Omeclamox®-Pak

OMEPRAZOLE DELAYED-RELEASE CAPSULES, USP, 20 mg, CLARITHROMYCIN TABLETS, USP, 500 mg, and AMOXICILLIN CAPSULES, USP, 500 mg

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Omeclamox®-Pak safely and effectively. See full prescribing information for Omeclamox®-Pak.

Omeclamox®-Pak

Initial U.S. Approval: 2011

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Omeclamox®-Pak and other antibacterial drugs, Omeclamox®-Pak should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

RECENT MAJOR CHANGES

Acute Interstitial Nephritis (5.6) 12/2014

INDICATIONS AND USAGE

Omeclamox®-Pak, a copackaged product containing a proton pump inhibitor, a macrolide antimicrobial, and a penicillin class antibacterial, is indicated for the treatment of patients with *Helicobacter pylori* infection and duodenal ulcer disease (active or up to one-year history) to eradicate *H. pylori.* (1.1)

DOSAGE AND ADMINISTRATION

- Adult regimen: omeprazole 20 mg plus clarithromycin 500 mg plus amoxicillin 1000 mg, each given twice daily for 10 days in the morning and evening before eating a meal. (2)
- Advise patients to swallow all tablets and capsules whole. (2)
- In patients with an ulcer present at initiation of therapy, an additional 18 days of omeprazole 20 mg once daily is recommended. (2)

DOSAGE FORMS AND STRENGTHS

Pack of 10 daily administration cards for morning and evening dosing, each containing:
- Two omeprazole delayed-release capsules, USP, 20 mg.
- Two clarithromycin tablets, USP, 500 mg.
- Four amoxicillin capsules, USP, 500 mg.

CONTRAINDICATIONS

- Known hypersensitivity to omeprazole, any macrolide antibiotic, any penicillin, or any component of the formulations. (4.1)
- Coadministration with pimozide, ergotamine or dihydroergotamine. (4.2, 7.2, 7.3)

WARNINGS AND PRECAUTIONS

- Fetal risk and clarithromycin: Based on animal data, may cause fetal harm. Use in pregnancy only when there is no appropriate alternative therapy. (5.1)
- Colchicine interaction: Concomitant use of clarithromycin and colchicine has resulted in deaths, especially in the elderly with renal insufficiency. Monitor patients for clinical symptoms of colchicine toxicity. (5.2, 7.1)
- Myasthenia gravis: Exacerbation of symptoms and new onset of symptoms reported with clarithromycin. Monitor patients for symptoms. (5.3)
- *Clostridium difficile*-associated diarrhea: Reported with use of clarithromycin and amoxicillin; evaluate if diarrhea occurs. (5.4)
- Risk of gastric malignancy: Symptomatic response does not preclude concomitant underlying malignancy. (5.5)
- Acute interstitial nephritis has been observed in patients taking PPIs. (5.6)

ADVERSE REACTIONS

Most frequent adverse reactions (> 7%) with triple therapy were diarrhea, taste perversion, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Cumberland Pharmaceuticals at 1-877-484-2700 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Antiarrythmics: Risk of torsades de pointes and other arrhythmias with concurrent use of clarithromycin and

quinidine, disopyramide, and digoxin. Monitor ECGs and serum digoxin concentrations. (7.4)
- Oral anticoagulants: Concomitant administration of omeprazole or clarithromycin may potentiate the anticoagulant effects of warfarin and other oral anticoagulants. Monitor prothrombin times and INR. (7.5)
- Atazanavir and nelfinavir: Omeprazole reduces plasma concentrations of atazanavir and nelfinavir. Concomitant use is not recommended. (7.6)
- Saquinavir: Omeprazole increases plasma concentrations of saquinavir. Monitor for toxicity and consider dose reduction of saquinavir. (7.6)
- Cilostazol: Omeprazole increases systemic exposure of cilostazol and one of its active metabolites. Consider dose reduction of cilostazol. (7.7)
- Tacrolimus: Omeprazole may increase serum concentrations of tacrolimus. Frequently monitor whole blood trough concentrations of tacrolimus. (7.8)
- Theophylline: Clarithromycin may increase serum concentrations of theophylline. Monitor serum theophylline concentrations. (7.9)
- Carbamazepine: Clarithromycin may increase plasma concentrations of carbamazepine. Monitor blood concentrations of carbamazepine. (7.10)
- Sildenafil: Clarithromycin may increase systemic exposure of sildenafil. Consider dose reduction of sildenafil. (7.11)
- HMG-CoA reductase inhibitors (statins): Clarithromycin may alter the effect of HMG-CoA reductase inhibitors (statins). (7.12)
- Drugs metabolized by cytochrome P450 (e.g., diazepam, warfarin, phenytoin, cyclosporine, disulfiram, benzodiazepines): Omeprazole can prolong their elimination. Monitor and determine need for dose adjustments. (7, 7.13)
- Probenecid: Probenecid may increase blood concentrations of the amoxicillin. (7.14)
- Omeprazole may interfere with drugs for which gastric pH affects bioavailability (e.g., ketoconazole, iron salts, ampicillin esters, digoxin, and mycophenolate mofetil). (7.15)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data for omeprazole and clarithromycin, may cause fetal harm. (8.1)
- Nursing Mothers: Discontinue nursing or express and discard milk during treatment. (8.3)
- Hepatic Impairment: Avoid use. (8.7)
- Asian Patients: Avoid use unless it is deemed that the benefits outweigh the risks. (8.8)

See 17 for PATIENT COUNSELING INFORMATION **Revised: 07/2014**

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Omeclamox®-Pak and other antibacterial drugs, Omeclamox®-Pak should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

1.1 Eradication of *Helicobacter pylori* in Patients with Active Duodenal Ulcer or History of Duodenal Ulcer Disease

Omeprazole delayed-release capsules, clarithromycin tablets, and amoxicillin capsules taken together are indicated for the treatment of patients with *Helicobacter pylori* infection and duodenal ulcer disease (active or one-year history) to eradicate *H. pylori* in adults. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence [*See Clinical Studies (14.1)*].

In patients who fail therapy with Omeclamox®-Pak, perform susceptibility testing. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, institute alternative antimicrobial therapy [*See Clinical Pharmacology, Microbiology (12.4)*].

2 DOSAGE AND ADMINISTRATION

The recommended adult oral regimen is omeprazole delayed-release capsules 20 mg plus clarithromycin 500 mg plus amoxicillin 1000 mg, each given twice daily, for 10 days, in the morning and evening before eating a meal. Inform patients that omeprazole, clarithromycin, and amoxicillin should not be crushed or chewed, and should be swallowed whole.

In patients with an ulcer present at the time of initiation of therapy, an additional 18 days of omeprazole 20 mg once daily is recommended for ulcer healing and symptom relief.

3 DOSAGE FORMS AND STRENGTHS

Omeclamox®-Pak is supplied in a carton containing ten individual daily administration cards. Each card contains:

Omeprazole Delayed-Release Capsules, USP, 20 mg

Two opaque, hard gelatin lavender and grey capsules, with ‘R 158’ and ‘OMEPRAZOLE 20 mg’ imprinted on the capsules in black ink, containing off-white to pale-yellow, elliptical spherical pellets.

Clarithromycin Tablets, USP, 500 mg

Two white, biconvex beveled-edge capsule-shaped coated tablets debossed with ‘54 312’ on one side and plain on the other side.

Amoxicillin Capsules, USP, 500 mg

Four opaque hard gelatin peach and orange capsules, marked ‘WC 731’. Each capsule contains amoxicillin trihydrate, equivalent to 500 mg amoxicillin.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Omeclamox®-Pak is contraindicated in patients with a history of hypersensitivity to omeprazole, any macrolide antibiotic, or any penicillin.

Hypersensitivity reactions to omeprazole may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, interstitial nephritis, and urticaria [*See Adverse Reactions (6.3)*].

Hypersensitivity reactions to clarithromycin may include anaphylaxis, Stevens-Johnson syndrome, and toxic epidermal necrolysis [*See Adverse Reactions (6.3)*].

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. Before initiating therapy with amoxicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens.

Hypersensitivity reactions to amoxicillin may include serum sickness like reactions, erythematous maculopapular rashes, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, hypersensitivity vasculitis and urticaria [*See Adverse Reactions (6.3)*].

