KONVOMEP- omeprazole and sodium bicarbonate
Azurity Pharmaceuticals, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KONVOMEPsafely and effectively. See full prescribing information for KONVOMEP.

KONVOMEP ®(omeprazole and sodium bicarbonate for oral suspension)
Initial U.S. Approval: 2004

INDICATIONS AND USAGE

KONVOMEP is a combination of omeprazole, a proton pump inhibitor (PPI) and sodium bicarbonate, indicated in adults for:
•Treatment of active benign gastric ulcer (1)
•Reduction of risk of upper gastrointestinal (GI) bleeding in critically ill patients (1)

DOSAGE AND ADMINISTRATION

Recommended doses of KONVOMEP in the table below are based upon the omeprazole content. (2.2)

Indication	Recommended Adult Dosage (2.2)
Active Benign Gastric Ulcer	40 mg once daily for 4 to 8 weeks
Reduction of Risk of Upper GI Bleeding in Critically Ill Patients	40 mg initially followed by 40 mg 6 to 8 hours later and 40 mg once daily thereafter for 14 days

DOSAGE FORMS AND STRENGTHS

For Oral Suspension: 2 mg omeprazole and 84 mg sodium bicarbonate per mL after reconstitution in 90 mL, 150 mL, or 300 mL bottles. (3)

CONTRAINDICATIONS

- Known hypersensitivity to any components of the formulation (4)
- Patients receiving rilpivirine-containing products (4, 7)

WARNINGS AND PRECAUTIONS

- Gastric Malignancy: In adults, symptomatic response does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing. (5.1)
- Acute Tubulointerstitial Nephritis: Discontinue treatment and evaluate patients. (5.2)
- Sodium Content: Take sodium content into consideration in patients on a sodium-restricted diet. Avoid in patients with Bartter's syndrome, hypokalemia, hypocalcemia, and problems with acid-base balance. (5.3)
- *Clostridium difficile*-Associated Diarrhea : PPI therapy may be associated with increased risk. (5.4)
- Bone Fracture: Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. (5.5)
- Severe Cutaneous Adverse Reactions: Discontinue at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation. (5.6)
- Cutaneous and Systemic Lupus Erythematosus: Mostly cutaneous; new onset or exacerbation of existing disease; discontinue KONVOMEP and refer to specialist for evaluation. (5.7)
- Interaction with Clopidogrel: Avoid concomitant use of KONVOMEP. (5.8)
- Cyanocobalamin (Vitamin B-12) Deficiency: Daily long-term use (e.g., longer than 3 years) may lead to malabsorption or a deficiency of cyanocobalamin. (5.9)
- Hypomagnesemia and Mineral Metabolism: Reported rarely with prolonged treatment with PPIs. (5.10)
- Interaction with St. John's Wort or Rifampin: Avoid concomitant use of KONVOMEP. (5.11, 7)
- Interactions with Diagnostic Investigations for Neuroendocrine Tumors: Increased Chromogranin A (CgA) levels may interfere with diagnostic investigations for neuroendocrine tumors; temporarily stop KONVOMEP at least 14 days before assessing CgA levels. (5.12)
- Interaction with Methotrexate: Concomitant use with PPIs may elevate and/or prolong serum concentrations of methotrexate and/or its metabolite, possibly leading to toxicity. With high dose methotrexate administration, consider a temporary withdrawal of KONVOMEP. (5.13, 7)
- Fundic Gland Polyps: Risk increases with long-term use, especially beyond one year. Use the shortest

duration of therapy. (5.14)

ADVERSE REACTIONS

Most common adverse reactions (≥2%) are: headache, abdominal pain, nausea, diarrhea, vomiting, and flatulence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contactAzurity Pharmaceuticals, Inc. at 1-800-461-7449or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

See Full Prescribing Information for a list of clinically important drug interactions. (7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 4/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

KONVOMEP is indicated in adults for:

- short-term treatment (4 to 8 weeks) of active benign gastric ulcer.
- reduction of risk of upper gastrointestinal (GI) bleeding in critically ill adult patients.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

•KONVOMEP is a kit of two bottles: one bottle containing omeprazole powder and one bottle of diluent containing sodium bicarbonate.

•KONVOMEP is for reconstitution by a healthcare provider for use in adults.

•After reconstitution, each mL of KONVOMEP contains 2 mg of omeprazole and 84 mg of sodium bicarbonate.

•Take the sodium content of KONVOMEP into consideration when prescribing this product *[see Warnings and Precautions (5.3)]* .

•Recommended doses throughout the labeling are based upon the omeprazole component of KONVOMEP.

2.2 Dosage Regimen

The recommended dosage regimen in adults of KONVOMEP by indication is summarized in Table 1. Recommended dosage is based upon the omeprazole content of KONVOMEP.

Table 1: Recommended Dosage Regimen of KONVOMEP for Adults by Indication

Indication	**Recommended Dosage**	**Treatment Duration**

Treatment of Benign Gastric Ulcer	40 mg once daily	4 to 8 weeks
Reduction of Risk of Upper GI Bleeding in Critically Ill Patients	40 mg initially; followed by 40 mg 6 to 8 hours later; and 40 mg once daily thereafter	14 days

2.3 Preparation and Administration

Preparation of Reconstituted Suspension by a Healthcare Provider Prior to Dispensing

1.Hold the neck of the bottle containing the omeprazole powder and tap all four of the bottom edges on a hard surface to loosen the powder.2.Shake the diluent containing sodium bicarbonate for a few seconds. Open the diluent bottle and transfer about one-third of the contents into the bottle containing omeprazole powder, replace the omeprazole powder cap, and shake the bottle vertically for approximately 30 seconds.3.Add a second one-third of the diluent into the omeprazole powder bottle and shake the bottle vigorously for approximately 30 seconds.4.Add the remaining diluent into the omeprazole powder bottle. Allow diluent to drain into the omeprazole powder bottle for 10 seconds and shake the omeprazole bottle vigorously for approximately 30 seconds.5.The reconstituted suspension contains 40 mg of omeprazole per 20 mL and should be pink to red and hazy.6.Instruct the patient to shake the reconstituted suspension well before each use. Use an oral dosing device that measures the appropriate volume.

Nasogastric or Orogastric Tube Administration (8 French or larger)

If KONVOMEP is administered via nasogastric or orogastric tube, suspend enteral feeding approximately 3 hours before and 1 hour after administration of KONVOMEP.

1.Reconstitute KONVOMEP according to the steps for preparation provided above.2.Use a catheter or oral tip syringe to administer KONVOMEP through the nasogastric or orogastric tube.3.Shake the bottle well prior to dispensing 20 mL of KONVOMEP into the syringe.4.Immediately inject the medication through the nasogastric or orogastric tube into the stomach.5.Refill the syringe with 20 mL of water.6.Flush any remaining medication from the nasogastric or orogastric tube into the stomach.

Storage of Reconstituted Suspension

Store the reconstituted KONVOMEP suspension under refrigerated conditions 2°C to 8°C (36°F to 46°F) for up to 30 days.

3 DOSAGE FORMS AND STRENGTHS

For Oral Suspension: 2 mg omeprazole and 84 mg sodium bicarbonate per mL of a pink to red hazy, strawberry-flavored liquid after reconstitution in 90 mL, 150 mL, or 300 mL bottles. Each kit contains a bottle of omeprazole as a white to off-white powder and a strawberry-flavored diluent containing sodium bicarbonate as a slightly hazy red liquid *[see Description (11) and How Supplied/Storage and Handling (16)]* .

4 CONTRAINDICATIONS

KONVOMEP is contraindicated in patients with known hypersensitivity to substituted benzimidazoles or to any components of the formulation. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute tubulointerstitial nephritis, and urticaria *[see Warnings and Precautions (5.2) and Adverse Reactions (6.2)]* .

Proton pump inhibitors (PPIs), including KONVOMEP, are contraindicated in patients receiving rilpivirine containing products *[see Drug Interactions (7)]* .

5 WARNINGS AND PRECAUTIONS

5.1 Presence of Gastric Malignancy

In adults, symptomatic response to therapy with KONVOMEP 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 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, 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 KONVOMEP and evaluate patients with suspected acute TIN *[see Contraindications (4)]* .

5.3 Sodium Content

Each mL of reconstituted KONVOMEP contains 84 mg of sodium bicarbonate (equivalent to 1 mEq/mL of sodium). The total content of sodium, from active and inactive ingredients per mL of reconstituted KONVOMEP is 26.3 mg (1.14 mEq). Total sodium content per 40 mg dose (volume of 20 mL) of KONVOMEP is 526 mg (22.8 mEq).

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 KONVOMEP should be taken into consideration when administering to patients on a sodium-restricted diet or those at risk for developing congestive heart failure.

Avoid KONVOMEP in patients with Bartter’s syndrome, hypokalemia, hypocalcemia, and problems with acid-base balance.

5.4 *Clostridium difficile*-Associated Diarrhea

Published observational studies suggest that PPI therapy like KONVOMEP 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 *[see Adverse Reactions (6.2)]* .

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 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 *[see Dosage and Administration (2.2) and Adverse Reactions (6.2)]* .

