
# Downoprazol

Hard gelatin capsules &
Packets powder for oral suspension

- 1 INDICATIONS AND USAGE

**1.1 Duodenal Ulcer**

DOWNOPRAZOL (omeprazole/sodium bicarbonate) is indicated for short-term treatment of active duodenal ulcer. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy.

**1.2 Gastric Ulcer**

DOWNOPRAZOL is indicated for short-term treatment (4-8 weeks) of active benign gastric ulcer.

**1.3 Treatment of Gastroesophageal Reflux Disease (GERD)**

*Symptomatic GERD*

DOWNOPRAZOL is indicated for the treatment of heartburn and other symptoms associated with GERD for up to 4 weeks.

*Erosive Esophagitis*

DOWNOPRAZOL is indicated for the short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy.

The efficacy of DOWNOPRAZOL used for longer than 8 weeks in these patients has not been established. If a patient does not respond to 8 weeks of treatment, it may be helpful to give up to an additional 4 weeks of treatment. If there is recurrence of erosive esophagitis or GERD symptoms (e.g., heartburn), additional 4-8 week courses of DOWNOPRAZOL may be considered.

**1.4 Maintenance of Healing of Erosive Esophagitis**

DOWNOPRAZOL is indicated to maintain healing of erosive esophagitis. Controlled studies do not extend beyond 12 months.

## 2 DOSAGE AND ADMINISTRATION

DOWNOPRAZOL (omeprazole/sodium bicarbonate) is available as a capsule and as a powder for oral suspension in 20 mg &40 mgstrength of omeprazole for adult use. Directions for use for each indication are summarized in Table 1. All recommended doses throughout the labeling are based upon omeprazole.

Since both the 20 mg and 40 mg **oral suspension** packets contain the same amount of sodium bicarbonate (1,680mg), two packets of 20 mg are **not** equivalent to one packet of DOWNOPRAZOL 40 mg; therefore, two 20 mg packets of Downoprazol should not be substituted for one packet of DOWNOPRAZOL 40 mg.

Since both the 20 mg and 40 mg **capsules** contain the same amount of sodium bicarbonate (1100 mg), two capsules of 20 mg are **not** equivalent to one capsule of DOWNOPRAZOL 40 mg; therefore, two 20 mg capsules of DOWNOPRAZOL should not be substituted for one capsule of DOWNOPRAZOL 40 mg.
DOWNOPRAZOL should be taken on an empty stomach at least one hour before a meal.

For patients receiving continuous Nasogastric (NG)/Orogastric (OG) tube feeding, enteral feeding should be suspended approximately 3 hours before and 1 hour after administration of DOWNOPRAZOL Powder for Oral Suspension.

Table 1: Recommended Doses of DOWNOPRAZOL by Indication for Adults 18 Years and Older

| Indication | Recommended Dose | Frequency |
|---|---|---|
| Short-Term Treatment of Active Duodenal Ulcer | 20 mg | Once daily for 4 weeks*,† |
| Benign Gastric Ulcer | 40 mg | Once daily for 4-8 weeks‡,† |
| Gastroesophageal Reflux Disease (GERD) | | |
| Symptomatic GERD (with no esophageal erosions) | 20 mg | Once daily for up to 4 weeks† |
| Erosive Esophagitis | 20 mg | Once daily for 4-8 weeks† |
| Maintenance of Healing of Erosive Esophagitis | 20 mg | Once daily‡ |
| Reduction of Risk of Upper Gastrointestinal Bleeding in Critically Ill Patients (40 mg oral suspension only) | 40 mg | 40 mg initially followed by40 mg 6-8 hours later and40 mg daily thereafter for14 days‡ |

* Most patients heal within 4 weeks. Some patients may require an additional 4 weeks of therapy.
† For additional information, *[See Indications and Usage (1)]*
‡ Controlled studies do not extend beyond 12 months

Special Populations

*Hepatic Insufficiency*

Consider dose reduction, particularly for maintenance of healing of erosive esophagitis.

Administration of Capsules
DOWNOPRAZOL Capsules should be swallowed intact with water. DO NOT USE OTHER LIQUIDS. DO NOT OPEN CAPSULE AND SPRINKLE CONTENTS INTO FOOD.

Preparation and Administration of Suspension
Directions for use: Empty packet contents into a small cup containing 1-2 tablespoons of water. DO NOT USE OTHER LIQUIDS OR FOODS. Stir well and drink immediately. Refill cup with water and drink.

