Warnings and Precautions, Fundic Gland Polyps (5.12) 06/2018

NEXIUM® (esomeprazole magnesium) for delayed-release oral suspension

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

• Treatment of gastrointestinal 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)

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Dosage and Administration

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

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)

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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)

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Contraindications

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

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Warnings and Precautions

• Gastric Malignancy: In adults, symptomatic response does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing. (5.1)
• Acute Interstitial Nephritis: Observed in patients taking PPIs. (5.2)
• Clostridium difficile-Associated Diarrhea: PPI therapy may be associated with increased risk. (5.3)
• 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. (5.4)
• Cutaneous and Systemic Lupus Erythematosus: Mostly cutaneous; new onset or exacerbation of existing disease; discontinue NEXIUM and refer to specialist for evaluation. (5.5)
• Interaction with Clopidogrel: Avoid concomitant use of NEXIUM. (5.6)
• Cyanocobalamin (Vitamin B-12): Deficiency: Daily long-term use (e.g., longer than 3 years) may lead to malabsorption or a deficiency of cyanocobalamin. (5.7)
• Hypomagnesemia: Reported rarely with prolonged treatment with PPIs. (5.8)
• Interaction with St. John’s Wort or Rifampin: Avoid concomitant use of NEXIUM. (5.9, 7.3)
• Interactions with Diagnostic Investigations for Neuroendocrine Tumors: Increased chromogranin A (CgA) levels may interfere with diagnostic investigations for neuroendocrine tumors; temporarily stop NEXIUM at least 14 days before assessing CgA levels. (5.10, 12.2)
• Interaction with Methotrexate: Concomitant use with PPIs may elevate or prolong serum concentrations of methotrexate and/or its metabolite, possibly leading to toxicity. With high dose methotrexate administration, consider temporary withdrawal of NEXIUM. (5.11, 7.7)
• Fundic Gland Polyps: Risk increases with long-term use, especially beyond one year. Use the shortest duration of therapy. (5.12)

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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, tachycardia, 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.

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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, digoxin and mycophenolate mofetil). Patients treated with NEXIUM and digoxin may need to be monitored for digoxin toxicity. (7.2)
• Combined inhibitor of CYP2C19 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 clofazimine 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: 06/2018
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 [see Dosage 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 [see Clinical 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 for NEXIUM

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosage Form</th>
<th>Route</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroesophageal Reflux Disease (GERD)</td>
<td>Delayed-Release Capsules</td>
<td>Oral</td>
<td>NEXIUM capsules can be swallowed whole.</td>
</tr>
<tr>
<td>Healing of Erosive Esophagitis</td>
<td>Doses over 1.33 mg/kg/day have not been studied.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintenance of Healing of Erosive Esophagitis</td>
<td>Doses over 1 mg/kg/day have not been studied.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic Gastroesophageal Reflux Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric GERD</td>
<td>Delayed-Release Capsules</td>
<td>Oral</td>
<td>NEXIUM capsules can be swallowed whole.</td>
</tr>
<tr>
<td>12 to 17 Year Olds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healing of Erosive Esophagitis</td>
<td>20 mg or 40 mg</td>
<td>Once Daily for 4 to 8 Weeks</td>
<td></td>
</tr>
<tr>
<td>Symptomatic GERD</td>
<td>20 mg</td>
<td>Once Daily for 4 to 8 Weeks</td>
<td></td>
</tr>
<tr>
<td>1 to 11 Year Olds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-term Treatment of Symptomatic GERD</td>
<td>10 mg</td>
<td>Once Daily for up to 8 Weeks</td>
<td></td>
</tr>
<tr>
<td>Healing of Esophageal Ulcer</td>
<td>weight &lt; 20 kg</td>
<td>10 mg or 15 mg</td>
<td>Once Daily for up to 8 Weeks</td>
</tr>
<tr>
<td>weight ≥ 20 kg</td>
<td>20 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 month to &lt; 1 year old</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erosive Esophagitis due to acid-mediated GERD</td>
<td>weight 3 kg to 5 kg</td>
<td>2.5 mg</td>
<td>Once Daily for up to 6 Weeks</td>
</tr>
<tr>
<td>weight &gt; 5 kg to 7.5 kg</td>
<td>5 mg</td>
<td>Once Daily for up to 8 Weeks</td>
<td></td>
</tr>
<tr>
<td>weight &gt; 7.5 kg to 12 kg</td>
<td>10 mg</td>
<td>Once Daily for up to 6 Weeks</td>
<td></td>
</tr>
<tr>
<td>Risk Reduction of NSAID-Associated Gastric Ulcer</td>
<td>20 mg or 40 mg</td>
<td>For Delayed-Release Oral Suspension</td>
<td>NEXIUM capsules can be swallowed whole.</td>
</tr>
<tr>
<td>H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple Therapy: NEXIUM</td>
<td>40 mg</td>
<td>Once Daily for 10 Days</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>1000 mg</td>
<td>Twice Daily for 10 Days</td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>500 mg</td>
<td>Twice Daily for 10 Days</td>
<td></td>
</tr>
</tbody>
</table>

