

Nolcer

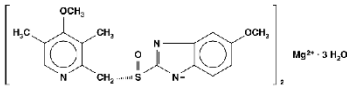
(Esomeprazole)

نولسر کپسولز
(اسوی پرازول)
۲۰ ملی گرام اور ۴۰ ملی گرام

20mg & 40mg Capsules

1 DESCRIPTION

The active ingredient in the proton pump inhibitor NOLCER® (esomeprazole magnesium) Delayed-Release Capsules for oral administration and NOLCER (esomeprazole magnesium) For Delayed-Release Oral Suspension is bis(5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfanyl)-1H-benzimidazole-1-yl) magnesium trihydrate. Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S- and R- isomers. (Initial U.S. approval of esomeprazole magnesium: 2001). Its molecular formula is (C 17 H 18 N 3 O 3 S) 2 Mg x 3 H 2 O with molecular weight of 767.2 as a trihydrate and 713.1 on an anhydrous basis. The structural formula is:



2 INDICATIONS AND USAGE

2.1 Treatment of Gastroesophageal Reflux Disease (GERD)

Healing of Erosive Esophagitis

NOLCER is indicated for the short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of diagnostically confirmed erosive esophagitis. For those patients who have not healed after 4 to 8 weeks of treatment, an additional 4 to 8 week course of NOLCER may be considered.

In infants 1 month to less than 1 year.

NOLCER is indicated for short-term treatment (up to 6 weeks) of erosive esophagitis due to acid-mediated GERD.

Maintenance of Healing of Erosive Esophagitis

NOLCER is indicated to maintain symptom resolution and healing of erosive esophagitis. Controlled studies do not extend beyond 6 months.

Symptomatic Gastroesophageal Reflux Disease

NOLCER is indicated for short-term treatment (4 to 8 weeks) of heartburn and other symptoms associated with GERD in adults and children 1 year or older.

2.2 Risk Reduction of NSAID-Associated Gastric Ulcer

NOLCER is indicated for the reduction in the occurrence of gastric ulcers associated with continuous NSAID therapy in patients at risk for developing gastric ulcers. Patients are considered to be at risk due to their age (> 60) and/or documented history of gastric ulcers. Controlled studies do not extend beyond 6 months.

2.3 H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence

Triple Therapy (NOLCER plus amoxicillin and clarithromycin): NOLCER, in combination with amoxicillin and clarithromycin, is indicated for the treatment of patients with H. pylori infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate H. pylori. Eradication of H. pylori has been shown to reduce the risk of duodenal ulcer recurrence [see Dosage and Administration (2) and Clinical Studies].

In patients who fail therapy, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted [see Clinical Pharmacology (12.4) and the prescribing information for clarithromycin].

2.4 Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

NOLCER is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome.

3 DOSAGE AND ADMINISTRATION

NOLCER is supplied as delayed-release capsules for oral administration or in packets for preparation of delayed-release oral suspensions. The recommended dosages are outlined in Table 1. NOLCER should be taken at least one hour before meals.

The duration of proton pump inhibitor administration should be based on available safety and efficacy data specific to the defined indication and dosing frequency, as described in the prescribing information, and individual patient medical needs. Proton pump inhibitor treatment should only be initiated and continued if the benefits outweigh the risks of treatment.

Table 1: Recommended Dosage Schedule of NOLCER

Indication	Dose	Frequency
Gastroesophageal Reflux Disease (GERD)		
Healing of Erosive Esophagitis	20 mg or 40 mg	Once Daily for 4 to 8 Week
Maintenance of Healing of Erosive Esophagitis	20 mg	Once Daily
Erosive Esophagitis	20 mg	Once Daily for 4 Weeks
Symptomatic Gastroesophageal Reflux Disease	20 mg	Once Daily for 4 Weeks
Pediatric GERD		
12 to 17 Year Olds		
Healing of Erosive Esophagitis	20 mg or 40 mg	Once Daily for 4 to 8 Weeks
Symptomatic GERD	20 mg	Once Daily for 4 Weeks
1 to 11 Year Olds⁺		
Short-term Treatment of Symptomatic GERD		
Healing of Erosive Esophagitis	10 mg	Once Daily for up to 8 Weeks
weight < 20 kg	10 mg	Once Daily for 8 Weeks
weight < 20 kg	10 mg or 20mg	Once Daily for 8 Weeks
1 month to < 1 year old⁺⁺⁺		
Erosive esophagitis due to acid-mediated GERD		
weight 3 kg to 5 kg	2.5 mg	Once Daily for up to 6 Weeks
weight > 5 kg to 7.5 kg	5 mg	Once Daily for up to 6 Weeks
weight > 7.5 kg to 12 kg	10 mg	Once Daily for up to 6 Weeks
Risk Reduction of NSAID-Associated Gastric Ulcer	20 mg or 40 mg	Once Daily for up to 6 months
H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence		
<i>Triple Therapy:</i>		
NOLCER	40 mg	Once Daily for 10 Days
Amoxicillin	1000 mg	Twice Daily for 10 Days
Clarithromycin	500 mg	Twice Daily for 10 Days
Pathological Hypersecretory Conditions Including Zollinger-Elison Syndrome	40 mg†	†Twice Daily

[See Clinical Studies] The majority of patients are healed within 4 to 8 weeks. For patients who do not heal after 4 to 8 weeks, an additional 4 to 8 weeks of treatment may be considered.

⁺Controlled studies did not extend beyond six months.

⁺⁺H. pylori symptoms do not resolve completely after 4 weeks, an additional 4 weeks of treatment may be considered.

⁺⁺⁺Doses over 1 mg/kg/day have not been studied.

[†]The dosage of NOLCER in patients with pathological hypersecretory conditions varies with the individual patient. Dosage regimens should be adjusted to individual patient needs.

[‡]Doses up to 240 mg daily have been administered [see Drug Interactions].

[§]Doses over 1.33 mg/kg/day have not been studied.

Please refer to amoxicillin and clarithromycin prescribing information for Contraindications, Warnings, and dosing in elderly and renally-impaired patients.

Special Populations

Hepatic Insufficiency

In patients with mild to moderate liver impairment (Child Pugh Classes A and B), no dosage adjustment is necessary. For patients with severe liver impairment (Child Pugh Class C), a dose of 20 mg of NOLCER should not be exceeded [see Clinical Pharmacology].

Directions for use specific to the route and available methods of administration for each of these dosage forms are presented in Table 2.

