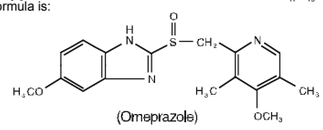
Risek®

(Omeprazole) Capsules 20mg, 40mg رائیزیک

DESCRIPTION
RISEK (Omeprazole) a substituted benzimidazole, is a proton pump inhibitor that inhibits gastric acid secretion.
Chemically omeprazole is 5-methoxy-2-[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1Hbenzimidazole. The molecular formula is $C_{17}H_{19}N_3O_3S$ and the structural formula is:



(Omeprazole)

QUALITATIVE & QUANTITATIVE COMPOSITION
RISEK (Omeprazole) is available for oral administration as:

1. RISEK Capsules 20mg
   Each capsule contains:
   Enteric-coated pellets of omeprazole equivalent to omeprazole Ph.Eur ... 20mg

2. RISEK Capsules 40mg
   Each capsule contains:
   Enteric-coated pellets of omeprazole equivalent to omeprazole Ph.Eur ... 40mg

CLINICAL PHARMACOLOGY
Mechanism of Action
Omeprazole reduces gastric acid secretion through a unique mechanism of action. Omeprazole belongs to a new class of anti-secretory compounds, the substituted benzimidazoles that do not exhibit anti-cholinergic or histamine antagonistic properties. It inhibits secretion of gastric acid by irreversibly blocking the enzyme system of hydrogen/potassium adenosine triphosphatase (H^+/K^+ ATPase), the proton pump of the gastric parietal cell. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus.

Pharmacokinetics
Absorption/Distribution
Omeprazole is acid-labile and is administered orally as enteric-coated pellets in capsules.
Omeprazole is rapidly but variably absorbed following oral administration, with peak plasma levels of omeprazole occurring within 0.5 to 3.5 hours. Absorption of omeprazole is not affected by food and also appears to be dose dependent. Increasing the dosage above 40mg has been reported to increase the plasma concentrations in a non-linear fashion because of saturable first pass metabolism. Absorption is higher after long- term administration. The apparent volume of distribution in healthy subjects is approximately 0.3 l/kg body weight. The systemic bioavailability of omeprazole is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. The plasma protein binding is approximately 95%.

Metabolism & Excretion
Following absorption, omeprazole is almost completely metabolized in the liver, primarily by the cytochrome P450 isoenzyme CYP2C19 to form hydroxy-omeprazole and to a small extent by CYP3A4 to form omeprazole sulfone. These metabolites are inactive and excreted mostly in the urine and to a lesser extent in the bile. The majority of the dose (about 77%) is eliminated in the urine and the remainder, recoverable in the feces. The elimination half-life from plasma is reported to be about 0.5 to 3 hours.

Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites.

Special Population
Pediatric
Available data from children (1 year and older) suggest that the pharmacokinetics within the recommended doses are similar to those reported in adults. At steady state, lower plasma levels of omeprazole were seen in some children. In children younger than 6 months, clearance of omeprazole is low due to low capacity to metabolize omeprazole.

Geriatric
The bioavailability of omeprazole may be increased in elderly patients. The metabolism rate of omeprazole is somewhat reduced in patients in between ages 75 to 79 years.

Renal Insufficiency
The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function. Therefore, dose adjustment is not required.

Hepatic Insufficiency
The area under the plasma concentration-time curve is increased in patients with impaired liver function, but no tendency to accumulation of omeprazole has been found.

THERAPEUTIC INDICATIONS
RISEK (Omeprazole) is indicated in adults for the treatment of:

1. Gastro-Esophageal Reflux Disease (GERD):
   - Treatment of erosive reflux esophagitis.
   - Long term management of patients with healed esophagitis to prevent relapse.
   - Symptomatic treatment of gastroesophageal reflux disease (GERD).
2. Gastric and duodenal ulcer.
3. Treatment and prophylaxis of NSAID-associated ulceration.
4. Eradication of *Helicobacter pylori* infection associated with peptic ulcer disease.
5. Zollinger-Ellison syndrome.
6. Dyspepsia.
7. Prophylaxis of acid aspiration.

Children over 1 year of age and ≥ 10 kg
Treatment of reflux oesophagitis.
Symptomatic treatment of heartburn and acid regurgitation in gastro-oesophageal reflux disease.

