**ESZOPICLONE**

**Brands**  • Lunesta  
*see index for additional brand names*

**Generic?** No

**Class**  • Non-benzodiazepine hypnotic; alpha 1 isof orm selective agonist of GABA-A/benzodiazepine receptors

**Commonly Prescribed for**  
(bold for FDA approved)  
• Insomnia  
• Primary insomnia  
• Chronic insomnia  
• Transient insomnia  
• Insomnia secondary to psychiatric or medical conditions  
• Residual insomnia following treatment with antidepressants

**How the Drug Works**  
• May bind selectively to a subtype of the benzodiazepine receptor, the alpha 1 isof orm  
• May enhance GABA inhibitory actions that provide sedative hypnotic effects more selectively than other actions of GABA  
• Boosts chloride conductance through GABA-regulated channels  
• Inhibitory actions in sleep centers may provide sedative hypnotic effects

**How Long Until It Works**  
• Generally takes effect in less than an hour

**If It Works**  
• Improves quality of sleep  
• Effects on total wake-time and number of nighttime awakenings may be decreased over time

**If It Doesn’t Work**  
• If insomnia does not improve after 7–10 days, it may be a manifestation of a primary psychiatric or physical illness such as obstructive sleep apnea or restless leg syndrome, which requires independent evaluation  
• Increase the dose  
• Improve sleep hygiene  
• Switch to another agent

| **Best Augmenting Combos** for Partial Response or Treatment Resistance |  
| • Generally, best to switch to another agent  
• Trazodone  
• Agents with antihistamine actions (e.g., diphenhydramine, tricyclic antidepressants)  
| **Tests** |  
| • None for healthy individuals |

**SIDE EFFECTS**

**How Drug Causes Side Effects**  
• Actions at benzodiazepine receptors that carry over to the next day can cause daytime sedation, amnesia, and ataxia  
*Chronic studies of eszopiclone suggest lack of notable tolerance or dependence developing over time

**Notable Side Effects**  
• Unpleasant taste  
• Sedation  
• Dizziness  
• Dose-dependent amnesia  
• Nervousness  
• Dry mouth, headache

**Life-Threatening or Dangerous Side Effects**  
• Respiratory depression, especially when taken with other CNS depressants in overdose  
• Rare angioedema

**Weight Gain**  
• Reported but not expected

**Sedation**  
• Many experience and/or can be significant in amount  
• Next day carryover sedation following nighttime dosing uncommon

**What to Do About Side Effects**  
• Wait
**DOSING AND USE**

**Usual Dosage Range**
- 2–3 mg at bedtime

**Dosage Forms**
- Tablet 1 mg, 2 mg, 3 mg

**How To Dose**
- No titration, take dose at bedtime

**Dosing Tips**
- Not restricted to short-term use
- No notable development of tolerance or dependence seen in studies up to 6 months
- Recent study adding eszopiclone to patients with major depression and only a partial response to fluoxetine showed improvement not only in residual insomnia, but in other residual symptoms of depression as well
- Most studies were done with 3 mg dose or less at night, but some patients with insomnia associated with psychiatric disorders may require higher dosing
- However, doses higher than 3 mg may be associated with carryover effects, hallucinations, or other CNS adverse effects
- To avoid problems with memory or carryover sedation, only take eszopiclone if planning to have a full night’s sleep
- Most notable side effect may be unpleasant taste
- Other side effects can include sedation, dizziness, dose-dependent amnesia, nervousness, dry mouth, and headache

**Best Augmenting Agents for Side Effects**
- Many side effects cannot be improved with an augmenting agent

**Overdose**
- Few reports of eszopiclone overdose, but probably similar to zopiclone overdose
- Rare fatalities have been reported in zopiclone overdose
- Symptoms associated with zopiclone overdose include clumsiness, mood changes, sedation, weakness, breathing trouble, unconsciousness

**Long-Term Use**
- No development of tolerance was seen in studies up to 6 months

**Habit Forming**
- Eszopiclone is a Schedule IV drug
- Some patients could develop dependence and/or tolerance with drugs of this class; risk may be theoretically greater with higher doses
- History of drug addiction may theoretically increase risk of dependence

**How to Stop**
- Rebound insomnia may occur the first night after stopping
- If taken for more than a few weeks, taper to reduce chances of withdrawal effects

**Pharmacokinetics**
- Metabolized by CYP450 3A4 and 2E1
- Terminal elimination half-life approximately 6 hours

**Drug Interactions**
- Increased depressive effects when taken with other CNS depressants
- Inhibitors of CYP450 3A4, such as nefazodone and fluvoxamine, could increase plasma levels of eszopiclone
- Inducers of CYP450 3A4, such as rifampicin, could decrease plasma levels of eszopiclone

**Other Warnings/Precautions**
- Insomnia may be a symptom of a primary disorder, rather than a primary disorder itself
- Some patients may exhibit abnormal thinking or behavioral changes similar to those caused by other CNS depressants
SPECIAL POPULATIONS

Renal Impairment
- Dose adjustment not generally necessary

Hepatic Impairment
- Dose adjustment not generally recommended for mild-to-moderate hepatic impairment
- For severe impairment, recommended initial dose 1 mg at bedtime; maximum dose 2 mg at bedtime

Cardiac Impairment
- Dosage adjustment may not be necessary

Elderly
- May be more susceptible to adverse effects
- Initial dose 1 mg at bedtime; maximum dose generally 2 mg at bedtime
- Eszopiclone should be administered only at bedtime

Children and Adolescents
- Safety and efficacy have not been established
- Long-term effects of eszopiclone in children/adolescents are unknown
- Should generally receive lower doses and be more closely monitored

Do Not Use
- If there is a proven allergy to eszopiclone or zopiclone
- Rare angioedema has occurred with sedative hypnotic use and could potentially cause fatal airway obstruction if it involves the throat, glottis, or larynx; thus if angioedema occurs treatment should be discontinued
- Sleep driving and other complex behaviors, such as eating and preparing food and making phone calls, have been reported in patients taking sedative hypnotics

Pregnancy
- Risk Category C [some animal studies show adverse effects; no controlled studies in humans]
- Infants whose mothers took sedative-hypnotics during pregnancy may experience some withdrawal symptoms
- Neonatal flaccidity has been reported in infants whose mothers took sedative hypnotics during pregnancy

Breast Feeding
- Unknown if eszopiclone is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages
- Primary insomnia
- Chronic insomnia
- Those who require long-term treatment
- Those with depression whose insomnia does not resolve with antidepressant treatment

Potential Disadvantages
- More expensive than some other sedative hypnotics

Primary Target Symptoms
- Time to sleep onset
- Nighttime awakenings
- Total sleep time

Pearls
- May be preferred over benzodiazepines because of its rapid onset of action, short duration of effect, and safety profile
- Eszopiclone is the best documented agent to be safe for long-term use, with little or no suggestion of tolerance, dependence, or abuse
- May even be safe to consider in patients with a past history of substance abuse who require treatment with a hypnotic
- May be preferred over benzodiazepine hypnotics, which all cause tolerance, dependence, and abuse as a class
ESZOPICLONE

- Not a benzodiazepine itself but binds to the benzodiazepine receptor
- May be a preferred agent in primary insomnia
- Targeting insomnia may prevent the onset of depression and maintain remission after recovery from depression
- Rebound insomnia does not appear to be common

Suggested Reading