NOLCER Delayed-Release Capsules

NOLCER Delayed-Release Capsules should be swallowed whole. Alternatively, for patients who have difficulty swallowing capsules, one tablespoon of applesauce can be added to an empty bowl and the NOLCER Delayed-Release Capsule can be opened, and the granules inside the capsule carefully emptied onto the applesauce. The granules should be mixed with the applesauce and then swallowed immediately; do not store for future use. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The granules should not be chewed or crushed. If the granules/applesauce mixture is not used in its entirety, the remaining mixture should be discarded immediately.

For patients who have a nasogastric tube in place, NOLCER Delayed-Release Capsules can be opened and the intact granules emptied into a 60 mL catheter tipped syringe and mixed with 50 mL of water. It is important to only use a catheter tipped syringe when administering NOLCER through a nasogastric tube. Replace the plunger and shake the syringe vigorously for 15 seconds. Hold the syringe with the tip up and check for granules remaining in the tip. Attach the syringe to a nasogastric tube and deliver the contents of the syringe through the nasogastric tube into the stomach. After administering the granules, the nasogastric tube should be flushed with additional water. Do not administer the granules if they have dissolved or disintegrated.

The mixture must be used immediately after preparation. NOLCER For Delayed-Release Oral Suspension

NOLCER For Delayed-Release Oral Suspension should be administered as follows:

- Empty the contents of a 2.5 mg or 5 mg packet into a container containing 5 mL of water. For the 10 mg, 20 mg, and 40 mg strengths, the contents of a packet should be emptied into a container containing 15 mL of water.
- Stir.
- Leave 2 to 3 minutes to thicken.
- Stir and drink within 30 minutes.
- If any medicine remains after drinking, add more water, stir, and drink immediately.
- In cases where there is a need to use two packets, they may be mixed in a similar
- way by adding twice the required amount of water or follow the mixing
- instructions provided by your pharmacist or doctor.

For patients who have a nasogastric or gastric tube in place, NOLCER For Delayed-Release Oral Suspension can be administered as follows:

- Add 5 mL of water to a catheter tipped syringe and then add the contents of a 2.5 mg or 5 mg NOLCER packet. For the 10 mg, 20 mg, and 40 mg strengths, the volume of water in the syringe should be 15 mL. It is important to only use a catheter tipped syringe when administering NOLCER through a nasogastric tube or gastric tube.
- Immediately shake the syringe and leave 2 to 3 minutes to thicken.
- Shake the syringe and inject through the nasogastric or gastric tube, French size 6
 - or larger, into the stomach within 30 minutes.
- Refill the syringe with an equal amount of water (5 mL or 15 mL).
- Shake and flush any remaining contents from the nasogastric or gastric tube into
- the stomach.

4 DOSAGE FORMS AND STRENGTHS

NOLCER Delayed-Release Capsules, 20 mg - opaque, hard gelatin, amethyst colored capsules with two radial bars in yellow on the cap and NOLCER 20 mg in yellow on the body.

NOLCER Delayed-Release Capsules, 40 mg - opaque, hard gelatin, amethyst colored capsules with three radial bars in yellow on the cap and NOLCER 40 mg in yellow on the body.

NOLCER For Delayed-Release Oral Suspension, 2.5 mg, 5 mg, 10 mg, 20 mg or 40 mg - unit dose packet containing a fine yellow powder, consisting of white to pale brownish esomeprazole granules and pale yellow inactive granules.

5 CONTRAINDICATIONS

NOLCER is contraindicated in patients with known hypersensitivity to substituted benzimidazoles or to any component of the formulation. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, and urticaria [see Adverse Reactions].

For information about contraindications of antibacterial agents (clarithromycin and amoxicillin) indicated in combination with NOLCER, refer to the CONTRAINDICATIONS section of their package inserts.

WARNINGS AND PRECAUTIONS

5.1 Concomitant Gastric Malignancy

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

5.2 Atrophic Gastritis

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole, of which esomeprazole is an enantiomer.

5.3 Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs including NOLCER. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue NOLCER if acute interstitial nephritis develops.

5.4 Cyanocobalamin (vitamin B-12) Deficiency

Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature.

This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

5.5 Clostridium difficile associated diarrhea

Published observational studies suggest that PPI therapy like NOLCER may be associated with an increased risk of Clostridium difficile associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve [see Adverse Reactions].

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents. For more information specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with NOLCER, refer to WARNINGS and PRECAUTIONS sections of those package inserts.

5.6 Interaction with Clopidogrel

Avoid concomitant use of NOLCER 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 esomeprazole, that inhibit CYP2C19 activity. Concomitant use of clopidogrel with 40 mg esomeprazole reduces the pharmacological activity of clopidogrel. When using NOLCER consider alternative anti-platelet therapy [see Drug Interactions (7.3) and Pharmacokinetics].

5.7 Bone Fracture

Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines [see Dosage and Administration (2) and Adverse Reactions].

5.8 Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically [see Adverse Reactions].

5.9 Concomitant use of NOLCER with St. John's Wort or Rifampin

Drugs which induce CYP2C19 or CYP3A4 (such as St. John's Wort or rifampin) can substantially decrease esomeprazole concentrations [see Drug Interactions (7.3)]. Avoid concomitant use of NOLCER with St. John's Wort or rifampin.

5.10 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. Healthcare providers should temporarily stop esomeprazole treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g. for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.]

5.11 Concomitant use of NOLCER with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration a temporary withdrawal of the PPI may be considered in some patients [see Drug Interactions (7.7)].

6 ADVERSE REACTIONS

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.

Adults

The safety of NOLCER was evaluated in over 15,000 patients (aged 18 to 84 years) in clinical trials worldwide including over 8,500 patients in the United States and over 6,500 patients in Europe and Canada. Over 2,900 patients were

treated in long-term studies for up to 6-12 months. In general, NOLCER was well tolerated in both short and long-term clinical trials.

The safety in the treatment of healing of erosive esophagitis was assessed in four randomized comparative clinical trials, which included 1,240 patients on NOLCER 20 mg, 2,434 patients on NOLCER 40 mg, and 3,008 patients on omeprazole 20 mg daily. The most frequently occurring adverse reactions ($\geq 1\%$) in all three groups were headache (5.5, 5, and 3.8, respectively) and diarrhea (no difference among the three groups). Nausea, flatulence, abdominal pain, constipation, and dry mouth occurred at similar rates among patients taking NOLCER or omeprazole.

