HYPNOTIC | C-IV

Zolpidem

Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist

Most-prescribed Z-drug hypnotic; sex-specific dosing, multiple formulations, and a boxed warning for complex sleep behaviors.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
5-10 mg PO qhs (IR)	2.5-3 h	CYP3A4, CYP2C9, CYP1A2	15-30 min; peak 1.6 h

⚠ FDA BOXED WARNING

Complex sleep behaviors including sleepwalking, sleep-driving, and engaging in other activities while not fully awake have occurred, sometimes resulting in serious injury or death. These events can occur after the first dose and at any dose. Discontinue immediately if a complex sleep behavior occurs.

INDICATIONS

- FDA-approved for short-term treatment of insomnia characterized by difficulty with sleep initiation in adults, using the immediate-release tablet.
- Ambien CR is approved for insomnia characterized by difficulties with both sleep onset and sleep maintenance in adults.
- Intermezzo sublingual tablets are approved for middle-of-the-night awakening with difficulty returning to sleep, when 4 hours of bed time remain.
- Edluar sublingual tablets and Zolpimist oral spray are approved for sleep-onset insomnia and act somewhat faster than the swallowed tablet.
- Cognitive behavioral therapy for insomnia is first line per the American Academy of Sleep Medicine and the American College of Physicians.
- Off-label reports of transient responsiveness in disorders of consciousness and in catatonia exist but are anecdotal and not a practice standard.

DOSING & TITRATION

- Immediate release: **5 mg for women and 5 or 10 mg for men**, once nightly immediately before bed with at least 7-8 hours of sleep opportunity.
- Extended release: **6.25 mg for women and 6.25 or 12.5 mg for men**, once nightly; swallow whole and do not divide, crush or chew.
- Intermezzo sublingual for middle-of-night awakening: **1.75 mg for women and 3.5 mg for men**, only with at least 4 hours of bed time remaining.
- Older adults, debilitated patients and any hepatic impairment: 5 mg immediate release or 6.25 mg extended release regardless of sex; avoid in severe hepatic disease.
- Do not exceed 10 mg/day of immediate release or 12.5 mg/day of extended release, and give only one dose per night by any route.
- After nightly use for weeks, taper stepwise rather than stopping abruptly to limit rebound insomnia and withdrawal symptoms.

MECHANISM OF ACTION

- Non-benzodiazepine imidazopyridine that binds the benzodiazepine site of GABA-A receptors, enhancing chloride conductance in the presence of GABA.
- Preferential affinity for alpha-1 subunit-containing receptors gives sedation and amnesia with relatively less anxiolytic and muscle relaxant effect.
- Alpha-1 selectivity is only partial, so ataxia, falls and next-day impairment still occur, and the drug retains reinforcing properties.
- Sleep architecture is largely preserved compared with benzodiazepines, with modest suppression of stage 3 and REM sleep at higher doses.
- Partial arousal from non-REM sleep with intact motor output but absent memory encoding is the presumed basis for complex sleep behaviors.

PHARMACOKINETICS

- Rapid absorption with peak levels near 1.6 hours; a meal delays absorption and lowers peak concentration, so dose on an empty stomach.
- Elimination half-life is about **2.5-3 hours**, short enough that residual next-day effects are usually modest at labeled doses.
- Metabolized by CYP3A4 with lesser contributions from CYP2C9 and CYP1A2 to three inactive metabolites cleared renally.
- Women clear zolpidem more slowly than men, producing roughly 45 percent higher morning blood levels and the sex-specific dose limits.
- Hepatic impairment markedly reduces clearance and prolongs half-life to about 10 hours in cirrhosis, requiring a lower dose or avoidance.

ADVERSE EFFECTS

- Drowsiness in about 8 percent, dizziness 5 percent and diarrhea 3 percent with immediate release; headache and nausea are also common.
- Complex sleep behaviors such as sleepwalking, sleep-driving, sleep-eating and sleep-sex with no memory of the event; these can be fatal.
- Next-morning psychomotor and driving impairment, worst with the extended-release form, with women and older adults most affected.
- Anterograde amnesia for events after dosing, hallucinations, and rarely confusional arousals or transient psychotic-like phenomena.
- Falls, fractures and delirium in older adults, plus a documented association between hypnotic use and motor vehicle crash risk.
- Angioedema and anaphylaxis after the first or subsequent doses, respiratory depression with opioids, and worsened depression or suicidality.

MONITORING

- Ask explicitly at every visit about sleepwalking, sleep-driving, nocturnal eating and any amnesia for nighttime events.
- Screen for and treat obstructive sleep apnea, restless legs, alcohol use, pain and mood disorder before or alongside hypnotic therapy.
- Reassess ongoing need at 2-4 weeks and periodically thereafter; the label supports short-term use, not indefinite nightly dosing.
- Assess next-morning alertness and counsel that driving may be impaired even when the patient feels fully awake.
- Check the prescription monitoring program and screen for substance use disorder before initiating this schedule IV hypnotic.

INTERACTIONS & CAUTIONS

- Contraindicated in patients who have previously experienced a complex sleep behavior on zolpidem, and in known hypersensitivity or angioedema.
- Additive respiratory depression and sedation with opioids, alcohol, benzodiazepines, gabapentinoids and sedating antihistamines.
- Strong CYP3A4 inhibitors such as ketoconazole and ritonavir raise exposure; avoid the combination or use the lowest dose available.
- Rifampin, carbamazepine and St. John's wort induce CYP3A4 and can substantially reduce efficacy of a given dose.
- Sertraline and fluvoxamine increase zolpidem concentrations modestly, and combined use raises the reported risk of complex sleep behaviors.

SPECIAL POPULATIONS

- Pregnancy: associated with low birth weight and preterm birth in cohort studies; late exposure can cause neonatal sedation and respiratory depression.
- Lactation: small amounts appear in milk with a short half-life; monitor the infant for sedation and consider dosing after the last feed.
- Pediatrics: not approved under age 18 and a controlled trial in pediatric insomnia showed no benefit with more hallucinations and dizziness.
- Older adults: the AGS Beers Criteria advise avoiding Z-drugs entirely given delirium, falls, fractures and emergency department visits.
- Hepatic impairment: reduce to 5 mg and avoid in severe disease; no dose adjustment is needed for renal impairment.

PRESCRIBING PEARLS

- Women get half the dose of men because they clear zolpidem more slowly and wake more impaired.
- Any episode of sleep-driving or sleepwalking makes zolpidem permanently contraindicated.
- Give on an empty stomach with a full 7-8 hour sleep opportunity or expect a poor result.

References

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NOTE

References follow APA 7th edition style. Dosing, boxed warnings, and interaction data change; confirm every clinical decision against the current FDA prescribing information (DailyMed) and your institution's formulary. This sheet is an educational quick reference and does not replace the full label or clinical judgment.