

# NEW DRUG UPDATE



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## Nexium® (esomeprazole magnesium)

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### Introduction:

Nexium® [esomeprazole magnesium, (es-oh-ME-pray-zol)], is a new proton pump inhibitor that was FDA approved in February 2001 for treatment of gastroesophageal reflux disease and erosive esophagitis. Esomeprazole is the S-enantiomer of omeprazole, which binds to hydrogen/potassium adenosine triphosphate in gastric parietal cells and blocks the final step of hydrochloric acid secretion by these cells, leading to a decrease in gastric acid secretion.

### Therapeutic Recommendation:

Esomeprazole is one of several proton pump inhibitors marketed as second line therapy for patients with gastroesophageal lesions unresponsive to maximum doses of H<sub>2</sub>-receptor antagonists. However in severe disease, proton pump inhibitors may be considered first-line treatment. Esomeprazole undergoes less first-pass hepatic metabolism than omeprazole, has a lower plasma clearance and greater oral bioavailability to enable more effective management of acid related disorders. Esomeprazole may be more effective than 20 mg omeprazole for the treatment of erosive

esophagitis in GERD patients. However, no clinical trials have been performed to evaluate its efficacy when compared to omeprazole 40 mg for the same indication. At this time the two are competitively priced, although omeprazole is going off patent soon and will be available generically.

Studies indicate that esomeprazole 20 and 40 mg demonstrated healing of erosive esophagitis after eight weeks of therapy to be statistically superior to omeprazole 20 mg. In comparison to placebo as maintenance therapy with completely healed erosive esophagitis, more patients were heartburn free at one month with esomeprazole than with placebo. This effect was dose-dependent. Patients with recurrent esophagitis have a longer time to recurrence at larger doses as compared to smaller doses (40 mg vs. 10 mg). A more rapid onset of heartburn relief was noted with esomeprazole 40 mg than with esomeprazole 20 mg or omeprazole.

### Dosing and Administration:

Esomeprazole is available in 20 mg (amethyst colored with 2 radial bars) and 40 mg (amethyst colored with 3 radial bars) delayed release capsules for oral intake. Each strength is supplied in bottles of 30 capsules, 90 capsules, 100 capsules, 1000 capsules and unit dose packages of 100 capsules. Esomeprazole should be taken at least one hour before eating once daily. The recommended adult dosage for treatment of erosive esophagitis is 20 or 40 mg once daily

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for 4 to 8 weeks. If healing is incomplete, esomeprazole can be given for an additional 4 to 8 weeks. For maintenance of healing, the recommended dose is 20 mg once daily, and controlled studies have not exceeded 6 months. For the treatment of GERD without erosive disease, 20 mg for 4 weeks is advised with an additional 4 weeks if symptoms persist. For eradication of *H. pylori* to reduce the risk of duodenal ulcer recurrence, 10 days of triple therapy with esomeprazole 40 mg once daily, amoxicillin 1000 mg twice daily and clarithromycin 500 mg twice daily is recommended.

**Cost Comparison:**

Medication/Dose	Cost*		
	<u>KMart</u>	<u>Rite Aid</u>	<u>CVS</u>
Nexium® (esomeprazole) 40 mg QD	109.59	119.19	136.99
Prilosec® (omeprazole) 20 mg QD	120.39	134.99	136.99
Prevacid® (lansoprazole) 30 mg QD	110.59	129.99	125.99
Protonix® (pantoprazole) 40 mg QD	83.99	113.69	102.99
Aciphex® (rabeprazole) 20 mg QD	105.99	143.69	134.99

\* Cost represents price to patients for a 30-day supply of medication at average doses used.

**Contraindications:**

Esomeprazole is contraindicated in patients who are known to have a hypersensitivity to esomeprazole, omeprazole, hydroxypropyl cellulose, magnesium stearate, or any other component of its formulation.

**Special populations:**

Hepatic Disease: Dosage adjustment is not required in patients with mild to moderate hepatic impairment. However for patients with severe hepatic impairment, the dose of esomeprazole should not exceed 20 mg.

Lactation: It may distribute into the breast milk and is therefore not recommended.

Pediatrics: There are no clinical trials to support the use of esomeprazole during childhood.

Pregnancy: Animal and human data are unavailable. Pregnancy category B.

Cross Reactivity: Patients with a history of allergic-type responses to lansoprazole, rabeprazole or pantoprazole should use esomeprazole with caution.

Geriatrics: There appears to be a slight increase in AUC and Cmax in elderly individuals, however dosage adjustment is not recommended.

Gender: The AUC and Cmax values were slightly higher for females, but dosage adjustment is not necessary.