If DOWNOPRAZOL is to be administered through a nasogastric (NG) or orogastric (OG) tube, the suspension should be constituted with approximately 20 mL of water. DO NOT USE OTHER LIQUIDS OR FOODS. Stir well and administer immediately. An appropriately-sized syringe should be used to instill the suspension in the tube. The suspension should be washed through the tube with 20 mL of water.

- 3 DOSAGE FORMS AND STRENGTHS
**DOWNOPRAZOL 20-mgor 40-mg Capsules:** Each hard gelatin capsule contains 20 mg or 40 mg omeprazole and 1100 mg sodium bicarbonate.
**DOWNOPRAZOL Powder for Oral Suspension** : Each packet contains either 20 mg or 40 mg omeprazole and 1680 mg sodium bicarbonate.

- 4 CONTRAINDICATIONS
DOWNOPRAZOL is contraindicated in patients with known hypersensitivity to any components of the formulation. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, and urticaria.

- 5 WARNINGS AND PRECAUTIONS
**5.1 Presence of Gastric Malignancy**

In adults, symptomatic response to therapy with Omeprazole does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing in adult patients who have a suboptimal response or an early symptomatic relapse after completing treatment with a proton pump inhibitor (PPI). In older patients, also consider an endoscopy.

**5.2 Acute Interstitial Nephritis**

Acute interstitial nephritis has been observed in patients taking PPIs including Omeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue Omeprazole if acute interstitial nephritis develops.

**5.3 Buffer Content**

Each DOWNOPRAZOL Capsule contains 1100 mg (13 mEq) of sodium bicarbonate. The total content of sodium in each capsule is 304 mg.

Each packet of DOWNOPRAZOL Powder for Oral Suspension contains 1680 mg (20 mEq) of sodium bicarbonate (equivalent to 460 mg of Na+).

The sodium content of DOWNOPRAZOL products should be taken into consideration when administering to patients on a sodium restricted diet.

Because DOWNOPRAZOL products contain sodium bicarbonate, they should be used with caution in patients with Bartter's syndrome, hypokalemia, hypocalcemia, and problems with acid-base balance. Long-term administration of bicarbonate with calcium or milk can cause milk-alkali syndrome.

Chronic use of sodium bicarbonate may lead to systemic alkalosis, and increased sodium intake can produce edema and weight increase.

### 5.4 Clostridium difficile-Associated Diarrhea

Published observational studies suggest that PPI therapy like Omeprazole 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.

### 5.5 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 the established treatment guidelines.

**5.6 Subacute cutaneous lupus erythematosus (SCLE)**: Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping omeprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

### 5.7 Interaction with Clopidogrel

Avoid concomitant use of Omeprazolewith 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 with concomitant medications, such as omeprazole, that interfere with CYP2C19 activity. Concomitant use of clopidogrel with 80 mg omeprazole reduces the pharmacological activity of clopidogrel, even when administered 12 hours apart. When using Omeprazole, consider alternative antiplatelet therapy.

### 5.8 Cyanocobalamin (Vitamin B-12) Deficiency

Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo-or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

### 5.9 Hypomagnesemia

Hypomagnesemia, symptomatic and 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, as potassium supplements alone did not improve potassium level.

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), healthcare professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

**5.10 Concomitant Use of** Omeprazole**with St. John's Wort or Rifampin**

Drugs which induce CYP2C19 or CYP3A4 (such as St. John's wort or rifampin) can substantially decrease omeprazole concentrations . Avoid concomitant use of Omeprazole with St. John's wort or rifampin.

5.11 Interactions with Investigations for 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. Providers should temporarily stop omeprazole treatment before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g., for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.

**5.12 Concomitant Use of** Omeprazole**with Methotrexate**

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients. [See Drug Interactions (7.8).]

**5.13 Fundic Gland Polyps**

PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond one year. Most PPIs users who developed fundic gland polyps were asymptomatic and fundic gland polyps were identified incidentally on endoscopy. Use the shortest duration of PPI therapy appropriate to the condition being treated.

