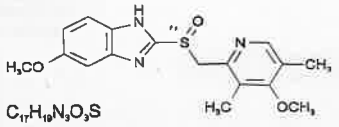
PRESCRIBING INFORMATION

1. PRODUCT DESCRIPTION

Omeprazole, the active ingredient in MEPRASIL® capsule, is a substituted benzimidazole. Omeprazole is a member of the Proton Pump Inhibitors (PPIs); a group of molecules which inhibit the final phase of gastric acid secretion. With a molecular weight of 345.42, its structure and molecular formula are shown below:



$C_{17}H_{19}N_3O_3S$

Omeprazole is a white to off-white crystalline powder that melts with decomposition at about 155 degrees Celsius. It is a weak base, freely soluble in ethanol and methanol, 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 acidic medium, but has acceptable stability under alkaline conditions.

MEPRASIL® is supplied as capsules for oral administration. Each capsule contains 20mg of omeprazole in the form of enteric-coated granules.

2. CLINICAL PHARMACOLOGY

2.1 Mechanism of Action

Omeprazole, the active ingredient in MEPRASIL® capsule, belongs to a class of antisecretory compounds, the substituted benzimidazoles, that suppress gastric acid secretion by specific inhibition of H^+/K^+ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme 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. 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.

2.2. Pharmacodynamics

Antisecretory Activity

After oral administration, the onset of antisecretory effect of omeprazole occurs within one hour, with the maximum effect occurring within two hours. Inhibition of secretion is about 50% of maximum at 24 hours and the duration of inhibition lasts up to 72hours. The antisecretory effect lasts far longer than would be expected from the very short (< 1 hr) half life, apparently due to the prolonged binding to the parietal H^+/K^+ATPase enzyme.

When the drug is discontinued, secretory activity returns gradually, over 3 to 5 days. The inhibitory effect of omeprazole on acid secretion increases with repeated once-daily dosing, reaching a plateau after four days. Single daily doses of omeprazole ranging from 10mg to 40mg have produced 100% inhibition of 24-hour acidity in some patients.

Other Effects

Systemic effects of omeprazole in the CNS, cardiovascular and respiratory systems have not been found to date. Omeprazole, given in oral doses of 30mg or 40mg for 2 to 4 weeks, had no effect on thyroid function, carbohydrate metabolism or circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin or secretin.

No effect on gastric emptying of the solid and liquid components of a test meal was demonstrated after a single dose of omeprazole 90 mg. As do other agents that elevate intragastric pH, omeprazole administered for 14 days in healthy subjects produced a significant increase in the intragastric concentration of viable bacteria. The pattern of the bacteria species was unchanged from that commonly found in saliva. All changes resolved within three days of stopping treatment.

2.3. Pharmacokinetics

Absorption

MEPRASIL® capsules contain an enteric–coated granule formulation of

omeprazole so that absorption of omeprazole begins only after the granules leave the stomach. Absorption is rapid, with peak plasma levels of omeprazole occurring within 0.5 to 3.5 hours. Peak plasma concentrations of omeprazole and AUC are approximately proportional to doses up to 40mg, but because of a saturated first-pass effect, a greater than linear response in peak plasma concentration and AUC occur with doses greater than 40mg. Absolute bioavailability (compared with intravenous administration) is about 30-40% at doses of 20-40mg, due in large part to presystemic metabolism. In healthy subjects, the plasma half-life is 0.5-1 hour, and the total body clearance is 500-600mL/min.

Distribution

Protein binding is approximately 95%

Metabolism

Omeprazole is extensively metabolized by the cytochrome P450 (CYP) enzyme system.

Excretion

Following single dose oral administration of a buffered solution of omeprazole, little if any, unchanged drug was excreted in urine. The majority of the dose (about 77%) was eliminated in urine as at least six metabolites. Two were identified as hydroxyomeprazole and the corresponding carboxylic acid. The remainder of the dose was recoverable in faeces. This implies a significant biliary excretion of the metabolites of omeprazole. Three metabolites have been identified in plasma- the sulfide and sulfone derivatives of omeprazole, and hydroxyomeprazole. These metabolites have very little or no antisecretory activity.

4. Special Population

Geriatrics

The elimination rate of omeprazole was somewhat decreased in the elderly, and bioavailability was increased. Omeprazole was 76% bioavailable when a single 40mg oral dose (buffered solution) was administered to healthy elderly volunteers, versus 58% in young volunteers given the same dose. Nearly 70% of the dose was recovered in urine as metabolites of omeprazole and no unchanged drug was detected. The plasma clearance of omeprazole was 250mL/min (about half that of young volunteers)

Hepatic Impairment

In patients with chronic hepatic disease, the bioavailability increased to approximately 100% compared with an IV dose, reflecting decreased first-pass effect, and the plasma half-life of the drug increased to nearly 3 hours compared with the half-life in normal subjects of 0.5-1 hour. Plasma clearance averaged 70mL/min, compared with 500-600mL/min in normal subjects. Dose reduction, particularly when maintenance of healing of erosive esophagitis is indicated, for the hepatically impaired should be considered.