4.2 Serious Drug Interactions (Cardiotoxicity, Ergotism)

Because of the clarithromycin component, Omeclamox®-Pak is contraindicated in patients taking ergotamine or dihydroergotamine and pimozide. Cardiac arrhythmias, some fatal, have been reported with the use of clarithromycin and/or erythromycin and pimozide. Arrhythmias have included QT prolongation, ventricular tachycardia, ventricular

fibrillation, and torsades de pointes, and are most likely due to inhibition of metabolism of these drugs by clarithromycin and/or erythromycin [*See Drug Interactions (7.2, 7.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Fetal Risk and Clarithromycin

Clarithromycin has demonstrated adverse effects on pregnancy outcomes and/or embryo-fetal development in monkeys, rats, mice, and rabbits at doses that produced plasma concentrations 2 to 17 times the serum concentrations achieved in humans at the maximum recommended human dose.

Clarithromycin should be used in pregnant women only in clinical circumstances where no alternative therapy is appropriate, and the potential benefit to the patient outweighs the potential risk to the fetus [*See Use in Specific Populations (8.1)*].

5.2 Colchicine Toxicity with Clarithromycin

There have been postmarketing reports of colchicine toxicity, some fatal, with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Monitor patients for clinical symptoms of colchicine toxicity [*See Drug Interactions (7.1)*].

5.3 Myasthenia Gravis

Exacerbation of symptoms of myasthenia gravis and new onset of symptoms of myasthenic syndrome have been reported in patients receiving clarithromycin therapy. Monitor patients for symptoms.

5.4 *Clostridium difficile*-associated diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of clarithromycin and amoxicillin, and may range in severity from mild diarrhea to fatal colitis [*See Adverse Reactions (6.3)*]. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile.*

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.

5.5 Concomitant Gastric Malignancy

Symptomatic response to therapy with omeprazole does not preclude the presence of gastric malignancy.

5.6 Acute Interstitial Nephritis

Acute interstitial nephritis (AIN) has been observed in patients taking PPIs including omeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue omeprazole if AIN develops. [*See Contraindications (4.1)].*

5.7 Development of Bacterial Superinfections

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy with Omeclamox®-Pak due to the clarithromycin and amoxicillin components. If superinfections occur, Omeclamox®-Pak should be discontinued and appropriate therapy instituted.

5.8 Mononucleosis and Ampicillin

A high percentage of patients with mononucleosis who receive ampicillin develop an erythematosus skin rash. Thus, administration of ampicillin-class antibiotics is not recommended in patients with mononucleosis.

5.9 Development of Drug Resistant Bacteria

Prescribing clarithromycin or amoxicillin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity [*See Contraindications (4.1)*]
- Myasthenia Gravis [*See Warnings and Precautions (5.3)*]
- *Clostridium difficile*-associated diarrhea [*See Warnings and Precautions (5.4)*]

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.

In clinical trials using triple therapy with omeprazole, clarithromycin, and amoxicillin, no adverse reactions unique to triple therapy were observed. Adverse reactions observed were limited to those previously reported with omeprazole, clarithromycin, or amoxicillin alone. The most frequent adverse reactions observed in clinical trials using combination therapy with omeprazole, clarithromycin, and amoxicillin (n = 274) were diarrhea (14%), taste perversion (10%), and headache (7%). None of these occurred at a higher frequency than that reported by patients taking antimicrobial agents alone.

6.2 Adverse Reactions from Labeling for the Individual Components of Omeclamox®-Pak

The safety data below reflect exposure to omeprazole delayed-release capsules and clarithromycin worldwide in clinical trials for various indications using doses and durations of therapy that may differ from how they are used as a component of Omeclamox®-Pak. For complete information on these reactions, see the full prescribing information for omeprazole delayed-release capsules and clarithromycin.

Omeprazole:

The most common adverse reactions reported (i.e., with an incidence rate ≥ 2%) in 3096 patients from omeprazole delayed-release capsules-treated patients enrolled in clinical trials included headache (6.9%), abdominal pain (5.2%), nausea (4.0%), diarrhea (3.7%), vomiting (3.2%), and flatulence (2.7%).

Additional adverse reactions that were reported with an incidence rate ≥ 1% included acid regurgitation (1.9%), upper respiratory infection (1.9%), constipation (1.5%), dizziness (1.5%), rash (1.5%), asthenia (1.3%), back pain (1.1%), and cough (1.1%).

The clinical trial safety profile in patients greater than 65 years of age was similar to that in patients 65 years of age or less.

Clarithromycin:

The most frequently reported events in adults were diarrhea (3%), nausea (3%), abnormal taste (3%), dyspepsia (2%), abdominal pain/discomfort (2%), and headache (2%). Most of these events were described as mild or moderate in severity. Of the reported adverse events, only 1% were described as severe. Fewer than 3% of adult patients without mycobacterial infections discontinued therapy because of drug-related side effects.

Amoxicillin:
[*See Adverse Reactions (6.3)*]

6.3 Post-Marketing Experience with the Individual Components of Omeclamox®-Pak

Because these reactions are voluntarily reported from a population of uncertain size, it is not always possible to reliably estimate their actual frequency or establish a causal relationship to drug exposure.

Omeprazole:

Body As a Whole: Hypersensitivity reactions including anaphylaxis, anaphylactic shock, angioedema, bronchospasm, interstitial nephritis, urticaria, (see also *Skin* below); fever; pain; fatigue; malaise.

Cardiovascular: Chest pain or angina, tachycardia, bradycardia, palpitations, elevated blood pressure, peripheral edema.

Endocrine: Gynecomastia.

Gastrointestinal: Pancreatitis (some fatal), anorexia, irritable colon, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, stomatitis, abdominal swelling, dry mouth. During treatment with omeprazole, gastric fundic gland polyps have been noted rarely. These polyps are benign and appear to be reversible when treatment is discontinued. Gastroduodenal carcinoids have been reported in patients with Zollinger-Ellison syndrome on long-term treatment with omeprazole. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors.

Hepatic: Liver disease including hepatic failure (some fatal), liver necrosis (some fatal), hepatic encephalopathy hepatocellular disease, cholestatic disease, mixed hepatitis, jaundice, and elevations of liver function tests [ALT, AST, GGT, alkaline phosphatase, and bilirubin].

Metabolic/Nutritional: Hypoglycemia, hyponatremia, weight gain.

Musculoskeletal: Muscle weakness, myalgia, muscle cramps, joint pain, leg pain.

Nervous System/Psychiatric: Psychiatric and sleep disturbances including depression, agitation, aggression, hallucinations, confusion, insomnia, nervousness, apathy, somnolence, anxiety, and dream abnormalities; tremors, paresthesia; vertigo.

Respiratory: Epistaxis, pharyngeal pain.

Skin: Severe generalized skin reactions including toxic epidermal necrolysis (some fatal), Stevens-Johnson syndrome, and erythema multiforme; photosensitivity; urticaria; rash; skin inflammation; pruritus; petechiae; purpura; alopecia; dry skin; hyperhidrosis.

Special Senses: Tinnitus, taste perversion.

Ocular: Optic atrophy, anterior ischemic optic neuropathy, optic neuritis, dry eye syndrome, ocular irritation, blurred vision, double vision.

Urogenital: Interstitial nephritis, hematuria, proteinuria, elevated serum creatinine, microscopic pyuria, urinary tract infection, glycosuria, urinary frequency, testicular pain.

Hematologic: Agranulocytosis (some fatal), hemolytic anemia, pancytopenia, neutropenia, anemia, thrombocytopenia, leukopenia, leucocytosis.

Clarithromycin:

Hypersensitivity Reactions: Allergic reactions ranging from urticaria and mild skin eruptions to rare cases of anaphylaxis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have occurred.

Gastrointestinal: Glossitis, stomatitis, oral moniliasis, anorexia, vomiting, pancreatitis, tongue discoloration.

Hematologic: Thrombocytopenia, leukopenia, neutropenia.

Other: There have been reports of tooth discoloration in patients treated with clarithromycin. Tooth discoloration is

usually reversible with professional dental cleaning.

Nervous System/Psychiatric: There have been isolated reports of hearing loss, which is usually reversible, occurring chiefly in elderly women. Reports of alterations of the sense of smell, usually in conjunction with taste perversion or taste loss have also been reported.

Transient CNS events including anxiety, behavioral changes, confusional states, convulsions, depersonalization, disorientation, hallucinations, insomnia, manic behavior, nightmares, psychosis, tinnitus, tremor, dizziness and vertigo have been reported during postmarketing surveillance. Events usually resolve with discontinuation of the drug.

Hepatic: Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been infrequently reported with clarithromycin. This hepatic dysfunction may be severe and is usually reversible. In very rare instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications.

