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## APPROVED PROTON PUMP INHIBITOR : A COMPARATIVE STUDY

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### ABSTRACT

*There are two major classes of drugs used for the inhibition of gastric acid secretion: the H<sub>2</sub> receptor antagonists, which were introduced in the 1970s,<sup>1</sup> and proton pump inhibitors (PPIs), which were introduced in the 1980s.<sup>2,48</sup> The developments of specific inhibitors of the proton pump inhibitor (PPI) in the acid secretion, which is known to be the final step in acid secretion are one of the most commonly prescribed classes of medications in the primary care setting and are considered a major advance in the treatment of acid-peptic disease. PPI have enabled improved treatment of various acid-peptic disorders, including gastro-esophageal reflux disease (GERD), peptic ulcer disease, and non-steroidal anti-inflammatory drug-induced gastropathy. Not only is the PPI good for treating the symptom of heartburn, but it also is good for protecting the esophagus from acid so that esophageal inflammation can heal. Proton pump inhibitors have minimal side effects and few significant drug interactions, and they are generally considered safe for long-term treatment. In this article we have reviewed all the comparative parameters including doses, drug interactions, side effects, absorption, distribution and lastly efficacy of the well known PPIs like omeprazole, lansoprazole, Pantoprazole, rabeprazole, and the recently approved esomeprazole--in the management of acid-related diseases.*

**KEYWORDS** : Proton Pump Inhibitors, Gastro-esophageal reflux disease.

### INTRODUCTION

Gastric acid has been known for many decades to be a key factor in normal gastrointestinal functions, including protein digestion and calcium and iron absorption, as well as providing some protein against bacterial infections. However,

inappropriate levels of gastric acid causes several widespread pathological conditions, including ulcers, gastroesophageal reflux disease (GERD) for which heartburn is the common symptom and Zollinger-Ellison syndrome and which only thirty years ago life threatening if untreated.

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Despite the development of potent medications for the treatment of GERD, antacids remain a mainstay of treatment. Antacids neutralize the acid in the stomach so that there is no acid to reflux. The problem with antacids is that their action is brief. Antacids may be aluminum, magnesium, or calcium based. Calcium-based antacids (usually calcium carbonate), unlike other antacids, stimulate the release of gastrin from the stomach and duodenum. Gastrin is the hormone that is primarily responsible for the stimulation of acid secretion by the stomach.

Although antacids can neutralize acid, they do so for only a short period of time. The medical treatment of acid release disease in particular ulcer and GERD had a break through in the late 1970s with the introduction of the first medication developed for more effective and convenient treatment of acid-related diseases, including GERD, was a histamine antagonist, specifically cimetidine (Tagamet). Histamine is an important chemical because it stimulates acid production by the stomach. Released within the wall of the stomach, histamine attaches to receptors (binders) on the stomach's acid-producing cells and stimulates the cells to produce acid. Other H<sub>2</sub> antagonists are ranitidine (Zantac), nizatidine (Axid), and famotidine, (Pepcid) and available over-the-counter (OTC), without the need for a prescription. The developments of specific inhibitors of the proton pump inhibitor (PPI) in the acid secretion, which is known to be the final step in acid secretion. A PPI blocks the secretion of acid into the stomach by the acid-secreting cells. The advantage of a PPI over an H<sub>2</sub> antagonist is that the PPI shuts off acid production more completely and for a longer period of time. Not only is the PPI good for treating the symptom of heartburn, but it also is good for protecting the esophagus from acid so that esophageal inflammation can heal.

PPIs are used when H<sub>2</sub> antagonists do not relieve symptoms adequately or when complications of GERD such as erosions or ulcers, strictures, or Barrett's esophagus exist. Five different PPIs are approved for the treatment of GERD, including omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole. A sixth PPI product consists of a combination of omeprazole and sodium bicarbonate (Zegerid). PPIs (except for Zegarid) are best taken an hour before meals. The reason for this timing is that the PPIs work best when the stomach is most actively producing acid, which occurs after meals. If the PPI is taken before the meal, it is at peak levels in the body after the meal when the acid is being made.

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### **Classification of Proton Pump Inhibitor**

There are two type of PPIs; Irreversible proton pump Inhibitor and Reversible proton pump Inhibitor. Irreversible proton pump inhibitors (PPIs) inhibit gastric acid secretion effectively throughout the day by irreversibly inhibiting the gastric proton pump, H<sup>+</sup>, K<sup>+</sup>-ATPase, in the parietal cells. Reversible gastric proton pump inhibitors are under development, but have not yet reached clinical use<sup>3</sup>.

Clinically used proton pump inhibitors:

- Omeprazole (brand names: Gasec, Losec, Prilosec, Zegerid, ocid, Lomac, Omepral, Omez,)
- Lansoprazole (brand names: Prevacid, Zoton, Monolium, Inhibitol, Levant, Lupizole)
- Dexlansoprazole (brand name: Kapidex, Dexilant)
- Esomeprazole (brand names: Nexium, Esotrex, esso)
- Pantoprazole (brand names: Protonix, Somac, Pantoloc, Pantozol, Zurcal, Zentro, Pan, Controloc)
- Rabeprazole (brand names: AcipHex, Pariet, Erraz, Zechin, Rabecid, Nzole-D, Rabeloc, Razo. Dorafem: combination with domperidone).
- Ilaprazole (brand names: Ilapro, Lupilla, Adiza)

### **Basic Pharmacology<sup>5</sup>**

PPIs are substituted benzimidazoles and are generally administered as enteric-coated tablets or capsules that pass through the stomach intact and are absorbed in the proximal small bowel. Once absorbed, all PPIs have a relatively short plasma half-life (about one to two hours). Their duration of

action is much longer because of their unique mechanism of action. PPIs are lipophilic weak bases that cross the parietal cell membrane and enter the acidic parietal cell canaliculus. In this acidic environment, the PPI becomes protonated, producing the activated sulphenamide form of the drug that binds covalently with the H<sup>+</sup>/K<sup>+</sup> ATPase enzyme that results in irreversible inhibition of acid secretion by the proton pump.<sup>6-8</sup> The parietal cell must then produce new proton pumps or activate resting pumps to resume its acid secretion.<sup>5,6</sup> In contrast to the other PPIs, rabeprazole (Aciphex) forms a partially reversible bond with the proton pump and is activated at a broader range of gastric pH. Therefore, it may have a more sustained acid-suppressing effect than the other PPIs.<sup>5,6,8</sup>

#### **Side Effects and Precautions<sup>2,9,10</sup>**

PPIs are generally well tolerated. The proton pump inhibitors (PPIs) as a class are remarkably safe and effective for persons with peptic ulcer disorders. However, the number of reported side effects and drug interactions involving PPIs has risen in recent years.

