NEXIUM® (esomeprazole magnesium) DELAYED-RELEASE CAPSULES

DESCRIPTION

The active ingredient in NEXIUM® (esomeprazole magnesium) Delayed-Release Capsules and NEXIUM® (esomeprazole magnesium) for Delayed-Release Oral Suspension is bis-[meta-2-[[2-(4-[meta-2-[[2-(4-ethylphenyl)phenylimino]-1-phenyl-1H-imidazol-5-yl]phenylimino]-1H-imidazol-5-yl]phenylimino]-1H-imidazol-5-yl]phenyl]ethylene ketene acetate, which is a mixture of the S- and R-isomers. Its empirical formula is C₃₇H₃₅N₇O₇S₂ and the molecular weight is 797.2 g/mol at a pH of 7.2 as a trihydrate and 713.1 g/mol as an anhydrous base. The structural formula is:

![NEXIUM Structural Formula]  

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

NEXIUM is supplied in delayed-release capsules and in packets for a delayed-release oral suspension. Each delayed-release capsule contains 20 mg or 40 mg of esomeprazole magnesium (esomeprazole magnesium trihydrate) in the form of enteric-coated granules with the following inactive ingredients: gelatin, monostearate, hydroxypropyl cellulose, hypromellos- lor, magnesium stearate, mineral oil, propylene glycol, polyethylene glycol, and D&C Yellow #10. Each packet of NEXIUM® for Delayed-Release Oral Suspension contains 20 mg or 40 mg of esomeprazole in the form of the same enteric-coated granules used in NEXIUM Delayed-Release Capsules, and also inactive granules. The inactive granules are composed of the following ingredients: dextrose, xanthan gum, crospovidone, citic acid, iron oxide, and hydroxypropyl cellulose. The enteric-coated granules and inactive granules are combined with water to form a suspension and are given by oral, nasogastric or gastric administration.

CLINICAL PHARMACOLOGY

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 48 healthy male and female volunteers under fasting conditions. After oral administration peak plasma levels (Cmax) occur at approximately 1.5 hours (Tmax). The exposure (AUC) increases proportionally with the dose 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 bioavailability of esomeprazole was approximately 99% on repeated dosing and increased by 48-53% after food intake compared to fasting conditions. Esomeprazole is not known to be metabolized to an extent of 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>CV (%)</th>
<th>NEXIUM 20 mg</th>
<th>NEXIUM 40 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax (h)</td>
<td>1.6</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Cmax (µmol/L)</td>
<td>2.8</td>
<td>4.2 (29%)</td>
<td>4.2 (29%)</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>4.7 (21%)</td>
<td>4.7 (21%)</td>
<td>4.7 (21%)</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 2-20 µmol/L. The apparent volume of distribution at steady state in healthy volunteers is approximately 16 L.

Metabolism

Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system. The metabolites of esomeprazole lack anti-secretory activity. The major part of esomeprazole’s metabolism is dependent upon the CYP2C19 isoenzyme, which forms the hydrolysis and deamidation metabolites. The remaining amount is dependent on CYP2A4 which forms the sulfone metabolite. CYP2C19 polymorphism hardly influences the metabolism of esomeprazole, since some 3% of Caucasians and 15-20% of Asians lack CYP2C19 and are 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.
**Nexium® (esomeprazole magnesium) Delayed-Release Capsules and Oral Suspension**

**Clinical Studies**

**Healing of Erosive Esophagitis**

The healing rates of NEXIUM 40 mg, NEXUM 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, active-controlled studies. The healing rates at weeks 4 and 8 were evaluated and are shown in the table below.

