Texas Vendor Drug Program

Drug Use Criteria: Proton Pump Inhibitors

Publication History

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Notes: Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with an asterisk [*]. The information contained is for the convenience of the public. The Texas Health and Human Services Commission is not responsible for any errors in transmission or any errors or omissions in the document.

Medications listed in the tables and non-FDA approved indications included in these retrospective criteria are not indicative of Vendor Drug Program formulary coverage.

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1 Dosage

Proton pump inhibitors (PPIs) are FDA-approved for managing duodenal and gastric ulcers, erosive esophagitis (EE), gastroesophageal reflux disease (GERD), hypersecretory conditions, and heartburn, preventing nonsteroidal anti-inflammatory drug (NSAID)-induced ulcers, and eradicating Helicobacter pylori (as a component of combination therapy).

Omeprazole/sodium bicarbonate combination therapy is FDA-approved for managing gastric and duodenal ulcer, EE, GERD, and upper gastrointestinal bleed risk reduction in critically ill patients.

Esomeprazole combined with naproxen is FDA-approved for use in osteoarthritis (OA), rheumatoid arthritis (RA), or ankylosing spondylitis (AS) in adult patients at greater risk for developing NSAID-induced gastric ulcers.

1.1 Adults

Maximum daily adult doses for PPIs when prescribed as acute and maintenance therapy, as well as components of combination treatments, are summarized in Tables 1 and 2. Dosages exceeding these recommended values will be reviewed.

Table 1: Adult Maximum Daily Acute Doses for Proton Pump Inhibitors (Monotherapy)

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
erosive esophagitis (EE)	dexlansoprazole (Dexilant®)	30 mg, 60 mg delayed- release capsules	60 mg/day
gastroesophageal reflux disease (GERD) - nonerosive			30 mg/day
EE	esomeprazole magnesium (Nexium®, generics)	20 mg, 40 mg delayed-release capsules; 2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg delayed-release powder for suspension	40 mg/day
GERD - nonerosive			20 mg/day
Helicobacter pylori eradication			80 mg/day

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
heartburn			20 mg/day
hypersecretory conditions			240 mg/day in divided doses
EE	esomeprazole strontium	49.3 mg (equivalent to 40 mg esomeprazole magnesium) delayed-release capsules	49.3 mg/day
Helicobacter pylori eradication			49.3 mg/day
hypersecretory conditions			295.8 mg/day in divided doses
duodenal ulcer	lansoprazole (Prevacid®, generics)	15 mg, 30 mg delayed-release capsules, 15 mg, 30 mg orally disintegrating tablets	15 mg/day
EE			30 mg/day
gastric ulcer			30 mg/day
GERD - nonerosive			15 mg/day
H. pylori eradication			90 mg/day (in divided doses)
heartburn			15 mg/day
hypersecretory conditions			180 mg/day in divided doses
NSAID-associated gastric ulcer			30 mg/day
duodenal ulcer	omeprazole (generics)	10 mg, 20 mg, 40 mg delayed-release capsule; 20 mg delayed-release orally disintegrating tablet; 2 mg/mL oral suspension	20 mg/day
EE			20 mg/day
gastric ulcer			40 mg/day
GERD - nonerosive			20 mg/day
heartburn			20 mg/day
H. pylori eradication			triple therapy: 40 mg/day in divided doses dual therapy: 40 mg/day
hypersecretory conditions			360 mg/day in divided doses

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
duodenal ulcer	omeprazole magnesium (Prilosec®)	2.5 mg, 10 mg packet with delayed-release granules for suspension	20 mg/day
EE			20 mg/day
gastric ulcer			40 mg/day
GERD - nonerosive			20 mg/day
H. pylori eradication			triple therapy: 40 mg/day in divided doses dual therapy: 40 mg/day
hypersecretory conditions			360 mg/day in divided doses
EE	pantoprazole (Protonix®, generics)	20 mg, 40 mg delayed-release tablets; 40 mg delayed-release granules for suspension	40 mg/day
hypersecretory conditions			240 mg/day in divided doses
duodenal ulcer	rabeprazole (Aciphex®, generics)	20 mg delayed-release tablet; 5 mg, 10 mg delayed-release sprinkle capsule	20 mg/day
EE			20 mg/day
GERD - nonerosive			20 mg/day
H. pylori eradication			40 mg/day (in divided doses)
hypersecretory conditions			120 mg/day in divided doses