The incidence of GERD is increasing and it is becoming more difficult to treat due to rising obesity levels, ageing populations, and greater use of non-steroidal anti-inflammatory drugs (NSAIDs) that irritate the gastric/oesophageal mucosa.<sup>11-15</sup>

The management of GERD is also more complicated in patients with co morbidities as they are often polymedicated.<sup>14,16,17</sup> The increased incidence of GERD will lead to a rise in the need for long-term treatment with PPI. This symposium addressed several key clinical questions regarding the long-term GERD patient management.

The most common adverse effects are headache, diarrhea, abdominal pain, and nausea. Except for diarrhea, the adverse effects of PPIs do not appear to be related to age, dosage, or duration of treatment.<sup>18,19</sup> PPI use is associated with the development of fundic gland polyps (FGP); stopping PPIs is associated with regression of FGP. In the absence of *Helicobacter pylori* infection, the long-term use of PPIs has not been convincingly proven to cause or be associated with the progression of pre-existing chronic gastritis or

gastric atrophy or intestinal metaplasia. Mild/modest hypergastrinemia is a physiological response to the reduction in gastric acid secretion due to any cause.

The diarrhea seems to be related to the profound acid suppression, which has been shown to alter the bacterial content of the gut. Nevertheless, the overall incidence of diarrhea is less than 5 percent, and this effect appears to be dosage and age-related<sup>18</sup>.

The long-term use of PPIs has not been convincingly proven to cause enterochromaffin-like cell hyperplasia or carcinoid tumors. PPIs increase the risk of community acquired pneumonia, but not of hospital acquired (nosocomial) pneumonia. There is no data to support particular care in prescribing PPI therapy due to concerns about risk of hip fracture with the long-term use of PPIs.

PPIs reduce gastric acidity, which is necessary to activate pepsinogen to pepsin to release vitamin B12 from B12-containing foods. PPIs used short-term may minimally reduce the absorption of protein-bound B12 in food<sup>20-22</sup>. Long-term use of PPIs does not lead to vitamin B12 deficiencies, except possibly in the elderly, or in persons with Zollinger-Ellison Syndrome who are on high doses of PPI for prolonged periods of time.

PPIs reduce gastric acidity, and in patients treated long-term with high dose PPIs duodenal absorption of organic and non-organic iron may be reduced<sup>23</sup>. It is believed that Acid (HCl) to be important mediator of calcium absorption in the small intestine, therefore without an appropriate acid environment, calcium might be retained in food reducing its absorption.

There is no convincingly proven data that PPIs increase the risk of *Clostridium difficile*-associated diarrhea in persons in the community. The discontinuation of PPIs may result in rebound symptoms requiring further and even continuous PPI use for suppression of symptoms.

Short-term safety (less than 12 weeks of treatment) of the oldest agents, omeprazole and lansoprazole, has been well established<sup>2</sup>. The safety profiles of the newer agents, rabeprazole and pantoprazole, appear to be similar to those of

the older agents.<sup>24,28</sup> PPIs are only contraindicated if the patient has a known history of hypersensitivity to them, and they should be used with caution in patients with severe hepatic disease.

Omeprazole is a pregnancy category C agent; the others are pregnancy category B medications. PPIs are not recommended for use in breastfeeding mothers<sup>24-28</sup>.

As with all medications, the key is to use PPIs only when clearly indicated, and to reassess continued use so that long-term therapy is used judiciously. Thus, in summary, the PPIs are a safe class of medications to use long-term in persons in whom there is a clear need for the maintenance of extensive acid inhibition.

## **DISORDERS DUE TO HYPER-SECRETION OF GASTRIC ACID**

### **Peptic Ulcers**

Peptic ulcers usually occur in patients with normal acid secretion and gastroduodenal mucosal defenses disrupted because of *Helicobacter pylori* infection or therapy with nonsteroidal anti-inflammatory drugs (NSAIDs), environmental factors, and malignancy. Duodenal ulcers can result from hypersecretion of gastrin. Studies of PPIs have demonstrated superior healing rates, shorter healing time, faster symptom relief and preventing recurrence of both Gastric and Duodenal ulcers than are obtained with H<sub>2</sub> blockers in these patients. 2-4 PPIs have been shown to heal peptic ulcers that may be refractory even to high-dose H<sub>2</sub>-receptor blockers, and they also exhibit antimicrobial activity against *H. pylori* in vitro.

### **NSAID-INDUCED GASTROPATHY**

NSAIDs cause peptic ulcers by inhibiting prostaglandin synthesis and weakening gastroduodenal mucosal defenses. Uncomplicated ulcers usually heal after discontinuation of NSAIDs and treatment with standard dosages of PPIs, H<sub>2</sub> blockers, or sucralfate (Carafate). PPIs are the treatment of choice for large or complicated ulcers,<sup>2,16</sup> and they may also be used for prevention of NSAID-induced ulcers.

## **5.3 Zollinger-Elison Syndrome (ZES)**

In these disease, a non beta-cell tumor of the pancreatic islets may produce gastrin in a quantity sufficient to stimulate secretion of gastric acid to life-threatening levels. These can lead to severe gastro-dudodenal ulcerations. *H. Pylori* is a gram-negative rod-shaped bacteria and has clearly been associated with gastritis, peptic ulcers, gastric adenocarcinoma, and gastric B-cell lymphoma. Gastric enterochromaffin-like (ECL) cell carcinoids are rare events that have been described in association with pernicious anemia and Zollinger-Elison Syndrome.

### **Gastro-Esophageal Reflux Disease (GERD) or acid reflux**

GERD is a chronic, relapsing disease that infrequently progresses but is associated with a range of potentially serious esophageal complications (esophageal ulcer, esophageal stricture, Barrett's esophagus or esophageal cancer) and extra-esophageal diseases such as respiratory problems, chest pain, angina, and increased mortality. It has been reported that about 10-44% have GERD-related symptoms once a month, and 10-20% once a week<sup>29</sup>.

