Texas Vendor Drug Program

Drug Use Criteria: Proton Pump Inhibitors

Publication History

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2. Revised **January 2023;** January 2021; December 2016; March 2015; June 2013; November 2011; September 2011; September 2009; June 2009; December 2005; November 2003; October 2002.

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).[1-9]

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.[1,2,10]

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.[1,2,11]

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 1-4. Dosages exceeding these recommended values will be reviewed.

Table 1. Adult Maximum Daily Acute Doses for Proton Pump Inhibitors – Monotherapy[1-9]

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
dexlansoprazole (Dexilant®)	30 mg, 60 mg delayed- release capsules	erosive esophagitis (EE)	60 mg/day
		gastroesophageal reflux disease (GERD) - nonerosive	30 mg/day

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
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	EE	40 mg/day
		GERD - nonerosive	20 mg/day
		Helicobacter pylori eradication	**40 mg/day***
		heartburn	20 mg/day
		hypersecretory conditions	240 mg/day in divided doses
lansoprazole (Prevacid®, generics)	15 mg, 30 mg delayed-release capsules, 15 mg, 30 mg orally disintegrating tablets	duodenal ulcer	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
omeprazole (Prilosec®, generics)	10 mg, 20 mg, 20.6 mg, 40 mg delayed-release capsule; 20 mg delayed-release orally disintegrating tablet	duodenal ulcer	20 mg/day
		EE	20 mg/day
		gastric ulcer	40 mg/day

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
		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
omeprazole magnesium (Prilosec®)	2.5 mg, 10 mg packet with delayed-release granules for suspension, 20.6 mg delayed-release capsule	duodenal ulcer	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
pantoprazole (Protonix®, generics)	20 mg, 40 mg delayed-release tablets; 40 mg delayed-release granules for suspension	EE	40 mg/day
		hypersecretory conditions	240 mg/day in divided doses
rabeprazole (Aciphex®, generics)	20 mg delayed-release tablet; 5 mg, 10 mg delayed-release sprinkle capsule	duodenal ulcer	20 mg/day

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
		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

Per ACG Guidelines, PPI dosing may be doubled depending on the regimen used for H. Pylori eradication[12]

Table 2. Adult Maximum Daily Acute Doses for Proton Pump Inhibitors – Combination Therapy[1,2,10]

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
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	duodenal ulcer	20 mg/day (as mg of omeprazole)
		EE	20 mg/day (as mg of omeprazole)
		gastric ulcer	40 mg/day (as mg of omeprazole)
		GERD - nonerosive	20 mg/day (as mg of omeprazole)
		heartburn	20 mg/day (as mg of omeprazole)
		upper GI bleed risk reduction in critically ill *(suspension only)*	**Day 1: 80 mg (in divided doses); Days 2-14: 40 mg/day (as mg of omeprazole)**

Table 3. Adult Maximum Daily Maintenance Dose for Proton Pump Inhibitors – Monotherapy[1-9]

Drug Name	Dosage Form/Strength	Treatment Indication	Maximum Recommended Dosage
dexlansoprazole (**Dexilant®**)	30 mg, 60 mg delayed- release capsules	erosive esophagitis (EE)	30 mg/day
		heartburn	30 mg/day
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	EE	20 mg/day
		hypersecretory conditions	240 mg/day in divided doses
		risk reduction of NSAID-associated gastric ulcer	40 mg/day
lansoprazole (Prevacid®, generics)	15 mg, 30 mg delayed-release capsules, 15 mg, 30 mg orally disintegrating tablets	duodenal ulcer	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
omeprazole (Prilosec®, generics)	10 mg, 20 mg, 40 mg delayed-release capsule; 20 mg delayed-release orally disintegrating tablet	EE	20 mg/day
		hypersecretory conditions	360 mg/day in divided doses
omeprazole magnesium (Prilosec®)	2.5 mg, 10 mg packet with delayed-release granules for suspension	EE	20 mg/day

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

Table 4. Adult Maximum Daily <u>Maintenance</u> Dose for Proton Pump Inhibitors – Combination Therapy [1,2,10,11]

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

1.2 Pediatrics

The safety and efficacy of dexlansoprazole and esomeprazole/naproxen in patients less than 12 years of age as well as omeprazole/sodium bicarbonate in patients less than 18 years of age have not been established.[1,2,8,10,11]

Esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole are FDA-approved for acute use in pediatric patients; doses are age-dependent.[1-7,13] **Omeprazole and dexlansoprazole are the only PPIs approved for erosive esophagitis maintenance therapy in pediatric patients.**[1,2,4,5,8] The maximum recommended daily pediatric doses for these PPIs are summarized in Tables 5-7. Dosages exceeding these recommendations will be reviewed.

