commission (HRC) to advise the Department of Human Services on this Plan.

In January of 2002 the HRC appointed a subcommittee to perform an evidence-based review of the use of proton pump inhibitors (PPIs) for reduction of stomach acid. Members of the subcommittee consisted of physicians, pharmacists, nurse practitioners, other health care professionals, consumers and advocates. The subcommittee held six meetings, two of which were general sessions of orientation and evidence-based analysis education. All meetings were held in public with appropriate notice provided.

Subcommittee members worked with Oregon Health and Science University's Evidence-based Practice Center (OHSU-EPC) to develop and finalize key questions for drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity, age, demographics, other medications and co-morbidities.

Using standardized methods, the OHSU-EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

In January of 2003 the HRC appointed a PPI update committee to perform an evidence-based review of the June 2002 *Proton Pump Inhibitors (PPI) Subcommittee Report* for new information or changes in the FDA package inserts. Members of the Update Committee consisted of one HRC member, one Oregon State University (OSU) pharmacist, one Office for Oregon Health Policy & Research (OHPR) physician, one OHSU-EPC pharmacist, and three PPI Subcommittee members. The Update Committee held one public meeting with appropriate notice provided. The PPI Update Committee members worked with the OHSU-EPC reviewing the new evidence for both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity, age, demographics, other medications and co-morbidities.

The OHSU EPC's Preliminary *Drug Class Review on Proton Pump Inhibitors Forth Update Report* was completed June 2006, circulated to the Standing Update Committee members and posted on the OHPR website at

[http://www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence\\_based\\_reports.shtml](http://www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml)

The Standing Update Committee met once on July 11, 2006 and reviewed the preliminary document and any additional evidence. By consensus, the committee members agreed to adopt the EPC's Drug Class Review on Proton Pump Inhibitors Updated Final Report #4. Time was allotted for public comment, questions, written and oral testimony. All available sources of information from the EPC's report that included information submitted by pharmaceutical manufacturers and public testimony were considered.

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This report is prepared to facilitate the HRC in providing recommendations to the Oregon Medical Assistance Program (OMAP) for the plan drug list (PDL). This update report does not recite or characterize all the evidence that was discussed by the OHSU EPC, the original PPI Subcommittee, the Standing Update Committee or the HRC. For further information provided during the committee process, readers are encouraged to review the source materials on the website.

The PPI Update Subcommittee of the HRC, working together with the EPC, OMAP, and the OSU College of Pharmacy, will continue to monitor medical evidence for new developments in this drug class. Approximately every year emerging pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PDL will be made. Significant new evidence for pharmaceuticals already on the PDL will be assessed and Federal Drug Administration (FDA) changes in indications and safety recommendations will be evaluated. The PPI Subcommittee Report will be amended if indicated. Substantive changes will be brought to the attention of the HRC, who may choose to approve the report, or reconvene the PPI Subcommittee.

This report and the OHSU EPC's draft update report, *Drug Class Review on Proton Pump Inhibitors Update Final Report # 4*, are all available on the Office for Oregon Health Policy & Research (OHPR), PMPDP website:

[http://egov.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence\\_based\\_reports.shtml](http://egov.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml)

Information regarding the HRC and its subcommittee policy and process can be found on the OHPR website: <http://www.oregon.gov/DAS/OHPPR/HRC/PMPDP.shtml>

You may also request more information, copies of the reports or copies of minutes and tapes from:

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Information dossiers submitted by pharmaceutical manufacturers are available upon request from by contacting OHSU Center for Evidence-based Policy:

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There will be a charge for copying and handling in providing documents from both OHPR and from OHSU Center for Evidence-based Policy.

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## ***Critical Policy:***

### ***Senate Bill 819***

“The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price.”

### ***Health Resources Commission***

“Clinical outcomes are the most important indicators of comparative effectiveness”;

“If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed.”

## ***Inclusion Criteria:***

- Patients with symptoms of gastro esophageal reflux, peptic ulcer or non-steroidal anti-inflammatory drug-induced ulcer. Studies of any degree of symptoms of gastro esophageal reflux or ulcer (mild, moderate, or severe) will be included.
- Studies in special populations, such as older patients, pregnant or lactating women and Southeast Asian patients, will be included.
- Intervention includes a PPI compared with another PPI, another anti-ulcer drug (such as an H2 receptor antagonist, another class of acid reducing drugs), placebo, surgery, or antibiotics alone.
- Studies of antibiotic combinations with a PPI or other anti-ulcer drug will be included, providing that other inclusion criteria are met.
- For effectiveness, the study is a randomized controlled trial in an outpatient setting and treatment period is at least 4 weeks duration.
- For adverse effects, study is a controlled clinical trial or observational study.
- Studies assessing multiple doses of a single PPI, with no other comparator will be included for assessing adverse effects (not efficacy). Drug-drug interaction studies will be included.
- Outcomes include symptoms, eradication rates, endoscopic healing, functional outcome, quality of life, or adverse effect (including drug interactions).