Additional adverse reactions that were reported as possibly or probably related to NOLCER with an incidence $< 1\%$ are listed below by body system:

Body as a Whole: abdomen enlarged, allergic reaction, asthenia, back pain, chest pain, substernal chest pain, facial edema, peripheral edema, hot flashes, fatigue, fever, flu-like disorder, generalized edema, leg edema, malaise, pain, rigors;

Cardiovascular: flushing, hypertension, tachycardia;

Endocrine: goiter;

Gastrointestinal: bowel irregularity, constipation aggravated, dyspepsia, dysphagia, dysplasia GI, epigastric pain, eructation, esophageal disorder, frequent stools, gastroenteritis, GI hemorrhage, GI symptoms not otherwise specified, hiccup, melena, mouth disorder, pharynx disorder, rectal disorder, serum gastrin increased, tongue disorder, tongue edema, ulcerative stomatitis, vomiting;

Hearing: earache, tinnitus;

Hematologic: anemia, anemia hypochromic, cervical lymphadenopathy, epistaxis, leukocytosis, leukopenia, thrombocytopenia;

Hepatic: bilirubinemia, hepatic function abnormal, SGOT increased, SGPT increased; **Metabolic/Nutritional:** glycosuria, hyperuricemia, hyponatremia, increased alkaline phosphatase, thirst, vitamin B12 deficiency, weight increase, weight decrease;

Musculoskeletal: arthralgia, arthritis aggravated, arthropathy, cramps, fibromyalgia syndrome, hernia, polymyalgia rheumatica;

Nervous System/Psychiatric: anorexia, apathy, appetite increased, confusion, depression aggravated, dizziness, hypertension, nervousness, hypoesthesia, impotence, insomnia, migraine, migraine aggravated, paresthesia, sleep disorder, somnolence, tremor, vertigo, visual field defect;

Reproductive: dysmenorrhea, menstrual disorder, vaginitis;

Respiratory: asthma aggravated, coughing, dyspnea, larynx edema, pharyngitis, rhinitis, sinusitis;

Skin and Appendages: acne, angioedema, dermatitis, pruritus, pruritus ani, rash, rash erythematous, rash maculo-papular, skin inflammation, sweating increased, urticaria;

Special Senses: otitis media, parosmia, taste loss, taste perversion;

Urogenital: abnormal urine, albuminuria, cystitis, dysuria, fungal infection, hematuria, micturition frequency, moniliasis, genital moniliasis, polyuria;

Visual: conjunctivitis, vision abnormal.

The following potentially clinically significant laboratory changes in clinical trials, irrespective of relationship to NOLCER, were reported in $\leq 1\%$ of patients: increased creatinine, uric acid, total bilirubin, alkaline phosphatase, ALT, AST, hemoglobin, white blood cell count, platelets, serum gastrin, potassium, sodium, thyroxine and thyroid stimulating hormone [see Clinical Pharmacology (12)]. Decreases were seen in hemoglobin, white blood cell count, platelets, potassium, sodium, and thyroxine.

Endoscopic findings that were reported as adverse reactions include: duodenitis, esophagitis, esophageal stricture, esophageal ulceration, esophageal varices, gastric ulcer, gastritis, hernia, benign polyps or nodules, Barrett's esophagus, and mucosal discoloration.

The incidence of treatment-related adverse reactions during 6-month maintenance treatment was similar to placebo. There were no differences in types of related adverse reactions seen during maintenance treatment up to 12 months compared to short-term treatment.

Two placebo-controlled studies were conducted in 710 patients for the treatment of symptomatic gastroesophageal reflux disease. The most common adverse reactions that were reported as possibly or probably related to NOLCER were diarrhea (4.3%), headache (3.8%), and abdominal pain (3.8%).

Pediatrics

The safety of NOLCER was evaluated in 316 pediatric and adolescent patients aged 1 to 17 years in four clinical trials for the treatment of symptomatic GERD [see Clinical Studies (14.2)]. In 109 pediatric patients aged 1 to 11 years, the most frequently reported (at least 1%) treatment-related adverse reactions in these patients were diarrhea (2.8%), headache (1.9%) and somnolence (1.9%). In 149 pediatric patients aged 12 to 17 years the most frequently reported (at least 2%) treatment-related adverse reactions in these patients were headache (8.1%), abdominal pain (2.7%), diarrhea (2%), and nausea (2%).

The safety of NOLCER was evaluated in 167 pediatric patients from birth to < 1 year of age in three clinical trials. In a study that included 26 pediatric patients

aged birth to 1 month there were no treatment related adverse reactions. In a study that included 43 pediatric patients age 1 to 11 months, inclusive the most frequently reported (at least 5%) adverse reactions, irrespective of causality, were irritability and vomiting. In a study that included 98 pediatric patients, age 1 to 11 months, inclusive exposed to esomeprazole for up to 6 weeks (including 39 patients randomized to the withdrawal phase), there were 4 treatment-related adverse reactions: abdominal pain (1%), regurgitation (1%), tachypnea (1%), and increased ALT (1%).

No new safety concerns were identified in pediatric patients.

Combination Treatment with Amoxicillin and Clarithromycin

In clinical trials using combination therapy with NOLCER plus amoxicillin and clarithromycin, no additional adverse reactions specific to these drug combinations were observed. Adverse reactions that occurred were limited to those observed when using NOLCER, amoxicillin, or clarithromycin alone.

The most frequently reported drug-related adverse reactions for patients who received triple therapy for 10 days were diarrhea (9.2%), taste perversion (6.6%), and abdominal pain (3.7%). No treatment-emergent adverse reactions were observed at higher rates with triple therapy than were observed with NOLCER alone.

For more information on adverse reactions with amoxicillin or clarithromycin, refer to their package inserts, Adverse Reactions sections.

In clinical trials using combination therapy with NOLCER plus amoxicillin and clarithromycin, no additional increased laboratory abnormalities particular to these drug combinations were observed.

For more information on laboratory changes with amoxicillin or clarithromycin, refer to their package inserts, Adverse Reactions section.

6.1 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of NOLCER.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reports are listed below by body system:

Blood And Lymphatic: agranulocytosis, pancytopenia;

Eye: blurred vision;

Gastrointestinal: pancreatitis; stomatitis; microscopic colitis

Hepatobiliary: hepatic failure, hepatitis with or without jaundice;

Immune System: anaphylactic reaction/shock;

Infections and Infestations: GI candidiasis; Clostridium difficile associated diarrhea;

Metabolism and nutritional disorders: hypomagnesemia, with or without hypocalcemia and/or hypokalemia

Musculoskeletal and Connective Tissue: muscular weakness, myalgia, bone fracture;

Nervous System: hepatic encephalopathy, taste disturbance;

Psychiatric: aggression, agitation, depression, hallucination;

Renal and Urinary: interstitial nephritis;

Reproductive System and Breast: gynecomastia;

Respiratory, Thoracic, and Mediastinal: bronchospasm;

Skin and Subcutaneous Tissue: alopecia, erythema multiforme, hyperhidrosis, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal).