Gastroesophageal reflux disease, commonly referred to as GERD or acid reflux, is a condition in which the liquid content of the stomach regurgitates (backs up or refluxes) into the esophagus. The liquid can inflame and damage the lining (cause esophagitis) of the esophagus although visible signs of inflammation occur in a minority of patients. The regurgitated liquid usually contains acid and pepsin that are produced by the stomach. (Pepsin is an enzyme that begins the digestion of proteins in the stomach.) The refluxed liquid also may contain bile that has backed-up into the stomach from the duodenum. (The duodenum is the first part of the small intestine that attaches to the stomach.) Acid is believed to be the most injurious component of the refluxed liquid. Pepsin and bile also may injure the esophagus, but their role in the production of esophageal inflammation and damage is not as clear as the role of acid. Upper gastrointestinal endoscopy (also known as

esophago-gastro-duodenoscopy or EGD) is a common way of diagnosing GERD.

GERD is a chronic condition. Once it begins, it usually is life-long. If there is injury to the lining of the esophagus (esophagitis), this also is a chronic condition. Moreover, after the esophagus has healed with treatment and treatment is stopped, the injury will return in most patients within a few months. Certain conditions make a person susceptible to GERD. For example, GERD can be a serious problem during pregnancy.

#### **Causes of GERD**

The cause of GERD is complex. There probably are multiple causes, and different causes may be operative in different individuals or even in the same individual at different times. A small number of patients with GERD produce abnormally large amounts of acid, but this is uncommon and not a contributing factor in the vast majority of patients. The factors that contribute to GERD are lower esophageal sphincter abnormalities, hiatal hernias, abnormal esophageal contractions, and slow or prolonged emptying of the stomach.

In addition to the above, some medications may cause or worsen GERD. Some common medications that may have this effect include anticholinergics, antihypertensives such as beta blockers or calcium channel blockers, bronchodilators, dopamine-active drugs, progestin, sedatives, and tricyclic antidepressants. Individuals should not stop taking these or any drugs that are prescribed until the prescribing doctor has discussed the potential GERD situation with them.

The symptoms of uncomplicated GERD are primarily heartburn (sometimes interpreted as chest pain), regurgitation, and dysphagia. It can also have atypical presentations such as odynophagia, hypersalivation, nausea and globus sensation, as well as extra-esophageal manifestations like chest pain and cough.

The liquid from the stomach that refluxes into the esophagus damages the cells lining the esophagus. The body responds in the way that it usually responds to damage, which is with inflammation (esophagitis). The purpose of inflammation is to neutralize the damaging agent and begin the

process of healing. If the damage goes deeply into the esophagus, an ulcer forms. An ulcer is simply a break in the lining of the esophagus that occurs in an area of inflammation. Ulcers and the additional inflammation they provoke may erode into the esophageal blood vessels and give rise to bleeding into the esophagus.

#### **Helicobacter Pylori (H. pylori)**

Around 40% of patients over 40 years age and with peptic ulcer disease are infected with *H. pylori* infection. *H. Pylori* is a gram-negative rod-shaped bacteria and has clearly been associated with gastritis, peptic ulcers, Gastric adenocarcinoma, and gastric B-cell lymphoma up to 80-90% of ulcers may be associated with *H. pylori* infection of stomach. This infection may lead to impaired production of somatostatin by D-cells. This leads to increased gastric acid secretion along with impaired duodenal bicarbonate production. *H. pylori* infection now proven to be the cause for gastric cancer.<sup>30</sup>

Based on randomized clinical trials (RCTs), the most effective first-line eradication therapy for *Helicobacter pylori* is a combination of proton pump inhibitor (PPI) and 2 antimicrobial agents. Yet there remains a significant treatment failure rate of 5% to 25%. Antibiotic resistance is the major impediment of cure.<sup>32</sup>

Thus, if initial attempts fail at eradication of *H. pylori* then quadruple therapy (an antisecretory agent, a bismuth compound, and 2 antimicrobials) or ranitidine-bismuth (Tritec) plus 2 antimicrobials is the most effective follow-up treatment. The latter approach is fairly expensive. For patients whose first course included only one antimicrobial, using 2 new antimicrobials is just as effective as quadruple or ranitidine bismuth-based therapy. These approaches will achieve eradication in 75% to 80% of resistant cases. The re-treatment eradication rate was greater when 2 new antimicrobials were included in the regimen than when a single new antimicrobial was added ( $P = .0064$ )<sup>33</sup>.

**Dosage and Administration**<sup>34-38</sup>

PPIs are inactivated by exposure to gastric juice and are delivered in delayed-release gelatin capsules containing enteric-coated granules (omeprazole and lansoprazole) or in delayed-release enteric-coated tablets (rabeprazole and pantoprazole).<sup>2,24-27</sup> Omeprazole is supplied in doses of 20, and 40 mg, and lansoprazole is supplied in doses of 15 and 30 mg. Both of these agents should be taken 30 minutes before meals, and their capsules should not be opened, chewed, or crushed, but should be swallowed whole.

Other methods of administering omeprazole, lansoprazole,<sup>2,24,25</sup> or esomeprazole<sup>28</sup> have been recommended for patients who are unable to swallow intact capsules. The capsules may be opened and the granules sprinkled over a tablespoon of applesauce, pudding, yogurt, or cottage cheese; the food must be swallowed immediately without stirring, crushing, or chewing. In patients with nasogastric or gastrostomy tubes, the granules in one capsule may be mixed with 40 mL of apple juice and injected through the tube.

Table- 1. The dosing regimens for FDA approved indications of the PPI's are summarized below.

