SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Risek Insta (Omeprazole + Sodium bicarbonate) 40mg + 1680mg Powder for Oral Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains:
Omeprazole USP…40mg
Sodium Bicarbonate USP
…1680mg (as buffer)

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

White to off-white granular powder filled in a printed sachet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Risek Insta for oral suspension are indicated in adults for the:

- short-term treatment of active duodenal ulcer. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy.
- short-term treatment (4 to 8 weeks) of active benign gastric ulcer.
- treatment of heartburn and other symptoms associated with GERD for up to 4 weeks.
- short-term treatment (4 to 8 weeks) of EE due to acid-mediated GERD which has been diagnosed by endoscopy in adults.
  - The efficacy of Risek Insta used for longer than 8 weeks in patients with EE has not been established. If a patient does not respond to 8 weeks of treatment, an additional 4 weeks of treatment may be given. If there is recurrence of EE or GERD symptoms (e.g., heartburn), additional 4 to 8-week courses of Risek Insta may be considered.
- maintenance of healing of EE due to acid-mediated GERD. Controlled studies do not extend beyond 12 months.

Risek Insta for oral suspension is indicated in adults for the:

- reduction of risk of upper GI bleeding in critically ill adult patients.

4.2. Posology and method of administration

Important Administration Instructions

- Risek Insta (omeprazole and sodium bicarbonate) is available as a powder for oral suspension in 20mg and 40mg strengths of omeprazole for adult use. All recommended doses throughout the labeling are based upon omeprazole.
- The sodium content of Risek Insta for oral suspension should be taken into

consideration when prescribing this product:

- Risek Insta for oral suspension: each 20mg and 40mg packet of contains 1,680mg (20 mEq) of sodium bicarbonate. The total content of sodium in each packet is 460mg.
- Due to the sodium bicarbonate content of Risek Insta:
- Do not substitute two packets of 20mg Risek Insta for oral suspension with one packet of 40mg Risek Insta for oral suspension.

Dosage Regimen

The recommended dosage regimen by indication in adults of Risek Insta for oral suspension is summarized in the table below.

Recommended Dosage Regimen of Risek Insta for Oral Suspension in Adults by Indication

Indication	Dosage of Risek Insta for oral suspension	Treatment Duration
Treatment of Active Duodenal Ulcer	20mg once daily	4 weeks[1,2]
Treatment of Active Benign Gastric Ulcer	40mg once daily	4 to 8 weeks
Treatment of Symptomatic GERD	20mg once daily	Up to 4 weeks
Treatment of EE due to Acid-Mediated GERD	20mg once daily	4 to 8 weeks[2]
Maintenance of Healing of EE due to Acid-Mediated GERD	20mg once daily	Controlled studies do not extend beyond 12 months.

[1] *Most patients heal within 4 weeks. Some patients may require an additional 4 weeks of therapy.*

[2] *The efficacy of Risek Insta used for longer than 8 weeks in patients with EE has not been established. If a patient does not respond to 8 weeks of treatment, an additional 4 weeks of treatment may be given. If there is recurrence of EE or GERD symptoms (e.g., heartburn), additional 4 to 8-week courses of Risek Insta may be considered.*

Only 40mg Risek Insta for oral suspension is indicated for the reduction of risk of upper GI bleeding in critically ill adult patients and the dosage regimen is summarized in the table below. All recommended dosages are based upon omeprazole content.

Recommended Dosage Regimen of 40mg Risek Insta for Oral Suspension in Adults by Indication

Indication	Dosage of 40mg Risek Insta for oral suspension	Treatment Duration

Reduction of Risk of Upper GI Bleeding in Critically ill Patients	40mg initially; followed by 40mg 6 to 8 hours later; and 40mg once daily thereafter	14 days

Risek Insta for Oral Suspension

- Risek Insta for oral suspension is intended to be mixed with water and administered orally or via a nasogastric (NG) or orogastric (OG) tube.
- If administered orally, take on an empty stomach at least one hour before a meal.
- If administered via NG or OG tube, suspend enteral feeding approximately 3 hours before and 1 hour after administration of Risek Insta for oral suspension.