5.6 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 *[see Adverse Reactions (6.2)]* . Discontinue KONVOMEP at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

5.7 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. 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 KONVOMEP, 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.

5.8 Interaction with Clopidogrel

Avoid concomitant use of KONVOMEP 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 80 mg omeprazole reduces the pharmacological activity of clopidogrel, even when administered 12 hours apart. When using KONVOMEP, consider alternative antiplatelet therapy *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]* .

5.9 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 KONVOMEP.

5.10 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 *[see Adverse Reactions (6.2)]* .

Consider monitoring magnesium and calcium levels prior to initiation of KONVOMEP 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.

5.11 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 *[see Drug Interactions (7)]* . Avoid concomitant use of KONVOMEP with St. John’s wort or rifampin.

5.12 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 KONVOMEP 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 *[see Drug Interactions (7)]* .

5.13 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 *[see Drug Interactions (7)]* .

5.14 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 PPI 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

The following serious adverse reactions are described below and elsewhere in labeling:

- Acute Tubulointerstitial Nephritis *[see Warnings and Precautions (5.2)]* .
- *Clostridium difficile*-Associated Diarrhea *[see Warnings and Precautions (5.4)]* .
- Bone Fracture *[see Warnings and Precautions (5.5)]* .
- Severe Cutaneous Adverse Reactions *[see Warnings and Precautions (5.6)]* .
- Cutaneous and Systemic Lupus Erythematosus *[see Warnings and Precautions (5.7)]* .
- Cyanocobalamin (Vitamin B-12) Deficiency *[see Warnings and Precautions (5.9)]* .
- Hypomagnesemia and Mineral Metabolism *[see Warnings and Precautions (5.10)]* .
- Fundic Gland Polyps *[see Warnings and Precautions (5.14)]* .

6.1 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 in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of KONVOMEP has been established, in part, based on oral studies of an oral delayed-release omeprazole product and another oral omeprazole and sodium bicarbonate product.

Clinical Trials with Omeprazole

In the U.S. clinical trial population of 465 adult patients, the adverse reactions summarized in Table 2were reported to occur in 1% or more of patients on therapy with omeprazole.

Table 2: Adverse Reactions Occurring in 1% or More of Adult Patients in US Clinical Trials of Omeprazole Therapy

	Omeprazole % (n = 465)	**Placebo % (n = 64)**	**Ranitidine % (n = 195)**

Headache	7	6	8
Diarrhea	3	3	2
Abdominal Pain	2	3	3
Nausea	2	3	4
Upper Respiratory Infection (URI)	2	2	3
Dizziness	2	0	3
Vomiting	2	5	2
Rash	2	0	0
Constipation	1	0	0
Cough	1	0	2
Asthenia	1	2	2
Back Pain	1	0	1

Table 3summarizes the adverse reactions that occurred in 1% or more of omeprazole-treated patients from international double-blind and open-label clinical trials in which 2631 patients and subjects received omeprazole.

Table 3: Adverse Reactions Occurring in 1% or More of Adult Patients in International Clinical Trials of Omeprazole Therapy

	Omeprazole % (n = 2631)	**Placebo % (n = 120)**
Abdominal Pain	5.2	3.3
Nausea	4.0	6.7
Diarrhea	3.7	2.5
Vomiting	3.2	10.0
Headache	2.9	2.5
Flatulence	2.7	5.8
Acid Regurgitation	1.9	3.3
Constipation	1.5	0.8
Asthenia	1.3	0.8

Clinical Trial of Another Omeprazole and Sodium Bicarbonate Product, 40 mg

Adverse reactions reported in at least 3% of critically ill adult patients in a clinical trial of 40 mg omeprazole and sodium bicarbonate for oral suspension compared to intravenous cimetidine for up to 14 days are presented in Table 4.

Table 4: Common Adverse Reactions [*] by Body System and Preferred Term in a Randomized Controlled Trial of Critically Ill Adult Patients Treated up to 14 Days

Body System **Preferred Term**	**Omeprazole and Sodium Bicarbonate for Oral Suspension, 40 mg (%) (n = 178)**	**Intravenous Cimetidine 1,200 mg per day (%) (n = 181)**
Blood and Lymphatic System Disorders		
Anemia NOS	7.9	7.7
Anemia NOS Aggravated	2.2	3.9
Thrombocytopenia	10.1	6.1
Cardiac Disorders		
Atrial Fibrillation	6.2	3.9
Bradycardia NOS	3.9	2.8
Supraventricular Tachycardia	3.4	1.1
Tachycardia NOS	3.4	3.3
Ventricular Tachycardia	4.5	3.3
Gastrointestinal Disorders [†]		
Constipation	4.5	4.4
Diarrhea NOS	3.9	8.3
Gastric Hypomotility	1.7	3.3
General Disorders and Administration Site Conditions		
Hyperpyrexia	4.5	1.7
Edema NOS	2.8	6.1
Pyrexia	20.2	16.0
Infections and Infestations		
Candidal Infection NOS	1.7	3.9
Oral Candidiasis	3.9	0.6
Sepsis NOS	5.1	5.0
Urinary Tract Infection	2.2	3.3
Investigations		
Liver Function Tests NOS Abnormal	1.7	3.3
Metabolism and Nutrition Disorders		
Fluid Overload	5.1	7.7

Hyperglycemia NOS	10.7	11.6
Hyperkalemia	2.2	3.3
Hypernatremia	1.7	5.0
Hypocalcemia	6.2	5.5
Hypoglycemia NOS	3.4	4.4
Hypokalemia	12.4	13.3
Hypomagnesemia	10.1	9.9
Hyponatremia	3.9	2.8
Hypophosphatemia	6.2	3.9
Psychiatric Disorders		
Agitation	3.4	8.8
Respiratory, Thoracic, and Mediastinal Disorders		
Acute Respiratory Distress Syndrome	3.4	3.9
Nosocomial Pneumonia	11.2	9.4
Pneumothorax NOS	0.6	4.4
Respiratory Failure	1.7	3.3
Skin and Subcutaneous Tissue Disorders		
Decubitus Ulcer	3.4	2.8
Rash NOS	5.6	6.1
Vascular Disorders		
Hypertension NOS	7.9	3.3
Hypotension NOS	9.6	6.6

NOS = Not otherwise specified.

* Reported in at least 3% of patients in either treatment group.
† In this trial, clinically significant upper gastrointestinal bleeding was considered a serious adverse reaction, but it is not included in this table.

6.2 Postmarketing Experience

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 (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. 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), ɣ-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:*Hypomagnesemia, hypocalcemia, hypokalemia, *[see Warnings and Precautions (5.10)]* , 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 (some fatal), 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 (some fatal), thrombocytopenia, neutropenia, leukopenia, anemia, leukocytosis, and hemolytic anemia have been reported.

Sodium Bicarbonate

Metabolic alkalosis, seizures, and tetany.

7 DRUG INTERACTIONS

Table 5and Table 6include drugs with clinically important drug interactions and interaction with diagnostics when administered concomitantly with omeprazole and instructions for preventing or managing them.

Consult the labeling of concomitantly used drugs to obtain further information about interactions with PPIs.

Table 5: Clinically Relevant Interactions Affecting Drugs Co-Administered with Omeprazole and Interaction with Diagnostics

Antiretrovirals	
Clinical Impact:	The effect of PPIs on antiretroviral drugs is variable. The clinical importance and the mechanisms behind these interactions are not always known. • Decreased exposure of some antiretroviral drugs (e.g., rilpivirine, atazanavir and nelfinavir) when used concomitantly with omeprazole may reduce antiviral effect and promote the development of drug resistance *[see Clinical Pharmacology (12.3)]* . • Increased exposure of other antiretroviral drugs (e.g., saquinavir) when used concomitantly with omeprazole may increase toxicity *[see Clinical Pharmacology (12.3)]* . • There are other antiretroviral drugs which do not result in clinically relevant interactions with omeprazole.
Intervention:	Rilpivirine-containing products: Concomitant use with KONVOMEP is contraindicated *[see Contraindications (4)]* . Atazanavir: Avoid concomitant use with KONVOMEP. See prescribing information for atazanavir for dosing information. Nelfinavir: Avoid concomitant use with KONVOMEP. See prescribing information for nelfinavir. Saquinavir: See the prescribing information for saquinavir for monitoring of potential saquinavir-related toxicities. Other antiretrovirals: See prescribing information for specific antiretroviral drugs.
Warfarin	
Clinical Impact:	Increased INR and prothrombin time in patients receiving PPIs, including omeprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death.
Intervention:	Monitor INR and prothrombin time and adjust the dose of warfarin, if needed, to maintain target INR range.
Methotrexate	
Clinical Impact:	Concomitant use of omeprazole with methotrexate (primarily at high dose) may elevate and prolong serum concentrations of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities. No formal drug interaction studies of high-dose methotrexate with PPIs have been conducted *[see Warnings and Precautions (5.13)]* .
Intervention:	A temporary withdrawal of KONVOMEP may be considered in some patients receiving high-dose methotrexate.