PPIs	Indication	Dosage Regimen
<b>Omeprazole</b>	Treatment of DU	20mg daily x 4 weeks
	Treatment of GU	40mg daily x 4-8 weeks
	Treatment of GERD	20mg daily x 4 weeks
	Treatment of EE	20mg daily x 4-8 weeks
	Maintenance of EE	20mg daily
	Hypersecretory conditions	60mg daily
	H. pylori eradication - triple therapy - dual therapy	20mg twice daily x 10 days 40mg daily x 14 days
<b>Lansoprazole</b>	Treatment of DU	15mg daily x 4 weeks
	Maintenance of healed DU	15mg daily
	Treatment of GU	30mg daily x 8 weeks
	Treatment of GERD	15mg daily x 8 weeks
	Treatment of EE	30mg daily x 8 weeks
	Maintenance of EE	15mg daily
	Hypersecretory conditions H. pylori eradication - triple therapy - dual therapy	60mg daily 30mg q12h x 10-14 days 30mg q8h x 14 days
<b>Pantoprazole</b>	Treatment of EE	40mg daily x 8 weeks
<b>Rabeprazole</b>	Treatment of DU	20mg daily x 4 weeks
	Treatment of GERD	20mg daily x 4-8 weeks
	Maintenance of GERD	20mg daily
	Treatment of EE	20mg daily x 4-8 weeks
	Maintenance of EE	20mg daily
	Treatment of hypersecretory conditions	60mg daily

## Structure Commonly Used PPIs

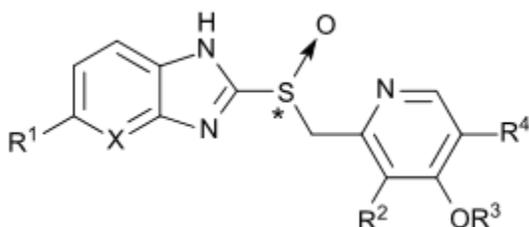


Table-2. Description of Different PPIs

Compound	Substituents					Form	First approval
	X	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>		
Omeprazole	CH	OCH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	Racemate	1989 in USA
Esomeprazole	CH	OCH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	S-enantiomer of omeprazole	2001 in USA
Lansoprazole	CH	H	CH <sub>3</sub>	CH <sub>2</sub> CF <sub>3</sub>	H	Racemate	1991 in Europe
Dexlansoprazole	CH	H	CH <sub>3</sub>	CH <sub>2</sub> CF <sub>3</sub>	H	R-enantiomer of lansoprazole	2009 in USA
Pantoprazole	CH	OCHF <sub>2</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	H	Racemate	1994 in Germany
Rabeprazole	CH	H	CH <sub>3</sub>	(CH <sub>2</sub> ) <sub>3</sub> OCH <sub>3</sub>	H	Racemate	1999 in USA
Tenatoprazole	N	OCH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	Racemate	—

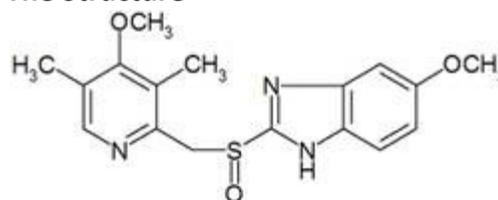
## Description of some commonly used PPIs

**OMEPRAZOLE**<sup>34,48</sup>

**Description:** Omeprazole is a substituted benzimidazole, that inhibits gastric acid secretion. Omeprazole is a white to off-white crystalline powder which melts with decomposition at about 155°C. It is a weak base, freely soluble in ethanol and methanol, and slightly soluble in acetone and isopropanol and very slightly soluble in water. The stability of omeprazole is a function of pH; it is rapidly degraded in acid media, but has acceptable stability under alkaline conditions.

**Indication :** It is used for the treatment of acid-reflux disorders (GERD) with or without esophageal lesion, gastric ulcer (GU), erosive esophagitis (EE), peptic ulcer disease, Maintenance therapy of EE, Eradication of *Helicobacter pylori* in triple therapy with clarithromycin and amoxicillin or in double therapy with clarithromycin only, and prevention of gastrointestinal bleeds with NSAID use.

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**The Structure**

**Toxicity:** Symptoms of overdose include confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, and dry mouth.

**Mechanism of Action** Omeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H<sup>+</sup>/K<sup>+</sup>-ATPase in the gastric parietal cell. By acting specifically on the proton pump, it belongs to a new class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H<sub>2</sub> histamine antagonistic properties. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production,

thus reducing gastric acidity. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after rapid disappearance from plasma, omeprazole can be found within the gastric mucosa for a day or more.

## LANSOPRAZOLE<sup>35, 48</sup>

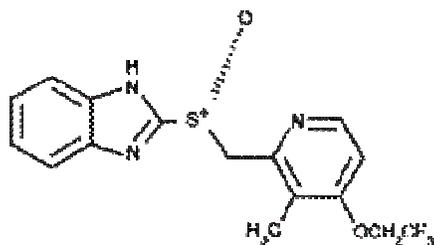
### Description

Lansoprazole is a proton pump inhibitor which prevents the stomach from producing acid. It is manufactured by TAP Pharmaceutical Products. Lansoprazole has been marketed for many years and is one of several PPI's available.

Lansoprazole is a white to brownish-white odorless crystalline powder which melts with decomposition at approximately 166°C. Lansoprazole is freely soluble in dimethylformamide; soluble in methanol; sparingly soluble in ethanol; slightly soluble in ethyl acetate, dichloromethane and acetonitrile; very slightly soluble in ether; and practically insoluble in hexane and water. Lansoprazole is stable when exposed to light for up to two months. The compound degrades in aqueous solution, the rate of degradation increasing with decreasing pH. At 25°C the  $t_{1/2}$  is approximately 0.5 hour at pH 5.0 and approximately 18 hours at pH 7.0.

Indication: For the treatment of acid-reflux disorders (GERD), peptic ulcer disease, Treatment of duodenal ulcer (DU), both *H. pylori* positive and negative, active benign GU, GERD, EE and pathological hypersecretory conditions, including Zollinger-Ellison syndrome (ZES), Maintenance therapy of DU and EE. Eradication of *H. pylori* in triple therapy with clarithromycin and amoxicillin, or in double therapy with amoxicillin only and prevention of gastrointestinal bleeds with NSAID use.

### The Structure



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Pharmacodynamics: Lansoprazole, an acid proton-pump inhibitor similar to omeprazole, is used as an antiulcer drug in the treatment and maintenance of healing of duodenal or gastric ulcers, erosive and reflux esophagitis, NSAID-induced ulcer, Zollinger-Ellison syndrome, and Barrett's esophagus. Lansoprazole is active against *Helicobacter pylori*. The plasma elimination half-life of lansoprazole does not reflect its duration of suppression of gastric acid secretion. Thus, the plasma elimination half-life is less than two hours, while the acid inhibitory effect lasts more than 24 hours.