**Drug Interactions:**

Metabolism of esomeprazole includes extensive hydroxylation by CYP2C19 and also by CYP3A4, and it is excreted in the urine. Coadministration of diazepam, a CYP2C19 substrate, may result in a 45% decrease in clearance of diazepam. However, this interaction is thought to be clinically irrelevant. Similar to other proton pump inhibitors, esomeprazole may interfere with the bioavailability of drugs dependent on an acidic pH for absorption, such as ketoconazole (Nizoral) or digoxin (Lanoxin).



**...A Primary Care  
Physician's Guide to  
Newly Released  
Medications...**

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### Common Adverse Drug Reactions:

The most common adverse drug reactions as with other proton pump inhibitors are headache, diarrhea, nausea, flatulence, abdominal pain, constipation and dry mouth.

### Pharmacology:

**Mechanism of Action:** Esomeprazole blocks the final pathway of hydrochloric acid secretion by binding to the hydrogen/potassium adenosine triphosphate in the gastric parietal cells. The active metabolite forms an irreversible covalent bond and the acid secretion is inhibited until additional enzymes are synthesized, leading to a prolonged duration of action. This mechanism results in a gastric pH of greater than 4.0, which is known to aid the healing of erosive esophagitis, heartburn and gastroesophageal reflux disease.

**Absorption/Distribution:** Esomeprazole comes as a delayed-release capsule that contains an enteric coated pellet formulation with peak plasma levels occurring in about 1.5 hours. It has a bioavailability that increases during multiple dose therapy. For example, the absolute bioavailability for a 40 mg capsule increased from 64 to 89% from day 1 to 5. Area under the curve data indicate nonlinear pharmacokinetics that increase following repeated oral daily doses, which is contributed to a reduced systemic clearance and decreased first-pass elimination. The area under the curve decreased by 33-53% after food consumption compared to fasting conditions. Esomeprazole should be taken at least one hour before meals. Esomeprazole is 97% bound to plasma proteins and has a volume of distribution of approximately 16L.

**Metabolism/Elimination:** There are two known metabolites with unknown activity, 5-hydroxyesomeprazole and esomeprazole sulfone. Hydroxylation in the liver by cytochrome P450-2C19 is a major pathway in the metabolism of esomeprazole to hydroxy and desmethyl metabolites. The remaining amount depends on cytochrome P450-3A4, which forms the sulfone metabolite. In comparison with the racemic omeprazole, esomeprazole undergoes less first-pass metabolism. Total body clearance decreases with repeated doses. The elimination half-life is approximately 1.5 hours. About 80% of the oral dose is excreted as inactive metabolites in the urine and the remainder as inactive metabolites in the feces.

### Patient Information:

1. Do not take this medication if you are allergic to esomeprazole or omeprazole, and use cautiously with a history of allergic-type responses to lansoprazole, rabeprazole, or pantoprazole.
2. Counsel patients to inform their prescribers and pharmacists of all other medications (prescription, non-prescription, dietary supplements and herbals) that they are taking.
3. Take esomeprazole once daily at least one hour before eating.
4. Headache, diarrhea, nausea, flatulence, abdominal pain, constipation and dry mouth are the most common adverse effects.
5. The safety of this medication when administered to a patient who is pregnant or breastfeeding is unknown and is not recommended.
6. Use cautiously if liver disease is present, or if currently taking anticoagulants, diazepam, or phenytoin.
7. If a dose is missed, take it as soon as possible. If it is almost time for the next dose, simply wait to the next dose and be sure not to double doses.
8. Antacids may be taken for relief of pain, unless otherwise instructed by the physician.
9. Store the medication in a cool, dry place away from children and pets.
10. If the condition does not improve or worsens, be certain to tell the physician.

### References:

1. Esomeprazole (nexium). The Medical Letter. 2001;43(1103):36-7
2. Hassan-Alin M, et al. Pharmacokinetics of esomeprazole after oral and intravenous administration of single and repeated doses to healthy subjects. European Journal of Pharmacology 2000; 56(9-10):665-70.
3. Nexium® prescribing information. AstraZeneca Pharmaceuticals, Inc., Wilmington, Delaware, January 2001.

**Geodon® (ziprasidone HCl)**

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**Introduction:**

Geodon® [ziprasidone HCL (zi-PRAY-si-done)] is a new atypical antipsychotic approved by the FDA in February 2001. Ziprasidone is indicated for the treatment of schizophrenia and shows efficacy against both positive and negative symptoms of this disorder.