**6 ADVERSE REACTIONS**

*Adverse Reactions Occurring in 1% or More of Patients on Omeprazole Therapy:*
*Headache, Diarrhea, Abdominal pain, Nausea, URI, Dizziness, Vomiting, Rash , Constipation, Cough, Asthenia, Back pain.*
*Incidence of Adverse Reactions ≥1% Causal Relations hip not Assessed*
*Abdominal pain, Asthenia, Digestive system : Constipation, Diarrhea, Flatulence, Nausea, Vomiting, Acid regurgitation , Headache.*
Number (%) of Critically Ill Patients with Frequently Occurring (≥3%) Advers e Events by Body System and Preferred Term:
**Blood and lymphatic system disorders**: Anemia NOS, Anemia NOS Aggravated , Thrombocytopenia.
**Cardiac disorders** : Atrial Fibrillation , Bradycardia NOS, SupraventricularTachycardia ,Tachycardia NOS ,Ventricular Tachycardia
**GASTROINTESTINAL DISORDERS**: Constipation, Diarrhea NOS, Gastric Hypomotility.
**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS**: Hyperpyrexia

, Edema NOS, Pyrexia.
**INFECTIONS AND INFESTATIONS**: Candidal Infection NOS, Oral Candidiasis, Sepsis NOS, Urinary Tract Infection NOS.
**Investigations**: Liver Function Tests NOS Abnormal.
**Metabolism and Nutrition Disorders**: Fluid Overload , Hyperglycaemia NOS, Hyperkalaemia, Hypernatraemia, Hypocalcaemia, Hypoglycaemia NOS, Hypokalaemia, Hypomagnesaemia, Hyponatraemia, Hypophosphataemia.
**Psychiatric Disorders**: Agitation.
**Respiratory , Thoracic and Mediastinal Disorders**: Acute Respiratory Distress Syndrome, Nosocomial Pneumonia, Pneumothorax NOS, Respiratory Failure.
**Skin and Subcutaneous Tissue Disorders:** Decubitus Ulcer, Rash NOS
**Vascular Disorders:** Hypertension NOS, Hypotension NOS
*Body as a Whole:* Hypersensitivity reactions, including anaphylaxis, anaphylactic shock, angioedema, bronchospasm, interstitial nephritis, urticaria (see also Skin below), fever, pain, fatigue, malaise.
*Cardiovascular:* Chest pain or angina, tachycardia, bradycardia, palpitation, elevated blood pressure, and peripheral edema.
*Gastrointestinal:* Pancreatitis (some fatal), anorexia, irritable colon, flatulence, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, dry mouth, stomatitis and abdominal swelling. During treatment with omeprazole, gastric fundic gland polyps have been noted rarely. These polyps are benign and appear to be reversible when treatment is discontinued. Gastroduodenal carcinoids have been reported in patients with Zollinger-Ellison syndrome on long-term treatment with omeprazole. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors.
*Hepatic:* Mild and, rarely, marked elevations of liver function tests [ALT (SGPT), AST (SGOT), γ-glutamyl transpeptidase, alkaline phosphatase, and bilirubin (jaundice)]. In rare instances, overt liver disease has occurred, including hepatocellular, cholestatic, or mixed hepatitis, liver necrosis (some fatal), hepatic failure (some fatal), and hepatic encephalopathy.
*Infections and Infestations: Clostridium difficile* associated diarrhea.
*Metabolism and Nutritional Disorders:* Hyponatremia, hypoglycemia, hypomagnesemia, and weight gain.
*Musculoskeletal:* Muscle cramps, myalgia, muscle weakness, joint pain, bone fracture, and leg pain.
*Nervous System/Psychiatric:* Psychic disturbances including depression, agitation, aggression, hallucinations, confusion, insomnia, nervousness, tremors, apathy, somnolence, anxiety, dream abnormalities; vertigo; paresthesia; and hemifacial dysesthesia.
*Respiratory:* Epistaxis, pharyngeal pain.
*Skin:* Severe generalized skin reactions including toxic epidermal necrolysis (TEN; some fatal), Stevens-Johnson syndrome, and erythema multiforme (some severe); purpura and/or petechiae (some with rechallenge); skin inflammation, urticaria, angioedema, pruritus, photosensitivity, alopecia, dry skin, and hyperhidrosis.
Skin and subcutaneous tissue disorders Frequency 'not known': Subacute cutaneous lupus erythematosus.
*Special Senses:* Tinnitus, taste perversion.
*Ocular:* Blurred vision, ocular irritation, dry eye syndrome, optic atrophy, anterior ischemic optic neuropathy, optic neuritis and double vision.

*Urogenital:* Interstitial nephritis (some with positive rechallenge), urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, hematuria, glycosuria, testicular pain, and gynecomastia.
*Hematologic:* Rare instances of pancytopenia, agranulocytosis (some fatal), thrombocytopenia, neutropenia, leukopenia, anemia, leucocytosis, and hemolytic anemia have been reported.
The incidence of clinical adverse experiences in patients greater than 65 years of age was similar to that in patients 65 years of age or less.