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Patients</th>
<th>Treatment Group</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Significance Level*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>556</td>
<td>NEXIUM 20 mg</td>
<td>69.7%</td>
<td>80.6%</td>
<td>N.S.</td>
</tr>
<tr>
<td></td>
<td>562</td>
<td>NEXIUM 20 mg</td>
<td>69.5%</td>
<td>88.3%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>654</td>
<td>NEXIUM 40 mg</td>
<td>78.9%</td>
<td>94.1%</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>660</td>
<td>NEXIUM 20 mg</td>
<td>70.5%</td>
<td>89.9%</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>3</td>
<td>576</td>
<td>NEXIUM 40 mg</td>
<td>71.5%</td>
<td>92.0%</td>
<td>N.S.</td>
</tr>
<tr>
<td></td>
<td>626</td>
<td>NEXIUM 20 mg</td>
<td>68.0%</td>
<td>89.9%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1216</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>1299</td>
<td>NEXIUM 20 mg</td>
<td>88.7%</td>
<td>84.2%</td>
<td></td>
</tr>
</tbody>
</table>

*Log-rank test vs omeprazole 20 mg

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 below.

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Patients</th>
<th>Treatment Group</th>
<th>Per-Protocol</th>
<th>Intention-To-Treat*</th>
</tr>
</thead>
<tbody>
<tr>
<td>191</td>
<td>184</td>
<td>Placebo</td>
<td>83.3%</td>
<td>88.2%</td>
</tr>
<tr>
<td></td>
<td>191</td>
<td>NEXIUM plus</td>
<td>84%</td>
<td>77%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>amoxicillin</td>
<td>(n=186)</td>
<td>(n=203)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clarithromycin</td>
<td>[48, 62]</td>
<td>[45, 59]</td>
</tr>
<tr>
<td>193</td>
<td>190</td>
<td>Placebo</td>
<td>85%</td>
<td>79%</td>
</tr>
<tr>
<td></td>
<td>193</td>
<td>NEXIUM plus</td>
<td>55%</td>
<td>52%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>amoxicillin</td>
<td>[48, 50]</td>
<td>[46, 54]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clarithromycin</td>
<td>[67, 87]</td>
<td>[67, 87]</td>
</tr>
</tbody>
</table>

**Maintenance of Healing Rates by Month (Study 177)**

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.

**INDICATIONS AND USAGE**

Treatment of Gastroesophageal Reflux Disease (GERD)

NEXIUM is indicated for the short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of diagnosed erosive esophagitis. For those patients who have not healed after 4–8 weeks of treatment, an additional 4–8 week course of NEXIUM may be considered.
Nexium® (esomeprazole magnesium) Delayed-Release Capsules and Oral Suspension

Eradication to Reduce the Risk of Duodenal Bilirubinemia, Hepatic Function Abnormal, SGOT Studies have shown that esomeprazole is not likely to inhibit goiter; and the clarithromycin package insert, human lymphocyte (esomeprazole magnesium) Delayed-Release Capsules and Oral Suspension and patients treated long-term with omeprazole, of which NEXIUM is an enantiomer. (Please refer to full prescribing information for amoxicillin.) Amoxicillin is contraindicated in patients with a known hypersensitivity to any component of the formulation or to substituted benzimidazoles. (See clarithromycin package insert.) Concomitant administration of clarithromycin and amoxicillin may range in severity from mild gastrointestinal symptoms to severe hypersecretory conditions, including Zollinger-Ellison Syndrome.

CONTRAINdications NEXIUM is contraindicated in patients with known hypersensitivity to any component of the formulation. Clarithromycin is contraindicated in patients with a known hypersensitivity to any macrolide antibiotic, including clarithromycin and amoxicillin. Amoxicillin is contraindicated in patients with a known hypersensitivity to any penicillin.

WARNINGS CLARITHROMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. CLARITHROMYCIN IS A MACROLIDE ANTIBIOTIC. THE PATIENT SHOULD BE ADVISED OF THE POTENTIAL HAZARD TO THE FETUS. (See WARNINGS in prescribing information for clarithromycin.) Amoxicillin is contraindicated in patients with known hypersensitivity to any penicillin. (See WARNINGS in prescribing information for amoxicillin.)

Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenicity and mutagenicity studies conducted with omeprazole in rats. In two 2-year oral carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.0 mg/kg/day (about 0.7 to 57 times the human dose on a body surface area basis) produced gastric ECL cells, carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which have a greater gastric cell mass, than in male rats at all dose levels except in the untreated rats. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of those studies, female rats were treated with 13.8 mg omeprazole/kg (about 5.6 times the human dose on a body surface area basis) for 1 year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of 1 year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for 2 years. For this strain of rat no similar tumor has been observed. ECL cell hyperplasia occurs in one tumor is difficult to interpret. A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. Esomeprazole was negative in the Ames mutation test, in the in vivo rat bone marrow cell chromosome aberration test, and in the in vivo mouse micronucleus test. Esomeprazole, however, was positive in the in vitro human lymphocyte chromosome aberration test. Omeprazole was positive in the in vitro human lymphocyte chromosome aberration test. 14-hydroxy-clarithromycin, the major circulating metabolite of clarithromycin, was inactive in the in vivo bone marrow cell chromosome aberration test, and in the in vivo mouse micronucleus test. The potential effects of esomeprazole on fertility and reproductive performance in animals have not been assessed. In both male and female rats doses up to 138 mg/kg/day in rats (about 56 times the human dose on a body surface area basis) was found to have no effect on reproductive performance of parental animals.

Pregnancy Teratogenic Effects. Pregnancy Category B Terminology studies have been performed in rats at oral doses up to 230 mg/kg/day (about 65 times the human dose on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 35 times the human dose on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to esomeprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Clinical studies conducted in rats at oral doses up to 138 mg/kg/day (about 56 times the human dose on a body surface area basis) and in rabbits at oral doses up to 69 mg/kg/day (about 56 times the human dose on a body surface area basis) did not reveal any evidence of an increased postnatal developmental toxicity of omeprazole in rats, omeprazole in a dose range of 6.0 to 69.1 mg/kg/day (about 5.0 to 56.0 times the human dose on a body surface area basis) and in dogs did not reveal any evidence of an increased postnatal developmental toxicity of omeprazole in dogs.

Eradication to Reduce the Risk of Duodenal Ulcer 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 the treatment of heartburn and other symptoms associated with pathological hypersecretory states in adults.

Applesauce and/or历史的文本内容
Nexium® (esomeprazole magnesium) Delayed-Release Capsules and Oral Suspension

disorder, somnolence, tremor, vertigo, visual field defect. Reproductive: dysmenorrhea, menstrual disorder, vaginitis; Respiratory: asthma, aggravated, coughing, dyspnea, laryngitis, pharyngitis, rhinitis, sinusitis. Skin and Appendages: acne, angioedema, dermatitis, pruritus, purpura ani, rash, rash erythematous, rash maculopapular, skin inflammation, sweating increased, urticaria. Special Senses: blurred vision, taste alteration, tinnitus, taste perversion; Unintentional: abdominal ulcer, albuminuria, cystitis, dysuria, fungal infection, hematuria, microlithiasis, moniliasis, genital moniliasis, polyuria; Visual confusion, vision abnormal.

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

The incidence of treatment-related adverse events during 6-month maintenance treatment was similar to placebo. There were no differences in median adverse event rates 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 event that were reported as possibly or probably related to NEXIUM were diarrhea (4.3%), 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 occurred rarely and are listed below by body system:

Blood and Lymphatic System Disorders: anemia, leukopenia, pancytopenia, eye disorders: blurred vision, Gastrointestinal Disorders: pancreatitis, gastroparesis, Hepatobiliary Disorders: hepatic failure, hepatitis with or without jaundice; Immune System Disorders: anaphylactic reaction/shock; Infections and Infestations: herpes zoster, Injuries and Poisoning: self-inflicted and Non-accidental Trauma Disorders: muscular weakness, myalgia, Nervous System Disorders: headache, anxiety, edema, hypertensive crisis, peripheral neuropathy; Reproductive System and Breast Disorders: dysmenorrhea; Respiratory, Thoracic and Mediastinal Disorders: bronchospasm; Skin and Subcutaneous Tissue Disorders: alopecia, erythema multiforme or hypopigmentation, hidrosis, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN, some fatal); Urinary and Reproductive System Disorders: oliguria, polyuria; 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 adverse events peculiar to these drug combinations were observed. Adverse events that have occurred have been limited to those that had been observed with NEXIUM, amoxicillin, or clarithromycin alone.

