HYPNOTIC · C-IV

Lemborexant

Dayvigo

Dual orexin receptor antagonist with 12-month efficacy data; outperformed zolpidem ER on sleep maintenance measures.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
5 mg PO qhs (max 10 mg)	17-19 h	CYP3A4, CYP3A5	~30 min; peak 1-3 h

No FDA boxed warning on the current US label.

INDICATIONS

- FDA-approved for the treatment of insomnia characterized by difficulties with sleep onset, sleep maintenance, or both, in adults.
- Efficacy and tolerability were maintained across 12 months in the SUNRISE-2 trial, supporting longer-term use than most hypnotics.
- In SUNRISE-1 it improved objective sleep-onset latency and sleep efficiency more than zolpidem extended release in adults over 55.
- It is a reasonable choice when a patient cannot tolerate Z-drugs or when complex sleep behaviors have already occurred on zolpidem.
- Off-label interest exists in irregular sleep-wake rhythm in Alzheimer disease, where orexin antagonists have preliminary support.
- Contraindicated in narcolepsy, since orexin signaling is already deficient and further blockade worsens cataplexy and sleep attacks.

DOSING & TITRATION

- Adults: **5 mg PO once nightly** immediately before going to bed, with at least 7 hours remaining before planned awakening.
- The dose may be increased to a maximum of **10 mg** once nightly based on response and tolerability after adequate trial at 5 mg.
- With a weak or moderate CYP3A inhibitor, cap the dose at 5 mg nightly; concomitant strong CYP3A inhibitors should be avoided.
- Moderate hepatic impairment: maximum 5 mg nightly; use in severe hepatic impairment is not recommended.
- No dose adjustment is needed for renal impairment at any stage, including severe renal impairment.
- No taper is required on discontinuation, and rebound insomnia and withdrawal are not seen as they are with benzodiazepines.

MECHANISM OF ACTION

- Dual orexin receptor antagonist with competitive binding at both OX1R and OX2R and faster dissociation from OX2R than OX1R.
- Blocks the wake-promoting orexin signal from lateral hypothalamus to histaminergic, noradrenergic and serotonergic arousal nuclei.
- Because it suppresses arousal rather than depressing the CNS globally, sleep architecture is preserved and REM sleep increases.
- No GABA-A activity means no muscle relaxation, no anticonvulsant effect, and less amnesia than benzodiazepine hypnotics produce.
- Orexin deficiency is the pathology of narcolepsy, which explains the contraindication and the sleep paralysis reported on treatment.

PHARMACOKINETICS

- Peak concentrations occur at 1-3 hours; a high-fat meal delays the peak by about 2 hours and lowers peak concentration by 23 percent.
- Elimination half-life is **17-19 hours** and is dose dependent, which is why next-morning residual effects are the dose-limiting issue.
- Metabolized principally by **CYP3A4** with a CYP3A5 contribution; the main metabolite M10 is active but circulates at low levels.
- Excretion is largely fecal at about 57 percent with roughly 29 percent in urine, and less than 1 percent is excreted unchanged.
- Exposure roughly doubles in moderate hepatic impairment, which caps the dose at 5 mg; severe hepatic impairment is not recommended.

ADVERSE EFFECTS

- Somnolence or fatigue in about 7 percent at 5 mg and 10 percent at 10 mg, headache 6 percent, and abnormal dreams or nightmares.
- Next-morning driving impairment demonstrated at the 10 mg dose, so counsel patients about morning activities requiring alertness.
- Sleep paralysis, hypnagogic and hypnopompic hallucinations, and mild cataplexy-like leg weakness reflecting orexin receptor blockade.
- Complex sleep behaviors including sleepwalking and sleep-driving have been reported, and any episode should prompt discontinuation.
- Worsening of depression and suicidal ideation have been reported; assess mood before starting and at each follow-up visit.
- Additive respiratory depression with opioids and alcohol, and caution is warranted in severe obstructive sleep apnea or COPD.

MONITORING

- Assess next-morning alertness and driving safety, particularly at the 10 mg dose and in the first weeks of treatment.
- Ask specifically about sleep paralysis, hallucinations on falling asleep or waking, leg weakness and complex sleep behaviors.
- Screen for depression and suicidal ideation before initiating and at each visit, since worsening mood has been reported.
- Evaluate and treat obstructive sleep apnea, restless legs, alcohol use and chronic pain before or alongside hypnotic therapy.
- Check the prescription monitoring program before prescribing this schedule IV agent and periodically reassess ongoing need.

INTERACTIONS & CAUTIONS

- Concomitant strong CYP3A inhibitors such as ketoconazole, itraconazole and clarithromycin should be avoided altogether.
- Weak and moderate CYP3A inhibitors including fluconazole, verapamil and diltiazem require capping the dose at 5 mg nightly.
- Strong and moderate CYP3A inducers such as rifampin, carbamazepine and efavirenz substantially reduce exposure and efficacy.
- Additive sedation and respiratory depression with opioids, alcohol, benzodiazepines, gabapentinoids and sedating antihistamines.
- Contraindicated in narcolepsy; use caution in patients with compromised respiratory function or severe untreated sleep apnea.

SPECIAL POPULATIONS

- Pregnancy: human data are insufficient and animal studies showed developmental effects; a pregnancy exposure registry is available.
- Lactation: lemborexant is present in animal milk and human data are lacking; monitor a nursing infant for sedation and poor feeding.
- Pediatrics: safety and effectiveness under age 18 are not established and use is not recommended in that age group.
- Older adults: not flagged for avoidance in the AGS Beers Criteria, but the long half-life makes next-day sedation and falls a real concern.
- Hepatic and renal impairment: cap at 5 mg in moderate hepatic disease, avoid in severe; no renal dose adjustment is required.

PRESCRIBING PEARLS

- The only hypnotic here with head-to-head objective superiority over zolpidem ER in older adults.
- A 17-19 hour half-life is the trade-off for maintenance benefit; 10 mg impairs morning driving.
- Contraindicated in narcolepsy, and stop it outright after any complex sleep behavior.

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.