Nexium® (esomeprazole magnesium) Delayed-Release Capsules

DESCRIPTION

The active ingredient in NEXIUM (esomeprazole magnesium) Delayed-Release Capsules is bis(s-methylthio)-2-(2-[(4-methoxy-3,3-dimethyl-2-pyridyl)methyl]sulfanyl)-1H-benzimidazole-1-yi magnesium trihydrate, a compound that inhibits gastric acid secretion. Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S- and R-isomers. Its empirical formula is (C17H18N3O3S)2Mg x 3 H2O with molecular weight of 767.2 as a trihydrate and 713.1 on an anhydrous basis. The structural formula is:

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 8.6 (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 as Delayed-Release Capsules for oral administration. 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 pellets with the following inactive ingredients: glycerin monostearate 45-50, hydroxypropyl cellulose, hypromellose, magnesium stearate, metacrylic acid copolymer type C, polysorbate 80, sugar spheres, talc, and triethyl citrate. The capsule shells have the following inactive ingredients: gelatin, FD&C Blue #1, FD&C Red #40, D&C Red #28, titanium dioxide, shells, ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, sodium hydroxide, polyvinyl pyrrolidone, and D&C Yellow #10.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption

NEXIUM Delayed-Release Capsules contain an enteric-coated pellet formulation of esomeprazole magnesium. 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 dose-related increase in Tmax 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 esomeprazole is decreased by 43-53% after food intake compared to fasting conditions. Esomeprazole should be taken at least one hour before meals. The pharmacokinetic profile of esomeprazole 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 following table:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NEXIUM 40 mg</th>
<th>NEXIUM 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (µmol*h/L)</td>
<td>12.6</td>
<td>4.2</td>
</tr>
<tr>
<td>Coefficient of variation (%)</td>
<td>42%</td>
<td>59%</td>
</tr>
<tr>
<td>Cmax (µmol/L)</td>
<td>4.7</td>
<td>2.1</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>

Values represent the geometric mean, except the Tmax which is the arithmetic mean.

Distribution

Esomeprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 2-200 µmol/L. The apparent volume of distribution at steady state in healthy volunteers is approximately 16 L.

Metabolism

Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system. The metabolites of esomeprazole lack antisecretory activity. The major part of esomeprazole's metabolism is dependent upon the CYP2C19 isoenzyme, which forms the hydroxy and 3S-methoxy metabolites. The remaining amount is dependent on CYP3A4 which forms the sulfone metabolite. CYP2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since up to 3% of the population (15-20% 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.

Elimination

The plasma elimination half-life of esomeprazole is approximately 1–1.5 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.

Special Populations

Geriatric

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

Pediatric

The pharmacokinetics of esomeprazole have not been studied in infants and children <18 years of age.

Gender

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

Hepatic Insufficiency

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

Renal Insufficiency

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

Pharmacodynamics

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 esomeprazole are protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the aromatic sulfenamide. By acting specifically in 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.

Antisecretory Action

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NEXIUM 40 mg</th>
<th>NEXIUM 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH (&lt;4) (%)</td>
<td>96.7</td>
<td>84.8</td>
</tr>
<tr>
<td>Median 24 Hour pH</td>
<td>4.9</td>
<td>4.1</td>
</tr>
</tbody>
</table>

| Coefficient of variation (%) | 10% | 27% |

A gastric pH of 4.0 or less was maintained by 96.7% and 84.8% of patients, respectively, on 40 mg and 20 mg daily dosing. The gastric acid suppression by 20 mg once daily was not significantly different from 40 mg once daily. This increased release protocol was achieved in two to three months of therapy and returned to baseline levels within four weeks after discontinuation of therapy.

Endocrine Effects

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

Microbiology

Esomeprazole magnesium, amoxicillin and clarithromycin triple therapy has been shown to be active against most strains of Helicobacter pylori (H. pylori) in vitro and in clinical infections as described in the Clinical Studies and INDICATIONS AND USAGE sections.