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***Definition of Proton Pump Inhibitors:***

<b><u>Generic</u></b>	<b><u>Brand</u></b>
Omeprazole	Prilosec Rx
Omeprazole Magnesium	Prilosec OTC
Omeprazole Sodium Bicarbonate	Zegerid
Lansoprazole	Prevacid
	Prevacid SoluTab
Pantoprazole	Protonix
Rabeprazole	Aciphex
Esomeprazole	Nexium

***Key Questions:***

1. What is the comparative efficacy of different PPIs in patients with symptoms of (GERD)?
  - a. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in healing esophagitis, reducing symptoms, and preventing relapse in adult patients with symptoms of GERD?
  - b. In comparisons of PPIs and H2-RAs what is the comparative effectiveness of different PPIs in healing esophagitis, reducing symptoms, and preventing relapse in adult patients with symptoms of GERD?
2. What is the comparative effectiveness of different proton pump inhibitors in patients with peptic ulcer or non-steroidal anti-inflammatory drug-induced ulcer?
  - a. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with **duodenal ulcer**?
  - b. In comparisons of PPIs and H2-RAs, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with **duodenal ulcer**?
  - c. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with **gastric ulcer**?
  - d. In comparisons of PPIs and H2-RAs, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with **gastric ulcer**?

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- e. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with **NSAID-induced ulcer**?
  - f. In comparisons of PPIs and H2-RAs, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with **NSAID-induced ulcer**?
  - g. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in preventing **NSAID-induced ulcer**?
  - h. In comparisons of PPIs and other drugs or placebo, what is the comparative effectiveness of different PPIs in preventing **NSAID-induced ulcer**?
  - i. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in improving eradication rates in adult patients with **Helicobacter pylori**?
  - j. In comparisons of PPIs and H2-RAs, what is the comparative effectiveness of different PPIs in improving eradication rates in adult patients with **Helicobacter pylori**?
3. What are the comparative incidence and nature of complications (serious or life-threatening or those that may adversely effect compliance) of different PPIs in adult patients being treated for symptoms of gastro esophageal reflux, peptic ulcer, or non-steroidal anti-inflammatory drug-induced ulcer?
  4. Are there subgroups of patients based on demographics, other medications, or co-morbidities (including patients with nasogastric tubes, or who cannot swallow solid oral medications) for which one medication or preparation is more effective or associated with fewer adverse effects?

### *New Findings of **Standing Update Committee, July 2006***

- This review adds children to the adult patients.
- Since the 3<sup>rd</sup> Update, there have been no new PPI drugs except omeprazole that is available as a combination with sodium bicarbonate (Zegerid), but no studies of this product met inclusion criteria.
- The public review process revealed 6 studies that were included for the 4<sup>th</sup> update.
- There were 13 new head-to-head trials, 12 new active-controlled trials, 4 new placebo-controlled trials, and 6 new systematic review trials added to this update.
- Three head-to-head trails in patients with endoscopy-negative GERD were added.
- One study comparing esomeprazole and ranitidine for relapse of erosive esophagitis was added.
- A new treatment regimen of “on demand” for prevention of relapse of non-erosive or empirically treated GERD was reviewed in two papers.
- Evidence in children is minimal since there are no direct comparisons of PPIs for reflux esophagitis in children. A fair quality placebo-controlled trial in infants

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failed to find omeprazole superior to placebo in controlling symptoms or acid-exposure time.<sup>1</sup>

- There is still controversy about whether dose comparisons in head-to-head trials of esomeprazole versus omeprazole were appropriate. It is argued that because of differences in drug chemistry and pharmacology, there is no equivalent dose of omeprazole and esomeprazole.<sup>2</sup>

## Summary of Results

### 1. WHAT IS THE COMPARATIVE EFFICACY OF DIFFERENT PPIs IN PATIENTS WITH SYMPTOMS OF GERD?

#### A. In head-to-head comparisons, what is the comparative efficacy of different PPIs in healing esophagitis, reducing symptoms, and preventing relapse in patients with symptoms of GERD?