Oral Administration

- Empty the contents of a packet into a small cup containing 5 to 10 mL of water. Do not mix with liquids or foods other than water.
- Stir well and drink immediately.
- Refill cup with water and drink immediately.

Nasogastric (NG) or Orogastric (OG) Tube Administration

- Add 20 mL of water to a catheter tipped syringe and then add the contents of a packet. Use an appropriately-sized catheter tipped syringe. Do not mix with liquids or foods other than water.
- Shake the syringe to dissolve the powder.
- Administer through the NG or orogastric tube into the stomach right away.
- Refill the syringe with an equal amount of water.

Shake and flush any remaining contents from the NG tube or orogastric tube into the stomach

4.3. Contraindications

Omeprazole + Sodium bicarbonate Powder for Oral Suspension is contraindicated in patients with known hypersensitivity to substituted benzimidazoles or to any component of the formulation. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute tubulointerstitial nephritis, and urticaria.
Proton pump inhibitors (PPIs), including Omeprazole + Sodium bicarbonate) 20mg + 1680mg Powder for Oral Suspension, are contraindicated in patients receiving rilpivirine containing products.

4.4. Special warnings and special precautions for use

Presence of Gastric Malignancy
In adults, symptomatic response to therapy with Omeprazole + Sodium bicarbonate) 20mg + 1680mg Powder 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 proton pump inhibitor (PPI). In older patients, also consider an endoscopy.

Acute Tubulointerstitial Nephritis
Acute tubulointerstitial nephritis (TIN) has been observed in patients taking PPIs and may occur at any point during PPI therapy. Patients may present with varying signs and symptoms from symptomatic hypersensitivity reactions to non-specific symptoms of decreased renal function (e.g., malaise, nausea and anorexia). In reported case series, some patients were diagnosed on biopsy and in the absence of extra-renal manifestations (e.g., fever, rash or arthralgia).
Discontinue Omeprazole + Sodium bicarbonate Powder for Oral Suspension and evaluate patients with suspected acute TIN.

Sodium Bicarbonate Buffer Content
Each 20mg and 40mg packet of Omeprazole + Sodium bicarbonate Powder for Oral Suspension for oral suspension contains 1,680mg (20 mEq) of sodium bicarbonate. The total content of sodium in each packet is 460mg.
Chronic 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 gain.
The sodium content of Omeprazole + Sodium bicarbonate) 20mg + 1680mg Powder for Oral Suspension products should be taken into consideration when administering to patients on a sodium-restricted diet or those at risk for developing congestive heart failure.
Avoid Omeprazole + Sodium bicarbonate) 20mg + 1680mg Powder for Oral Suspension in patients with Bartter's syndrome, hypokalemia, hypocalcemia, and problems with acid-base balance.

Clostridium difficile-Associated Diarrhea
Published observational studies suggest that PPI therapy like Omeprazole + Sodium bicarbonate) 20mg + 1680mg Powder 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.

Severe Cutaneous Adverse Reactions
Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and

systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported in association with the use of PPIs. Discontinue Omeprazole + Sodium bicarbonate Powder for Oral Suspension at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

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 erythematosus 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. Generally, histological findings were observed without organ involvement.

Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported.

Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving Omeprazole + Sodium bicarbonate Powder for Oral Suspension, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks. Serological testing (e.g., ANA) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

Interaction with Clopidogrel

Avoid concomitant use of Omeprazole + Sodium bicarbonate Powder 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. Concomitant use of clopidogrel with 80mg omeprazole reduces the pharmacological activity of clopidogrel, even when administered 12 hours apart. When using Omeprazole + Sodium bicarbonate Powder for Oral Suspension, consider alternative antiplatelet 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 in patients treated with Omeprazole + Sodium bicarbonate Powder for Oral Suspension.