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Route</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed-Release Capsules</td>
<td>Oral</td>
<td>NEXIUM capsules can be swallowed whole.</td>
</tr>
<tr>
<td>Chronic Gastritis</td>
<td>Doses over 1.33 mg/kg/day have not been studied.</td>
<td></td>
</tr>
<tr>
<td>Reflux Esophagitis</td>
<td>Doses over 1 mg/kg/day have not been studied.</td>
<td></td>
</tr>
<tr>
<td>Gastric Ulcers</td>
<td>Doses over 1 mg/kg/day have not been studied.</td>
<td></td>
</tr>
<tr>
<td>Gastroduodenal Ulcers</td>
<td>The dosage of NEXIUM in patients with pathological hypersecretory conditions varies with the individual patient. Dosage regimens should be adjusted to individual patient needs.</td>
<td></td>
</tr>
<tr>
<td>Doses up to 240 mg daily have been administered [see Drug Interactions (7)].</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Specific 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 [see Clinical 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

Dosage Form

<table>
<thead>
<tr>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed-Release Capsules</td>
<td>NEXIUM capsules can be swallowed whole.</td>
</tr>
<tr>
<td>Oral</td>
<td>NEXIUM capsules can be swallowed whole.</td>
</tr>
<tr>
<td>Nasogastric Tube</td>
<td>NEXIUM capsules can be opened and the intact granules emptied into a syringe and delivered through the nasogastric tube.</td>
</tr>
<tr>
<td>Oral Suspension</td>
<td>NEXIUM capsules can be swallowed whole.</td>
</tr>
<tr>
<td>Nasogastric or Gastric Tube</td>
<td>NEXIUM capsules can be opened and the intact granules emptied into a syringe and delivered through the nasogastric tube.</td>
</tr>
</tbody>
</table>

NEXIUM Delayed-Release Capsules

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 syringe. 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 within 30 minutes.
- For the 10 mg, 20 mg and 40 mg strengths, add 15 mL of water, and follow the instructions above.
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 substituted benzimidazoles or to any component of the formulation. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, and urticaria [see Adverse Reactions (6)].

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 Presence of Gastric Malignancy
In adults, symptomatic response to therapy with NEXIUM does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing in adults who have a suboptimal response or an early symptomatic relapse after completing treatment with a PPI. In older patients, also consider an endoscopy.

5.2 Acute Intestinal Nephritis
Acute intestinal nephritis has been observed in patients taking PPIs including NEXIUM. Acute intestinal nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue NEXIUM if acute intestinal nephritis develops [see Contraindications (4)].

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 difficile-associated diarrhea (CDDA) 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 section of the corresponding prescribing information.

5.4 Bone Fracture
Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines [see Dosage and Administration (2) and Adverse Reactions (6.2)].

5.5 Cutaneous and Systemic Lupus Erythematosus
Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs, including esomeprazole. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematosus cases were CLE.

The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after discontinuing treatment primarily in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement.

Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash, however, arthralgia and cytopenia were also reported.

Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving NEXIUM, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks. Serological testing (e.g., ANA) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

5.6 Interaction with Clopidogrel
Avoid concomitant use of NEXIUM with clopidogrel. Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is entirely due to its 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 Clinical Pharmacology (12.3)].

5.7 Cyanocobalamin (Vitamin B-12) Deficiency
Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

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

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically [see Adverse Reactions (6.2)].

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

5.10 Interactions with Diagnostic Investigations for Neuroendocrine Tumors
Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Healthcare providers should temporarily stop esomeprazole treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g., for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary [see Clinical Pharmacology (12.2)].