Metabolism: Hepatic. Two metabolites have been identified in measurable quantities in plasma (the hydroxylated sulfinyl and sulfone derivatives of lansoprazole). These metabolites have very little or no antisecretory activity. Lansoprazole is thought to be transformed into two active species which inhibit acid secretion by  $(H^+, K^+)$ -ATPase within the parietal cell canaliculus, but are not present in the systemic circulation.

Route of elimination: Following single-dose oral administration of PREVACID, virtually no unchanged lansoprazole was excreted in the urine. In one study, after a single oral dose of 14C-lansoprazole, approximately one-third of the administered radiation was excreted in the urine and two-thirds was recovered in the feces. This implies a significant biliary excretion of the lansoprazole metabolites.

Half life: 1.5 ( $\pm$  1.0) hours

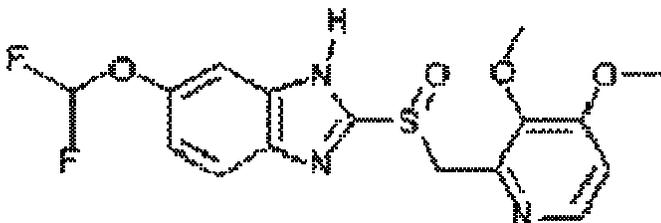
### Mechanism of action

Lansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or histamine H<sub>2</sub>-receptor antagonist properties, but that suppress gastric acid secretion by specific inhibition of the  $(H^+, K^+)$ -ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the parietal cell, lansoprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus.

**PANTOPRAZOLE**<sup>36, 48</sup>**Description**

Pantoprazole sodium (PROTONIX) is a substituted benzimidazole, sodium 5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole sesquihydrate, a compound that inhibits gastric acid secretion. Its empirical formula is  $C_{16}H_{14}F_2N_3NaO_4 \cdot 1.5 H_2O$ , with a molecular weight of 432.4. Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production.

Indication: Short-term (up to 16 weeks) treatment of erosive esophagitis, treatment of EE associated with GERD. The manufacturer of pantoprazole IV is also pursuing the GERD indication for this formulation.

**The Structure**

Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder and is racemic. Pantoprazole has weakly basic and acidic properties. Pantoprazole sodium sesquihydrate is freely soluble in water, very slightly soluble in phosphate buffer at pH 7.4, and practically insoluble in n-hexane. The stability of the compound in aqueous solution is pH-dependent. The rate of degradation increases with decreasing pH. At ambient temperature, the degradation half-life is approximately 2.8 hours at pH 5.0 and approximately 220 hours at pH 7.8.

**Mechanism of Action**

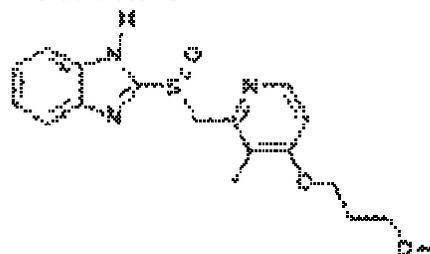
*Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by forming a covalent bond to two sites of the (H<sup>+</sup>,K<sup>+</sup>)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The binding to the (H<sup>+</sup>,K<sup>+</sup>)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours. The main metabolic*

*pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity.*

**RABEPRAZOLE**<sup>37, 48</sup>**Description**

Rabeprazole sodium (ACIPHEX) is a substituted benzimidazole that inhibits gastric acid secretion. Rabeprazole sodium is known chemically as 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1H-benzimidazole sodium salt. It has an empirical formula of  $C_{18}H_{20}N_3NaO_3S$  and a molecular weight of 381.43.

Rabeprazole sodium is a white to slightly yellowish-white solid. It is very soluble in water and methanol, freely soluble in ethanol, chloroform and ethyl acetate and insoluble in ether and n-hexane. The stability of rabeprazole sodium is a function of pH; it is rapidly degraded in acid media, and is more stable under alkaline conditions.

**The Structure**

ACIPHEX is available for oral administration as delayed-release, enteric-coated tablets containing 20 mg of rabeprazole sodium. Inactive ingredients are mannitol, hydroxypropyl cellulose, magnesium oxide, low-substituted hydroxypropyl cellulose, magnesium stearate, ethylcellulose, hydroxypropyl methylcellulose phthalate, diacetylated monoglycerides, talc, titanium dioxide, carnauba wax, and ferric oxide (yellow) as a coloring agent.

**Indication**

Rabeprazole blocks the final step of gastric acid secretion. For the treatment of acid-reflux disorders (GERD), DU and hypersecretory syndromes including ZES, peptic ulcer disease, H. Treatment of erosive or ulcerative GERD, - Maintenance of erosive or ulcerative GERD. pylori

eradication, and prevention of gastrointestinal bleeds with NSAID use.

### Pharmacology

#### Mechanism of Action

Rabeprazole belongs to a class of antisecretory compounds (substituted benzimidazole proton-pump inhibitors) that do not exhibit anticholinergic or histamine H<sub>2</sub>-receptor antagonist properties, but suppress gastric acid secretion by inhibiting the gastric H<sup>+</sup>, K<sup>+</sup>ATPase at the secretory surface of the gastric parietal cell. Because this enzyme is regarded as the acid (proton) pump within the parietal cell, rabeprazole has been characterized as a gastric proton-pump inhibitor. Rabeprazole blocks the final step of gastric acid secretion.

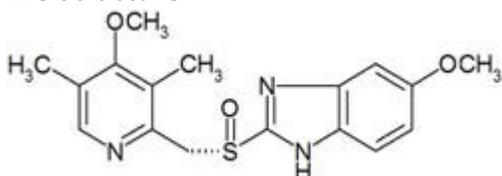
### ESOMEPRAZOLE<sup>38, 48</sup>

#### Description

Esomeprazole sodium (NEXIUM) for Injection is (S)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl]-methyl]sulfinyl]-1H-benzimidazole sodium a compound that inhibits gastric acid secretion. Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S and R-isomers. Its empirical formula is C<sub>17</sub>H<sub>18</sub>N<sub>3</sub>O<sub>3</sub>Na with molecular weight of 367.4 g/mol (sodium salt) and 345.4 g/mol (parent compound).

Esomeprazole sodium is very soluble in water and freely soluble in ethanol (95%).

#### The Structure



#### Mechanism of Action

Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H<sup>+</sup>/K<sup>+</sup>-ATPase in the gastric parietal cell. The S- and R-isomers of omeprazole are protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphenamide. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity. This effect is dose-related

up to a daily dose of 20 to 40 mg and leads to inhibition of gastric acid secretion.