Hypomagnesemia and Mineral Metabolism

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.
Hypomagnesemia may lead to hypocalcemia and/or hypokalemia and may exacerbate underlying hypocalcemia in at-risk patients. 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.
Consider monitoring magnesium and calcium levels prior to initiation of Omeprazole + Sodium bicarbonate Powder for Oral Suspension and periodically while on treatment in patients with a preexisting risk of hypocalcemia (e.g., hypoparathyroidism). Supplement with magnesium and/or calcium as necessary. If hypocalcemia is refractory to treatment, consider discontinuing the PPI.

Interaction 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 + Sodium bicarbonate Powder for Oral Suspension with St. John's wort or rifampin.

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 + Sodium bicarbonate Powder for Oral Suspension treatment for at least 14 days 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.

Interaction 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.

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.

4.5. Interaction with other medicinal products and other forms of Interactions

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 (150mg, daily) and omeprazole (20mg, daily), AUC was decreased by 40%, C_{max} by 40%, and C_{min} by 33% for rilpivirine.

Nelfinavir: Following multiple doses of nelfinavir (1250mg, twice daily) and omeprazole (40mg daily), AUC was decreased by 36% and 92%, C_{max} by 37% and 89% and C_{min} by 39% and 75% respectively for nelfinavir and M8.
Atazanavir: Following multiple doses of atazanavir (400mg, daily) and omeprazole (40mg, daily, 2 hours before atazanavir), AUC was decreased by 94%, C_{max} by 96%, and C_{min} by 95%.
Saquinavir: Following multiple dosing of saquinavir/ritonavir (1000/100mg) twice daily for 15 days with omeprazole 40mg daily co-administered days 11 to 15.
AUC was increased by 82%, C_{max} by 75%, and C_{min} 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 PRILOSEC.

Clopidogrel: In a clinical study, healthy subjects were administered clopidogrel (300mg loading dose followed by 75mg per day) alone and with omeprazole (80mg 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 (300mg loading dose/75mg daily maintenance dose) and omeprazole 80mg 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, healthy subjects were given the same doses of clopidogrel and 80mg 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 20mg twice daily for 4 days and a single 1000mg 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 C_{max} 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 C_{max} and AUC of cilostazol by 18% and 26% respectively. The C_{max} 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 20mg once daily and diazepam 0.1mg/kg given intravenously resulted in 27% decrease in clearance and 36% increase in diazepam half-life.

Digoxin

Concomitant administration of omeprazole 20mg 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 (400mg every 12 hours for one day, followed by 200mg once daily for 6 days) was given with omeprazole (40 mg once daily for 7 days) to healthy subjects, the steadystate C_{max} 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.

4.6. Fertility, pregnancy and lactation Pregnancy

Risk Summary

There are no adequate and well-controlled studies with Omeprazole + Sodium bicarbonate Powder for Oral Suspension in pregnant women.

Omeprazole

There are no adequate and well-controlled studies with omeprazole 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. Reproduction studies in rats and rabbits resulted in dose-dependent embryo-lethality at omeprazole doses that were approximately 3.4 to 34 times an oral human dose of 40 mg (based on a body surface area for a 60 kg person).

Teratogenicity was not observed in animal reproduction studies with administration of oral esomeprazole (an enantiomer of omeprazole) magnesium in rats and rabbits during organogenesis with doses about 68 times and 42 times, respectively, an oral human dose of 40 mg esomeprazole or 40 mg omeprazole (based on body surface area for a 60 kg person).

Changes in bone morphology were observed in offspring of rats dosed through most of pregnancy and lactation at doses equal to or greater than approximately 34 times an oral human dose of 40 mg esomeprazole or 40mg omeprazole. When

maternal administration was confined to gestation only, there were no effects on bone physeal morphology in the offspring at any age.

