IMPORTANT SAFETY INFORMATION

KONVOMEP® (omeprazole and sodium bicarbonate for oral suspension)

KONVOMEP is a combination of omeprazole, a proton pump inhibitor (PPI) and sodium bicarbonate, indicated in adults for:

- Treatment of active benign gastric ulcer
- Reduction of risk of upper gastrointestinal (GI) bleeding in critically ill patients

Instruct patients to shake the reconstituted suspension well before each use. A calibrated measuring device is recommended to measure and deliver the prescribed dose accurately. A household teaspoon or tablespoon is not an adequate measuring device.

ADDITIONAL IMPORTANT SAFETY INFORMATION

Contraindications

- Known hypersensitivity to any components of the formulation
- Patients receiving rilpivirine-containing products

Warnings and Precautions

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 PPI. In older patients, also consider an endoscopy.

Acute Tubulointerstitial Nephritis: Acute tubulointerstitial nephritis (TIN) has been observed in patients taking PPIs and may occur at any point during PPI therapy. Patients may present with varying signs and symptoms from symptomatic hypersensitivity reactions to non-specific symptoms of decreased renal function (e.g., malaise, nausea, 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.

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 in 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.

***Clostridium difficile*-Associated Diarrhea:** 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. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

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. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to the established treatment guidelines.

Severe Cutaneous Adverse Reactions: Severe cutaneous adverse reactions (SCAR), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported in association with the use of PPIs. Discontinue at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

Cutaneous and Systemic Lupus Erythematosus: Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs, including omeprazole. These events have occurred as both new onset and an exacerbation of an existing autoimmune disease. The majority of PPI-induced lupus erythematosus cases were CLE, with the most common form being subacute CLE. PPI-associated SLE is usually milder than non-drug-induced SLE. 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.

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. When using KONVOMEP, consider alternative antiplatelet therapy.

Cyanocobalamin (Vitamin B-12) Deficiency: Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin caused by hypo- or achlorhydria. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed in patients treated with KONVOMEP.

Hypomagnesemia and Mineral Metabolism: Symptomatic and asymptomatic hypomagnesemia has been reported in patients treated with PPIs for at least three months, and 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. For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically. Consider monitoring magnesium and calcium levels prior to initiation of 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.

Interaction with St. John's Wort or Rifampin: Avoid concomitant use of KONVOMEP with St. John's wort or rifampin. Drugs that induce CPY2C19 or CYP3A4, such as St. John's wort or rifampin, can substantially decrease omeprazole concentrations.

Interactions with Diagnostic 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. Temporarily stop KONVOMEP at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high.

Interaction with Methotrexate: Concomitant use of PPIs with methotrexate may elevate and prolong serum concentrations of methotrexate and/or metabolite, possibly leading to toxicity. With high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients.

Fundic Gland Polyps: PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond one year. Use the shortest duration of PPI therapy appropriate to the condition being treated.

Adverse Reactions

The most common side effects in (≥2%) or more of adult patients are:

- Headache
- Abdominal Pain
- Diarrhea
- Nausea

- Vomiting
- Flatulence

These are not all the possible side effects of KONVOMEP. Please see Full Prescribing Information for a full list.

Drug Interactions

Antiretrovirals: The effect of PPIs on antiretroviral drugs is variable. The clinical importance and the mechanisms behind these interactions are not always known.

When used concomitantly with omeprazole, may:

- Reduce antiviral effect and promote the development of drug resistance (e.g., rilpivirine, atazanavir and nelfinavir).
- Increased exposure of other antiviral (e.g., saquinavir) which may increase toxicity
- Not result in clinically relevant interactions (other antiretroviral drugs)

Concomitant use with KONVOMEP is contraindicated with rilpivirine-containing products, atazanavir, nelfinavir, saquinavir, and other antiretrovirals. See prescribing information for specific antiretroviral drugs.

Warfarin: 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. Monitor INR and prothrombin time and adjust the dose of warfarin, if needed, to maintain the target INR range.

Methotrexate: 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. 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:** Concomitant use of omeprazole 80 mg results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition. Avoid concomitant use with KONVOMEP. Consider the use of alternative anti-platelet therapy.
- **Citalopram:** Increased exposure to citalopram leads to an increased risk of QT prolongation. Limit the dose of citalopram to a maximum of 20 mg per day. See prescribing information for citalopram.
- **Cilostazol:** Increased exposure of one of the active metabolites of cilostazol (3,4-dihydro-cilostazol). Reduce the dose of cilostazol to 50 mg twice daily. See prescribing information for cilostazol.

- **Phenytoin:** Potential for increased exposure to phenytoin. Monitor phenytoin serum concentrations. Dose adjustment may be needed to maintain therapeutic drug concentrations. See prescribing information for phenytoin.
- **Diazepam:** Increased exposure to diazepam. Monitor patients for increased sedation and reduce the dose of diazepam as needed.

Digoxin: Potential for increased exposure to digoxin. Monitor digoxin concentrations. Dose adjustments 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): Omeprazole can reduce the absorption of other drugs due to its effect on reducing intragastric acidity.

- **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). Use KONVOMEP with caution in transplant patients receiving MMF. See prescribing information for other drugs dependent on gastric pH for absorption.

Tacrolimus: Potential for increased exposure of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19. 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: 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. 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.

Interaction with Secretin Stimulation Test: Hyper-response in gastrin secretion in response to secretin stimulation test, falsely suggesting gastrinoma. Temporarily stop KONVOMEP treatment at least 14 days before assessing to allow gastrin levels to return to baseline

False Positive Urine Tests for THC: There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs. An alternative confirmatory method should be considered to verify positive results.

CYP2C19 or CYP3A4 Inducers (St. John's Wort, rifampin, ritonavir-containing products): Decreased exposure of omeprazole when used concomitantly with strong inducers. Avoid concomitant use with KONVOMEP**.** See prescribing information for specific drugs.

CYP2C19 or CYP3A4 Inhibitors (voriconazole): Increased exposure to omeprazole. Dosage adjustment of KONVOMEP is not usually required. See full prescribing information for voriconazole.

Other: There have been clinical reports of interactions with other drugs metabolized via the cytochrome P450 system (e.g., cyclosporine, disulfiram). Monitor patients to determine if it is necessary to adjust the dosage of these other drugs when taken concomitantly with KONVOMEP.

See full prescribing information for Specific Drugs and Interactions.

Use in Specific Populations

Pregnancy: There are no adequate and well-controlled studies on KONVOMEP in pregnant women. Based on animal data, may cause fetal harm.

Lactation: KONVOMEP 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.

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

Geriatric: 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 the greater sensitivity of some older individuals cannot be ruled out. Pharmacokinetic studies with buffered omeprazole have shown the elimination rate was decreased and bioavailability was increased in the elderly. However, no dosage adjustment is necessary for the elderly.

The Important Safety Information does not include all the information needed to use KONVOMEP safely and effectively. Please see accompanying full Prescribing Information for KONVOMEP.

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

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