LOVANZO INSTA
(Omeprazole + Sodium Bicarbonate)

20mg+1680mg & 40mg+1680mg

Sachet

COMPOSITION

Lovanzo Insta Sachet 20mg+1680mg
Each sachet contains:
Omeprazole 20mg
Sodium bicarbonate 1680mg

Lovanzo Insta Sachet 40mg+1680mg
Each sachet contains:
Omeprazole 40mg
Sodium bicarbonate 1680mg

THERAPEUTIC INDICATIONS

Duodenal Ulcer
Omeprazole and Sodium Bicarbonate for oral suspension 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.

Gastric Ulcer
Omeprazole and Sodium Bicarbonate for oral suspension is indicated for short-term treatment (4 to 8 weeks) of active benign gastric ulcer.

Treatment of Gastroesophageal Reflux Disease (GERD)
Symptomatic GERD
Omeprazole and Sodium Bicarbonate for oral suspension is indicated for the treatment of heartburn and other symptoms associated with GERD.

Erosive Esophagitis
Omeprazole and Sodium Bicarbonate is indicated for the short-term treatment (4 to 8 weeks) of erosive esophagitis which has been diagnosed by endoscopy. The efficacy of Omeprazole and Sodium Bicarbonate used for longer than 8 weeks in these patients has not been established. In the rare instance of a patient not responding 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 omeprazole may be considered.

Maintenance of Healing of Erosive Esophagitis
Omeprazole and Sodium Bicarbonate is indicated to maintain healing of erosive esophagitis. Controlled studies do not extend beyond 12 months.

Reduction of Risk of Upper Gastrointestinal Bleeding in Critically Ill Patients (40 mg Oral Suspension only)
Omeprazole and Sodium Bicarbonate for Oral Suspension 40 mg/1680 mg is indicated for the reduction of risk of upper GI bleeding in critically ill patients.

DOSAGE AND ADMINISTRATION

Omeprazole and Sodium Bicarbonate is available for oral suspension in 20 mg and 40 mg strengths for adult use. Directions for use is 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 (1680 mg), two packets of 20 mg are not equivalent to one packet of Omeprazole and Sodium Bicarbonate 40 mg; therefore, two 20 mg packets of Omeprazole and Sodium Bicarbonate should not be substituted for one packet of Omeprazole and Sodium Bicarbonate 40 mg.
Omeprazole and Sodium Bicarbonate for oral suspension should be taken on an empty stomach at least one hour before to a meal.
For patients receiving continuous NG/OG tube feeding, enteral feeding should be suspended approximately 3 hours before and 1 hour after administration of Omeprazole and Sodium Bicarbonate for Oral Suspension.

Table 1: Recommended Doses of Omeprazole and Sodium Bicarbonate 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 [1]
Benign Gastric Ulcer	40 mg	Once daily for 4 to 8 weeks [2]
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 to 8 weeks
Maintenance of Healing of Erosive Esophagitis	20 mg	Once daily[2]
Reduction of Risk of Upper Gastrointestinal Bleeding in Critically Ill Patients (40 mg oral suspension only)	40mg	40 mg initially followed by 40 mg 6 to 8 hours later and 40 mg daily thereafter for 14 days [2]

[1]Most patients heal within 4 weeks. Some patients may require an additional 4 weeks of therapy.
[2] Controlled studies do not exceed beyond 12 months.

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 Omeprazole and Sodium Bicarbonate is to be administered through a nasogastric or orogastric tube, the suspension should be constituted with approximately 20 mL of water. 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.

USE IN SPECIAL POPULATION

Pediatric Use
Safety and effectiveness of Omeprazole and Sodium Bicarbonate have not been established in pediatric patients less than 18 years of age.

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 the same as that in nonelderly, healthy subjects taking Omeprazole and Sodium Bicarbonate. However, no dosage adjustment is necessary in the elderly.

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

Renal Impairment
No dose reduction is necessary.

Asian Population
Recommended dose reduction, particularly for maintenance of healing of erosive esophagitis.