Table 5. Pediatric Maximum Daily Acute Doses for Proton Pump Inhibitors – Monotherapy[1-8,13]

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
dexlansoprazole (Dexilant®)	30 mg, 60 mg delayed- release capsules	erosive esophagitis (EE)	*12 to 17 years of age:* 60 mg/day
		gastroesophageal reflux disease (GERD) - nonerosive	*12 to 17 years of age:* 30 mg/day
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	EE due to only acid-mediated GERD	*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:* ○ ≥ 20 kg: 20 mg/day ○ < 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

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
lansoprazole (Prevacid®, generics)	15 mg, 30 mg delayed-release capsules, 15 mg, 30 mg orally disintegrating tablets	EE	*1 to 11 years of age:* ○ ≥ 30 kg: 30 mg/day* ○ < 30 kg: 15 mg/day ***12 to 17 years of age**:* 30 mg/day*
		GERD - nonerosive	*1 to 11 years of age:* ○ ≤ 30 kg: 15 mg/day ○ > 30 kg: 30 mg/day ***12 to 17 years of age:*** 15 mg/day
omeprazole (Prilosec®, generics)	10 mg, 20 mg, 40 mg delayed-release capsule; 20 mg delayed-release orally disintegrating tablet	EE	*1 to 16 years of age:* ○ 5 kg to < 10 kg: 5 mg once daily ○ 10 kg to < 20 kg: 10 mg once daily ○ ≥ 20 kg: 20 mg once daily
		GERD - nonerosive	*1 to 16 years of age:* ○ 5 kg to < 10 kg: 5 mg once daily ○ 10 kg to < 20 kg: 10 mg once daily ○ ≥ 20 kg: 20 mg once daily
omeprazole magnesium (Prilosec®)	2.5 mg, 10 mg packet with delayed-release granules for suspension	EE	*1 month to < 1 year of age:* ○ 3 kg to < 5 kg: 2.5 mg once daily ○ 5 kg to < 10 kg: 5 mg once daily ○ ≥ 10 kg: 10 mg once daily *1 to 16 years of age:* ○ 5 kg to < 10 kg: 5 mg once daily ○ 10 kg to < 20 kg: 10 mg once daily ○ ≥ 20 kg: 20 mg once daily

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
		GERD - nonerosive	*1 to 16 years of age:* ○ 5 kg to < 10 kg: 5 mg once daily ○ 10 kg to < 20 kg: 10 mg once daily ○ ≥ 20 kg: 20 mg once daily
pantoprazole (Protonix®, generics)	20 mg, 40 mg delayed-release tablets; 40 mg delayed-release granules for suspension	EE	*≥ 5 years of age:* ○ 15 kg to < 40 kg: 20 mg/day ○ ≥ 40 kg: 40 mg/day
rabeprazole (Aciphex®, generics)	20 mg delayed-release tablet; 5 mg, 10 mg delayed-release sprinkle capsule	GERD - nonerosive	*1 to 11 years of age:* ○ < 15 kg: 5 mg/day+ ○ ≥ 15 kg: 10 mg/day *≥ 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[6]

+*may increase to 10 mg daily in those with inadequate response to 5 mg dose using the delayed-release sprinkle capsule*[13]

Table 6. Pediatric Maximum Daily Maintenance Doses for Proton Pump Inhibitors – Monotherapy[1,2,4,5,8]

Drug Name	Dosage Form/Strength	Treatment Indication	Maximum Recommended Dosage
dexlansoprazole (Dexilant®)	30 mg, 60 mg delayed- release capsules	erosive esophagitis (EE)	12 to 17 years of age: 30 mg/day
omeprazole (Prilosec®, generics)	10 mg, 20 mg, 40 mg delayed-release capsule; 20 mg delayed-release orally disintegrating tablet	EE	*1 to 16 years of age:* ○ 5 kg to < 10 kg: 5 mg once daily ○ 10 kg to < 20 kg: 10 mg once daily ○ ≥ 20 kg: 20 mg once daily

Drug Name	Dosage Form/Strength	Treatment Indication	Maximum Recommended Dosage
omeprazole magnesium (Prilosec®)	**2.5 mg, 10 mg packet with delayed-release granules for suspension**	**EE**	***1 to 16 years of age:*** ○ **5 kg to < 10 kg: 5 mg once daily** ○ **10 kg to < 20 kg: 10 mg once daily** ○ **≥ 20 kg: 20 mg once daily**

