NEXIUM- esomeprazole magnesium capsule, delayed release
Bryant Ranch Prepack

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NEXIUM safely and effectively. See full prescribing information for NEXIUM.
NEXIUM (esomeprazole magnesium) Delayed-Release Capsules, for Oral Use
NEXIUM (esomeprazole magnesium) For Delayed-Release Oral Suspension
Initial U.S. Approval: 1989 (omeprazole)

RECENT MAJOR CHANGES

Warnings and Precautions, Interaction with Clopidogrel (5.4) 10/2012
Warnings and Precautions, Clostridium difficile associated diarrhea (5.3) 09/2012
Warnings and Precautions, Concomitant use of NEXIUM with Methotrexate (5.9) 01/2012
Indications and Usage, Treatment of GERD (1.1) 12/2011
Dosage and Administration (2) 12/2011

INDICATIONS AND USAGE

NEXIUM is a proton pump inhibitor indicated for the following:

- Treatment of gastroesophageal reflux disease (GERD) (1.1)
- Risk reduction of NSAID-associated gastric ulcer (1.2)
- H. pylori eradication to reduce the risk of duodenal ulcer recurrence (1.3)
- Pathological hypersecretory conditions, including Zollinger-Ellison syndrome (1.4)

DOSAGE AND ADMINISTRATION

Indication	Dose	Frequency
Gastroesophageal Reflux Disease (GERD)		
Adults	20 mg or 40 mg	Once daily for 4 to 8 weeks
12 to 17 years	20 mg or 40 mg	Once daily for up to 8 weeks
1 to 11 years	10 mg or 20 mg	Once daily for up to 8 weeks
1 month to less than 1 year: 2.5 mg, 5 mg or 10 mg (based on weight). Once daily, up to 6 weeks for erosive esophagitis (EE) due to acid-mediated GERD only.		
Risk Reduction of NSAID-Associated Gastric Ulcer		
	20 mg or 40 mg	Once daily for up to 6 months
***H. pylori* Eradication** *(Triple Therapy):*		
NEXIUM	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		
	40 mg	Twice daily

See full prescribing information for administration options (2)
Patients with severe liver impairment-do not exceed dose of 20 mg (2)

DOSAGE FORMS AND STRENGTHS

- NEXIUM Delayed-Release Capsules: 20 mg and 40 mg (3)
- NEXIUM For Delayed-Release Oral Suspension: 2.5 mg, 5 mg, 10 mg, 20 mg, and 40 mg (3)

CONTRAINDICATIONS

Patients with known hypersensitivity to proton pump inhibitors (PPIs) (angioedema and anaphylaxis have occurred) (4)

WARNINGS AND PRECAUTIONS

- Symptomatic response does not preclude the presence of gastric malignancy. (5.1)
- Atrophic gastritis has been noted with long-term omeprazole therapy. (5.2)
- PPI therapy may be associated with increased risk of *Clostridium difficile* associated diarrhea. (5.3)
- Avoid concomitant use of NEXIUM with clopidogrel. (5.4)

- Bone Fracture: Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. (5.5)
- Hypomagnesemia has been reported rarely with prolonged treatment with PPIs (5.6)
- Avoid concomitant use of NEXIUM with St John's Wort or rifampin due to the potential reduction in esomeprazole levels (5.7) (7.3)
- Interactions with diagnostic investigations for Neuroendocrine Tumors: Increases in intragastric pH may result in hypergastrinemia and enterochromaffin-like cell hyperplasia and increased chromogranin A levels which may interfere with diagnostic investigations for neuroendocrine tumors. (5.8, 12.2)

ADVERSE REACTIONS

Most common adverse reactions (6.1):

- Adults (≥ 18 years) (incidence ≥ 1%) are headache, diarrhea, nausea, flatulence, abdominal pain, constipation, and dry mouth
- Pediatric (1 to 17 years) (incidence ≥ 2%) are headache, diarrhea, abdominal pain, nausea, and somnolence
- Pediatric (1 month to less than 1 year) (incidence 1%) are abdominal pain, regurgitation, tachypnea, and increased ALT

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- May affect plasma levels of antiretroviral drugs – use with atazanavir and nelfinavir is not recommended; if saquinavir is used with NEXIUM, monitor for toxicity and consider saquinavir dose reduction (7.1)
- May interfere with drugs for which gastric pH affects bioavailability (e.g., ketoconazole, iron salts, erlotinib, and digoxin). Patients treated with NEXIUM and digoxin may need to be monitored for digoxin toxicity. (7.2)
- Combined inhibitor of CYP 2C19 and 3A4 may raise esomeprazole levels (7.3)
- Clopidogrel: NEXIUM decreases exposure to the active metabolite of clopidogrel. (7.3)
- May increase systemic exposure of cilostazol and an active metabolite. Consider dose reduction (7.3)
- Tacrolimus: NEXIUM may increase serum levels of tacrolimus (7.5)
- Methotrexate: NEXIUM may increase serum levels of methotrexate (7.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2012

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Gastroesophageal Reflux Disease (GERD)

Healing of Erosive Esophagitis

NEXIUM 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 NEXIUM may be considered.

In infants 1 month to less than 1 year, NEXIUM is indicated for short-term treatment (up to 6 weeks) of erosive esophagitis due to acid-mediated GERD.

Maintenance of Healing of Erosive Esophagitis

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

Symptomatic Gastroesophageal Reflux Disease

NEXIUM 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.

1.2 Risk Reduction of NSAID-Associated Gastric Ulcer

NEXIUM 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.

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

Triple Therapy (NEXIUM plus amoxicillin and clarithromycin): NEXIUM, 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 [*seeDosage and Administration (2) and Clinical Studies (14)*].

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 [*seeClinical Pharmacology (12.4) and the prescribing information for clarithromycin*].