Metabolic: There have been rare reports of hypoglycemia, some of which have occurred in patients taking oral hypoglycemic agents or insulin.

Cardiac: As with other macrolides, clarithromycin has been associated with QT prolongation and ventricular arrhythmias, including ventricular tachycardia and torsades de pointes.

Renal: There have been reports of interstitial nephritis coincident with clarithromycin use.

Amoxicillin:

Gastrointestinal: Nausea, vomiting, diarrhea, and hemorrhagic/*Clostridium difficile*-associated colitis. Onset of *Clostridium difficile*-associated diarrhea may occur during or after antibiotic treatment [*See Warnings and Precautions (5.4)*].

Hypersensitivity Reactions: Serum sickness like reactions, erythematous maculopapular rashes, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, hypersensitivity vasculitis and urticaria have been reported. Reactions are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria.

Hepatic: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted, but the significance of this finding is unknown. Hepatic dysfunction including cholestatic jaundice, hepatic cholestasis and acute cytolytic hepatitis have been reported.

Renal: Crystalluria has also been reported [*See Overdosage (10)*].

Hemic and Lymphatic Systems: Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

Nervous System/Psychiatric: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

Miscellaneous: Tooth discoloration (brown, yellow, or gray staining) has been rarely reported. Most reports occurred in pediatric patients. Discoloration was reduced or eliminated with brushing or dental cleaning in most cases.

Changes in Laboratory Values: Changes in laboratory values with possible clinical significance were as follows: Hepatic – elevated SGPT (ALT) less than 1%, SGOT (AST) less than 1%, GGT less than 1%, alkaline phosphatase less than 1%, LDH less than 1%, total bilirubin less than 1%; Hematologic – decreased WBC less than 1%, elevated prothrombin time 1%; Renal – elevated BUN 4%, elevated serum creatinine less than 1%. GGT, alkaline phosphatase, and prothrombin time data are from adult studies only.

7 DRUG INTERACTIONS

Effect of Omeprazole

Omeprazole is a substrate and an inhibitor of CYP2C19 *in vivo,* a substrate of CYP3A4 *in vivo,* and an inhibitor of

CYP2C19 *in vitro.* Therefore, omeprazole may affect the metabolism and plasma concentrations of drugs that are metabolized by these CYP enzymes. Although in healthy subjects no interaction with theophylline or propranolol was reported, there have been reports of an interaction with other drugs metabolized via the CYP enzyme system (e.g., cyclosporine, disulfiram, benzodiazepines). Carefully monitor patients taking these drugs to determine if dosage adjustments of these drugs are necessary when taken concomitantly with omeprazole.

Effect of Clarithromycin

Clarithromycin is a substrate and inhibitor of CYP3A enzymes. Coadministration of clarithromycin with drugs metabolized by CYP3A may be associated with elevations in drug concentrations that could increase the therapeutic and adverse effects of the concomitant drug. There have been reports of CYP3A-based interactions of erythromycin and/or clarithromycin with cyclosporine, tacrolimus, alfentanil, rifabutin, methylprednisolone, cilostazol, and bromocriptine. In addition, there have been reports of interactions
of erythromycin or clarithromycin with drugs not thought to be metabolized by CYP3A, including: hexobarbital, phenytoin, and valproate.

7.1 Colchicine

Concurrent use of colchicine and Omeclamox®-Pak may increase plasma colchicine concentrations. Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). The clarithromycin component of Omeclamox®-Pak is known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased plasma exposure to colchicine. Monitor patients for clinical symptoms of colchicine toxicity [*See Warnings and Precautions (5.2)*].

7.2 Ergotamine/Dihydroergotamine

Ergotamine/dihydroergotamine plasma concentrations may increase when administered concomitantly with Omeclamox®-Pak. Post-marketing reports indicate that coadministration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin with ergotamine or dihydroergotamine is contraindicated [*See Contraindications (4.2)*].

7.3 Pimozide

The coadministration of pimozide and Omeclamox®-Pak may increase the pimozide plasma concentrations due to an interaction with the clarithromycin component of Omeclamox®-Pak. Post-marketing reports indicate that coadministration of clarithromycin with pimozide has been associated with cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes). Two sudden deaths have been reported when clarithromycin was added to ongoing pimozide therapy. Pimozide is metabolized partly by CYP3A4. When clarithromycin and pimozide are administered together, inhibition of CYP3A4 by clarithromycin may lead to increased plasma exposure to pimozide. Omeclamox®-Pak is contraindicated in patients receiving pimozide [*See Contraindications (4.2)*].

7.4 Antiarrhythmics

Concurrent use of antiarrhythmic drugs and Omeclamox®-Pak may potentiate the antiarrhythmic effects due to an interaction with the clarithromycin component of Omeclamox®-Pak. There have been post-marketing reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have also been reported in post-marketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Monitor electrocardiograms for QTc prolongation during coadministration of Omeclamox®-Pak with antiarrhythmic drugs. Serum concentrations of antiarrhythmics, including digoxin, should also be monitored.

7.5 Anticoagulants

The simultaneous administration of anticoagulants and Omeclamox®-Pak may alter the anticoagulant effects of warfarin and other oral anticoagulants due to an interaction with the omeprazole and clarithromycin components of Omeclamox®-Pak. Monitor prothrombin time and INR in patients receiving Omeclamox®-Pak and oral anticoagulants simultaneously.

There have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including omeprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death.

Spontaneous reports in the post-marketing period suggest that concomitant administration of clarithromycin and oral anticoagulants may potentiate the effects of the oral anticoagulants.

7.6 Antiretroviral Drugs

Concurrent use of antiretroviral agents and Omeclamox®-Pak may alter the antiretroviral effects due to interactions with the omeprazole or clarithromycin components of Omeclamox®-Pak. Omeprazole has been reported to interact with some antiretroviral drugs such as atazanavir, nelfinavir, and saquinavir.

Concomitant use of atazanavir or nelfinavir with omeprazole is not recommended unless the benefits of taking atazanavir or nelfinavir with Omeclamox®-Pak outweigh the risks. Coadministration of atazanavir or nelfinavir with proton pump inhibitors is expected to substantially decrease atazanavir or nelfinavir plasma concentrations and thereby reduce the therapeutic effect of either of these drugs [*See Clinical Pharmacology (12.3)*].

Coadministration of saquinavir with omeprazole may increase the serum concentrations of saquinavir. Dose reduction of saquinavir should be considered when coadministered with Omeclamox®-Pak [*See Clinical Pharmacology (12.3)*].

7.7 Cilostazol

Concomitant administration of Omeclamox®-Pak and cilostazol may increase systemic exposure of cilostazol due to an interaction with the omeprazole component of Omeclamox®-Pak. Therefore, a dose reduction of cilostazol by 50% should be considered when concomitantly administered with Omeclamox®-Pak [*See Clinical Pharmacology (12.3)*].

7.8 Tacrolimus

Concomitant administration of Omeclamox®-Pak and tacrolimus may increase the serum concentrations of tacrolimus due to an interaction with the omeprazole component of Omeclamox®-Pak. Frequent monitoring of whole blood trough concentrations of tacrolimus is recommended when concomitantly administered with Omeclamox®-Pak.

7.9 Theophylline

Omeclamox®-Pak use in patients who are receiving theophylline may be associated with an increase of serum theophylline concentrations due to an interaction with the clarithromycin component of Omeclamox®-Pak. Monitoring of serum theophylline concentrations should be considered for patients receiving high doses of theophylline or with baseline concentrations in the upper therapeutic range [*See Clinical Pharmacology (12.3)*].

7.10 Carbamazepine

The simultaneous administration of carbamazepine and Omeclamox®-Pak may alter the effect of carbamazepine due to an interaction with the clarithromycin component of Omeclamox®-Pak. Concomitant administration of single doses of clarithromycin and carbamazepine has been shown to result in increased plasma concentrations of carbamazepine. Blood level monitoring of carbamazepine should be considered when administered concomitantly with Omeclamox®-Pak.

7.11 Sildenafil

The systemic exposure of sildenafil may increase when it is administered concomitantly with Omeclamox®-Pak due to an interaction with the clarithromycin component of Omeclamox®-Pak; consider a reduction in sildenafil dosage (see sildenafil full prescribing information).

7.12 HMG-CoA Reductase Inhibitors (Statins)

Concurrent use of HMG-CoA reductase inhibitors (statins) and Omeclamox®-Pak may alter the effect of HMG-CoA

due to an interaction with the clarithromycin component of Omeclamox®-Pak. As with other macrolides, clarithromycin has been reported to increase concentrations of statins (e.g., lovastatin and simvastatin). Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly.

