

# Proton Pump Inhibitors

## Clinical Pearls for the Washington Rx Therapeutic Interchange Program (TIP)

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### Background

Following recommendations by the Washington State Pharmacy and Therapeutics Committee (P&T), the agency directors of the Department of Social and Health Services - Medical Assistance Administration (DSHS-MAA), Labor and Industries (LNI), and the Health Care Authority - Uniform Medical Plan (UMP) have named omeprazole Over-the-Counter (OTC) as their preferred drug in the drug class of Proton Pump Inhibitors (PPIs). This change is effective May 1, 2004. Furthermore, patients presenting with prescriptions for non-preferred agents from “endorsing practitioners” (i.e., providers that have signed the TIP agreement) may be automatically converted to preferred agents by pharmacists.

### Purpose

The purpose of this document is to inform pharmacists of the clinical, safety and cost rationale for these policy changes and to optimize their ability to assure safe and effective conversion of patients to the appropriate agents.

#### *PPIs Available in US*

Generic name	Omeprazole*^	Esomeprazole	Lansoprazole	Pantoprazole	Rabeprazole
Brand name	Prilosec	Nexium	Prevacid	Protonix	Aciphex
Manufacturer	Multiple	AstraZeneca	Tap Pharma	Wyeth-Ayerst	Eisai/Janssen
Dosage forms / strengths	10, 20, 40mg DR C	20, 40mg DR C	15, 30mg C 15, 30mg DR ODT 15, 30mg DR Susp (30ml)	20, 40mg DR EC T 40mg/vial IV injection	20mg DR EC T

DR=delayed release, EC=enteric coated, C=capsule, T=tablet, ODT=orally disintegrating tablet, IV = intravenous

\*Omeprazole is available in generic forms in 10 and 20mg capsules and over the counter as omeprazole magnesium (Prilosec 1, Procter and Gamble) in 20.6mg tablets equivalent to 20mg omeprazole, and in brand forms as 10,20 & 40mg capsules (Prilosec, AstraZeneca)

^Washington State Preferred Drug List Agents

### Clinical Pearls regarding PPI Efficacy

- Proton pump inhibitors (PPIs) reduce gastric acid by blocking the proton pump of the parietal cell. They are used to treat peptic ulcers, gastroesophageal reflux disease (GERD), and medication induced ulcers caused by aspirin or NSAIDs.
- Evidence to date suggests that all PPIs are similar in efficacy and safety. Studies also support the fact that PPIs are superior to histamine-2 receptor antagonists for the above conditions.
- In general, all PPIs are considered to be equivalent at their standard doses. No evidence exists to support clinical superiority of any PPI over another.
- Rabeprazole has been reported to have a faster onset of effect than other PPIs, however this is of limited clinical significance as all PPIs require several days for steady state proton pump inhibition and therapy is most often chronic.
- Patient variability in response may result in some loss of therapeutic effect when converting from one PPI to another, making dose adjustments necessary.
- Studies evaluating therapeutic interchange of PPIs support the ability to successfully convert patients from one PPI to another 72-95% of the time. The most common reasons for unsuccessful conversion are adverse effects and lack of efficacy.

### PPI Safety Summary

#### Adverse events

- Although no head to head studies exist that compare adverse events among PPIs, comparison trials indicate the safety and tolerability of all PPIs is similar. The incidence of all and serious adverse events in clinical trials is low, as are the drop out rates due to adverse events.
- The most common reported side effects with PPIs are gastrointestinal upset, headache, and diarrhea.

**Most frequently reported side effects (> 2% for at least one PPI) per package inserts**

Side Effect	Frequency of side effect (%)				
	Omeprazole	Esomeprazole	Lansoprazole	Pantoprazole	Rabeprazole
Abdominal pain	2.4-5.2*	3.8	2.1*	1	Listed as side effect, but frequency not reported
Diarrhea	3.0-3.7*	4.3	3.8*	4*	Listed as side effect, but frequency not reported
Flatulence	2.7	Not listed as side effect	<1	2	Listed as side effect, but frequency not reported
Nausea	2.2-4.0*	Not listed as side effect	1.3*	2	Listed as side effect, but frequency not reported
Vomiting	1.5	Not listed as side effect	<1	2	Listed as side effect, but frequency not reported
Headache	2.9-6.9	3.8	>1	6	2.4*

\* greater than placebo

Frequencies listed should not be compared between PPIs as they represent different clinical trials. Methods used to assess adverse events may have differed between clinical trials.