7 DRUG INTERACTIONS

7.1 Interference with Antiretroviral Therapy

Concomitant use of atazanavir and nelfinavir with proton pump inhibitors is not recommended. Co-administration of atazanavir with proton pump inhibitors is expected to

substantially decrease atazanavir plasma concentrations and may result in a loss of therapeutic effect and the development of drug resistance. Co-administration of saquinavir with proton pump inhibitors is expected to increase saquinavir concentrations, which may increase toxicity and require dose reduction.

Omeprazole, of which esomeprazole is an enantiomer, has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19.

Reduced concentrations of atazanavir and nelfinavir

For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. Following multiple doses of nelfinavir (1250 mg, twice daily) and omeprazole (40 mg daily), AUC was decreased by 36% and 92%, C_{max} by 37% and 89% and C_{min} by 39% and 75% respectively for nelfinavir and M8. Following multiple doses of atazanavir (400 mg, daily) and omeprazole (40 mg, daily, 2 hr before atazanavir), AUC was decreased by 94%, C_{max} by 96%, and C_{min} by 95%.

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is therefore not recommended.

Increased concentrations of saquinavir

For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported, with an increase in AUC by 82%, in C_{max} by 75%, and in C_{min} by 106%, following multiple dosing of saquinavir/ritonavir (1000/100 mg) twice daily for 15 days with omeprazole 40 mg daily co-administered days 11 to 15. Therefore, clinical and laboratory monitoring for saquinavir toxicity is recommended during concurrent use with NOLCER. Dose reduction of saquinavir should be considered from the safety perspective for individual patients.

There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

7.2 Drugs for Which Gastric pH Can Affect Bioavailability

Due to its effects on gastric acid secretion, esomeprazole can reduce the absorption of drugs where gastric pH is an important determinant of their bioavailability. Like with other drugs that decrease the intragastric acidity, the absorption of drugs such as ketoconazole, atazanavir, iron salts, erlotinib, and mycophenolate mofetil (MMF) can decrease, while the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Esomeprazole is an enantiomer of omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (30% in two subjects). Co-administration of digoxin with NOLCER is expected to increase the systemic exposure of digoxin. Therefore, patients may need to be monitored when digoxin is taken concomitantly with NOLCER.

Co-administration of omeprazole in healthy subjects and in transplant patients receiving MMF has been reported to reduce the exposure to the active metabolite, mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH. The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients receiving NOLCER and MMF. Use NOLCER with caution in transplant patients receiving MMF.

7.3 Effects on Hepatic Metabolism/Cytochrome P-450 Pathways

Esomeprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4. In vitro and in vivo studies have shown that esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1, and 3A4. No clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Drug interaction studies have shown that esomeprazole does not have any clinically significant interactions with phenytoin, warfarin, quinidine, clarithromycin, or amoxicillin.

However, post-marketing reports of changes in prothrombin measures have been received among patients on concomitant warfarin and esomeprazole therapy. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Esomeprazole may potentially interfere with CYP2C19, the major esomeprazole metabolizing enzyme. Co-administration of esomeprazole 30 mg and diazepam, a CYP2C19 substrate, resulted in a 45% decrease in clearance of diazepam.

Clopidogrel

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of esomeprazole 40 mg results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition. Avoid concomitant administration of NOLCER with clopidogrel. When using NOLCER, consider use of alternative anti-platelet therapy.

Omeprazole acts as an inhibitor of CYP2C19. Omeprazole, given in doses of 40 mg daily for one week to 20 healthy subjects in cross-over study, increased C_{max} and AUC of closetazol by 18% and 26% respectively. C_{max} and AUC of one of its active metabolites, 3,4-dihydro- closetazol, which has 4-7 times the activity of closetazol, were increased by 29% and 69% respectively. Co-administration of closetazol with esomeprazole is expected to increase concentrations of closetazol and its above mentioned active metabolite. Therefore a dose reduction of closetazol from 100 mg twice daily to 50 mg twice daily should be considered.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. Dose adjustment of esomeprazole is not normally required. However, in patients with Zollinger-Elison's Syndrome, who may require higher doses up to 240 mg/day, dose adjustment may be considered.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampin) may lead to decreased esomeprazole serum levels. Omeprazole, of which esomeprazole is an enantiomer, has been reported to interact with St. John's Wort an inducer of CYP3A4. In a cross-over study in 12 healthy male subjects, St. John's Wort (300 mg three times daily for 14 days) significantly decreased the systemic exposure of omeprazole in CYP2C19 poor metabolisers (C_{max} and AUC decreased by 37.5% and 37.9%, respectively) and extensive metabolisers

(C_{max} and AUC decreased by 49.6% and 43.9%, respectively). Avoid concomitant use of St. John's Wort or rifampin with NOLCER.

7.4 Interactions With Investigations of Neuroendocrine Tumors

Drug-induced decrease in gastric acidity results in enterochromaffin-like cell hyperplasia and increased Chromogranin A levels which may interfere with investigations for neuroendocrine tumors [see Warnings and Precautions (5.10) and Clinical Pharmacology].

7.5 Tacrolimus

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

7.6 Combination Therapy with Clarithromycin

Co-administration of esomeprazole, clarithromycin, and amoxicillin has resulted in increases in the plasma levels of esomeprazole and 14-hydroxyclarithromycin.

Concomitant administration of clarithromycin with other drugs can lead to serious adverse reactions due to drug interactions [see Warnings and Precautions in prescribing information for clarithromycin]. Because of these drug interactions, clarithromycin is contraindicated for co-administration with certain drugs [see Contraindications in prescribing information for clarithromycin].

7.7 Methotrexate

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with NOLCER in pregnant women. Esomeprazole is the S-isomer of omeprazole. Available epidemiologic data fail to demonstrate an increased risk of major congenital malformations or other adverse pregnancy outcomes with first trimester omeprazole use.

Teratogenicity was not observed in animal reproduction studies with administration of oral esomeprazole magnesium in rats and rabbits with doses about 68 times and 42 times, respectively, an oral human dose of 40 mg (based on a body surface area basis for a 60 kg person). However, changes in bone morphology were observed in offspring of rats dosed through most of pregnancy and lactation at doses equal to or greater than approximately 34 times an oral human dose of 40 mg (see Animal Data). Because of the observed effect at high doses of esomeprazole magnesium on developing bone in rat studies, NOLCER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human Data

Esomeprazole is the S-isomer of omeprazole. Four epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy with the frequency of abnormalities among infants of women exposed to H₂-receptor antagonists or other controls.