**Metabolism:** Esomeprazole is completely metabolized by the cytochrome P450 system via CYP2C19 and CYP3A4. Metabolism produces inactive hydroxy and desmethyl metabolites, which have no effect on gastric acid secretion. Less than 1% of the parent drug is excreted in urine.

### PHARMACOKINETICS<sup>39-41,50</sup>

#### Absorption

Omeprazole and lansoprazole are formulated as enteric-coated granules, whereas rabeprazole and pantoprazole are enteric-coated tablets. Upon leaving the stomach, the granules and tablets are rapidly absorbed once the preparation enters the small intestine. All the products achieve peak concentrations of approximately 0.5 to 2mg/ml. All of the PPI's undergo low rates of hepatic first pass metabolism. The absolute bioavailability of pantoprazole is approximately 77% due to the first pass effect. Omeprazole shows a saturable first pass effect such that at doses greater than 40mg, the maximum concentration and the absolute bioavailability are greater than would be expected. NEXIUM Delayed-Release Capsules contain an enteric-coated pellet formulation of esomeprazole magnesium. After oral administration peak plasma levels (C<sub>max</sub>) occur at approximately 1.5 hours (T<sub>max</sub>). The C<sub>max</sub> increases proportionally when the dose is increased, and there is a three-fold increase in the area under the plasma concentration-time curve (AUC) from 20 to 40 mg. At repeated once-daily dosing with 40 mg, the systemic bioavailability is approximately 90% compared to 64% after a single dose of 40 mg. The mean exposure (AUC) to esomeprazole increases from 4.32 mmol\*hr/L on day 1 to 11.2 mmol\*hr/L on day 5 after 40 mg once daily dosing.

#### Distribution

Protein binding of all the PPI's is 95% or greater. Rabeprazole, omeprazole and lansoprazole have been found in the breast-milk of lactating humans. The approximate volume of distribution of pantoprazole is 11 to 23.6L (mean 0.16L/kg) indicating distribution mainly in the extracellular

fluid, and limited tissue distribution. Omeprazole is found in fetal tissues at concentrations similar to that achieved in maternal plasma. In animal studies the highest concentrations of omeprazole were found in the liver, kidneys, duodenum, stomach and thyroid gland following intravenous administration of omeprazole. Penetration into red blood cells was found to be low, as well as penetration across the blood-brain barrier. Following oral administration the stomach and duodenal tissues had the highest concentrations of omeprazole. The volume of distribution of omeprazole is 0.24L/kg in elderly, and 0.34-0.37L/kg in adult subjects. The volume of distribution of lansoprazole is ~0.39L/kg. Esomeprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 2-20 mmol/L. The apparent volume of distribution at steady state in healthy volunteers is approximately 16 L.

#### Metabolism

All of the PPI's are extensively metabolized in the liver to inactive metabolites. Certain sub-

populations with deficiency of CYP2C19 have been shown to have slow metabolism of pantoprazole.

#### Half-life of PPIs

PPIs have a rather short half-life in human plasma (60–90 min), but because they covalently bind to the pump, their half-life of inhibition of gastric acid secretion is substantially longer. The half-life at the site of action is estimated to be approximately 24h. Dissociation of the inhibitory complex is probably due to the effect of the endogenous antioxidant glutathione which leads to the release of omeprazole sulfide and reactivation of the enzyme.<sup>42,43,44</sup>

#### Elimination

All of the PPI's undergo elimination in urine and feces and have elimination half-lives of 1.5 hours or less. All of the drugs are cleared mainly as metabolites due to their high degree of metabolism. Certain slow metabolizers of PPI's clear the drug more slowly than normal metabolizers, and have longer drug elimination half-lives.

**Table- 3. Comparative Study of Commonly used PPIs**<sup>31</sup>

PPIs Parameters	Omeprazole	Lansoprazole	Pantoprazole	Rabeprazole	Esomeprazole
IUPAC	5-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)methylsulfanyl]-3H-benzimidazole	2-[(3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methylsulfanyl]-1H-benzimidazole	5-(difluoromethoxy)-2-[(3,4-dimethoxypyridin-2-yl)methylsulfanyl]-3H-benzimidazole	2-[(4-(3-methoxypropoxy)-3-methylpyridin-2-yl)methylsulfanyl]-1H-benzimidazole	(S)-5-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)methylsulfanyl]-3H-benzimidazole
Chemical Name	C <sub>17</sub> H <sub>19</sub> N <sub>3</sub> O <sub>3</sub> S	C <sub>16</sub> H <sub>14</sub> F <sub>3</sub> N <sub>3</sub> OS	C <sub>16</sub> H <sub>15</sub> F <sub>2</sub> N <sub>3</sub> O <sub>4</sub> S	C <sub>18</sub> H <sub>21</sub> N <sub>3</sub> O <sub>3</sub> S	C <sub>17</sub> H <sub>19</sub> N <sub>3</sub> O <sub>3</sub> S
Molecular weight	345.4	369.363	383.371	359.444	345.417
Duration of Effect	22 - 72 hr	> 24 hr	22 - 72 hr	24 hr	22 - 27 hr
Bioavailability	30–40%	>80%	77%	52%	50–90%
Metabolism	Hepatic (via CYP2C19)	Hepatic (via CYP2C19, CYP3A4)	Hepatic (via CYP2C19, CYP3A)	Hepatic (via CYP2C19, CYP3A)	Hepatic (via CYP2C19,

			4)	4)	CYP3A4)
<b>Half-life</b>	0.5 – 1.0 hrs	1.5 ( $\pm$ 1.0) hrs	1 hour	1 – 2 hours	1–1.5 hours
<b>Tmax</b>	0.5-3.5	1.7	2.5	2-5	0.5-3.5
<b>Excretion</b>	80% Renal 20% Faecal	Renal- 33% Biliary/feces- 66%	Renal- 71% as metabolites Feces- 18% as metabolites	Renal- 90% as metabolites Feces- 10% as metabolites	80% Renal 20% Faecal
<b>Proprietary Name</b>	PRILOSEC	PREVACID	PROTONIX	ACIPHEX	NEXIUM
<b>Year of Approval (USFDA)</b>	Jan 15, 1998	May 10, 1995	Feb 2000	Aug 19, 1999	Feb 20, 2001
<b>Route of Administration</b>	Oral, IV	Oral, IV	Oral, IV	Oral	Oral, IV
<b>pK<sub>b</sub> (in vitro)</b>	9	9	8.6	-	9