**Drug-interactions**

- There are few clinically relevant drug interactions with the PPIs.
- All PPIs share drug interactions with drugs whose absorption is affected by elevated gastric pH (ketoconazole, itraconazole, ampicillin, indinavir, digoxin, and iron salts).
- Omeprazole is known to inhibit CYPs 2C19 and 2C9 leading to decreases in the clearance of diazepam (levels increased 25-200%), phenytoin (levels increased 15-25%), and S-warfarin. Patients taking these medications who are started on or switched to omeprazole should be monitored for signs of adverse effects due to increased levels.
- Esomeprazole appears to reduce diazepam clearance by 45% and reduce phenytoin and warfarin metabolism. The clinical significance of these interactions is unclear, however patients should be monitored for adverse effects due to increased levels of diazepam, phenytoin, and warfarin when started on or switched to esomeprazole.
- Although rare, post-marketing reports of omeprazole, lansoprazole, and pantoprazole interactions with warfarin exist. This suggests a class effect for interactions between warfarin and PPIs. Patients taking warfarin who are started on a PPI should be monitored for increases in INR values.

**Special populations**

- PPIs do not require special dosing in the elderly, in renal impairment, or in mild to moderate hepatic impairment.
- All PPIs should be used with caution in severe hepatic impairment (Child Pugh Class C).
- Lansoprazole and omeprazole are reported to be safe and effective for treating acid-related disorders in children. Lansoprazole is approved for the treatment of GERD in children 1-11 years of age. Recommended starting doses are 1.5mg/kg/day.

**Cost Considerations and Comparisons**

- PPIs cost significantly more than histamine-2 receptor antagonists; however, studies support the cost-effectiveness of PPIs over histamine-2 receptor antagonists in the treatment and maintenance of GERD, healing and maintenance of peptic ulcer disease, and eradication of *Helicobacter pylori*.
- Omeprazole is the only PPI currently available as a generic and as an OTC product.

Agent / Dose	Cost for 30-Days Supply*
Omeprazole OTC 20mg daily	\$20
Esomeprazole 40mg daily Lansoprazole 30mg daily Omeprazole 20mg daily (generic Rx) Pantoprazole 40mg daily Rabeprazole 40mg daily	\$89 – 125 Note: Co-pays are typically \$20-30

\*Based on DSHS reimbursement formulas.

## Miscellaneous Considerations

### Patients with trouble swallowing tablets / capsules

- Omeprazole, esomeprazole, and lansoprazole capsules may be opened and sprinkled on food or mixed in orange juice. The stability of generic omeprazole mixed in orange juice has not been established.
- Omeprazole OTC tablets should not be crushed or mixed in juices.
- Lansoprazole is available as an orally disintegrating tablet and as granules.

## Converting Patients to the Preferred PPI

### Patient Assessment

- Intra-patient differences may make it necessary to adjust the dose of a PPI after converting from one agent to another. Patients should watch for recurrence or loss of symptom control such as worsening heartburn after eating or when lying down, reflux, or nausea. Loss of symptom control may occur less than a week after switching medications.
- Patients should be instructed to call the pharmacy about recurrence or worsening of symptoms. If the post-conversion dose of the new PPI is ineffective in controlling symptoms, an increase in dose may be needed. The pharmacist should consult with the prescriber for any dose adjustments.
- Adverse effects to one PPI may warrant switching to another PPI. This may require DSHS prior authorization.

### Patient Education and Consultation

Important patient education for managing GERD

- Avoid foods and beverages that aggravate heartburn
- Decrease the size of portions at mealtimes
- Avoid tight fitting clothing
- Lose weight if overweight
- Take the evening meal at least three hours before bedtime
- Avoid lying down after eating

### What to tell patients who are switched to omeprazole OTC

- You are being switched to a new PPI (proton pump inhibitor), similar to (previous PPI).
- Results from scientific studies show that all PPIs are similar in effectiveness and side effects.
- This medication replaces (previous PPI) and you should only be taking the new medication.
- Follow the directions on the bottle carefully, as the number of pills you take each day may have changed.
- This medication should be taken in the morning, ½ to 1 hour before the first meal of the day.
- Omeprazole OTC tablets should not be crushed or chewed.
- Call your pharmacy if you have any questions about the new medication. If your heartburn worsens talk to your pharmacist or physician.

