

*For the use of only a Registered Medical Practitioner or a Hospital or a Laboratory*

*Not to be sold by retail without the prescription of a Registered Medical Practitioner*

## **Prescribing Information**

### **1. Generic Name**

Esomeprazole Gastro-resistant Tablets IP

(Brand Name: S-PPI® 40 Tablets)

### **2. Qualitative and Quantitative Composition**

Each Gastro-resistant Tablet Contains:

Esomeprazole Magnesium Trihydrate IP

equivalent to Esomeprazole ..... 40 mg

Excipients ..... q.s.

Colours: Lake of Sunset Yellow FCF

### **3. Dosage Form and Strength**

Dosage Form: Tablets.

Dosage Strength: Esomeprazole 40 mg (in a gastro resistant form) per tablet.

### **4. Clinical Particulars**

#### **4.1 Therapeutic Indication**

S-PPI Tablets are indicated in the following:

- Erosive esophagitis associated with gastro-esophageal reflux disease (GERD).
- Prevention of rebleeding of gastric or duodenal ulcers following therapeutic endoscopy in adults.
- Prevention of non-steroidal anti-inflammatory drug (NSAID)-associated gastric or duodenal ulcers in patients at risk.
- Pathological hypersecretory conditions including Zollinger-Ellison syndrome.

#### **4.2 Posology and Method of Administration**

For oral administration in adults and adolescents ( $\geq 12$  years of age).

- 1) **Erosive Esophagitis Associated with GERD:** 40 mg once daily for 4 weeks. An additional 4 weeks treatment is recommended for patients in whom esophagitis has not healed or who have persistent symptoms.
- 2) **Prevention of Rebleeding of Peptic Ulcers Following Endoscopy:** 40 mg once daily for 4 weeks.
- 3) **Prevention of NSAID-Associated Gastric or Duodenal Ulcer in Patients at Risk** (age > 60 years, previous history of peptic ulcers or upper gastrointestinal/GI bleeding): 20 mg or 40 mg once daily for up to 6 months.

- 4) **Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome:**  
The recommended initial dose is 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Based on the clinical data available, the majority of patients can be controlled on doses between 80 to 160 mg esomeprazole daily. With doses above 80 mg daily, the dose should be divided and given twice daily.

S-PPI Tablets should be administered on empty stomach, preferably in the morning or at least 1 hour prior to meal. S-PPI Tablets should be swallowed whole with water and not to be cut, crush or chew.

Or, as prescribed by the physician.

### 4.3 Contraindications

S-PPI Tablets are contraindicated in the following conditions:

- Known hypersensitivity to esomeprazole or to substituted benzimidazoles or to any component of the formulation.
- Concomitant use with nelfinavir.

### 4.4 Special Warnings and Precautions for Use

**Gastric Malignancy:** In the presence of any alarm symptom (e.g., significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

***Helicobacter Pylori* Eradication:** When prescribing esomeprazole for eradication of *Helicobacter pylori*, possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4, such as cisapride.

**Gastrointestinal Infections/Gastritis:** Treatment with PPIs may lead to a slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*. Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole, of which esomeprazole is an enantiomer.

***Clostridium Difficile*-Associated Diarrhea (CDAD):** Published observational studies suggest that PPI therapy like esomeprazole may be associated with an increased risk of *Clostridium difficile*-associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

**Absorption of Vitamin B<sub>12</sub>:** Esomeprazole, like all acid-blocking medicines, may reduce the absorption of vitamin B<sub>12</sub> (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B<sub>12</sub> absorption on long-term therapy.

**Risk of Bone Fracture:** Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related

fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose (defined as multiple daily doses), and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines and they should have an adequate intake of vitamin D and calcium.

**Subacute Cutaneous Lupus Erythematosus (SCLE):** PPIs have been associated with cases of SCLE, although very infrequently. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and esomeprazole therapy should be stopped immediately. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

**Hypomagnesemia:** Hypomagnesemia (symptomatic/asymptomatic), has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), it is recommended to monitor magnesium levels prior to initiation of PPI treatment, and periodically thereafter.