7.13 Triazolobenziodidiazepines (e.g., triazolam and alprazolam) and related Benzodiazepines (e.g., midazolam)

The effect of triazolobenziodidiazepines/related benzodiazepines may be altered when administered concomitantly with Omeclamox®-Pak due to an interaction with the clarithromycin component. There have been postmarketing reports of drug interactions and CNS effects (e.g., somnolence and confusion) with the concomitant use of clarithromycin and triazolam.

7.14 Probenecid

Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use of Omeclamox®-Pak and probenecid may result in increased and prolonged blood concentrations of the amoxicillin component of Omeclamox®-Pak.

7.15 Drugs for which Gastric pH can affect Bioavailability

Due to its effects on gastric acid secretion, omeprazole can reduce the absorption of drugs where gastric pH is an important determinant of their bioavailability. As with other drugs that decrease the intragastric acidity, the absorption of drugs such as ketoconazole, atazanavir, iron salts, erlotinib, and mycophenolate mofetil can decrease, while the absorption of drugs such as digoxin can increase during treatment with omeprazole.

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

Coadministration of omeprazole in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the exposure to mycophenolic acid (MPA), the active moiety, possibly due to a decrease in MPA solubility at an increased gastric pH. The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients receiving proton pump inhibitors (PPIs) and mycophenolate mofetil. Use omeprazole with caution in transplant patients receiving mycophenolate mofetil [*See Clinical Pharmacology (12.3)*].

7.16 Drug-Laboratory Test Interactions

High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using Clinitest,® Benedict's Solution or Fehling's Solution. Since this effect may also occur with amoxicillin, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix®) be used.

Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estradiol, estriol-glucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with amoxicillin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C (based on animal studies of omeprazole and clarithromycin)

There are no adequate and well controlled studies of omeprazole, clarithromycin, or amoxicillin (used separately or together) in pregnant women. Clarithromycin demonstrated adverse developmental effects in four animal species at clinically relevant doses. Omeprazole increased embryo-fetal loss in rabbits, but animal studies and multiple human studies do not show an increased risk for major malformations. Omeclamox®-Pak should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus and there is no appropriate alternative therapy [*See Warnings and Precautions (5.1)*].

Omeprazole:

Multiple cohort studies in pregnant women exposed to omeprazole during the first trimester do not show an increased risk of congenital malformations. The majority of experience with omeprazole use during human pregnancy includes first trimester exposure and the duration of use is rarely specified. Three epidemiological studies compared the frequency of congenital malformations among infants born to women who used omeprazole during pregnancy with the frequency of malformations among infants of women exposed to H2-receptor antagonists or controls. One population-based prospective cohort study from the Swedish Medical Birth Registry, reported 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. *In utero* exposure to omeprazole was not associated with an increased risk of malformations (odds ratio 0.82, 95% CI 0.50-1.34), low birth weight or low Apgar score. While the number of stillbirths and infants born with ventricular septal defects were slightly higher in the omeprazole-exposed group, these findings may have been due to chance and do not establish a causal relationship to omeprazole exposure.

A retrospective cohort study reported on 689 pregnant women exposed to either H2-blockers or omeprazole in the first trimester (134 exposed to omeprazole). The overall malformation rate was 4.4% (95% CI 3.6-5.3) and the malformation rate for first trimester exposure to omeprazole was 3.6% (95% CI 1.5-8.1). The relative risk of malformations associated with first trimester exposure to omeprazole compared with non-exposed women was 0.9 (95% CI 0.3-2.2). The study could effectively rule out a relative risk greater than 2.5 for all malformations. Rates of preterm delivery or growth retardation did not differ between the groups.

A controlled prospective observational study followed 113 women exposed to omeprazole during pregnancy (89% first trimester exposures). The reported rates of major congenital malformations was 4% for the omeprazole group, 2% for controls exposed to non-teratogens, and 2.8% in disease-paired controls (background incidence of major malformations 1-5%). Rates of spontaneous and elective abortions, preterm deliveries, gestational age at delivery, and mean birth weight did not differ among the groups. The sample size in this study had 80% power to detect a 5-fold increase in the rate of major malformations.

Reproductive and developmental toxicology studies conducted in rats and rabbits during organogenesis at oral omeprazole doses up to 28 times the human dose of 40 mg/day did not show any evidence of fetal structural abnormalities. However, dose-related increases in embryo-lethality, fetal resorptions, and pregnancy loss occurred when pregnant rabbits received omeprazole at doses about 2.8 to 28 times the human dose of 40 mg/day. In a peri- and post-natal development study, when pregnant rats received omeprazole at doses about 2.8 to 28 times the human dose of 40 mg/day, dose-related embryo/fetal toxicity and postnatal developmental toxicity occurred in offspring.

Clarithromycin:

When pregnant monkeys received 70 mg/kg/day oral clarithromycin (approximately equivalent to the maximum recommended human dose (MRHD) on a mg/m^2 basis) fetal growth retardation occurred at plasma concentrations that were 2 times the human serum concentrations achieved at the MRHD.

A low incidence of cardiovascular anomalies were observed in fetuses in two rat embryo-fetal studies of clarithromycin administered orally to dams on gestation days 6 to 15 at doses of 150 mg/kg/day, which resulted in plasma concentrations approximately 2 times the human serum concentrations achieved at the MRHD.

Four embryo-fetal studies in mice revealed a variable incidence of cleft palate following oral doses of 500 mg/kg/day and 1000 mg/kg/day (2 and 4 times the MRHD on a mg/m^2 basis, respectively) during organogenesis (gestation days 6 to 15). The 1000 mg/kg/day exposure resulted in plasma concentrations 17 times the human serum concentrations achieved at the MRHD.

No teratogenic effects occurred in offspring from two studies in pregnant rabbits that received oral clarithromycin doses up to 125 mg/kg/day (approximately 2 times the maximum recommended human dose on a mg/m^2 basis) or intravenous doses of 30 mg/kg/day during the period of major organogenesis.

Amoxicillin:

Reproduction studies have been performed in mice and rats at doses up to 10 times the human dose and revealed no evidence of impaired fertility or harm to the fetus due to amoxicillin.

8.2 Labor and Delivery

Omeprazole:

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.

Amoxicillin:

Oral ampicillin-class antibiotics are poorly absorbed during labor. Studies in guinea pigs showed that intravenous administration of ampicillin slightly decreased the uterine tone and frequency of contractions, but moderately increased the height and duration of contractions. However, it is not known whether amoxicillin affects labor or delivery in humans.

8.3 Nursing Mothers

Omeclamox®-Pak contains omeprazole, clarithromycin, and amoxicillin. Information on use of each product during lactation is provided below.

Omeprazole:

Breast milk concentrations of omeprazole were measured in the breast milk of one woman following oral administration of 20 mg. The peak concentration was 20 mcg/L, less than 7% of the peak maternal serum concentration. Based on this information, the estimated infant daily dose in an exclusively human-milk fed infant is 3 mcg/kg/day. However, due to the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or express and discard milk during Omeclamox®-Pak treatment.

Clarithromycin:

It is not known whether clarithromycin is excreted in human milk. However, other macrolide antibiotics are excreted in human milk. Clarithromycin is found in animal milk. Caution should be exercised when clarithromycin is administered to a nursing woman.

Amoxicillin:

Penicillins are excreted in human milk. Amoxicillin use by nursing mothers may lead to sensitization of infants. Caution should be exercised when amoxicillin is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of Omeclamox®-Pak for pediatric patients with *H. pylori* have not been established.

8.5 Geriatric Use

Omeprazole:

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

Pharmacokinetic studies 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 volunteers) and its plasma half-life averaged one hour, about twice that of young healthy volunteers. However, no dosage adjustment is necessary in the elderly [*See Clinical Pharmacology (12.3)*].

Clarithromycin:

In a steady-state study in which healthy elderly subjects (age 65 to 81 years old) were given 500 mg every 12 hours, the maximum serum concentrations and area under the curves of clarithromycin and 14-OH clarithromycin were increased compared to those achieved in healthy young adults. These changes in pharmacokinetics parallel known age-related decreases in renal function. In clinical trials, elderly patients did not have an increased incidence of

adverse events when compared to younger patients.