CYP2C19 Substrates (e.g., clopidogrel, citalopram, cilostazol, phenytoin, diazepam)	
Clopidogrel	
Clinical Impact:	Concomitant use of omeprazole 80 mg results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition *[see Clinical Pharmacology (12.3)]* .
	There are no adequate combination studies of a lower dose of omeprazole or a higher dose of clopidogrel in comparison with the approved dose of clopidogrel.
Intervention:	Avoid concomitant use with KONVOMEP. Consider use of alternative anti-platelet therapy *[see Warnings and Precautions (5.8)]* .
Citalopram	
Clinical Impact:	Increased exposure of citalopram leading to an increased risk of QT prolongation *[see Clinical Pharmacology (12.3)]* .
Intervention:	Limit the dose of citalopram to a maximum of 20 mg per day. See prescribing information for citalopram.
Cilostazol	
Clinical Impact:	Increased exposure of one of the active metabolites of cilostazol (3,4-dihydro-cilostazol) *[see Clinical Pharmacology (12.3)]* .
Intervention:	Reduce the dose of cilostazol to 50 mg twice daily. See prescribing information for cilostazol.
Phenytoin	
Clinical Impact:	Potential for increased exposure of phenytoin.
Intervention:	Monitor phenytoin serum concentrations. Dose adjustment may be needed to maintain therapeutic drug concentrations. See prescribing information for phenytoin.
Diazepam	
Clinical Impact:	Increased exposure of diazepam *[see Clinical Pharmacology (12.3)]* .
Intervention:	Monitor patients for increased sedation and reduce the dose of diazepam as needed.
Digoxin	
Clinical Impact:	Potential for increased exposure of digoxin *[see Clinical Pharmacology (12.3)]* .
Intervention:	Monitor digoxin concentrations. Dose adjustment may be needed to maintain therapeutic drug concentrations. See digoxin prescribing information.
Drugs Dependent on Gastric pH for Absorption (e.g., iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetil, ketoconazole/itraconazole)	
Clinical Impact:	Omeprazole can reduce the absorption of other drugs due to its effect on reducing intragastric acidity.
Intervention:	Mycophenolate mofetil (MMF): 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 KONVOMEP and MMF. Use KONVOMEP with caution in transplant patients receiving MMF *[see Clinical Pharmacology (12.3)]* . See the prescribing information for other drugs dependent on gastric pH for absorption.
Tacrolimus	
Clinical Impact:	Potential for increased exposure of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.
Intervention:	Monitor tacrolimus whole blood concentrations. Dose adjustment may be needed to maintain therapeutic drug concentrations. See prescribing information for tacrolimus.
Interactions with Investigations of Neuroendocrine Tumors	
Clinical Impact:	Serum chromogranin A (CgA) levels increase secondary to PPI-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors *[see Warnings and Precautions (5.12) and Clinical Pharmacology (12.2)]* .
Intervention:	Temporarily stop KONVOMEP treatment 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 Secretin Stimulation Test	
Clinical Impact:	Hyper-response in gastrin secretion in response to secretin stimulation test, falsely suggesting gastrinoma.
Intervention:	Temporarily stop KONVOMEP treatment at least 14 days before assessing to allow gastrin levels to return to baseline *[see Clinical Pharmacology (12.2)]* .
False Positive Urine Tests for THC	
Clinical Impact:	There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs.
Intervention:	An alternative confirmatory method should be considered to verify positive results.
Other	
Clinical Impact:	There have been clinical reports of interactions with other drugs metabolized via the cytochrome P450 system (e.g., cyclosporine, disulfiram).
Intervention:	Monitor patients to determine if it is necessary to adjust the dosage of these other drugs when taken concomitantly with KONVOMEP.

Table 6: Clinically Relevant Interactions Affecting Omeprazole when Co-Administered with Other Drugs

CYP2C19 or CYP3A4 Inducers	
Clinical Impact:	Decreased exposure of omeprazole when used concomitantly with strong inducers *[see Clinical Pharmacology (12.3)]* .
Intervention:	St. John's Wort, rifampin: Avoid concomitant use with KONVOMEP *[see Warnings and Precautions (5.11)]* . Ritonavir-containing products: see prescribing information for specific drugs.
CYP2C19 or CYP3A4 Inhibitors	
Clinical Impact:	Increased exposure of omeprazole *[see Clinical Pharmacology (12.3)]* .
Intervention:	Voriconazole: Dosage adjustment of KONVOMEP is not usually required. See full prescribing information for voriconazole.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies with KONVOMEP in pregnant women. KONVOMEP contains omeprazole and sodium bicarbonate.

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 (*see Data*). 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 40-mg omeprazole. When maternal administration was confined to gestation only, there were no effects on bone physeal morphology in the offspring at any age (*see Data*).

Sodium Bicarbonate

Available data with sodium bicarbonate use in pregnant women have not identified 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. In the U.S. general population, 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 KONVOMEP 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 H_2-receptor antagonists or other controls.

A population-based retrospective cohort epidemiological study from the Swedish Medical Birth Register, covering approximately 99% of pregnancies, from 1995 to 99, reported on 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester, and 131 exposed after the first trimester) whose mothers used omeprazole during pregnancy. The number of infants exposed *in-utero*to omeprazole that had any malformation, low birth weight, low Apgar score or hospitalization was similar to the number observed in this population. The number of infants born with ventricular septal defects and the number of stillborn infants was slightly higher in the omeprazole-exposed infants than the expected number in this population.

A population-based retrospective cohort study covering all live births in Denmark from 1996 to 2009 reported on 1,800 live births whose mothers used omeprazole during the first trimester of pregnancy and 837,317 live births whose mothers did not use any PPI. The overall rate of birth defects in infants born to mothers with first trimester exposure to omeprazole was 2.9% and 2.6% in infants born to mothers not exposed to any PPI during the first trimester.

A retrospective cohort study reported on 689 pregnant women exposed to either H_2-blockers or omeprazole in the first trimester (134 exposed to omeprazole) and 1,572 pregnant women unexposed to either during the first trimester. The overall malformation rate in offspring born to mothers with first trimester exposure to omeprazole, an H_2-blocker, or were unexposed was 3.6%, 5.5%, and 4.1%, respectively.

A small prospective observational cohort study followed 113 women exposed to omeprazole during pregnancy (89% first trimester exposures). The reported rate of major congenital malformations was 4% in the omeprazole group, 2% in controls exposed to non-teratogens, and 2.8% in disease-paired controls. Rates of spontaneous and elective abortions, preterm deliveries, gestational age at delivery, and mean birth weight were similar among the groups.

Several studies have reported no apparent adverse short-term effects on the infant when single-dose oral or intravenous omeprazole was administered to over 200 pregnant women as premedication for cesarean section under general anesthesia.

Animal Data

Omeprazole

Reproductive studies conducted with omeprazole in rats at oral doses up to 138 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis) and in rabbits at doses up to 69.1 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis) during organogenesis did not disclose any evidence for a teratogenic potential of omeprazole. In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (about 3.4 to 34 times an oral human dose of 40 mg on a body surface area basis) administered during organogenesis produced dose-related increases in embryo-lethality, fetal resorptions, and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8 to 138.0 mg/kg/day (about 3.4 to 34 times an oral human dose of 40 mg on a body surface area basis), administered prior to mating through the lactation period.

Esomeprazole

The data described below was generated from studies using esomeprazole, an enantiomer of omeprazole. The animal to human dose multiples are based on the assumption of equal systemic exposure to esomeprazole in humans following oral administration of either 40 mg esomeprazole or 40 mg omeprazole.

No effects on embryo-fetal development were observed in reproduction studies with esomeprazole magnesium in rats at oral doses up to 280 mg/kg/day (about 68 times an oral human dose of 40 mg on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 42 times an oral human dose of 40 mg of esomeprazole or 40 mg omeprazole on a body surface area basis) administered during organogenesis.

A pre- and postnatal developmental toxicity study in rats with additional endpoints to evaluate bone development were performed with esomeprazole magnesium at oral doses of 14 to 280 mg/kg/day (about 3.4 to 68 times an oral human dose of 40 mg of esomeprazole or 40 mg omeprazole on a body surface area basis). Neonatal/early postnatal (birth to weaning) survival was decreased at doses equal to or greater than 138 mg/kg/day (about 34 times an oral human dose of 40 mg esomeprazole or 40 mg omeprazole on a body surface area basis). Body weight and body weight gain were reduced and neurobehavioral or general developmental delays in the immediate post-weaning timeframe were evident at doses equal to or greater than 69 mg/kg/day (about 17 times an oral human dose of 40 mg esomeprazole or 40 mg omeprazole on a body surface area basis). In addition, decreased femur length, width and thickness of cortical bone, decreased thickness of the tibial growth plate and minimal to mild bone marrow hypocellularity were noted at doses of esomeprazole magnesium equal to or greater than 14 mg/kg/day (about 3.4 times an oral human dose of 40 mg esomeprazole or 40 mg omeprazole on a body surface area basis). Physeal dysplasia in the femur was observed in offspring of rats treated with oral doses of esomeprazole magnesium at doses equal to or greater than 138 mg/kg/day (about 34 times an oral human dose of 40 mg esomeprazole or 40 mg omeprazole on a body surface area basis).