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

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

ClinicalTriumph Susceptibility Test Results and Clinical/Bacteriologic Outcomes: The baseline H. pylori clarithromycin susceptibility results and the H. pylori eradication results at the Day 38 visit are shown in the table below:

<table>
<thead>
<tr>
<th>Clarithromycin Susceptibility Test Results and Clinical/Bacteriologic Outcomes</th>
<th>H. pylori clarithromycin susceptibility results</th>
<th>H. pylori eradication results at the Day 38 visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin Pre-treatment</td>
<td>H. pylori negative (Eradicated)</td>
<td>H. pylori positive (Not Eradicated)</td>
</tr>
<tr>
<td>Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Resistant</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>S'</th>
<th>P'</th>
<th>N0</th>
<th>MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible</td>
<td>182</td>
<td>162</td>
<td>4</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Resistant</td>
<td>29</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

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

** Susceptible (H) MIC ≤0.25 µg/mL, Intermediate (I) MIC 0.25-5 µg/mL, Resistant (R) MIC ≥5 µg/mL.
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Patients not eradicated of H. pylori following esomeprazole magnesium/amoxicillin/clarithromycin triple therapy will likely have clarithromycin-resistant H. pylori isolates. Therefore, clarithromycin susceptibility testing should be done, when possible. Patients with clarithromycin resistant H. pylori should not be re-treated with a clarithromycin-containing regimen.

Akmolin Susceptibility Test Results and Clinical/Bacteriological Outcomes: In the esomeprazole magnesium/amoxicillin/clarithromycin clinical trials, 83% (176/212) of the patients in the esomeprazole magnesium/amoxicillin/clarithromycin treatment group who had pretreatment amoxicillin susceptible MICs (<0.25 µg/mL) were eradicated of H. pylori, and 17% (36/212) were not eradicated of H. pylori. Of the 36 patients who were not eradicated of H. pylori on triple therapy, 16 had no post-treatment susceptibility test results and 20 had post-treatment H. pylori isolates with amoxicillin susceptible MICs. Fifteen of the patients who were not eradicated of H. pylori on triple therapy also had post-treatment H. pylori isolates with clarithromycin resistant MICs. There were no patients with H. pylori isolates who developed treatment emergent resistance to amoxicillin.

Susceptibility Test for Helicobacter pylori: The reference method for susceptibility testing of H. pylori is agar dilution MICs. One to three microliters of an inoculum equivalent to a 0.2 McFarland standard (1 x 10^-1 – 1 x 10^0 CFU/mL for H. pylori) are inoculated directly onto freshly prepared antimicrobial containing Mueller-Hinton agar plates with 5% defibrinated sheep blood (≤2 weeks old). The agar plates are incubated at 35°C in a microaerobic environment produced by a gas generating system suitable for Campylobacter. After 3 days of incubation, the MICs are recorded as the lowest concentration of antimicrobial agent required to inhibit growth of the organism. The clarithromycin and amoxicillin MIC values should be interpreted according to the following criteria:

<table>
<thead>
<tr>
<th>Clarithromycin MIC (µg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.25</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>0.5</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>&gt;1.0</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Amoxicillin MIC (µg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.25</td>
<td>Susceptible (S)</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Antimicrobial Agent</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. pylori ATCC</td>
<td>Clarithromycin</td>
<td>0.016 – 0.12</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin</td>
<td>0.016 – 0.12</td>
</tr>
</tbody>
</table>

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

Clinical Studies

Healing of Erosive Esophagitis

The healing rates of NEXIUM 20 mg, NEXIUM 40 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 below:

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Treatment Groups</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Significance Level*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>573</td>
<td>NEXIUM 20 mg</td>
<td>68.7%</td>
<td>92.2%</td>
<td>N.S.</td>
</tr>
<tr>
<td></td>
<td>555</td>
<td>Omeprazole 20 mg</td>
<td>69.5%</td>
<td>83.8%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>621</td>
<td>NEXIUM 40 mg</td>
<td>75.9%</td>
<td>94.1%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>620</td>
<td>Omeprazole 20 mg</td>
<td>70.5%</td>
<td>89.9%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>568</td>
<td>NEXIUM 40 mg</td>
<td>71.5%</td>
<td>92.2%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>551</td>
<td>Omeprazole 20 mg</td>
<td>66.7%</td>
<td>89.8%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1187</td>
<td>NEXIUM 40 mg</td>
<td>81.7%</td>
<td>93.7%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>1188</td>
<td>Omeprazole 20 mg</td>
<td>76.7%</td>
<td>84.2%</td>
<td></td>
</tr>
</tbody>
</table>

- The log-rank test vs omeprazole 20 mg

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, 7–8 days for NEXIUM 20 mg and 7–9 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=1174), 20 mg (n=180), 10 mg (n=168) and placebo (n=171) once daily over six months.

The percentage of patients that maintained healing of erosive esophagitis at the various time points are shown in the figure below:

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Treatment Groups</th>
<th>Week 14</th>
<th>Week 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>71.5%</td>
<td>N.S.</td>
</tr>
<tr>
<td></td>
<td>555</td>
<td>Omeprazole 20 mg</td>
<td>68.7%</td>
<td>82.3%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>621</td>
<td>NEXIUM 40 mg</td>
<td>68.7%</td>
<td>74.2%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>620</td>
<td>Omeprazole 20 mg</td>
<td>65.7%</td>
<td>70.1%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>568</td>
<td>NEXIUM 40 mg</td>
<td>65.5%</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>73.2%</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>Omeprazole 20 mg</td>
<td>63.5%</td>
<td>70.8%</td>
<td></td>
</tr>
</tbody>
</table>

- Defined as 7 consecutive days with no heartburn reported in daily diary
- Defined as the cumulative proportion of patients who have reached the start of sustained resolution

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, 7–8 days for NEXIUM 20 mg and 7–9 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.

Maintenance of Healing Rates by Month (Study 178)

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.

H. pylori eradication rates at 4 Weeks after 10 Day Treatment Regimen

In a third multicenter open label study of 808 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.

A Gastroesophageal Reflux Disease (GERD) Two multicenter, randomized, double-blind, placebo-controlled studies were conducted in a total of 1177 patients comparing four weeks of treatment with NEXIUM 20 mg or 40 mg once daily versus placebo for resolution of GERD symptoms. Patients had ≥6-month history of heartburn episodes, no erosive esophagitis by endoscopy, and heartburn on at least four of the seven days immediately preceding randomization.

The percentage of patients who 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 figure below:

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

Study Treatment Group Per-Protocol 95% Confidence Interval (Number of patients)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Group</th>
<th>Per-Protocol</th>
<th>95% CI</th>
<th>(Number of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>191</td>
<td>NEXIUM plus</td>
<td>84%*</td>
<td>[76, 93]</td>
<td>[71, 82]</td>
</tr>
<tr>
<td></td>
<td>amoxicillin</td>
<td>7%*</td>
<td></td>
<td>(n=190)</td>
</tr>
<tr>
<td></td>
<td>and</td>
<td></td>
<td></td>
<td>(n=192)</td>
</tr>
<tr>
<td></td>
<td>clarithromycin</td>
<td></td>
<td></td>
<td>(n=191)</td>
</tr>
<tr>
<td>193</td>
<td>NEXIUM plus</td>
<td>55%*</td>
<td>[46, 62]</td>
<td>[45, 59]</td>
</tr>
<tr>
<td></td>
<td>amoxicillin</td>
<td>52%</td>
<td></td>
<td>(n=187)</td>
</tr>
<tr>
<td></td>
<td>and</td>
<td></td>
<td></td>
<td>(n=188)</td>
</tr>
<tr>
<td></td>
<td>clarithromycin</td>
<td></td>
<td></td>
<td>(n=187)</td>
</tr>
</tbody>
</table>

Patients were included in the analysis if they had H. pylori infection documented at baseline, had at least one endoscopically documented 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 event related to the study drug were included in the analysis as not H. pylori eradicated.

