Oral Proton Pump Inhibitors in Children

Esomeprazole (Nexium® – AstraZeneca)
Lansoprazole (Prevacid® – TAP Pharmaceuticals)
Omeprazole (Prilosec® – AstraZeneca; Zegerid® – Santarus; Generics)
Pantoprazole (Protonix® – Wyeth)
Rabeprazole (Aciphex® – Eisai Inc.)
AHFS 56:28.36, Proton Pump Inhibitors

There are currently five oral proton pump inhibitors (PPIs) available in the US – esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole. Omeprazole is the only PPI available as a generic product. Three of the agents are labeled for use in children, as follows:[1-6]

- Lansoprazole is indicated for the treatment of gastroesophageal reflux disease (GERD) and erosive esophagitis in children ages 1 to 17 years.[2]
- Omeprazole is indicated for the treatment of GERD and erosive esophagitis in children 2 to 16 years.[4]
- Esomeprazole is indicated for treatment of GERD in adolescents 12 to 17 years.[1]

Of the acid-related disorders occurring in children, GERD is more common than peptic ulcer disease or gastropathies.[7] Table 1 summarizes the labeled indications for the available oral PPIs. Table 2 compares the oral PPIs with regard to availability, pharmacokinetics, dosing and administration in children.

Table 1. Labeled Indications for the Oral PPIs[1-6]

Use	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Treatment of GERD	X - adult X - pediatric	X - adult X - pediatric	X - adult X - pediatric		X - adult
Helicobacter pylori eradication to reduce the risk of duodenal ulcer recurrence	X - adult	X - adult	X - adult		X - adult
Short-term (i.e., 8 weeks) treatment of erosive esophagitis associated with GERD	X - adult	X - adult X - pediatric	X - adult X - pediatric	X - adult	X - adult
Duodenal ulcer		X - adult	X – adult		X - adult
Gastric ulcer		X - adult	X - adult		
Maintenance healing of erosive esophagitis	X - adult	X - adult	X - adult X- pediatric	X - adult	X - adult
Pathological hypersecretory conditions	X - adult	X - adult	X - adult	X - adult	X - adult
Healing and risk reduction of NSAID associated gastric ulcer	X - adult	X - adult			
Reduction of risk for upper GI bleeding in critically ill patients			X - adult		

Table 2. Comparison of Available Oral Proton Pump Inhibitors in Children[1-6, 8-20]

Parameter	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Dosage Forms Available	Delayed-release Capsules: 20 mg, 40 mg Delayed-release Oral Suspension: 20 mg packet, 40 mg packets	Delayed-release Capsules: 15 mg, 30 mg Delayed-release Orally Disintegrating Tablets: 15 mg, 30 mg (Prevacid® SoluTab™) Delayed-release Oral Suspension: 15 mg packet, 30 mg packet Oral Combinations: Amoxicillin / Clarithromycin / Lansoprazole (Prevpac®); Lansoprazole / Naproxen (Naprapac®)	Immediate-release Capsules: 20 mg, 40 mg (Zegerid®, contains sodium bicarbonate) Immediate-release Powder for Oral Suspension: 20 mg packet, 40 mg packet (Zegerid®, contains sodium bicarbonate) Delayed-release Capsules: 10 mg, 20 mg, 40 mg (Prilosec®, generics) Delayed-release Tablets: 20 mg (Prilosec® OTC)	Delayed-release Tablets: 20 mg, 40 mg	Delayed-release Tablets: 20 mg
Oral Bioavailability	Initial dose: 64% Repeat doses: 90%	> 80%	Initial dose: 30% – 40% Repeat doses: 65%[21, 22]	77%	52%
Absorption	Tmax 1.75 – 2 hours Cmax after repeated doses: 20 mg: 1.45 microMol/L 40 mg: 5.13 microMol/L	Tmax 1.5 – 1.7 hours Cmax after 15 mg daily for 5 days: Children 1 – 11 years: 791 mcg/L Adolescents:[23] 415 mcg/L	Tmax: 2 hours Cmax after repeated doses of 1 mg/kg/day: Age 2 – 5 years: 539 ng/mL Age 6 – 16 years: 851 ng/mL	Adults Tmax 2.5 hours Cmax after 40 mg/day repeated doses: 2.5 mcg/mL.	Adults Tmax: 2 to 5 hours
Elimination Half-Life	1.2 – 1.5 hours	Adults: 1.5 hours Children:[23] 0.68 – 0.95 hours	1 hour	1 hour	1 – 2 hours
Duration of action[10]	> 24 hours	> 24 hours	> 24 hours	> 24 hours	24 hours
Gastric pH effects	No data in children Percent of 24 hour period intragastric pH above 4: 53% for 20 mg for 5 days and 70% for 40 mg.	Percent of 24 hour period intragastric pH above 4: 47% for 15 mg.	Percent of 24 hour period intragastric pH above 4: 72% for 0.6 mg/kg/day[24]	Percent of 24 hour period intragastric pH above 3: 39% on pantoprazole 20 mg/day.	No data in children In adults, percent of 24 hour period intragastric pH above 4, 60.3% on 20 mg daily for 8 days.
Route of Elimination	Metabolized by CYP 2C19, 3A4. Excreted 80% urine, 20% feces.	Metabolized by CYP 2C19, 3A4. Excreted 33% urine, 67% feces.	Metabolized by CYP 2C19, 3A4. Excreted 77% urine, 23% feces.	Metabolized by CYP 2C19, 3A4. Excreted 71% urine, 18% feces.	Metabolized by CYP 2C19, 3A. Excreted 90% urine, 10% feces.