1.4 Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

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

2 DOSAGE AND ADMINISTRATION

NEXIUM 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. NEXIUM 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 NEXIUM

Indication	Dose	Frequency
Gastroesophageal Reflux Disease (GERD)		
Healing of Erosive Esophagitis	20 mg or 40 mg	Once Daily for 4 to 8 Weeks*
Maintenance of Healing of Erosive Esophagitis	20 mg	Once Daily†
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	10 mg	Once Daily for up to 8 Weeks
Healing of Erosive Esophagitis		
weight < 20 kg	10 mg	Once Daily for 8 Weeks
weight ≥ 20 kg	10 mg or 20 mg	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**		
Triple Therapy:		
NEXIUM	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-Ellison	40 mg[¶]	[#] Twice

Syndrome	40 mg ¶	Daily

* [*SeeClinical Studies (14.1)*]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.

‡ If 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 NEXIUM 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 [*seeDrug Interactions (7)*].

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 NEXIUM should not be exceeded [*seeClinical Pharmacology (12.3)*].

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

Table 2: Administration Options

Administration Options (See text following table for additional instructions.)		
Dosage Form	**Route**	**Options**
Delayed-Release Capsules	Oral	Capsule can be swallowed whole. -or- Capsule can be opened and mixed with applesauce.
Delayed-Release Capsules	Nasogastric Tube	Capsule can be opened and the intact granules emptied into a syringe and delivered through the nasogastric tube.
For Delayed-Release Oral Suspension	Oral	For the 2.5 mg and 5 mg strengths, mix the contents of packet with 5 mL of water, leave 2 to 3 minutes to thicken, stir and drink within 30 minutes. For the 10 mg, 20 mg and 40 mg strengths, mix contents of packet with 15 mL of water, and follow the instructions above.
For Delayed-Release Oral Suspension	Nasogastric or Gastric Tube	For the 2.5 mg and 5 mg strengths, add 5 mL of water to a syringe and then add contents of packet. Shake the syringe; leave 2 to 3 minutes to thicken. Shake the syringe and inject through the nasogastric or gastric tube within 30 minutes. For the 10 mg, 20 mg and 40 mg strengths, add 15 mL of water, and follow the instructions above.

<u>NEXIUM Delayed-Release Capsules</u>

NEXIUM 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 NEXIUM 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, NEXIUM 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 NEXIUM 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.

NEXIUM For Delayed-Release Oral Suspension

NEXIUM 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, NEXIUM 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 NEXIUM 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 NEXIUM 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.

3 DOSAGE FORMS AND STRENGTHS

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

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

NEXIUM 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.

4 CONTRAINDICATIONS

NEXIUM is contraindicated in patients with known hypersensitivity to proton pump inhibitors. Hypersensitivity reactions, e.g., angioedema and anaphylactic shock, have been reported with NEXIUM use.

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

5 WARNINGS AND PRECAUTIONS

5.1 Concurrent Gastric Malignancy

Symptomatic response to therapy with NEXIUM 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 *Clostridium difficile* associated diarrhea

Published observational studies suggest that PPI therapy like NEXIUM may be associated with an increased risk of *Clostridium difficile* associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve [*see Adverse Reactions (6.2)*].

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

Clostridium diffficile 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 NEXIUM, refer to WARNINGS and PRECAUTIONS sections of those package inserts.

5.4 Interaction with Clopidogrel

Avoid concomitant use of NEXIUM 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 NEXIUM consider alternative anti-platelet therapy. [see *Drug Interactions (7.3)and Pharmacokinetics (12.3)*]

5.5 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. [*seeDosage and Administration (2) and Adverse Reactions (6.2)*]

5.6 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. [*SeeAdverse Reactions (6.2)*]

5.7 Concomitant use of NEXIUM 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. [*seeDrug Interactions (7.3)*] Avoid concomitant use of NEXIUM with St John's Wort, or rifampin.

5.8 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. Providers should temporarily stop esomeprazole treatment 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.

5.9 Concomitant use of NEXIUM 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 NEXIUM 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, NEXIUM 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 NEXIUM 20 mg, 2,434 patients on NEXIUM 40 mg, and 3,008 patients on omeprazole 20 mg daily. The most frequently occurring adverse reactions (≥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 NEXIUM or omeprazole.

Additional adverse reactions that were reported as possibly or probably related to NEXIUM 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 flushes, 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, hypertonia, 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 NEXIUM, were reported in ≤ 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 [*seeClinical 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 NEXIUM were diarrhea (4.3%), headache (3.8%), and abdominal pain (3.8%).

Pediatrics

The safety of NEXIUM was evaluated in 316 pediatric and adolescent patients aged 1 to 17 years in four clinical trials for the treatment of symptomatic GERD [*seeClinical 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 NEXIUM was evaluated in 167 pediatric patients from birth to <1 year of age in three clinical trials. [*See Clinical Studies (14.3)*] 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 NEXIUM 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 NEXIUM, 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 NEXIUM 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 NEXIUM 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.

6.2 Postmarketing Experience

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

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 CYP 2C19.

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 NEXIUM. 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

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

7.3 Effects on Hepatic Metabolism/Cytochrome P-450 Pathways

Esomeprazole is extensively metabolized in the liver by CYP 2C19 and CYP 3A4. *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 CYP 2C19, the major esomeprazole metabolizing enzyme. Coadministration of esomeprazole 30 mg and diazepam, a CYP 2C19 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 NEXIUM with clopidogrel. When using NEXIUM, consider use of alternative anti-platelet therapy [*seePharmaokinetics (12.3)*].

