HYPNOTIC C-IV

Daridorexant

Quviviq

Newest dual orexin receptor antagonist, approved 2022; shortest half-life in its class with daytime functioning data.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
25-50 mg PO qhs	~8 h	CYP3A4	~30 min; peak 1-2 h

No FDA boxed warning on the current US label.

INDICATIONS

- FDA-approved in 2022 for the treatment of insomnia characterized by difficulties with sleep onset, sleep maintenance, or both, in adults.
- Pivotal phase 3 trials showed improvement in objective and subjective sleep measures plus daytime functioning at the 50 mg dose.
- Its roughly 8-hour half-life is the shortest among orexin antagonists, which limits next-day carryover relative to lemborexant.
- Reasonable when Z-drugs are contraindicated after a complex sleep behavior or when benzodiazepine exposure should be avoided.
- Off-label interest exists in insomnia comorbid with anxiety or depression, where orexin antagonists are under active study.
- Contraindicated in narcolepsy, since orexin transmission is already deficient and further blockade worsens the disorder.

DOSING & TITRATION

- Adults: **25 or 50 mg PO once nightly** within 30 minutes of going to bed, with at least 7 hours remaining before planned awakening.
- The **50 mg** dose is the labeled maximum and is the dose that carried the daytime functioning benefit in the phase 3 program.
- With a moderate CYP3A4 inhibitor such as verapamil, diltiazem or fluconazole, the maximum recommended dose is 25 mg nightly.
- Concomitant use with strong CYP3A4 inhibitors such as ketoconazole, itraconazole or clarithromycin should be avoided.
- Moderate hepatic impairment: maximum 25 mg nightly; use in severe hepatic impairment is not recommended. No renal adjustment is needed.
- No taper is required on stopping, and neither rebound insomnia nor a withdrawal syndrome has been demonstrated in trials.

MECHANISM OF ACTION

- Dual orexin receptor antagonist that competitively blocks orexin A and orexin B binding at both OX1R and OX2R.
- Suppresses the hypothalamic wake drive to histaminergic, noradrenergic, serotonergic and cholinergic arousal nuclei rather than sedating broadly.
- Sleep architecture is largely preserved with proportional increases across sleep stages, including REM, unlike benzodiazepine hypnotics.
- No activity at GABA-A receptors, so there is no muscle relaxation, no anticonvulsant effect and less amnesia than with Z-drugs.
- Rapid receptor dissociation combined with a short half-life is intended to deliver overnight effect without morning residual blockade.

PHARMACOKINETICS

- Rapidly absorbed with peak concentrations at 1-2 hours and absolute bioavailability of about 62 percent after oral dosing.
- Elimination half-life is roughly **8 hours**, about half that of lemborexant, which is the basis of its lower carryover profile.
- Metabolized almost entirely by **CYP3A4**, accounting for about 89 percent of clearance, with excretion split between feces and urine.
- A high-fat high-calorie meal delays the peak by about 1.3 hours and lowers peak concentration, blunting the sleep-onset effect.
- Exposure roughly doubles in moderate hepatic impairment, which caps the dose; pharmacokinetics are unchanged in renal impairment.

ADVERSE EFFECTS

- Headache in about 6-7 percent and somnolence or fatigue in about 6 percent, with nausea and dizziness less frequent.
- Next-morning residual sleepiness is less than with lemborexant or suvorexant, but driving impairment can still occur at 50 mg.
- Sleep paralysis, hypnagogic and hypnopompic hallucinations, and mild cataplexy-like leg weakness attributable to orexin blockade.
- Complex sleep behaviors including sleepwalking and sleep-driving have been reported and require immediate discontinuation.
- Worsening of depression and suicidal ideation have been reported with hypnotics generally; assess mood before and during treatment.
- Additive respiratory depression with opioids and alcohol, and caution is warranted in severe sleep apnea or advanced COPD.

MONITORING

- Assess next-morning alertness and driving safety after initiation and after any dose increase to 50 mg nightly.
- Ask specifically about sleep paralysis, hallucinations at sleep transitions, leg weakness and any complex sleep behaviors.
- Screen for depression and suicidal ideation before starting and at each follow-up visit during ongoing therapy.
- 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 reassess ongoing need periodically.

INTERACTIONS & CAUTIONS

- Avoid concomitant strong CYP3A4 inhibitors; moderate inhibitors require the reduced maximum dose of 25 mg nightly.
- Strong and moderate CYP3A4 inducers including rifampin, carbamazepine, phenytoin and efavirenz markedly 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 untreated severe sleep apnea.
- No clinically meaningful interaction with citalopram was observed, making combination with an SSRI generally straightforward.

SPECIAL POPULATIONS

- Pregnancy: human data are insufficient; animal studies showed no clear teratogenicity but exposure margins were modest.
- Lactation: daridorexant 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: studied in adults 65 and older with efficacy maintained; it is not among the agents the AGS Beers Criteria flag for avoidance.
- Hepatic and renal impairment: cap at 25 mg in moderate hepatic disease and avoid in severe; no renal dose adjustment is needed.

PRESCRIBING PEARLS

- Shortest half-life of the orexin antagonists at about 8 hours, so less morning carryover.
- The 50 mg dose carried the daytime functioning benefit; 25 mg is mainly a sleep measure dose.
- Like the whole class, absolutely contraindicated in narcolepsy and a schedule IV substance.

References

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U.S. National Library of Medicine. (2022). *Daridorexant*. MedlinePlus. https://medlineplus.gov/druginfo/meds/a622034.html

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.