Additional adverse reactions that could be caused by sodium bicarbonate include metabolic alkalosis, seizures, and tetany.

- 7 DRUG INTERACTIONS

**7.1 Drugs for Which Gastric pH Can Affect Bioavailability**

Due to its effects on gastric acid secretion, omeprazole can reduce the absorption of drugs where gastric pH is an important determinant of their bioavailability. Like with other drugs that decrease the 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 omeprazole.

Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (30% in two subjects). Coadministration of digoxin with DOWNOPRAZOL is expected to increase the systemic exposure of digoxin. Therefore, patients may need to be monitored when digoxin is taken concomitantly with DOWNOPRAZOL.

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 DOWNOPRAZOL and MMF. Use DOWNOPRAZOL with caution in transplant patients receiving MMF.

**7.2 Drugs Metabolized by Cytochrome P450 (CYP)**

Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. There have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including omeprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin may need to be monitored for increases in INR and prothrombin time.

Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P-450 system (e.g., cyclosporine, disulfiram, benzodiazepines). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with DOWNOPRAZOL.

Concomitant administration of omeprazole and voriconazole (a combined inhibitor of CYP2C19 and CYP3A4) resulted in more than doubling of the omeprazole exposure. Dose adjustment of omeprazole is not normally required. When voriconazole (400 mg every 12 hours for one day, then 200 mg for 6 days) was given with omeprazole (40 mg once daily for 7 days) to healthy subjects, it

significantly increased the steady-state Cmax and AUC0-24 of omeprazole, an average of 2 times (90% CI: 1.8, 2.6) and 4 times (90% CI: 3.3, 4.4) respectively as compared to when omeprazole was given without voriconazole.

Drugs known to induce CYP2C19 or CYP3A4 (such as rifampin) may lead to decreased omeprazole serum levels. In a cross-over study in 12 healthy male subjects, St John's wort (300 mg three times daily for 14 days), an inducer of CYP3A4, decreased the systemic exposure of omeprazole in CYP2C19 poor metabolisers (Cmax and AUC decreased by 37.5% and 37.9%, respectively) and extensive metabolisers (Cmax and AUC decreased by 49.6% and 43.9%, respectively). Avoid concomitant use of St. John's Wort or rifampin with omeprazole.

Omeprazole acts as an inhibitor of CYP 2C19. Omeprazole, given in doses of 40 mg daily for week to 20 healthy subjects in cross-over study, increased C max and AUC of citostazol by 18% and 26% respectively. C max and AUC of one of its active metabolites, 3,4-dihydrocitostazol. Which has 4- 7 times the activity of citostazol, were increased by 29% and 69% respectively. Therefore a dose reduction of cilostazol from 100 mg b.i.d to 50 mg b.i.d should be considered.

**7.3 Antiretroviral Agents**

Concomitant administration of atazanavir and proton pump inhibitors is not recommended. Co-administration of atazanavir with proton pump inhibitors is expected to substantially decrease atazanavir plasma concentrations and thereby reduce its therapeutic effect.

Omeprazole has been reported to interact with some antiretroviral drugs. 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 CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. Following multiple doses of nelfinavir (1250 mg, twice daily) and omeprazole (40 mg, daily), AUC was decreased by 36% and 92%, Cmax by 37% and 89% and Cmin by 39% and 75% respectively for nelfinavir and M8. Following multiple doses of atazanavir (400 mg, daily) and omeprazole (40 mg, daily, 2 hours before atazanavir), AUC was decreased by 94%, Cmax by 96%, and Cmin by 95%. Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is therefore not recommended.

*Increased Concentration of Saquinavir*

For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported with an increase in AUC by 82%, in Cmax by 75% and in Cmin by 106% following multiple dosing of saquinavir/ritonavir (1000/100 mg) twice daily for 15 days with omeprazole 40 mg daily co-administered days 11 to 15. Dose reduction of saquinavir should be considered from the safety perspective for individual patients. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

**7.4 Combination Therapy with Clarithromycin**

Concomitant administration of clarithromycin with other drugs can lead to serious adverse reactions due to drug interaction [See *Warnings and Precautions* in prescribing information for clarithromycin]. Because of these drug interactions, clarithromycin is contraindicated for co-administration with certain drugs [See *Contraindications* in prescribing information for clarithromycin].