* p<0.05 compared to placebo

* p<0.05 compared to NEXIUM alone
Nexium® (esomeprazole magnesium) Delayed-Release Capsules

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=150) respectively, in the 191 and 193 studies (per-protocol analysis).

INDICATIONS AND USAGE

Treatment of Gastroesophageal Reflux Disease (GERD) Healing of Esophageal Erosions

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

Maintenance of Healing of Esophageal Erosions

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 treatment of heartburn and other symptoms associated with GERD.

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 Clinical Studies and Dosage and Administration.)

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: Microbiology and the clarithromycin package insert, Clinical Pharmacology, Microbiology.)

CONTRAINDICATIONS

Nexium® is contraindicated in patients with known hypersensitivity to any component of the formulation or to substituted benzimidazoles.

Clarithromycin is contraindicated in patients with a known hypersensitivity to any macrolide antibiotic.

Concomitant administration of clarithromycin with pimozide is contraindicated. There have been post-marketing reports of drug interactions when clarithromycin and/or erythromycin are co-administered with pimozide resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsade de pointes) most likely due to inhibition of hepatic metabolism of pimozide by clarithromycin and erythromycin. Fatalities have been reported. (See Reference for prescribing information for clarithromycin.)

Amodiaquine is contraindicated in patients with a known hypersensitivity to any pincillin. (See Reference for prescribing information for amoxicillin.)

WARNINGS

CLARITHROMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE, IF PREGNANCY OCCURS WHILE TAKING CLARITHROMYCIN, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. (See WARNINGS in prescribing information for clarithromycin.)

Amodiaquine: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on pincillin therapy. These reactions are more apt to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of pincillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before initiating cephalosporin therapy, any patient with a history of allergy to penicillin should be carefully inquired into to be made concerning previous hypersensitivity reactions to pincillin, cephalosporins, and other allergens. If an allergic reaction occurs, amoxicillin should be discontinued and the appropriate therapy instituted.

SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE: OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANEUVERS. IN TREATMENT OF ANAPHYLACTIC SHOCK, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin and amoxicillin, and may range from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. Treatment with antibacterial agents alters the normal flora of the gastrointestinal tract, including the overgrowth of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. The role of vancomycin and other recommendations should be reserved for treatment failures or when the diagnosis is in doubt. Vancomycin is effective against Gram-positive bacteria and is generally effective against drug-resistant strains. Vancomycin should be administered intravenously and usually is effective in the treatment of pseudomembranous colitis.

PRECAUTIONS

General

Symptomatic response to therapy with NEXIUM does not preclude the presence of gastric malignancy. Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole, of which NEXIUM is an enantiomer.

Information for Patients

Patients should be informed of the following:

NEXIUM Delayed-Release Capsules should be taken at least one hour before meals.

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 pellets inside the capsule carefully and completely emptied onto the applesauce. The pellets should not be mixed with the applesauce and then swallowed immediately. The applesauce should not be hot and should be soft enough to be swallowed without chewing. The pellets should not be chewed or crushed. The pellets/applesauce mixture should not be stored for future use.

Antacids may be used while taking NEXIUM.

Drug Interactions

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, 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 inhibit the following CYP enzymes: phenytoin, warfarin, quinidine, clarithromycin or amoxicillin.

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

Esomeprazole may potentially interfere with CYP2C19, the major esomeprazole metabolizing enzyme. Co-administration of esomeprazole 30 mg and diazepam in CYP2C19 substrate produced a 43% decrease in clearance of diazepam. Increased plasma levels of diazepam were observed 12 hours after dosing and onwards. However, at that time plasma levels of diazepam were below the therapeutic interval, and this interaction thus is unlikely to be of clinical relevance.