<b>PPIs Parameters</b>	<b>Omeprazole</b>	<b>Lansoprazole</b>	<b>Pantoprazole</b>	<b>Rabeprazole</b>	<b>Esomeprazole</b>
<b>Affected organism</b>	Humans and other mammals	Humans and other mammals	Humans and other mammals	Humans and other mammals	Humans and other mammals
<b>Route of elimination (U = Urine F = Feces)</b>	U = 77 F = 33 (Urinary excretion is a primary route of excretion of omeprazole metabolites)	U = 35 F = 65 (This implies a significant biliary excretion of the lansoprazole metabolites)	U = 71 F = 18 (Urinary excretion is a primary route of excretion of omeprazole metabolites)	U = 90 F = 10 (In the urine, primarily as thioether carboxylic acid; its glucuronide, and mercapturic acid metabolites)	U = 80 F = 20 (major part of the administered dose is excreted as metabolites in urine and the remaining is excreted in feces)
<b>Plasma Protein binding</b>	95%	97%	98%	96.3%	97% is constant over the concentration range of 2-20 mmol/L
<b>Volume of distribution</b>	0.24L/kg in elderly, and 0.34-0.37L/kg in adult subjects, the	~0.39L/kg, found in the breast-milk of lactating humans.	11.0 to 23.6 L (mean 0.16L/kg) indicating distribution mainly in the	52% found in the breast-milk of lactating humans.	16 L [at steady state in healthy volunteers ]

	stomach and duodenal tissues had the highest concentrations		extracellular fluid, and limited tissue distribution.		
Absorption	Absorption is rapid, absolute bioavailability (compared to intravenous administration) is about 30-40% at doses of 20-40 mg.	The absorption of lansoprazole is rapid, with mean $C_{max}$ occurring approximately 1.7 hrs after oral dosing, and relatively complete with absolute bioavailability over 80%.	Pantoprazole is well absorbed. It undergoes little first-pass metabolism resulting in an absolute bioavailability of approximately 77%.	Absolute bioavailability is approximately 52%.	90%
Toxicity	Symptoms of overdose include confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, and dry mouth.	Symptoms of overdose include abdominal pain, nausea and diarrhea.	Single intravenous doses of pantoprazole at 378, 230, and 266 mg/kg (38, 46, and 177 times the recommended human dose based on body surface area) were lethal to mice, rats and dogs, respectively. The symptoms of toxicity included hypoactivity, ataxia, hunched sitting, limb-splay, lateral position, segregation, absence of ear reflex, and tremor. There is limited	Symptoms of a serious allergic reaction include: rash, itching/swelling (especially of the face/tongue/throat), dizziness, trouble breathing etc.	Blurred vision, confusion, drowsiness, dry mouth, flushing headache, nausea, rapid heartbeat, sweating etc.

			experience regarding cases of human overdose, and treatment should be symptomatic and supportive.		
Clearance	Not available	Not available	7.6-14.0 L/h	Not Available	Not Available

**DRUG INTERACTIONS**<sup>45,48</sup>

PPIs cause significant increases in gastric pH, which may alter the absorption of weak acids or bases. They may inhibit the absorption of drugs such as griseofulvin (Grisactin), ketoconazole (Nizoral), itraconazole (Sporanox), iron salts, vitamin B12, cefpodoxime (Vantin), and enoxacin (Penetrex), many of which are weak bases and require acid for absorption.<sup>46,47</sup>

The PPI's are metabolized by the cytochrome P450 isoenzymes and therefore can be expected to

interact with other drugs that are substrates for that enzyme system. Omeprazole is, however, the only PPI with known interactions with drugs that are substrates of the CYP2C19, including diazepam, warfarin and phenytoin. Lansoprazole interacts with theophylline through CYP1A1 isoenzyme induction. The PPI's may also affect the absorption of certain drugs that require an acidic environment for optimal absorption to occur. The drug interactions of the PPI's are summarized below.

**Table- 4. Drug Interactions of different PPIs.**

Proton Pump Inhibitor	Interacting Drug(s)	Nature of Interaction
<b>Omeprazole</b>	Clarithromycin	Increase plasma levels of omeprazole, clarithromycin and 14-hydroxylclarithromycin
	Sucralfate	Delayed absorption/Decrease bioavailability of omeprazole; administer at least 30 minutes prior to sucralfate.
	Diazepam	Decrease diazepam clearance 25-50%;130% increase in half-life and increase plasma levels of diazepam
	Phenytoin	15-20% decrease clearance and 18-25% increase AUC and 17% increase half-life of phenytoin.
	Warfarin	Elimination of warfarin may be prolonged
<b>Lansoprazole</b>	Theophylline	10% increase in theophylline clearance and 13% decrease in AUC may require dosage adjustment
	Sucralfate	Delayed absorption/Decrease bioavailability of lansoprazole; administer lansoprazole at least 30 minutes prior to sucralfate.
	Ketoconazole Ampicillin esters Iron salts	Absorption of these drugs may be decrease by the change in gastric pH.
<b>Pantoprazole</b>	It does not significantly affect the kinetics of the drugs as in the case of other PPI's. In vivo studies, digoxin, ethanol, glyburide, antipyrine, and caffeine had no clinically relevant interactions with pantoprazole.	
<b>Rabeprazole</b>	Digoxin	19% increase in digoxin bioavailability, 20% increase in digoxin trough levels, 29% increase in digoxin Cmax
	Ketoconazole	30% decrease in bioavailability of ketoconazole

	Cyclosporine	Increase cyclosporine plasma Levels
<b>Esomeprazole</b>	Diazepam	45% decrease in clearance of diazepam.
	Warfarin	Increase in INR and prothrombin time
	Ketoconazole, iron salts and digoxin	interfere with the absorption

### Other Proton Pump Inhibitor

#### Dexlansoprazole (brand names: Kapidex, Dexilant)

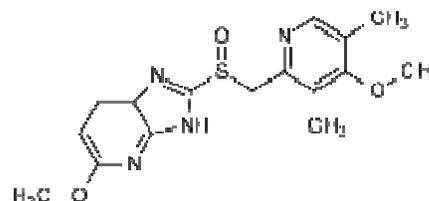
Dexlansoprazole was launched as a follow up of lansoprazole in 2009. dexlansoprazole is an *R*-enantiomer of lansoprazole, marketed as Dexilant. After oral appliance of the racemic lansoprazole, the circulating drug is 80% dexlansoprazole. Moreover, both enantiomers have similar effects on the proton pump. Consequently, the main advantage of Dexilant is not the fact that it is an enantiopure substance. The advantage is the pharmaceutical formulation of the drug, which is based on a dual release technology, with the first quick release producing a blood plasma peak concentration about one hour after application, and the second retarded release producing another the proton pump inhibitor tenatoprazole.