Renal Impairment

In patients with chronic renal impairment, whose creatinine clearance ranged between 10 and 62 mL/min, the disposition of omeprazole was very similar to that in healthy volunteers, although there was a slight increase in bioavailability. Because urinary excretion is a primary route of excretion of omeprazole metabolites, their elimination slowed in proportion to the decreased creatinine clearance. No dose reduction is necessary in patients with renal impairment.

3. INDICATIONS AND USAGE

3.1 Duodenal Ulcers

MEPRASIL® is indicated for short-term treatment of active duodenal ulcer in adults. Most patients heal within four weeks. Some patients may require additional four weeks of therapy.

In combination with appropriate antibacterial agents, MEPRASIL® is indicated for treatment of patients with *H. pylori* infection and duodenal ulcer (active or up to 1-year history) to eradicate *H. pylori* in adults.

3.2. Gastric Ulcers

MEPRASIL® is indicated for short-term treatment (4-8 weeks) of active benign gastric ulcer in adults.

3.3. Gastroesophageal Reflux Disease (GERD) -Symptomatic GERD

MEPRASIL® is indicated for the treatment of heartburn and other symptoms associated with GERD - Erosive Esophagitis.

The efficacy of MEPRASIL® use for longer than 8 weeks in these patients has not been established. If a patient does not respond to 8 weeks of treatment, an additional 4 weeks of treatment may be given. If there is recurrence of erosive esophagitis or GERD.

Symptoms (eg. Heartburn), an additional 4-8 weeks course of MEPRASIL® may be considered.

3.4. Maintenance of Healing of Erosive Esophagitis.
MEPRASIL® is indicated for the maintenance of healing of erosive esophagitis.

3.5. Pathologic Hyperscretory Conditions
MEPRASIL® is indicated for the long-term treatment of pathologic hypersecretory conditions (eg, Zollinger-Ellison syndrome, multiple endocrine adenomas and systemic mastocystitis) in adults

4. DOSAGE AND ADMINISTRATION

4.1. Active Duodenal Ulcer
For short-term treatment of active duodenal ulcer, the recommended adult oral dose of MEPRASIL® is 20mg once daily. Most patients heal within four weeks. Some patients may require additional four weeks of therapy.

4.2. Gastric Ulcer
The recommended adult dose is 40mg once daily for 4-8 weeks.

4.3. GERD
The recommended oral dose for the treatment of patients with symptomatic GERD and no esophageal lesions is 20mg daily for up to 4 weeks. The recommended adult oral dose for the treatment of patients with erosive esophagitis and accompanying symptoms due to GERD is 20mg daily for 4 to 8 weeks.

4.4. Maintenance of Healing of Erosive Esophagitis
The recommended adult oral dose is 20mg daily.

4.5. *H.pylori* **Eradication for the Reduction of the Risk of Duodenal Ulcer Recurrence**

1. Triple Therapy: The recommended adult oral regimen is MEPRASIL 20mg plus clarithromycin 500mg plus amoxicillin 1000mg each given twice daily for 10 days. In patients with an ulcer present at the time of initiation of therapy, an additional 18 days of MEPRASIL® 20mg once daily is recommended for ulcer healing and symptom relief.

2. Dual Therapy: The recommended adult oral regimen is MEPRASIL® 20mg plus clarithromycin 500mg three times daily for 14 days. In patients with an ulcer at the time of initiation of therapy, an additional 14 days of MEPRASIL® 20mg once daily is recommended for ulcer healing and symptom relief.

Pathological Hypersecretory Conditions
The dosage of MEPRASIL® in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60mg once daily. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to 120mg three times daily have been administered. Daily dosage of greater than 80mg should be administered in divided doses.

Pediatric Patients
For the treatment of GERD and maintenance of healing of erosive esophagitis, the recommended daily dose for pediatric patients 1 to 16 years of age is as follows:

Patient Weight	Daily Dose
5<10kg	5mg
10<20kg	10mg
More than /equal to 20kg	20mg

On a per kg basis, the doses of omeprazole required to heal erosive esophagitis in pediatric patients are greater than those for adults

5. DRUG INTERACTIONS

5.1. Use with Clopidogrel
Co-administration of clopidogrel with 80mg or more of omeprazole reduces the pharmacological activity of clopidogrel if given concomitantly.

6. CONTRAINDICATIONS
MEPRASIL® is contraindicated in patients with known hypersensitivity to substituted benzimidazoles or to any component of the formulation. Hypersensitivity reactions may include anaphylactic shock, anaphylaxis, angioedema, bronchospasm, interstitial nephritis, and urticaria.

7. PRESENTATION AND STORAGE
i. 2 x 10 capsules
ii. 20 x 10 capsules

MEPRASIL® capsules should be stored below 30°C in a dry place
Protect from light.
Keep all medicines out of reach of children.

Manufactured by:
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