Effects on maternal bone were observed in pregnant and lactating rats in a pre- and postnatal toxicity study when esomeprazole magnesium was administered at oral doses of 14 to 280 mg/kg/day (about 3.4 to 68 times an oral human dose of 40 mg esomeprazole or 40 mg omeprazole on a body surface area basis). When rats were dosed from gestational Day 7 through weaning on postnatal Day 21, a statistically significant decrease in maternal femur weight of up to 14% (as compared to placebo treatment) was observed at doses of esomeprazole magnesium equal to or greater than

138 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis).

A pre- and postnatal development study in rats with esomeprazole strontium (using equimolar doses compared to esomeprazole magnesium study) produced similar results in dams and pups as described above.

A follow up developmental toxicity study in rats with further time points to evaluate pup bone development from postnatal Day 2 to adulthood was performed with esomeprazole magnesium at oral doses of 280 mg/kg/day (about 68 times an oral human dose of 40 mg on a body surface area basis) where esomeprazole administration was from either gestational Day 7 or gestational Day 16 until parturition. When maternal administration was confined to gestation only, there were no effects on bone physeal morphology in the offspring at any age.

8.2 Lactation

Risk Summary

Available data from the published literature suggest both components of KONVOMEP, 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 KONVOMEP and any potential adverse effects on the breastfed infant from KONVOMEP or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of KONVOMEP have not been established in pediatric patients.

Juvenile Animal Data

Esomeprazole, an enantiomer of omeprazole, was shown to decrease body weight, body weight gain, femur weight, femur length, and overall growth at oral doses about 34 to 68 times a daily human dose of 40 mg esomeprazole or 40 mg omeprazole based on body surface area in a juvenile rat toxicity study. The animal to human dose multiples are based on the assumption of equal systemic exposure to esomeprazole in humans following oral administration of either 40 mg esomeprazole or 40 mg omeprazole.

A 28-day toxicity study with a 14-day recovery phase was conducted in juvenile rats with esomeprazole magnesium at doses of 70 to 280 mg/kg/day (about 17 to 68 times a daily oral human dose of 40 mg esomeprazole or 40 mg omeprazole on a body surface area basis). An increase in the number of deaths at the high dose of 280 mg/kg/day was observed when juvenile rats were administered esomeprazole magnesium from postnatal Day 7 through postnatal Day 35. In addition, doses equal to or greater than 140 mg/kg/day (about 34 times a daily oral human dose of 40 mg esomeprazole or 40 mg omeprazole on a body surface area basis), produced treatment-related decreases in body weight (approximately 14%) and body weight gain, decreases in femur weight and femur length, and affected overall growth. Comparable findings described above have also been observed in this study with another esomeprazole salt, esomeprazole strontium, at equimolar doses of esomeprazole.

8.5 Geriatric Use

Omeprazole was administered to over 2000 elderly individuals (65 years of age or older) 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 omeprazole. However, no dosage adjustment is necessary in the elderly *[see Clinical Pharmacology (12.3)]* .

10 OVERDOSAGE

If over-exposure occurs, call your Poison Control Center at 1-800-222-1222 for current information on the management of poisoning or overdosage.

Omeprazole

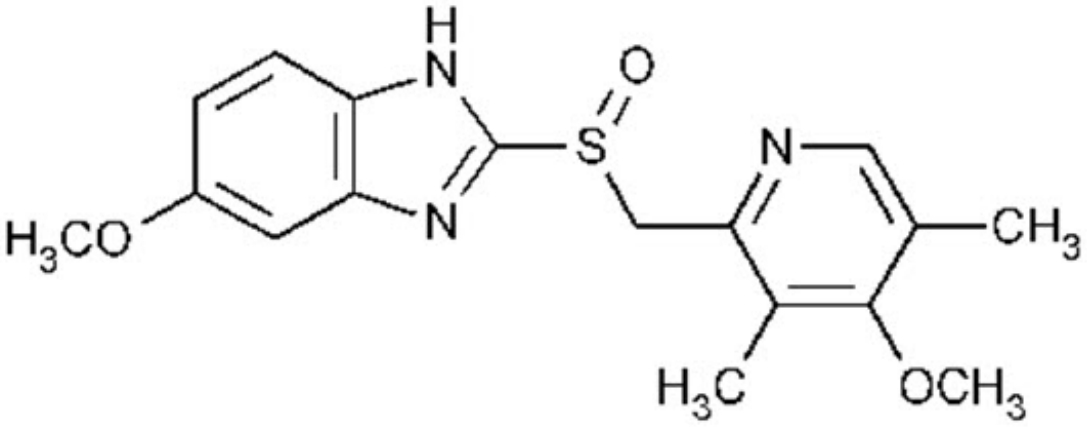
Reports have been received of overdosage with omeprazole in humans. Doses ranged up to 2400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, vomiting, diaphoresis, flushing, headache, dry mouth and other adverse reactions similar to those seen in normal clinical experience with the recommended dosage *[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 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.

11 DESCRIPTION

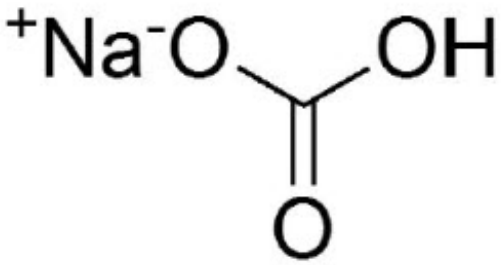
KONVOMEP (omeprazole and sodium bicarbonate for oral suspension) is a combination of omeprazole, a PPI, and sodium bicarbonate, an antacid. Omeprazole is a substituted benzimidazole, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1 *H*-benzimidazole, a racemic mixture of two enantiomers that inhibits gastric acid secretion. Its empirical formula is $C_{17}H_{19}N_3O_3S$, with a molecular weight of 345.42. The structural formula is:



Omeprazole is a white to off-white crystalline powder which melts with decomposition at about 155°C. It is a weak base, freely soluble in ethanol and methanol, slightly soluble in acetone and isopropanol and very slightly soluble in water. The stability of omeprazole is a function of pH; it is rapidly degraded in acid media but has acceptable stability under alkaline conditions. Sodium bicarbonate raises the gastric pH and protects the omeprazole from acid degradation.

Sodium bicarbonate is a white crystalline powder. It is soluble in water and insoluble in alcohol. One gram of sodium bicarbonate dissolves in 12 mL of water at 25ºC. The pH of a freshly prepared 0.1 molar aqueous solution is 8.3 at 25ºC. Aqueous solutions slowly convert to sodium carbonate through loss of carbon dioxide.

The molecular formula is $NaHCO_3$ and the molecular weight is 84.01. The structural formula is:



KONVOMEP is supplied as a kit. Each kit is comprised of 1 bottle of pre-weighed omeprazole powder and 1 bottle of pre-measured strawberry-flavored diluent to be reconstituted for oral administration. The strawberry-flavored diluent contains sodium bicarbonate and the following inactive ingredients: benzyl alcohol, carboxymethylcellulose sodium, FD&C Red No. 40, poloxamer 188, purified water, simethicone emulsion, sodium citrate (dihydrate), sorbitol solution, strawberry flavor (natural and artificial flavors, propylene glycol, and glycerin), and sucralose. After reconstitution each mL contains 2 mg omeprazole and 84 mg sodium bicarbonate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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.

12.2 Pharmacodynamics

Antisecretory Activity

Results from a pharmacokinetic/pharmacodynamic (PK/PD) study of the antisecretory effect of repeated once-daily dosing of 40 mg omeprazole and 1,680 mg sodium bicarbonate for oral suspension in healthy subjects are shown in Table 7.

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

Parameter	**Once Daily Dosage of Omeprazole and Sodium Bicarbonate**
	40 mg Omeprazole and 1680 mg Sodium Bicarbonate (n = 24)
% Decrease from Baseline for Integrated Gastric Acidity (mmol•hr/L)	84%
Coefficient of Variation	20%
% Time Gastric pH > 4 (Hours)	77% (18.6 hours)
Coefficient of Variation	27%
Median pH	5.2
Coefficient of Variation	17%
Note: Values represent medians. All parameters were measured over a 24-hour period.	

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.

Enterochromaffin-like (ECL) Cell Effects

Human gastric biopsy specimens have been obtained from more than 3000 patients treated with omeprazole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies increased with time; however, no case of ECL cell carcinoids, dysplasia,

or neoplasia has been found in these patients. These studies are of insufficient duration and size to rule out the possible influence of long-term administration of omeprazole on the development of any premalignant or malignant conditions.

Serum Gastrin Effects

In studies involving more than 200 patients, serum gastrin levels increased during the first 1 to 2 weeks of once-daily administration of therapeutic doses of omeprazole in parallel with inhibition of acid secretion. No further increase in serum gastrin occurred with continued treatment. Gastrin values returned to pretreatment levels, usually within 1 to 2 weeks after discontinuation of therapy.

Increased gastrin causes enterochromaffin-like cell hyperplasia and increased serum Chromogranin A (CgA) levels. The increased CgA levels may cause false positive results in diagnostic investigations for neuroendocrine tumors *[see Warnings and Precautions (5.12)]* .

Other Effects

Systemic effects of omeprazole in the Central Nervous System (CNS), cardiovascular, and respiratory systems have not been found to date. Omeprazole, given in oral doses of 30 or 40 mg for 2 to 4 weeks, had no effect on thyroid function, carbohydrate metabolism, or circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin or secretin.