Children and adolescents over 4 years of age
In combination with antibiotics in treatment of duodenal ulcer caused by *Helicobacter pylori.*

DOSAGE & ADMINISTRATION
RISEK (Omeprazole) capsule is given by mouth, which should be swallowed whole and not crushed or chewed.

Symptomatic gastro-esophageal reflux disease (GERD) without esophagitis:
The recommended adult oral dose is 20mg daily for up to 4 weeks.

Erosive esophagitis:
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.

Maintenance of healing of erosive esophagitis:
The recommended adult oral dose is 20 mg daily.

Dosage for children in GERD:
In children, doses in the ranges 0.7 to 1.4mg per kg body weight daily, up to a maximum daily dose of 40mg have been given for 4 to 12 weeks.

Children over 1 year of age and ≥ 10 kg

Treatment of reflux oesophagitis
Symptomatic treatment of heartburn and acid regurgitation in gastro-oesophageal reflux disease

Age	Weight	Dosage
≥ 1 year of age	10-20 kg	10mg once daily or 20mg once daily if required.
≥ 2 years of age	> 20 kg	20mg once daily or 40mg once daily if required.

Reflux oesophagitis: The treatment time is 4-8 weeks.

Symptomatic treatment of heartburn and acid regurgitation in gastro-oesophageal reflux disease: The treatment time is 2–4 weeks. If symptom control has not been achieved after 2–4 weeks the patient should be investigated further.

Children and adolescents over 4 years of age

Treatment of duodenal ulcer caused by Helicobacter pylori

Weight	Dosage
15-30 kg	Combination with two antibiotics: Omeprazole 10mg, amoxicillin 25mg/kg body weight and clarithromycin 7.5mg/kg body weight are all administrated together two times daily for one week.
31-40 kg	Combination with two antibiotics:Omerprazole 20mg, amoxicillin 750 mg and clarithromycin 7.5 mg/kg body weight are all administrated two times daily for one week.
> 40 kg	Combination with two antibiotics: Omeprazole 20mg, amoxicillin 1g and clarithromycin 500mg are all administrated two times daily for one week.

Gastric and duodenal ulcer:
A single daily dose of 20mg by mouth or 40mg in severe cases is given. Treatment is continued for 4 weeks for duodenal ulcer and 8 weeks for gastric ulcer. Where appropriate, a dose of 10mg to 20mg once daily may be given for maintenance.

Prevention of relapse of duodenal ulcers:
For the prevention of relapse of duodenal ulcer in *Helicobacter pylori* negative patients or when *Helicobacter pylori* eradication is not possible the recommended dose is 20mg once daily. In some patients a daily dose of 10mg may be sufficient. In case of therapy failure, the dose can be increased to 40mg.

Prevention of relapse of gastric ulcers:
For the prevention of relapse in patients with poorly responsive gastric ulcer the recommended dose is 20mg once daily. If needed the dose can be increased to 40mg once daily.

NSAID-associated ulceration:
Doses of 20mg daily are used in the treatment of NSAID-associated ulceration. A

dose of 20mg daily may also be used for prophylaxis in patients with a previous history of gastroduodenal lesions who require continued NSAID treatment.

Helicobacter pylori eradication:
For the eradication of *Helicobacter pylori* in peptic ulceration omeprazole 40mg daily may be combined with antibacterials in dual therapy or omeprazole 20mg twice daily may be combined with antibacterials in triple therapy. omeprazole alone may be continued for a further 2 to 8 weeks.

Zollinger-Ellison syndrome:
The initial recommended dosage is 60mg by mouth once daily, adjusted as required. The majority of patients are effectively controlled by doses in the range 20mg to 120mg daily, but doses up to 120mg threetimes daily have been used. Daily doses above 80mg should be administered in divided doses.

Dyspepsia:
For the relief of acid-related dyspepsia omeprazole is given in usual doses of 10mg or 20mg daily by mouth for 2 to 4 weeks.

Prophylaxis of acid aspiration:
Omeprazole is also used for the prophylaxis of acid aspiration during general anesthesia, in a dose of 40mg the evening before surgery and a further 40mg two to six hours before the procedure.

Dosage for Hepatic Impaired Patients:
A maximum daily dose of 20mg is recommended for patients with impaired hepatic function.

ADVERSE EFFECTS
Omeprazole is well tolerated and the adverse reactions have generally been mild and reversible.

Common
Central and peripheral nervous system: Headache.
Gastrointestinal: Diarrhea, constipation, abdominal pain, nausea/vomiting and flatulence.