Omeprazole acts as an inhibitor of CYP 2C19. Omeprazole, given in doses of 40 mg daily for one week to 20 healthy subjects in cross-over study, increased C_{max} and AUC of cilostazol by 18% and 26% respectively. C_{max} and AUC of one of its active metabolites, 3,4-dihydrocilostazol, which has 4-7 times the activity of cilostazol, were increased by 29% and 69% respectively. Co-administration of cilostazol with esomeprazole is expected to increase concentrations of cilostazol and its above mentioned active metabolite. Therefore a dose reduction of cilostazol from 100 mg twice daily to 50 mg twice daily should be considered.

Concomitant administration of esomeprazole and a combined inhibitor of CYP 2C19 and CYP 3A4, 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-Ellison'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 NEXIUM.

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. [*seeWarnings and Precautions (5.7) and Clinical Pharmacology (12.2)*]

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 [*seeClinical Pharmacology (12.4)*].

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 [*seeWarnings and Precautions (5.8)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Reproductive studies in rats and rabbits with NEXIUM (esomeprazole) and multiple cohort studies in pregnant women with omeprazole use during the first trimester do not show an increased risk of congenital anomalies or adverse pregnancy outcomes. There are, however, no adequate and well controlled studies of NEXIUM use in pregnancy. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Esomeprazole is the s-isomer of omeprazole. In four population-based cohort studies that included 1226 women exposed during the first trimester of pregnancy to omeprazole there was no increased risk of congenital anomalies.

Reproductive studies with esomeprazole have been performed in rats at doses up to 57 times the human dose and in rabbits at doses up to 35 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus. [*SeeAnimal Toxicology and/or Pharmacology (13.2)*]

Reproductive studies conducted with omeprazole on rats at oral doses up to 56 times the human dose and in rabbits at doses up to 56 times the human dose did not show any evidence of teratogenicity. In pregnant rabbits, omeprazole at doses about 5.5 to 56 times the human dose produced dose-related increases in embryo-lethality, fetal resorptions, and pregnancy loss. In rats treated with omeprazole at doses about 5.6 to 56 times the human dose, dose-related embryo/fetal toxicity and postnatal developmental toxicity occurred in offspring.

8.3 Nursing Mothers

Omeprazole concentrations have been measured in breast milk of one woman taking omeprazole 20 mg per day. However, the excretion of esomeprazole in milk has not been studied. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for NEXIUM in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of NEXIUM 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 NEXIUM 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 NEXIUM have not been established in patients less than 1 month of age.

1 to 17 years of age

Use of NEXIUM 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 [*seeClinical Pharmacology (12.3), Dosage and Administration (2), Adverse Reactions (6.1), and Clinical*

Studies (14.3)]. The safety and effectiveness of NEXIUM 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 NEXIUM 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 [*seeClinical Pharmacology (12.3), Dosage and Administration (2), Adverse Reactions (6.1), and Clinical Studies, (14.3)*].

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

There was no statistically significant difference between NEXIUM 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 NEXIUM 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 NEXIUM 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 NEXIUM 1 mg/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 [*seeClinical 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 NEXIUM 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 NEXIUM in neonates have not been established.

8.5 Geriatric Use

Of the total number of patients who received NEXIUM 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.

10 OVERDOSAGE

A single oral dose of esomeprazole at 510 mg/kg (about 103 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 NEXIUM overdose (limited experience of doses in excess of 240 mg/day) are transient. Single doses of 80 mg of esomeprazole were uneventful. Reports of overdosage 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 overdosage, 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 contact a Poison Control Center at 1–800–222–1222.

11 DESCRIPTION

The active ingredient in the proton pump inhibitor NEXIUM® (esomeprazole magnesium) Delayed-Release Capsules for oral administration and NEXIUM (esomeprazole magnesium) For Delayed-Release Oral Suspension is bis(5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-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 $(C_{17}H_{18}N_3O_3S)_2Mg$ x 3 H_2O with molecular weight of 767.2 as a trihydrate and 713.1 on an anhydrous basis. The structural formula is:

Figure 1

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.

NEXIUM 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: glyceryl monostearate 40-55, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer type C, polysorbate 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 NEXIUM 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 NEXIUM 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.

12 CLINICAL PHARMACOLOGY

12.1 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.

12.2 Pharmacodynamics

Antisecretory Activity

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

Table 3: Effect on Intragastric pH on Day 5 (N=36)

Parameter	NEXIUM 40 mg	NEXIUM 20 mg
% Time Gastric pH >4*(Hours)	70%† (16.8 h)	53% (12.7 h)
Coefficient of variation	26%	37%
Median 24 Hour pH	4.9†	4.1
Coefficient of variation	16%	27%

* Gastric pH was measured over a 24-hour period

† p< 0.01 NEXIUM 40 mg vs. NEXIUM 20 mg

In a second study, the effect on intragastric pH of NEXIUM 40 mg administered once daily over a five day period was similar to the first study, (% time with pH > 4 was 68% or 16.3 hours).

Serum Gastrin Effects

The effect of NEXIUM 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.

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 [*seeNonclinical 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 H_2-receptor antagonists.

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

In over 1,000 patients treated with NEXIUM (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

NEXIUM had no effect on thyroid function when given in oral doses of 20 or 40 mg for 4 weeks. Other effects of NEXIUM 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.

12.3 Pharmacokinetics

Absorption

NEXIUM Delayed-Release Capsules and NEXIUM 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 NEXIUM is decreased by 43% to 53% after food intake compared to fasting conditions. NEXIUM should be taken at least one hour before meals.

The pharmacokinetic profile of NEXIUM was determined in 36 patients with symptomatic gastroesophageal reflux disease following repeated once daily administration of 20 mg and 40 mg capsules of NEXIUM over a period of five days. The results are shown in the Table 4:

Table 4: Pharmacokinetic Parameters of NEXIUM on Day 5 Following Oral Dosing for 5 Days

Parameter * (CV)	NEXIUM 40 mg	NEXIUM 20 mg
AUC (µmol*h/L)	12.6 (42%)	4.2 (59%)
C_{max} (µmol/L)	4.7 (37%)	2.1 (45%)
T_{max} (h)	1.6	1.6
$t_{1/2}$ (h)	1.5	1.2

* Values represent the geometric mean, except the T_{max}, which is the arithmetic mean; CV = Coefficient of variation

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.

