ESZOPICLONE

THERAPEUTICS

Brands • Lunesta
see index for additional brand names

Generic? Yes

Class
• Neuroscience-based Nomenclature: GABA positive allosteric modulator (GABA-PAM)
• Non-benzodiazepine hypnotic; alpha 1 isoform 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 isoform
• 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, TCAs)

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

261
ESZOPICLONE (continued)

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

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

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

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 (i.e., either depressant actions or disinhibiting actions)
- Some depressed patients may experience a worsening of suicidal ideation
- Use only with caution in patients with impaired respiratory function or obstructive sleep apnea
- Eszopiclone should only be administered at bedtime

**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**
- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- 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

- Recommended either to discontinue drug or bottle feed

**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

**Children and Adolescents**
- Safety and efficacy have not been established

**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
Suggested Reading


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
- 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