Sodium Bicarbonate
Available data with sodium bicarbonate use in pregnant women are insufficient to identify a drug associated risk of major birth defects or miscarriage. Published animal studies report that sodium bicarbonate administered to rats, mice or rabbits during pregnancy did not cause adverse developmental effects in offspring.
The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. The estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data
Human Data
There are no adequate and well-controlled studies with Omeprazole + Sodium bicarbonate Powder for Oral Suspension in pregnant women. Four published epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy with the frequency of abnormalities among infants of women exposed to H2-receptor antagonists or other controls.

Lactation
Risk Summary
Available data from the published literature suggest both components of Omeprazole + Sodium bicarbonate Powder for Oral Suspension, omeprazole and sodium bicarbonate, are present in human milk. There are no clinical data on the effects of omeprazole or sodium bicarbonate on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Omeprazole + Sodium bicarbonate Powder for Oral Suspension and any potential adverse effects on the breastfed infant from Omeprazole + Sodium bicarbonate Powder for Oral Suspension or from the underlying maternal condition.

Pediatric Use
Safety and effectiveness of Omeprazole + Sodium bicarbonate Powder for Oral Suspension have not been established in pediatric patients.

Geriatric Use
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 Omeprazole + Sodium bicarbonate Powder for Oral Suspension.
However, no dosage adjustment is necessary in the elderly.

Hepatic Impairment
In patients with hepatic impairment (Child-Pugh Class A, B, or C) exposure to

omeprazole substantially increased compared to healthy subjects. Avoid use of Omeprazole + Sodium bicarbonate Powder for Oral Suspension in patients with hepatic impairment for maintenance of healing of erosive esophagitis.

Asian Population
In studies of healthy subjects, Asians had approximately a four-fold higher exposure than Caucasians. Avoid use of Omeprazole + Sodium bicarbonate 20mg + 1680mg Powder for Oral Suspension in Asian patients for maintenance of healing of erosive esophagitis.

4.7. Effects on ability to drive and use machines

Not available

4.8. Undesirable effects

The following adverse reactions were reported*:*

*Postmarketing Experienc*e

The following adverse reactions have been identified during post-approval use of omeprazole and sodium bicarbonate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Omeprazole
Body as a Whole: Hypersensitivity reactions, including anaphylaxis, anaphylactic shock, angioedema, bronchospasm, 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, 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. 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, hepatic failure, and hepatic encephalopathy.

Infections and Infestations: Clostridium difficile-associated diarrhea.

Metabolism and Nutritional Disorders: Hypomagnesemia, hypocalcemia, hypokalemia, hyponatremia, hypoglycemia, 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 TEN, SJS, DRESS, AGEP, 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: Tubulointerstitial nephritis, urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, hematuria, glycosuria, testicular pain, gynecomastia, and erectile dysfunction

Hematologic: Rare instances of pancytopenia, agranulocytosis, thrombocytopenia, neutropenia, leukopenia, anemia, leukocytosis, and hemolytic anemia have been reported.

Sodium Bicarbonate

Metabolic alkalosis, seizures, and tetany.

The following adverse reactions have been identified during post-approval use of omeprazole and sodium bicarbonate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Omeprazole

Body as a Whole: Hypersensitivity reactions, including anaphylaxis, anaphylactic shock, angioedema, bronchospasm, urticaria (see also *Skin* below), fever, pain, fatigue, malaise, and systemic lupus erythematosus.

Cardiovascular: Chest pain or angina, tachycardia, bradycardia, palpitation,

elevated blood pressure, and peripheral edema.

Gastrointestinal: Pancreatitis, 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. 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, hepatic failure, and hepatic encephalopathy.

Infections and Infestations: Clostridium difficile-associated diarrhea.

Metabolism and Nutritional Disorders: Hypomagnesemia, hypocalcemia, hypokalemia, hyponatremia, hypoglycemia, 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 TEN, SJS, DRESS, AGEP, 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: Tubulointerstitial nephritis, urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, hematuria, glycosuria, testicular pain, gynecomastia, and erectile dysfunction

Hematologic: Rare instances of pancytopenia, agranulocytosis, thrombocytopenia, neutropenia, leukopenia, anemia, leukocytosis, and

hemolytic anemia have been reported.