CONTRAINDICATIONS
Proton pump inhibitors (PPIs) are contraindicated in patients receiving rilpivirine-containing products. Omeprazole and Sodium Bicarbonate is contraindicated in patients with known hypersensitivity to any components of the formulation.
Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, interstitial nephritis, and urticaria.

WARNINGS AND PRECAUTIONS

Presence of Gastric Malignancy
In adults, symptomatic response to therapy with Omeprazole and Sodium Bicarbonate for oral suspension 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 PPI. In older patients, also consider an endoscopy.

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

Clostridium difficile - Associated Diarrhea
Published observational studies suggest that PPI therapy like Omeprazole and Sodium Bicarbonate for oral suspension 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.

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.

Interaction with Clopidogrel
Avoid concomitant use of Omeprazole and Sodium Bicarbonate for oral suspension 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 with concomitant medications, such as omeprazole, that interfere with CYP2C19 activity. When using Omeprazole and Sodium Bicarbonate for oral suspension, consider alternative anti-platelet therapy.

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.

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

Concomitant Use of Omeprazole and Sodium Bicarbonate for Oral Suspension with St. John's Wort or rifampin
Drugs which induce CYP2C19 OR CYP34A (such as St. John's Wort or rifampin) can substantially decrease omeprazole concentrations. Avoid concomitant use of Omeprazole and Sodium Bicarbonate for oral suspension with St. John's Wort or rifampin.

Concomitant Use of Omeprazole and Sodium Bicarbonate for Oral Suspension with Methotrexate
Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; 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.

Atrophic gastritis
Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole.

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. omeprazole treatment should be temporarily stop 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.

Buffer Content
Each sachet contains 1680 mg (20 mEq) of sodium bicarbonate (equivalent to 460 mg of Na+). The sodium content of the product should be taken into consideration when administering to patients on a sodium restricted diet or those at risk for developing congestive heart failure. Because product contain sodium bicarbonate, it 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 an increased sodium intake can produce edema and weight increase.

Cutaneous and Systemic Lupus Erythematosus
Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs, including omeprazole. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematous cases were CLE. The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly.

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. Use the shortest duration of PPI therapy appropriate to the condition being treated.

ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in labeling:
- Acute Interstitial Nephritis
- Clostridium difficile-Associated Diarrhea
- Bone Fracture
- Cutaneous and Systemic Lupus Erythematosus
- Cyanocobalamin (Vitamin B-12) Deficiency
- Hypomagnesemia
- Fundic Gland Polyps

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates the rates observed in practice. During various clinical trials the most commonly reported ADRs were Headache, Abdominal Pain, Diarrhea, Nausea, Dizziness, Vomiting, Rash, Constipation, Cough, Flatulence, Upper respiratory tract infection, Asthenia & Back Pain.

Post marketing Experience
The following adverse reactions have been identified during post-approval use of omeprazole and sodium bicarbonate.
Omeprazole
Body as a Whole: Hypersensitivity reactions, including anaphylaxis, anaphylactic shock, angioedema, bronchospasm, interstitial nephritis,

urticaria, fever, pain, fatigue, malaise, and systemic lupus erythematosus.
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, abdominal swelling and fundic gland polyps. Gastroduodenal carcinoids have been reported in patients with Zollinger-Ellison syndrome on long-term treatment with omeprazole.
Hepatic: Mild and, rarely, marked elevations of liver function tests [ALT (SGPT), AST (SGOT), _-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, cutaneous lupus erythematosus and erythema multiforme (some severe); purpura and/or petechiae (some with rechallenge); skin inflammation, urticaria, angioedema, pruritus, photosensitivity, alopecia, dry skin, and hyperhidrosis.
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, leukocytosis, and hemolytic anemia have been reported.
Sodium Bicarbonate
metabolic alkalosis, seizures, and tetany.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at pv@searlecompany.com

PREGNANCY AND LACTATION

Pregnancy - Category C

There are no adequate and well controlled studies on the use of omeprazole in pregnant women. Omeprazole should be used during pregnancy only if the potential benefit to pregnant women justifies the potential risk to the fetus.