Table 2: Adult Maximum Daily Acute Doses for Proton Pump Inhibitors (Combination Therapy)

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
duodenal ulcer	omeprazole/ sodium bicarbonate (Zegerid®, generics)	20 mg/1100 mg, 40 mg/1100 mg capsules; 20 mg/1680 mg, 40 mg/1680 mg packets for suspension	20 mg/day
EE			20 mg/day
gastric ulcer			40 mg/day

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
GERD - nonerosive			20 mg/day
heartburn			20 mg/day
upper GI bleed risk reduction in critically ill (suspension only)			40 mg/day

Table 3: Adult Maximum Daily Maintenance Dose for Proton Pump Inhibitors (Monotherapy)

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
erosive esophagitis (EE)	dexlansoprazole	30 mg, 60 mg delayed- release capsules	30 mg/day
heartburn			30 mg/day
EE	esomeprazole magnesium (Nexium®, generics)	20 mg, 40 mg delayed-release capsules; 2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg delayed-release powder for suspension	20 mg/day
hypersecretory conditions			240 mg/day in divided doses
risk reduction of NSAID-associated gastric ulcer			40 mg/day
hypersecretory conditions	esomeprazole strontium	49.3 mg (equivalent to 40 mg esomeprazole magnesium) delayed-release capsules	295.8 mg/day in divided doses
risk reduction of NSAID-associated gastric ulcer			49.3 mg once daily
duodenal ulcer	lansoprazole (Prevacid®, generics)	15 mg, 30 mg delayed-release capsules, 15 mg, 30 mg orally disintegrating tablets	15 mg/day
EE			15 mg/day
hypersecretory conditions			180 mg/day in divided doses
risk reduction of NSAID-associated gastric ulcer			15 mg/day

Treatment Indication	Drug Name	Dosage Form/Strength	Maximum Recommended Dosage
EE	omeprazole (Prilosec®, generics)	10 mg, 20 mg, 40 mg delayed-release capsule; 20 mg delayed-release orally disintegrating tablet; 2 mg/mL oral suspension	20 mg/day
hypersecretory conditions			360 mg/day in divided doses
EE	omeprazole magnesium (Prilosec®)	2.5 mg, 10 mg packet with delayed-release granules for suspension	20 mg/day
hypersecretory conditions			360 mg/day in divided doses
EE	pantoprazole (Protonix®, generics)	20 mg, 40 mg delayed-release tablets; 40 mg delayed-release granules for suspension	40 mg/day
hypersecretory conditions			240 mg/day in divided doses
EE	rabeprazole (Aciphex®, generics)	20 mg delayed-release tablet; 5 mg, 10 mg delayed-release sprinkle capsule	20 mg/day
hypersecretory conditions			120 mg/day in divided doses

Table 4: Adult Maximum Daily Maintenance Dose for Proton Pump Inhibitors (Combination Therapy)

Treatment Indication	Drug Name	Dosage Form/Strength	Maximum Recommended Dosage
prevention of NSAID-associated gastric ulcer in patients with osteoarthritis, rheumatoid arthritis, ankylosing spondylitis	esomeprazole/ naproxen (Vimovo®)	20 mg immediate-release/375 mg delayed-release, 20 mg immediate-release/500 mg delayed-release tablets	40 mg/1000 mg//day in divided doses
EE	omeprazole/ sodium bicarbonate (Zegerid®, generics)	20 mg/1100 mg, 40 mg/1100 mg capsules; 20 mg/1680 mg, 40 mg/1680 mg packets for suspension	20 mg/day

1.2 Pediatrics

Safety and efficacy of dexlansoprazole in patients less than 12 years of age as well as omeprazole/sodium bicarbonate and esomeprazole/naproxen in patients less than 18 years of age have not been established.

Esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole are FDA-approved for acute use in pediatric patients; doses are age-dependent. Omeprazole is the only PPI approved for erosive esophagitis maintenance therapy in pediatric patients. The maximum recommended daily pediatric doses for these PPIs are summarized in Tables 3 and 4. Dosages exceeding these recommendations will be reviewed.

Table 5: Pediatric Maximum Daily Acute Doses for Proton Pump Inhibitors

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
erosive esophagitis (EE)	dexlansoprazole (Dexilant®)	30 mg, 60 mg delayed- release capsules	12 to 17 years of age: 60 mg/day
gastroesophageal reflux disease (GERD) - nonerosive			12 to 17 years of age: 30 mg/day
EE due to only acid-mediated GERD	esomeprazole magnesium (Nexium®, generics)	20 mg, 40 mg delayed-release capsules; 2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg delayed-release powder for suspension	1 to 11 months of age: ○ 3 kg to 5 kg: 2.5 mg once daily ○ 5 kg to 7.5 kg: 5 mg once daily ○ 7.5 kg to 12 kg: 10 mg once daily
EE			1 to 11 years of age: ○ greater than or equal to 20 kg: 20 mg/day ○ Less than 20 kg: 10 mg/day 12 to 17 years of age: 40 mg/day
GERD - nonerosive			1 to 11 years of age: 10 mg/day 12 to 17 years of age: 20 mg/day

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
EE	lansoprazole (Prevacid®, generics)	15 mg, 30 mg delayed-release capsules, 15 mg, 30 mg orally disintegrating tablets	1 to 11 years of age: ○ greater than or equal to 30 kg: 30 mg/day* ○ Less than 30 kg: 15 mg/day greater than or equal to 12 years of age: 30 mg/day*
GERD - nonerosive			1 to 11 years of age: ○ less than 30 kg: 15 mg/day ○ greater than or equal to 30 kg: 30 mg/day greater than or equal to 12 years of age: 15 mg/day
EE	omeprazole (Prilosec®, generics)	10 mg, 20 mg, 40 mg delayed-release capsule; 20 mg delayed-release orally disintegrating tablet	1 month to less than 1 year of age: ○ 3 kg to less than 5 kg: 2.5 mg once daily ○ 5 kg to less than 10 kg: 5 mg once daily ○ greater than or equal to 10 kg: 10 mg once daily 1 to 16 years of age: ○ 5 kg to less than 10 kg: 5 mg once daily ○ 10 kg to less than 20 kg: 10 mg once daily ○ greater than or equal to 20 kg: 20 mg once daily
GERD - nonerosive			1 to 16 years of age: ○ 5 kg to less than 10 kg: 5 mg once daily ○ 10 kg to less than 20 kg: 10 mg once daily ○ greater than or equal to 20 kg: 20 mg once daily

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
EE	omeprazole magnesium (Prilosec®)	2.5 mg, 10 mg packet with delayed-release granules for suspension	1 month to less than 1 year of age: ○ 3 kg to less than 5 kg: 2.5 mg once daily ○ 5 kg to less than 10 kg: 5 mg once daily ○ greater than or equal to 10 kg: 10 mg once daily 1 to 16 years of age: ○ 5 kg to less than 10 kg: 5 mg once daily ○ 10 kg to less than 20 kg: 10 mg once daily ○ greater than or equal to 20 kg: 20 mg once daily
GERD - nonerosive			1 to 16 years of age: ○ 5 kg to less than 10 kg: 5 mg once daily ○ 10 kg to less than 20 kg: 10 mg once daily ○ greater than or equal to 20 kg: 20 mg once daily
EE	pantoprazole (Protonix®, generics)	20 mg, 40 mg delayed-release tablets; 40 mg delayed-release granules for suspension	greater than or equal to 5 years of age: ○ 15 kg to less than 40 kg: 20 mg/day ○ greater than or equal to 40 kg: 40 mg/day
GERD - nonerosive	rabeprazole (Aciphex®, generics)	20 mg delayed-release tablet; 5 mg, 10 mg delayed-release sprinkle capsule	1 to 11 years of age: ○ less than 15 kg: 5 mg/day+ ○ greater than or equal to 15 kg: 10 mg/day greater than or equal to 12 years of age: 20 mg/day