Abbreviations: Cmax = peak plasma concentration; CYP = cytochrome P450; Tmax = time to peak plasma concentration.

Table 2. Comparison of Available Oral Proton Pump Inhibitors in Children (continued)

Parameter	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Dosing per product labeling	Ages 12 – 17 years: 20 mg or 40 mg once daily for 8 weeks.	Ages 1 – 11 years: Weight ≤ 30 kg: 15 mg once daily for up to 12 weeks. Weight > 30 kg: 30 mg once daily for up to 12 weeks. (Can increase to twice daily if needed) Ages 12 – 17 years: Nonerosive GERD: 15 mg once daily for 8 weeks. Erosive GERD: 30 mg once daily for 8 weeks.	Ages 2 and older: Weight < 20 kg: 10 mg/d Weight ≥ 20 kg: 20 mg/d	Not labeled.	No data.
Dosing – other references	Esomeprazole 5 to 10 mg/day has been given to children ages 1 – 5 years, and esomeprazole 10 to 20 mg/day has been given to children ages 6 – 11 years.[25]	Guidelines recommend a starting dose of 1.4 mg/kg/day for GERD in infants and children.[26]	Omeprazole doses of 0.7 to 3.5 mg/kg/day have been used in uncontrolled studies.[27]	In children ages 5 – 17 years, pantoprazole 20 mg to 80 mg/day has been used.[28]	No data.
Dosage Adjustments for Hepatic or Renal Insufficiency	No dosage adjustment needed in renal or mild to moderate hepatic impairment. For severe liver impairment, do not exceed 20 mg/day.	No dosage adjustment needed in renal or mild to moderate hepatic impairment. For severe liver impairment, consider using a lower dose.	No dosage adjustment needed in renal or mild to moderate hepatic impairment. For severe liver impairment, consider using a lower dose.	No dosage adjustment needed in renal or hepatic impairment. No dosage adjustment for hemodialysis.	No dosage adjustment needed in renal or mild to moderate hepatic impairment.
Genetic polymorphism (occurs in 3% of Caucasians or African-Americans; and in 17 – 23% of Asians)	Drug exposure increases 2-fold.	Drug exposure increases 2-fold.	Drug exposure increases 4-fold.	Half-life increases to 3.5 to 10 hours. Less than 23% accumulation.	Drug exposure increases 50% to 60%
Effect of food on absorption	Drug exposure decreased 43 – 53% after food intake.	Drug exposure decreased 50 – 70% if taken with food.	Minimal effect	Minimal effect	Minimal effect

Abbreviations: Cmax = peak plasma concentration; CYP = cytochrome P450; Tmax = time to peak plasma concentration.