Esomeprazole inhibits gastric acid secretion. Therefore, esomeprazole may interfere with the action of other drugs where gastric pH is an important determinant of bioavailability (eg, ketoconazole, iron salts and digoxin).

Gastrulation of oral contraceptives, diazepam, phenytoin, or warfarin. Pharmacokinetics: Combination Therapy with Antimicrobials

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, Pharmacokinetics: Combination Therapy with Antimicrobials.)

Concomitant administration of clarithromycin with pimozide is contraindicated. (See clarithromycin package insert.)

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of esomeprazole was assessed using omeprazole studies. Omeprazole was positive in the mouse micronucleus test. Esomeprazole, however, was negative in the in vitro human lymphocyte chromosome aberration test. Omeprazole was positive in the in vitro human lymphocyte chromosome aberration test, and the in vivo mouse micronucleus test. The potential effects of esomeprazole on fertility and reproductive performance were assessed using omeprazole studies. Omeprazole at oral doses up to 280 mg/kg/day (about 57 times the human dose on a body surface area basis) has been shown to reduce fertility in rats. Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy.

Amodiaquine

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Adverse reactions were seen in 65 to 74 years and 124 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 that would limit the use of NEXIUM in patients over 65 years of age. In general, NEXIUM was well tolerated in both short- and long-term clinical trials.

ADVERSE REACTIONS

The safety of NEXIUM was evaluated in over 10,000 patients (aged 18-84 years) in clinical trials worldwide including over 7,000 patients in clinical trials in the United States and over 2,600 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.
Nexium® (esomeprazole magnesium) Delayed-Release Capsules

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, 2,424 patients on omeprazole 20 mg, and 3,008 patients on omeprazole 20 mg daily. The most frequently occurring adverse events (≥1%) in all three groups were headache (5.5, 5.0, 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 events 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, chest pain submaximal, facial edema, peripheral edema, flushing, hot flushes, fever, flushing, cold sweat, generalized edema, leg edema, malaise, pain, rigor, cardiovascular: flushing; hypertension, tachycardia.

**Endocrine:** goiter, gastrointestinal: bowel incontinence, constipation aggravated, dyspepsia, dysphagia, dysphonia, G1, epigastric pain, eructation, esophageal disorder, frequent stools, nausea, vomiting, constipation, diarrhea, diarrhea aggravated, paresthesia, sleep disorder, somnolence, tremor, vertigo, visual field defect; reproductive: dysmenorrhea, menstrual disorder, vaginitis.

**Nervous System/Psychiatric:** angina, angina pectoris, anxiety, angina pectoris, agitation, anxiety, apathy, appetite increased, confusion, depression, depressed, diziness, dizziness, hypertension, nervousness, hypotension, impotence, insomnia, migraine, migraine aggravated, paresthesia, sleep disorder, somnolence, tremor, vertigo, visual field defect; Reproductive: dysmenorrhea, menstrual disorder, vaginitis.

**Respiratory:** asthmatic, asthmatic reactions, cough, coughing, dyspnea, larynx edema, pharyngitis, sinusitis. Skin and Appendages: acanthosis nigricans, acne, angioedema, dermatitis, pruritus, pruritus ani, rash, rash erythematous, rash maculopapular, skin infection, swelling increased, urticaria; Special Senses: otitis media, paranoia, taste loss, taste disturbance, VDRL: positive. Vision: conjunctivitis, vision abnormality.

Endoscopic findings that were reported as adverse events include: duodenitis, esophagitis, esophageal stricture, esophageal ulceration, esophageal varices, gastric ulceration, hemorrhage, hiatal hernia, benign polypos or nodules, Barrett’s esophagus, and mucosal discoloration.

The incidence of related adverse events during 6-month maintenance treatment was similar to placebo. There were no differences in types of related adverse events 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 events that were reported as possibly or probably related to NEXIUM were diarrhea (3.3%), headache (3.8%), and abdominal pain (3.8%).

