**THERAPEUTICS**

**Brands**
- Ambien, Ambien CR
- Intermezzo

*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*
- Short-term treatment of insomnia (controlled-release indication is not restricted to short-term)
- As needed for the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep and there are at least 4 hours of bedtime remaining before the planned time of wakening (Intermezzo)

**How the Drug Works**
- Binds 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
- CR formulation may allow sufficient drug to persist at receptors to improve total sleep time and to prevent early morning awakenings that can be associated with the immediate-release formulation of zolpidem

**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

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**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
- Long-term adaptations of zolpidem immediate-release not well studied, but chronic studies of zolpidem CR and other alpha 1 selective non-benzodiazepine hypnotics suggest lack of notable tolerance or dependence developing over time

**Notable Side Effects**
- Sedation
- Dizziness, ataxia
- Dose-dependent amnesia
- Hyperexcitability, nervousness
- Rare hallucinations
- Diarrhea, nausea
- 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

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**815 ZOLPIDEM**
ZOLPIDEM (continued)

Sedation

- Many experience and/or can be significant in amount

What to Do About Side Effects

- Wait
- To avoid problems with memory, only take zolpidem or zolpidem CR if planning to have a full night’s sleep
- Lower the dose
- Switch to a shorter-acting sedative hypnotic
- Administer flumazenil if side effects are severe or life-threatening

Best Augmenting Agents for Side Effects

- Many side effects cannot be improved with an augmenting agent

Dosing Tips

- Zolpidem is not absorbed as quickly if taken with food, which could reduce onset of action
- Patients with lower body weights may require only a 5-mg dose immediate-release or 6.25 mg controlled-release
- Zolpidem should generally not be prescribed in quantities greater than a 1-month supply; however, zolpidem CR is not restricted to short-term use
- Risk of dependence may increase with dose and duration of treatment
- However, treatment with alpha 1 selective non-benzodiazepine hypnotics may cause less tolerance or dependence than benzodiazepine hypnotics
- Controlled-release tablets should be swallowed whole and should not be divided, crushed, or chewed

Overdose

- No fatalities reported with zolpidem monotherapy; sedation, ataxia, confusion, hypotension, respiratory depression, coma

Long-Term Use

- Original studies with zolpidem immediate-release did not assess long-term use
- Zolpidem CR is not restricted to short-term use
- Increased wakefulness during the latter part of night (wearing off) or an increase in daytime anxiety (rebound) may occur with immediate-release and be less common with controlled-release

Habit Forming

- Zolpidem is a Schedule IV drug
- Some patients may develop dependence and/or tolerance; risk may be greater with higher doses
- History of drug addiction may increase risk of dependence

How to Stop

- Although rebound insomnia could occur, this effect has not generally been seen

DOSING AND USE

Usual Dosage Range

- 10 mg/day at bedtime for 7–10 days (immediate-release)
- 12.5 mg/day at bedtime (controlled-release)

Dosage Forms

- Immediate-release tablet 5 mg
- Controlled-release tablet 6.25 mg, 12.5 mg
- Sublingual tablet 1.75 mg, 3.5 mg, 5 mg, 10 mg
- Oral spray 5 mg

How to Dose

- Men: 10 mg at bedtime for 7–10 days (immediate-release); 12.5 mg at bedtime for 7–10 days (controlled-release); 3.5 mg sublingually in the middle of the night if more than 4 hours of bedtime remain (Intermezzo)
- Women: 5 mg at bedtime for 7–10 days (immediate-release); 6.25 mg at bedtime for 7–10 days (controlled-release); 1.75 mg sublingually in the middle of the night if more than 4 hours of bedtime remain (Intermezzo)
- Intermezzo formulation is administered sublingually in the middle of the night; it should be placed under the tongue and allowed to dissolve completely before swallowing
- Intermezzo formulation should not be taken more than once per night

Sedation

- Many experience and/or can be significant in amount

What to Do About Side Effects

- Wait
- To avoid problems with memory, only take zolpidem or zolpidem CR if planning to have a full night’s sleep
- Lower the dose
- Switch to a shorter-acting sedative hypnotic
- Administer flumazenil if side effects are severe or life-threatening

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How to Stop

- Although rebound insomnia could occur, this effect has not generally been seen
with therapeutic doses of zolpidem or zolpidem CR
• If taken for more than a few weeks, taper to reduce chances of withdrawal effects

**Pharmacokinetics**
• Short elimination half-life (approximately 2.5 hours)

**Drug Interactions**
• Increased depressive effects when taken with other CNS depressants
• Sertraline may increase plasma levels of zolpidem
• Rifampin may decrease plasma levels of zolpidem
• Ketoconazole may increase plasma levels of zolpidem
• Use with imipramine or chlorpromazine may be associated with decreased alertness

**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 extreme caution in patients with impaired respiratory function or obstructive sleep apnea
• Zolpidem and zolpidem CR should only be administered at bedtime
• Temporary memory loss may occur at doses above 10 mg/night
• 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

**Do Not Use**
• If there is a proven allergy to zolpidem
• For Intermezzo, if the patient has fewer than 4 hours of bedtime remaining before the planned time of waking

### SPECIAL POPULATIONS

**Renal Impairment**
• No dose adjustment necessary
• Patients should be monitored

**Hepatic Impairment**
• Recommended dose 5 mg (immediate-release), 6.25 mg (controlled-release), 1.75 mg (Intermezzo)
• Patients should be monitored

**Cardiac Impairment**
• No available data

**Elderly**
• Recommended initial dose: 5 mg (immediate-release), 6.25 mg (controlled-release), 1.75 mg (Intermezzo)
• Elderly may have increased risk for falls, confusion

**Children and Adolescents**
• Safety and efficacy have not been established
• Long-term effects of zolpidem or zolpidem CR in children/adolescents are unknown
• Should generally receive lower doses and be more closely monitored
• Hallucinations in children ages 6-17 have been reported

**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 (PLLRR or final rule) applies only to prescription drugs and will be...

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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
- Some drug is found in mother’s breast milk
* Recommended either to discontinue drug or bottle feed

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages
- Patients who require long-term treatment, especially CR formulation

Potential Disadvantages
- More expensive than some other sedative hypnotics

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

Pearls
* One of the most popular sedative hypnotic agents in psychopharmacology
- Zolpidem has been shown to increase the total time asleep and to reduce the amount of nighttime awakenings

Suggested Reading