Amoxicillin:

An analysis of clinical studies of amoxicillin was conducted to determine whether subjects aged 65 and over respond differently from younger subjects. Of the 1811 subjects treated with amoxicillin, 85% were < 60 years old, 15% were ≥ 61 years old and 7% were ≥ 71 years old. This analysis and other reported clinical experience have not identified differences in responses between the elderly and younger patients, but a greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Renal Impairment

In the presence of severe renal impairment with or without coexisting hepatic impairment, prolonged dosing intervals for the clarithromycin component may be appropriate.

8.7 Hepatic Impairment

It is recommended to avoid the use of Omeclamox®-Pak in patients with hepatic impairment [*See Clinical Pharmacology (12.3)*].

8.8 Asian Patients

It is recommended to avoid the use of Omeclamox®-Pak in Asian patients unless it is deemed that the benefits outweigh the risks [*See Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

In case of an overdose, patients should contact a physician, poison control center, or emergency room. There is neither a pharmacologic basis nor data suggesting an increased toxicity of the combination compared to individual components.

As with the management of any overdose, the possibility of multiple drug ingestion should be considered. For current information on treatment of any drug overdose, contact your local Poison Control Center at 1-800-222-1222.

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 [*See Adverse Reactions (6.3)*]. 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.

Single oral doses of omeprazole at 1350, 1339, and 1200 mg/kg were lethal to mice, rats, and dogs, respectively. Animals given these doses showed sedation, ptosis, tremors, convulsions, and decreased activity, body temperature, and respiratory rate and increased depth of respiration.

Clarithromycin:

Overdosage of clarithromycin can cause gastrointestinal symptoms such as abdominal pain, vomiting, nausea, and diarrhea.

Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, clarithromycin serum concentrations are not expected to be appreciably affected by hemodialysis or peritoneal dialysis.

Amoxicillin:

In case of overdosage, discontinue medication, treat symptomatically, and institute supportive measures as required. If the overdosage is very recent and there is no contraindication, an attempt at emesis or other means of removal of drug from the stomach may be performed. A prospective study of 51 pediatric patients at a poison-control center suggested that overdosages of less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms and do not require gastric emptying.[1]

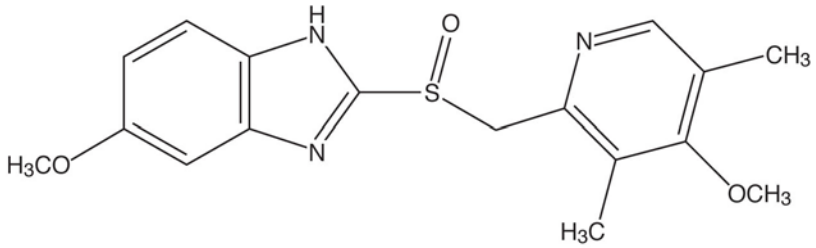
Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after overdosage with amoxicillin. Crystalluria, in some cases leading to renal failure, has also been reported after amoxicillin overdosage in adult and pediatric patients. In case of overdosage, adequate fluid intake and diuresis should be maintained to reduce the risk of amoxicillin crystalluria. Renal impairment appears to be reversible with cessation of drug administration. High blood concentrations may occur more readily in patients with impaired renal function because of decreased renal clearance of amoxicillin. Amoxicillin can be removed from circulation by hemodialysis.

11 DESCRIPTION

Omeclamox®-Pak consists of a pack of ten individual daily administration cards, each card containing two omeprazole delayed-release 20 mg capsules, USP, two clarithromycin 500 mg tablets, USP, and four amoxicillin 500 mg capsules, USP, for oral administration.

Omeprazole Delayed-Release Capsules, USP:

The active ingredient in omeprazole delayed-release capsules is a substituted benzimidazole, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl]1*H*-benzimidazole, a compound 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:

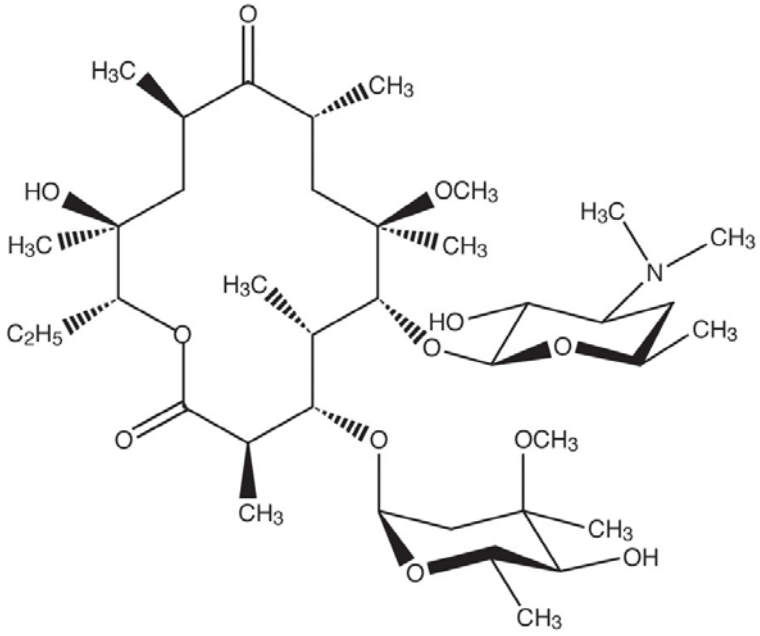


Omeprazole is a white to off-white crystalline powder that melts with decomposition at about 155°C. It is a weak base, freely soluble in ethanol and methanol, and slightly soluble in acetone and isopropanol, and very slightly soluble in water. The stability of omeprazole is a function of pH; it is rapidly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

Each omeprazole delayed-release capsule contains 20 mg of omeprazole in the form of enteric-coated granules with the following inactive ingredients: crospovidone, hypromellose, lactose, magnesium stearate, mannitol, meglumine, methacrylic acid copolymer, poloxamer, povidone and triethyl acetate. The capsule shells contain: D&C Red #28, FD&C Blue No. 1, FD&C Red No. 40, FD&C Yellow No. 6, yellow iron oxide, gelatin, silicon dioxide, sodium lauryl sulfate and titanium dioxide. Imprinting ink contains: D&C Yellow No. 10 aluminum lake, FD&C Blue No. 1 aluminum lake, FD&C Blue No. 2 aluminum lake, FD&C Red No. 40 aluminum lake, n-butyl alcohol, pharmaceutical glaze, propylene glycol, SDA-3A alcohol and synthetic black iron oxide.

Clarithromycin Tablets, USP:

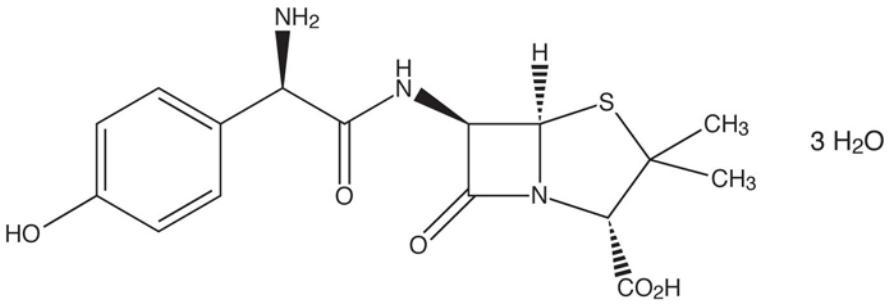
Clarithromycin is a semi-synthetic macrolide antibiotic. Chemically, it is 6-*O*-methylerythromycin. The molecular formula is $C_{38}H_{69}NO_{13}$, and the molecular weight is 747.96. Clarithromycin has the following structural formula:



Clarithromycin is a white to off-white crystalline powder. It is soluble in acetone, slightly soluble in methanol, ethanol, and acetonitrile, and practically insoluble in water. Each tablet for oral administration contains 500 mg of clarithromycin and the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, Opadry II (White), povidone, stearic acid, and talc. Opadry II (White) contains hypromellose, polyethylene glycol, polydextrose, titanium dioxide and triacetin.

Amoxicillin Capsules, USP:

Amoxicillin, a semisynthetic antibiotic, is an analogue of ampicillin, with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Chemically it is (2S, 5R, 6R)-6-[(R)-(-)-2-amino-2-(p-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0] heptane-2-carboxylic acid trihydrate. Its empirical formula is $C_{16}H_{19}N_3O_5S \cdot 3H_2O$ with a molecular weight of 419.45. Amoxicillin has the following structural formula:



Amoxicillin capsules contain amoxicillin trihydrate equivalent to 500 mg of amoxicillin. Amoxicillin capsules USP also contain magnesium stearate and sodium lauryl sulfate. The capsule shell contains D&C Red No. 33, FD&C Blue No. 1, FD&C Red No. 40, FD&C Yellow No. 6, gelatin, sodium lauryl sulfate and titanium dioxide. Each 500 mg capsule contains up to 0.0052 mEq (0.119 mg) of sodium.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Omeprazole is an antisecretory drug whereas clarithromycin and amoxicillin are antibacterial drugs [*See Clinical*

Pharmacology (12.4)].