Postmarketing Reports – There have been spontaneous reports of adverse events with postmarketing use of esomeprazole. These reports have included cases of anaphylactic reaction. Other adverse events not observed with NEXIUM, but occurring with omeprazole can be found in the omeprazole package insert, ADVERSE REACTIONS section.

**Combination Treatment with Amoxicillin and Clarithromycin**

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.

**OVERDOSE**

A single oral dose of esomeprazole at 510 mg/kg (about 103 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience (see esomeprazole 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, a certified Regional Poison Control Center should be contacted. Telephone numbers are listed in the Physicians’ Desk Reference (PDR) or local physician telephone book.

**DOSE AND ADMINISTRATION**

The recommended adult dosages are outlined in the table below. NEXIUM Delayed-Release Capsules should be swallowed whole and taken at least one hour before eating. For patients who have difficulty swallowing capsules, one tablespoon of applesauce can be added to an empty bowl and the NEXIUM Delayed-Release Capsules should be swallowed without breaking.

**Recommended Adult Dosage Schedule of NEXIUM**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroesophageal Reflux Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GERD</td>
<td>20 mg</td>
<td>Once Daily for 4 to 8 Weeks*</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>40 mg</td>
<td>Once Daily **</td>
</tr>
<tr>
<td>Maintenance of Healing of Erosive Esophagitis</td>
<td>20 mg</td>
<td>Once Daily **</td>
</tr>
<tr>
<td>Symptomatic Gastroesophageal Reflux Disease</td>
<td>20 mg</td>
<td>Once Daily for 4 Weeks ***</td>
</tr>
<tr>
<td><strong>H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple Therapy: NEXIUM</td>
<td>40 mg</td>
<td>Once Daily for 10 Days</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>1000 mg</td>
<td>Twice Daily for 10 Days</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>500 mg</td>
<td>Twice Daily for 10 Days</td>
</tr>
</tbody>
</table>

* (see CLINICAL STUDIES): The majority of patients are healed within 4 to 8 weeks. For patients who do not heal after 4–8 weeks, an additional 4–8 weeks of treatment may be considered.
** Controlled trials did not extend beyond six months.
*** If symptoms do not resolve completely after 4 weeks, an additional 4 weeks of treatment may be considered.

Please refer to amoxicillin and clarithromycin full prescribing information for CONTRAINDICATIONS, WARNINGS and dosing in elderly and renally-impaired patients.

**Special Populations**

**Genetics:** No dosage adjustment is necessary. (See CLINICAL PHARMACOLOGY, Pharmacokinetics.)

**Renal Insufficiency:** No dosage adjustment is necessary. (See CLINICAL PHARMACOLOGY, Pharmacokinetics.)

**Liver Insufficiency:** No dosage adjustment is necessary in patients with mild to moderate liver impairment (Child Pugh Classes A and B). For patients with severe liver impairment (Child Pugh Class C), a dose of 20 mg of NEXIUM should not be exceeded. (See CLINICAL PHARMACOLOGY, Pharmacokinetics.)

**Gender:** No dosage adjustment is necessary. (See CLINICAL PHARMACOLOGY, Pharmacokinetics.)

**HOW SUPPLIED**

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

NDC 0186-5020-31 unit of use bottles of 30
NDC 0186-5022-28 unit dose packages of 100
NDC 0186-5020-54 bottles of 90
NDC 0186-5020-82 bottles of 1000
NEXIUM Delayed-Release Capsules, 40 mg, are opaque, hard gelatin, amethyst colored capsules with three radial bars in yellow on the cap and 40 mg in yellow on the body. They are supplied as follows:

NDC 0186-5040-31 unit of use bottles of 30
NDC 0186-5040-28 unit dose packages of 100
NDC 0186-5040-54 bottles of 90
NDC 0186-5040-82 bottles of 1000

**Storage**

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

**REFERENCES**


**NEXIUM** is a trademark of the AstraZeneca group © AstraZeneca 2003

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Wilmington, DE 19850

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Product of France

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