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 1.0 mg/kg esomeprazole in 1 to 11 month old infants are summarized in Table 5.

Table 5: Summary of PK parameters in 1 month to < 1 year Olds with GERD Following 7/8 Days of Once-Daily Oral Esomeprazole Treatment

	1 month to < 1 year
Parameter	1.0 mg/kg
AUC (µmol*h/L) (n=7)*	3.51
$C_{,max}$ (µmol/L) (n=15)*	0.87
$t_{½}$ (hours) (n=8)*	0.93
t_{max} (hours) (n=15)†	3.0

* *Geometric mean*

† *Median*

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.

Table 6: Summary of PK Parameters in 1 to 11 Year Olds with GERD following 5 Days of Once-Daily Oral Esomeprazole Treatment

	1 to 5 Year Olds	**6 to 11 Year Olds**	
Parameter	**10 mg (N=8)**	**10 mg (N=7)**	**20 mg (N=6)**
AUC (µmol*h/L)*	4.83	3.70	6.28
C_{max} (µmol/L)*	2.98	1.77	3.73
t_{max} (h)†	1.44	1.79	1.75
$t_{½λz}$ (h)*	0.74	0.88	0.73
Cl/F (L/h)*	5.99	7.84	9.22

* Geometric mean;

† arithmetic mean

12 to 17 Years of Age

The pharmacokinetics of NEXIUM were studied in 28 adolescent patients with GERD aged 12 to 17 years inclusive, in a single center study. Patients were randomized to receive NEXIUM 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, NEXIUM pharmacokinetics in adolescent patients aged 12 to 17 years were similar to those observed in adult patients with symptomatic GERD. See Table 7.

Table 7: Comparison of PK Parameters in 12 to 17 Year Olds with GERD and Adults with Symptomatic GERD Following the Repeated Daily Oral Dose Administration of Esomeprazole*

	12 to 17 Year Olds (N=28)		**Adults (N=36)**	
	20 mg	**40 mg**	**20 mg**	**40 mg**
AUC (µmol*h/L)	3.65	13.86	4.2	12.6
C_{max} (µmol/L)	1.45	5.13	2.1	4.7
t_{max} (h)	2.00	1.75	1.6	1.6
$t_{½λz}$ (h)	0.82	1.22	1.2	1.5

Data presented are geometric means for AUC, C_{max} and $t_{½λz}$, and median value for t_{max}.

* Duration of treatment for 12 to 17 year olds and adults were 8 days and 5 days, respectively. Data were obtained from two independent studies.

Gender

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 [*seeDosage and Administration (2)*].

Renal Insufficiency

The pharmacokinetics of NEXIUM 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

Coadministration 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.

12.4 Microbiology

NEXIUM, 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.

Pretreatment Resistance: Clarithromycin pretreatment resistance rate (MIC ≥ 1 mcg/mL) to *H. pylori* was 15% (66/445) at baseline in all treatment groups combined. A total of > 99% (394/395) of patients had *H. pylori* isolates that were considered to be susceptible (MIC ≤ 0.25 mcg/mL) to amoxicillin at baseline. One patient had a baseline *H. pylori* isolate with an amoxicillin MIC = 0.5 mcg/mL.

Clarithromycin Susceptibility Test Results and Clinical/Bacteriologic Outcomes: The baseline *H. pylori* clarithromycin susceptibility results and the *H. pylori* eradication results at the Day 38 visit are shown in the Table 8:

Table 8: Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes* for Triple Therapy - (Esomeprazole magnesium 40 mg once daily/amoxicillin 1000 mg twice daily/clarithromycin 500 mg twice daily for 10 days)

Clarithromycin Pretreatment Results	*H. pylori* negative (Eradicated)		*H. pylori* positive (Not Eradicated) Post-treatment susceptibility results			
			S †	I†	R †	No MIC
Susceptible† 182	162		4	0	2	14
Intermediate† 1	1		0	0	0	0
Resistant† 29	13		1	0	13	2

* Includes only patients with pretreatment and post-treatment clarithromycin susceptibility test results

† Susceptible (S) MIC ≤ 0.25 mcg/mL, Intermediate (I) MIC = 0.5 mcg/mL, Resistant (R) MIC ≥ 1.0 mcg/mL

Patients not eradicated of *H. pylori* following NEXIUM/amoxicillin/clarithromycin triple therapy will likely have clarithromycin resistant *H. pylori* isolates. Therefore, clarithromycin susceptibility testing should be done, when possible. Patients with clarithromycin resistant *H. pylori* should not be re-treated with a clarithromycin-containing regimen.

Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes:

In the NEXIUM/amoxicillin/clarithromycin clinical trials, 83% (176/212) of the patients in the NEXIUM/amoxicillin/clarithromycin treatment group who had pretreatment amoxicillin susceptible MICs (≤ 0.25 mcg/mL) were eradicated of *H. pylori*, and 17% (36/212) were not eradicated of *H. pylori*. Of the 36 patients who were not eradicated of *H. pylori* on triple therapy, 16 had no post-treatment susceptibility test results and 20 had post-treatment *H. pylori* isolates with amoxicillin susceptible MICs. Fifteen of the patients who were not eradicated of *H. pylori* on triple therapy also had post-treatment *H. pylori* isolates with clarithromycin resistant MICs. There were no patients with *H. pylori* isolates who developed treatment emergent resistance to amoxicillin.

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of NEXIUM 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 141 mg/kg/day (about 0.7 to 57 times the human dose of 20 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 5.6 times the human dose 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, 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 56 times the human dose on a body surface area basis) was found to have no effect on reproductive performance of parental animals.