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

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

A retrospective cohort study reported on 689 pregnant women exposed to either H₂-blockers or omeprazole in the first trimester (134 exposed to omeprazole) and 1,572 pregnant women unexposed to either during the first trimester. The overall malformation rate in offspring born to mothers with first trimester exposure to omeprazole, an H₂-blocker, or were unexposed was 3.6%, 5.5%, and 4.1% respectively.

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

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

Animal Data

Reproduction studies have been performed with esomeprazole magnesium in rats at oral doses up to 280 mg/kg/day (about 68 times an oral human dose of 40 mg on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 41 times an oral human dose of 40 mg on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to esomeprazole magnesium.

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

Effects on maternal bone were observed in pregnant and lactating rats in a pre- and postnatal toxicity study when esomeprazole magnesium was administered at oral doses of 14 to 280 mg/kg/day (about 3.4 to 68 times an oral human dose of 40 mg on a body surface area basis). When rats were dosed from gestational day 7 through weaning on postnatal day 21, a statistically significant decrease in maternal femur weight of up to 14% (as compared to placebo treatment) was observed at doses equal to or greater than 138 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis).

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

8.3 Nursing Mothers

Esomeprazole is likely present in human milk. Esomeprazole is the S-isomer of omeprazole and limited data indicate that maternal doses of omeprazole 20 mg daily produce low levels in human milk. Caution should be exercised when NOLCER is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of NOLCER have been established in pediatric patients 1 to 17 years of age for short-term treatment (up to eight weeks) of GERD. The safety and effectiveness of NOLCER have been established in pediatric patients 1 month to less than 1 year for short-term treatment (up to 6 weeks) of erosive esophagitis due to acid-mediated GERD. However, the safety and effectiveness of NOLCER have not been established in patients less than 1 month of age.

1 to 17 years of age

Use of NOLCER in pediatric and adolescent patients 1 to 17 years of age for short-term treatment (up to eight weeks) of GERD is supported by extrapolation of results from adequate and well-controlled studies for adults and safety and pharmacokinetic studies performed in pediatric and adolescent patients [see Dosage and Administration (2), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.3)]. The safety and effectiveness of NOLCER for other pediatric uses have not been established.

Erosive esophagitis due to acid-mediated GERD in infants 1 month to less than one year of age

Use of NOLCER in pediatric patients 1 month to less than 1 year of age for treatment (up to 6 weeks) of erosive esophagitis due to acid-mediated GERD is supported by extrapolation of results from adequate and well-controlled studies for adults and safety, pharmacokinetic, and pharmacodynamic studies performed in pediatric patients [see, Dosage and Administration (2), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies.

Symptomatic GERD in infants 1 month to less than one year of age

There was no statistically significant difference between NOLCER and placebo in the rate of discontinuation due to symptom worsening in a multicenter, randomized, double-blind, controlled, treatment-withdrawal study of 98 patients ages 1 to 11 months, inclusive. Patients were enrolled if they had either a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD. Twenty of 98 enrolled patients underwent endoscopy, and 6 patients were found to have erosive esophagitis on endoscopy at baseline. All patients received NOLCER Delayed-Release Oral Suspension once daily during a two-week, open-label phase of the study.

There were 80 patients who attained a pre-specified level of symptom improvement and who entered the double-blind phase, in which they were randomized in equal proportions to receive NOLCER or placebo for the next four weeks. Efficacy was assessed by observing the time from randomization to study discontinuation due to symptom worsening during the four-week, treatment-withdrawal phase.

The following pharmacokinetic and pharmacodynamic information was obtained in pediatric patients with GERD aged birth to less than one year of age. In infants (1 to 11 months old, inclusive) given NOLCER 1mg/kg once daily, the percent time with intragastric pH > 4 increased from 29% at baseline to 69% on Day 7, which is similar to the pharmacodynamic effect in adults [see Clinical Pharmacology (12.2)]. Apparent clearance (CL/F) increases with age in pediatric patients from birth to 2 years of age.

Neonates 0 to 1 month of age

Following administration of oral NOLCER in neonates the geometric mean (range) for the apparent clearance (CL/F) was 0.55 L/h/kg (0.25-1.6 L/h/kg).

The safety and effectiveness of NOLCER in neonates have not been established.

Juvenile Animal Data

In a juvenile rat toxicity study, esomeprazole was administered with both magnesium and strontium salts at oral doses about 34 to 68 times a daily human dose of 40 mg based on body surface area. Increases in death were seen at the high dose, and at all doses of esomeprazole, there were decreases in body weight, body weight gain, femur weight and femur length, and decreases in overall growth.

8.2 Geriatric Use

Of the total number of patients who received NOLCER in clinical trials, 1459 were 65 to 74 years of age and 354 patients were ≥ 75 years of age.

No overall differences in safety and efficacy were observed between the elderly and younger individuals, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

9 OVERDOSAGE

A single oral dose of esomeprazole at 510 mg/kg (about 124 times the human dose on a body surface area basis), was lethal to rats. The major signs of acute toxicity were reduced motor activity, changes in respiratory frequency, tremor, ataxia, and intermittent clonic convulsions.

The symptoms described in connection with deliberate NOLCER overdose (limited experience of doses in excess of 240 mg/day) are transient. Single doses of 80 mg of esomeprazole were uneventful. Reports of overdose with omeprazole in humans may also be relevant. Doses ranged up to 2,400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience (see omeprazole package insert – Adverse Reactions). No specific antidote for esomeprazole is known. Since esomeprazole is extensively protein bound, it is not expected to be removed by dialysis. In the event of overdose, treatment should be symptomatic and supportive.

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.

The magnesium salt is a white to slightly colored crystalline powder. It contains 3 moles of water of solvation and is slightly soluble in water. The stability of esomeprazole magnesium is a function of pH; it rapidly degrades in acidic media, but it has acceptable stability under alkaline conditions. At pH 6.8 (buffer), the half-life of the magnesium salt is about 19 hours at 25°C and about 8 hours at 37°C.

NOLCER is supplied in delayed-release capsules and in packets for a delayed-release oral suspension. Each delayed-release capsule contains 20 mg, or 40 mg of esomeprazole (present as 22.3 mg, or 44.5 mg esomeprazole magnesium trihydrate) in the form of enteric-coated granules with the following inactive ingredients: glycerol monostearate 40-55, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer type C, polyorbate 80, sugar spheres, talc, and triethyl citrate. The capsule shells have the following inactive

ingredients: gelatin, FD&C Blue #1, FD&C Red #40, D&C Red #28, titanium dioxide, shellac, ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, sodium hydroxide, polyvinyl pyrrolidone, and D&C Yellow #10.