## 4.5 Drug Interactions

### Interference with Antiretroviral Therapy

**Reduced Concentrations of Atazanavir and Nelfinavir:** Concomitant use of atazanavir and nelfinavir with PPIs is not recommended. Co-administration of atazanavir with PPIs is expected to substantially decrease atazanavir plasma concentrations and may result in a loss of therapeutic effect and the development of drug resistance. If the combination of atazanavir with a PPI is unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; esomeprazole 20 mg should not be exceeded.

**Increased Concentrations of Saquinavir:** Co-administration of saquinavir with PPIs is expected to increase saquinavir concentrations, which may increase toxicity and require dose reduction. Omeprazole, of which esomeprazole is an enantiomer, has been reported to interact with other antiretroviral drugs, too. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19.

### Drugs for Which Gastric PH Can Affect Bioavailability (ketoconazole, atazanavir, iron salts, erlotinib, mycophenolate mofetil, digoxin)

Esomeprazole inhibits gastric acid secretion. Therefore, esomeprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability. Like with other drugs that decrease intragastric acidity, the absorption of drugs such as ketoconazole, atazanavir, iron salts, erlotinib, and mycophenolate mofetil (MMF) can decrease, while the absorption of drugs such as digoxin can increase during treatment with esomeprazole.

**Digoxin:** Concomitant treatment with omeprazole (20 mg daily), of which esomeprazole is an enantiomer, and digoxin in healthy subjects increased the bioavailability of digoxin by 10%. Co-administration of digoxin with esomeprazole is expected to increase the systemic exposure of digoxin. Therefore, patients may need to be monitored when digoxin is taken concomitantly with esomeprazole.

**Mycophenolate Mofetil (MMF):** Co-administration of omeprazole in healthy subjects and in transplant patients receiving MMF has been reported to reduce the exposure to the active metabolite, mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH. The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients receiving esomeprazole and MMF. Use esomeprazole with caution in transplant patients receiving MMF.

### **Effects on Hepatic Metabolism/Cytochrome P-450 Pathways**

Esomeprazole is extensively metabolized in the liver by CYP 2C19 and CYP 3A4. *In-vitro* and *in-vivo* studies have shown that esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1, and 3A4. No clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Drug interaction studies have shown that esomeprazole does not have any clinically significant interactions with quinidine, clarithromycin, or amoxicillin.

**Warfarin:** Patients treated with PPIs and warfarin concomitantly may need to be monitored for increases in INR (International Normalized Ratio) and prothrombin time. Increases in INR and prothrombin time may lead to abnormal bleeding.

**Clopidogrel:** Avoid concomitant use of esomeprazole with clopidogrel. Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is entirely due to an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by use of concomitant medications, such as esomeprazole, that inhibit CYP2C19 activity. Concomitant use of clopidogrel with esomeprazole 40 mg reduces the pharmacological activity of clopidogrel. As a precaution, concomitant use of esomeprazole and clopidogrel should be discouraged or when using esomeprazole consider alternative anti-platelet therapy.

**Diazepam:** Esomeprazole may potentially interfere with CYP2C19, the major esomeprazole metabolizing enzyme. Co-administration of esomeprazole and diazepam, a CYP2C19 substrate, resulted in a 45% decrease in clearance of diazepam.

**Phenytoin:** Concomitant administration of esomeprazole 40 mg resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

**Cilostazol:** Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, of which esomeprazole is an enantiomer, given in doses of 40 mg to healthy subjects in a cross-over study, increased  $C_{max}$  and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69%, respectively.

**Cisapride:** In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ( $t_{1/2}$ ) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of

cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole.

**Voriconazole:** Concomitant administration of esomeprazole and a combined inhibitor of CYP 2C19 and CYP3A4, such as voriconazole, may result in a more than doubling of the esomeprazole exposure. Dose adjustment of esomeprazole is not normally required. However, in patients with Zollinger-Ellison's Syndrome, who may require higher doses (up to 240 mg/day), dose adjustment may be considered.

**Rifampicin:** Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampin) may lead to decreased esomeprazole serum levels. Avoid concomitant use of rifampin with esomeprazole.