- * dose increased to 30 mg twice daily in some children who remained symptomatic after 2 weeks of therapy at lower doses conditions
- + may increase to 10 mg daily in those with inadequate response to 5 mg dose

Table 6: Pediatric Maximum Daily Maintenance Doses for Proton Pump Inhibitors

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
Monotherapy			

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
erosive esophagitis (EE)	dexlansoprazole (Dexilant®)	30 mg, 60 mg delayed- release capsules	12 to 17 years of age: 30 mg/day
EE	omeprazole (Prilosec®, generics)	10 mg, 20 mg, 40 mg delayed-release capsule; 20 mg delayed-release orally disintegrating tablet	1 to 16 years of age: ○ 5 kg to less than 10 kg: 5 mg once daily ○ 10 kg to less than 20 kg: 10 mg once daily ○ greater than or equal to 20 kg: 20 mg once daily
Combination Therapy			
juvenile idiopathic arthritis	esomeprazole/ naproxen (Vimovo®)	20 mg immediate-release/375 mg delayed-release, 20 mg immediate-release/500 mg delayed-release tablets	greater than or equal to 12 years: ○ 38 kg to less than 50 kg: 40 mg/750 mg/day in two divided doses ○ greater than or equal to 50 kg: 40 mg/1000 mg/day in two divided doses

Although not FDA-approved due to limited availability of guidelines and well-designed clinical trials, select proton pump inhibitors have been utilized in combination with antibiotic therapy to manage H. pylori in pediatric patients. The 2016 European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) guidelines for H. pylori management in pediatric patients recommend PPI doses of 1-2 mg/kg/day for 10 to 14 days as combination therapy or sequential therapy. Pediatric dosage recommendations for H. pylori management are summarized in Table 5.

Table 7: ESPGHAN / NASPGHAN Pediatric H. pylori Treatment Recommendations

Treatment Option	Maximum Recommended Dosage
Option 1: amoxicillin clarithromycin PPI	15-24 kg: 500 mg twice daily; 25-34 kg: 750 mg twice daily; greater than or equal to 35 kg: 1 g twice daily 15-24 kg: 250 mg twice daily; 25-34 kg: 500 mg in morning, 250 mg in evening; greater than or equal to 35 kg: 500 mg twice daily 15-24 kg: 20 mg twice daily; 25-34 kg: 30 mg twice daily; greater than or equal to 35 kg: 40 mg twice daily