12.3 Pharmacokinetics

Pharmacokinetics when all three of the Omeclamox®-Pak components were coadministered has not been studied. Studies have shown the low risk of clinically significant interactions of omeprazole and amoxicillin or omeprazole and clarithromycin when administered together. There is no information about the gastric mucosal concentrations of omeprazole, clarithromycin and amoxicillin after administration of these drugs concomitantly. The systemic pharmacokinetic information presented below is based on studies in which each product was administered alone, or in combination of two components.

Omeprazole Delayed-Release Capsules, USP:

Absorption and Distribution

Omeprazole delayed-release capsules contain an enteric-coated granule formulation of omeprazole (because omeprazole is acid-labile), so that absorption of omeprazole begins only after the granules leave the stomach. Absorption is rapid, with peak plasma concentrations of omeprazole occurring within 0.5 to 3.5 hours. Peak plasma concentrations of omeprazole and AUC are approximately proportional to doses up to 40 mg, but because of a saturable first-pass effect, a greater than linear response in peak plasma concentration and AUC occurs with doses greater than 40 mg. Absolute bioavailability (compared with intravenous administration) is about 30-40% at doses of 20-40 mg, due in large part to presystemic metabolism. In healthy subjects the plasma half-life is 0.5 to 1 hour, and the total body clearance is 500-600 mL/min.

The bioavailability of omeprazole increases slightly upon repeated administration of omeprazole delayed-release capsules.

Omeprazole delayed-release capsules 40 mg was bioequivalent when administered with and without applesauce. However, omeprazole delayed-release capsules 20 mg was not bioequivalent when administered with and without applesauce. When administered with applesauce, a mean 25% reduction in C_{max} was observed without a significant change in AUC for omeprazole delayed-release capsules 20 mg. The clinical relevance of this finding is unknown. Protein binding is approximately 95%.

Metabolism and Excretion

Omeprazole is extensively metabolized by the cytochrome P450 (CYP) enzyme system. Following single dose oral administration of a buffered solution of omeprazole, little if any unchanged drug was excreted in urine. The majority of the dose (about 77%) was eliminated in urine as at least six metabolites. Two were 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.

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 volunteers, versus 58% in young volunteers 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 volunteers) and its plasma half-life averaged one hour, about twice that of young healthy volunteers.

Hepatic Impairment

In patients with chronic hepatic disease, the bioavailability of omeprazole increased to approximately 100% compared with an IV dose, reflecting decreased first-pass effect, and the plasma half-life of the drug increased to nearly 3 hours compared with the half-life in normals of 0.5-1 hour. Plasma clearance averaged 70 mL/min, compared with a value of 500-600 mL/min in normal subjects. It is recommended to avoid the use of Omeclamox®-Pak in patients with hepatic impairment.

Renal Impairment

In patients with chronic renal impairment, whose creatinine clearance ranged between 10 and 62 mL/min/1.73m,^{2} the disposition of omeprazole was very similar to that in healthy volunteers, although there was a slight increase in bioavailability. Because urinary excretion is a primary route of excretion of omeprazole metabolites, their elimination slowed in proportion to the decreased creatinine clearance. No dose reduction is necessary in patients with renal impairment.

Asian Patients

In pharmacokinetic studies of single 20 mg omeprazole doses, an increase in AUC of approximately four-fold was noted in Asian subjects compared with Caucasians. It is recommended to avoid the use of Omeclamox®-Pak in Asian patients unless it is deemed that the benefits outweigh the risks.

Clarithromycin Tablets, USP:

Clarithromycin is rapidly absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability of 250 mg clarithromycin tablets was approximately 50%. For a single 500 mg dose of clarithromycin, food slightly delays the onset of clarithromycin absorption, increasing the peak time from approximately 2 to 2.5 hours. Food also increases the clarithromycin peak plasma concentration by about 24%, but does not affect the extent of clarithromycin bioavailability. Food does not affect the onset of formation of the antimicrobially active metabolite, 14-OH clarithromycin or its peak plasma concentration but does slightly increase the extent of metabolite formation, indicated by an 11% decrease in area under the plasma concentration-time curve (AUC). Therefore, clarithromycin tablets may be given without regard to food.

In nonfasting healthy human subjects (males and females), peak plasma concentrations were attained within 2 to 3 hours after oral dosing. Steady-state peak plasma clarithromycin concentrations were attained within 3 days and were approximately 3 to 4 µg/mL with a 500 mg dose administered every 8 to 12 hours. The elimination half-life of clarithromycin was 5 to 7 hours with 500 mg administered every 8 to 12 hours. The nonlinearity of clarithromycin pharmacokinetics is slight at the recommended dose of 500 mg administered every 8 to 12 hours. With a 500 mg every 8 to 12 hours dosing, the peak steady-state concentration of 14-OH clarithromycin is up to 1 µg/mL, and its elimination half-life is about 7 to 9 hours. The steady-state concentration of this metabolite is generally attained within 3 to 4 days.

After a 500 mg tablet every 12 hours, the urinary excretion of clarithromycin is approximately 30%. The renal clearance of clarithromycin approximates the normal glomerular filtration rate. The major metabolite found in urine is 14-OH clarithromycin, which accounts for an additional 10% to 15% of the dose with a 500 mg tablet administered every 12 hours.

The steady-state concentrations of clarithromycin in subjects with impaired hepatic function did not differ from those in normal subjects; however, the 14-OH clarithromycin concentrations were lower in the hepatically impaired subjects. The decreased formation of 14-OH clarithromycin was at least partially offset by an increase in renal clearance of clarithromycin in the subjects with impaired hepatic function when compared to healthy subjects.

The pharmacokinetics of clarithromycin was altered in subjects with impaired renal function. In the presence of severe renal impairment with or without coexisting hepatic impairment, prolonged dosing intervals for clarithromycin may be appropriate.

Amoxicillin Capsules, USP:

Amoxicillin is stable in the presence of gastric acid and may be given without regard to meals. It is rapidly absorbed after oral administration. It diffuses readily into most body tissues and fluids, with the exception of brain and spinal fluid, except when meninges are inflamed. The half-life of amoxicillin is 61.3 minutes. Most of the amoxicillin is excreted unchanged in the urine; its excretion can be delayed by concurrent administration of probenecid. In blood serum, amoxicillin is approximately 20% protein-bound.

Orally administered doses of 500 mg amoxicillin capsules result in average peak blood concentrations 1 to 2 hours after administration in the range of 5.5 µg /mL to 7.5 µg /mL. Detectable serum concentrations are observed up to 8 hours after an orally administered dose of amoxicillin. Approximately 60% of an orally administered dose of amoxicillin is excreted in the urine within 6 to 8 hours.

Combination Therapy of Omeprazole with Antimicrobials:

Omeprazole 40 mg daily was given in combination with clarithromycin 500 mg every 8 hours to healthy adult male

subjects. The steady-state plasma concentrations of omeprazole were increased (C_{max}, AUC_{0-24}, and $T_{1/2}$ increases of 30%, 89% and 34% respectively) by the concomitant administration of clarithromycin. The observed increases in omeprazole plasma concentration were associated with the following pharmacological effects. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when coadministered with clarithromycin.

The plasma concentrations of clarithromycin and 14-hydroxy-clarithromycin were increased by the concomitant administration of omeprazole. For clarithromycin, the mean C_{max} was 10% greater, the mean C_{min} was 27% greater, and the mean AUC_{0-8} was 15% greater when clarithromycin was administered with omeprazole than when clarithromycin was administered alone. Similar results were seen for 14-hydroxy-clarithromycin, the mean C_{max} was 45% greater, the mean C_{min} was 57% greater, and the mean AUC_{0-8} was 45% greater. Clarithromycin concentrations in the gastric tissue and mucus were also increased by concomitant administration of omeprazole.