The most frequently reported drug-related adverse events for patients who received triple therapy for 10 days were diarrhea (0.2%), taste perversion (0.2%), abdominal pain (0.6%), and abnormal pain (3.7%). No treatment-emergent adverse events were observed at higher rates with triple therapy than were observed with NEXIUM alone.

For more information on adverse events with amoxicillin or clarithromycin, refer to their package inserts, ADVERSE REACTIONS sections.

Laboratory Events

The following potentially clinically significant laboratory changes in clinical trials, irrespective of relationship to NEXIUM, were reported in ≤5% of patients: increased alkaline phosphatase, AST, ALT, bilirubin, BUN, creatinine, direct bilirubin, glucose, hemoglobin, white blood cell count, platelets, serum gastrin, potassium, sodium, thymol turbidity test, total bilirubin. (See CLINICAL PHARMACOLOGY, Pharmacokinetics.)

Gastric: NEXIUM alone.

Hepatic: Increases in liver enzymes

Renal: NEXIUM alone.

Special Populations

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

Hypersensitivity: If a hypersensitivity reaction occurs during treatment with NEXIUM, treatment should be discontinued and appropriate therapy initiated.

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

Administration Options

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

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

DNC 0186-5242-33 unit of dose packets of 30
DNC 0186-5242-36 unit of dose packets of 100
DNC 0186-5242-40 unit of dose packets of 1000

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

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 light resistant container if the product package is subdivided.

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 NEXIUM 20 mg in yellow on the body. They are supplied as follows:

DNC 0186-5230-33 unit of dose packets of 30
DNC 0186-5233-83 unit of dose packets of 100
DNC 0186-5236-82 bottles of 100

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

DNC 0186-5240-31 unit of dose packets of 30
DNC 0186-5240-34 unit of dose packets of 100
DNC 0186-5240-54 bottles of 90
DNC 0186-5240-52 bottles of 100

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

DNC 0186-4020-01 unit of dose packets of 20 mg packets
DNC 0186-4020-01 unit of dose packets of 40 mg packets

NEXIUM® (esomeprazole magnesium) is available orally as a delayed-release capsule or as a delayed-release oral suspension. The recommended dosages are outlined in the table below. NEXIUM should be taken at least one hour before meals.

<table>
<thead>
<tr>
<th>Type</th>
<th>Route</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed-Release Capsule</td>
<td>Oral</td>
<td>Can be swallowed whole</td>
</tr>
<tr>
<td>Delayed-Release Capsule</td>
<td>Oral Suspension</td>
<td>Mix contents of packet with 1 tablespoon (15 mL) of water, leave 2 to 3 minutes to thicken, stir and drink within 30 minutes.</td>
</tr>
<tr>
<td>Delayed-Release Oral Suspension</td>
<td>Oral</td>
<td>N/A</td>
</tr>
<tr>
<td>Delayed-Release Oral Suspension</td>
<td>Nasogastric or Gastric Tube</td>
<td>Add 15 mL of water to a catheter tipped syringe and then the contents of a 20 mg or 40 mg NEXIUM packet. It is important to only use a catheter tipped syringe when administering NEXIUM through a nasogastric tube or gastric tube.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immediately shake the syringe and leave 2 to 3 minutes to thicken.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Shake the syringe and inject through the nasogastric or gastric tube.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>French size #6 or larger, into the stomach within 30 minutes.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Refill the syringe with 15 mL of water.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Shake and flush any remaining contents from the nasogastric tube into the stomach.</td>
</tr>
</tbody>
</table>

References


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Product of France

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