## PPI dosing conversion guide

To use this chart, match the dose of the current PPI to the recommended dose for the preferred PPI. These are not absolute equivalent doses, but rather estimates based on approved dosage regimens and clinical trials comparisons. Considerations should be given for the patient's current status and inpatient variability in response.

omeprazole*	esomeprazole	lansoprazole	pantoprazole	rabeprazole
10mg daily	20mg daily	15mg daily	20mg daily	20mg daily
20mg daily	20mg daily	30mg daily	40mg daily	20mg daily
20mg bid or 40mg daily	40mg daily	30mg bid	40mg bid	20mg bid
40mg bid	80mg daily	60mg bid	80mg bid	40mg bid

\*MAA-DSHS Preferred PPI

## FDA approved indications and off-label uses

Indication	Omeprazole	Esomeprazole	Lansoprazole	Pantoprazole	Rabeprazole
<b>Duodenal Ulcers</b>					
Active treatment	20mg daily x 4-8 weeks	-----	15mg daily x 4 weeks	40mg daily x 2-4 weeks (OLU)	20mg daily x $\geq$ 4 weeks
Maintenance treatment	10-20mg daily (OLU)	-----	15mg daily	-----	-----
<i>Helicobacter pylori</i> eradication	20mg bid x 10 days in combination with amoxicillin and clarithromycin  or 40mg daily x 14 days in combination with clarithromycin	40mg daily x 10 days in combination with amoxicillin and clarithromycin	30mg bid x 10 or 14 days in combination with amoxicillin and clarithromycin  and 30mg q 8h x 14 days in combination with amoxicillin	-----	20mg bid x 7 days in combination with amoxicillin and clarithromycin
<b>Gastric Ulcers</b>					
Short term active treatment (non NSAID related)	40mg daily x 4-8 weeks		30mg daily x $\leq$ 8 weeks	40mg daily x 4 or 8 weeks (OLU)	20mg daily x 3 or 6 weeks (OLU)
Short term active treatment (NSAID related)	20mg daily x 4-8 weeks		30mg daily x 8 weeks	40mg daily x 12 weeks (OLU)	
Reduce risk (NSAID related)	20mg daily x 12 weeks (OLU)		15mg daily x $\leq$ 12 weeks	40mg daily x 12 weeks (OLU)	
<b>GERD</b>					
Symptomatic relief	20mg daily x 4 weeks	20mg daily x 4 weeks	15mg daily x $\leq$ 8 weeks	40mg daily x 4 or 8 weeks (OLU)	20mg daily x 4-8 weeks
Healing of erosive or ulcerative esophagitis	20mg daily x 4-8 weeks	20 or 40mg daily x 4-8 weeks	30mg daily x 8-16 weeks	40mg daily x 8-16 weeks	20mg daily x 4-8 weeks
Maintenance healing of erosive or ulcerative esophagitis	20mg daily	20mg daily	15mg daily	40mg daily	20mg daily
<b>Hypersecretory condition</b>					
Long term treatment of pathological hypersecretory conditions	60-360mg daily in 1 to 3 divided doses		60-180mg daily in one or two divided doses	80mg daily (PO) or 160mg daily (IV) in 2 divided doses up to 240mg daily	60 or 120mg daily in 1 or 2 divided doses

## References and Resources

- <http://www.gastromd.com/education/gerd.html>
- <http://www.aboutgerd.org/treatment.html>
- <http://www.oregonrx.org/OHPPRREPORTS.htm>
- VHA pharmacy Benefits management strategic healthcare group and the medical advisory panel. Abbreviated drug class review. Proton Pump Inhibitors. Available on line at [www.vapbm.org/reviews/ppiabbreviatedreview.pdf](http://www.vapbm.org/reviews/ppiabbreviatedreview.pdf)
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