Table 1 Mean ± SD Clarithromycin Tissue Concentrations 2 hours after Dose

Tissue	Clarithromycin (µg/g)	Clarithromycin+Omeprazole (µg/g)
Antrum	10.48 ± 2.01 (n = 5)	19.96 ± 4.71 (n=5)
Fundus	20.81 ± 7.64 (n = 5)	24.25 ± 6.37 (n= 5)
Mucus	4.15 ± 7.74 (n = 4)	39.29 ± 32.79 (n=4)

Drug Interactions:

Antiretroviral Drugs and Omeprazole

The clinical importance and the mechanisms behind interactions between omeprazole and antiretroviral drugs are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via inhibition of CYP2C19.

Following multiple doses of nelfinavir (1250 mg twice daily) and omeprazole (40 mg once daily), AUC of nelfinavir and the M8 metabolite was decreased by 36% and 92%, C_{max} by 37% and 89% and C_{min} by 39% and 75%.

Following multiple doses of atazanavir (400 mg once daily) and omeprazole (40 mg once daily 2 hours before atazanavir), AUC of atazanavir was decreased by 94%, C_{max} by 96%, and C_{min} by 95%. Concomitant administration with omeprazole and atazanavir is not recommended.

Saquinavir serum AUC, C_{max} and C_{min} increased by 82%, 75% and 106%, respectively, following multiple dosing of saquinavir/ritonavir (1000/100 mg) twice daily for 15 days with omeprazole 40 mg once daily coadministered days 11 to 15 [*See Drug Interactions (7.6)*].

Cilostazol and Omeprazole

Omeprazole acts as an inhibitor of CYP2C19. Omeprazole, given in doses of 40 mg daily for one week to 20 healthy subjects in crossover study, increased C_{max} and AUC of cilostazol by 18% and 26% respectively. C_{max} and AUC of one of its active metabolites, 3,4-dihydro-cilostazol, which has 4-7 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 its above mentioned active metabolite. Therefore a dose reduction of cilostazol from 100 mg b.i.d. to 50 mg b.i.d. should be considered [*See Drug Interactions (7.7)*].

Theophylline and Clarithromycin

Theophylline is metabolized by CYP1A2 and CYP3A4. Clarithromycin will increase theophylline plasma concentrations when it is administered concomitantly. In two studies in which theophylline was administered with clarithromycin (theophylline sustained-release formulation dosed at either 6.5 mg/kg or 12 mg/kg together with 250 or 500 mg every 12 hours clarithromycin), the steady-state C_{max}, C_{min}, and AUC of theophylline increased about 20%. Monitoring of serum theophylline concentrations should be considered for patients receiving high doses of theophylline or with baseline concentrations in the upper therapeutic range [*See Drug Interactions (7.9)*].

Voriconazole and Omeprazole

Voriconazole is an inhibitor of CYP2C19, CYP2C9, and CYP3A4. Coadministration of voriconazole and omeprazole will increase omeprazole plasma exposure. When voriconazole (400 mg every 12 hours x 1 day, then 200 mg x 6

days) was given with omeprazole (40 mg once daily x 7 days) to healthy subjects, it significantly increased the steady-state C_{max} and AUC_{0-24} of omeprazole, an average of 2 times (90% CI: 1.8, 2.6) and 4 times (90% CI: 3.3, 4.4) respectively as compared to when omeprazole was given without voriconazole. Dose adjustment of omeprazole is not normally required.

Mycophenolate mofetil

Administration of omeprazole 20 mg twice daily for 4 days and a single 1000 mg dose of mycophenolate mofetil approximately one hour after the last dose of omeprazole to 12 healthy subjects in a cross-over study resulted in a 52% reduction in the Cmax and 23% reduction in the AUC of mycophenolic acid.

12.4 Microbiology

Mechanism of Action:

Omeprazole, an antisecretory drug with the substituted benzimidazoles, suppresses 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-dependent and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Omeprazole can also exhibit anti-bacterial activity depending on the culture conditions. Animal studies indicate that after rapid disappearance from plasma, omeprazole can be found within the gastric mucosa for a day or more.

Clarithromycin exerts its antibacterial activity by binding to the 50S ribosomal subunit of susceptible microorganisms resulting in inhibition of protein synthesis.

Amoxicillin acts through the inhibition of biosynthesis of cell wall mucopeptide.

Activity *in vitro* and *in vivo*:

Triple therapy with omeprazole, clarithromycin and amoxicillin has been shown to be active against most strains of *Helicobacter pylori in vitro* and in clinical infections as indicated [*See Indications and Usage (1.1)*].

In vitro studies show that chloramphenicol, macrolides, sulfonamides, and tetracyclines may interfere with bactericidal effects of penicillin; however, the clinical significance of this interaction is not well documented.

Drug Resistance:

Helicobacter pylori Pretreatment Resistance

Clarithromycin pretreatment resistance rates were 9.3% (41/439) in omeprazole/clarithromycin/amoxicillin triple therapy studies [*See Clinical Studies (14.1)*].

Amoxicillin pretreatment susceptible isolates (≤ 0.25 µg/mL) were found in 99.3% (436/439) of the patients in the omeprazole/clarithromycin/amoxicillin triple therapy studies (1, 2, and 3). Amoxicillin pretreatment minimum inhibitory concentrations (MICs) > 0.25 µg/mL occurred in 0.7% (3/439) of the patients, all of whom were in the clarithromycin and amoxicillin study arm. One patient had an unconfirmed pretreatment amoxicillin minimum inhibitory concentration (MIC) of > 256 µg/mL by Etest.®

Table 2
Pre-treatment and post-treatment clarithromycin susceptibility test results and clinical/bacteriological outcomes in patients treated with triple therapy*

Clarithromycin Pre-treatment Results			Clarithromycin Post-treatment Results			
		H. pylori negative – eradicated	*H. pylori* positive – not eradicated Post-treatment susceptibility results			
			S[a]	I[a]	R[a]	No MIC
Susceptible[a]	171	153	7	0	3	8
Intermediate[a]	0	0	0	0	0	0
Resistant[a]	14	4	1	0	6	3

[a]Susceptible (S) MIC ≤ 0.25 µg/mL, Intermediate (I) MIC 0.5 µg/mL, Resistant (R) MIC ≥ 1 µg/mL.
*Treatment with omeprazole 20 mg twice daily/clarithromycin 500 mg twice daily/amoxicillin 1 g twice daily for 10 days (Studies 1, 2 and 3) followed by omeprazole 20 mg once daily for another 18 days (Studies 1 and 2).

Patients not eradicated of *H. pylori* following omeprazole/clarithromycin/amoxicillin triple therapy will likely have clarithromycin resistant *H. pylori* isolates. Therefore, clarithromycin susceptibility testing should be done, if possible. Patients with clarithromycin-resistant *H. pylori* should not be treated with any of the following: omeprazole/clarithromycin dual therapy, omeprazole/clarithromycin/amoxicillin triple therapy, or other regimens which include clarithromycin as the sole antimicrobial agent.

Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes

In the triple therapy clinical trials, 84.9% (157/185) of the patients in the omeprazole/clarithromycin/amoxicillin treatment group who had pretreatment amoxicillin susceptible MICs (≤ 0.25 µg/mL) were eradicated of *H. pylori* and 15.1% (28/185) failed therapy. Of the 28 patients who failed triple therapy, 11 had no post-treatment susceptibility test results and 17 had post-treatment *H. pylori* isolates with amoxicillin susceptible MICs. Eleven of the patients who failed triple therapy also had post-treatment *H. pylori* isolates with clarithromycin resistant MICs.

Susceptibility Test for *Helicobacter pylori*:

The reference methodology for susceptibility testing of *H. pylori* is agar dilution MICs [*See References (15)*]. One to three microliters of an inoculum equivalent to a No. 2 McFarland standard ($1 \times 10^7 - 1 \times 10^8$ CFU/mL for *H. pylori*) are inoculated directly onto freshly prepared antimicrobial containing Mueller-Hinton agar plates with 5% aged defibrinated sheep blood (≥ 2 weeks old). The agar dilution plates are incubated at 35°C in a microaerobic environment produced by a gas generating system suitable for campylobacters. After 3 days of incubation, the MICs are recorded as the lowest concentration of antimicrobial agent required to inhibit growth of the organism. The clarithromycin and amoxicillin MIC values should be interpreted according to the following criteria:

Table 3 *In vitro* Susceptibility Interpretive Criteria for Clarithromycin and Amoxicillin

Clarithromycin MIC (µg/mL)[a]	Interpretation
≤ 0.25	Susceptible (S)
0.5	Intermediate (I)
≥ 1.0	Resistant (R)
Amoxicillin MIC (µg/mL)[a,b]	**Interpretation**
≤ 0.25	Susceptible (S)

[a]These are breakpoints for the agar dilution methodology and they should not be used to interpret results obtained using alternative methods.
[b]There were not enough organisms with MICs > 0.25 µg/mL to determine a resistance breakpoint.