Treatment Option	Maximum Recommended Dosage
Option 2: amoxicillin metronidazole PPI	15-24 kg: 500 mg twice daily; 25-34 kg: 750 mg twice daily; greater than or equal to 35 kg: 1 g twice daily 15-24 kg: 250 mg twice daily; 25-34 kg: 500 mg in morning, 250 mg+ in evening; greater than or equal to 35 kg: 500 mg twice daily 15-24 kg: 20 mg twice daily; 25-34 kg: 30 mg twice daily; greater than 35 kg: 40 mg twice daily
Option 3: bismuth salts amoxicillin metronidazole	less than 10 years: 262 mg four times daily; greater than or equal to 10 years: 524 mg four times daily 15-24 kg: 500 mg twice daily; 25-34 kg: 750 mg twice daily; greater than or equal to 35 kg: 1 g twice daily 15-24 kg: 250 mg twice daily; 25-34 kg: 500 mg in morning, 250 mg+ in evening; greater than or equal to 35 kg: 500 mg twice daily
Sequential therapy*: PPI + amoxicillin followed by PPI + metronidazole + clarithromycin	15-24 kg: 20 mg twice daily; 25-34 kg: 30 mg twice daily; greater than or equal to 35 kg: 40 mg twice daily 1 15-24 kg: 500 mg twice daily; 25-34 kg: 750 mg twice daily; greater than or equal to 35 kg: 1 g twice daily 15-24 kg: 20 mg twice daily; 25-34 kg: 30 mg twice daily; greater than or equal to 35 kg: 40 mg twice daily 1 15-24 kg: 250 mg twice daily; 25-34 kg: 500 mg in morning, 250 mg+ in evening; greater than or equal to 35 kg: 500 mg twice daily 15-24 kg: 250 mg twice daily; 25-34 kg: 500 mg in morning, 250 mg in evening; greater than or equal to 35 kg: 500 mg twice daily

- * sequential therapy = PPI + amoxicillin x 5 days followed by PPI + metronidazole + clarithromycin x 5 days
- + if oral metronidazole suspension used, dose may be divided equally every 12 hours

1.3 Dosage in Renal Impairment

Dosage adjustments are not necessary when PPIs are prescribed as monotherapy to patients with renal impairment. Omeprazole/sodium bicarbonate therapy also does not require dosage adjustments in renally impaired patients. However, the esomeprazole/naproxen combination is not recommended for use in patients with a creatinine clearance below 30 ml/min due to the potential for naproxen/naproxen metabolite accumulation and increased risk for adverse events.

2 Duration of Therapy

PPI acute treatment durations for both adult and pediatric patients based on FDA-approved indications are summarized in **Tables 5 and 6**.

Table 8: PPI Acute Duration of Therapy for Adult Patients

Treatment Indication	Drug Name	Maximum Therapy Duration
Monotherapy		
erosive esophagitis (EE)	dexlansoprazole (Dexilant®)	8 weeks
gastroesophageal reflux disease (GERD) - nonerosive		4 weeks
EE	esomeprazole magnesium (Nexium®, generics)	8 weeks^
GERD		4 weeks+
heartburn		14 days*
EE	esomeprazole strontium	8 weeks^
GERD		4 weeks+
duodenal ulcer	lansoprazole (Prevacid®, generics)	4 weeks
EE		8 weeks#
gastric ulcer		8 weeks
GERD		8 weeks
heartburn		14 days*
NSAID-associated gastric ulcer		without prior gastric ulcer: 8 weeks with prior gastric ulcer: 12 weeks
duodenal ulcer	omeprazole (Prilosec®, generics)	4 weeks+
EE		8 weeks#
gastric ulcer		8 weeks
GERD		4 weeks
heartburn		14 days*
duodenal ulcer	omeprazole magnesium (Prilosec®)	4 weeks+
EE		8 weeks#

Treatment Indication	Drug Name	Maximum Therapy Duration
gastric ulcer		8 weeks
GERD		4 weeks
EE	pantoprazole (Protonix®, generics)	8 weeks#
duodenal ulcer	rabeprazole (Aciphex®, generics)	4 weeks+
EE		8 weeks#
GERD		4 weeks+
Combination Therapy		
duodenal ulcer	omeprazole/ sodium bicarbonate (Zegerid®, generics)	4 weeks+
EE		8 weeks#
gastric ulcer		8 weeks
GERD		4 weeks

- ^ may consider an additional 4- to 8-week treatment course in patients who do not heal with initial treatment
- + may consider an additional 4-week treatment course in patients who do not heal with initial treatment
- # may consider an additional 8-week treatment course in patients with incomplete healing or EE recurrence after initial treatment
- * PPI treatment duration should not exceed 14 days during a 4-month period, unless alternate instructions are provided by a physician
- ~ treatment longer than 14 days has not been studied in critically ill patients