#### Tenatoprazole

Tenatoprazole (TU-199), an imidazopyridine proton pump inhibitor, is a novel compound that has been designed as a new chemical entity with a substantially prolonged plasma half-life (7h), but otherwise has similar activity as other PPIs.<sup>49</sup> The difference in the structural backbone of tenatoprazole compared to benzimidazole PPIs, is its imidazo[4,5-*b*]pyridine moiety, which reduces the rate of metabolism, allowing a longer plasma residence time but also decreases the pKa of the fused imidazole N as compared to the current PPIs.<sup>50</sup> Tenatoprazole has the same substituents as omeprazole, the methoxy groups at position 6 on the imidazopyridine and at position 4 on the pyridine part as well as two methyl groups at position 3 and 5 on the pyridine. The bioavailability of tenatoprazole is double for the *S*-tenatoprazole sodium salt hydrate form when compared to the free form in dogs. This increased bioavailability is due to differences in the crystal structure and hydrophobic nature of the two forms, and

therefore its more likely to be marketed as the pure *S*-enantiomer.

Structure



### Conceivable of Future Drugs

Despite the fact that PPIs have revolutionized the treatment of GERD, there is still room for improvement in the speed of onset of acid suppression as well as mode of action that is independent of an acidic environment and also better inhibition of the proton pump.<sup>51</sup> The antisecretory drugs may be replaced by drugs that act more specifically in the treatment of some acid-related diseases.

Patient with gastrin producing tumour-ZES are often treated with rather high dose of a PPI. A specific antigastrin drug would change the situation.

Peptic ulcers induced by the use of Non Steroidal Anti-Inflammatory Drugs (NSAIDs) are might be reduced by the use of newer NSAIDs, such as cyclooxygenase-2 (COX2) inhibitors and the nitric oxide donating NSAIDs.

Time will come when a vaccine or a specific monotherapy against *H. Pylori* might represent a future therapeutic strategy for peptic ulcer treatment and a possible preventative measure against the development of gastric malignancy.

### New Generation of PPI

Therefore, a new class of PPIs, potassium-competitive acid blockers or acid pump antagonists, have been under development the past years and will most likely be the next generation of drugs that suppress gastric activity.<sup>52</sup> These new agents can in a reversible and

competitive fashion inhibit the final step in the gastric acid secretion with respect to  $K^+$  binding to the parietal cell gastric  $H^+,K^+$ -ATPase. That is, they block the action of the  $H^+,K^+$ -ATPase by binding to or near the site of the  $K^+$  channel. Since the binding is competitive and reversible these agents have the potential to achieve faster inhibition of acid secretion and longer duration of action compared to PPIs, resulting in quicker symptom relief and healing.<sup>53</sup> The imidazopyridine based compound SCH28080 was the prototype of this class.

Other activity that PPIs may modulate is v-type  $H^+$ -ATPase activity, which is widely distributed in a variety of cells in the human body. Hence, there is still much potential for research on the pharmacological and clinical aspects of PPI treatment.<sup>54</sup>

#### SUMMARY AND CONCLUSION

The proton pump inhibitors are substituted benzimidazoles and are generally administered as enteric-coated tablets or capsules that inhibit gastric acid secretion via inhibition of the  $H^+/K^+$  ATPase pump. Although  $H_2$  blockers are less expensive than PPIs, PPIs provide superior acid suppression, healing rates and symptom relief. This includes *H. pylori* treatment where  $\geq 90\%$  eradication can be achieved with a PPI in combination with 2 antibiotics alone. The PPI's are also used for the treatment of Zollinger-Ellison Syndrome (ZES). The PPI's offer convenient once-daily dosing for most indications. Therefore, PPIs may be more cost-effective than  $H_2$  blockers, especially in patients with more severe acid-peptic disorders, because of their lower and less frequent dosing requirements and their comparatively shorter duration of required therapy. When deciding which PPI to use, physicians should consider the patient's age, medications, and diagnosis, as well as the expense of therapy.

Although there are some differences in pharmacokinetics and binding affinity for the pump, all five PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole) are comparatively similar in their efficacy in treatment of various acid-peptic disorders. Rabeprazole

shows faster rate of inhibition and shorter duration of action. Esomeprazole is the s-isomer of omeprazole. It is more bioavailability and oral potency inhibiting gastric acid secretion in man owing to stereoselective metabolism compare to omeprazole as the result of a lesser first-pass effect and slower plasma clearance. Esomeprazole in dosages of 20 and 40 mg produces higher 24-hour intragastric pH levels than omeprazole, thus possibly resulting in superior acid control. The incidence and types of adverse effects appear to be similar to those of omeprazole.

Comparative studies with lansoprazole and pantoprazole suggest that they have potency similar to that of omeprazole. Compared with lansoprazole, the onset of action of rabeprazole was fastest and its duration of action was shorter as determined by measuring acid output and microsomal enzyme activity<sup>55</sup>. The PPIs are clearly more potent than  $H_2$ -receptor antagonists with clinically their doses being 15 times lower than those of  $H_2$ -receptor antagonists in the treatment of duodenal ulcers<sup>56</sup>.

Unlike omeprazole which has several significant drug interactions, the newer agents, rabeprazole and pantoprazole, seem to have fewer drug interactions. This is a particularly important consideration in older patients who are already taking several other medications.

While the average wholesale prices of all agents in this class are similar, Pantoprazole has only one indication at this time, and is the most cost effective of the group for that indication. Lansoprazole has the largest number of FDA approved indications of the group and for most of those indications is more cost effective than the other agents. The PPI's, as a class are primarily used for a limited duration of time i.e., 4-8 weeks. Avoiding excessive duration of use should be advocated to minimize drug interactions, long term suppression of gastric acid and potential for severe unexpected toxicity.

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