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

Reproductive studies have been performed in rats at oral doses up to 280 mg/kg/day (about 57 times the human dose on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 35 times the human dose on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to esomeprazole.

Reproductive studies conducted with omeprazole in rats at oral doses up to 138 mg/kg/day (about 56 times the human dose on a body surface area basis) and in rabbits at doses up to 69 mg/kg/day (about 56 times the human dose on a body surface area basis) did not disclose any evidence for a teratogenic potential of omeprazole. In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (about 5.5 to 56 times the human dose on a body surface area basis) produced dose-related increases in embryo-lethality, fetal resorptions, and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8 to 138.0 mg/kg/day (about 5.6 to 56 times the human dose on a body surface area basis).

14 CLINICAL STUDIES

14.1 Healing of Erosive Esophagitis

The healing rates of NEXIUM 40 mg, NEXIUM 20 mg, and omeprazole 20 mg (the approved dose for this indication) were evaluated in patients with endoscopically diagnosed erosive esophagitis in four multicenter, double-blind, randomized studies. The healing rates at Weeks 4 and 8 were evaluated and are shown in the Table 9:

Table 9: Erosive Esophagitis Healing Rate (Life-Table Analysis)

Study	No. of Patients	Treatment Groups	Week 4	Week 8	Significance Level *
1	588	NEXIUM 20 mg	68.7%	90.6%	N.S.†
	588	Omeprazole 20 mg	69.5%	88.3%	
2	654	NEXIUM 40 mg	75.9%	94.1%	$p < 0.001$
	656	NEXIUM 20 mg	70.5%	89.9%	$p < 0.05$
	650	Omeprazole 20 mg	64.7%	86.9%	
3	576	NEXIUM 40 mg	71.5%	92.2%	N.S.†
	572	Omeprazole 20 mg	68.6%	89.8%	
4	1216	NEXIUM 40 mg	81.7%	93.7%	$p < 0.001$
	1209	Omeprazole 20 mg	68.7%	84.2%	

* log-rank test vs. omeprazole 20 mg

† N.S. = not significant ($p > 0.05$)

In these same studies of patients with erosive esophagitis, sustained heartburn resolution and time to sustained heartburn resolution were evaluated and are shown in the Table 10:

Table 10: Sustained Resolution* of Heartburn (Erosive Esophagitis Patients)

			Cumulative Percent† with Sustained Resolution		
Study	No. of Patients	Treatment Groups	Day 14	Day 28	Significance Level ‡
1	573	NEXIUM 20 mg	64.3%	72.7%	N.S.§

	555	Omeprazole 20 mg	64.1%	70.9%	
2	621	NEXIUM 40 mg	64.8%	74.2%	p <0.001
	620	NEXIUM 20 mg	62.9%	70.1%	N.S.§
	626	Omeprazole 20 mg	56.5%	66.6%	
3	568	NEXIUM 40 mg	65.4%	73.9%	N.S.§
	551	Omeprazole 20 mg	65.5%	73.1%	
4	1187	NEXIUM 40 mg	67.6%	75.1%	p <0.001
	1188	Omeprazole 20 mg	62.5%	70.8%	

* Defined as 7 consecutive days with no heartburn reported in daily patient diary.

† Defined as the cumulative proportion of patients who have reached the start of sustained resolution

‡ log-rank test vs. omeprazole 20 mg

§ N.S. = not significant (p > 0.05)

In these four studies, the range of median days to the start of sustained resolution (defined as 7 consecutive days with no heartburn) was 5 days for NEXIUM 40 mg, 7 to 8 days for NEXIUM 20 mg and 7 to 9 days for omeprazole 20 mg.

There are no comparisons of 40 mg of NEXIUM with 40 mg of omeprazole in clinical trials assessing either healing or symptomatic relief of erosive esophagitis.

Long-Term Maintenance of Healing of Erosive Esophagitis

Two multicenter, randomized, double-blind placebo-controlled 4-arm trials were conducted in patients with endoscopically confirmed, healed erosive esophagitis to evaluate NEXIUM 40 mg (n=174), 20 mg (n=180), 10 mg (n=168) or placebo (n=171) once daily over six months of treatment.

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

The percentages of patients that maintained healing of erosive esophagitis at the various time points are shown in the Figures 2 and 3:

Figure 2: Maintenance of Healing Rates by Month (Study 177)

s= scheduled visit

Figure 3: Maintenance of Healing Rates by Month (Study 178)

s= scheduled visit

Patients remained in remission significantly longer and the number of recurrences of erosive esophagitis was significantly less in patients treated with NEXIUM compared to placebo.

In both studies, the proportion of patients on NEXIUM who remained in remission and were free of heartburn and other GERD symptoms was well differentiated from placebo.

In a third multicenter open label study of 808 patients treated for 12 months with NEXIUM 40 mg, the percentage of patients that maintained healing of erosive esophagitis was 93.7% for six months and 89.4% for one year.

14.2 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 NEXIUM 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 NEXIUM groups compared to placebo at all follow-up visits (Weeks 1, 2, and 4).

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

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

Figure 4: Percent of Patients Symptom-Free of Heartburn by Day (Study 225)

Figure 5: Percent of Patients Symptom-Free of Heartburn by Day (Study 226)

In three European symptomatic GERD trials, NEXIUM 20 mg and 40 mg and omeprazole 20 mg were evaluated. No significant treatment related differences were seen.

14.3 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 NEXIUM 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 NEXIUM 5 mg or 10 mg
weight ≥ 20 kg: once daily treatment with NEXIUM 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 NEXIUM 20 mg or NEXIUM 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.