Twenty-six head-to-head randomized controlled trials compared one or more PPIs to another for healing of endoscopically-proven esophagitis and gastro-esophageal reflux symptom relief. Two are unpublished, and two publications are supplemented with additional data provided by the manufacturer. One study reported racial and ethnic diversity in the population but distinct results were not reported for these groups. Four systematic reviews of good quality compared PPIs.

#### Esophagitis healing

A large study by Castell et al. with 5241 patients found an overall 3.8% statistically significant improvement in healing of biopsy proven erosive esophagitis when comparing the effects of esomeprazole (40 mg) to lansoprazole (30 mg).<sup>3</sup> Twenty-six patients would be needed to treat (NNT) with esomeprazole as compared to lansoprazole to make a difference in esophagitis healing in all groups. However, it was the consensus of the PPI Update Subcommittee that these differences were so small (albeit “statistically significant”) as to be clinically irrelevant. A second, smaller, fair-quality trial of lansoprazole 30 mg vs. esomeprazole 40 mg found the two to be equivalent at healing esophagitis at 8 weeks.<sup>4</sup> Two trials showed esomeprazole 40 mg had higher healing rates than omeprazole 20 mg, but there were no head-to-head comparisons of comparable doses of omeprazole 40 mg vs. esomeprazole 40 mg.<sup>5,6</sup>

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<sup>1</sup> Moore DJ, Tao BS, Lines DR, et al. Double-blind placebo-controlled trial of omeprazole in irritable infants with gastroesophageal reful. *Journal of Pediatrics* 2003;143(2):219-223.

<sup>2</sup> FDA. Medical Review of Nexium (Esomeprazole Magnesium) Delayed-Release Capsules. 2001. Available at: [http://www.fda.gov/cder/foi/nda/2001/21154\\_Nexium.htm](http://www.fda.gov/cder/foi/nda/2001/21154_Nexium.htm). Accessed 4/29/2004.

<sup>3</sup> Castell DO, Kahrilas PJ, Richter JE, et al. Esomeprazole (40 mg) compared with lansoprazole (30 mg) in the treatment of erosive esophagitis. *American Journal of Gastroenterology* 2002;97(3):575-83

<sup>4</sup> Howden CW, Ballard EDI, Robieson W. Evidence for therapeutic equivalence of lansoprazole 30 mg and esomeprazole 40 mg in the treatment of erosive esophagitis. *Clinical Drug Investigation*. 2002;22(2):99-109.

<sup>5</sup> Kahrilas PJ, Falk GW, Johnson DA, et al. Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux esophagitis patients: a randomized controlled trial. The Esomeprazole Study Investigators. *Alimentary Pharmacology & Therapeutics* 2000;14(10):1249-58.

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Thus three of the four trials that compare esomeprazole to another PPI concluded that esomeprazole was more effective, but because of concerns over lack of equivalence in doses use (omeprazole), method of reporting and analyzing results, and relatively small difference in the healing rates, the PPI subcommittee agrees that these trials do not provide sufficient evidence that esomeprazole is more efficacious than any other PPI.

To determine an estimate of healing rates for each drug, the OH&SU EPC pooled data from head-to-head trials, using a random effects model to control for the effect of the study. For Esomeprazole 20 or 40 mg, Lansoprazole 30 mg, Omeprazole 20 or 40 mg, and Pantoprazole 40 mg, healing rates were similar and confidence intervals overlapped, indicating no significant differences between PPIs.<sup>7</sup>

No difference in healing rates between omeprazole, lansoprazole, rabeprazole, and pantoprazole was demonstrated in head-to-head trials. Consistent results were found from four new head-to-head trials of PPIs in patients with erosive esophagitis. Lansoprazole 30 mg vs. esomeprazole 40 mg or pantoprazole 40 mg vs. omeprazole 40 mg showed no differences in healing rates for healing of esophagitis at 4 and 8 weeks.

In one of three new systematic reviews of studies of patients with GERD, esomeprazole vs. lansoprazole was compared; whereas, the other two reviews included head-to-head trials for all PPIs. In two of these three reviews the conclusions are based on studies previously examined in the first PPI update. The third systematic (good) review concluded that in more severe esophagitis esomeprazole 40 mg compared with lansoprazole 30 mg provided an additional 5% increased healing at 4 weeks and 4% at 8 weeks.

One fair small (N=48) new Chinese head-to-head trial<sup>8</sup> comparing esomeprazole vs. omeprazole found that the healing rate at 8 weeks was lower than other studies for both treatment groups (64% esomeprazole 40 mg vs. 45.5% omeprazole 20 mg ) The addition of the Chen study to the calculated pooled risk difference from 3 other studies slightly decreased the NNT from 20 to 17 in favor of esomeprazole.