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 taken 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.

DRUG INTERACTIONS

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.

Drugs metabolized by cytochrome P450 (CYP)

Patients treated with proton pump inhibitors and warfarin may need to be monitored for increases in INR and prothrombin time. 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. Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver.

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.

Combination therapy with Clarithromycin

Concomitant administration of clarithromycin with other drugs can lead to serious adverse reactions due to drug interaction. Because of these drug interactions, clarithromycin is contraindicated for co-administration with certain drugs.

Clopidogrel

Omeprazole is an inhibitor of CYP2C19 enzyme. Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Avoid concomitant administration of Omeprazole and Sodium Bicarbonate for oral suspension with clopidogrel. When using Omeprazole and Sodium Bicarbonate

for oral suspension, consider use of alternative anti-platelet therapy.

Tacrolimus

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

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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

ADVERSE DRUG REACTIONS

OVERDOSE

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. Symptoms were transient, and no serious clinical outcome has been reported when omeprazole was taken alone. 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. As with the management of any overdose, the possibility of multiple drug ingestion should be considered. 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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. Omeprazole and Sodium Bicarbonate Capsules are immediate-release formulations that contain sodium bicarbonate which raises the gastric pH and thus protects omeprazole from acid degradation.

PHARMACODYNAMICS

Antisecretory Activity

Results from a PK/PD study of the antisecretory effect of repeated once-daily dosing of 40 mg and 20 mg of omeprazole and sodium bicarbonate oral suspension in healthy subjects are shown in Table below.

Table 2: Effect of Omeprazole and Sodium Bicarbonate Oral Suspension on Intragastric pH, Day 7

Parameter	**Omeprazole/Sodium Bicarbonate**	
	40 mg/1680 mg (n = 24)	**20 mg/1680 mg (n = 28)**
% Decrease from Baseline for Integrated Gastric Acidity (mmol·hr/L)	84%	82%
Coefficient of variation	20%	24%
% Time Gastric pH > 4* (Hours)*	77 (18.6 h)	51 (12.2 h)
Coefficient of variation	27%	43%
Median pH	5.2	4.2
Coefficient of variation	17%	37%

Note: Values represent medians. All parameters were measured over a 24-hour period.

*p < 0.05 20 mg vs. 40 mg

Results from a separate PK/PD study of antisecretory effect on repeated once daily dosing of 40 mg/1100 mg and 20 mg/1100 mg of Omeprazole and Sodium Bicarbonate Capsules in healthy subjects show similar effects in general on the above three PD parameters as those for omeprazole and sodium bicarbonate 40 mg/1680 mg and 20 mg/1680 mg oral suspension, respectively.

The antisecretory effect lasts longer than would be expected from the very short (1 hour) plasma half-life, apparently due to irreversible binding to the parietal H+/K+ ATPase enzyme.

Pharmacokinetic properties

Absorption

In separate in vivo bioavailability studies, when omeprazole and sodium bicarbonate oral suspension 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 omeprazole and sodium bicarbonate powder for oral suspension (compared to I.V. administration) is about 30-40% at doses of 20 to 40 mg, due in large part to pre-systemic metabolism. When omeprazole and sodium bicarbonate 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 omeprazole and sodium bicarbonate 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 omeprazole and sodium bicarbonate increases upon repeated administration. When omeprazole and sodium bicarbonate 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 hydroxy-omeprazole 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 hydroxy-omeprazole. 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.

Specific Populations

Geriatric Patients

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.

Male and Female Patients

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

Patients with Renal Impairment

In patients with chronic renal impairment (creatinine clearance between 10 and 62 mL/min/1.73 m2), the disposition of omeprazole 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. This increase in bioavailability is not considered to be clinically meaningful.