14.4 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 NEXIUM 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 NEXIUM 40 mg over NEXIUM 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	191	NEXIUM 20 mg	95.4
	194	NEXIUM 40 mg	96.7
	184	Placebo	88.2
2	267	NEXIUM 20 mg	94.7
	271	NEXIUM 40 mg	95.3
	257	Placebo	83.3

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

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

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

NEXIUM plus clarithromycin or NEXIUM alone group. The results are shown in Table 12:

Table 12: H. pylori Eradication Rates at 4 Weeks after 10 Day Treatment Regimen % of Patients Cured [95% Confidence Interval] (Number of Patients)

Study	Treatment Group	Per-Protocol*	Intent-to-Treat†
191	NEXIUM plus amoxicillin and clarithromycin	84%‡ [78, 89] (n=196)	77%‡ [71, 82] (n=233)
	NEXIUM plus clarithromycin	55% [48, 62] (n=187)	52% [45, 59] (n=215)
193	NEXIUM plus amoxicillin and clarithromycin	85%§ [74, 93] (n=67)	78%§ [67, 87] (n=74)
	NEXIUM	5% [0, 23] (n=22)	4% [0, 21] (n=24)

* 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 NEXIUM plus clarithromycin.

§ $p < 0.05$ compared to NEXIUM alone.

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

14.6 Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

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, NEXIUM 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.

Table 13: Adequate Acid Suppression at Final Visit by Dose Regimen

NEXIUM 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

NEXIUM Delayed-Release Capsules, 20 mg, are opaque, hard gelatin, amethyst colored capsules with two radial bars in yellow on the cap and NEXIUM 20 mg in yellow on the body. They are supplied as follows:

NDC 0186-5020-31 unit of use bottles of 30

NDC 0186-5022-28 unit dose packages of 100

NDC 0186-5020-54 bottles of 90

NDC 0186-5020-82 bottles of 1000

NEXIUM Delayed-Release Capsules, 40 mg, are opaque, hard gelatin, amethyst colored capsules with three radial bars in yellow on the cap and NEXIUM 40 mg in yellow on the body. They are supplied as follows:

NDC 0186-5040-31 unit of use bottles of 30

NDC 0186-5042-28 unit dose packages of 100

NDC 0186-5040-54 bottles of 90

NDC 0186-5040-82 bottles of 1000

NDC 0186-5040-35 unit of use bottles of 30

NDC 0186-5042-25 unit dose packages of 100

NDC 0186-5040-55 bottles of 90

NDC 0186-5040-85 bottles of 1000

NEXIUM For Delayed-Release Oral Suspension is supplied as a unit dose packet containing a fine yellow powder, consisting of white to pale brownish esomeprazole granules and pale yellow inactive granules. NEXIUM unit dose packets are supplied as follows:

NDC 0186-4025-01 unit dose packages of 30: 2.5 mg packets

NDC 0186-4050-01 unit dose packages of 30: 5 mg packets

NDC 0186-4010–01 unit dose packages of 30: 10 mg packets

NDC 0186-4020–01 unit dose packages of 30: 20 mg packets

NDC 0186-4040–01 unit dose packages of 30: 40 mg packets

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

17 PATIENT COUNSELING INFORMATION

“See FDA-Approved Medication Guide”

- Advise patients to let you know if they are taking, or begin taking, other medications, because NEXIUM can interfere with antiretroviral drugs and drugs that are affected by gastric pH changes [*see Drug Interactions (7.1)*].
- Let patients know that antacids may be used while taking NEXIUM.
- Advise patients to take NEXIUM at least one hour before a meal.
- For patients who are prescribed NEXIUM Delayed-Release Capsules, advise them not to chew or crush the capsules.
- Advise patients that, if they open NEXIUM Delayed-Release Capsules to mix the granules with

food, the granules should only be mixed with applesauce. Use with other foods has not been evaluated and is not recommended.

- For patients who are advised to open the NEXIUM Delayed-Release Capsules before taking them or who are prescribed NEXIUM For Delayed-Release Oral Suspension, instruct them in the proper technique for administration [*see Dosage and Administration (2)*] and tell them to follow the dosing instructions in the PATIENT INFORMATION insert included in the package. Instruct patients to rinse the syringe with water after each use.
- For patients who are prescribed NEXIUM for Delayed-Release Oral Suspension and need to use more than one packet for their dose, instruct them regarding the correct amount of water to use when mixing their dose.

Advise patients to immediately report and seek care for diarrhea that does not improve. This may be a sign of *Clostridium difficile* associated diarrhea [*see Warnings and Precautions (5.3)*].

Advise patients to immediately report and seek care for any cardiovascular or neurological symptoms including palpitations, dizziness, seizures, and tetany as these may be signs of hypomagnesemia [*see Warnings and Precautions (5.6)*].

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Medication Guide

NEXIUM® (nex-e-um)

(esomeprazole magnesium)

Delayed-Release Capsules

NEXIUM® (nex-e-um)

(esomeprazole magnesium)

For Delayed-Release
Oral Suspension

Read the Medication Guide that comes with NEXIUM before you start taking NEXIUM and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about NEXIUM?

NEXIUM may help your acid-related symptoms, but you could still have serious stomach problems. Talk with your doctor.

NEXIUM can cause serious side effects, including:

- **Diarrhea**. NEXIUM may increase your risk of getting severe diarrhea. This diarrhea may be caused by an infection *(Clostridium difficile)* in your intestines.
  Call your doctor right away if you have watery stool, stomach pain, and fever that does not go away.

- **Bone fractures**. People who take multiple daily doses of Proton Pump Inhibitor medicines for a long period of time (a year or longer) may have an increased risk of fractures of the hip, wrist, or spine. You should take NEXIUM exactly as prescribed, at the lowest dose possible for your treatment and for the shortest time needed. Talk to your doctor about your risk of bone fracture if you take NEXIUM.

  NEXIUM can have other serious side effects. See "**What are the possible side effects of NEXIUM**?"