5.11 Interaction 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)].

5.12 Fundic Gland Polyps
PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond one year. Most PPI users who developed fundic gland polyps were asymptomatic and fundic gland polyps were identified incidentally on endoscopy. Use the shortest duration of PPI therapy appropriate to the condition being treated.

6 ADVERSE REACTIONS
The following serious adverse reactions are described below and elsewhere in labeling:
• Acute Intestinal Nephritis [see Warnings and Precautions (5.2)]
• Clostridium difficile-Associated Diarrhea [see Warnings and Precautions (5.3)]
• Bone Fracture [see Warnings and Precautions (5.4)]
• Cutaneous and Systemic Lupus Erythematosus [see Warnings and Precautions (5.5)]
• Cyanocobalamin (Vitamin B-12) Deficiency [see Warnings and Precautions (5.7)]
• Hypomagnesemia [see Warnings and Precautions (5.8)]
• Fundic Gland Polyps [see Warnings and Precautions (5.12)]

5.1 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 commonly 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, asthma, back pain, chest pain, subternal chest pain, facial edema, peripheral edema, hot flushed, 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, dysphagia GI, epigastric pain, eructation, esophageal disorder, frequent stools, gastro-enteritis, 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, hypernatremia, 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, hypotonia, nervousness, hyperesthesia, 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, microurinary frequency, mononucleosis, genitourinary infection, pyelonephritis, 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 [see Clinical Pharmacology (12)]. Decreases were seen in hemoglobin, white blood cell count, platelets, potassium, sodium, and thyroid hormone.

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 possible 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 [see Clinical Studies (14.2)]. In 109 pediatric patients aged 1 to 11 years, the most frequently reported (at least 1%) treatment-related adverse reactions in these patients were diarrhea (2.8%), headache (1.9%) and somnolence (1.9%). In 149 pediatric patients aged 12 to 17 years the most frequently reported (at least 2%) treatment-related adverse reactions in these patients were headache (6.1%), 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.

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

7.3 Effects on Hepatic Metabolism/Cytochrome P-450 Pathways
Esomeprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4. In vitro and in vivo studies have shown that esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1, and 3A4. No clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Drug interaction studies have shown that esomeprazole does not have any clinically significant interactions with phenytoin, warfarin, quinidine, clarithromycin, or amoxicillin.

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

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

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 [see Clinical Pharmacology (12.3)].
Omeprazole acts as an inhibitor of CYP2C19. Omeprazole, given in doses of 40 mg daily for one week to 20 healthy subjects in cross-over study, increased C<sub>max</sub> and AUC of citalostazol by 18% and 26% respectively. C<sub>max</sub> and AUC of one of its active metabolites, 3,4-dihydrocitalostazol, which has 4-7 times the activity of citalostazol, were increased by 29% and 69%, respectively. Co-administration of citalostazol with esomeprazole is expected to increase concentrations of citalostazol and its above mentioned active metabolite. Therefore, a dose reduction of citalostazol from 100 mg twice daily to 50 mg twice daily should be considered.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. Dose adjustment of esomeprazole is not normally required. However, in patients with Zollinger-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<sub>max</sub> and AUC decreased by 37.5% and 37.9%, respectively) and extensive metabolisers (C<sub>max</sub> 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 [see Warnings and Precautions (5.10) 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 [see Clinical 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 [see Warnings and Precautions (5.11)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies with NEXIUM in pregnant women. Esomeprazole is the S-isomer of omeprazole. Available epidemiologic data fail to demonstrate an increased risk of major congenital malformations or other adverse pregnancy outcomes with first trimester omeprazole use. Reproduction studies in rats and rabbits resulted in dose-dependent embryo-lethality at omeprazole doses that were approximately 3.4 to 34 times an oral human dose of 40 mg (based on a body surface area for a 60 kg person).

Teratogenicity was not observed in animal reproduction studies with administration of oral esomeprazole magnesium in rats and rabbits with doses about 68 times and 42 times, respectively, an oral human dose of 40 mg (based on a body surface area basis for a 60 kg person). Changes in bone morphology were observed in offspring of rats dosed through most of pregnancy and lactation at doses equal to or greater than approximately 34 times an oral human dose of 40 mg. When maternal administration was confined to gestation only, there were no effects on bone physical morphology in the offspring at any age [see Data]. The estimated background risk of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

Esomeprazole is the S-isomer of omeprazole. Four epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy with the frequency of abnormalities among infants of women exposed to H<sub>2</sub>-receptor antagonists or other controls.