Each packet of NOLCER For Delayed-Release Oral Suspension contains 2.5 mg, 5 mg, 10 mg, 20 mg, or 40 mg of esomeprazole, in the form of the same enteric-coated granules used in NOLCER Delayed-Release Capsules, and also inactive granules. The inactive granules are composed of the following ingredients: dextrose, xanthan gum, crospovidone, citric acid, iron oxide, and hydroxypropyl cellulose. The esomeprazole granules and inactive granules are constituted with water to form a suspension and are given by oral, nasogastric, or gastric administration.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H⁺/K⁺-ATPase in the gastric parietal cell. The S- and R-isomers of omeprazole are protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphenamide. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity. This effect is dose-related up to a daily dose of 20 to 40 mg and leads to inhibition of gastric acid secretion.

10.2 Pharmacodynamics

Antisecretory Activity

The effect of NOLCER on intragastric pH was determined in patients with symptomatic gastroesophageal reflux disease in two separate studies. In the first study of 36 patients, NOLCER 40 mg and 20 mg capsules were administered over 5 days. The results are shown in the Table 3:

Serum Gastrin Effects

The effect of NOLCER on serum gastrin concentrations was evaluated in approximately 2,700 patients in clinical trials up to 8 weeks and in over 1,300 patients for up to 6 to 12 months. The mean fasting gastrin level increased in a dose-related manner. This increase reached a plateau within two to three months of therapy and returned to baseline levels within four weeks after discontinuation of therapy.

Increased gastrin causes enterochromaffin-like cell hyperplasia and increased serum Chromogranin A (CgA) levels. The increased CgA levels may cause false positive results in diagnostic investigations for neuroendocrine tumors. Healthcare providers should temporarily stop esomeprazole treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high.

Enterochromaffin-like (ECL) Cell Effects

In 24-month carcinogenicity studies of omeprazole in rats, a dose-related significant occurrence of gastric ECL cell carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals [see Nonclinical Toxicology (13.1)]. Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of H₂-receptor antagonists.

Human gastric biopsy specimens have been obtained from more than 3,000 patients (both children and adults) treated with omeprazole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies increased with time; however, no case of ECL cell carcinoids, dysplasia, or neoplasia has been found in these patients.

In over 1,000 patients treated with NOLCER (10, 20 or 40 mg/day) up to 6 to 12 months, the prevalence of ECL cell hyperplasia increased with time and dose. No patient developed ECL cell carcinoids, dysplasia, or neoplasia in the gastric mucosa.

Endocrine Effects

NOLCER had no effect on thyroid function when given in oral doses of 20 or 40 mg for 4 weeks. Other effects of NOLCER on the endocrine system were assessed using omeprazole studies. Omeprazole given in oral doses of 30 or 40 mg for 2 to 4 weeks had no effect on carbohydrate metabolism, circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin, or secretin.

10.3 Pharmacokinetics

Absorption

NOLCER Delayed-Release Capsules and enteric-coated For Delayed-Release Oral Suspension contain a bioequivalent enteric-coated granule formulation of esomeprazole magnesium. Bioequivalency is based on a single dose (40 mg) study in 94 healthy male and female volunteers under fasting condition. After oral administration peak plasma levels (C_{max}) occur at approximately 1.5 hours (T_{max}). The C_{max} increases proportionally when the dose is increased, and there is a three-fold increase in the area under the plasma concentration-time curve (AUC) from 20 to 40 mg. At repeated once-daily dosing with 40 mg, the systemic bioavailability is approximately 90% compared to 64% after a single dose

of 40 mg. The mean exposure (AUC) to esomeprazole increases from 4.32 μmol*hr/L on Day 1 to 11.2 μmol*hr/L on Day 5 after 40 mg once daily dosing.

The AUC after administration of a single 40 mg dose of NOLCER is decreased by 43% to 53% after food intake compared to fasting conditions. NOLCER should be taken at least one hour before meals.

Distribution

Esomeprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 2 to 20 μmol/L. The apparent volume of distribution at steady state in healthy volunteers is approximately 16 L.

Metabolism

Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system. The metabolites of esomeprazole lack antisecretory activity. The major part of esomeprazole's metabolism is dependent upon the CYP 2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on CYP 3A4 which forms the sulphone metabolite. CYP 2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15 to 20% of Asians lack CYP 2C19 and are termed Poor Metabolizers. At steady state, the ratio of AUC in Poor Metabolizers to AUC in the rest of the population (Extensive Metabolizers) is approximately 2.

Following administration of equimolar doses, the S- and R-isomers are metabolized differently by the liver, resulting in higher plasma levels of the S- than of the R-isomer.

Excretion

The plasma elimination half-life of esomeprazole is approximately 1 to 1.5 hours. Less than 1% of parent drug is excreted in the urine. Approximately 80% of an oral dose of esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces.

Pharmacokinetics: Combination Therapy with Antimicrobials

Esomeprazole magnesium 40 mg once daily was given in combination with clarithromycin 500 mg twice daily and amoxicillin 1000 mg twice daily for 7 days to 17 healthy male and female subjects. The mean steady state AUC and C_{max} of esomeprazole increased by 70% and 18%, respectively during triple combination therapy compared to treatment with esomeprazole alone. The observed increase in esomeprazole exposure during co-administration with clarithromycin and amoxicillin is not expected to produce significant safety concerns.

The pharmacokinetic parameters for clarithromycin and amoxicillin were similar during triple combination therapy and administration of each drug alone. However, the mean AUC and C_{max} for 14-hydroxyclarithromycin increased by 19% and 22%, respectively, during triple combination therapy compared to treatment with clarithromycin alone. This increase in exposure to 14-hydroxyclarithromycin is not considered to be clinically significant.

Concomitant Use with Clopidogrel

Results from a crossover study in healthy subjects have shown a pharmacokinetic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. once daily) when co-administered for 30 days. Exposure to the active metabolite of clopidogrel was reduced by 35% to 40% over this time period. Pharmacodynamic parameters were also measured and demonstrated that the change in inhibition of platelet aggregation was related to the change in the exposure to clopidogrel active metabolite.

Concomitant Use with Mycophenolate Mofetil

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

Special Populations

Geriatric

The AUC and C_{max} values were slightly higher (25% and 18%, respectively) in the elderly as compared to younger subjects at steady state. Dosage adjustment based on age is not necessary.

