Market feasibility study of Rabeprazole Sodium

Bipon Chandra Das
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A Research paper submitted to the department of pharmacy, East West University in conformity with the requirements for the Bachelor of Pharmacy

Dedicated
TO
My parents

Acknowledgement

All praise is for the almighty Allah, who has given me the ability to complete my B. Pharm thesis on market feasibility study of Rabeprazole Sodium. Then I would like to thank my instructor and following individuals for their help and support during the preparation of this paper.

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Abstract

A peptic ulcer is damage to the lining of the stomach, duodenum, or esophagus due to corrosion caused by gastric acid or digestive juices secreted by stomach cells. Among all classes of drugs, proton pump inhibitors are the most effective for the management of peptic ulcer diseases. Rabeprazole sodium is one of the prominent proton pump inhibitors. It is commonly used in the world for the treatment of peptic ulcer. It functions by inhibiting the enzyme H^+/K^+ ATPase which is responsible for the secretion of gastric acid. The purpose of this study is to analyze the market feasibility study of Rabeprazole sodium. Many books, journals and different articles were used to know efficacy and safety profile of drugs. Rabeprazole sodium blocks acid production in the stomach. It is prescribed for the short-term (4 to 8 weeks) treatment of sores and inflammation in the upper digestive canal (esophagus). It is more effective in the treatment of duodenal ulcer, *H. pylori*, gastric ulcer, erosive esophagitis, GERD, and pathological hypersecretory conditions, including Zollinger-Ellison syndrome. By the study of market, feasibility among all PPIs Rabeprazole market value is 26,568,572 taka. Rabeprazole market growth is 2.29%, which is comparatively less among other PPIs. To increase overall market growth I can introduce Rabeprazole sodium, which is a delayed–release tablet. Because of its D-R property I hope that with in one year it will become a superior drug for the treatment of peptic ulcer.

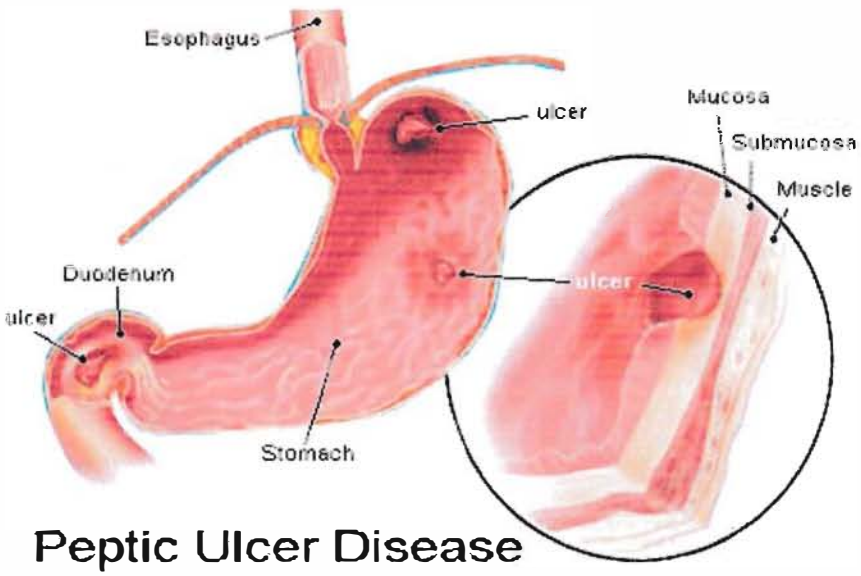
Table of contents

1. Introduction

A good number of classes of drugs have been discovered for the treatment of peptic ulcer. A peptic ulcer is damage to the lining of the stomach, duodenum, or esophagus due to corrosion caused by digestive juices secreted by stomach cells. Various pathophysiologic mechanisms of peptic ulcer disease and thus clinical management require multiple pharmacologic agents. Ulcers develop when digestive juices produced in the stomach, intestines, and digestive glands damage the lining of the stomach or duodenum. Gastritis includes a marked disorder that involves inflammatory changes in the gastric mucosa, including erosive gastritis caused by *Helicobacter pylori* bacterial infections. For more than many years, peptic ulcer disease was most often managed surgically. Effective pharmacologic suppression of gastric acid secretion began with the introduction of histamine H_2-receptor antagonists. The class includes antacid, H_2 receptor antagonists, carbonicanhydrase inhibitors and proton pump inhibitors. Among all classes of drugs, proton pump inhibitors are the most effective for the management of peptic ulcer diseases. Proton pump inhibitors are a group of drugs widely used in the treatment of peptic ulcer. PPIs are used for the prevention and treatment of acid-related conditions such as ulcers, gastro esophageal reflux disease (GERD), and Zollinger-Ellison syndrome. They also are used in combination with antibiotics for eradicating *Helicobacter pylori*. Rabeprazole sodium is one of the prominent proton pump inhibitors. It is commonly used in the world for the treatment of peptic ulcer. It functions by inhibiting the enzyme H^+/K^+ ATPase which is responsible for the secretion of gastric acid. Rabeprazole sodium, a substituted benzimidazole that inhibits gastric acid secretion. Due to its mechanism of action dosage frequency is less, so chance of dose missing is minimized. Patient will get desired action by taking this drug.

1.1. Peptic ulcer

A peptic ulcer is a hole in the gut lining of the stomach, duodenum, or esophagus. A peptic ulcer of the stomach is called a gastric ulcer; of the duodenum, a duodenal ulcer; and of the esophagus, an esophageal ulcer. Acid peptic diseases include peptic ulcer, gastro esophageal reflux, Zollinger-Ellison syndrome. The medical cost of treating peptic ulcer and its complications runs in the billions of money annually. Improved and expanded treatment options are now available (David EG, 2004; Chey WD, Wong 2007; Bortoli M, Leonardi G, Ciancia E, 2007).



Peptic Ulcer Disease

1.1.1. Causes and risk factors of peptic ulcers

The stomach produces acid to help with digestion. The lining of the stomach and first part of the small intestine (duodenum) have ways to protect acid naturally from stomach. When these stop working the acid can eat into the stomach lining causing a peptic ulcer. Duodenal ulcers affect about one in 10 people at some point in their lives, usually between the ages of 45 and 65. Stomach ulcers are less common, and usually affect people aged over 65. Nearly all ulcers are caused by *Helicobacter pylori* infection or NSAID use. Symptoms typically include burning epigastric pain that is often relieved by

food (Melvin JE, Yule D, Shuttleworth T, Begenisich T, 2005; Turnberg LA, Fordtran JS, Carter NW, Rector FC, 1970).

There are various causes for peptic ulcers which include:

- ***Helicobacter pylori*:**

Helicobacter pylori are small, microaerophilic, spiral-shaped, gram-negative bacteria which cause duodenal ulcer, a type of peptic ulcer. The bacterium weakens the protective mucous coating of the stomach and duodenum. It helps the acids and bacteria to irritate the lining of the stomach and cause a sore or ulcer. It is important to note here that *Helicobacter pylori* survives the strong stomach acid by secreting enzymes that neutralize the acid (Guyton 2007; Laine L, Curtis SP, Cryer B, 2007).

- **Drugs:**

Nonsteroidal Anti-Inflammatory Drugs (NSAID's) such as aspirin, ibuprofen, naproxen and etodolac are painkillers, but also the causal agents for ulcers by interfering with prostaglandin (Philip S, 2008).

- **Alcohol:**

Over consumption of alcohol irritates and erodes the mucous lining of stomach leading to increased production of acid consequently causing ulcerations. H. pylori cause ulcers is not well understood, but elimination of these bacteria by antibiotics has clearly been shown to heal ulcers and prevent ulcer recurrence (Rang HP, Dale MM, Ritter JM, Moore PK, 2003).

- **Smoking:**

Cigarette smoking causes ulcers and increases the risk of ulcer bleeding, stomach obstruction and perforation. Smoking also leads to failure in ulcers medication treatment (Moberly JB, Harris SI, Diff DS, 2007).