Table 9: PPI Acute Duration of Therapy for Pediatric Patients

Treatment Indication	Drug Name	Maximum Therapy Duration
Monotherapy		
erosive esophagitis (EE)	dexlansoprazole (Dexilant®)	12 to 17 years of age: 8 weeks
EE due to only acid-mediated GERD	esomeprazole magnesium (Nexium®, generics)	1 to 11 months of age: 6 weeks

Treatment Indication	Drug Name	Maximum Therapy Duration
EE		1 to 11 years of age: 8 weeks 12 to 17 years of age: 8 weeks
symptomatic GERD - nonerosive		1 to 11 years of age: 8 weeks 12 to 17 years of age: 4 weeks
EE	lansoprazole (Prevacid®, generics)	1 to 11 years of age: 12 weeks 12 to 17 years of age: 8 weeks
GERD		1 to 11 years of age: 12 weeks 12 to 17 years of age: 8 weeks
EE	omeprazole (Prilosec®, generics)	1 month to less than 1 year of age: 6 weeks 1 to 16 years of age: 12 weeks∞
EE	omeprazole magnesium (Prilosec®)	1 month to less than 1 year of age: 6 weeks 1 to 16 years of age: 8 weeks^
GERD		1 to 16 years of age: 4 weeks
EE	pantoprazole (Protonix®, generics)	greater than or equal to 5 years of age: 8 weeks
GERD	rabeprazole (Aciphex®, generics)	1 to 11 years of age: 12 weeks 12 to 17 years of age: 8 weeks

- ^ may consider an additional 4- to 8-week treatment course in patients who do not heal with initial treatment
- ∞ may consider additional 4- to 8-week treatment course with EE or GERD recurrence

In the acute setting in both adult and pediatric patients older than 11 months of age, 8 weeks of PPI therapy will treat EE and will heal most non-H. pylori duodenal and gastric ulcers. The prescribing health care provider may continue acute dosage

regimens for longer than 8 weeks in patients with hypersecretory disease states, esophagitis, or GERD, as well as those patients with risk factors for gastric ulcer treatment failure such as smoking. PPI acute dosage regimens may also exceed 8 weeks in patients with risk factors for delayed duodenal ulcer healing such as daily ethanol use, large ulcers, signs of upper GI bleeding, and/or a previous history of duodenal ulcer. Patients with refractory ulcers, defined as ulcers that do not respond to up to 12 weeks of anti-ulcer therapy, may also require extended PPI therapy. Treatment regimens at acute dosage levels lasting longer than four months (16 weeks) in patients with a diagnosis of acute duodenal or gastric ulcer will be reviewed.

Clinical trials support dexlansoprazole efficacy for maintenance of healed EE and heartburn relief for up to six months in adults and up to 16 weeks in pediatric patients 12 to 17 years of age.

Esomeprazole, when prescribed for risk reduction of NSAID-associated gastric ulcer, may be administered for up to six months, as controlled studies for this indication do not extend beyond this time period. Treatment regimens for NSAID-associated gastric ulcers extending beyond designated treatment times for esomeprazole and lansoprazole will be reviewed.

Unless otherwise specified, maintenance therapy, at the recommended daily maintenance dose (Tables 2 and 4), may be continued indefinitely based on patient need. Omeprazole treatment for EE and GERD in pediatric patients may continue indefinitely.

PPI treatment duration in adults for H. pylori eradication is summarized in Table 7. PPI therapy is prescribed for a maximum of 14 days in most patients, as treatment durations exceeding 14 days do not significantly increase eradication rates. In treatment failures, retreatment with an alternate antibiotic regimen has been beneficial. In these circumstances, patients may receive PPI therapy for a maximum of 28 days.