**St. John's Wort:** Omeprazole, of which esomeprazole is an enantiomer, has been reported to interact with St. John's wort, an inducer of CYP3A4. Avoid concomitant use of St. John's wort with esomeprazole.

### **Concomitant Administration with Other Drugs**

**Tacrolimus:** Concomitant administration of esomeprazole and tacrolimus may increase the serum levels of tacrolimus.

**Combination Therapy with Clarithromycin:** Co-administration of esomeprazole, clarithromycin, and amoxicillin has resulted in an increase in plasma levels of esomeprazole and 14-hydroxyclearithromycin.

**Methotrexate:** Concomitant administration of PPIs and methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, leading to a risk of methotrexate toxicity. In high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients.

### **Drug / Laboratory Tests Interactions**

**Interactions with Investigations of Neuroendocrine Tumors:** Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. To avoid this interference, esomeprazole treatment should be stopped for at least 5 days before CgA measurements; consider repeating the test if initial CgA levels are high.

## **4.6 Use in Special Populations**

### **Pregnant Women**

Pregnancy Category C. Animal studies with esomeprazole do not indicate direct or indirect harmful effects with respect to reproductive toxicity (embryonal/fetal development). Also, animal studies with the racemic mixture (i.e., omeprazole) do not indicate direct or indirect harmful effects with respect to pregnancy, parturition or postnatal development. A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicates no malformative or fetoneonatal toxicity of esomeprazole. There are however, no adequate and well controlled studies available for use of esomeprazole during pregnancy. Thus, caution should be exercised when prescribing esomeprazole to pregnant women.

### **Lactating Women**

Esomeprazole is likely to present in human milk. Esomeprazole is the S-isomer of omeprazole and limited data indicate that maternal doses of omeprazole 20 mg daily produce low levels in human milk. There is insufficient information on the effects of esomeprazole in newborns/infants. Caution should be exercised when esomeprazole is administered to a nursing woman.

### **Paediatric Patients**

The safety and effectiveness of esomeprazole have been established in paediatric patients between 1 to 17 years of age for short-term treatment of GERD (up to 8 weeks). However, S-PPi Tablets are not recommended for use in this population, as dosage feasibility with this formulation is not possible. The safety and effectiveness of esomeprazole for other paediatric uses have not been established. Thus, S-PPi Tablets are not recommended for use in children.

### **Geriatric Patients**

With esomeprazole, no dosage adjustment is generally necessary in the elderly population. No overall differences in safety and efficacy were observed between the elderly and younger individuals, but greater sensitivity of some older individuals cannot be ruled out.

### **Renal Impairment Patients**

S-PPi Tablets can be administered in patients with mild to moderate renal impairment; dose adjustment is not required in these patients. However, there is lack of data on use of esomeprazole in patients with severe renal insufficiency; thus, such patients should be treated with caution.

### **Hepatic Impairment Patients**

Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, a maximum dose of 20 mg esomeprazole should not be exceeded.

## **4.7 Effect on Ability to Drive and Use Machines**

Esomeprazole has a minor influence on the ability to drive or use machines. Adverse reactions such as dizziness and blurred vision have been reported rarely with esomeprazole. If affected, patients should not drive or use machines.

## **4.8 Undesirable Effects**

### **Clinical Trials Experience**

The most frequently reported ( $\geq 1\%$ ) adverse reactions with esomeprazole were headache, diarrhea, nausea, flatulence, abdominal pain, constipation, and dry mouth.

Additional adverse reactions that were reported as possibly or probably related to esomeprazole with an incidence  $< 1\%$  are as follows:

Body as a Whole: Enlarged abdomen, allergic reaction, asthenia, back pain, chest pain, substernal chest pain, facial edema, peripheral edema, hot flushes, fatigue, fever, flu-like symptoms, generalized edema, leg edema, malaise, pain, rigors.

Cardiovascular: Flushing, hypertension, tachycardia.

Endocrine: Goiter.