**Therapeutic Recommendation:**

Ziprasidone is classified as an atypical antipsychotic that acts as both a serotonin and dopamine receptor antagonist. Ziprasidone has the highest 5HT<sub>2a</sub>/D<sub>2</sub> receptor-binding ratio of any of the atypical antipsychotics, which has been associated with a lower risk of movement disorders. Because ziprasidone is a moderate inhibitor of norepinephrine and serotonin reuptake, it may theoretically improve depressive symptoms in this patient population; however, this has not yet been clinically evaluated.

Five clinical studies have been performed evaluating the efficacy of oral ziprasidone versus placebo. In four of the five trials, psychological rating scores for ziprasidone were superior to placebo. Currently, studies have not been completed comparing the efficacy of ziprasidone to other antipsychotics. The FDA did not approve ziprasidone in 1998 due to QT<sub>c</sub> interval prolongation concerns; therefore, the manufacturer performed a study comparing QT interval changes of ziprasidone versus risperidone, olanzapine, quetiapine, and haloperidol. The mean QT<sub>c</sub> interval increase compared to baseline was approximately 9 to 14 msec greater for ziprasidone than the other atypical antipsychotics. QT interval prolongation has been associated with the development of torsades de pointes and sudden death. Patients with disease states or medications that predispose patients to arrhythmias should not take ziprasidone. The risk of sudden death with ziprasidone may be greater than with other atypical antipsychotics. This outcome should be con-

sidered when deciding on drug therapy. Careful evaluation of predisposing conditions and medications is essential before starting therapy with ziprasidone.

When ziprasidone was compared to placebo in short-term trials, 10% of ziprasidone patients experienced a weight gain of ≥7% of body weight compared to 4% of placebo. The median weight change in ziprasidone patients was 0.5 kg. Compared to other atypical antipsychotics, ziprasidone shows the lowest potential for weight gain.

**Dosing and Administration:**

Ziprasidone is supplied in 20 mg (blue/white), 40 mg (blue/blue) and 60 mg (white/white) capsules for oral administration. All strengths are available in bottles of 60 capsules. An injectable formulation of ziprasidone is currently under final FDA review.

For the initial treatment of a schizophrenic episode, the recommended starting dose is 20 mg given twice daily with food. The dose may be titrated up to 80 mg twice daily as needed and tolerated to control symptoms. Dosage increases should be limited to intervals of no less than two days as steady state levels are reached within 1 to 3 days. To maintain the lowest effective treatment dose, ideally patient response should be monitored over several weeks before increasing the dose. Dosage adjustments are not required for patients based on age, gender, race, and renal or hepatic impairment.

**Cost Comparison:**

Medication/Dose	Cost*		
	Drug Emporium	Kroger	Rite Aid
Geodon® (ziprasidone) 20 mg BID	230.46	279.59	257.99
Risperdal® (risperidone) 1 mg BID	153.38	183.99	204.69
Zyprexa® (olanzapine) 5 mg QD	171.14	204.39	208.99

\*Cost to patient for a 30-day supply at the initial starting dose.

**Contraindications:**

Ziprasidone is contraindicated in patients who have a known hypersensitivity to ziprasidone or any of its components.

Because ziprasidone shows a dose-related prolongation of the QT interval, ziprasidone is contraindicated in patients at risk for development or who have a history of QT interval prolongation. Zip-

prazosin is contraindicated in patients with congenital long QT syndrome, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. Ziprasidone is also contraindicated in patients receiving other drugs that prolong the QT interval such as quinidine, erythromycin, tricyclic antidepressants, dofetilide, pimozone, sotalol, thioridazine, moxifloxacin, and sparfloxacin.

### General Warnings:

Torsades de pointes and sudden unexplained death have been associated with drugs that prolong the QT interval. Although premarketing studies with ziprasidone have not documented the occurrence of torsades de pointes, clinical information is limited and one may not rule out an increased risk. Because hypokalemia and/or hypomagnesemia may increase the risk for QT prolongation, patients at risk for these electrolyte imbalances should be closely monitored while taking ziprasidone.

All patients receiving antipsychotics should be monitored for the development of neuroleptic malignant syndrome, a potentially life threatening disorder. Tardive dyskinesia has also been associated with the use of antipsychotic medications, especially with higher doses and/or prolonged durations.

### Special populations:

**Pregnancy:** Ziprasidone is classified as pregnancy category C. Animal studies have shown developmental toxicity at doses similar to human doses. The use of ziprasidone in pregnant women should be based on the benefit versus the risk.

**Lactation:** Because of limited information regarding transfer of ziprasidone or its metabolites into breast milk, breast-feeding is not recommended.

**Pediatrics:** There is no evidence to evaluate the safety and effectiveness of ziprasidone in this population.

**Geriatrics:** Limited data does not suggest differences in tolerability or clearance of ziprasidone within this population. The manufacturer suggests using lower starting doses, slower titrations, and close monitoring within this population due to the possibility of age-related factors contributing to an adverse event.