Sodium Bicarbonate

Metabolic alkalosis, seizures, and tetany.

'Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org'

4.9. Overdose

Omeprazole
Reports have been received of overdosage with omeprazole in humans. Doses ranged up to 2,400mg (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 clinical experience with the recommended dosage. 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.

Sodium Bicarbonate
Overdosage of sodium bicarbonate can cause electrolyte abnormalities (hypocalcemia, hypokalemia, hypernatremia), metabolic alkalosis, and seizures. Institute supportive care and correct electrolyte abnormalities.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Omeprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, 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.

5.2. Pharmacokinetic properties

Absorption
Following single or repeated once-daily dosing, peak plasma concentrations (Cmax) of omeprazole from Omeprazole + Sodium bicarbonate Powder for Oral Suspension were approximately proportional from 20 to 40mg doses. A greater than dose proportional increase in mean steady-state AUC was observed when

doubling the dose to 40mg. The bioavailability of omeprazole from Omeprazole + Sodium bicarbonate Powder for Oral Suspension increases upon repeated administration. The percent changes in C_{max} and AUC between steady-state and single dose indicate omeprazole is a time-dependent auto inhibitor of CYP2C19. When Omeprazole + Sodium bicarbonate Powder for Oral Suspension 40mg 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 T_{max} was approximately 30 minutes for both Dose 1 and Dose 2.
When Omeprazole + Sodium bicarbonate Powder for Oral Suspension 40 mg is administered one hour after a meal, the omeprazole AUC is reduced by approximately 27% and 22%, respectively, relative to administration one hour prior to a meal.

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

Elimination
Metabolism
Omeprazole is extensively metabolized by the cytochrome P450 (CYP) enzyme system. The major part of its metabolism is dependent on the polymorphically expressed CYP2C19, responsible for the formation of hydroxyomeprazole, the major metabolite in plasma. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone.
The mean plasma omeprazole half-life following administration of Omeprazole + Sodium bicarbonate Powder for Oral Suspension in healthy subjects is approximately 1 hour (range 0.4 to 4.2 hours), and the total body clearance is 500 to 600 mL/min.

Excretion
Following single-dose oral administration of a buffered solution 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.

<u>Specific Populations</u>
Geriatric Patients
The elimination rate of omeprazole was somewhat decreased in the elderly, and bioavailability was increased.
Omeprazole was 76% bioavailable when a single 40mg oral dose 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 m^2), 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.

5.3. Preclinical safety data

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44 and 140.8mg/kg/day (approximately 0.4 to 34.2 times the human dose of 40mg/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 13.8mg omeprazole/kg/day (approximately 3.36 times the human dose of 40mg/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 16mg/kg/day (about 0.1 to 3.9 times the human dose of 40mg/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 140.8mg/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 vivo bone 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 138mg/kg/day (about 33.6 times the human dose of 40mg/day on a body surface area basis) was found to have no effect on the fertility and general reproductive performance in rats.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

- Mannitol
- Xanthan Gum
- Mint Flavor
- Sucralose

6.2. Incompatibilities

None

6.3. Shelf-life

3 years
The expiration date refers to the product correctly stored at the required conditions.

6.4. Special precautions for storage

- Store at 25°C. (Excursions permitted to 15°C - 30°C).
- Protect from sunlight and moisture.
- Keep out of the reach of children.

6.5. Nature and contents of container

Risek Insta (Omeprazole + Sodium bicarbonate) 40mg+1680mg powder for oral suspension is available as Aluminum foil sachet pack of 10's packed in a printed unit carton along with a package insert.

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESS

Getz Pharma (Private) Limited
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8. MARKETING AUTHORIZATION NUMBER

H2014/CTD1400/054/R1

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

2025 September 26

10. DATE OF REVISION OF THE TEXT

2025 September 26