HYPNOTIC C-IV

Eszopiclone

Lunesta

Cyclopyrrolone Z-drug for sleep onset and maintenance, with six-month efficacy data and a signature metallic taste.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
1-3 mg PO qhs	~6 h (9 h in elderly)	CYP3A4, CYP2E1	~30 min; peak ~1 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 the treatment of insomnia in adults, improving both sleep latency and sleep maintenance in placebo-controlled trials.
- Unlike most hypnotics the label carries no explicit duration limit, and nightly efficacy has been demonstrated over six months of use.
- The 6-hour half-life makes it a reasonable choice when middle-of-the-night awakening rather than sleep onset is the dominant complaint.
- Cognitive behavioral therapy for insomnia remains first line by both American Academy of Sleep Medicine and American College of Physicians guidance.
- Off-label use in insomnia comorbid with depression or generalized anxiety has trial support as an adjunct to antidepressant therapy.
- Not indicated for pediatric insomnia; a controlled pediatric trial in children with ADHD-associated insomnia failed to show benefit.

DOSING & TITRATION

- Adults: start **1 mg PO immediately before bedtime** with at least 7-8 hours of sleep opportunity remaining before planned awakening.
- May increase to 2 mg or **3 mg** if clinically indicated; 3 mg is the labeled maximum and produces the most next-day impairment.
- Older adults or debilitated patients: start at 1 mg and do not exceed **2 mg**, given prolonged half-life and greater sensitivity.
- Severe hepatic impairment: start at 1 mg and do not exceed 2 mg; the same limits apply when a strong CYP3A4 inhibitor is co-prescribed.
- Do not take with or immediately after a heavy or high-fat meal, since delayed absorption blunts the sleep-onset effect.
- Taper stepwise after prolonged nightly use rather than stopping abruptly, since rebound insomnia and withdrawal symptoms can occur.

MECHANISM OF ACTION

- Cyclopyrrolone that acts as a positive allosteric modulator at the benzodiazepine site of GABA-A receptors, enhancing chloride conductance.
- It is the active S-enantiomer of zopiclone and binds a partly different domain than benzodiazepines, though the functional effect is similar.
- Less alpha-1 subunit selectivity than zolpidem, which contributes to a longer duration of action and some anxiolytic effect.
- Sleep architecture is largely preserved with modest reduction of REM latency changes compared with benzodiazepine hypnotics.
- Partial arousal from non-REM sleep with motor activity but no memory encoding underlies the complex sleep behaviors in the boxed warning.

PHARMACOKINETICS

- Rapidly absorbed with peak concentrations near 1 hour; a high-fat meal delays the peak by about an hour and blunts sleep-onset effect.
- Elimination half-life is roughly **6 hours** in adults and lengthens to about 9 hours in older patients, raising next-day carryover risk.
- Oxidized and demethylated by CYP3A4 and CYP2E1 to desmethyl-eszopiclone, which is weakly active, and to an inactive N-oxide.
- Less than 10 percent is excreted unchanged in urine, so no dose adjustment is required for renal impairment at any stage.
- Severe hepatic impairment reduces clearance substantially and requires both a lower starting dose and a lower maximum dose.

ADVERSE EFFECTS

- Unpleasant metallic or bitter taste is the hallmark effect, reported by 8 percent at 1 mg and up to 34 percent at 3 mg, and often limits adherence.
- Headache in about 21 percent, somnolence 10 percent, dizziness 7 percent, dry mouth 7 percent and respiratory infection symptoms.
- Complex sleep behaviors including sleepwalking, sleep-driving and sleep-eating without recall, which mandate immediate permanent discontinuation.
- Next-morning psychomotor and driving impairment, demonstrated at 3 mg even when patients report feeling fully alert.
- Anterograde amnesia, hallucinations, abnormal thinking and behavior changes, plus worsening of depression and suicidal ideation.
- Angioedema and anaphylaxis can occur after the first dose, and respiratory depression is additive with opioids and alcohol.

MONITORING

- Ask directly at each visit about sleepwalking, sleep-driving, nocturnal eating and amnesia for nighttime events.
- Screen for and address sleep apnea, restless legs, alcohol use, chronic pain and untreated mood disorder before or alongside therapy.
- Assess next-morning alertness and warn against driving the following morning after the 3 mg dose in particular.
- Reassess response and continued need within 7-10 days; if insomnia persists beyond 7-10 days, evaluate for a comorbid condition.
- Check the prescription drug monitoring program and screen for substance use disorder before starting this schedule IV hypnotic.

INTERACTIONS & CAUTIONS

- Contraindicated in patients who have experienced a complex sleep behavior on eszopiclone and in known hypersensitivity or prior angioedema.
- Strong CYP3A4 inhibitors such as ketoconazole, ritonavir, clarithromycin and nefazodone roughly double exposure; cap the dose at 2 mg.
- Rifampin, carbamazepine and St. John's wort induce CYP3A4 and can reduce eszopiclone exposure enough to eliminate benefit.
- Additive sedation and respiratory depression with opioids, alcohol, benzodiazepines, gabapentinoids and sedating antihistamines.
- Olanzapine co-administration reduced psychomotor performance in study conditions, so combine sedating psychotropics cautiously.

SPECIAL POPULATIONS

- Pregnancy: limited human data; late third-trimester exposure carries theoretical risk of neonatal sedation and respiratory depression.
- Lactation: it is not known whether eszopiclone is excreted in human milk; monitor the infant for sedation if breastfeeding continues.
- Pediatrics: safety and effectiveness under age 18 are not established and a pediatric trial did not demonstrate efficacy.
- Older adults: the AGS Beers Criteria advise avoiding Z-drugs because of delirium, falls, fractures and motor vehicle crashes.
- Hepatic and renal impairment: cap at 2 mg in severe hepatic disease; no adjustment is required at any level of renal impairment.

PRESCRIBING PEARLS

- The metallic aftertaste is the most common reason patients quit; warn them before the first dose.
- One of the few hypnotics with placebo-controlled nightly efficacy data out to six months.
- Avoid dosing after a heavy meal; delayed absorption defeats the sleep-onset effect entirely.

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.