What is NEXIUM?

NEXIUM is a prescription medicine called a proton pump inhibitor (PPI). NEXIUM reduces the amount of acid in your stomach.

NEXIUM is used in adults:

- for 4 to 8 weeks to treat the symptoms of gastroesophageal reflux disease (GERD). NEXIUM may also be prescribed to heal acid-related damage to the lining of the esophagus (erosive esophagitis), and to help continue this healing.
- GERD happens when acid in your stomach backs up into the tube (esophagus) that connects your mouth to your stomach. This may cause a burning feeling in your chest or throat, sour taste, or burping.
- for up to 6 months to reduce the risk of stomach ulcers in some people taking pain medicines called non-steroidal anti-inflammatory drugs (NSAIDs).
- to treat patients with a stomach infection (Helicobacter pylori), along with the antibiotics amoxicillin and clarithromycin.
- for the long-term treatment of conditions where your stomach makes too much acid, including Zollinger-Ellison Syndrome. Zollinger-Ellison Syndrome is a rare condition in which the stomach produces a more than normal amount of acid.

For children and adolescents 1 year to 17 years of age, NEXIUM may be prescribed for up to 8 weeks for short-term treatment of GERD.

In children ages 1 month to less than 1 year of age, NEXIUM is only used to treat GERD with acid-related damage to the esophagus (erosive esophagitis) for up to 6 weeks.

It is not known if NEXIUM is effective in children under 1 month of age.

Who should not take NEXIUM?

Do not take NEXIUM if you:

- are allergic to esomeprazole magnesium or any of the ingredients in NEXIUM. See the end of this Medication Guide for a complete list of ingredients in NEXIUM.
- are allergic to any other Proton Pump Inhibitor (PPI) medicine.

What should I tell my doctor before taking NEXIUM?

Before you take NEXIUM, tell your doctor if you:

- have been told that you have low magnesium levels in your blood
- have liver problems
- are pregnant or plan to become pregnant. It is not known if NEXIUM can harm your unborn baby.
- are breastfeeding or planning to breastfeed. It is not known if NEXIUM passes into your breastmilk. You and your doctor should decide if you will take NEXIUM or breastfeed. You

should not do both. Talk to your doctor about the best way to feed your baby if you take NEXIUM.

Tell your doctor about all of the medicines you take, including prescription and non-prescription drugs, vitamins and herbal supplements. NEXIUM may affect how other medicines work, and other medicines may affect how NEXIUM works.

- Especially tell your doctor if you take:
- warfarin (Coumadin, Jantoven)
- ketoconazole (Nizoral)
- voriconazole (Vfend)
- atazanavir (Reyataz)
- nelfinavir (Viracept)
- saquinavir (Fortovase)
- products that contain iron
- digoxin (Lanoxin)
- St.John's Wort (Hypericum perforatum)
- Rifampin (Rimactane, Rifater, Rifamate)
- cilostazol (Pletal)
- diazepam (Valium)
- tacrolimus (Prograf)
- erlotinib (Tarceva)
- methotrexate
- clopidogrel (Plavix)

How should I take NEXIUM?

- Take NEXIUM exactly as prescribed by your doctor.
- Do not change your dose or stop NEXIUM without talking to your doctor.
- Take NEXIUM at least 1 hour before a meal.
- Swallow NEXIUM capsules whole. **Never chew or crush NEXIUM.**
- If you have difficulty swallowing NEXIUM capsules, you may open the capsule and empty the contents into a tablespoon of applesauce. Do not crush or chew the granules. Be sure to swallow the applesauce right away. Do not store it for later use.
- If you forget to take a dose of NEXIUM, take it as soon as you remember. If it is almost time for your next dose, do not take the missed dose. Take the next dose on time. Do not take a double dose to make up for a missed dose.
- If you take too much NEXIUM, call your doctor or local poison control center right away, or go to the nearest hospital emergency room.
- See the "Instructions for Use" at the end of this Medication Guide for instructions how to take NEXIUM For Delayed-Release Oral Suspension, and how to mix and give NEXIUM Delayed-Release Capsules and NEXIUM For Delayed-Release Oral Suspension, through a nasogastric tube or gastric tube.

What are the possible side effects of NEXIUM?

NEXIUM can cause serious side effects, including:

- See "**What is the most important information I should know about NEXIUM?"**
- **Chronic (lasting a long time) inflammation of the stomach lining (Atrophic Gastritis)**. Using

NEXIUM for a long period of time may increase the risk of inflammation to your stomach lining. You may or may not have symptoms. Tell your doctor if you have stomach pain, nausea, vomiting, or weight loss.

- **Low magnesium levels in your body.** This problem can be serious. Low magnesium can happen in some people who take a proton pump inhibitor medicine for at least 3 months. If low magnesium levels happen, it is usually after a year of treatment. You may or may not have symptoms of low magnesium.
  Tell you doctor right away if you have any of these symptoms:

  - seizures
  - dizziness
  - abnormal or fast heart beat
  - jitteriness
  - jerking movements or shaking (tremors)
  - muscle weakness
  - spasms of the hands and feet
  - cramps or muscle aches
  - spasm of the voice box

Your doctor may check the level of magnesium in your body before you start taking NEXIUM or during treatment if you will be taking NEXIUM for a long period of time.

The most common side effects with NEXIUM may include:

- headache
- diarrhea
- nausea
- gas
- abdominal pain
- constipation
- dry mouth
- drowsiness

Other side effects:

Serious allergic reactions. Tell your doctor if you get any of the following symptoms with NEXIUM:

- rash
- face swelling
- throat tightness
- difficulty breathing

Your doctor may stop NEXIUM if these symptoms happen.

Tell your doctor if you have any side effects that bother you or that do not go away. These are not all the possible side effects with NEXIUM.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store NEXIUM?