No effect on gastric emptying of the solid and liquid components of a test meal was demonstrated after a single dose of omeprazole 90 mg. In healthy subjects, a single intravenous dose of omeprazole (0.35 mg/kg) had no effect on intrinsic factor secretion. No systematic dose-dependent effect has been observed on basal or stimulated pepsin output in humans. However, when intragastric pH is maintained at 4.0 or above, basal pepsin output is low, and pepsin activity is decreased.

As do other agents that elevate intragastric pH, omeprazole administered for 14 days in healthy subjects produced a significant increase in the intragastric concentrations of viable bacteria. The pattern of the bacterial species was unchanged from that commonly found in saliva. All changes resolved within three days of stopping treatment.

The course of Barrett’s esophagus in 106 patients was evaluated in a U.S. double-blind controlled study of omeprazole 40 mg twice daily for 12 months followed by 20 mg twice daily for 12 months or ranitidine 300 mg twice daily for 24 months. No clinically significant impact on Barrett’s mucosa by antisecretory therapy was observed. Although neosquamous epithelium developed during antisecretory therapy, complete elimination of Barrett’s mucosa was not achieved. No significant difference was observed between treatment groups in development of dysplasia in Barrett’s mucosa, and no patient developed esophageal carcinoma during treatment. No significant differences between treatment groups were observed in development of ECL cell hyperplasia, corpus atrophic gastritis, corpus intestinal metaplasia, or colon polyps exceeding 3 mm in diameter.

12.3 Pharmacokinetics

Absorption

The bioavailability and pharmacokinetics of KONVOMEP was assessed in 57 healthy male and female volunteers following a 40 mg dose under fasted conditions. The absorption

of omeprazole was rapid with a median time to peak plasma concentration of 0.33 hour (range 0.17 to 1.3 hr.). The mean peak plasma concentration (SD) was 1250 ng/mL (470) and the AUC $_{(0\text{-inf})}$(SD) was 1640 h*ng/mL (1050).

Omeprazole is a time-dependent autoinhibitor of CYP2C19. The bioavailability of omeprazole from omeprazole and sodium bicarbonate for oral suspension increases upon repeated administration.

Following repeated once-daily dosing of omeprazole at a dose of 40 mg with sodium bicarbonate, a higher omeprazole mean C $_{max}$(1.4-fold on Day 7) and increased AUC (2-fold on Day 7) were observed. The increase in mean steady-state AUC (on Day 7) for omeprazole at a dose of 40 mg was greater than dose proportional relative to a lower dose.

When omeprazole and sodium bicarbonate for oral suspension 40 mg was administered in a two-dose loading regimen, the omeprazole AUC $_{0\text{-inf}}$(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 and sodium bicarbonate 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 *[see Dosage and Administration (2.3)]* .

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 *[see Clinical Pharmacology (12.5)]* , 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 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.

Special 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.

Racial or Ethnic Groups

[see Clinical Pharmacology (12.5)] .

Patients with Renal Impairment

In patients with chronic renal impairment (creatinine clearance ranged 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 mean half-life of 0.5 to 1 hour in healthy subjects. 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 *[see Drug Interactions (7)]* .

Antiretrovirals

For some antiretroviral drugs, such as rilpivirine, atazanavir and nelfinavir, decreased serum concentrations have been reported when given together with omeprazole *[see Drug Interactions (7)]* .

*Rilpivirine:*Following multiple doses of rilpivirine (150 mg, daily) and omeprazole (20 mg, daily), AUC was decreased by 40%, $C_{max}$by 40%, and $C_{min}$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%, $C_{max}$by 37% and 89% and $C_{min}$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%, $C_{max}$by 96%, and $C_{min}$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%, $C_{max}$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 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 *[see Warnings and Precautions (5.8), Drug Interactions (7)]* .

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 $C_{max}$and 23% reduction in the AUC of MPA *[see Drug Interactions (7)]* .

Cilostazol

Omeprazole acts as an inhibitor of CYP2C19. Omeprazole, given in doses of 40 mg daily for one week to 20 healthy subjects in cross-over 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 *[see Drug Interactions (7)]* .

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 *[see Drug Interactions (7)]* .

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) *[see Drug Interactions (7)]* .

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 C_{max} and AUC_{0-24} 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 *[see Drug Interactions (7)]* .

12.5 Pharmacogenomics

CYP2C19, a polymorphic enzyme, is involved in the metabolism of omeprazole. The CYP2C19*1 allele is fully functional while the CYP2C19*2 and *3 alleles are nonfunctional. There are other alleles associated with no or reduced enzymatic function. Patients carrying two fully functional alleles are extensive metabolizers and those carrying two loss-of-function alleles are poor metabolizers. In extensive metabolizers, omeprazole is primarily metabolized by CYP2C19. The systemic exposure to omeprazole varies with a patient's metabolism status: poor metabolizers > intermediate metabolizers > extensive metabolizers. Approximately 3% of Caucasians and 15 to 20% of Asians are CYP2C19 poor metabolizers.

In pharmacokinetic studies of single 20 mg omeprazole dose, the AUC of omeprazole in Asian subjects was approximately four-fold of that in Caucasians.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 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 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 proton pump inhibitors or high doses of H_2-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.

14 CLINICAL STUDIES

14.1 Active Benign Gastric Ulcer

The effectiveness of KONVOMEP has been established, in part, based on studies of an oral delayed-release omeprazole product for the treatment of active benign gastric ulcer.

In a U.S. multicenter, double-blind study of two doses of omeprazole and placebo in 520 patients with endoscopically diagnosed gastric ulcer, the following results were obtained with 40 mg omeprazole and placebo. (see Table 8.)

Table 8: Treatment of Gastric Ulcer % of Patients Healed

	% of Patients Healed	
	Omeprazole 40 mg once daily (n = 214)	**Placebo (n = 104)**
Week 4	55.6 *	30.8
Week 8	82.7 *	48.1

* $p < 0.01$ omeprazole 40 mg versus placebo

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 the lower omeprazole dosage was detected at either 4 or 8 weeks. For patients with ulcer size greater than 1 cm, 40 mg omeprazole was significantly more effective than the lower omeprazole dosage at 8 weeks.

In a foreign, multinational, double-blind study of 602 patients with endoscopically diagnosed gastric ulcer, two doses of omeprazole and ranitidine 150 mg twice a day were evaluated. The following results were obtained with 40 mg omeprazole and ranitidine (see Table 9).

Table 9: Treatment of Gastric Ulcer % of Patients Healed

	% of Patients Healed	
	Omeprazole 40 mg once daily (n = 187)	**Ranitidine 150 mg twice daily (n = 199)**
Week 4	78.1 *	56.3
Week 8	91.4 *	78.4

* $p < 0.01$ omeprazole 40 mg versus ranitidine

14.2 Reduction of Risk of Upper Gastrointestinal Bleeding in Critically Ill Patients

The effectiveness of KONVOMEP has been established, in part, based on studies of another omeprazole and sodium bicarbonate oral suspension product for the reduction of risk of upper GI bleeding in critically ill adult patients.

A double-blind, multicenter, randomized, non-inferiority clinical trial was conducted to compare omeprazole and sodium bicarbonate oral suspension 40 mg/1680 mg 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 minutes lavage, or persistent Gastroccult positive coffee grounds for 8 consecutive hours which did not clear with 100 mL lavage. Omeprazole and sodium bicarbonate oral suspension was administered as two doses of 40 mg omeprazole and 1680 mg sodium bicarbonate 6 to 8 hours apart on the first day via orogastric or nasogastric tube, followed by 40 mg omeprazole and 1680 mg sodium bicarbonate once daily thereafter. Cimetidine was administered intravenously as a 300 mg bolus, followed by 50 to 100 mg/hour continuously thereafter. Treatment was administered for up to 14 days (mean = 6.8 days). A total of 359 patients were studied, age range 16 to 91 years (mean age of 56 years), 58.5% were males, and 64% were Caucasians. The results of the study showed that omeprazole and sodium bicarbonate oral suspension was non-inferior to intravenous cimetidine, 7/178 (3.9%) patients in the omeprazole and sodium bicarbonate oral suspension group vs. 10/181 (5.5%) patients in the cimetidine group experienced clinically significant upper GI bleeding.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

KONVOMEP (omeprazole and sodium bicarbonate for oral suspension) 2 mg/84 mg per mL is supplied as:

A kit containing two bottles:
- one bottle with child resistant closure of omeprazole USP, a white to off-white powder and
- one bottle of pre-measured strawberry-flavored slightly hazy red diluent containing sodium bicarbonate (see table below).

Prior to dispensing, reconstitute KONVOMEP for oral suspension *[see Dosage and Administration (2.3)]* .