A population-based retrospective cohort epidemiological study from the Swedish Medical Birth Registry, covering approximately 99% of pregnancies, from 1995 to 1999, reported on 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester, and 131 exposed after the first trimester) whose mothers used omeprazole during pregnancy. The number of infants exposed in utero to omeprazole that had any malformation, low birth weight, low Apgar score, or hospitalization was similar to the number observed in this population. The number of infants born with ventricular septal defects and the number of stillborn infants was slightly higher in the omeprazole-exposed infants than the expected number in this population.

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

A retrospective cohort study reported on 689 pregnant women exposed to either H<sub>2</sub>-blockers or omeprazole in the first trimester (134 exposed to omeprazole) and 1,575 pregnant women unexposed to either during the first trimester. The overall malformation rate in offspring born to mothers with first trimester exposure to omeprazole, an H<sub>2</sub>-blocker, or were unexposed was 3.6%, 5.5%, and 4.1% respectively.

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

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

Animal Data

Omeprazole

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

Esomeprazole

No effects on embryo/fetal development were observed in reproduction studies with esomeprazole magnesium in rats at oral doses up to 280 mg/kg/day (about 68 times an oral human dose of 40 mg on a body surface area basis) or in rabbits at oral doses up to 86 mg/kg/day (about 41 times an oral human dose of 40 mg on a body surface area basis), administered prior to mating through the lactation period.

A pre- and postnatal developmental toxicity study in rats with additional endpoints to evaluate bone development was performed with esomeprazole magnesium at oral doses of 14 to 280 mg/kg/day (about 3.4 to 68 times an oral human dose of 40 mg on a body surface area basis). Neonatal/early postnatal (birth to weaning) survival was decreased at doses of 280 mg/kg/day or greater than an oral human dose of 138 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis). Body weight and body weight gain were reduced and neurobehavioral or general developmental delays in the immediate post-weaning timeframe were evident at doses equal to or greater than 69 mg/kg/day (about 17 times an oral human dose of 40 mg on a body surface area basis). In addition, decreased femur length, width and thickness of cortical bone, decreased thickness of the tibial growth plate and an increase in mild bone marrow dysplasia were noted at doses equal to or greater than 14 mg/kg/day (about 3.4 times an oral human dose of 40 mg on a body surface area basis). Physial dysplasia in the femur was observed in offspring of rats treated with oral doses of esomeprazole magnesium at doses equal to or greater than 138 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis). Effects on maternal bone were observed in pregnant and lactating rats in a pre- and postnatal toxicity study when esomeprazole magnesium was administered at oral doses of 14 to 280 mg/kg/day (about 3.4 to 68 times an oral human dose of 40 mg on a body surface area basis). When rats were dosed from gestational day 7 through weaning on postnatal day 21, a statistically significant decrease in maternal femur weight of up to 14% (as compared to placebo treatment) was observed at doses equal to or greater than 138 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis).

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

A follow up developmental toxicity study in rats with further time points to evaluate pup bone development from postnatal day 2 to adulthood was performed with esomeprazole magnesium at oral doses of 280 mg/kg/day (about 68 times an oral human dose of 40 mg on a body surface area basis) where esomeprazole administration was from either gestational day 7 or gestational day 16 until parturition. When maternal administration was confined to gestation only, there were no effects on bone physical morphology in the offspring at any age.
8.2. Lactation
Risk Summary
Esomeprazole is the S-isomer of omeprazole and limited data suggest that omeprazole may be present in human milk. There are no clinical data on the effects of esomeprazole on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for NEXIUM and any potential adverse effects on the breastfed infant from NEXIUM or from the underlying maternal condition.

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 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 and pharmacokinetic studies performed in pediatric and adolescent patients [see Dosage and Administration (2), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.3)]. The safety and effectiveness of 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 one year of age for treatment (up to 6 weeks) of erosive esophagitis due to acid-mediated GERD is supported by extrapolation of results from adequate and well-controlled studies for adults and safety, pharmacokinetic, and pharmacodynamic studies performed in pediatric patients [see Dosage and Administration (2), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (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 have not been established.