Table 10: Proton Pump Inhibitor Recommended Therapy Duration in Adults for H. pylori Eradication

Drug Name	Recommended Therapy Duration
esomeprazole	with triple therapy: 10 days
lansoprazole	with dual therapy: 14 days with triple therapy: 10-14 days

Drug Name	Recommended Therapy Duration
omeprazole	with ulcer present at treatment initiation dual or triple therapy: 28 days without ulcer present at treatment initiation dual therapy: 14 days triple therapy: 10 days
rabeprazole	with triple therapy: 7 days

Pediatric treatment regimens for *H. pylori* eradication reported in guidelines and clinical trials should be administered for 10 to 14 days. Pediatric sequential therapy for *H. pylori* eradication is comprised of a PPI plus amoxicillin administered for 5 days, followed by a PPI plus metronidazole plus clarithromycin given for 5 days.

3 Duplicative Therapy

The combination of two or more PPIs is not supported by the current literature. Additional clinical benefit is not realized when multiple PPIs are prescribed adjunctively. Therefore, concurrent use of multiple PPIs will be reviewed.

4 Drug-Drug Interactions

Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions. Drug-drug interactions considered clinically relevant for PPIs are summarized in Table 7. Only those drug-drug interactions identified as clinical significance level 1 or contraindicated, or those considered life-threatening which have not yet been classified will be reviewed.