### ***Analysis of healing rates by baseline severity of esophagitis***

The PPI subcommittee asked the EPC to provide more detail about esophageal healing based on severity of esophagitis upon entry into the study. Eighteen head-to-head trials reported information about esophagitis healing rates separately by baseline

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<sup>6</sup> Richter JE, Kahrilas PJ, Johanson J, et al. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. *American Journal of Gastroenterology* 2001;96(3):656-65.

<sup>7</sup> McDonagh, MS, Carson S, Drug class review on proton pump inhibitors, Oregon Evidence-based Practice Center, May 2005. p. 15

<sup>8</sup> Chen C-Y, Lu C-L, Luo J-C, et al. Esomeprazole tablet vs. omeprazole capsule in treating erosive esophagitis. *World Journal of Gastroenterology* May 28, 2005;11(20):3112-3117.



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severity of esophagitis. To estimate healing rates for each drug at 4 and 8 weeks for patients with moderate to severe esophagitis, the EPC conducted a random effects meta-analysis of data from 9 studies reporting the number healed/total by baseline severity<sup>9</sup>.

Esomeprazole 40 mg vs. Omeprazole 20mg (3 studies) was a pooled significant relative risk of 16% at 4 weeks and 13% at 8 weeks, but similar (2 studies) with both drugs at 20 mg. There were no comparisons of esomeprazole at any dose to omeprazole 40 mg.

Esomeprazole 40 mg vs. Lansoprazole 30 mg (2 studies) was a pooled significant relative risk of 8% (NNT=13) at 4 weeks and 9% (NNT=11) at 8 weeks. A third study reported the combined outcome of healing or improvement of at least two grades in the subgroup of patients with moderate to severe esophagitis at 8 weeks. There was a non-significant trend reported favoring Lansoprazole (published by the maker) at 10%.

Esomeprazole 40 mg vs. Pantoprazole 40 mg in patients with moderate esophagitis at baseline had a 22% higher healing rate at 8-10 weeks. However, another study showed a 14% difference favoring Esomeprazole after 4 weeks, but did not report 8 week data.

Lansoprazole 30 mg vs. Omeprazole 20 mg (3 studies) was a pooled insignificant relative risk of healing rates at both 4 and 8 weeks.

### ***Relief of symptoms***

Four head-to-head comparisons of PPIs measured symptom relief as a primary outcome and 13 reported symptoms as a secondary outcome at varying lengths of time, generally two and/or six weeks of treatment. The study conclusions are difficult to interpret and compare because data was recorded differently, diary reports were inconsistent and incomplete, and symptoms evaluated varied from study to study. Similar concerns about dosing of omeprazole vs. esomeprazole applied to relief of symptoms from esophagitis.

A random effects meta-analysis performed by the OH&SU EPC revealed that esomeprazole 40 mg compared to omeprazole 20 mg significantly favored esomeprazole 40 mg; for every 10 persons treated with esomeprazole 40 mg vs. omeprazole 20 mg, one additional patient would be symptom-free at four weeks in the esomeprazole group (NNT=10). However, the pooled data for esomeprazole 40 mg versus either lansoprazole 30 mg or pantoprazole 40 mg did not indicate a significant difference between the drugs.<sup>10</sup>

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<sup>9</sup>McDonagh, MS, Carson S, Drug class review on proton pump inhibitors, Oregon Evidence-based Practice Center, May 2005. Table 9 p. 18

<sup>10</sup>McDonagh, MS, Carson S, Drug class review on proton pump inhibitors, Oregon Evidence-based Practice Center, May 2005. Table 3, p. 12

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## ***Non-Erosive Esophagitis***

Three fair-quality head-to-head trials in patients with endoscopy negative reflux disease (ENRD) all compared esomeprazole to another PPI (omeprazole<sup>11</sup>, rabeprazole<sup>12</sup>, and pantoprazole<sup>13</sup>). A fourth head-to-head trial of lansoprazole vs. omeprazole included patients with both erosive and nonerosive esophagitis, but did not report results separately for these patient populations. The three used different outcomes measures, but all found esomeprazole to be similar in efficacy to the comparator PPI.