Final Volume of KONVOMEP after reconstitution	**Kit Contents**	**NDC Numbers**
90 mL	Bottle of 0.18 g omeprazole powder	65628-270-03
	Bottle of diluent containing sodium bicarbonate 7.56 g per 90 mL	65628-271-03
	Konvomep Kit	65628-272-03
150 mL	Bottle of 0.3 g omeprazole powder	65628-270-05
	Bottle of diluent containing sodium bicarbonate 12.6 g per 150 mL	65628-271-05
	Konvomep Kit	65628-272-05
300 mL	Bottle of 0.6 g omeprazole powder	65628-270-10
	Bottle of diluent containing sodium bicarbonate 25.2 g per 300 mL	65628-271-10
	Konvomep Kit	65628-272-10

Storage
- Store KONVOMEP kit in the refrigerator, 2°C to 8°C (36°F to 46°F).
- Store reconstituted suspension of KONVOMEP in the refrigerator, 2°C to 8°C (36°F to 46°F); discard unused reconstituted suspension after 30 days.
- Keep containers tightly closed.
- Protect containers from light.
- Protect containers from freezing.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Acute Tubulointerstitial Nephritis

Advise the patient to call their healthcare provider immediately if they experience signs

and/or symptoms associated with acute tubulointerstitial nephritis *[see Warnings and Precautions (5.2)]* .

Sodium Bicarbonate Buffer Content

Inform patients on a sodium-restricted diet or patients at risk of developing congestive heart failure of the sodium content of KONVOMEP (526 mg or 22.8 mEq total sodium per 40 mg dose).

Advise patients that:

- chronic use of bicarbonate with calcium or milk can cause milk-alkali syndrome
- chronic use of sodium bicarbonate may cause systemic alkalosis
- increased sodium intake can cause swelling and weight gain

If any of these occur, instruct patients to contact their healthcare provider *[see Warnings and Precautions (5.3)]* .

Clostridium difficile-Associated Diarrhea

Advise the patient to immediately call their healthcare provider if they experience diarrhea that does not improve *[see Warnings and Precautions (5.4)]* .

Bone Fracture

Advise the patient to report any fractures, especially of the hip, wrist, or spine, to their healthcare provider *[see Warnings and Precautions (5.5)]* .

Severe Cutaneous Adverse Reactions

Advise the patient to immediately call their healthcare provider for any new or worsening of symptoms associated with cutaneous or systemic lupus erythematosus *[see Warnings and Precautions (5.6)]* .

Cutaneous and Systemic Lupus Erythematosus

Advise the patient to immediately call their healthcare provider for any new or worsening of symptoms associated with cutaneous or systemic lupus erythematosus *[see Warnings and Precautions (5.7)]* .

Cyanocobalamin (Vitamin B-12) Deficiency

Advise the patient to report any clinical symptoms that may be associated with cyanocobalamin deficiency to their healthcare provider if they have been receiving KONVOMEP for longer than 3 years *[see Warnings and Precautions (5.9)]* .

Hypomagnesemia and Mineral Metabolism

Advise the patient to report any clinical symptoms that may be associated with hypomagnesemia, hypocalcemia, and/or hypokalemia to their healthcare provider, if they have been receiving KONVOMEP for at least 3 months *[see Warnings and Precautions (5.10)]* .

Drug Interactions

Advise patients to report to their healthcare provider if they start treatment with rilpivirine-containing products, clopidogrel, St. John’s wort or rifampin, or if they take high-dose methotrexate *[see Contraindications (4) and Warnings and Precautions (5.8, 5.11and 5.13)]* .

Administration

- Instruct the patient or caregiver to shake the reconstituted suspension well before each use.
- Advise patients that KONVOMEP may be administered orally, or via a nasogastric or orogastric tube.
- Instruct patients or caregivers to suspend enteral feeding approximately 3 hours before and 1 hour after administration of KONVOMEP by nasogastric or orogastric tube *[see Dosage and Administration (2.3)]* .

Store reconstituted KONVOMEP suspension in the refrigerator. Discard the reconstituted KONVOMEP suspension after 30 days.

KONVOMEP is a registered trademark of Azurity Pharmaceuticals, Inc.

Manufactured for:
Azurity Pharmaceuticals, Inc.
Woburn, MA 01801 USA

Patent: https://azurity.com/patents

This product's labeling may have been updated. For current Full Prescribing Information, please visit *www.konvomep.com*

PN: 65628-0288

Rev: 04 04/2024

Medication Guide

MEDICATION GUIDE
KONVOMEP ®(Kan-vo-mep)
(omeprazole and sodium bicarbonate for oral suspension)

What is the most important information I should know about KONVOMEP?
KONVOMEP may help your acid-related symptoms, but you could still have serious stomach problems. Talk with your doctor.
KONVOMEP can cause serious side effects, including:

- **A type of kidney problem (acute tubulointerstitial nephritis).**Some people who take proton pump inhibitor (PPI) medicines, including KONVOMEP, may develop a kidney problem called acute tubulointerstitial nephritis that can happen at any time during treatment with KONVOMEP. Call your doctor right away if you have a decrease in the amount that you urinate or if you have blood in your urine.
- **KONVOMEP contains sodium bicarbonate.**Long-term use of bicarbonate with calcium or milk can cause a condition called "milk-alkali syndrome". Long-term use of sodium bicarbonate can cause a condition called "systemic alkalosis". Talk to your doctor about any questions you may have. Too much sodium can cause swelling and weight gain. Tell your doctor if you are on a low-sodium diet or if you have Bartter's Syndrome (a rare kidney disorder). Tell your doctor right away if you have confusion, shaking hands, dizziness, muscle twitching, nausea, vomiting, and numbness or tingling in the face, arms, or legs.
- **Diarrhea caused by an infection (*Clostridium difficile*) in your intestines.**

Call your doctor right away if you have watery stools or stomach pain that does not go away. You may or may not have a fever.

- **Bone fractures (hip, wrist, or spine).**Bone fractures in the hip, wrist or spine may happen in people who take multiple daily doses of PPI medicines and for a long period of time (a year or longer). Tell your doctor if you have bone fracture, especially in the hip, wrist, or spine.
- **Certain types of lupus erythematosus.**Lupus erythematosus is an autoimmune disorder (the body's immune cells attack other cells or organs in the body). Some people who take PPI medicines, including KONVOMEP, may develop certain types of lupus erythematosus or have worsening of the lupus they already have. Call your doctor right away if you have new or worsening joint pain or a rash on your cheeks or arms that gets worse in the sun.

Talk to your doctor about your risk of these serious side effects.
KONVOMEP can have other serious side effects. See **"What are the possible side effects of KONVOMEP?"**

What is KONVOMEP?
KONVOMEP is a combination of omeprazole, a proton pump inhibitor (PPI) and sodium bicarbonate.
KONVOMEPis used:

- in adults for up to 8 weeks for the healing of stomach ulcers.
- in critically ill adults to lower the risk of stomach bleeding.

It is not known if KONVOMEP is safe and effective in children.

Do not take KONVOMEP if you are:

- allergic to omeprazole, any other PPI medicine, or any of the ingredients in KONVOMEP. See the end of this Medication Guide for a complete list of ingredients in KONVOMEP.
- taking a medicine that contains rilpivirine, used to treat HIV-1 (Human Immunodeficiency Virus).

Before taking KONVOMEP, tell your doctor about all of your medical conditions, including if you:

- have low magnesium, calcium, or potassium levels in your blood.
- have problems with the acid-base (pH) balance in your body.
- have heart failure.
- are on a low-sodium diet.
- have Bartter's syndrome (a rare kidney problem).
- are pregnant or plan to become pregnant. It is not known if KONVOMEP will harm your unborn baby.
- are breastfeeding or plan to breastfeed. KONVOMEP can pass into your breast milk. Talk with your doctor about the best way to feed your baby if you take KONVOMEP.

Tell your doctor about all the medicines you take,including prescription and over-the counter medications, vitamins and herbal supplements.
Especially tell your doctor if you take:

- digoxin
- clopidogrel
- St. John's wort (*Hypericum perforatum*)

- rifampin
- methotrexate

Ask your doctor or pharmacist for a list of these medicines, if you are not sure. Know the medicines that you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take KONVOMEP?

- Take KONVOMEP exactly as prescribed by your doctor.
- KONVOMEP is mixed (reconstituted) by a healthcare provider, and you will receive KONVOMEP as an oral suspension that can be taken by mouth or given through a nasogastric or orogastric tube.
- Shake the KONVOMEP oral suspension well before each use.
- Measure the KONVOMEP oral suspension with an accurate measuring device. Ask your pharmacist to recommend a measuring device and for instructions on how to measure the correct dose.
- If KONVOMEP is given through a nasogastric or orogastric tube, it is important to stop enteral feeding at least **3 hours before**giving KONVOMEP. You can start enteral feeding again at least **1 hour after**giving KONVOMEP.
- Do not change your dose or stop taking KONVOMEP without talking to your doctor.
- If you miss a dose of KONVOMEP, take it as soon as you remember. If it is almost time for your next dose, do not take the missed dose. Take the next dose at your regular time. Do not take two doses to make up for a missed dose.
- If you take too much KONVOMEP, call your doctor or Poison Control Center at 1-800-222-1222 right away, or go to the nearest hospital emergency room.