Table 2. Comparison of Available Oral Proton Pump Inhibitors in Children (continued)

Parameter	**Esomeprazole**	**Lansoprazole**	**Omeprazole**	**Pantoprazole**	**Rabeprazole**
Comments	Give 1 hour before meals. Delayed-release capsules: Swallow whole. If needed, capsules can be opened and sprinkled on semisolid food or mixed with acidic fruit juice, then given immediately. Intact granules may mixed with water or acidic fruit juice and poured down gastric tube; flush tube with additional liquid after giving. Oral Suspension: Mix oral suspension packets with 15 mL water. Allow to thicken for 2 – 3 minutes, then stir or shake. Give orally or via nasogastric or gastric tube within 30 minutes. Add additional water to the mixing container to flush any remaining contents, mix, and give immediately.	Give before meals. Delayed-release capsules: Swallow whole. If needed, capsules can be opened and sprinkled on semisolid food or mixed with acidic fruit juice. Intact granules may be mixed with acidic juice and poured down gastric tube; flush tube with additional juice after giving. Orally disintegrating tablet: Contains phenylalanine. Place on tongue and allow to disintegrate; may swallow particles after disintegration. If needed, may be given via oral syringe or nasogastric tube. Put a single tablet in a syringe and draw up appropriate amount of water: 4 mL for 15 mg SoluTab, 10 mL for 30 mg SoluTab. Gently shakesyringe to disperse tablet, then given within 15 minutes. Draw an additional 2 – 5 mL water into the syringe to give any remaining contents and flush tube. Oral suspension: Mix packet contents with 30 mL water, stir well, and give immediately. Add additional water to mixing container to flush any remaining contents, mix, and give immediately. Do not give through enteral feeding tubes.	Give 1 hour before meals. Do not use immediate-release products (Zegerid) in patients with metabolic alkalosis and hypocalcemia. Use immediate-release products with caution in patients with acid-base disorders or patients on sodium restriction. Immediate-release capsules: Contains sodium bicarbonate 13 mEq/capsule. Swallow capsule whole. Do not open capsules, mix with liquids, or sprinkle on food. Immediate-release suspension: Mix packet contents with appropriate amount of water: 15 – 30 mL for oral administration, 20 mL for gastric tubes. Stir well and give immediately. Add additional water to mixing container to flush any remaining contents, mix, and give immediately. For patients on enteral feeding, hold feeds for 3 hours before and 1 hour after giving. Contains sodium bicarbonate 20 mEq/packet. Delayed-release capsules: Swallow whole. If needed, can be opened and sprinkled on semisolid food or mixed with acidic fruit juice, then given immediately. Intact granules may be mixed with acidic fruit juice and poured down gastric tube; flush tube with additional juice after giving. Delayed-release tablets: Do not crush, chew, or split tablets.	Give before meals so proton pumps are maximally activated. Delayed-release tablets should not be crushed, chewed or split.	Give before meals so proton pumps are maximally activated. Delayed-release tablets should not be crushed, chewed or split.

Abbreviations: Cmax = peak plasma concentration; CYP = cytochrome P450; Tmax = time to peak plasma concentration.

Are there differences in the pharmacokinetic profiles of the PPIs in children compared to adults?

The pharmacokinetic profiles of the PPIs vary between children and adults. Lansoprazole and omeprazole are the best studied PPIs in pediatrics,[9, 10, 24, 29-37] although esomeprazole has also been evaluated.[38, 39] Litalien et al have published an extensive review of the pharmacokinetic profiles of the PPIs in children.[40] Children have age-related enhanced metabolic capacity. Children under 10 years of age often require higher doses on a per-kilogram basis than adults.[29, 38] Adolescents, age 12 to 17 years, have similar pharmacokinetic profiles to adults. One reason for the difference in pharmacokinetics in children has to do with the metabolic activity in the liver of the cytochrome P450 isoenzymes, 2C19 and 3A4. These enzymes have reduced activity at birth but reach adult levels in early infancy (about 3 months of age) and then exceed adult levels in childhood. Enzymatic activity returns to adult levels after puberty.[29, 41] Another factor that affects PPI activity in children is the immaturity of parietal cells during the first months of life. Grahnquist et al has demonstrated the H+/K+ ATPase is present from week 25 of gestation and activity increases with gestational age, continuing for the first 3 months of life.[42] By six months of age, maximal acid output is about the same level as older children and adults.[40] Bioavailability of the PPIs is potentially affected by altered gastric emptying and gut transit time in infants and children.[43] Further studies of the PPIs in different pediatric age groups are needed to fully understand the differences in pharmacokinetic profiles between adults and children.