## ***Prevention of relapse***

Although a trial by Lauritsen et al. demonstrated that esomeprazole 20 mg was 9% more effective than lansoprazole 15 mg in maintaining healed reflux esophagitis for 6 months, there was not a head-to-head comparison of comparable dosing of esomeprazole 40 mg vs. lansoprazole 30 mg.<sup>14</sup> The use of low dose PPI for maintenance is not commonly practiced in the US and therefore the relevance of this European study to clinical practice in Oregon is limited. A head to head trial of omeprazole, lansoprazole and pantoprazole in endoscopically diagnosed reflux esophagitis patients at 8 weeks maintenance therapy found equivalence in decreasing symptoms between omeprazole and pantoprazole, but not for lansoprazole. Two head-to-head trials found no differences in endoscopic or symptomatic relapse rates for lansoprazole vs. omeprazole after 48 weeks and rabeprazole vs. omeprazole after 13, 26, and 1 and 5 years. A head-to-head trial of rabeprazole 10 or 20 mg vs. omeprazole 20 mg for maintenance of GERD over 5 years revealed similar efficacy and safety with both groups.<sup>15</sup>

In patients with non-erosive or empirically treated GERD, a 6 month head-to-head trial of on-demand esomeprazole 20 mg vs. continuous lansoprazole 15 mg, more patients discontinued lansoprazole than esomeprazole. (13% vs. 6%, p=0.001).<sup>16</sup>

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<sup>11</sup> Armstrong D, Talley NJ, Lauritsen K, et al. The role of acid suppression in patients with endoscopy-negative reflux disease: the effect of treatment with esomeprazole or omeprazole. *Alimentary Pharmacology & Therapeutics*.2004;20(4):413-421.

<sup>12</sup> Fock KM, Teo EI, Ang TL et al. Rabeprazole vs esomeprazole in non-erosive gastro-esophageal reflux disease: a randomized, double-blind study in urban Asia. *World Journal of Gastroenterology:WJG* 2005;11(20):3091-3098.

<sup>13</sup> Monnikes H, Pfaffenberger B, Gatz G, et al. Novel measurement of rapid treatment success with ReQuest: first and sustained symptom relief as outcome parameters in patients with endoscopy-negative GERD receiving 20 mg pantoprazole or 20 mg esomeprazole. *Digestion*. 2005;71(3):152-158.

<sup>14</sup> Lauritsen K, Deviere J, Bigard MA, et al. Esomeprazole 20 mg and lansoprazole 15 mg in maintaining healed reflux oesophagitis:Metropole study results. *Alimentary Pharmacology & Therapeutics* 2003;17(3):333-41

<sup>15</sup> Thjodleifsson B, Rindi G, Fiocca R et al. A randomized, double-blind trial of the efficacy and safety of 10 or 20 mg rabeprazole compared with 20 mg omeprazole in the maintenance of gastro-esophageal reflux disease over 5 years. *Alimentary Pharmacology & Therapeutics* 2003;17(3):343-51.

<sup>16</sup> Tsai HH, Chapman R, Shepard A, et al. Esomeprazole 20 mg on-demand is more acceptable to patients than continuous lansoprazole 15 mg in the long-term maintenance of endoscopy-negative gastro-esophageal reflux patients; the COMMAND Study. *Alimentary pharmacology & therapeutics*. 2004;20 (6): 657-665.

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On-demand rabeprazole 10 mg, on-demand esomeprazole 20 mg, and continuous omeprazole 10 mg were significantly more effective than placebo in prevention of relapse of symptoms over 6 months in patients with endoscopically negative GERD.<sup>17 18 19</sup>

A systematic review found, in studies comparing PPIs to placebo or ranitidine, similar remission rates for lansoprazole, rabeprazole, and omeprazole over 6 and 12 months of treatment.

### ***Esophagitis in Children***

There are no head-to-head trials of PPIs in children. A fair quality placebo-controlled trial of omeprazole (10 to 20 mg/day) in infants (3-12 months) with gastroesophageal reflux defined as a pH <4 for 5% of the monitoring time and/or abnormal esophageal histology found a significant improvement in histological and pH measurements between omeprazole and placebo, but no difference in the cry/fuss time or parent assessment of infant irritability.<sup>20</sup>

#### ***B. In comparisons of PPIs and H2-RAs, what is the comparative efficacy of different PPIs in healing esophagitis, reducing symptoms, and preventing relapse of GERD?***

No difference was found amongst the PPIs in the systematic review and the 31 studies comparing PPIs to H2-receptor antagonists. All the PPIs studied were more effective than H2-receptor antagonists, but there were no differences amongst PPIs.

***The Standing Update Subcommittee agrees by consensus:***

- ***There is no overall clinically significant difference between PPIs for esophagitis healing, relief of symptoms or prevention of relapse in adult patients with GERD***
- ***There is no comparative evidence for different PPIs in infants with GERD.***

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<sup>17</sup> Bytzer P, Blum A, De Herdt D, et al. Six-month trial of on-demand rabeprazole 10 mg maintains symptom relief in patients with non-erosive reflux disease. *Aliment Pharmacol Ther.* 2004;20(2):181-188.