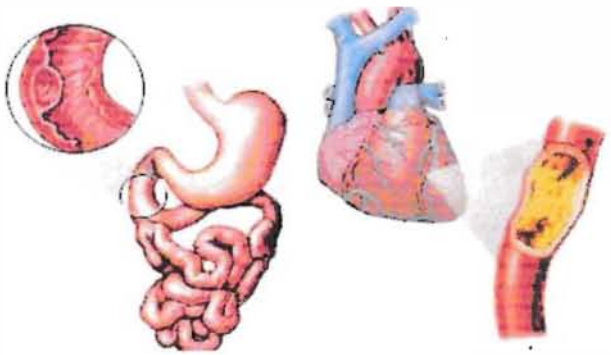


Fig: Tobacco use is associated with increased risk of peptic ulcer

1.1.2. Symptoms of ulcer

Symptoms of ulcer disease are variable. Many ulcer patients experience minimal indigestion or no discomfort at all. Some report upper abdominal burning or hunger pain one to three hours after meals and in the middle of the night. The pain of ulcer disease correlates poorly with the presence or severity of active ulceration (Malagelada JR, Martin EJ, Blaser J, 2007).

1.1.3. Signs of ulcer

- Pain or discomfort
- Bloating
- A feeling of fullnessp, people with severe dyspepsia are unable to drink as much fluid as people with mild or no dyspepsia
- Hunger and an empty feeling in the stomach, often 1 - 3 hours after a meal
- Mild nausea (vomiting, in fact, may relieve symptoms)
- Regurgitation (sensation of acid backing up into the throat)
- Belching (Feret B, Quercia R, Cappa J, 2000).

1.1.4. Diagnosis of ulcer

The diagnosis of an ulcer is made by either a barium upper GI x-ray or an upper endoscopy. Barium is visible on x- ray, and outlines the stomach on x-ray film. However, barium x-rays are less accurate and may not detect ulcers up to 20% of the time. An upper endoscopy is more accurate.

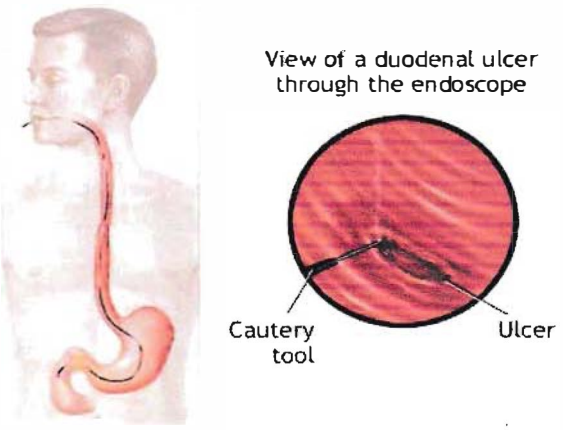


Fig: Peptic ulcer diagnosis

It involves sedation of the patient and which includes insertion of a flexible tube through the mouth to inspect the stomach, esophagus, and duodenum. While virtually all duodenal ulcers are benign, gastric ulcers can occasionally be cancerous. Therefore, biopsies are often performed on gastric ulcers to exclude cancer (Moberly JB, Harris SI, Diff DS, 2007).

1.1.5. Different type of complications of ulcer

The major problems resulting from ulcers are related to ulcer complications, such as ulcer bleeding, ulcer perforation, and gastric obstruction. Patients with persistent or severe bleeding may require blood transfusions. An upper endoscopy is performed to establish the bleeding site. It is also require to stop active ulcer bleeding with the aid of heated instruments. Many patients report a sudden onset of abdominal pain, which is worsened

by any type of motion. Abdominal muscles become rigid. Urgent surgery is usually required. Ulcer perforation helps to cause leakage of gastric contents into the abdominal cavity, resulting in acute peritonitis (infection of the abdominal cavity) (Chey WD, Wong BC, 2007; Rang HP, Dale MM, Ritter JM, Moore PK, 2003).

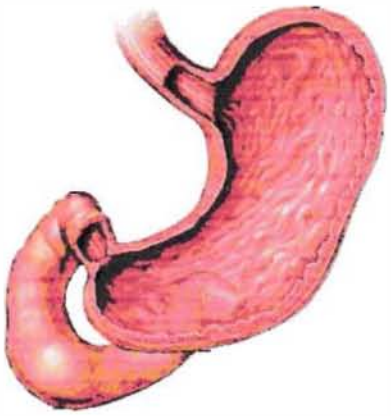


Fig: Peptic ulcer occur in stomach (gastric) or in the duodenum (duodenal)

Symptoms depend on ulcer location and patient age, many patients, particularly elderly patients, have few or no symptoms.

- **Gastric ulcer**

Symptoms often do not follow a consistent pattern. This is especially true for pyloric channel ulcers, which are often associated with symptoms of obstruction (e.g. bloating, nausea, vomiting) caused by edema and scarring (Richardson P, Hawkey C, Stack W, 1998).

- **Duodenal ulcers**

Most function of duodenal ulcer to produce more consistent pain. Pain does not present when the patient awakens but appears in mid-morning. Which help to relieved by food, but recurs 2 to 3 hour after a meal. Pain that awakens a patient at night is common and is highly suggestive of duodenal ulcer (Richardson P, Hawkey C, Stack W, 1998).

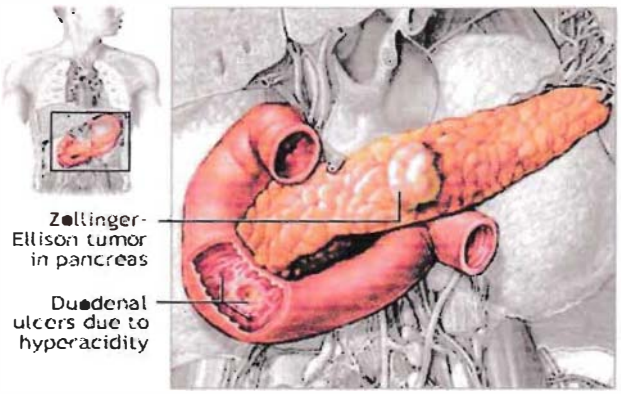
1.2. Problem arises with Hyperacidity

Hyperacidity means increase acid secretion in the stomach. These are related with different type of diseases such are given bellow:

1. Zollinger- Ellison Syndrome
2. Gas Esophageal Reflux Disease (GERD)
3. Peptic ulcer

1.2.1. Zollinger- Ellison Syndrome

Zollinger-Ellison syndrome is a rare disorder that causes tumors in the pancreas and duodenum. This gastrin-secreting tumor of the non-beta endocrine cells of the pancreas leads to increase acid secretion (David EG, 2005). It also causes ulcers in the stomach and duodenum. The pancreas is a gland located behind the stomach. It produces enzymes and hormones. These enzymes cause break down fat, protein, and carbohydrates from food and hormones like insulin that break down sugar. The duodenum is the first part of the small intestine. The tumors secrete the gastrin hormone that increases the production of acid in the stomach. Then that will turn to cause stomach and duodenal ulcers (peptic ulcers). There is a chance of developing ECL hyperplasia in case of Zollinger-Ellison syndrome patients and also some development of carcinoid tumors (Sharon G, 2008).



Causes of Zollinger-Ellison Syndrome

ZES is caused by a tumor is called gastrinoma. The tumor is usually present in the pancreas and the upper small bowel (duodenum). These tumors produce the hormone gastrin and are called gastrinomas. High levels of gastrin cause overproduction of stomach acid. That causes increase in acidity which leads to the development of peptic ulcers in the stomach and duodenum (Sharon G, 2008; Omudhome O, 2008).

Symptoms of Zollinger-Ellison Syndrome

- Gnawing, burning pain in the abdomen: This pain is usually located in the area between the breastbone and the navel.
- Sensation of pressure, bloating, or fullness: This pain usually develops 30 to 90 minutes after a meal, and is often relieved by antacids.
- Vomiting: The vomit may contain blood or resemble coffee grounds.
- Diarrhea: Stools may be foul smelling.
- Black, tarry stools: Blood in the stools will turn them dark red or black, and make them tarry or sticky.
- Other: Nausea, Fatigue, Weakness, Weight loss (Sharon G, 2008).