Pediatric (1 to 11 month of age)

The pharmacokinetic parameters following repeated dose administration of 10 mg/kg esomeprazole in 1 to 11 month old infants are summarized in Table 5.

Subsequent pharmacokinetic simulation analyses showed that a dosage regimen of 2.5 mg once-daily for pediatric patients with body weight 3-5 kg, 5.0 mg once-daily for >5 to 7.5 kg and 10 mg once-daily for >7.5 to 12 kg would achieve comparable steady-state plasma exposures (AUC) to that observed after 10 mg in 1 to 11 year olds, and 20 mg in 12 to 18 year-olds as well as adults.

1 to 11 Years of Age

The pharmacokinetics of esomeprazole were studied in pediatric patients with GERD aged 1 to 11 years. Following once daily dosing for 5 days, the total exposure (AUC) for the 10 mg dose in patients aged 6 to 11 years was similar to

that seen with the 20 mg dose in adults and adolescents aged 12 to 17 years. The total exposure for the 10 mg dose in patients aged 1 to 5 years was approximately 30% higher than the 10 mg dose in patients aged 6 to 11 years. The total exposure for the 20 mg dose in patients aged 6 to 11 years was higher than that observed with the 20 mg dose in 12 to 17 year-olds and adults, but lower than that observed with the 40 mg dose in 12 to 17 year-olds and adults. See Table 6.

12 to 17 Years of Age

The pharmacokinetics of NOLCER were studied in 28 adolescent patients with GERD aged 12 to 17 years inclusive, in a single center study. Patients were randomized to receive NOLCER 20 mg or 40 mg once daily for 8 days. Mean C_{max} and AUC values of esomeprazole were not affected by body weight or age; and more than dose-proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, NOLCER pharmacokinetics in adolescent patients aged 12 to 17 years were similar to those observed in adult patients with symptomatic GERD. See Table 7.

The AUC and C_{max} values were slightly higher (13%) in females than in males at steady state. Dosage adjustment based on gender is not necessary.

Hepatic Insufficiency

The steady state pharmacokinetics of esomeprazole obtained after administration of 40 mg once daily to 4 patients each with mild (Child Pugh A), moderate (Child Pugh Class B), and severe (Child Pugh Class C) liver insufficiency were compared to those obtained in 36 male and female GERD patients with normal liver function. In patients with mild and moderate hepatic insufficiency, the AUCs were within the range that could be expected in patients with normal liver function. In patients with severe hepatic insufficiency the AUCs were 2 to 3 times higher than in the patients with normal liver function. No dosage adjustment is recommended for patients with mild to moderate hepatic insufficiency (Child Pugh Classes A and B). However, in patients with severe hepatic insufficiency (Child Pugh Class C) a dose of 20 mg once daily should not be exceeded.

Renal Insufficiency

The pharmacokinetics of NOLCER in patients with renal impairment are not expected to be altered relative to healthy volunteers as less than 1% of esomeprazole is excreted unchanged in urine.

Other pharmacokinetic observations

Co-administration of oral contraceptives, diazepam, phenytoin, or quinidine did not seem to change the pharmacokinetic profile of esomeprazole.

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant changes in the pharmacokinetic profiles of esomeprazole or these NSAIDs.

10.4 Microbiology

NOLCER, amoxicillin, and clarithromycin triple therapy has been shown to be active against most strains of *Helicobacter pylori* (*H. pylori*) in vitro and in clinical infections [see Indications and Usage (1) and Clinical Studies (14)].

Helicobacter pylori: Susceptibility testing of *H. pylori* isolates was performed for amoxicillin and clarithromycin using agar dilution methodology, and minimum inhibitory concentrations (MICs) were determined.

Susceptibility Test for *Helicobacter pylori*: For susceptibility testing information about *Helicobacter pylori*, see Microbiology section in prescribing information for clarithromycin and amoxicillin.

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* and possibly *Clostridium difficile* in hospitalized patients.

11 NONCLINICAL TOXICOLOGY

11.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of NOLCER was assessed using studies of omeprazole, of which esomeprazole is an enantiomer. In two 24-month oral carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44, and 140.8 mg/kg/day (about 0.4 to 34 times the human dose of 40 mg/day expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 3.4 times the human dose of 40 mg/day on a body surface area basis) for 1 year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of 1 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 2 years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive.

Esomeprazole was negative in the Ames mutation test, in the in vivo rat bone marrow cell chromosome aberration test, and the in vivo mouse micronucleus test. Esomeprazole, however, was positive in the in vitro human lymphocyte chromosome aberration test. Omeprazole was positive in the in vitro human lymphocyte chromosome aberration test, in the in vivo mouse bone marrow cell chromosome aberration test, and the in vivo mouse micronucleus test.

The potential effects of esomeprazole on fertility and reproductive performance were assessed using omeprazole studies. Omeprazole at oral doses up to 138 mg/kg/day in rats (about 34 times the human dose of 40 mg/day on a body surface area basis) was found to have no effect on reproductive performance of parental animals.

11.2 Animal Toxicology and/or Pharmacology

Reproduction Studies

Reproduction studies have been performed in rats at oral doses up to 280 mg/kg/day (about 68 times an oral human dose of 40 mg on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 42 times an oral human dose of 40 mg on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to esomeprazole [see Pregnancy, Animal Data].

Juvenile Animal Study

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

11.3 Symptomatic Gastroesophageal Reflux Disease (GERD)

Two multicenter, randomized, double-blind, placebo-controlled studies were conducted in a total of 717 patients comparing four weeks of treatment with NOLCER 20 mg or 40 mg once daily versus placebo for resolution of GERD symptoms. Patients had ≥ 6-month history of heartburn episodes, no erosive esophagitis by endoscopy, and heartburn on at least four of the seven days immediately preceding randomization.

The percentage of patients that were symptom-free of heartburn was significantly higher in the NOLCER groups compared to placebo at all follow-up visits (Weeks 1, 2, and 4).

No additional clinical benefit was seen with NOLCER 40 mg over NOLCER 20 mg.

The percent of patients symptom-free of heartburn by day are shown in the Figures 4 and 5:

11.4 Pediatric Gastroesophageal Reflux Disease (GERD)

1 to 11 Years of Age

In a multicenter, parallel-group study, 109 pediatric patients with a history of endoscopically-proven GERD (1 to 11 years of age; 53 female; 89 Caucasian, 19 Black, 1 Other) were treated with NOLCER once daily for up to 8 weeks to evaluate safety and tolerability. Dosing by patient weight was as follows:

weight < 20 kg: once daily treatment with NOLCER 5 mg or 10 mg
weight > 20 kg: once daily treatment with NOLCER 10 mg or 20 mg

Patients were endoscopically characterized as to the presence or absence of erosive esophagitis.