<sup>18</sup> Talley MJ, Lauritsen K, Tunturi-Hignala H, et al. Esomeprazole 20 mg maintains symptom control in endoscopy-negative gastro-oesophageal reflux disease: a controlled trial of 'on-demand' therapy for 6 months. *Alimentary Pharmacology & Therapeutics* 2001;15(3):347-354.

<sup>19</sup> Venables TL, Newland RD, Patel AC, et al. Maintenance treatment for gastro-oesophageal reflux disease. A placebo-controlled evaluation of 10 mg omeprazole once daily in general practice. *Scandinavian Journal of Gastroenterology.* 1997;32(7):627-632.

<sup>20</sup> Moore DJ, Tao BS, Lines DR, et al. Double-blind placebo-controlled trial of omeprazole in irritable infants with gastroesophageal reflux. *Journal of Pediatrics.* 2003;143(2):219-223.

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## **2. WHAT IS THE COMPARATIVE EFFICACY OF DIFFERENT PROTON PUMP INHIBITORS IN ADULT PATIENTS WITH PEPTIC ULCER OR NON-STEROIDAL ANTI-INFLAMATORY DRUG-INDUCED ULCER?**

### ***A. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with duodenal ulcer?***

Nine randomized controlled trials of fair quality compared one PPI to another. All PPIs have been compared to omeprazole. No significant differences were found in healing rates. Symptoms were assessed in seven studies. One found a significant difference in daytime pain between rabeprazole and omeprazole at four weeks, but no difference in nighttime pain or number of patients that are pain free. Antacid use, GI symptoms and overall well-being were not different in any of the studies. Relapse rates were not significantly different in three studies comparing a PPI to placebo or ranitidine.

### ***B. In comparisons of PPIs and H2-RAs, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with duodenal ulcer?***

Twenty-seven randomized controlled trials were reviewed. PPIs were more effective at healing than H2-RAs but there were no significant differences in healing rates among the PPIs. One indirect comparison showed pantoprazole to have a significantly higher healing rate than rabeprazole but the confidence interval was large.

### ***C. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with gastric ulcer?***

One study (N=227) of fair quality compared rabeprazole to omeprazole. There was no difference in healing rates. No significant differences in pain resolution or improvement were found in nine of twelve comparisons; minor symptom relief improvement for rabeprazole was shown in three comparisons but no difference in overall well being.

A fair quality study (N=80) compared rabeprazole 10 mg/day and omeprazole 20 mg/day and evaluated the impact of CYP2C19 genotype on healing rates.<sup>21</sup> The overall healing rate at 8 weeks (risk difference 1.94%, 95% CI – 1.34% to 1.71%) did not show a difference between the drugs.

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<sup>21</sup> Ando T, Kato H, Sugimoto N, et al. A comparative study on endoscopic ulcer healing of omeprazole versus rabeprazole with respect to CYP2C19 genotypic differences. *Digestive Diseases & Sciences*. Sep 2005;50(9):1625-1631.

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***D. In comparisons of PPIs and H2-RAs what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with gastric ulcer?***

Fifteen studies compared a PPI to an H2-RA for treatment of gastric ulcer. Confidence intervals for PPIs compared to H2-receptor antagonists all overlap. Pain scales were not consistent across studies or not described.

***E. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with non-steroidal anti-inflammatory drug-induced ulcer?***

No head-to-head study comparing one PPI to another was identified.

***F. In comparisons of PPIs and misoprostol or H2-RAs, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in adult patients with non-steroidal anti-inflammatory drug-induced ulcer?***

Four studies assessed PPIs compared to another drug in non-steroidal anti-inflammatory drug-induced ulcer. A good quality systematic review of prevention and treatment of NSAID induced ulcers was also found.<sup>22</sup> All confidence intervals overlap, regardless of the comparison. Results for symptoms did not include all indicators that were measured.

***G. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in preventing non-steroidal anti-inflammatory drug-induced ulcer?***

No head-to-head study comparing one PPI to another was identified. A good quality systematic review and seven subsequently published trials compared PPIs to placebo or other drugs. Based on development of new ulcers or serious erosions and on symptoms, there did not appear to be differences in the PPIs studied (omeprazole, lansoprazole and pantoprazole). However because of differences in patient populations, comparison groups, and outcome measured definitions, confidence in this finding is low.

