HYPNOTIC

Ramelteon

Rozerem

Selective melatonin MT1/MT2 agonist for sleep-onset insomnia; not scheduled, not habit forming, and modest in effect.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
8 mg PO qhs	1-2.6 h (M-II 2-5 h)	CYP1A2 (also 2C, 3A4)	~30 min; peak 0.75 h

No FDA boxed warning on the current US label.

INDICATIONS

- FDA-approved for the treatment of insomnia characterized by difficulty with sleep onset in adults, with no limit on treatment duration.
- It is the preferred hypnotic when a patient has a substance use disorder, since it is not a controlled substance and shows no abuse liability.
- The American Academy of Sleep Medicine gives it a weak recommendation for sleep-onset insomnia based on small but consistent latency reductions.
- Off-label for circadian rhythm disorders such as delayed sleep-wake phase and non-24-hour sleep-wake disorder in some practice settings.
- Off-label for delirium prevention in hospitalized older adults, supported by a randomized trial showing reduced delirium incidence.
- It does not meaningfully improve sleep maintenance or total sleep time, so it is a poor choice for middle-of-the-night awakening.

DOSING & TITRATION

- Adults: **8 mg PO within 30 minutes of bedtime**; this is both the recommended and the maximum dose, and higher doses add nothing.
- Do not take with or immediately after a high-fat meal, since delayed absorption undercuts the sleep-onset effect.
- No dose adjustment is required for older adults, though exposure is somewhat higher and effect may be modestly greater.
- Use with caution in mild to moderate hepatic impairment; ramelteon is **contraindicated in severe hepatic impairment**.
- No dose adjustment is needed at any degree of renal impairment, including patients on chronic hemodialysis.
- No taper is required on discontinuation, since ramelteon causes neither physical dependence nor rebound insomnia.

MECHANISM OF ACTION

- Potent selective agonist at melatonin MT1 and MT2 receptors in the suprachiasmatic nucleus, with no measurable affinity for GABA-A receptors.
- MT1 activation attenuates the circadian wake-promoting signal of the suprachiasmatic nucleus, which shortens time to sleep onset.
- MT2 activation shifts circadian phase, providing the rationale for use in delayed sleep-wake phase and shift work disorder.
- Because it does not act on GABA-A, it produces no muscle relaxation, no anticonvulsant effect, no amnesia and no reinforcement.
- The absence of GABAergic action explains why abrupt discontinuation causes neither rebound insomnia nor a withdrawal syndrome.

PHARMACOKINETICS

- Absorbed rapidly with peak levels near 45 minutes, but absolute bioavailability is only about 1.8 percent due to extensive first-pass metabolism.
- Parent half-life is 1-2.6 hours; the active metabolite M-II has a 2-5 hour half-life and circulates at 20-100 times parent concentration.
- Oxidized principally by **CYP1A2**, with minor contributions from CYP2C and CYP3A4, then glucuronidated and excreted mostly in urine.
- A high-fat meal delays the peak by about 45 minutes and raises total exposure, so avoid dosing with or right after a heavy meal.
- Exposure roughly doubles in mild to moderate hepatic impairment and rises much further in severe disease, where it is contraindicated.

ADVERSE EFFECTS

- Somnolence in about 5 percent, dizziness 5 percent, fatigue 4 percent, nausea 3 percent, and worsened insomnia in about 3 percent.
- Effect size is modest, reducing subjective sleep latency by roughly 10-15 minutes, and many patients judge it insufficient.
- Endocrine changes including decreased testosterone and increased prolactin, with reports of amenorrhea, galactorrhea and reduced libido.
- Complex sleep behaviors, hallucinations and abnormal thinking have been reported in postmarketing use, though there is no boxed warning.
- Anaphylaxis and angioedema, including tongue and throat swelling, can occur after the first dose and preclude any rechallenge.
- Worsening depression and suicidal ideation have been reported; monitor patients with a history of mood disorder after starting.

MONITORING

- Reassess sleep latency and total sleep time after 7-10 nights; failure to improve should prompt evaluation for a comorbid disorder.
- Check prolactin and testosterone if amenorrhea, galactorrhea, decreased libido or fertility problems emerge during therapy.
- Assess for depression and suicidal ideation at follow-up, since worsening mood has been reported with hypnotic therapy generally.
- Screen for and treat obstructive sleep apnea, restless legs, alcohol use and untreated mood disorder before or alongside treatment.
- No routine laboratory monitoring is otherwise required, and no prescription monitoring program check is needed since it is not scheduled.

INTERACTIONS & CAUTIONS

- Concurrent **fluvoxamine is contraindicated**; strong CYP1A2 inhibition raises ramelteon exposure roughly 190-fold and produces marked sedation.
- Other CYP1A2 inhibitors including ciprofloxacin and cimetidine raise levels meaningfully and should be combined only with caution.
- Rifampin and other strong inducers reduce exposure by about 80 percent and can abolish any clinical benefit.
- Fluconazole and ketoconazole increase exposure modestly through CYP2C9 and CYP3A4 inhibition; monitor for excess sedation.
- Alcohol produces additive psychomotor impairment; also contraindicated in patients with a history of angioedema on ramelteon.

SPECIAL POPULATIONS

- Pregnancy: human data are insufficient; animal studies showed developmental toxicity at high doses, so use only if clearly needed.
- Lactation: it is not known whether ramelteon is excreted in human milk, so monitor the nursing infant for sedation and poor feeding.
- Pediatrics: safety and effectiveness are not established under age 18, and pediatric trials in neurodevelopmental disorders were negative.
- Older adults: not flagged for avoidance by the AGS Beers Criteria, unlike benzodiazepines and Z-drugs, making it a reasonable geriatric option.
- Hepatic impairment: contraindicated in severe disease and used cautiously in mild to moderate; no renal adjustment is required.

PRESCRIBING PEARLS

- Not a controlled substance and not habit forming, so it is the hypnotic of choice in addiction.
- Fluvoxamine is an absolute contraindication; it raises ramelteon levels roughly 190-fold.
- Real effect is about 10-15 minutes of sleep latency, so set expectations before prescribing.

References

Hatta, K., Kishi, Y., Wada, K., Takeuchi, T., Odawara, T., Usui, C., & Nakamura, H. (2014). Preventive effects of ramelteon on delirium: A randomized placebo-controlled trial. *JAMA Psychiatry, 71*(4), 397-403. https://doi.org/10.1001/jamapsychiatry.2013.3320

Qaseem, A., Kansagara, D., Forciea, M. A., Cooke, M., & Denberg, T. D. (2016). Management of chronic insomnia disorder in adults: A clinical practice guideline from the American College of Physicians. *Annals of Internal Medicine, 165*(2), 125-133. https://doi.org/10.7326/M15-2175

Sateia, M. J., Buysse, D. J., Krystal, A. D., Neubauer, D. N., & Heald, J. L. (2017). Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: An American Academy of Sleep Medicine clinical practice guideline. *Journal of Clinical Sleep Medicine, 13*(2), 307-349. https://doi.org/10.5664/jcsm.6470

Stahl, S. M. (2021). *Stahl's essential psychopharmacology* (5th ed.). Cambridge University Press.

Takeda Pharmaceuticals America. (2023). *Rozerem (ramelteon) [Prescribing information]*. U.S. Food and Drug Administration. https://dailymed.nlm.nih.gov/dailymed/

U.S. National Library of Medicine. (2021). *Ramelteon*. MedlinePlus. https://medlineplus.gov/druginfo/meds/a605038.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.