What are the possible side effects of KONVOMEP?
KONVOMEP may cause serious side effects, including:

- See **“What is the most important information I should know about KONVOMEP?”**
- **Low vitamin B-12 levels**in your body can happen in people who have taken KONVOMEP for a long time (more than 3 years). Tell your doctor if you have symptoms of low vitamin B-12 levels, including shortness of breath, lightheadedness, irregular heartbeat, muscle weakness, pale skin, feeling tired, mood changes, and tingling or numbness in the arms and legs.
- **Low magnesium levels in your body can happen in people who have taken KONVOMEP**for at least 3 months. Tell your doctor right away if you have symptoms of low magnesium levels, including seizures, dizziness, irregular heartbeat, jitteriness, muscle aches or weakness, and spasms of hands, feet, or voice.
- **Stomach growths (fundic gland polyps).**People who take PPI medicines for a long time have an increased risk of developing a certain type of stomach growths called fundic gland polyps, especially after taking PPI medicines for more than 1 year.
- **Severe skin reactions.**KONVOMEP can cause rare but severe skin reactions that may affect any part of your body. These serious skin reactions may need to be treated in a hospital and may be life threatening:
  - Skin rash which may have blistering, peeling or bleeding on any part of your skin (including your lips, eyes, mouth, nose, genitals, hands or feet).
  - You may also have fever, chills, body aches, shortness of breath, or enlarged lymph nodes.

Stop taking KONVOMEP and call your doctor right away. These symptoms may be the first sign of a severe skin reaction.

The most common side effects of KONVOMEP include:

- headache
- abdominal pain
- nausea
- diarrhea
- vomiting
- gas

These are not all the possible side effects of KONVOMEP. Call your doctor for medical advice about side effects. You may report side effect to FDA at 1-800-FDA-1088.
You may also report side effects to Azurity Pharmaceuticals, Inc. at 1-800-461-7449.

How should I store KONVOMEP?

- Store KONVOMEP oral suspension in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Keep the KONVOMEP container tightly closed. Protect the container from light.
- Do not freeze KONVOMEP.
- Throw away (discard) any unused KONVOMEP oral suspension after 30 days.

Keep KONVOMEP and all medicines out of the reach of children.

General information about the safe and effective use of KONVOMEP.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use KONVOMEP for any condition for which it was not prescribed. Do not give KONVOMEP to other people, even if they have the same symptoms that you have. It may harm them.
You can also ask your doctor or pharmacist for information about KONVOMEP that is written for health professionals.

What are the ingredients in KONVOMEP?

Active ingredients: omeprazole and sodium bicarbonate
Inactive ingredients in KONVOMEP:benzyl alcohol, carboxymethylcellulose sodium, FD&C Red No. 40, poloxamer 188, purified water, simethicone emulsion, sodium citrate (dihydrate), sorbitol solution, strawberry flavor (natural and artificial flavors, propylene glycol and glycerin) and sucralose.
Manufactured for:
Azurity Pharmaceuticals, Inc.
Woburn, MA 01801 USA
For more information, go to www.azurity.com or call 1-800-461-7449.

This Medication Guide has been approved by the U.S. Food and Drug Administration

Issued: 08/2023
PN: MC-00691
REV: 01 08/2023

PRINCIPAL DISPLAY PANEL – Carton Label

NDC 65628-272-10

Rx Only

KONVOMEP ®
(omeprazole and sodium bicarbonate
for oral suspension)

2 mg/84 mg per mL*

*300 mL final volume. When reconstituted, each mL contains
2 mg omeprazole, USP, and 84 mg sodium bicarbonate, USP.

EACH KIT INCLUDES:

- One bottle containing 0.6 g omeprazole powder
- One bottle containing 25.2 g sodium bicarbonate in 300 mL strawberry-flavored Diluent
- One Full Prescribing Information
- One Medication Guide

Shake well before each use

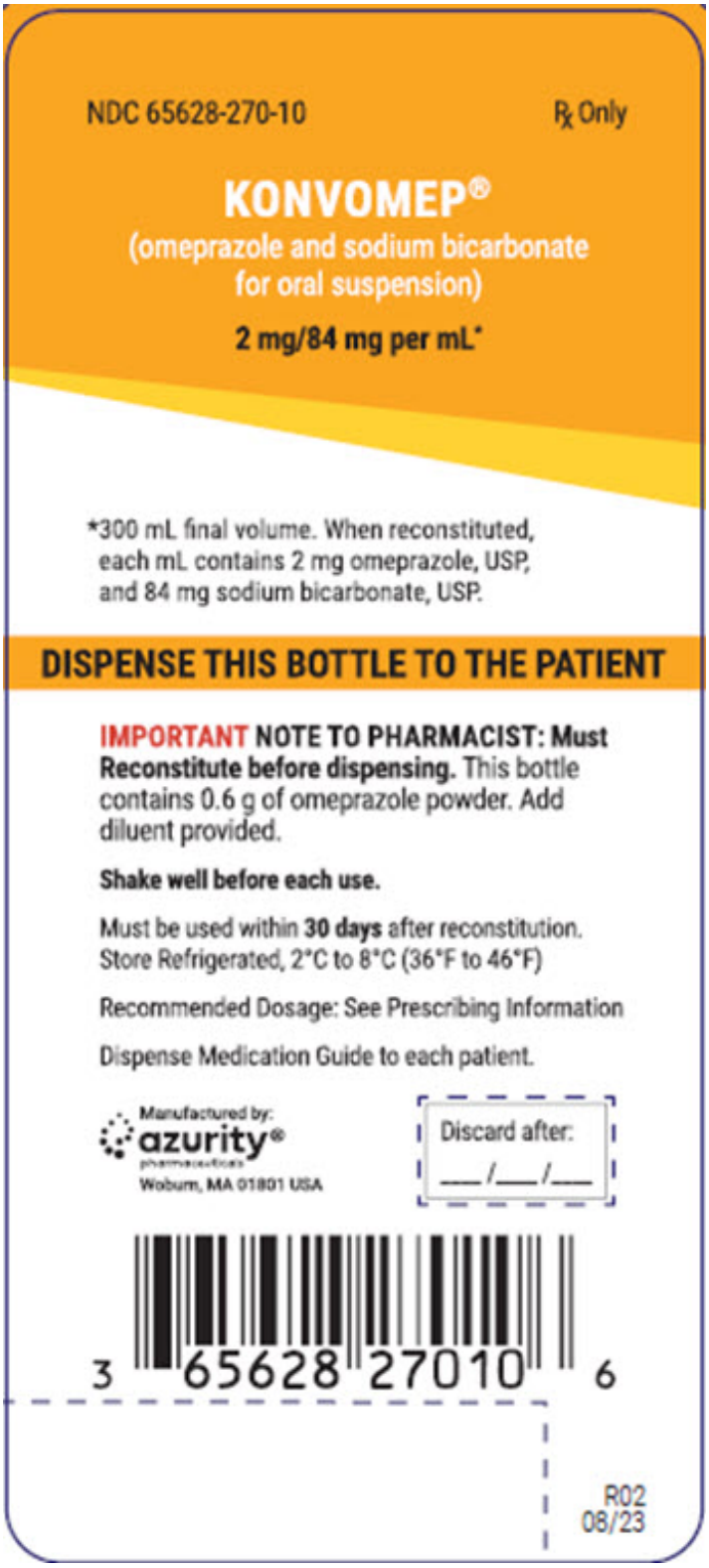
IMPORTANT NOTE TO PHARMACIST:
Must Reconstitute before dispensing

azurity ®
pharmaceuticls

Dispense Medication Guide to each patient.

300 mL final volume after reconstitution

PRINCIPAL DISPLAY PANEL – Drug Product Label



NDC 65628-270-10

Rx Only

KONVOMEP ®
(omeprazole and sodium bicarbonate
for oral suspension)

2 mg/84 mg per mL*

* 300 mL final volume. When reconstituted, each mL contains 2 mg omeprazole, USP, and 84 mg sodium bicarbonate, USP.

DISPENSE THIS BOTTLE TO THE PATIENT

IMPORTANT NOTE TO PHARMACIST: Must Reconstitute before dispensing. This bottle contains 0.6 g of omeprazole powder. Add diluent provided.

Shake well before each use.