Gastrointestinal (GI): Bowel irregularity, constipation aggravated, dyspepsia, dysphagia, GI dysplasia, epigastric pain, eructation, esophageal disorders, frequent stools, gastroenteritis, GI hemorrhage, GI symptoms not otherwise specified, hiccup, melena, mouth disorders, pharyngeal disorders, rectal disorders, increase in serum gastrin, tongue disorders, tongue edema, ulcerative stomatitis, vomiting.

Hearing: Earache, tinnitus.

Hematologic: Anemia, cervical lymphadenopathy, epistaxis, leukocytosis, leukopenia, thrombocytopenia.

Hepatic: Abnormalities in hepatic function, including bilirubinemia, increase in AST (aspartate aminotransferase) and ALT (alanine aminotransferase).

Metabolic/Nutritional: Glycosuria, hyperuricemia, hyponatremia, increased alkaline phosphatase, thirst, vitamin B<sub>12</sub> deficiency, weight increase/decrease.

Musculoskeletal: Arthropathy, cramps, fibromyalgia syndrome, hernia, polymyalgia rheumatica.

Nervous System/Psychiatric: Anorexia, apathy, increased appetite, confusion, depression aggravated, dizziness, hypertonia, nervousness, hypoesthesia, impotence, insomnia, migraine, paresthesia, sleep disorder, somnolence, tremor, vertigo, visual field defect.

Reproductive: Dysmenorrhea, menstrual disorders, vaginitis.

Respiratory: Aggravated asthma, coughing, dyspnea, laryngeal edema, pharyngitis, rhinitis, sinusitis.

Skin and Appendages: Acne, angioedema, dermatitis, pruritus, rash, urticaria, sweating.

Special Senses: Otitis media, parosmia, taste loss, taste perversion.

Urogenital: Albuminuria, cystitis, dysuria, fungal infection, hematuria, frequent micturition, moniliasis, polyuria.

Visual: Conjunctivitis, abnormal vision.

### **Laboratory Abnormalities**

The following clinically significant laboratory changes in clinical trials, irrespective of relationship to esomeprazole, were reported in  $\leq 1\%$  of patients: Increased creatinine, uric acid, total bilirubin, alkaline phosphatase, ALT, AST, hemoglobin, white blood cell count, platelets, serum gastrin, potassium, sodium, thyroxine and thyroid stimulating hormone. Decreased levels of hemoglobin, white blood cell count, platelets, potassium, sodium, and thyroxine.

### **Post-Marketing Experience**

Acute kidney injury as an adverse drug reaction reported with the use of proton pump inhibitors. The following adverse reactions have been identified during post-marketing use of esomeprazole. Because these reactions are reported voluntarily from a population of

uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic: Agranulocytosis, pancytopenia.

Eye: Blurred vision.

Gastrointestinal: Pancreatitis, stomatitis, microscopic colitis.

Hepatobiliary: Hepatitis with or without jaundice, hepatic failure.

Immune System: Anaphylactic reaction/shock.

Infections and Infestations: GI candidiasis, *Clostridium difficile*-associated diarrhea.

Metabolism and Nutritional Disorders: Hypomagnesemia.

Musculoskeletal and Connective Tissue: Muscular weakness, myalgia, fractures.

Nervous System: Hepatic encephalopathy, taste disturbance.

Psychiatric: Aggression, agitation, depression, hallucination.

Renal and Urinary: Interstitial nephritis.

Reproductive System and Breast: Gynecomastia.

Respiratory, Thoracic, and Mediastinal: Bronchospasm.

Skin and Subcutaneous Tissue: Alopecia, erythema multiforme, hyperhidrosis, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis (sometime fatal), cutaneous lupus erythematosus.

## 4.9 Overdose

**Symptoms:** There is very limited experience with deliberate overdose of esomeprazole. The symptoms described in connection with deliberate overdose (limited experience of doses in excess of 240 mg/day) are transient. Single doses of 80 mg of esomeprazole were uneventful. Symptoms of esomeprazole overdose were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, and dry mouth.

**Treatment:** No specific antidote for esomeprazole is known. Since esomeprazole is extensively protein bound, it is not able to be removed by dialysis. In the event of overdose, treatment should be symptomatic and supportive.