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 [see Clinical Pharmacology (12.2)]. Apparent clearance (CL/F) increases with age in pediatric patients from birth to 2 years of age.

Neonates 0 to 1 month of age.

Following administration of oral 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.

Juvenile Animal Data
In a juvenile rat toxicity study, esomeprazole was administered with both magnesium and strontium salts at oral doses about 34 to 68 times a daily human dose of 40 mg based on body surface area. Increases in death were seen at the high dose, and at all doses of esomeprazole, there were decreases in body weight, body weight gain, femur weight and femur length, and decreases in overall growth [see Nonclinical Toxicology (13.2)].

8.5. Geriatric Use
Of the total number of patients who received NEXIUM in clinical trials, 1,458 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 OVERDOSE
A single oral dose of esomeprazole at 510 mg/kg (about 124 times the human dose on a body surface area basis), was lethal to rats. The major signs of acute toxicity were reduced motor activity, changes in respiratory frequency, tremor, ataxia, and intermittent convulsive clonusions.

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 overdose with omeprazole in humans may also be relevant. Doses ranged up to 2,400 mg (120 times the usual recommended clinical dose). These observations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience (see omeprazole package insert - Adverse Reactions). No specific antidote for esomeprazole is known. Since esomeprazole is extensively protein bound, it is not expected to be removed by dialysis. In the event of overdose, treatment should be symptomatic and supportive.

As with the management of any overdose, the possibility of multiple drug ingestion should be considered. For current information on treatment of any drug overdose 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-[3,5-dimethyl-2-pyridinyl]methyl]-1-H-benzoimidazole-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 (C₉₂H₸₄O₇N₄S)₂Mg x 3 H₂O 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 6.6 (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: glycerol monostearate 40-55, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer type C, polysorbate 80, sugar spheres, tate, 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, croscarmellose, citric acid, iron oxide, and hydroxypropyl cellulose. The esomeprazole 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 Table 3:

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NEXIUM 40 mg</th>
<th>NEXIUM 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Time Gastric pH &gt;4 (Hours)</td>
<td>70%² (16.8 h)</td>
<td>53% (12.7 h)</td>
</tr>
<tr>
<td>Coefficient of variation</td>
<td>26%</td>
<td>37%</td>
</tr>
<tr>
<td>Median 24 Hour pH</td>
<td>4.9 ¹</td>
<td>4.1</td>
</tr>
<tr>
<td>Coefficient of variation</td>
<td>16%</td>
<td>27%</td>
</tr>
</tbody>
</table>

¹: 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 for 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. Healthcare providers should temporarily stop esomeprazole treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high.

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

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

In over 1,000 patients treated with 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 carboxyhydrate 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. Bioequivalence 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 (Cmax) occur at approximately 1.5 hours (Tmax). The Cmax 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*h/L on Day 1 to 11.2 µmol*h/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>
<thead>
<tr>
<th>Parameter' (CV)</th>
<th>NEXIUM 40 mg</th>
<th>NEXIUM 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (µmol*h/L)</td>
<td>12.6 (42%)</td>
<td>4.2 (59%)</td>
</tr>
<tr>
<td>Cmax (µmol/L)</td>
<td>4.7 (37%)</td>
<td>2.1 (45%)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>1.5</td>
<td>1.2</td>
</tr>
</tbody>
</table>

1 Values represent the geometric mean, except the Tmax, 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.

Elimination
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 CYP2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on CYP3A4 which forms the sulphone metabolite. CYP2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15 to 20% of Asians lack CYP2C19 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.

Combination Therapy with Antibiotics
Esomeprazole magnesium 40 mg once daily was given in combination with clarithromycin and amoxicillin. 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>
<thead>
<tr>
<th>Parameter</th>
<th>1 month to &lt; 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (µmol*h/L)</td>
<td>3.51</td>
</tr>
<tr>
<td>Cmax (µmol/L)</td>
<td>0.87</td>
</tr>
<tr>
<td>Tmax (hours)</td>
<td>0.93</td>
</tr>
<tr>
<td>t1/2 (hours)</td>
<td>3.0</td>
</tr>
</tbody>
</table>