Uncommon
Central and peripheral nervous system: Dizziness, paraesthesia, somnolence, insomnia and vertigo.
Hepatic: Increased liver enzymes
Skin: Rash and/or pruritis, urticaria
Other: Malaise

Rare
Central and peripheral nervous system: Reversible mental confusion, agitation, aggression, depression and hallucinations, predominantly in severely ill patients.
Endocrine: Gynecomastia
Gastrointestinal: Dry mouth, stomatitis and gastrointestinal candidiasis.
Hematological: Leukopenia, thrombocytopenia, agranulocytosis and pancytopenia.

Gastro-duodenal carcinoids have been reported in patients with Zollinger-Ellison syndrome on long-term treatment with omeprazole.

CONTRAINDICATIONS
Omeprazole is contraindicated in patients with known hypersensitivity to any component of the formulation or to substituted benzimidazoles. Omeprazole must not be used concomitantly with nelfinavir.

PRECAUTIONS
General:
- When gastric ulcer is suspected, the possibility of malignancy should be excluded as treatment may alleviate symptoms and delay diagnosis.
- Prior to initiation of dual or triple therapy, the physician should consider the patient with known hypersensitivity reactions to penicillin, macrolides and other antibiotics.
- Omeprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B_{12} (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B_{12} absorption on long-term therapy.
- Severe hypomagnesemia has been reported in patients treated with proton pump inhibitors (PPIs) like omeprazole for at least three months, and in most cases for a year.
- Proton pump inhibitors, especially if used in high doses and over long durations of greater than one year, may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognized risk factors.

Hepatic impairment:
Consideration should be given to reducing the dose of omeprazole in patients with impaired hepatic function as bioavailability and half-life can increase.

Pregnancy:
There are no adequate or well-controlled studies in pregnant women. Omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers:
It is not known whether omeprazole is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from omeprazole, a decision should be made whether, to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Drug Interactions
- In common with the use of other inhibitors of acid secretion or antacids, the absorption of ketoconazole and itraconazole can decrease during treatment with omeprazole due to decreased intragastric acidity during treatment with omeprazole.

- Omeprazole is metabolized by CYP2C19. Thus, when omeprazole is combined with drugs metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these drugs may be increased and a dose reduction could be needed.

Atazanavir
The plasma levels of atazanavir are decreased in case of co-administration with omeprazole therefore concomitant administration of omeprazole with atazanavir is not recommended.

Digoxin
Concomitant treatment with omeprazole (20mg daily) and digoxin increased the bioavailability of digoxin by 10%. Caution should be exercised when omeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should be then be reinforced.

Clopidogrel
Omeprazole is a CYP2C19 inhibitor. When starting or ending treatment with omeprazole, the potential for interactions with drugs metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and omeprazole. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged.

Other active substances
The absorption of posaconazole, erlotinib, ketoconazole and itraconazole is significantly reduced and thus clinical efficacy may be impaired. For posaconazole and erlotinib concomitant use should be avoided.

Saquinavir
Concomitant administration of omeprazole with saquinavir resulted in increased plasma levels up to approximately 70% for saquinavir associated with good tolerability in HIV-infected patients.

Tacrolimus
Concomitant administration of omeprazole has been reported to increase the serum levels of tacrolimus. A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dosage of tacrolimus adjusted if needed.

Methotrexate
When given together with proton-pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Inhibitors CYP2C19 and/or CYP3A4
Active substances known to inhibit CYP2C19 or CYP3A4 (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing omeprazole rate of metabolism. Concomitant voriconazole treatment resulted in more than doubling of the omeprazole exposure. As high doses of omeprazole have been well-tolerated adjustment of the omeprazole dose is not generally required. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Inducers of CYP2C19 and/or CYP3A4
Active substances known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing omeprazoles rate of metabolism.

OVERDOSAGE
Symptoms:
Nausea, vomiting, dizziness, abdominal pain, diarrhea and headache have been reported. Also apathy, depression and confusion have been described in single cases. The symptoms described have been transient and no serious outcome has been reported.

Treatment:
No specific antidote for omeprazole overdosage is known. Omeprazole is extensively protein bound and is, therefore, not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive.

STORAGE
Store below 30°C. Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
RISEK (Omeprazole) 20mg capsules are available in blister pack of 14's.
RISEK (Omeprazole) 40mg capsules are available in blister pack of 14's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:

Getz pharma (PVT) LIMITED
www.getzpharma.com
29-30/27, K.I.A., Karachi, Pakistan

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