Quality Control

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin and amoxicillin powders should provide the following MIC values:

Table 4 Quality Control for Susceptibility Testing

Microorganism[a]	Antimicrobial Agent	MIC (µg/mL)
H. pylori ATCC 43504	Clarithromycin	0.015-0.012
H. pylori ATCC 43504	Amoxicillin	0.015-0.012

[a]These are quality control ranges for the agar dilution methodology and they should not be used to control test results obtained using alternative methods.

Effects on Gastrointestinal Microbial Ecology:

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella and Campylobacter.*

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Omeprazole:

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 (about 0.7 to 57 times a human dose of 20 mg/day, as expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both males and females; the incidence of this effect was markedly higher in female rats, which had higher blood concentrations 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 (about 6 times a human dose of 20 mg/day, based on body surface area) for one year, and 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 vs. 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs. 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 0.2 to 6.5 times the human dose on a body surface area basis). No astrocytomas were observed in female rats in this study or in males or females from a 2-year carcinogenicity study in Sprague-Dawley rats at the high dose of 140.8 mg/kg/day (about 57 times the human dose 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.

Omeprazole at oral doses up to 138 mg/kg/day in rats (about 56 times the human dose on a body surface area basis) was found to have no effect on fertility and reproductive performance.

14 CLINICAL STUDIES

14.1 *H. pylori* associated Duodenal Ulcer Disease

Three U.S., randomized, double-blind clinical studies in patients with *H. pylori* infection and duodenal ulcer disease (n = 558) compared omeprazole plus clarithromycin plus amoxicillin with clarithromycin plus amoxicillin. Two studies (1 and 2) were conducted in patients with an active duodenal ulcer, and the other study (3) was conducted in patients with a history of a duodenal ulcer in the past 5 years but without an ulcer present at the time of enrollment. The dose regimen in the studies was omeprazole 20 mg twice daily plus clarithromycin 500 mg twice daily plus amoxicillin 1 g twice daily for 10 days; or clarithromycin 500 mg twice daily plus amoxicillin 1 g twice daily for 10 days. In studies 1 and 2, patients who took the omeprazole regimen also received an additional 18 days of omeprazole 20 mg once daily. Endpoints studied were eradication of *H. pylori* and duodenal ulcer healing (studies 1 and 2 only). *H. pylori* status was determined by CLOtest,® histology and culture in all three studies. For a given patient, *H. pylori* was considered eradicated if at least two of these tests were negative and none was positive.

The combination of omeprazole plus clarithromycin plus amoxicillin, was effective in eradicating *H. pylori.*

Table 5

Per-Protocol and Intent-to-Treat *H. pylori* Eradication Rates
% of Patients Cured [95% Confidence Interval]

Per-Protocol and Intent-to-Treat *H. pylori* Eradication Rates % of Patients Cured [95% Confidence Interval]				
	omeprazole + clarithromycin + amoxicillin		clarithromycin + amoxicillin	
	Per-Protocol†	Intent-to-Treat‡	Per-Protocol†	Intent-to-Treat‡
Study 1	*77 [64, 86] (n = 64)	*69 [57, 79] (n = 80)	43 [31, 56] (n = 67)	37 [27, 48] (n = 84)
Study 2	*78 [67, 88] (n = 65)	*73 [61, 82] (n = 77)	41 [29, 54] (n = 68)	36 [26, 47] (n = 83)
Study 3	*90 [80, 96] (n = 69)	*83 [74, 91] (n = 84)	33 [24, 44] (n = 93)	32 [23, 42] (n = 99)

†Patients were included in the analysis if they had confirmed duodenal ulcer disease (active ulcer, studies 1 and 2; history of ulcer within 5 years, study 3) and *H. pylori* infection at baseline defined as at least two of three positive endoscopic tests from CLOtest,® histology, and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the analysis as failures of therapy. The impact of eradication on ulcer recurrence has not been assessed in patients with a past history of ulcer.

‡Patients were included in the analysis if they had documented *H. pylori* infection at baseline and had confirmed duodenal ulcer disease. All dropouts were included as failures of therapy.

*($p < 0.05$) versus clarithromycin plus amoxicillin.

15 REFERENCES

1. Swanson-Biearman B, Dean BS, Lopez G, Krenzelok EP. The effects of penicillin and cephalosporin ingestions in children less than six years of age. *Vet Hum Toxicol.* 1988;30:66-67.
2. Clinical Laboratory Standards Institute. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard- Eighth Edition.* CLSI document M07-A8. Wayne, PA: Clinical and Laboratory Standards Institute; 2009.

16 HOW SUPPLIED/STORAGE AND HANDLING

Omeclamox®-Pak is supplied in a carton containing ten individual daily administration cards. Each card contains the morning dose and the evening dose of the following three drugs:

Omeprazole Delayed-Release Capsules, USP, 20 mg
- Two opaque hard gelatin lavender and grey capsules, with ‘R 158’ and ‘OMEPRAZOLE 20 mg’ imprinted on the capsules in black ink, containing off-white to pale-yellow, elliptical spherical pellets.

Clarithromycin Tablets, USP, 500 mg
- Two white, biconvex beveled-edge capsule-shaped coated tablets debossed with ‘54 312’ on one side and plain on the other side.

Amoxicillin Capsules, USP, 500 mg
- Four opaque hard gelatin peach and orange capsules, marked ‘WC 731’. Each capsule contains amoxicillin trihydrate equivalent to 500 mg amoxicillin.

NDC 65224-707-11	Carton containing 10 daily administration cards
NDC 65224-707-00	Daily administration card

Store at controlled room temperature between 20°C and 25°C (68°F and 77°F). Protect from light and moisture.

17 PATIENT COUNSELING INFORMATION

17.1 Administration

Inform patients that each dose of Omeclamox®-Pak contains four pills: one opaque lavender/grey capsule

(omeprazole), one white tablet (clarithromycin) and two opaque, peach/orange capsules (amoxicillin).

Take each dose of four pills in the morning and four pills in the evening before eating a meal, for 10 days. Capsules and tablets should not be crushed or chewed, and should be swallowed whole [*See Dosage and Administration (2)*].

17.3 Drug Interactions

Patients should be advised to report to their doctor the use of any other medications while taking Omeclamox®-Pak [*See Drug Interactions (7)*].

The simultaneous administration of any of the following drugs with Omeclamox®-Pak may result in clinically significant adverse reactions or even death:

- Colchicine
- Ergotamine/dihydroergotamine
- Pimozide
- Antiarrhythmic drugs (e.g., quinidine, disopyramide)
- Digoxin
- Anticoagulants (e.g., warfarin)
- Atazanavir
- Nelfinavir
- Saquinavir
- Cilostazol
- Tacrolimus
- Theophylline
- Carbamazepine
- Sildenafil
- HMG-CoA reductase inhibitors (also known as statins)
- Triazolobenziodidiazepines (e.g., triazolam and alprazolam) and related benzodiazepines (e.g., midazolam)
- Probenecid
- Drugs for which gastric pH can affect bioavailability

17.4 *Clostridium difficile*-associated Diarrhea

Advise patients that diarrhea is a common problem caused by omeprazole and antibiotics that usually ends when the drug is discontinued. Sometimes after starting treatment, patients can develop severe diarrhea with watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the drug. If this occurs, patients should contact a physician as soon as possible [*See Warnings and Precautions (5.4)*].

17.5 Antibacterial Resistance

Counsel patients that antibacterial drugs including Omeclamox®-Pak should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Omeclamox®-Pak is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Omeclamox-Pak™ or other antibacterial drugs in the future.

Omeclamox®-Pak is distributed by CUMBERLAND PHARMACEUTICALS INC, Nashville, TN 37203.

Omeprazole Delayed-Release Capsules, USP, 20 mg
Manufactured by Dr. Reddy's Laboratories, Limited, Bachepalli, 502 325, INDIA

Clarithromycin Tablets, USP, 500 mg
Manufactured by Roxane Laboratories, Inc., a division of Boehringer Ingelheim, Columbus, OH 43228, U.S.A.

Amoxicillin Capsules, USP, 500 mg
Manufactured by Suir Pharma Ireland Ltd., Clonmel, IRELAND

Promoted by:

For inquiries contact Cumberland® Pharmaceuticals 1-877-484-2700

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