1 Geometric mean
2 Median

Subsequent pharmacokinetic simulation analyses showed that a dosage regimen of 2.5 mg once-daily for pediatric patients with body weight 3 to 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>
<thead>
<tr>
<th>Parameter</th>
<th>1 to 5 Year Olds</th>
<th>6 to 11 Year Olds</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (µmol*h/L)</td>
<td>4.83</td>
<td>3.70</td>
</tr>
<tr>
<td>Cmax (µmol/L)</td>
<td>2.98</td>
<td>1.77</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.44</td>
<td>1.79</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>0.74</td>
<td>0.88</td>
</tr>
<tr>
<td>Cmax (µmol/L)</td>
<td>5.99</td>
<td>7.84</td>
</tr>
</tbody>
</table>

1 Geometric mean
2 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 Cmax and AUC values of esomeprazole were not affected by body weight or age; and more than dose-proportional increases in mean Cmax 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.
Susceptibility testing of *Helicobacter pylori*: Indications and Usage (1) and Clinical Studies (14)

NEXIUM, amoxicillin, and clarithromycin triple therapy has been shown to be active against *H. pylori* infections.

### Microbiology

The pharmacokinetics of NEXIUM in patients with renal impairment are not expected to be significantly altered.

#### Renal Insufficiency

In patients with severe hepatic insufficiency (Child-Pugh Class C), a dose of 20 mg once daily should not be exceeded.

#### Hepatic Insufficiency

The AUC and C max values were slightly higher (13%) in females than in males at steady state.

### Other pharmacokinetic observations

- Co-administration of esomeprazole and rifampicin (non-selective NSAID) or rifabutin (COX-2 selective NSAID) did not identify any clinically relevant changes in the pharmacokinetic profiles of esomeprazole or these NSAIDs.

### Carcinogenesis, Mutagenesis, Impairment of Fertility

#### Animal Toxicology and/or Pharmacology

Reproduction studies have been performed in rats at oral doses up to 280 mg/kg/day (about 34 times the human dose of 40 mg/day on a body surface area basis). An increase in the number of tumors in both sexes was found to be due to esomeprazole.

#### Effects on Gastrointestinal Microbial Ecology

Treatment with proton pump inhibitors may lead to slight increases in the risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

### Clinical Studies

In the NEXIUM/amoxicillin/clarithromycin clinical trials, 83% (176/212) of the patients in whom *H. pylori* was eradicated of *H. pylori* isolates that were considered to be susceptible had 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.

### 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, and 140.8 mg/kg/day (about 0.4 to 34 times the human dose of 40 mg/day expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole.

Animal Toxicology and/or Pharmacology

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

#### 13.2 Animal Toxicology and/or Pharmacology

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

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*.

### 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.
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 Resolution1 of Heartburn (Erosive Esophagitis Patients)

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Treatment Groups</th>
<th>Day 14</th>
<th>Day 28</th>
<th>Significance Level?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>573</td>
<td>NEXIUM 20 mg</td>
<td>64.3%</td>
<td>72.7%</td>
<td>N.S.</td>
</tr>
<tr>
<td></td>
<td>555</td>
<td>Omeprazole 20 mg</td>
<td>64.1%</td>
<td>70.9%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>621</td>
<td>NEXIUM 40 mg</td>
<td>64.8%</td>
<td>74.2%</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>620</td>
<td>NEXIUM 20 mg</td>
<td>62.9%</td>
<td>70.1%</td>
<td>N.S.</td>
</tr>
<tr>
<td></td>
<td>626</td>
<td>Omeprazole 20 mg</td>
<td>56.5%</td>
<td>66.6%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>568</td>
<td>NEXIUM 40 mg</td>
<td>65.4%</td>
<td>73.9%</td>
<td>N.S.</td>
</tr>
<tr>
<td></td>
<td>551</td>
<td>Omeprazole 20 mg</td>
<td>65.5%</td>
<td>73.1%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1187</td>
<td>NEXIUM 40 mg</td>
<td>67.6%</td>
<td>75.1%</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>1188</td>
<td>NEXIUM 20 mg</td>
<td>62.5%</td>
<td>70.8%</td>
<td></td>
</tr>
</tbody>
</table>

1 Defined as 7 consecutive days with no heartburn reported in daily patient diary.
2 Defined as the cumulative proportion of patients who have reached the start of sustained resolution.
3 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)