Table 11: Major PPI Drug-Drug Interactions

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level#
dexlansoprazole, esomeprazole, lansoprazole, omeprazole	tacrolimus	adjunctive administration may result in increased tacrolimus serum levels as tacrolimus is metabolized by CYP3A4, and select PPIs are substrates for CYP3A4 and CYP2C19	avoid combination, if possible; if concurrent therapy necessary, monitor serum tacrolimus levels and observe for adverse events; adjust doses as needed	major, moderate (DrugReax) 3-moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level#
esomeprazole, omeprazole	cilostazol (Pletal®)	adjunctive use may increase cilostazol serum levels and enhance cilostazol pharmacologic/adverse effects as cilostazol is metabolized by CYP2C19 as esomeprazole and omeprazole are CYP2C19 inhibitors	reduce cilostazol dose by 50% when given concurrently with omeprazole and monitor for enhanced cilostazol pharmacologic/ adverse effects	moderate (DrugReax) 2-major (CP)
esomeprazole, omeprazole	citalopram (Celexa®)	adjunctive use may increase citalopram serum levels and enhance citalopram, pharmacologic/adverse effects (including QT interval prolongation) as citalopram is metabolized by CYP2C19 and esomeprazole and omeprazole are CYP2C19 inhibitors	citalopram dose should not exceed 20 mg/day if this drug combination is utilized; monitor for enhanced citalopram pharmacologic/ adverse effects	major (DrugReax) 2-major (CP)
esomeprazole, omeprazole, pantoprazole	methotrexate (MTX)	concurrent administration of select PPIs and MTX (primarily high-dose MTX) may result in elevated MTX parent and metabolite concentrations and the potential for enhanced pharmacologic and adverse effects; these PPIs reduce renal MTX elimination	use combination cautiously; monitor MTX levels and observe patients for signs/symptoms of adverse events; may use alternative PPI or H2RA that does not interact; may not occur with lower MTX doses	major (DrugReax) 2-major (CP)
PPIs	select azole antifungals (e.g., itraconazole, ketoconazole, posaconazole)	combined administration may decrease antifungal absorption and effectiveness; itraconazole, ketoconazole, and posaconazole dependent on acidic environment for favorable absorption and PPIs increase gastric pH	avoid concurrent administration, if possible; if PPI-antifungal combination necessary, may administer antifungal with acidic beverage (e.g., Coke) to increase absorption; monitor closely for continued antifungal efficacy	moderate (DrugReax) 2-major (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level#
PPIs	clopidogrel (Plavix®)	combined administration may attenuate clopidogrel effects on platelet aggregation, increase potential risk of secondary acute cardiovascular events following percutaneous coronary intervention or acute coronary syndrome; exact mechanism for interaction unknown, but PPIs may delay or minimize clopidogrel conversion to its active form by competitively inhibiting CYP2C19	avoid combined use, if possible; H2RAs# other than cimetidine or pantoprazole (has less CYP2C19 inhibitory activity) are suitable alternatives for acid suppressive therapy in patients requiring clopidogrel	major (DrugReax) 2-major (CP)
PPIs	dasatinib (Sprycel®)	adjunctive administration for extended duration may result in reduced dasatinib exposure and serum levels as dasatinib dependent on acidic gastric pH for solubility and absorption	combined use not recommended; alternative acid suppressives (e.g., antacids) should be given 2 hours before or 2 hours after dasatinib dose for optimal efficacy	major (DrugReax) 2-major (CP)
PPIs	delavirdine	combined use for extended treatment duration may result in reduced delavirdine absorption, decreased delavirdine serum levels, and attenuated delavirdine efficacy as delavirdine is dependent on an acidic gastric pH for absorption; separating drug doses may not improve delavirdine absorption as PPIs affect gastric pH for prolonged time period	concomitant use not recommended; antacids may be alternative acid suppressive therapy, with antacid and delavirdine doses separated by at least one hour	major (DrugReax) 2-major (CP)
PPIs	erlotinib (Tarceva®)	adjunctive administration may decrease erlotinib absorption and reduce effectiveness as erlotinib solubility, which is pH dependent, is reduced with PPI therapy	avoid combination, if possible; if adjunctive therapy necessary, use lowest effective PPI dose, monitor for reduced erlotinib efficacy, and adjust erlotinib dose as needed; may use alternate acid suppressive therapy (e.g., H2RAs, antacids); antacid and erlotinib doses should be separated by several hours	major (DrugReax)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level#
PPIs	mycophenolate	combined administration may result in decreased mycophenolic acid serum levels and reduced therapeutic efficacy, most likely due to decreased mycophenolate absorption with increased gastric pH	avoid combined use, if possible; if adjunctive therapy necessary, closely monitor mycophenolic acid serum levels and adjust mycophenolate doses as necessary	major (DrugReax)
PPIs	select protease inhibitors (e.g., atazanavir, indinavir, nelfinavir)	concurrent administration may result in reduced protease inhibitor serum levels and effectiveness and increased potential for resistance, as PPIs may interfere with protease inhibitor solubility and absorption by increasing gastric pH	avoid PPI and atazanavir, indinavir, or nelfinavir combinations	major (DrugReax) 1-severe: atazanavir, nelfinavir; 2-major: indinavir (CP)
PPIs	rilpivirine (Edurant®)	adjunctive administration may promote rilpivirine treatment failure and potential for impaired virologic response and rilpivirine/NNRI† resistance as rilpivirine requires more acidic gastric pH for absorption	combined administration contraindicated	contraindicated (DrugReax) 1-severe (CP)
PPIs	other agents with solubility affected by changes in gastric pH (e.g., bosutinib, ponatinib, vismodegib)	concomitant administration may result in reduced bioavailability and activity of agents requiring low gastric pH for solubility as PPIs increase gastric pH	avoid combination, if possible; if adjunctive therapy necessary, use lowest effective PPI dose, monitor for reduced efficacy of agents requiring low gastric pH for solubility, and adjust dose as needed; may use alternate acid suppressive therapy (e.g., H2RAs, antacids); antacid and doses for agents with solubility issues should be separated by several hours	major (DrugReax)
PPIs	vitamin K antagonists (e.g., warfarin)	concurrent administration may result in elevated INR^ levels and prothrombin time and enhanced anticoagulant effects; warfarin is metabolized by CYP2C19 and omeprazole is a CYP2C19 inhibitor, but mechanism for other PPIs is not well known	monitor INR levels and observe for bleeding issues/adverse effects; adjust warfarin doses as needed	moderate (DrugReax) 3-moderate (CP)

- *CP = Clinical Pharmacology

- # histamine (H2) receptor antagonists
- † non-nucleoside reverse transcriptase inhibitor
- ^ International Normalized Ratio

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