Table 7. Pediatric Maximum Daily Maintenance Doses for Proton Pump Inhibitors – Combination Therapy[1,2,11]

Drug Name	Dosage Form/Strength	Treatment Indication	Maximum Recommended Dosage
esomeprazole/ naproxen (Vimovo®, **generics**)	20 mg immediate-release/375 mg delayed-release, 20 mg immediate-release/500 mg delayed-release tablets	juvenile idiopathic arthritis	≥ 12 years: ○ 38 kg to < 50 kg: 40 mg/750 mg/day in two divided doses ○ ≥ 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 are summarized in Table 8.[14]**

Table 8. ESPGHAN/NASPGHAN Pediatric *H. pylori* Treatment Recommendations[14]

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

[#]if patient is resistant or allergic to amoxicillin and is > 8 years old, may substitute amoxicillin with a tetracycline antibiotic

1.3 Dosage in Renal Impairment

Dosage adjustments are not necessary when PPIs are prescribed as monotherapy to patients with renal impairment.[1-9,13] Omeprazole/sodium bicarbonate therapy also does not require dosage adjustments in renally impaired patients.[1,2,10]

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.[1,2,11]

2 Duration of Therapy

PPI acute treatment durations for both adult and pediatric patients based on FDA-approved indications are summarized in Tables 9-11.

Table 9. PPI Acute Duration of Therapy for Adult Patients – Monotherapy[1-9]

Drug Name	Treatment Indication	Maximum Therapy Duration
dexlansoprazole (Dexilant®)	erosive esophagitis (EE)	8 weeks
	gastroesophageal reflux disease (GERD) - nonerosive	4 weeks
esomeprazole magnesium (Nexium®, generics)	EE	8 weeks^
	GERD	4 weeks+
	heartburn	14 days*
esomeprazole strontium	EE	8 weeks^
	GERD	4 weeks+
lansoprazole (Prevacid®, generics)	duodenal ulcer	4 weeks
	EE	8 weeks#
	gastric ulcer	8 weeks
	GERD	8 weeks
	heartburn	14 days*

Drug Name	Treatment Indication	Maximum Therapy Duration
	NSAID-associated gastric ulcer	*without prior gastric ulcer:* 8 weeks *with prior gastric ulcer:* 12 weeks
omeprazole (Prilosec®, generics)	duodenal ulcer	4 weeks[+]
	EE	8 weeks[#]
	gastric ulcer	8 weeks
	GERD	4 weeks
	heartburn	14 days[*]
omeprazole magnesium (Prilosec®)	duodenal ulcer	4 weeks[+]
	EE	8 weeks[#]
	gastric ulcer	8 weeks
	GERD	4 weeks
pantoprazole (Protonix®, generics)	EE	8 weeks[#]
rabeprazole (Aciphex®, generics)	duodenal ulcer	4 weeks[+]
	EE	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

Table 10. PPI Acute Duration of Therapy for Adult Patients – Combination Therapy[1,2,10]

Drug Name	Treatment Indication	Maximum Therapy Duration
omeprazole/ sodium bicarbonate (Zegerid®, generics)	duodenal ulcer	4 weeks[+]
	EE	8 weeks[#]
	gastric ulcer	8 weeks
	GERD	4 weeks

[+]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

Table 11. PPI Acute Duration of Therapy for Pediatric Patients – Monotherapy[1-8,13]

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

Drug Name	Treatment Indication	Maximum Therapy Duration
	GERD	*1 to 11 years of age:* 12 weeks *12 to 17 years of age:* 8 weeks
omeprazole (Prilosec®, generics)	EE	*1 to 16 years of age:* 12 weeks∞
omeprazole magnesium (Prilosec®)	EE	*1 month to < 1 year of age:* 6 weeks *1 to 16 years of age:* **12 weeks^**
	GERD	*1 to 16 years of age:* 4 weeks
pantoprazole (Protonix®, generics)	EE	*≥ 5 years of age:* 8 weeks
rabeprazole (Aciphex®, generics)	GERD	*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 gastric ulcers**, and **at least 4 weeks of PPI therapy** will heal most non-*H. pylori* duodenal ulcers. [1-9,13] 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.[1-9, 13, 15,16] 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.[15,16] 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.[15,16] 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.[8]

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.[3] **Lansoprazole, when prescribed for risk reduction of NSAID-associated gastric ulcer, may be administered for up to 12 weeks, as controlled studies for this indication do not extend beyond this time. If lansoprazole is prescribed for healing NSAID-associated gastric ulcer, it may be administered for up to 8 weeks, as controlled studies for this indication do not extend beyond this time.[6]** 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.[4,5]