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

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 a 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 (≥80 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 1. 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 
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>191</td>
<td>NEXIUM 20 mg</td>
<td>95.4</td>
</tr>
<tr>
<td></td>
<td>194</td>
<td>NEXIUM 40 mg</td>
<td>96.7</td>
</tr>
<tr>
<td></td>
<td>184</td>
<td>Placebo</td>
<td>88.2</td>
</tr>
<tr>
<td>2</td>
<td>267</td>
<td>NEXIUM 20 mg</td>
<td>94.7</td>
</tr>
<tr>
<td></td>
<td>271</td>
<td>NEXIUM 40 mg</td>
<td>95.3</td>
</tr>
<tr>
<td></td>
<td>257</td>
<td>Placebo</td>
<td>83.3</td>
</tr>
</tbody>
</table>

% = 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Group</th>
<th>Per-Protocol1</th>
<th>Intent-to-Treat2</th>
</tr>
</thead>
<tbody>
<tr>
<td>191</td>
<td>NEXIUM plus amoxicillin and clarithromycin</td>
<td>84%2 (n=196)</td>
<td>77%2 (n=233)</td>
</tr>
<tr>
<td></td>
<td>NEXIUM plus clarithromycin</td>
<td>55%2 (n=187)</td>
<td>52%2 (n=215)</td>
</tr>
<tr>
<td>193</td>
<td>NEXIUM plus amoxicillin and clarithromycin</td>
<td>85%3 (n=67)</td>
<td>78%3 (n=74)</td>
</tr>
<tr>
<td></td>
<td>NEXIUM</td>
<td>5%2 (n=22)</td>
<td>4%2 (n=24)</td>
</tr>
</tbody>
</table>

1 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.

2 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.

3 p < 0.05 compared to NEXIUM plus clarithromycin.

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 Hypersecretry 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 hypersecretery 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/h 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

<table>
<thead>
<tr>
<th>Dose</th>
<th>BAO under adequate control at the Month 12 visit (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 mg twice daily</td>
<td>13/15</td>
</tr>
<tr>
<td>80 mg twice daily</td>
<td>4/4</td>
</tr>
<tr>
<td>80 mg three times daily</td>
<td>1/1</td>
</tr>
</tbody>
</table>

1 One patient was not evaluated.
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 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. NEXIUM may pass into your breast milk. 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)

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:

- A type of kidney problem (acute interstitial nephritis). Some people who take proton pump inhibitor (PPI) medicines, including NEXIUM, may develop a kidney problem called acute interstitial nephritis that can happen at any time during treatment with NEXIUM. Call your doctor if you have a decrease in the amount that you urinate or if you have blood in your urine.
- 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 PPI 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.
- Certain types of lupus erythematos. Lupus erythematosus is an autoimmune disorder (the body’s immune cells attack other cells or organs in the body). Some people who take PPI medicines, including NEXIUM, may develop certain types of lupus erythematosus or have worsening of the lupus they already have. Call your doctor right away if you have new or worsening joint pain or a rash on your cheeks or arms that gets worse in the sun.

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.

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:

- A type of kidney problem (acute interstitial nephritis). Some people who take proton pump inhibitor (PPI) medicines, including NEXIUM, may develop a kidney problem called acute interstitial nephritis that can happen at any time during treatment with NEXIUM. Call your doctor if you have a decrease in the amount that you urinate or if you have blood in your urine.
- 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 PPI 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.
- Certain types of lupus erythematos. Lupus erythematosus is an autoimmune disorder (the body’s immune cells attack other cells or organs in the body). Some people who take PPI medicines, including NEXIUM, may develop certain types of lupus erythematosus or have worsening of the lupus they already have. Call your doctor right away if you have new or worsening joint pain or a rash on your cheeks or arms that gets worse in the sun.

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- 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.
• Low magnesium levels in your body. Low magnesium can happen in some people who take a PPI 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 your doctor right away if you have any of these symptoms:
  - seizures
  - muscle weakness
  - dizziness
  - spasms of the hands and feet
  - abnormal or fast heart beat
  - cramps or muscle aches
  - jitteriness
  - spasm of the voice box
  - jerking movements or shaking (tremors)

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.

• Stomach growths (fundic gland polyps). People who take PPI medicines for a long time have an increased risk of developing a certain type of stomach growths called fundic gland polyps, especially after taking PPI medicines for more than 1 year.

The most common side effects with NEXIUM may include:
  - headache
  - abdominal pain
  - diarrhea
  - constipation
  - nausea
  - dry mouth
  - gas
  - drowsiness

Other side effects:

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

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