Summary of differences in pharmacokinetic profiles of PPIs in children compared to adults:

- Decreased PPI metabolism in newborns.
- Increased metabolism of PPIs in children between the ages of 1 year and onset of puberty.
- Faster clearance of PPIs in children compared to adults.
- Children require greater doses of PPIs on a milligram per kilogram basis.

Clinical Efficacy

Most of the efficacy data for using PPIs in pediatric patients are with omeprazole (26 studies)[31, 44-68] or lansoprazole (11 studies).[11, 35-37, 69-77] Published data with esomeprazole (excluding abstracts) are limited to one pharmacokinetic study in children aged 1 – 11 years,[38]one pharmacokinetic study in adolescents,[39] a descriptive study using esomeprazole to control cysteamine-induced gastric hypersecretion in 12 patients with cystinosis,[78] and a descriptive study comparing the effect of esomeprazole and ranitidine on asthma exacerbations in 44 patients with asthma and GERD.[79] Published data with pantoprazole are limited to one randomized trial in adolescents with GERD,[80] and one descriptive study in 15 patients with reflux esophagitis.[81] There are no published data for rabeprazole.

GERD

There are six experimental studies evaluating the PPIs in children with GERD,[36, 44, 45, 67, 68, 80] one observational case-control study,[31] and 16 descriptive, non-comparative studies.[11, 35, 37, 46-54, 66, 69-72, 81] No study compared different PPIs. In the only study directly comparing a PPI with an H_2-antagonist, omeprazole and ranitidine were equally effective at preventing relapse in 46

patients randomized to 6 months of maintenance therapy after initial treatment with omeprazole for 3 months.[68] The experimental studies indicate that PPIs (lansoprazole and omeprazole) can significantly increase intragastric pH compared to baseline in children and adolescents and can decrease reflux time in infants. Pantoprazole relieves GERD symptoms in adolescents although effects on intragastric pH have not been evaluated. There are no randomized controlled trials that describe esophageal healing rates in pediatric patients with esophagitis. In descriptive open-label, non-randomized studies, healing rates for omeprazole range from 40% to 95% and healing rates for lansoprazole range from 75% to 78%.

- *Is any one PPI superior to another for the treatment of GERD in children?*

No data are available comparing one PPI to another in children with GERD.

Helicobacter pylori Infection

There are 20 published studies describing the use of PPIs in combination with antibiotics for the eradication of *H. pylori* infection.[55-65, 73-77, 82-85] In both experimental and descriptive studies, eradication rates for an omeprazole based triple therapy regimen range from 69% to 94% and for a lansoprazole based triple therapy regimen range from 54% to 87%. Treatment of *H. pylori* is recommended for children who have endoscopically diagnosed duodenal or gastric ulcer and *H. pylori* present on histology or if they have an active *H. pylori* infection and a history of duodenal or gastric ulcer. Proton pump inhibitors are preferred over H_2-antagonists in triple therapy regimens for *H. pylori*. There are no comparative trials between the PPIs.

- *Is any one PPI superior to another for the treatment of Helicobacter pylori infection in children?*

No data are available comparing one PPI to another in children with *H. pylori* infection.

Are there patient subgroups based on demographics (racial groups, gender), other medications, or co-morbidities for which any one PPI is more effective or safer than another?

There are no pediatric data describing differences between the PPIs in patients of various racial groups or genders, or in patients with renal or hepatic dysfunction.