- Store NEXIUM at room temperature between 68°F to 77°F (20°C to 25°C).

- Keep the container of NEXIUM closed tightly.

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

General information about NEXIUM

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NEXIUM for a condition for which it was not prescribed. Do not give NEXIUM to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about NEXIUM. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about NEXIUM that is written for health professionals.

For more information, go to www.purplepill.com or call 1-800-463-9486.

What are the ingredients in NEXIUM?

Active ingredient: esomeprazole magnesium trihydrate

Inactive ingredients in NEXIUM Delayed-Release Capsules (including the capsule shells): glyceryl monostearate 40-55, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer type C, polysorbate 80, sugar spheres, talc, triethyl citrate, 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.

Inactive granules in NEXIUM For Delayed-Release Oral Suspension: dextrose, xanthan gum, crospovidone, citric acid, iron oxide, and hydroxypropyl cellulose.

Instructions for Use

For instructions on taking Delayed-Release Capsules, see the section of this leaflet called "**How should I take NEXIUM?**"

Take NEXIUM For Delayed-Release Oral Suspension as follows:

- NEXIUM For Delayed-Release Oral Suspension comes in foil packets containing 2.5 mg, 5 mg, 10 mg, 20 mg, or 40 mg strengths.
- You should use an oral syringe to measure the amount of water needed to mix your dose. Ask your pharmacist for an oral syringe.
- If your prescribed dose is 2.5 mg or 5 mg, add 5 mL of water to a container, then add the contents of a foil packet containing the dose prescribed by your doctor.
- If your prescribed dose is 10 mg, 20 mg, or 40 mg, add 15 mL of water to a container, then add the contents of a foil packet containing the dose prescribed by your doctor.
- If you or your child are instructed to use more than one foil packet for the prescribed dose, follow the mixing instructions provided by your pharmacist or doctor.
- Stir.
- Leave 2 to 3 minutes to thicken.
- Stir and take dose within 30 minutes. If not used within 30 minutes, throw away this dose and mix a new dose.
- If any medicine remains after drinking, add more water, stir, and take dose right away.
- For young children, you can give the dose with an oral syringe. Rinse the oral syringe with water after each use.

NEXIUM Delayed-Release Capsules and NEXIUM For Delayed-Release Oral Suspension may be given through a nasogastric tube (NG tube) or gastric tube, as prescribed by your doctor. Follow the instructions below:

NEXIUM Delayed-Release Capsules:

- Open the capsule and empty the granules into a 60 mL catheter tipped syringe. Mix with 50 mL of water. Use only a catheter tipped syringe to give NEXIUM through a NG tube.
- Replace the plunger and shake the syringe well for 15 seconds. Hold the syringe with the tip up and check for granules in the tip.
- Give the medicine right away.
- Do not give the granules if they have dissolved or have broken into pieces.
- Attach the syringe to the NG tube. Give the medicine in the syringe through the NG tube into the stomach.
- After giving the granules, flush the NG tube with more water.

NEXIUM For Delayed-Release Oral Suspension:

- NEXIUM For Delayed-Release Oral Suspension comes in foil packets containing 2.5 mg, 5 mg, 10 mg, 20 mg, or 40 mg strengths.
- Use only a catheter tipped syringe to give NEXIUM through a NG tube or gastric tube
- If your prescribed dose is 2.5 mg or 5 mg, add 5 mL of water to a catheter tipped syringe, then add the contents of a foil packet containing the dose prescribed by your doctor.
- If your prescribed dose is 10 mg, 20 mg, or 40 mg, add 15 mL of water to a catheter tipped syringe, then add the contents of a foil packet containing the dose prescribed by your doctor.
- Shake the syringe right away and then leave it for 2 to 3 minutes to thicken.
- Shake the syringe and give the medicine through the NG or gastric tube (French size 6 or larger) into the stomach within 30 minutes.
- Refill the syringe with the same amount of water (either 5 mL or 15 mL of water depending on your dose).
- Shake the syringe and flush any remaining medicine from the NG tube or gastric tube into the stomach.

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

AstraZeneca Pharmaceuticals LP

Wilmington, DE 19850

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NEXIUM

esomeprazole magnesium capsule, delayed release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:63629-3347(NDC:0186-5020)
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ESOMEPRAZOLE MAGNESIUM (UNII: R6DXU4WAY9) (ESOMEPRAZOLE - UNII:N3PA6559FT)	ESOMEPRAZOLE	20 mg

Inactive Ingredients

Ingredient Name	Strength
GLYCERYL MONOSTEARATE (UNII: 230OU9XXE4)	
HYDROXYPROPYL CELLULOSE (UNII: RFW2ET671P)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
METHACRYLIC ACID (UNII: 1CS02G8656)	
TALC (UNII: 7SEV7J4R1U)	
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
GELATIN (UNII: 2G86QN327L)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
D&C RED NO. 28 (UNII: 767IP0Y5NH)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
ALCOHOL (UNII: 3K9958V90M)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
POLYETHYLENE GLYCOLS (UNII: 3WJQ0SDW1A)	

SODIUM HYDROXIDE (UNII: 55X04QC32I)	
POVIDONES (UNII: FZ989GH94E)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	

Product Characteristics

Color	PURPLE (Amethyst)	**Score**	no score
Shape	CAPSULE	**Size**	14mm
Flavor		**Imprint Code**	NEXIUM20mg
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63629-3347-1	30 in 1 BOTTLE		
2	NDC:63629-3347-2	10 in 1 BOTTLE		
3	NDC:63629-3347-3	90 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021153	03/19/2001	

Labeler - Bryant Ranch Prepack (171714327)

Registrant - Bryant Ranch Prepack (171714327)

Establishment

Name	Address	ID/FEI	Business Operations
Bryant Ranch Prepack		171714327	REPACK(63629-3347) , RELABEL(63629-3347)