1.2.2. Gastro Esophageal Reflux Disease (GERD)

Gastro esophageal reflux occurs in almost everybody. Gastro esophageal reflux occurs when the stomach contents reflux or back up into the esophagus and/or mouth. People with gastro esophageal reflux disease experience with some symptoms as a result of the reflux. These symptoms are heartburn, vomiting, or pain with swallowing. The reflux of stomach acid can adversely affect the vocal cords (Peter JK, 2008; Omudhome O, 2008).

Factors contributing to pathological reflux include:

- Incompetence of the gastro esophageal sphincter.
- Delayed esophageal clearance of acid.
- Delayed gastric emptying (Bennett PN, Brown MJ, 9th Edition).

Reflux considered gastro esophageal reflux disease when it shows bothersome symptoms or injury to the esophagus. The esophagus expand and contract to propel food to the stomach through a series of wave-like movements called peristalsis. At the lower end of the esophagus, there is a circular ring of muscle called the lower esophageal sphincter (LES). In this part it joins to the stomach. After swallowing, the LES relaxes to allow food to enter the stomach. After that it contracts to prevent the back-up of food and acid into the esophagus. This is most commonly occurred after meals, are brief, and do not cause symptoms. Normally, reflux should occur only rarely during sleep (Peter JK, 2008).

Symptoms

People having heartburn at least two to three times a week may have gastro esophageal reflux disease, or GERD.

- Unexplained weight loss
- Chest pain
- Choking
- Bleeding (vomiting blood or dark-colored stools)
- Stomach pain (pain in the upper abdomen)
- Painful swallowing (called odynophagia)
- Persistent sore throat
- Chronic cough, new onset asthma, or asthma only at night
- Worsening dental disease (Peter JK, 2008).

1.3. Regulation of acid secretion

Histamine can be release by gastrin from enterochrommafin-like cells (ECL, in green) appears to be the major physiologic mechanism. For this reason gastrin stimulates acid secretion, although parietal cells (in blue) also have gastrin receptors. In addition, the ECL cells integrate stimulatory messages from cholinergic nerves. Inhibition occurs by locally released somatostatin (Johnson LR, Christensen MJ, Jackson ED, 1994).

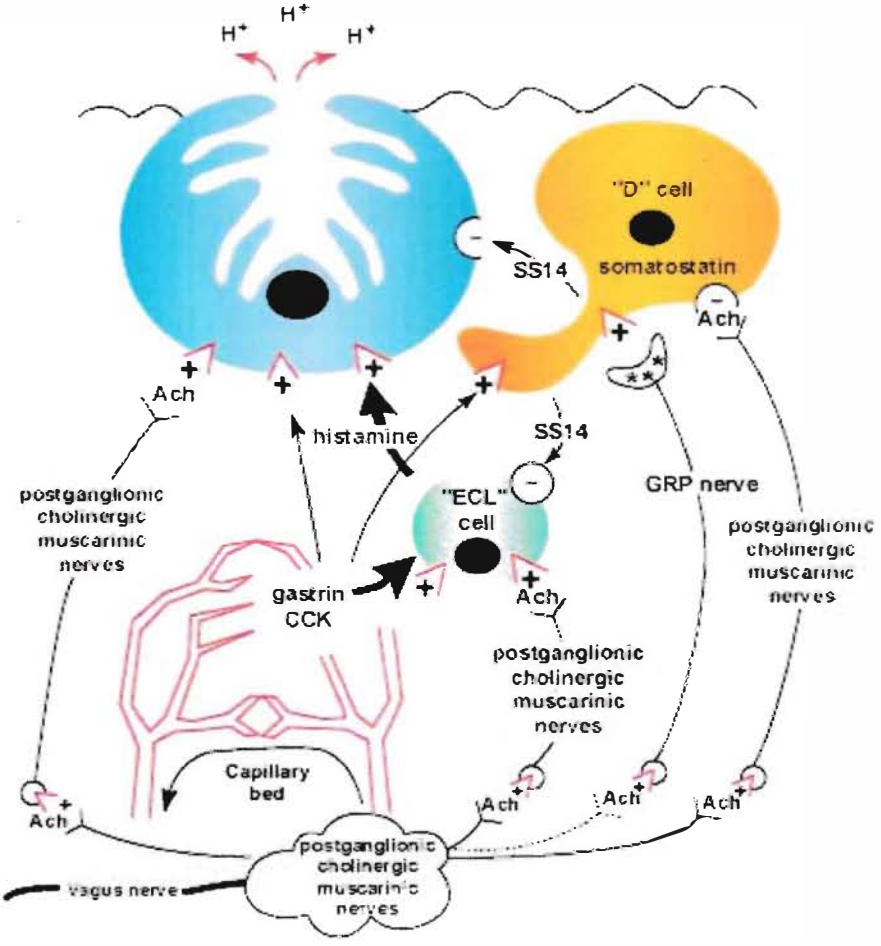


Fig: Regulation of acid secretion

1.4. Treatment

Ulcer cannot treat fully. People suffering from any type of hyperacidity, he must treat with long term therapy even life time. The following drugs are sometimes used in the treatments of ulcers caused by either NSAIDs or H. pylori.

1.4.1. Antacids

Many antacids are available without prescription and are the first drugs recommended to relieve heartburn and mild dyspepsia. They play no major role in either the prevention or healing of ulcers, but help in the following ways:

- They neutralize stomach acid by relying on various combinations of three basic compounds -- magnesium, calcium, or aluminum.
- They may defend the stomach by increasing bicarbonate and mucus secretion.
- It is generally believed that liquid antacids work faster and are more potent than tablets, although some evidence suggests that both forms work equally well (Rang HP, Dale MM, Ritter JM, Moore PK, 2003).

Basic Salts Used in Antacids

- Magnesium. Magnesium compounds are available in the form of magnesium carbonate, magnesium trisilicate, and, most commonly, magnesium hydroxide (Milk of Magnesia).
- Calcium. Calcium carbonate is a potent and rapid-acting antacid, but it can cause constipation.
- Aluminum. The most common side effect of antacids containing aluminum compounds is constipation. People who have recently experienced GI bleeding should not use aluminum compounds (Ramakrishnan K, Salinas RC, 2007).

Interactions of Antacids with Other Drugs

Antacids can reduce the absorption of a number of drugs. Conversely, some antacids increase the potency of certain drugs. The interactions can be avoided by taking these other drugs 1 hour before or 3 hours after taking the antacid (Gancz H, Jones KR, Merrell DS, 2008).

1.4.2. Antibiotics

H. pylori are usually highly sensitive to certain antibiotics, particularly amoxicillin, and to antibiotics in the macrolide class, such as clarithromycin.

- Amoxicillin is a form of penicillin. It is inexpensive, but some people are allergic to it.
- Clarithromycin is a macrolide antibiotic. It is the most expensive antibiotic used against H. pylori infection. It is very effective, but there is growing bacterial resistance to this drug.
- Tetracycline is effective, but this medicine has unique side effects, including tooth discoloration in children. Pregnant women cannot take tetracycline.
- Ciprofloxacin, a fluoroquinolone, is also sometimes used in ulcer regimens.
- Metronidazole was the mainstay in initial combination regimens for H. pylori (Ramakrishnan K, Salinas RC, 2007).

Side Effects of Antibiotics

The most common side effects of nearly all antibiotics are gastrointestinal problems such as cramps, nausea, vomiting, and diarrhea.

- Allergic reactions can also occur with all antibiotics, but are most common with medications derived from penicillin or sulfa drugs.

- Some drugs, including certain over-the-counter medications, interact with antibiotics; patients should report to all medications they are taking to their doctor.
- Antibiotics double the risk of vaginal yeast infections (Saif MW, Elfiky A, Salem RR, 2007).

1.4.3. Bismuth

Compounds that contain bismuth are often used in the three-drug treatment programs. They destroy the cell walls of H. pylori bacteria. High doses can cause vomiting and depression of the central nervous system, but the doses given for ulcer patients rarely cause side effects (Kona MS, 2007).