Patients with Hepatic Impairment

In patients with chronic hepatic disease classified as Child-Pugh Class A (n=3), B (n=4) and C (n=1), the bioavailability of omeprazole increased to approximately 100% compared to healthy subjects, reflecting decreased first-pass effect, and the plasma half-life of the drug increased to nearly 3 hours compared to the in healthy subjects of 0.5 to 1 hour. Plasma clearance averaged 70 mL/min, compared to a value of 500 to 600 mL/min in healthy subjects.

Drug Interactions Studies

Effect of Omeprazole on Other Drugs

Omeprazole is a time-dependent inhibitor of CYP2C19 and can increase the systemic exposure of co-administered drugs that are CYP2C19 substrates. In addition, administration of omeprazole increases intragastric pH and can alter the systemic exposure of certain drugs that exhibit pH-dependent solubility.

Antiretrovirals

For some antiretroviral drugs, such as rilpivirine, atazanavir and nelfinavir, decreased serum concentrations have been reported when given together with omeprazole.

Rilpivirine: Following multiple doses of rilpivirine (150 mg, daily) and omeprazole (20 mg, daily), AUC was decreased by 40%, Cmax by 40%, and Cmin by 33% for rilpivirine.

Nelfinavir: 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.

Atazanavir: 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%.

Saquinavir: 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.

AUC was increased by 82%, Cmax by 75%, and Cmin by 106%. The mechanism behind this interaction is not fully elucidated. Therefore, clinical and laboratory monitoring for saquinavir toxicity is recommended during concurrent use with omeprazole.

Clopidogrel

In a crossover clinical study, 72 healthy subjects were administered clopidogrel (300 mg loading dose followed by 75 mg per day) alone and with omeprazole (80 mg at the same time as clopidogrel) for 5 days. The exposure to the active metabolite of clopidogrel was decreased by 46% (Day 1) and 42% (Day 5) when clopidogrel and omeprazole were administered together.

Results from another crossover study in healthy subjects showed a similar pharmacokinetic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole 80 mg daily when coadministered for 30 days. Exposure to the active metabolite of clopidogrel was reduced by 41% to 46% over this time period.

In another study, 72 healthy subjects were given the same doses of clopidogrel and 80 mg omeprazole, but the drugs were administered 12 hours apart; the results were similar, indicating that administering clopidogrel and omeprazole at different times does not prevent their interaction.

Mycophenolate Mofetil

Administration of omeprazole 20 mg twice daily for 4 days and a single 1000 mg dose of MMF approximately one hour after the last dose of omeprazole to 12 healthy subjects in a crossover study resulted in a 52% reduction in the Cmax and 23% reduction in the AUC of MPA.

Cilostazol

Omeprazole acts as an inhibitor of CYP2C19. Omeprazole, given in doses of 40 mg daily for one week to 20 healthy subjects in crossover study, increased Cmax and AUC of cilostazol by 18% and 26% respectively. The Cmax and AUC of one of the active metabolites, 3,4-dihydro-cilostazol, which has 4 to 7 times the activity of cilostazol, were increased by 29% and 69%, respectively. Co-administration of cilostazol with omeprazole is expected to increase concentrations of cilostazol and the above-mentioned active metabolite.

Diazepam

Concomitant administration of omeprazole 20 mg once daily and diazepam 0.1 mg/kg given intravenously resulted in 27% decrease in clearance and 36% increase in diazepam half-life.

Digoxin

Concomitant administration of omeprazole 20 mg once daily and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (30% in two subjects)

Effect of Other Drugs on Omeprazole

Voriconazole

Concomitant administration of omeprazole and voriconazole (a combined inhibitor of CYP2C19 and CYP3A4) resulted in more than doubling of the omeprazole exposure. When voriconazole (400 mg every 12 hours for one day, followed by 200 mg once daily for 6 days) was given with omeprazole (40 mg once daily for 7 days) to healthy subjects, the steady-state Cmax and AUC0-24 of omeprazole significantly increased: 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

Summary of clinical studies

The effectiveness of OMEPRAZOLE has been established, in part, based on studies of an oral delayed-release omeprazole product for the treatment of active duodenal ulcer, active benign gastric ulcer, symptomatic GERD, EE due to acid-mediated GERD, and maintenance of healing of EE due to acid-mediated GERD.