### 7.5 Clopidogrel

When used concomitantly with Clopidogrel it decrease its efficacy. Omeprazole is an inhibitor of CYP2C19 enzyme. Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of omeprazole 80 mg results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition. Avoid concomitant administration of DOWNOPRAZOL with clopidogrel. When using DOWNOPRAZOL, consider use of alternative anti-platelet therapy.

### 7.6 Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

### 7.7 Interactions with Investigations of Neuroendocrine Tumors

Drug-induced decrease in gastric acidity results in enterochromaffin-like cell hyperplasia and increased Chromogranin A levels which may interfere with investigations for neuroendocrine tumors.

### 7.8 Methotrexate

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted. *[See WARNINGS AND PRECAUTIONS (5.12)]*

- 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

*Pregnancy Category C*

Risk Summary

There are no adequate and well-controlled studies on the use of DOWNOPRAZOL in pregnant women. Available epidemiologic data fail to demonstrate an increased risk of major congenital malformations or other adverse pregnancy outcomes with first trimester omeprazole use. DOWNOPRAZOL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### 8.3 Nursing Mothers

Omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. The peak concentration of omeprazole in breast milk was less than 7% of the peak serum concentration. The concentration will correspond to 0.004 mg of omeprazole in 200 mL of milk. Because omeprazole is excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. In addition, sodium bicarbonate should be used with caution in nursing mothers.

### 8.4 Pediatric Use

Safety and effectiveness of DOWNOPRAZOL have not been established in pediatric patients less than 18 years of age.

**8.5 Geriatric Use**

Omeprazole was administered to over 2000 elderly individuals (≥ 65 years of age) in clinical trials in the U.S. and Europe. There were no differences in safety and effectiveness between the elderly and younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Pharmacokinetic studies with buffered omeprazole have shown the elimination rate was somewhat decreased in the elderly and bioavailability was increased. The plasma clearance of omeprazole was 250 mL/min (about half that of young subjects). The plasma half-life averaged one hour, about twice that in nonelderly, healthy subjects taking DOWNOPRAZOL. However, no dosage adjustment is necessary in the elderly.

**8.6 Hepatic Impairment**

Consider dose reduction, particularly for maintenance of healing of erosive esophagitis.

**8.7 Renal Impairment**

No dose reduction is necessary.

**8.8 Asian Population**

Recommend dose reduction, particularly for maintenance of healing of erosive esophagitis.

- 9. OVERDOSAGE

Reports have been received of overdosage with omeprazole in humans. Doses ranged up to 2400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, vomiting, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience *[See ADVERSE REACTIONS (6)]*. Symptoms were transient, and no serious clinical outcome has been reported when omeprazole was taken alone. No specific antidote for omeprazole overdose is known. Omeprazole is extensively protein bound and is, therefore, not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive. Single oral doses of omeprazole at 1350, 1339, and 1200 mg/kg were lethal to mice, rats, and dogs, respectively. Animals given these doses showed sedation, ptosis, tremors, convulsions, and decreased activity, body temperature, and respiratory rate and increased depth of respiration.

In addition, a sodium bicarbonate overdose may cause hypocalcemia, hypokalemia, hypernatremia, and seizures.

- 10 DESCRIPTION

DOWNOPRAZOL (omeprazole/sodium bicarbonate) is a combination of omeprazole, a proton-pump inhibitor, and sodium bicarbonate, an antacid.

DOWNOPRAZOL is supplied as immediate-release capsules and unit-dose packets as powder for oral suspension. Each capsule contains either 40 mg or 20 mg of omeprazole and 1100 mg of sodium bicarbonate with the following excipients: Croscarmellose sodium - Magnesium stearate - Titanium dioxide – Gelatin - Methyl parapen - Propyl paraben- Brilliant Blue for 20 mg only .

Packets of powder for oral suspension contain either 20 mg or 40 of omeprazole and 1680 mg of sodium bicarbonate with the following excipients: Aspartam - carboxymethyl celloulose sodium - orange flavor –mint flavor – Sucrose.

Downoprazol packets contain a source of phenylalanine. may be harmful for people with phenylketonuria.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

## 11 CLINICAL PHARMACOLOGY

### 11.1 Mechanism of Action

Omeprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H2 histamine antagonistic properties, but that suppress 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. 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.
Omeprazole is acid labile and thus rapidly degraded by gastric acid. DOWNOPRAZOL Capsules and Powder for Oral Suspension are immediate-release formulations that contain sodium bicarbonate which raises the gastric pH and thus protects omeprazole from acid degradation.