Disability. GERD occurs frequently in children with intellectual and physical disability (eg, mental retardation, cerebral palsy). Omeprazole has been found safe and effective in children with intellectual disability, GERD and Grade I to IV esophagitis. Empiric therapy with PPIs may be more frequently employed in this population because endoscopy may be too stressful for these patients.[46, 48, 86]

Adverse Drug Reactions

Safety data for the use of PPIs in pediatrics come from the product labeling of lansoprazole, omeprazole, and esomeprazole, and a few clinical trials.[1-6, 28] The PPIs are well-

tolerated in short term trials. Drug discontinuation rates are not reported in any of the product labeling for the PPIs.[1-6]

What are the common adverse effects associated with the PPIs in pediatric patients?

For esomeprazole, the most frequently reported adverse events are headache (8.1%), abdominal pain (2.7%), diarrhea (2%), and nausea (2%).[1] For lansoprazole the most frequently reported adverse events are constipation (5%) and headache (3%) in children ages 1 to 11 years. For adolescents, the most frequent adverse events are headache (7%), abdominal pain (5%), nausea (3%), and dizziness (3%).[2] For omeprazole, respiratory system adverse events occurred in 46% of children ages 0 to 2 years and 18.5% of children ages 2 to 16 years. Otitis media was reported in 22.6% of children.[4] For pantoprazole, the most common treatment emergent adverse effect was headache (35%).[28] Other rarely reported adverse effects with the PPIs include abdominal pain, constipation, flatulence, dizziness and an increase in liver enzymes.

What are the long-term safety concerns for PPIs in pediatric patients?

Elevated gastrin levels and parietal cell hyperplasia can occur in both adults and children treated with long-term PPIs. The concern with elevated gastrin levels is that they will stimulate enterochromaffin-like (ECL) cells to grow and potentially turn into carcinoid tumors. In adults, an increased risk of gastric carcinoid tumors has not been found to date. The concern with parietal cell hyperplasia is that the enlarged parietal cells will obstruct the neck of the fundic glands and precipitate fundic cysts and polyps. The significance of this is unknown in the pediatric population.[1, 2, 4, 5, 43]

Which PPIs are available in dosage forms suitable for administration to children or other patients who are unable to swallow whole tablets or capsules?

Esomeprazole, lansoprazole, and omeprazole are the most appropriate PPIs for use in children or other patients who are unable to swallow whole tablets or capsules.[1-4, 12-20] All three drugs are available in oral suspension dosage forms. In addition, the agents are available as delayed-release capsules which may be opened and administered as intact granules if needed; the intact granules are either sprinkled on semisolid food or mixed with liquid immediately prior to administration (refer to Table 2 for specific instructions).[1-4, 12-20] Lansoprazole is also available as an orally disintegrating tablet which is allowed to dissolve in the mouth prior to swallowing.[2]

Pantoprazole and rabeprazole are available only as delayed-release tablets, which may not be chewed, crushed, or split.[5, 6] No alternate dosage forms of pantoprazole or rabeprazole are available for use in children or other patients who are unable to swallow tablets.

Summary

There are five PPIs (esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole) available in the United States. Three of the available agents are labeled for use in children – lansoprazole, omeprazole, and esomeprazole.

There are differences in pharmacokinetic profiles of PPIs in children compared to adults. These differences include: decreased PPI metabolism in newborns; increased metabolism of PPIs in children between the ages of 1 year and onset of puberty; and faster clearance of PPIs in children. Overall, children require greater doses of PPIs on a milligram per kilogram basis. There are no published trials comparing one PPI to another in children, for any indication. The PPIs are well tolerated in the pediatric population. The most common adverse events include headache, abdominal pain and nausea. Respiratory system adverse events (eg, otitis media) occur more frequently in children than in adults.

Esomeprazole, lansoprazole, and omeprazole are the most appropriate PPIs for use in children or other patients who are unable to swallow whole tablets or capsules, based on the types of dosage forms available. No alternate dosage forms of pantoprazole or rabeprazole are available for use in children or other patients who are unable to swallow tablets.

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