OMEPRAZOLE for oral suspension was studied for the reduction of risk of upper GI bleeding in critically ill adult patients.

Active Duodenal Ulcer

In a multicenter, double-blind, placebo-controlled study of 147 patients with endoscopically documented duodenal ulcer, the percentage of patients healed (per protocol) at 2 and 4 weeks was significantly higher with omeprazole delayed-release capsules 20 mg once a day than with placebo ($p \leq 0.01$)

Complete daytime and nighttime pain relief occurred significantly faster ($p \leq 0.01$) in patients treated with omeprazole 20 mg than in patients treated with placebo. At the end of the study, significantly more patients who had received omeprazole had complete relief of daytime pain ($p \leq 0.05$) and nighttime pain ($p \leq 0.01$).

In a multicenter, double-blind study of 293 patients with endoscopically documented duodenal ulcer, the percentage of patients healed (per protocol) at 4 weeks was significantly higher with omeprazole 20 mg once a day than with ranitidine 150 mg twice daily ($p < 0.01$)

Healing occurred significantly faster in patients treated with omeprazole than in those treated with ranitidine 150 mg twice daily ($p < 0.01$).

In a foreign multinational randomized, double-blind study of 105 patients with endoscopically documented duodenal ulcer, 40 mg and 20 mg of omeprazole were compared to 150 mg twice daily of ranitidine at 2, 4 and 8 weeks. At 2 and 4 weeks both doses of omeprazole were statistically superior (per protocol) to ranitidine, but 40 mg was not superior to 20 mg of omeprazole, and at 8 weeks there was no significant difference between any of the active drugs

For the stratified groups of patients with ulcer size less than or equal to 1 cm, no difference in healing rates between 40 mg and 20 mg was detected at either 4 or 8 weeks. For patients with ulcer size greater than 1 cm, 40 mg was significantly more effective than 20 mg at 8 weeks.

In a foreign, multinational, double-blind study of 602 patients with endoscopically diagnosed gastric ulcer, omeprazole 40 mg once a day, 20 mg once a day, and ranitidine 150 mg twice a day were evaluated

Symptomatic GERD

A placebo-controlled study was conducted in Scandinavia to compare the efficacy of omeprazole 20 mg or 10 mg once daily for up to 4 weeks in the treatment of heartburn and other symptoms in GERD patients without EE. % Successful Symptomatic Outcome Defined as complete resolution of heartburn is higher in 20 mg group than 10 mg group and placebo.

In a U.S. multicenter, double-blind, placebo-controlled study of 40 mg or 20 mg of omeprazole delayed-release capsules in patients with symptoms of GERD and endoscopically diagnosed erosive esophagitis of grade 2 or above. In this study, the 40 mg dose was not superior to the 20 mg dose of omeprazole in the percentage healing rate. Other controlled clinical trials have also shown that omeprazole is effective in severe GERD. In comparisons with histamine H2-receptor antagonists in patients with erosive esophagitis, grade 2 or above, omeprazole in a dose of 20 mg was significantly more effective than the active controls. Complete daytime and nighttime heartburn relief occurred significantly faster ($p < 0.01$) in patients treated with omeprazole than in those taking placebo or histamine H2-receptor antagonists.

In this and five other controlled GERD studies, significantly more patients taking 20 mg omeprazole (84%) reported complete relief of GERD symptoms than patients receiving placebo (12%).

Maintenance of Healing of EE Due to Acid-Mediated GERD

In a U.S. double-blind, randomized, multicenter, placebo-controlled study; two dose regimens of omeprazole were studied in patients with endoscopically confirmed healed esophagitis. Omeprazole 20 mg once daily show more percentage of remission at 6 months than omeprazole 20 mg 3 days per week or placebo

In an international, multicenter, double-blind study, omeprazole 20 mg daily and 10 mg daily were compared to ranitidine 150 mg twice daily in patients with endoscopically confirmed healed esophagitis, results reveal that In patients who initially had grades 3 or 4 erosive esophagitis, for maintenance after healing 20 mg daily of omeprazole was effective, while 10 mg did not demonstrate effectiveness.