PPI treatment duration in adults for *H. pylori* eradication is summarized in Table 12. 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.[12]

Table 12. Proton Pump Inhibitor Recommended Therapy Duration in Adults for *H. pylori* Eradication[3-6,9]

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

Drug Name	Recommended Therapy Duration
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.[14,17] 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.[14,17]

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 13. 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 13. Major PPI Drug-Drug Interactions[1-11,13]

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
dexlansoprazole, esomeprazole, lansoprazole, omeprazole	tacrolimus	adjunctive administration may result in increased tacrolimus serum levels **especially in intermediate or poor metabolizers of CYP2C19** as tacrolimus is metabolized by **CYP3A** 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)
esomeprazole, omeprazole	cilostazol (Pletal®)	adjunctive use may increase cilostazol **and one of its active metabolites** 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 **or esomeprazole** and monitor for enhanced cilostazol pharmacologic/ adverse effects	**major (Micromedex)** 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, **and citalopram should be discontinued in patients with persistent QTc measurements > 500 ms**; monitor for enhanced citalopram pharmacologic/ adverse effects	major (DrugReax), **3-moderate** (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
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	**major (Micromedex)** 2-major (CP)
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)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
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	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), **2-major (CP)**
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), 3-moderate (CP)
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-contraindicated**: atazanavir; 2-major: **nelfinavir,** indinavir (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
PPIs	**Atezolizumab (Tecentriq®)**	**use within 30 days of taking a PPI may decrease microbiota alpha diversity associated with enhanced antitumor immune activity of atezolizumab**	**Avoid concurrent use, if possible**	**Major (Micromedex)**
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-**contraindicated** (CP)
PPIs	other agents with solubility affected by changes in gastric pH (e.g., **acalabrutinib,** bosutinib, **pazopanib,** ponatinib, **tyrosine kinase inhibitors,** 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)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
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 **CYP450 (eg 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

5 References

1. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www-micromedexsolutions-com.libproxy.uthscsa.edu/ (cited: **November 21, 2022**).
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; **2022**. Available at: http://clinicalpharmacology-ip.com.ezproxy.lib.utexas.edu/. Accessed **November 21, 2022**.
3. Esomeprazole (Nexium®) package insert. AstraZeneca Pharmaceuticals LP, **March 2022**.
4. **Omeprazole (Prilosec®) package insert. Lannett Company, February 2022.**
5. Omeprazole magnesium delayed-release oral suspension (Prilosec®) package insert. Covis Pharma, **March 2022.**
6. Lansoprazole (Prevacid®) package insert. Takeda Pharmaceuticals America, Inc., **March 2022.**
7. Pantoprazole (Protonix®) package insert. Pfizer, **March 2022**.
8. Dexlansoprazole (Dexilant®) package insert. Takeda Pharmaceuticals America, Inc., **March 2022**.
9. Rabeprazole (Aciphex®) package insert. **Woodward Pharma Services, March 2022.**
10. Omeprazole/sodium bicarbonate (Zegerid®) package insert. Santarus, Inc., **March 2022**.

11. Naproxen/esomeprazole (Vimovo®) package insert. Horizon Pharma USA Inc., **March 2022.**
12. **Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: Treatment of Helicobacter pylori Infection [published correction appears in Am J Gastroenterol. 2018 Jul;113(7):1102]. Am J Gastroenterol. 2017;112(2):212-239. doi:10.1038/ajg.2016.563**
13. **Rabeprazole (Aciphex®) package insert. Sarras Health, December 2020.**
14. Jones NL, Koletzko S, Goodman K, et al., on behalf of ESPGHAN, NASPGHAN. Joint ESPGHAN/NASPGHAN guidelines for the management of *Helicobacter pylori* in children and adolescents (update 2016). J Pediatr Gastroenterol Nutr. 2017;64:991-1003.
15. **Love BL. Peptic ulcer disease and related disorders. In: DiPiro JT, Yee GC, Posey L, Haines ST, Nolin TD, Ellingrod V. eds. Pharmacotherapy: A Pathophysiologic Approach, 12e. McGraw-Hill; Accessed November 29, 2022. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=267240133**
16. **Ramakrishnan K, Salinas RC. Peptic ulcer disease. Am Fam Physician. 2007;76(7):1005-1012**.
17. Ertem D. Clinical practice: Helicobacter pylori infection in childhood. Eur J Pediatr. 2013;172(11):1427-34.