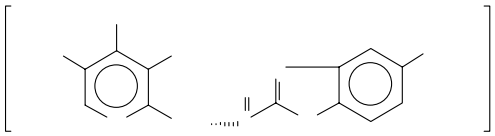
NEXIUM™
(esomeprazole magnesium)

Rx only

DESCRIPTION

The active ingredient in NEXIUM™ (esomeprazole magnesium) Delayed-Release Capsules is bis(5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1 -benzimidazole-1-yl) 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 $(C_{17}H_{18}N_3O_3S)_2Mg$ x 3 H_2O with molecular weight of 767.2 as a trihydrate and 713.1 on an anhydrous basis. The structural formula is:



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

NEXIUM is supplied 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: glyceryl monostearate 40-50, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methacrylic acid copolymer type C, polysorbate 80, sugar spheres, talc, and triethyl citrate. The capsule shells have the following inactive ingredients: gelatin, FD&C Blue #1, FD&C Red #40, D&C Red #28, titanium dioxide, shellac, ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, sodium hydroxide, polyvinyl pyrrolidone, and D&C Yellow #10.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption

NEXIUM Delayed-Release Capsules contain an enteric-coated pellet formulation of esomeprazole magnesium. After oral administration peak plasma levels (C_{max}) occur at approximately 1.5 hours (T_{max}). The C_{max} increases proportionally when the dose is increased, and there is a three-fold increase in the area under the plasma concentration-time curve (AUC) from 20 to 40 mg. At repeated once-daily dosing with 40 mg, the systemic bioavailability is approximately 90% compared to 64% after a single dose of 40 mg. The mean exposure (AUC) to esomeprazole increases from 4.32 µmol*hr/L on day 1 to

11.2 µmol*hr/L on day 5 after 40 mg once daily dosing.
The AUC after administration of a single 40 mg dose of esomeprazole is decreased by 33-53% 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:

Pharmacokinetic Parameters of NEXIUM Following Oral Dosing for 5 days

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

Values represent the geometric mean, except the T_{max}, which is the arithmetic mean.

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 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 15-20% 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 1-1.5 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 C_{max} values were slightly higher (25% and 18%, respectively) in the elderly as compared

Pediatric
The pharmacokinetics of esomeprazole have not been studied in patients < 18 years of age.

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

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

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

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

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 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

Antisecretory Activity

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:

Effect on Intragastric pH On Day 5 (N=36)

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

† Gastric pH was measured over a 24-hour period
*p< 0.01 NEXIUM 40 mg vs NEXIUM 20 mg

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

Serum Gastrin Effects

The effect of NEXIUM on serum gastrin concentrations was evaluated in approximately 2,700 patients in clinical trials up to 8 weeks and in over 1,300 patients for up to 6-12 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.

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 **PRECAUTIONS,** Carcinogenesis, Mutagenesis, Impairment of Fertility). Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of H_2-receptor antagonists.

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

In over 1,000 patients treated with NEXIUM (10, 20 or 40 mg/day) up to 6-12 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

given in oral doses of 30 or 40 mg for 2 to 4 weeks had no effect on carbohydrate metabolism, circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin or secretin.

Microbiology

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

Helicobacter

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

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

The baseline clarithromycin susceptibility results and the eradication results at the Day 38 visit are shown in the table below:

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