***H. In comparisons of PPIs and H2-RAs, what is the comparative effectiveness of different PPIs in preventing non-steroidal anti-inflammatory drug induced ulcer?***

One recent, good quality systematic review showed a PPI to be superior to an H2-RA but no head-to-head comparisons of PPIs were identified and no studies were designed to evaluate the effectiveness of PPIs in preventing serious ulcer complications. Symptom

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<sup>22</sup> Rostom A, Dube C, Jolicoeur E, et al. Gastroduodenal ulcers associated with the use of non-steroidal anti-inflammatory drugs: a systematic review of preventive pharmacological interventions. *Health Technol Assess.* 2004(12).

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assessment and reporting was variable and were not the same at baseline. Evidence is insufficient to identify any differences between PPIs.

***I. In head-to-head comparisons what is the comparative efficacy of different PPIs in improving eradication rates in adult patients with Helicobacter pylori?***

Three head-to-head trials of PPIs combined with antibiotics for the eradication of Helicobacter pylori revealed that rabeprazole and lansoprazole had similar eradication rates. A good-quality meta-analysis reviewed 20 head to head trials of PPIs combined with antibiotics in triple therapy regimens for H.pylori eradication. Six newer combination therapies comparing lansoprazole vs. omeprazole (4), two doses of lansoprazole (1) or esomeprazole vs. pantoprazole added no new information due to the heterogeneity of the studies. Using omeprazole as the reference for comparison, no difference was found in eradication rates among any of the PPIs.<sup>23</sup>

***J. In comparisons of PPIs and H2-RAs, what is the comparative effectiveness of different PPIs in improving eradication rates in adult patients with Helicobacter pylori?***

Four fair-quality systematic reviews showed similar eradication rates for the PPIs compared to the H2-RAs.

*The Standing Update Subcommittee agrees by consensus there is no evidence that any PPI has been shown to be superior in comparing outcomes of treatment for gastric ulcer disease, non-steroidal anti-inflammatory drug-induced ulcer, duodenal ulcer, or eradication of Helicobacter pylori.*

**3. WHAT ARE THE COMPARATIVE INCIDENCE AND NATURE OF COMPLICATIONS (SERIOUS OR LIFE-THREATENING OR THOSE THAT MAY ADVERSELY EFFECT COMPLIANCE) OF DIFFERENT PPIs IN ADULT PATIENTS BEING TREATED FOR SYMPTOMS OF GASTROESOPHAGEAL REFLUX, PEPTIC ULCER OR NON-STEROIDAL ANTI-INFLAMMATORY DRUG-INDUCED ULCER?**

***A. Adverse Events***

No head-to-head long-term comparison studies designed to assess adverse events among PPIs were identified. Although hyperplasia of enterchromaffin-like (ECL) cells occurs, there has been no progression to ECL carcinoids. Atrophic gastritis is increased with long-term PPI therapy, but progression to intestinal metaplasia and gastric cancer has not been shown. Gastric bacterial overgrowth does occur, but a higher rate of gastric Adenocarcinoma has not been shown. No studies were found assessing the risk of esophageal

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<sup>23</sup> Vergara M, Vallve M, Gisbert JP et al. Meta-analysis: comparative efficacy of different proton-pump inhibitors in triple therapy for Helicobacter pylori eradication. *Alimentary Pharmacology & Therapeutics* 2003;18(6):647-54.

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cancer. Several long-term maintenance studies showed similar withdrawal rates. Head-to-head comparisons of PPIs for short-term treatment show very low withdrawal due to adverse events, and there were no differences amongst them. New trials designed to assess maintenance treatment for GERD **have** provide additional information about **the paucity of** long-term adverse effects in patients taking omeprazole, pantoprazole, rabeprazole, or omeprazole.

### **Children**

Reporting of adverse events in children is limited to short-term trials and one open-label uncontrolled study with longer term follow up. In a before-after study of omeprazole for esophageal reflux, 15 children were followed for a mean of 12 months. Seven (47%) had elevation of liver enzymes and eleven (73%) had hypergastrinemia.<sup>24</sup> A more recent short-term before-after study of pantoprazole reported elevated liver enzymes in 1 of 18 (6%) and 5 of 18 (28%) had hypergastrinemia.<sup>25</sup>

#### **B. Drug Interactions**

No head-to-head comparative studies of drug interactions with PPIs were identified. Uncontrolled studies in healthy patients may show newer PPIs have less interactions with other drugs than omeprazole, but clinically significant interactions are few and dose monitoring is the only action that needs to be taken.