### 11.2 Pharmacokinetics

*Absorption*
In separate *in vivo* bioavailability studies, when DOWNOPRAZOL Oral Suspension and Capsules are administered on an empty stomach 1 hour prior to a meal, the absorption of omeprazole is rapid, with mean peak plasma levels (% CV) of omeprazole being 1954 ng/mL (33%) and 1526 ng/mL (49%), respectively, and time to peak of approximately 30 minutes (range 10-90 min) after a single-dose or repeated-dose administration. Absolute bioavailability of DOWNOPRAZOL Powder for Oral Suspension (compared to I.V. administration) is about 30-40% at doses of 20 – 40 mg, due in large part to presystemic metabolism.
When DOWNOPRAZOL Oral Suspension 40 mg/1680 mg was administered in a two-dose loading regimen, the omeprazole AUC (0-inf) (ng●hr/mL) was 1665 after Dose 1 and 3356 after Dose 2, while Tmax was approximately 30 minutes for both Dose 1 and Dose 2.

Following single or repeated once daily dosing, peak plasma concentrations of omeprazole from DOWNOPRAZOL are approximately proportional from 20 to 40 mg doses, but a greater than linear mean AUC (three-fold increase) is observed when doubling the dose to 40 mg. The bioavailability of omeprazole from DOWNOPRAZOL increases upon repeated administration.

When DOWNOPRAZOL is administered 1 hour after a meal, the omeprazole AUC is reduced by approximately 24% relative to administration 1 hour prior to a meal.

*Distribution*
Omeprazole is bound to plasma proteins. Protein binding is approximately 95%.

*Metabolism*

Following single-dose oral administration of omeprazole, the majority of the dose (about 77%) is eliminated in urine as at least six metabolites. Two metabolites have been identified as hydroxyomeprazole and the corresponding carboxylic acid. The remainder of the dose was recoverable in feces. 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.

*Excretion*
Following single-dose oral administration of omeprazole, little if any, unchanged drug is excreted in urine. The mean plasma omeprazole half-life in healthy subjects is approximately 1 hour (range 0.4 to 3.2 hours) and the total body clearance is 500-600 mL/min.

**Special Populations**
*Geriatric*
The elimination rate of omeprazole was somewhat decreased in the elderly, and bioavailability was increased. Omeprazole was 76% bioavailable when a single 40-mg oral dose of omeprazole (buffered solution) was administered to healthy elderly subjects, versus 58% in young subjects 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 250 mL/min (about half that of young subjects) and its plasma half-life averaged one hour, similar to that of young healthy subjects.

*Pediatric*
The pharmacokinetics of DOWNOPRAZOL has not been studied in patients < 18 years of age.

*Gender*
There are no known differences in the absorption or excretion of omeprazole between males and females.

*Hepatic Insufficiency*
In patients with chronic hepatic disease, the bioavailability of omeprazole from a buffered solution increased to approximately 100% compared to an I.V. dose, reflecting decreased first-pass effect, and the mean plasma half-life of the drug increased to nearly 3 hours compared to the mean half-life of 1 hour in normal subjects. Plasma clearance averaged 70 mL/min, compared to a value of 500-600 mL/min in normal subjects. Dose reduction, particularly where maintenance of healing of erosive esophagitis is indicated, for the hepatically impaired should be considered.

*Renal Insufficiency*
In patients with chronic renal impairment, whose creatinine clearance ranged between 10 and 62 mL/min/1.73 m2, the disposition of omeprazole from a buffered solution was very similar to that in healthy subjects, 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.

*Asian Population*

In pharmacokinetic studies of single 20-mg omeprazole doses, an increase in AUC of approximately four-fold was noted in Asian subjects compared to Caucasians. Dose adjustment, particularly where maintenance of healing of erosive esophagitis is indicated, for Asian subjects should be considered.

- 12 HOW SUPPLIED/STORAGE AND HANDLING

Downoprazol 20 mg and 40 mg hard gelatin capsule: Carton box contains 1 ( pvdc/ Aluminum) strip , each strip has 14 hard gelatin capsules with an insert leaflet.
Downoprazol 20 mg and 40 mg packets: Carton box containing 7 packets, each packet (paper, aluminum and plastic) contains 6 gm powder for oral suspension with an insert leaflet.

**Storage**
keep out of reach OF children.
Store at a temperature not exceeding 30°C in a dry place.

For capsules Produced by: Future pharmaceutical industries for Utopia pharmaceuticals.

For powder for suspension Produced by: Future pharmaceutical industries for Utopia pharmaceuticals.