Of the 109 patients, 53 had erosive esophagitis at baseline (51 had mild, 1 moderate, and 1 severe esophagitis). Although most of the patients who had a follow up endoscopy at the end of 8 weeks of treatment healed, spontaneous healing cannot be ruled out because these patients had low grade erosive esophagitis prior to treatment, and the trial did not include a concomitant control.

12 to 17 Years of Age

In a multicenter, randomized, double-blind, parallel-group study, 149 adolescent patients (12 to 17 years of age; 89 female; 124 Caucasian, 15 Black, 10 Other) with clinically diagnosed GERD were treated with either NOLCER 20 mg or NOLCER 40 mg once daily for up to 8 weeks to evaluate safety and tolerability. Patients were not endoscopically characterized as to the presence or absence of erosive esophagitis.

11.5 Risk Reduction of NSAID-Associated Gastric Ulcer

Two multicenter, double-blind, placebo-controlled studies were conducted in patients at risk of developing gastric and/or duodenal ulcers associated with continuous use of non-selective and COX-2 selective NSAIDs. A total of 1429 patients were randomized across the 2 studies. Patients ranged in age from 19 to 89 (median age 66.0 years) with 70.7% female, 29.3% male, 82.9% Caucasian, 5.5% Black, 3.7% Asian, and 8.0% Others. At baseline, the patients in these studies were endoscopically confirmed not to have ulcers but were determined to be at risk for ulcer occurrence due to their age (>60 years) and/or history of a documented gastric or duodenal ulcer within the past 5 years. Patients receiving NSAIDs and treated with NOLCER 20 mg or 40 mg once-a-day experienced significant reduction in gastric ulcer occurrences relative to placebo treatment at 26 weeks. See Table 11. No additional benefit was seen with NOLCER 40 mg over NOLCER 20 mg. These studies did not demonstrate significant reduction in the development of NSAID-associated duodenal ulcer due to the low incidence.

Table 11: Cumulative percentage of patients without gastric ulcers at 26 weeks:

Study	No. of Patients	Treatment Group	% of Patients Remaining Gastric Ulcer Free ¹
1	191	NOLCER 20 mg	95.4
	194	40 mg Placebo	96.7
	184		88.2
2	267	NOLCER 20 mg	94.7
	271	40 mg Placebo	95.3
	257		83.3

¹% = Life Table Estimate. Significant difference from placebo (p<0.01).

11.6 Helicobacter pylori (H. pylori) Eradication in Patients with Duodenal Ulcer Disease

Triple Therapy (NOLCER/amoxicillin/clarithromycin): Two multicenter, randomized, double-blind studies were conducted using a 10 day treatment regimen. The first study (191) compared NOLCER 40 mg once daily in combination with amoxicillin 1000 mg twice daily and clarithromycin 500 mg twice daily to NOLCER 40 mg once daily plus clarithromycin 500 mg twice daily. The second study (193) compared NOLCER 40 mg once daily in combination with amoxicillin 1000 mg twice daily and clarithromycin 500 mg twice daily to NOLCER 40 mg once daily. H. pylori eradication rates, defined as at least two negative tests and no positive tests from CLOtest3, histology and/or culture, at 4 weeks post-therapy were significantly higher in the NOLCER plus amoxicillin and clarithromycin group than in the NOLCER plus clarithromycin or NOLCER alone group.

† Patients were included in the analysis if they had H. pylori infection documented at baseline, had at least one endoscopically verified duodenal ulcer ≥ 0.5 cm in diameter at baseline or had a documented history of duodenal ulcer disease within the past 5 years, and were not protocol violators. Patients who dropped out of the study due to an adverse reaction related to the study drug were included in the analysis as not H. pylori eradicated.

‡ Patients were included in the analysis if they had documented H. pylori infection at baseline, had at least one documented duodenal ulcer at baseline, or had a documented history of duodenal ulcer disease, and took at least one dose of study medication. All dropouts were included as not H. pylori eradicated.

*p < 0.05 compared to NOLCER plus clarithromycin

**p < 0.05 compared to NOLCER alone

The percentage of patients with a healed baseline duodenal ulcer by 4 weeks after the 10 day treatment regimen in the NOLCER plus amoxicillin and clarithromycin group was 75% (n=156) and 57% (n=60) respectively, in the 191 and 193 studies (per-protocol analysis).

In a multicenter, open-label dose-escalation study of 21 patients (15 males and 6 females, 18 Caucasian and 3 Black, mean age of 55.5 years) with pathological hypersecretory conditions, such as Zollinger-Ellison Syndrome, NOLCER significantly inhibited gastric acid secretion. Initial dose was 40 mg twice daily in 19/21 patients and 80 mg twice daily in 2/21 patients. Total daily doses ranging from 80 mg to 240 mg for 12 months maintained gastric acid output below the target levels of 10 mEq/h in patients without prior gastric acid-reducing surgery and below 5 mEq/hr in patients with prior gastric acid-reducing surgery. At the Month 12 final visit, 18/20 (90%) patients had Basal Acid Output (BAO) under satisfactory control (median BAO = 0.17 mmol/hr). Of the 18 patients evaluated with a starting dose of 40 mg twice daily, 13 (72%) had their BAO controlled with the original dosing regimen at the final visit. See Table 13.

NOLCER dose at the Month 12 visit	BAO under adequate control at the Month 12 visit (N=20)*
40 mg twice daily	13/15
80 mg twice daily	4/4
80 mg three times daily	1/1

*One patient was not evaluated.

12 HOW SUPPLIED/STORAGE AND HANDLING

- NOLCER (Esomeprazole) Capsule 20mg are available in blister packs of 7's.

- NOLCER (Esomeprazole) Capsule 40mg are available in blister packs of 7's.

13 STORAGE CONDITIONS

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F). Keep NOLCER Delayed-Release Capsules container tightly closed. Dispense in a tight container if the NOLCER Delayed-Release Capsules product package is subdivided.

نولسر کپسولز

تورک: دو کا استعمال گانا کھانے سے پہلے کریں۔

ایک کپسول روزانہ، شدید بیماری کی حالت میں

دو کپسول روزانہ دو ہفتے تک یا ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

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صرف مسٹر ڈاکٹر کے نسخے پر فروخت کی جائے۔

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