1.4.4. H_2 Blockers

H_2 blockers interfere with acid production by blocking histamine. It is a substance produced by the body that encourages acid secretion in the stomach. H_2 blockers were the standard treatment for peptic ulcers until proton pump inhibitor and antibiotic regimens against H. pylori were developed. Four H_2 blockers are currently available over-the-counter famotidine, cimetidine, ranitidine, and nizatidine. All have good safety profiles and few side effects. There are some differences between these drugs (Mercer DW, Robinson EK, 2007).

- **Famotidine:** Famotidine is the most potent H_2 blocker. The most common side effect is headache, which occurs in 4.7% of people who take it. Famotidine is virtually free of drug interactions, but it may have significant adverse effects in patients with kidney problems.
- **Cimetidine:** Cimetidine has few side effects; about 1% of people taking cimetidine experience mild temporary diarrhea, dizziness, rash, or headache.
- **Nizatidine:** Nizatidine is nearly free of side effects and drug interactions.

- **Ranitidine:** Ranitidine interacts with very few drugs. In one study, ranitidine provided more pain relief and healed ulcers more quickly. It is more effective in below 60 years old, but there was no difference in older patients.
- The **PPIs** are more effective than the H_2 blockers in healing ulcers in people who take NSAIDs. Treatment efficacy for PPIs runs between 100% versus 85% or H_2 blockers, depending on which agents are being used.

Side Effects of H_2 Blockers

Long-Term Concerns, in most cases, these H_2 blockers have good safety profiles and few side effects. Because H_2 blockers can interact with other drugs (Bortoli M, Leonardi G, Ciancia E, 2007; David E, 2004).

- Liver damage: - This is more likely with ranitidine than other H_2 blockers, but is rare. Increased risk for pneumonia in hospitalized patients.
- Kidney-related central nervous system complications:- With famotidine, adverse effects on the central nervous system in patients with even moderate kidney insufficiency have been reported, resulting in anxiety, depression, and mental disturbances.
- Ulcer perforation and bleeding:- Some experts are concerned that the use of acid-blocking drugs may actually increase the risk for serious complications by masking the ulcer's symptoms (Philip MD, 2008).

1.4.5. Proton-Pump Inhibitors (PPIs)

Actions against ulcers PPIs suppress the production of stomach acid by blocking the gastric acid pump. The molecule present in the stomach glands that is responsible for acid secretion. PPIs can be used either as part of a multi drug regimen for H. pylori or alone for preventing and healing NSAID-caused ulcers. They are also useful in treating ulcers caused by Zollinger-Ellison syndrome also considered to be more effective than H_2 blockers (O'Brien DP, Romero-Gallo J, Schneider BG, 2008).

1.5. Proton-Pump Inhibitors

Proton pump inhibitors were introduced in 1980 for the treatment of heartburn, ulcers and Gastroesophageal reflux disease (GERD). Omeprazole was the first drug in this class, introduced in 1989. Since then, four other PPIs viz lansoprazole, rabeprazole, pantoprazole and esomeprazole have been introduced in 1995, 1999, 2000 and 2001 respectively. Most PPIs are available by prescription as oral drugs. There is no evidence that one brand of PPI works better than another. Brands approved for ulcer prevention and treatment include.

1.5.1. Mechanism of Action

Omeprazole belongs to a new class of antisecretory compounds. These substituted benzimidazoles that do not exhibit anticholinergic or H_2 histamine antagonistic properties. It causes suppression of 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 gastric mucosa. Omeprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production.

- Omeprazole
- Esomeprazole
- Lansoprazole
- Rabeprazole
- Pantoprazole
- Dexlansoprazole

Possible Adverse Effects

Side effects are uncommon, but may include headache, diarrhea, constipation, nausea, and itching. Pregnant women and nursing mothers should avoid taking PPIs. Although

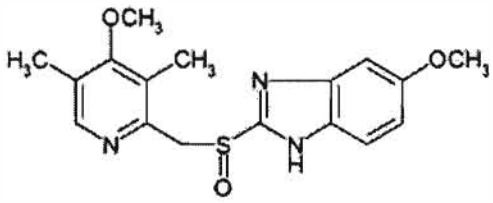
recent studies suggest that these drugs do not increase the risk of birth defects, their safety during pregnancy is not yet proven (Chey WD, Wong BC, 2007). PPIs may interact with certain drugs, such as antiseizure agents (such as phenytoin), antianxiety drugs (such as diazepam), and blood thinners (such as warfarin). Long-term use of high-dose PPIs may produce vitamin B12 deficiency (Pietroiusti A, Forlini A, Magrini A, 2006).

1.5.2. OMEPRAZOLE

Description

Omeprazole is a substituted benzimidazole, 5-methoxy-2-[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1Hbenzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{17}H_{19}N_3O_3S$, with a molecular weight of 345.42.

Chemical Structure



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.

Indications

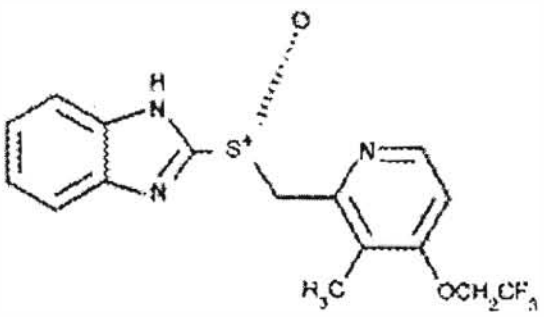
- Treatment of gastric ulcer (GU), erosive esophagitis (EE), gastroesophageal reflux disease (GERD) with or without esophageal lesion.
- Maintenance therapy of EE.
- Eradication of *H. pylori* in triple therapy with clarithromycin and amoxicillin or in double therapy with clarithromycin only (Sreedhar D, Dlip K, Manthan DJ, 2006).

1.5.3. LANSOPRAZOLE

Description

Lansoprazole is a substituted benzimidazole, 2-[[[3-methyl-4-(2, pyridyl] methyl] sulfinyl] benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_3N_3OS$ with a molecular weight of 369.37.

Chemical Structure



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.

Indication

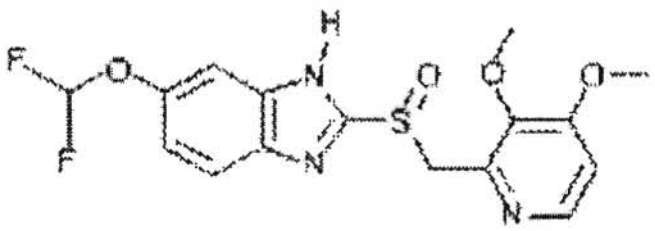
- Treatment of duodenal ulcer, in H. pylori infection. It is more effective in GU, GERD, EE and ZES.
- Maintenance therapy of DU and EE.
- Eradication of H. pylori in triple therapy with clarithromycin and amoxicillin, or in double therapy with amoxicillin only (Sreedhar D, Dlip K, Ajay P, Manthan DJ, Subramanian D, Udupa N, 2006).

1.5.4. PANTOPRAZOLE

Description

Pantoprazole sodium 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 $C_{16}H_{14}F_2N_3NaO_4S$ x 1.5 H_2O, with a molecular weight of 432.4.

Chemical 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.

Indication

Treatment of EE associated with GERD.

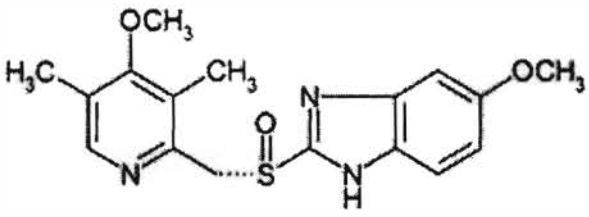
- Now pantoprazole IV is faster action in pursuing the GERD indication (Sreedhar D, Dlip K, Ajay P, Manthan DJ, Subramanian D, Udupa N, 2006).