**Hepatic impairment:** Ziprasidone is significantly metabolized by the liver. A small clinical study revealed an increased AUC in patients with clinically significant cirrhosis. Until more evidence is obtained, dosage adjustment in hepatic insufficiency is not recommended.

**Renal Impairment:** Less than 1% of ziprasidone is excreted unchanged in the urine. No adjustment in renal impairment is recommended.

### Drug Interactions:

Ziprasidone has shown little inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 in *in vitro* studies. CYP3A4 is the major enzyme responsible for the metabolism of ziprasidone. Carbamazepine, a potent inducer of CYP3A4, decreased the AUC for ziprasidone by 35% when given concomitantly. Ketoconazole, a potent inhibitor of CYP3A4, increased the AUC and C<sub>max</sub> of ziprasidone by approximately 35-40% when administered together. Drugs with similar inhibitory or inducing properties are expected to have similar effects on the clearance of ziprasidone. Cimetidine, beztropine, propranolol, and lorazepam did not interact with ziprasidone in clinical trials. Ziprasidone also did not affect the pharmacokinetics of lithium, oral contraceptives, or dextromethorphan.

### Common Adverse Drug Reactions:

The most common adverse event associated with discontinuation of treatment in short-term, placebo-controlled trials was rash (4.1% of treatment group). Adverse events occurring at a rate greater than 5% or over twice the rate of placebo included somnolence (14%), extrapyramidal syndrome (5%), and respiratory disorder (5%). Dose dependent adverse reactions included asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision. A significant number of patients in controlled trials experienced weight gain ( $\geq 7\%$  increase in body weight) compared to placebo (10% versus 4%). The median weight change in ziprasidone patients was 0.5 kg. Due to ziprasidone's antagonism of dopamine receptors, ziprasidone elevates prolactin levels. Patients with a past history of breast cancer should use caution.

### Pharmacology:

**Mechanism of Action:** *In vitro* studies reveal that ziprasidone has a high affinity for dopamine receptors (D<sub>2</sub> and D<sub>3</sub>), serotonin receptors (5HT<sub>2A</sub>, 5HT<sub>2C</sub>, 5HT<sub>1A</sub>, 5HT<sub>1D</sub>), and alpha-1-adrenergic receptors. Ziprasidone acts as an antagonist on the

D<sub>2</sub>, 5HT<sub>2A</sub>, and 5HT<sub>1D</sub> receptors and as an agonist at the 5HT<sub>1A</sub> receptor. Its main pharmacological efficacy is believed to be a result of ziprasidone's antagonism of D<sub>2</sub> and 5HT<sub>2</sub> receptors. The drug has moderate affinity for histamine H<sub>1</sub> receptors, which could explain the incidence of somnolence in test subjects. Its antagonism of alpha-adrenergic receptors may also be associated with the incidence of orthostatic hypotension. Ziprasidone also inhibited the reuptake of serotonin and norepinephrine.

**Absorption /Distribution:** After oral administration of ziprasidone, peak plasma concentration is reached after 6 to 8 hours. The absolute bioavailability of a 20 mg dose given with food was approximately 60%. In the presence of food, the absorption of ziprasidone is doubled when compared to fasting. Ziprasidone is highly bound to plasma proteins (>99%) and has an apparent volume of distribution of 1.5L/kg.

**Metabolism/Excretion:** Ziprasidone is extensively metabolized to primarily four metabolites. Less than one third of the drug is metabolized by the cytochrome P450 system while two thirds of the dose is reduced by aldehyde oxidase. CYP 3A4 is the predominant CYP metabolizing enzyme with a small fraction of the dose being metabolized by CYP 1A2. After oral administration, less than 1% of the dose is excreted unchanged in the urine and less than 4 % is unchanged in feces.

## Patient Information:

1. Notify your doctor if you have any type of heart condition, family history of heart disease, or problems with fainting or dizziness. Immediately talk to your doctor if you experience side effects of fainting or irregular heart beats.
2. While your body is adjusting to your medication, you may feel dizziness when you stand up too quickly due to a drop in your blood pressure. Use caution in standing and notify your doctor if you experience this problem.
3. Some medications are unsafe to use while you are taking ziprasidone. Always inform your doctor of all medications you are taking including prescription medications, over-the-counter products, vitamins, and herbals.
4. Ziprasidone capsules should be taken twice a day with food.
5. The benefits of ziprasidone may take several weeks to be noticed. Continue to take your medication even if you feel better.

## References:

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2. Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, Weiden PJ. Antipsychotic-induced weight gain: a comprehensive research synthesis. *American Journal of Psychiatry* 1999 Nov;156 (11):1686-96
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