

## MEPRAL

Capsules

### Composition

Each capsule contains Omeprazole 20 mg In enteric coated granule form.

### Action

Omeprazole reduces gastric acid secretion through a highly targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. It is rapid acting and provides control through reversible inhibition of gastric acid secretion with once daily dosing.

### Site and mechanism of action

Omeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the intracellular canaliculi within the parietal cell, where it inhibits the enzyme H<sup>+</sup>,K<sup>+</sup>-ATPase, the acid pump. This effect on the final step of the gastric acid formation process is dose-dependent and provides for highly effective inhibition of both basal acid secretion and stimulated acid secretion, irrespective of the stimulus.

All pharmacodynamic effects observed can be explained by the effect of omeprazole on acid secretion.

### Effect on gastric acid secretion

Mepal once daily provides rapid and effective inhibition of daytime and nighttime gastric acid secretion with maximum effect achieved within 4 days of treatment. With Omeprazole 20 mg, a mean decrease of at least 80% in 24-hour intragastric acidity is then maintained in duodenal ulcer patients, with the mean decrease in peak acid output after pentagastrin stimulation being about 70% twenty-four hours after dosing.

Mepal 20 mg maintains an intragastric pH of  $\geq 3$  for a mean time of 17 hours of the 24-hour period in duodenal ulcer patients. Because of reduced acid secretion and intragastric acidity, omeprazole dose-dependently reduces/normalizes acid exposure of the oesophagus in patients with gastro-esophageal reflux disease.

The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) of omeprazole and not to the actual plasma concentration at a given time. No tachyphylaxis has been observed during treatment with omeprazole.

### Effect on *Helicobacter pylori*

*Helicobacter pylori* is associated with acid peptic disease, including duodenal and gastric ulcer disease, in which about 95% and 70% of patients respectively are infected with this bacterium. *H. pylori* is a major factor in the development of gastritis. *H. pylori* together with gastric acid are major factors in the development of peptic ulcer disease. *H. pylori* has been found to play a causal role in the development of gastric carcinoma.

Omeprazole has a bactericidal effect on *H. pylori in vitro*.

Eradication of *H. pylori* with omeprazole and antimicrobials is associated with rapid symptom relief, high rates of healing of any mucosal lesions, and long-term remission of peptic ulcer disease thus reducing complications such as gastrointestinal bleeding as well as the need for prolonged anti-secretory treatment.

### Pharmacokinetics

#### *Absorption and distribution*

Omeprazole and omeprazole magnesium are acid labile and is therefore administered orally as enteric-coated pellets

Absorption of omeprazole takes place in the small intestine and is usually completed within 3-6 hours. The systemic bioavailability of Omeprazole from a single oral dose is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. The apparent volume of distribution in healthy subjects is approximately 0.3 L/kg and a similar value seen in patients with

renal insufficiency. In elderly patients, and in patients with hepatic insufficiency, the volume of distribution is slightly decreased. Concomitant intake of food has no influence on the bioavailability. The plasma protein binding of omeprazole is about 95%.

#### *Metabolism and excretion*

After oral administration, the plasma elimination half-life of omeprazole is usually shorter than one hour and there is no change in half-life during long-term treatment.

Omeprazole is completely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphically expressed, specific isoform CYP2C19 (S-mephenytoin hydroxylase), responsible for the formation of hydroxyomeprazole, the major metabolite in plasma. In accordance with this, because of competitive inhibition, there is a potential for metabolic drug-drug interactions between omeprazole and other substrates for CYP2C19.

No metabolite has been found to have any effect on gastric acid secretion. Almost 80% of an orally given dose is excreted as metabolites in the urine, and the remainder is found in the faeces, primarily originating from bile secretion.

The systemic bioavailability and elimination of omeprazole is unchanged in patients with reduced renal function. The area under the plasma concentration-time curve and the elimination half-life are increased in patients with impaired liver function, but omeprazole has not shown any tendency to accumulate with once daily dosing.

### **Indications**

Mepral indicated for the treatment of:

- Acute duodenal and gastric ulcer (up to 8 weeks)
- Reflux esophagitis (up to 8 weeks)
- Zollinger-Ellison syndrome.
- Ulcer caused by *Helicobacter Pylori*.

### **Contraindications**

Known hypersensitivity to omeprazole.

### **Warnings**

#### **Pregnancy and Breastfeeding**

Animal studies have not shown evidence of any hazard from the administration of omeprazole during pregnancy and breastfeeding, and there is no evidence of fetal toxicity or teratogenic effect. Mepral can be used during pregnancy. Omeprazole is excreted in breast milk but is not likely to influence the child when therapeutic doses are used.