1.5.5. ESOMEPRAZOLE

Description

Esomeprazole sodium for Injection is (S)-5-methoxy-2[[(4-methoxy-3, 5-dimethyl-2-pyridinyl)-methyl] sulfinyl] - 1 H-benzimidazole sodium a compound that inhibits gastric acid secretion. Esomeprazole is the S-isomer of omeprazole, which is a mixture of the Sand R- isomers. Its empirical formula is $C_{17}H_{18}N_3O_3SNa$ with molecular weight of 367.4 g/mol and 345.4 g/mol. Esomeprazole sodium is very soluble in water and freely soluble in ethanol (95%).

Chemical Structure



Indications

- GERD, healing of EE, maintenance of healing of EE, H. pylori Eradication.
- It is reducing the risk of duodenal ulcer recurrence in triple therapy with clarithromycin and amoxicillin (Sreedhar D, Dlip K, Ajay P, Manthan DJ, Subramanian D, Udupa N, 2006).

1.5.6. RABEPRAZOLE

Description

Rabeprazole is a substituted benzimidazole that inhibits gastric acid secretion. Rabeprazole sodium is known chemically as 2-[[[4-(3-methoxypropoxy)-3-methyl-2-

Pharmacokinetics

Dexlansoprazole leading to prolonged plasma concentrations than the Lansoprazole. It is almost double of Lansoprazole. Dexlansoprazole resulted in extended drug exposure compared to Lansoprazole. It also provides a prolonged pH profile across all dose levels compared to Lansoprazole (Zhang WJ, 2008).

Indication

Dexlansoprazole is mainly used in the treatment of the following diseases. These are given below:

- Acid-related disorders
- The treatment and maintenance of patients with erosive oesophagitis
- Non-erosive reflux disease, i.e. gastro-esophageal reflux disease.
- Treatment of peptic ulcer.
- Zollinger-Ellison syndrome (Zhang WJ, 2008; Sreedhar D, Dlip K, Ajay P, Manthan DJ, Subramanian D, Udupa N, 2006).

1.5.8. Overall indication of PPIs

Table 1: All PPIs are compare bellow according to their indication and dosage regimen:

PPIs	Indication	Dosage Regimen
Omeprazole	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
Lansoprazole	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	60mg daily
	H. pylori eradication - triple therapy - dual therapy	 30mg q12h x 10-14 days 30mg q8h x 14 days
Pantoprazole	Treatment of EE	40mg daily x 8 weeks
Rabeprazole	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	60mg daily

(Sreedhar D, Dlip K, Ajay P, Manthan DJ, Subramanian D, Udupa N, 2006).

1.5.9. Interactions of PPIs with other drug

The PPI's are metabolized by the cytochrome P450 isoenzymes. It 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 isoenyzme 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 2: PPIs shows some interaction with other drug, which are given bellow:

Proton Pump Inhibitor	Interacting Drug(s)	Nature of Interaction
Omeprazole	Clarithromycin	Increase plasma levels of omeprazole, clarithromycin and 14-hydroxyclarithromycin.
	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.
Lansoprazole	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.
Pantoprazole	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.	
Rabeprazole	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.
Esomeprazole	Diazepam	45% decrease in clearance of diazepam.
	Warfarin	Increase in INR and prothrombin time.
	Ketoconazole, iron salts and digoxin	Interfere with the absorption.

(Sreedhar D, Dlip K, Ajay P, Manthan DJ, Subramanian D, Udupa N, 2006).

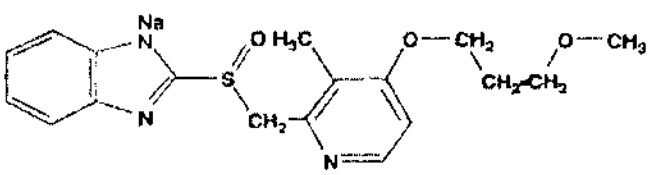
1.6. RABEPRAZOLE SODIUM (rabeprazole delayed-release tablets)

Rabeprazole sodium is one of the prominent proton pump inhibitors. It is commonly used in the world for the treatment of peptic ulcer. It functions by inhibiting the enzyme H^+/ K^+ ATPase which is responsible for the secretion of gastric acid. The active ingredient in Rabeprazole Delayed-Release Tablets is rabeprazole sodium, a substituted benzimidazole that inhibits gastric acid secretion. So, some brief descriptions of rabeprazole are given bellow:

1.6.1. Description

Rabeprazole sodium works by blocking acid production in the stomach. It is known as a proton pump inhibitor (PPI). It is used to treat acid-related stomach/intestinal and throat (esophagus) problems (e.g., acid reflux or GERD, ulcers, erosive esophagitis, Zollinger-Ellison syndrome) (Mayer MD, Vakily M, Witt G, Mulford DJ. 2008). The active ingredient in Rabeprazole Delayed-Release Tablets is rabeprazole sodium, 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 (Roche VF. 2005; Baltimore MD: Lippincott Williams & Wilkins; 2002).

1.6.2. Chemical Structure



RABEPRAZOLE SODIUM

Rabeprazole is available for oral administration as delayed-release, enteric coated tablets containing 20 mg of rabeprazole sodium. Inactive ingredients are carnauba wax, crospovidone, diacetylated monoglycerides, ethylcellulose, hydroxypropyl cellulose,

hypromellose phthalate, mannitol, sodium hydroxide, sodium stearyl fumarate, talc, titanium dioxide, and yellow ferric oxide as a coloring agent (Zhang WJ, 2008).

1.6.3. Mechanism of action

This PPI is the most highly reactive of those currently marketed. The high parietal cell concentration of rabeprazole compared to the other PPIs is certainly one factor in its superior anti-secretory activity (Alsharif NZ, Theesen KA, Roche VF, 1997). Rabeprazole has the lowest dependence of all PPIs on CYP isoforms for its biotransformation and is primarily inactivated through nonenzymatic conversion to the thioether. No CYP-mediated drug-drug interactions involving rabeprazole have been noted in the literature (Roche VF, 1985).

1.6.4. Pharmacology

Suppresses gastric acid secretion by blocking acid (proton) pump within gastric parietal cells (Zhang W, Wu J, 2008).

1.6.5. Pharmacokinetics

a. Absorption: - T_{max} is 2 to 5 hour. Oral bioavailability is about 52%.
b. Distribution: - Protein binding is 96.3%.
c. Metabolism: - Extensively metabolized in liver by CYP3A to sulfone metabolite and CYP2C19 to desmethyl rabeprazole. Thioether metabolite is formed by reduction of rabeprazole. These metabolites do not have significant antisecretory activity. Poor metabolizers of rabeprazole, CYP2C19 exhibit genetic polymorphism (Zhang W, Wu J, 2008).
d. Elimination: - Plasma $t_{½}$ is 1 to 2 hour. Eliminated in urine (90% as thioether carboxylic acid, glucuronide and mercapturic acid) remainder recovered in feces. No unchanged drug recovered.

1.6.6. Dose

The activation half-life of rabeprazole in acidic media is approximately 1.3 minutes, which is the shortest of all the PPIs. In 20-mg doses, rabeprazole exhibits the highest level of gastric acid secretion control within the first 24 hours of therapy. It takes a 40-mg dose of esomeprazole to provide the same degree of relief from gastric acid-induced discomfort that is obtained from 20 mg of rabeprazole. When used in combination with amoxicillin and clarithromycin for the eradication of H. pylori, rabeprazole produces positive results in 7 days compared to the 10-14 day course of therapy recommended for esomeprazole and lansoprazole, respectively (Mayer MD, Vakily M, Witt G, Mulford DJ, 2008; Zhang WJ, 2008).

1.6.7. Indications

-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).

- Rabeprazole sodium is indicated for short-term (up to four weeks) treatment in the healing and symptomatic relief of duodenal ulcers and EE.
- Eradication of H. pylori in triple therapy with clarithromycin and amoxicillin, or in double therapy with amoxicillin only (Dr, Sreedhar, Dlip Kumer, Ajay Pise, Manthan D Janodia, D Subramanian, Dr.06-11-2006).
- Rabeprazole sodium is indicated for maintaining healing and reduction in relapse rates heartburn symptoms (Howden CW, Perez MC, Larsen LM, 2008).