Reduction of Risk of Upper Gastrointestinal Bleeding in Critically Ill Patients

A double-blind, multicenter, randomized, non-inferiority clinical trial was conducted to compare OMEPRAZOLE oral suspension and intravenous cimetidine for the reduction of risk of upper gastrointestinal (GI) bleeding in critically ill patients (mean APACHE II score = 23.7). The primary endpoint was significant upper GI bleeding defined as bright red blood which did not clear after adjustment of the nasogastric tube and a 5-to-10-minute lavage, or persistent Gastroccult-positive coffee grounds for 8 consecutive hours which did not clear with 100 mL lavage. OMEPRAZOLE oral suspension was administered as 40 mg (two doses administered 6 to 8 hours apart on the first day via orogastric or nasogastric tube, followed by 40 mg once daily thereafter) and intravenous cimetidine (300 mg bolus, followed by 50 to 100 mg/hr continuously thereafter) for up to 14 days (mean = 6.8 days). A total of 359 patients were studied, age range 16 to 91 (mean = 56 years), 58.5% were males, and 64% were Caucasians. The results of the study showed that OMEPRAZOLE oral suspension was non-inferior to intravenous cimetidine, 7/178 (3.9%) patients in the OMEPRAZOLE group vs. 10/181 (5.5%) patients in the cimetidine group experienced clinically significant upper GI bleeding.

PRECLINICAL SAFETY DATA

Carcinogenesis, Mutagenesis, Impairment of Fertility

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44 and 140.8 mg/kg/day (approximately 0.4 to 34.2 times the human dose of 40 mg/day 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. Gastric carcinoids seldom occur in the untreated rat. 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 (approximately 3.36 times the human dose of 40 mg/day on a body surface area basis) for one 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 one year (94% treated versus 10% controls). By the second year the difference between treated and control rats was much smaller (46% versus 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. In a 52-week toxicity study in Sprague Dawley rats, brain astrocytomas were found in a small number of males that received omeprazole at dose levels of 0.4, 2, and 16 mg/kg/day (about 0.1 to 3.9 times the human dose of 40 mg/day on a body surface area basis). No astrocytomas were observed in female rats in this study. In a 2-year carcinogenicity study in Sprague Dawley rats, no astrocytomas were found in males and females at the high dose of 140.8 mg/kg/day (about 34 times the human dose of 40 mg/day on a body surface area basis). A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. A 26-week p53 (+/-) transgenic mouse carcinogenicity study was not positive.

Omeprazole was positive for clastogenic effects in an in vitro human lymphocyte chromosomal aberration assay, in one of two in vivo mouse micronucleus tests, and in an in vivobone marrow cell chromosomal aberration assay. Omeprazole was negative in the in vitro Ames test, an in vitro mouse lymphoma cell forward mutation assay and an in vivo rat liver DNA damage assay.

In a 24-month carcinogenicity studies in rats, a dose-related significant increase in gastric carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals. Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other PPIs or high doses of H2-receptor antagonists.

Omeprazole at oral doses up to 138 mg/kg/day (about 33.6 times the human dose of 40 mg/day on a body surface area basis) was found to have no effect on the fertility and general reproductive performance in rats.

PRESENTATION

Lovanzo Insta Sachet 20mg+1680mg are available in pack of 10's.

Lovanzo Insta Sachet 40mg+1680mg are available in pack of 10's.

INSTRUCTIONS

- To be sold on the prescription of a registered medical practitioner only.
- Protect from sunlight, moisture and heat.
- Store below 30°C.
- Keep all medicines out of the sight & reach of children.

REGISTRATION NUMBER

Lovanzo Insta Sachet 20mg+1680mg: 093059

Lovanzo Insta Sachet 40mg+1680mg: 092821

Manufacturing License No.**:** 000016

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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F-319, S.I.T.E., Karachi-Pakistan.

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