Must be used within **30 days**after reconstitution.
Store Refrigerated, 2°C to 8°C (36°F to 46°F)

Recommended Dosage: See Prescribing Information

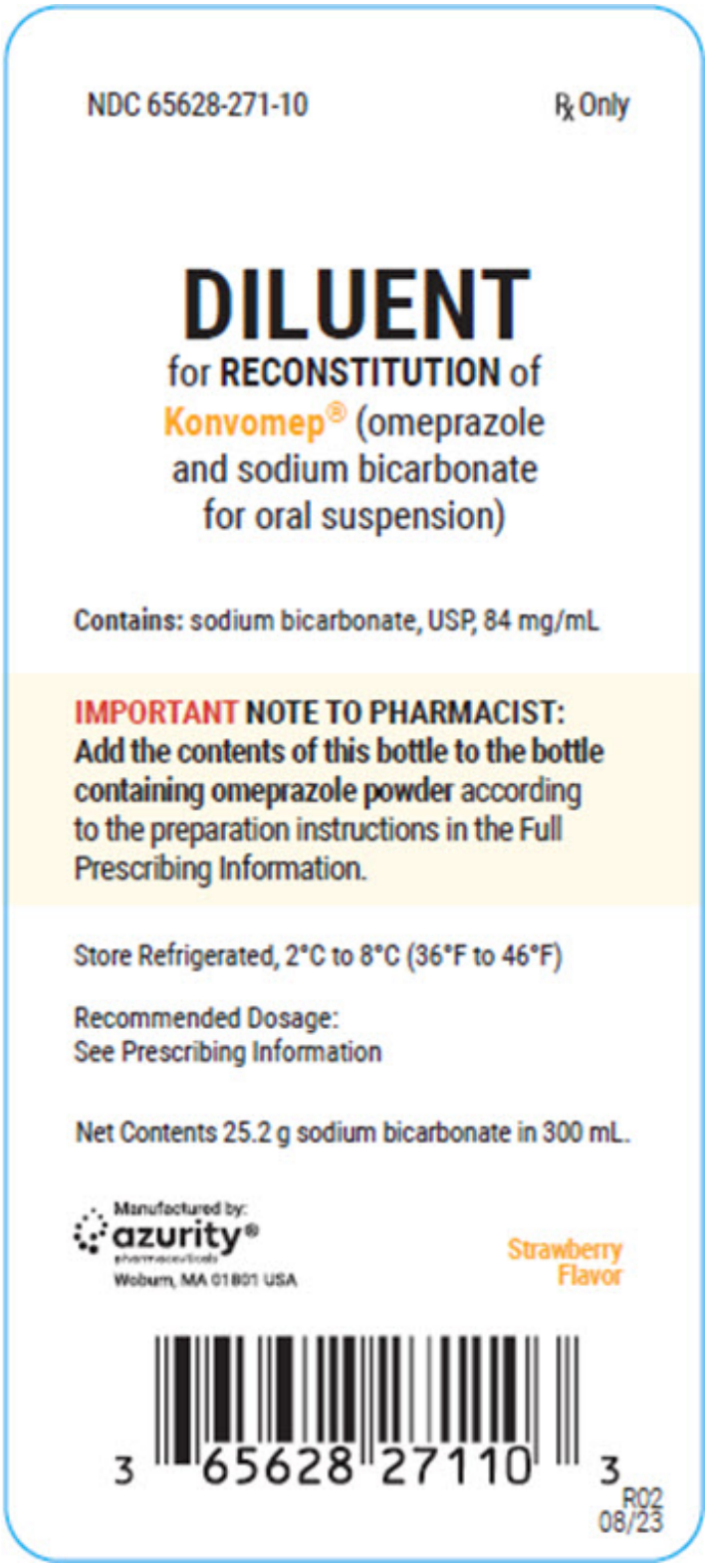
Dispense Medication Guide to each patient.

Manufactured by:
azurity ®
pharmaceuticals
Woborn, MA 01801 USA

Discard after:
____/____/____

R02
08/23

PRINCIPAL DISPLAY PANEL – Diluent Label



NDC 65628-271-10

Rx Only

DILUENT
for **RECONSTITUTION**of
Konvomep ®(omeprazole
and sodium bicarbonate
for oral suspension)

Contains:sodium bicarbonate, USP, 84 mg/mL

IMPORTANT NOTE TO PHARMACIST:
Add the contents of this bottle to the bottle containing omeprazole powder according to the preparation instructions in the Full Prescribing Information.

Store Refrigerated, 2°C to 8°C (36°F to 46°F)

Recommended Dosage:
See Prescribing Information

Net Contents 25.2 g sodium bicarbonate in 300 mL.

Manufactured for:
azurity ®
pharmaceuticals
Woborn, MA 01801 USA

Strawberry
Flavor

R02
08/23

KONVOMEP

omeprazole and sodium bicarbonate kit

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:65628-272

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:65628-272-03	1 in 1 CARTON; Type 0: Not a Combination Product	02/15/2023	
2	NDC:65628-272-05	1 in 1 CARTON; Type 0: Not a Combination Product	02/15/2023	
3	NDC:65628-272-10	1 in 1 CARTON; Type 0: Not a Combination Product	02/15/2023	

Quantity of Parts		
Part #	**Package Quantity**	**Total Product Quantity**
Part 1	1 BOTTLE	90 mL
Part 2	1 BOTTLE	90 mL
Part 3	1 BOTTLE	150 mL
Part 4	1 BOTTLE	150 mL
Part 5	1 BOTTLE	300 mL
Part 6	1 BOTTLE	300 mL

Part 1 of 6

KONVOMEP

omeprazole suspension

Product Information	
Item Code (Source)	NDC:65628-270
Route of Administration	ORAL

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
OMEPRAZOLE (UNII: KG60484QX9) (OMEPRAZOLE - UNII:KG60484QX9)	OMEPRAZOLE	2 mg in 1 mL

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:65628-270-03	90 mL in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA213593	02/15/2023	

Part 2 of 6

SODIUM BICARBONATE

sodium bicarbonate solution

Product Information	
Item Code (Source)	NDC:65628-271
Route of Administration	ORAL

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
SODIUM BICARBONATE (UNII: 8MDF5V39QO) (BICARBONATE ION -	SODIUM	84 mg

UNII:HN1ZRA3Q20)	BICARBONATE	in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
BENZYL ALCOHOL (UNII: LKG8494WBH)	
CARBOXYMETHYLCELLULOSE SODIUM, UNSPECIFIED FORM (UNII: K679OBS311)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
POLOXAMER 188 (UNII: LQA7B6G8JG)	
WATER (UNII: 059QF0KO0R)	
DIMETHICONE (UNII: 92RU3N3Y1O)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
TRISODIUM CITRATE DIHYDRATE (UNII: B22547B95K)	
SORBITOL SOLUTION (UNII: 8KW3E207O2)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
GLYCERIN (UNII: PDC6A3C0OX)	
SUCRALOSE (UNII: 96K6UQ3ZD4)	

Product Characteristics			
Color		**Score**	
Shape		**Size**	
Flavor	STRAWBERRY	**Imprint Code**	
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:65628-271-03	90 mL in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA213593	02/15/2023	

Part 3 of 6

KONVOMEP

omeprazole suspension

Product Information	
Item Code (Source)	NDC:65628-270
Route of Administration	ORAL

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
OMEPRAZOLE (UNII: KG60484QX9) (OMEPRAZOLE - UNII:KG60484QX9)	OMEPRAZOLE	2 mg in 1 mL

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:65628-270-05	150 mL in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA213593	02/15/2023	

Part 4 of 6

SODIUM BICARBONATE

sodium bicarbonate solution

Product Information	
Item Code (Source)	NDC:65628-271
Route of Administration	ORAL

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
SODIUM BICARBONATE (UNII: 8MDF5V39QO) (BICARBONATE ION - UNII:HN1ZRA3Q20)	SODIUM BICARBONATE	84 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
BENZYL ALCOHOL (UNII: LKG8494WBH)	
CARBOXYMETHYLCELLULOSE SODIUM, UNSPECIFIED FORM (UNII: K679OBS311)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
POLOXAMER 188 (UNII: LQA7B6G8JG)	
WATER (UNII: 059QF0KO0R)	
DIMETHICONE (UNII: 92RU3N3Y1O)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	

TRISODIUM CITRATE DIHYDRATE (UNII: B22547B95K)	
SORBITOL SOLUTION (UNII: 8KW3E207O2)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
GLYCERIN (UNII: PDC6A3C0OX)	
SUCRALOSE (UNII: 96K6UQ3ZD4)	

Product Characteristics			
Color		**Score**	
Shape		**Size**	
Flavor	STRAWBERRY	**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:65628-271-05	150 mL in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA213593	02/15/2023	

Part 5 of 6

KONVOMEP

omeprazole suspension

Product Information

Item Code (Source)	NDC:65628-270
Route of Administration	ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
OMEPRAZOLE (UNII: KG60484QX9) (OMEPRAZOLE - UNII:KG60484QX9)	OMEPRAZOLE	2 mg in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:65628-270-	300 mL in 1 BOTTLE; Type 0: Not a Combination		

1	10	Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA213593	02/15/2023	

Part 6 of 6

SODIUM BICARBONATE

sodium bicarbonate solution

Product Information

Item Code (Source)	NDC:65628-271
Route of Administration	ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
SODIUM BICARBONATE (UNII: 8MDF5V39QO) (BICARBONATE ION - UNII:HN1ZRA3Q20)	SODIUM BICARBONATE	84 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
BENZYL ALCOHOL (UNII: LKG8494WBH)	
CARBOXYMETHYLCELLULOSE SODIUM, UNSPECIFIED FORM (UNII: K679OBS311)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
POLOXAMER 188 (UNII: LQA7B6G8JG)	
WATER (UNII: 059QF0KO0R)	
DIMETHICONE (UNII: 92RU3N3Y1O)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
TRISODIUM CITRATE DIHYDRATE (UNII: B22547B95K)	
SORBITOL SOLUTION (UNII: 8KW3E207O2)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
GLYCERIN (UNII: PDC6A3C0OX)	
SUCRALOSE (UNII: 96K6UQ3ZD4)	

Product Characteristics

Color		**Score**	
Shape		**Size**	
Flavor	STRAWBERRY	**Imprint Code**	

Contains	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:65628-271-10	300 mL in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA213593	02/15/2023	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA213593	02/15/2023	

Labeler - Azurity Pharmaceuticals, Inc. (117505635)

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