#### **Use in Paediatrics**

Appropriate studies with omeprazole have not been performed in children.

#### **Liver Disease**

Dosage reduction may be required due to the increased half-life in chronic hepatic disease.

### **Adverse Reactions**

Omeprazole is well tolerated. The following reactions have been reported, but in the majority of cases a consistent relationship between them and treatment with omeprazole has not been established.

#### **Dermatological**

Rash, urticaria and/or pruritus have been reported on rare occasions.

#### **Musculoskeletal**

Arthralgia, muscular weakness and myalgia have been reported in isolated cases.

**Central Nervous System,**

Headache, Dizziness, paresthesia, somnolence, insomnia and vertigo have been reported rarely. Reversible mental confusion, agitation, depression and hallucinations have been reported in isolated cases, predominantly in severely ill patients.

**Gastrointestinal**

Diarrhea, constipation, abdominal pain, nausea/ vomiting and flatulence. Stomatitis and gastrointestinal candidiasis have been reported in isolated cases.

**Hepatic**

Increased liver enzymes, with or without increased bilirubin values, have been reported in isolated cases.

**Endocrine**

Gynecomastia has been reported in isolated cases.

**Hematological**

Leukopenia and thrombocytopenia have been reported in isolated cases.

**Other**

Malaise has been reported on rarely. Peripheral edema, tachycardia, bradycardia, palpitation, chest pain, blurred vision, taste perversion and weight gain have been reported in isolated cases.

**Drug Interactions***Omeprazole/ Diazepam/ Phenytoin*

Omeprazole can prolong the elimination of drugs that metabolize by oxidation in the liver, e.g. diazepam and phenytoin. It is recommended to monitor patients receiving phenytoin concomitantly with omeprazole. A reduction of the phenytoin dose may be necessary.

*Omeprazole/ Theophylline/ Warfarin*

No interaction with theophylline has been found, but there may be interactions with other drugs also metabolized via the cytochrome P-450 enzyme system, such as warfarin.

*Omeprazole/ Antacids*

No interaction with concomitantly administered antacids has been found.

*Omeprazole/ Drugs whose Absorption is pH-Dependent*

By increasing gastric pH, omeprazole has the potential to affect the bioavailability of any medication whose absorption is pH-dependent (e.g. Ketoconazole, Ampicillin esters and iron salts).

**Dosage and Administration**

Mepal should be taken before meals, preferably before breakfast. No dosage adjustment is required when administered to elderly patients. No geriatric-specific information is available. However, a somewhat decreased rate of elimination and an increased bioavailability are more likely to occur in geriatric patients taking omeprazole. No dose adjustment is required in patients, with impaired renal or liver function.

**Duodenal Ulcer**

The recommended dosage is 20 mg once daily. Symptom relief is rapid and in most patients, healing occurs within 2 weeks. For those patients who may not have fully healed after the initial course, healing usually occurs during a further 2-week treatment period. In patients with poorly responsive duodenal ulcer, a dosage of 40 mg Mepal once daily has been used with healing usually achieved within 4 weeks.

**Gastric Ulcer**

The recommended dosage is 20 mg once daily. Symptom relief is rapid and in most patients, healing occurs within 4 weeks. For those patients who may not have fully healed after the initial course, healing usually occurs during a further 4-week treatment period. In patients with poorly responsive gastric ulcer, a dosage of 40 mg Mepral once daily has been used with healing usually achieved within 8 weeks.

#### **Reflux Esophagitis**

In patients with erosive reflux esophagitis, the recommended dosage is 20 mg Mepral once daily, given for 4 weeks.

For maintenance of healing of erosive esophagitis, the recommended dose is 20 mg Mepral once daily. Controlled studies do not extend beyond 12 months.

#### **Zollinger-Ellison Syndrome**

The recommended initial dosage is 60 mg, once daily. Dosage should be adjusted individually, and treatment continued as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. With doses above 80 mg daily, the dose should be divided and given twice daily.

#### **Ulcer caused by Helicobacter pylori**

The recommended adult oral dose is Amoxitid (amoxicillin) 2 grams daily in divided doses and Mepral once daily for 2 weeks. The treatment is to be continued for another 2 weeks with Mepral 20 mg once daily.

#### **Over Dosage**

There is no information available on the effects of oral over dosage in humans and specific recommendations for treatment cannot be given. Single oral doses of up to 160 mg have been well tolerated. Treatment should be symptomatic and supportive.

No specific antidote is known. Omeprazole is extensively protein-bound, and is therefore not readily dialyzable.

#### **Pharmaceutical Precautions**

The patient should be instructed to close the container firmly after each use, not to bite or open the capsule.

#### **Presentation**

##### **Mepral 20 Capsules**

Box 14 capsules.