## 5. Pharmacological Properties

### 5.1 Mechanism of Action

Esomeprazole is a proton pump inhibitor (PPI) that suppresses gastric acid (hydrochloric acid - HCl) secretion by specific inhibition of the H<sup>+</sup>/K<sup>+</sup>-ATPase enzyme system at the secretory surface of the gastric parietal cell. Esomeprazole is a weak base and is concentrated and converted to the active form (i.e., the achiral sulphenamide) in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H<sup>+</sup>/K<sup>+</sup>-ATPase (the acid/proton pump), and inhibits both basal and stimulated acid secretion. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thereby reducing gastric acidity.

### 5.2 Pharmacodynamic Properties

Esomeprazole is the S-isomer of omeprazole. Esomeprazole reduces gastric acid secretion through a specific targeted mechanism of action i.e., inhibition of the acid pump in the gastric



parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity.

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for 5 days, mean peak acid output decreases by 90% when measured 6 to 7 hours after dosing on day five. After 5 days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GERD patients. The proportion of patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours respectively were 76%, 54% and 24% for esomeprazole 20 mg. Corresponding proportions for esomeprazole 40 mg were 97%, 92% and 56%.

Esomeprazole increases the mean fasting gastrin level in a dose-related manner. This increase reached a plateau within two to three months of therapy and returned to baseline levels within four weeks after discontinuation of therapy.

### 5.3 Pharmacokinetic Properties

**Absorption:** Like other PPIs, esomeprazole is an acid-labile drug and therefore, administered orally in the form of gastro-resistant tablets. Absorption of esomeprazole therefore, begins only after the gastro-resistant tablet leaves the stomach. Esomeprazole is rapidly absorbed after oral administration. Onset of effect occurs within one hour after oral dosing with esomeprazole 20 mg and 40 mg. Peak plasma levels ( $C_{max}$ ) occur approximately 1 to 2 hours ( $T_{max}$ ) after oral dose. The  $C_{max}$  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.

Food intake both delays and decreases the absorption of esomeprazole. Thus, esomeprazole should be administered at least one hour before meals.

**Distribution:** Esomeprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 2 to 20  $\mu\text{mol/l}$ . The apparent volume of distribution at steady state in healthy volunteers is approximately 16 liters.

**Metabolism:** Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system. The metabolites of esomeprazole lack antisecretory activity. The major part of esomeprazole's metabolism is dependent upon the CYP2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on CYP3A4 which forms the sulphone metabolite.

**Excretion:** Total plasma clearance is about 17 l/h after a single dose and about 9 l/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once daily dosing. Esomeprazole is completely eliminated from plasma with no tendency for accumulation during once-daily administration. Approximately 80% of an oral dose of esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces. Less than 1% of parent drug is excreted in the urine.

## 6. Nonclinical Properties

### 6.1 Animal Toxicology

**Carcinogenicity:** The carcinogenic potential of esomeprazole magnesium was assessed using studies of omeprazole, of which esomeprazole is an enantiomer. In two 24-month oral carcinogenicity studies in rats, omeprazole at daily doses of 1.7 mg/kg/day, 3.4 mg/kg/day, 13.8 mg/kg/day, 44 mg/kg/day, and 140.8 mg/kg/day (about 0.4 to 34 times the human dose of 40 mg/day expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole.

In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 3.4 times the human dose of 40 mg/day on a body surface area basis) for 1 year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of 1 year (94% treated vs. 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs. 26%) but still showed more hyperplasia in the treated group.

**Mutagenesis:** Esomeprazole was negative in the Ames mutation test, in the *in vivo* rat bone marrow cell chromosome aberration test, and the *in vivo* mouse micronucleus test. Esomeprazole, however, was positive in the *in vitro* human lymphocyte chromosome aberration test.

**Impairment of Fertility:** The potential effects of esomeprazole on fertility and reproductive performance were assessed using omeprazole studies. Omeprazole at oral doses up to 138 mg/kg/day in rats (about 34 times the human dose of 40 mg/day on a body surface area basis) was found to have no effect on reproductive performance of parental animals.