1.6.8. Contraindications

It produces hypersensitivity reaction to substituted benzimidazoles.

1.6.9. Storage/Stability

Store tablets at controlled room temperature (59° to 86°F). Protect from moisture.

1.6.10. Adverse Reactions

- **Cardiovascular**

Hypertension, MI, migraine (Zhang WJ, 2008).

- **Dermatologic**

Rash, sweating, alopecia, severe dermatologic reactions (Zhang WJ, 2008).

- **CNS**

Headache (2%), insomnia, anxiety, dizziness, depression, nervousness, vertigo, convulsion, abnormal dream, libido decreased, neuropathology, tremor, disorientation (Mayer MD, Vakily M, Witt G, Mulford DJ, 2008).

1.6.11. Precautions

- Pregnancy: Category B.
- Lactation: Undetermined.
- Children: Safety and efficacy not established.
- Gastric malignancy Symptomatic response to rabeprazole sodium does not preclude gastric malignancy.

1.6.12. Patient Information

- Instruct patient to take each dose without regard to meals but to take with food if stomach upset occurs.
- Instruct patient to swallow tablets whole and not to split, crush, or chew the tablets.
- Remind patient that rabeprazole is to be taken every day and not as needed or only when symptoms are present.
- Remind patient that antacids may be taken concurrently with rabeprazole (Sharma P, Shaheen NJ, Perez MC, Pilmer B, 2008).

2. Purpose

The purpose of this study is to determine the market feasibility study of Rabeprazole Sodium and to establish a new molecule. I can get desired action from that molecule, to treat all type of peptic ulcer. Among all type of PPIs Rabeprazole market growth is increase very promptly because of its molecular feature. Molecular study is done depending on its (Rabeprazole Sodium) indication and clinical response comparing with other PPI. It can be done by considering the market analysis of all PPIs and to establish a proposal about the market growth rate of that drug. Main purpose is to develop a hypothesis on Rabeprazole Sodium or how it can compete with other PPI.

3. Hypothesis

A research question poses a relationship between two or more variables but phrases the relationship as a question; a hypothesis represents a declarative statement of the relations between two or more variables (Kerlinger, 1979; Krathwohl, 1988). Rabeprazole sodium is the most effective drug among all PPIs for the treatment of peptic ulcer. Rabeprazole sodium can be cover maximum market share due to its duration of action.

4. Method

There are different types of methods were used to establish this hypothesis, which are given bellow:

- Many website were used to collect all information about the drug. For example, Google.com, Pubmed.com etc.
- Many books, journals, articles were also used to know efficacy and safety profile of drugs.
- MS Excel was used to calculate market growth and to plot graph.
- International Market Strategy (IMS) data was used to determine the market size.
- Comparison of Rabeprazole Sodium with other PPI was done on the basis of their efficacy and market strategy.
- This paper was prepared with authorized person and their publishing year.

5. Result and Discussion

Rabeprazole sodium can become a lead molecule among all PPIs because its dosage frequency is less. It is safer drug in the treatment of gastric ulcer.

5.1. Efficacy

Rabeprazole sodium is one of the prominent proton pump inhibitors. It is commonly used in the world for the treatment of peptic ulcer. Its T_{max} is 2 to 5 hour, oral bioavailability is about 52% and plasma $t_{½}$ is 1 to 2 hour. The activation half-life of rabeprazole sodium in acidic media is approximately 1.3 minutes, which is the shortest of all the PPIs. In 20-mg doses, rabeprazole exhibits the highest level of gastric acid secretion control within the first 24 hours of therapy. When used in combination with amoxicillin and clarithromycin for the eradication of H. pylori, rabeprazole produces positive results in 7 days compared to the 10-14 day course of therapy recommended for esomeprazole and lansoprazole, respectively (Mayer MD, Vakily M, Witt G, Mulford DJ, 2008; Zhang WJ, 2008). Extended duration of Rabeprazole sodium causes a progressive increase in the pharmacodynamic response (Vakily M, Zhang WJ, Atkinson SN, Mulford D, 2009). The Rabeprazole sodium Delayed release tablet formulation may improve acid suppression and offer benefits over conventional single release PPI formulations (Metz DC, Vakily M, Dixit T, Mulford D, 2009). Patient gets desired action by taking this. It is more effective in the treatment of duodenal ulcer, *H. pylori*, gastric ulcer, erosive esophagitis, GERD, and pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

5.2. Market Scenario

Table 4: Total market value of antiulcerant and PPI With their growth (Source, IMS Data):

		1-Q 2008 MAT Value TK	1-Q 2007 MAT Value TK	1-Q 2006 MAT Value TK
Total Market	Total Value	40,587,191,000	36,369,963,671	35,574,308,870
	Increased %	11.60	2.24	
Antiulcerant	Total Value	5,630,812,000	4,497,446,717	4,570,457,243
	Increased %	25.20	-1.60	
Acid Pump Inhibitor	Total Value	2,887,017,108	2,601,900,191	2,446,267,349
	Increased %	10.96	6.36	

Observation: From this table we get that, total Pharma market is changing in every year. The growth rate is 2.24% in year 2007 but in year 2008 it has been increased and the rate is11.60%. The antiulcerant drug cover cover 12.85% in year 2006, in year 2007 cover 12.36% and in year 2008 cover 13.87% of the total Pharma market. That means there is no significant change. It is a large market value in over all Pharma market. The total antiulcerant market value is also varying in every year. For example the growth rate is -1.60% in year 2007 but there is huge increase in 2008 to 25.20%. That means market value of total antiulcerant drugs is significantly reduced in year 2007. From this table we also can see that, the Proton Pump Inhibitors cover 6.87% in year 2006, 7.15% in year 2007 and 7.11% in year 2008 of the total Pharma market. The Proton Pump Inhibitors also cover 53.52% in year 2006, 57.85% in year 2007, 51.27% in year 2008 of the total Antiulcerant market. So the Proton Pump Inhibitors have covered a large market all over the Antiulcerant Drug. The Growth rate of Proton Pump Inhibitor is 6.36% in year 2007, 10.96% in year 2008. It is huge increased in the PPI market.

From the table 1, I can plot following graphs:

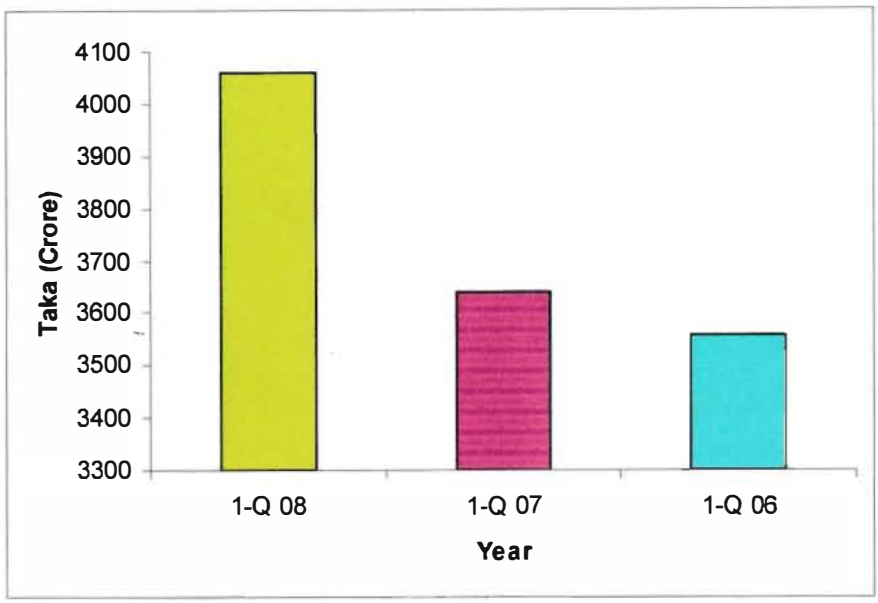


Fig: Graphical Presentation of Total Pharma Market Size in last three years

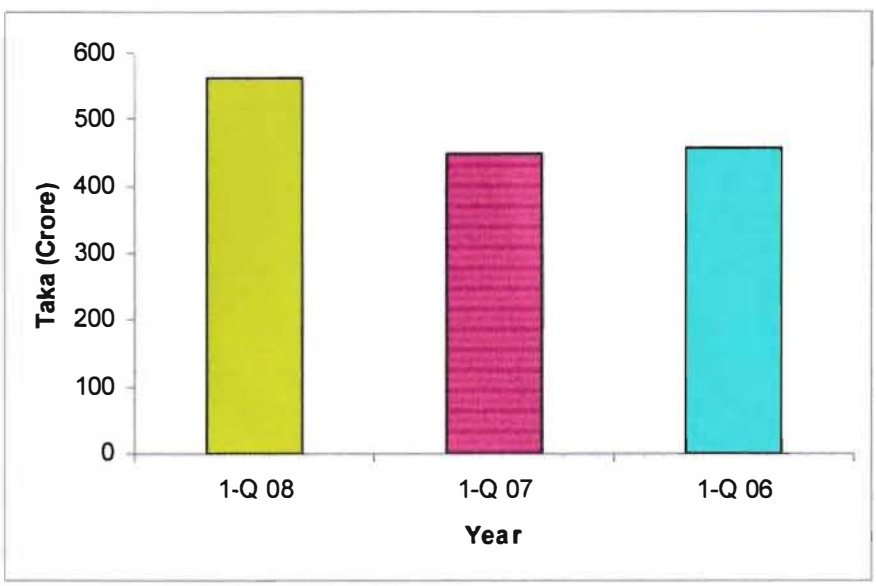


Fig: Graphical Presentation of Total Antiulcerants Market Size in last three years

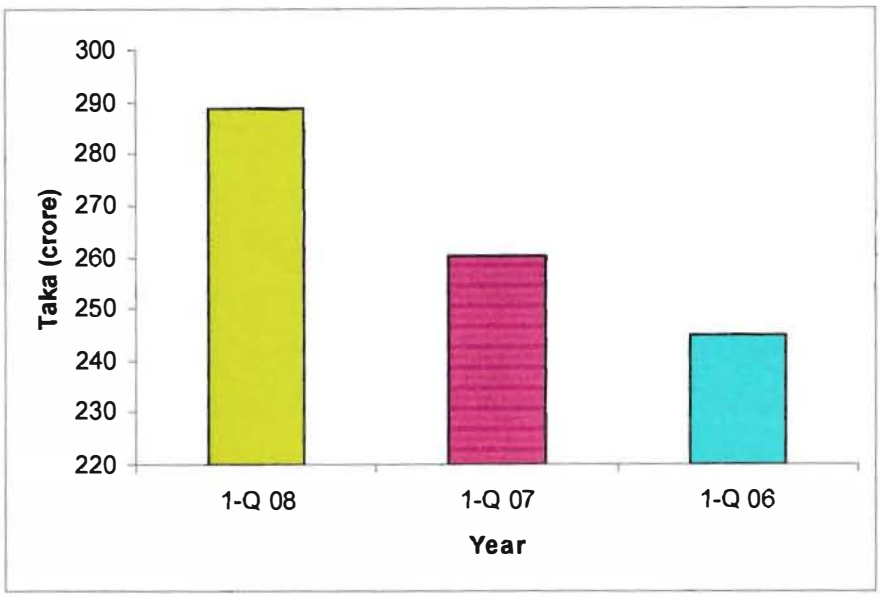


Fig: Graphical Presentation of Total PPIs Market Size in last 3 years

Table 5: Total market value of all Proton pump market Inhibitor and their growth (Source, IMS Data):

		1-Q 08 MAT Value TK	1-Q 07 MAT Value TK	1-Q 06 MAT Value TK
Omeprazole	Total Value	1,791,153,108	1,760,463,166	1,783,963,913
	Increased %	1.74	-1.32	
Pantoprazole	Total Value	510,828,000	405,361,198	278,442,595
	Increased %	26.02	45.58	
Esomeprazole	Total Value	422,014,000	295,593,153	250,653,316
	Increased %	42.77	17.93	
Lansoprazole	Total Value	96,841,000	96,563,144	106,638,952
	Increased %	-0.74	-8.51	
Rabeprazole	Total Value	66,181,000	42,919,530	26,568,572
	Increased %	54.20	61.54	

Observation: From this table we find that, the growth rate of Omeprazole in year 2007 has been decreased to -1.32 but it is very minutely increased to 1.74%. It cover 72.92% in year 2006, 67.66% in year 2007, 62.04% in year 2008 of the total PPI market. So it covers the highest market of the total PPI market. The growth rate of Pantoprazole is 45.58% in year 2007 but it has been reduced to 26.02% in year 2008. It cover 11.38% in year 2006, 15.57% in year 2007, 17.69% in year 2008 of the total PPI market. The growth rate of Esomeprazole is 17.93% in year 2007 but the growth rate of Esomeprazole has been improved to 42.77% in year 2008. That means it take over the Pantoprazole market. It cover 10.25% in year 2006, 11.36% in year 2007, 14.62% in year 2008 of the total PPI market. The growth rate of Lansoprazole is -8.51% in year 2007 although it has been increased to -0.74 but it is not a very high market value. It cover 4.36% in year 2006, 3.71% in year 2007, 3.35% in year 2008 of the total PPI market. The growth rate of Rabeprazole is 61.54% in year 2007. It is a very large market value though it is reduced to 54.20% in year 2008. It cover 1.09% in year 2006, 1.65% in year 2007, 2.29% in year 2008 of the total PPI market.

From table 2, I can plot following graphs:

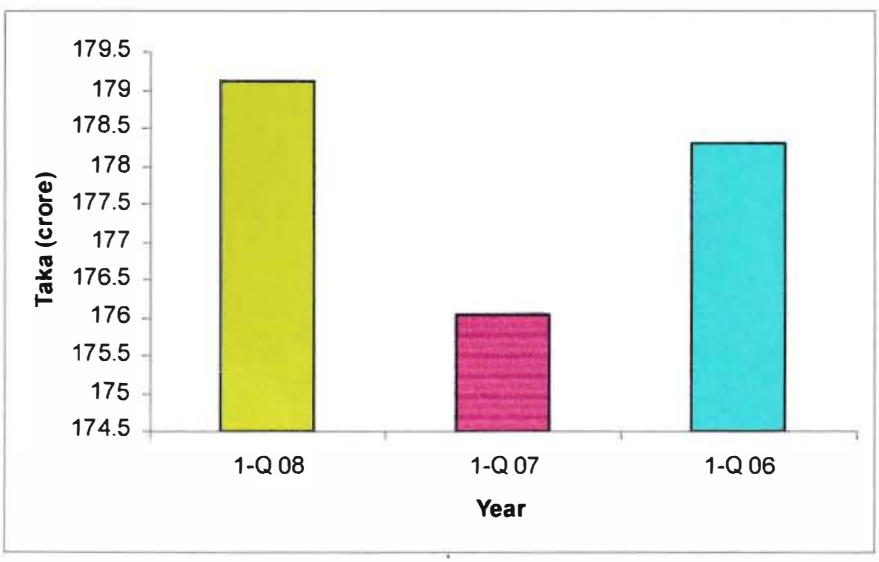


Fig: Graphical Presentation of Total Omeprazole Market Size in last three years

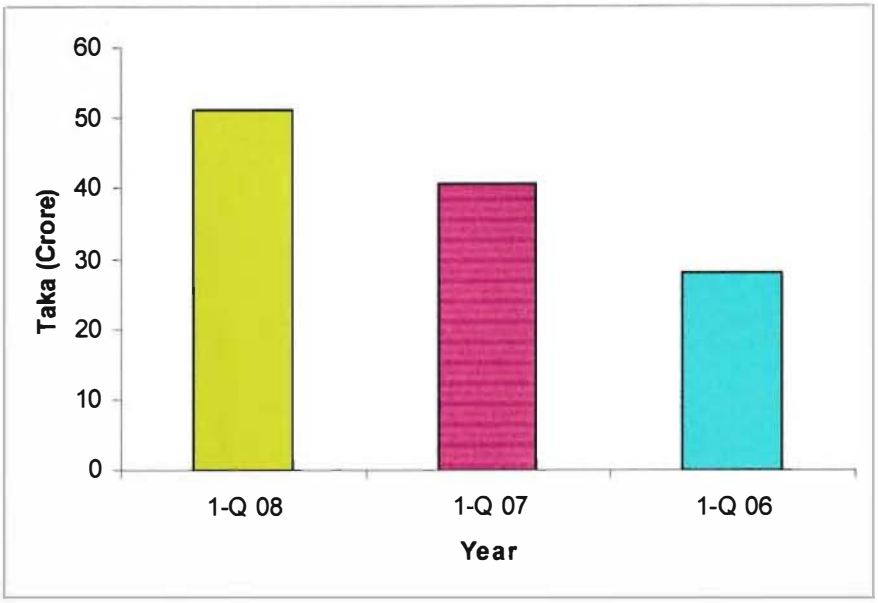


Fig: Graphical Presentation of Total Pantoprazole Market Size in last three years

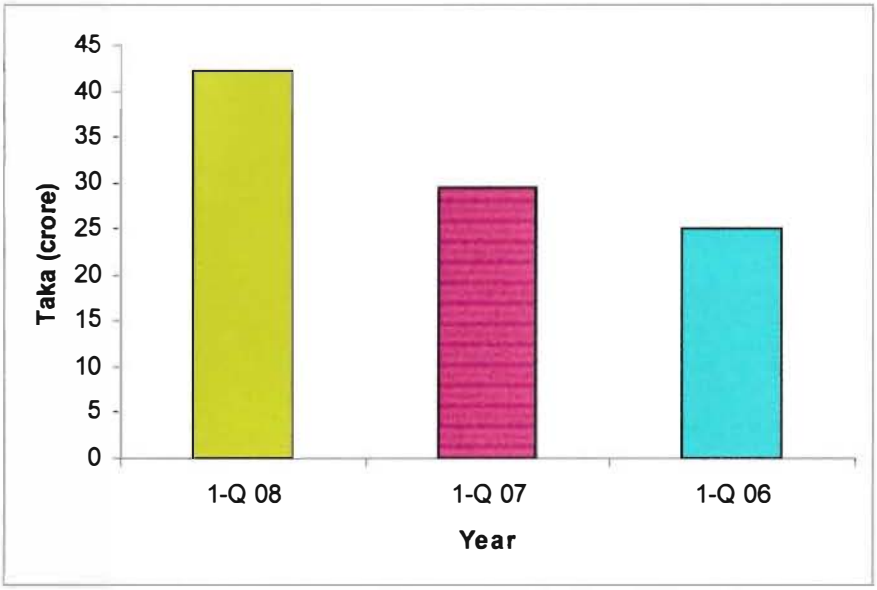


Fig: Graphical Presentation of Total Esomeprazole Market Size in last three years

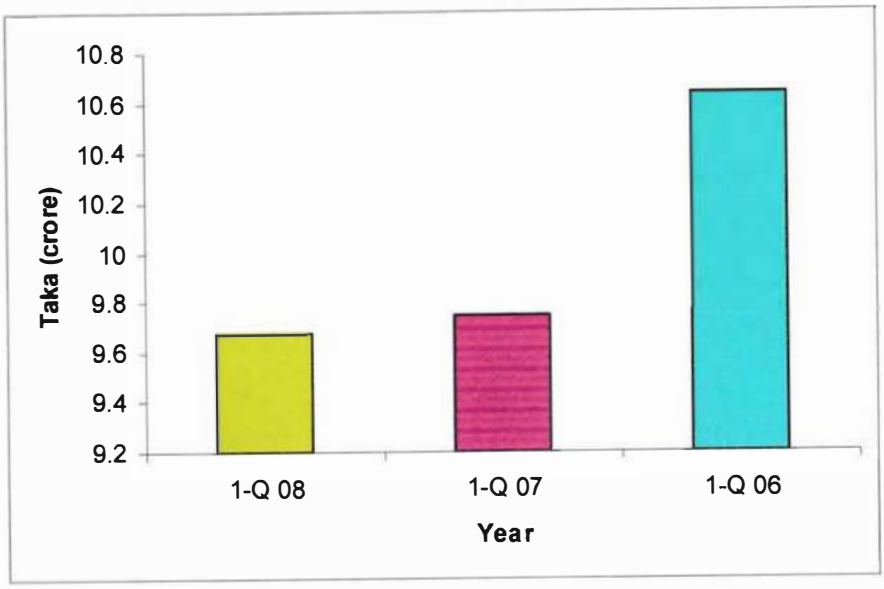


Fig: Graphical Presentation of Total Lansoprazole Market Size in last three years

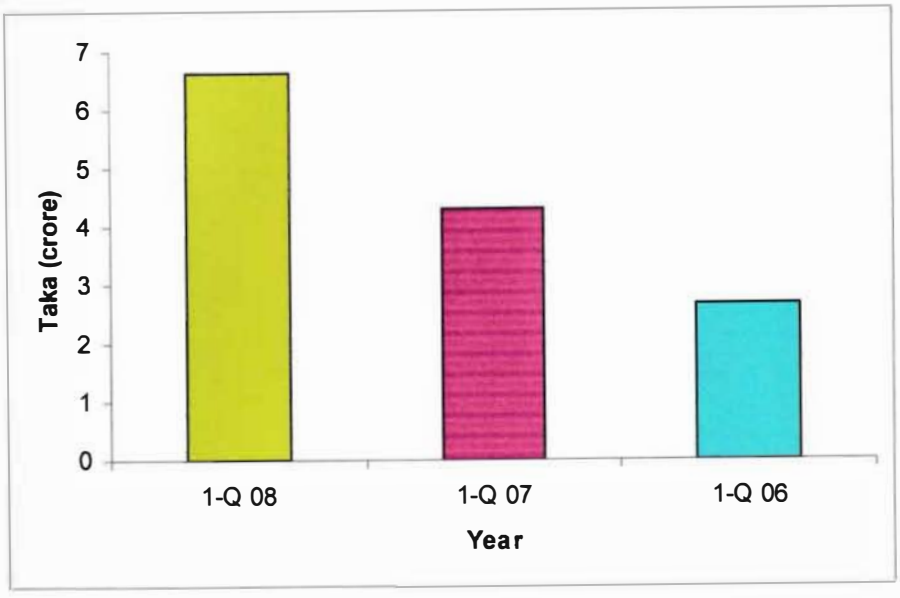


Fig: Graphical Presentation of Total Rabeprazole Market Size in last three years

6. Conclusion

PPIs are the lead molecule for the treatment of peptic ulcer. Rabeprazole sodium is a proton pump inhibitor which shows better efficacy in the treatment of duodenal ulcer, H. pylori, gastric ulcer, erosive esophagitis, GERD, and pathological hypersecretory conditions, including Zollinger-Ellison than the other proton pump inhibitors. To increase overall market growth I can introduce Rabeprazole sodium. Due to its D-R property it will become a superior molecule in PPI market.

7. Limitation

During the market feasibility of rabeprazole sodium some limitation were observed which are given bellow:

a. No clinical trial was done.
b. Data collect from website, which is not always perfect and optimum.
c. There are no survey study was done.
d. Hypothesis was not well developed.
e. Result was not accurate in compare to market study.
f. Comparative study was done on the basis of clinical data collect from website.

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8. Significance of the study

a. From this study I understood that how to launch a new product in competitive pharma market.
b. It helps me to acquire a brief knowledge about the total Pharma market.
c. To some extent of information about the nearest competitive product can be known.
d. I can get an overall idea about market position of any drugs.
e. We can also know how a product can improve its market position.
f. It gives an idea about the limitation of any drugs in the market.

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