***The Standing Update Subcommittee agrees by consensus:***

- No evidence by comparative trials supports a significant difference in the incidence and nature of adverse effects. Based on uncontrolled studies in healthy adults, omeprazole may have more interactions with other drugs than newer PPI's, but monitoring for needed dose adjustments is the only action required.***
- Two before-after studies in infants treated with omeprazole for esophageal reflux show a disturbing trend towards elevated liver enzymes and hypergastrinemia.***

#### **4. ARE THERE SUBGROUPS OF PATIENTS BASED ON DEMOGRAPHICS, OTHER MEDICATIONS OR CO-MORBIDITIES FOR WHICH ONE MEDICATION OR PREPARATION IS MORE EFFECTIVE OR ASSOCIATED WITH FEWER ADVERSE EFFECTS?**

Two trials showed no impact of age, gender and race on the incidence of adverse effects. Studies of non-steroidal anti-inflammatory drug-induced ulcer included more women than men, likely due to greater prevalence of diseases requiring non-steroidal anti-inflammatory drugs in women, but no gender-based analyses were done. Although 17-

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<sup>24</sup> Gunasekaran TS, Hassall EG. Efficacy and safety of omeprazole for severe gastroesophageal reflux in children. *Journal of Pediatrics* 1993;123(1):148-154.

<sup>25</sup> Madrazode la Garze A, Dibildox M, Vargas A, et al. Efficacy and safety of oral pantoprazole 20 mg given once daily for reflux esophagitis in children. *Journal of Pediatric Gastroenterology & Nutrition*. 2003;36(2):261-265.

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25% of Asian population has a higher incidence of deficiency of the liver enzymes that metabolize PPIs giving the drugs a longer half-life, the adverse effect profiles of the drugs do not differ. Older patients also metabolize PPIs more slowly. One placebo-controlled trial assessed the safety and efficacy of pantoprazole used for 12 months in patients over age 64. No accumulation of drugs has been demonstrated and no dose adjustment is required in either population.

### ***Pregnancy***

A multicenter, prospective cohort study enrolled 410 pregnant women who had sought counseling after exposure to omeprazole (N=295), lansoprazole (N=62), or pantoprazole (N=53) between 1992 and 2001<sup>26</sup> with a control group of 868 women without exposure to teratogenic drugs. There was no difference in the rate of major anomalies between each of the PPI groups compared to the control risk. (RR was 0.95%, CI 0.46-1.98 for omeprazole; 1.04, CI 0.25-4.21 for lansoprazole; and 0.55 CI 0.08-3.95 for pantoprazole.) Although there was a reduction of 60 grams in median birth weight in omeprazole exposed vs. control groups, there was no difference in median gestational age at delivery, rate of preterm births, and rate of miscarriages, ectopic pregnancies, or stillbirths in exposed vs. control groups.

***The Standing Update Subcommittee agrees by consensus:***

- ***Evidence supporting differences in efficacy or adverse events in subpopulations by gender, race, ethnicity or comorbidities was not found.***
- ***Although older people and Asians may metabolize proton pump inhibitors more slowly, it is not of clinical significance.***
- ***There was no significant difference in the rates of major anomalies compared to controls in children born of pregnant women exposed to omeprazole, lansoprazole, or pantoprazole***

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<sup>26</sup> Ohkusa T, Maekawa T, Arakawa T, et al. Effect of CYP2C19 polymorphism on the safety and efficacy of omeprazole in Japanese patients with recurrent reflux oesophagitis *Alimentary Pharmacology & Therapeutics*. Jun 1 2005;21(11):1331-1339.



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## Conclusion

In a series of public meetings with the opportunity for public questions, comment and testimony, the Update Subcommittee for Proton Pump Inhibitors of the Health Resources Commission, reviewed the medical evidence comparing the effectiveness and safety of proton pump inhibitors. All available sources of information including OHSU's Evidence-based Practice Center report, *Drug Class Review on Proton Pump Inhibitors*, and additional information presented in public testimony were considered. Using all available sources of information, the subcommittee arrived at the following conclusions as supported by analysis of the medical literature.

*It is the decision of the PPI Update Subcommittee that the evidence does not demonstrate a clinical difference in efficacy to justify selection of any PPI as clinically superior to the other drugs in the class.*

*This includes consideration of comparative effectiveness and incidence and nature of adverse events between omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole. There are no clinically demonstrable differences amongst the PPIs whether treatment is for GERD, peptic ulcer, non-steroidal ulcer, duodenal ulcer, or eradication of *Helicobacter Pylori*.*

*No evidence supports difference in efficacy or adverse effects in subpopulations by race and ethnicity, age, gender, or co-morbidities.*

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## Health Resources Commission

The State of Oregon's Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative; two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The Commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the Commission subject to approval by a majority of the Commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.