**Reproduction Studies:** Reproduction studies have been performed in rats at oral doses up to 280 mg/kg/day (about 68 times an oral human dose of 40 mg on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 42 times an oral human dose of 40 mg on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to esomeprazole.

## 7. Description

S-PPi Tablets are Orange colour, capsules shaped, enteric coated tablet & plain on both side.

Each tablet of S-PPi contains 40 mg of esomeprazole (in a gastro-resistant form) for oral administration.

Esomeprazole magnesium is the magnesium salt of esomeprazole, the S-isomer of omeprazole, with gastric proton pump inhibitor activity.

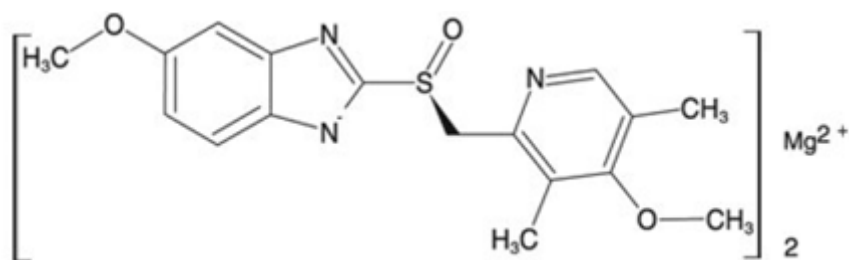
Esomeprazole magnesium salt is off-white to pale cream colored powder. It is slightly soluble in water.

Molecular Weight: 713.12 g/mol.

Molecular Formula: C<sub>34</sub>H<sub>36</sub>MgN<sub>6</sub>O<sub>6</sub>S<sub>2</sub>.

Chemical Name: 5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]benzimidazole, magnesium salt (2:1).

Structural Formula:



Inactive ingredients (excipients) of S-PPi Tablets contain Light Magnesium Carbonate, Cross Povidone XL-10, Croscarmellose Sodium, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Dummy Granules, Talcum, Magnesium Stearate, Instacoat Sol, Isopropyl Alcohol, Methylene Chloride & Instacoat EN Super IV Orange.

## 8. Pharmaceutical Particulars

### 8.1 Incompatibilities

None known.

### 8.2 Shelf-life

24 Months

### 8.3 Packaging Information

15 tablets per strip.

### 8.4 Storage and Handling Instructions

Store protected from light and moisture.

Keep out of reach of children.

## 9. Patient Counseling Information

### Instructions to Patients

- Take S-PPi Tablets exactly as prescribed by your doctor, at the lowest dose possible and for the shortest time needed. Do not change the dose or stop therapy without consulting your doctor.
- Swallow S-PPi Tablets whole with water, on empty stomach, preferably in the morning or at least 1 hour prior to meal. Do not split, chew, or crush tablets.
- If you miss a dose of S-PPi Tablets, take it as soon as possible. If it is almost time for your next dose, do not take the missed dose. Take the next dose at your regular time. Do not take 2 doses/tablets at the same time to make up for the missed dose.
- Instruct patients not to take this medicine during pregnancy and lactation unless advised by their healthcare professionals.

- Esomeprazole can be used in children above 1 year of age, however, S-PPi Tablets are not recommended for use in children because there is no dosage feasibility with this formulation (children can use other pediatric dosage formulations of esomeprazole).
- Instruct patients not to share this medication with other people even though symptoms are similar. It may harm them.
- Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. S-PPi Tablets and certain other medicines can interact with each other causing serious side effects.

## **10. Details of Manufacturer**

Pure & Cure Healthcare Pvt. Ltd.

(A subsidiary of Akums Drugs & Pharmaceuticals Ltd.)

Plot No. 26A, 27-30, Sector-8A, I.I.E., SIDCUL, Ranipur,  
Haridwar – 249 403, Uttarakhand.

## **11. Details of Permission or License Number with Date**

Mfg. Lic. No. : 31/UA/2013, Date of Product Permission: 03/06/2020

## **12. Date of Revision**

February 2023.

Marketed by:



Division of

**BLUE CROSS LABORATORIES PVT LTD.**

A-12, M.I.D.C., NASHIK-422 010.

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