**RAMELTEON**

**Brands** • Rozerem 
*see index for additional brand names*

**Generic?** No

**Class**
- Neuroscience-based Nomenclature: 
  - melatonin receptor agonist (Mel-RA) 
  - Melatonin 1 and 2 receptor agonist

**Commonly Prescribed for** 
(bold for FDA approved)
- Insomnia (difficulty with sleep onset) 
- Primary insomnia 
- Chronic insomnia 
- Transient insomnia 
- Insomnia associated with shift work, jet lag, or circadian rhythm disturbances

**How the Drug Works**
- Binds selectively to melatonin 1 and melatonin 2 receptors as a full agonist

**How Long Until It Works**
- Generally takes effect in less than an hour

**If It Works**
- Reduces time to sleep onset 
- Increases total sleep time 
- May improve quality of sleep

**If It Doesn’t Work**
- If insomnia does not improve after 7–10 days, it may be a manifestation of a primary psychiatric or physical illness such as obstructive sleep apnea or restless leg syndrome, which requires independent evaluation 
- Increase the dose 
- Improve sleep hygiene 
- Switch to another agent

**Best Augmenting Combos for Partial Response or Treatment Resistance**
- Generally, best to switch to another agent 
- Eszopiclone, zolpidem 
- Trazodone 
- Agents with antihistamine actions (e.g., diphenhydramine, TCAs)

**Tests**
- None for healthy individuals 
- For patients presenting with unexplained amenorrhea, galactorrhea, decreased libido, or problems with fertility, could consider measuring prolactin and testosterone levels

**SIDE EFFECTS**

**How Drug Causes Side Effects**
- Actions at melatonin receptors that carry over to the next day could theoretically cause daytime sedation, fatigue, and sluggishness, but this is not common

**Notable Side Effects**
- ✽ Sedation 
- ✽ Dizziness 
- ✽ Fatigue 
- ✽ Headache

**Life-Threatening or Dangerous Side Effects**
- Respiratory depression, especially when taken with other CNS depressants in overdose 
- Rare angioedema

**Weight Gain**
- Reported but not expected

**Sedation**
- Many experience and/or can be significant in amount 
- May experience sedation or sleepiness immediately after dosing, but not commonly after awakening from a night’s sleep

**What to Do About Side Effects**
- Wait 
- To avoid problems with memory, only take ramelteon if planning to have a full night’s sleep 
- Lower the dose 
- Switch to a non-benzodiazepine sedative hypnotic

**Best Augmenting Agents for Side Effects**
- Many side effects cannot be improved with an augmenting agent
### Pharmacokinetics
- Metabolized predominantly by CYP450 1A2
- CYP450 3A4 and 2C are also involved in metabolism of ramelteon
- Mean elimination half-life of parent drug 1–2.6 hours
- Mean elimination half-life of major metabolite, M-II, is 2–5 hours

### Drug Interactions
- Inhibitors of CYP450 1A2, such as fluvoxamine, could increase plasma levels of ramelteon
- Inducers of CYP450, such as rifampin, could decrease plasma levels of ramelteon
- Inhibitors of CYP450 3A4, such as ketoconazole, could increase plasma levels of ramelteon
- Inhibitors of CYP450 2C9, such as fluconazole, could increase plasma levels of ramelteon
- Exercise caution if combining with alcohol
- No interaction with fluoxetine (CYP450 2D6 inhibitor)

### Other Warnings/Precautions
- Insomnia may be a symptom of a primary disorder, rather than a primary disorder itself
- Use only with extreme caution in patients with impaired respiratory function or obstructive sleep apnea
- Ramelteon should only be administered at bedtime
- May decrease testosterone levels or increase prolactin levels, but the clinical significance of this is unknown
- Patients who develop angioedema after treatment with ramelteon should not be rechallenged

### Do Not Use
- With fluvoxamine
- In patients with severe hepatic impairment
- If there is a proven allergy to ramelteon

### SPECIAL POPULATIONS

#### Renal Impairment
- Dose adjustment not generally necessary
Hepatic Impairment
- Use with caution in patients with moderate hepatic impairment
- Not recommended for use in patients with severe impairment

Cardiac Impairment
- Dosage adjustment may not be necessary

Elderly
- No adjustment necessary
- Greater absorption and higher plasma drug concentrations but no increase in side effects

Children and Adolescents
- Safety and efficacy have not been established

Pregnancy
- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLL or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women

Breast Feeding
- Unknown if ramelteon is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
✿ Recommended either to discontinue drug or bottle feed

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages
- Those who require long-term treatment
- Those who need a hypnotic but have a past history of substance abuse

Potential Disadvantages
- Possibly for circadian rhythm disturbances

Primary Target Symptoms
- Time to sleep onset

Pearls
- First in a new class of agents, chronohypnotics, that act upon circadian rhythms by stimulating melatonin receptors in the brain’s “pacemaker,” namely the suprachiasmatic nucleus
- Theoretically, stimulation of melatonin 1 receptors mediates the suppressive effects of melatonin on the suprachiasmatic nucleus
- Theoretically, stimulation of melatonin 2 receptors mediates the phase shifting effect of melatonin
- Ramelteon may act by promoting the proper maintenance of circadian rhythms underlying a normal sleep-wake cycle
- Thus, ramelteon may also prove effective for treatment of circadian rhythm disturbances such as shift work sleep disorder and jet lag
- Lack of actions on GABA systems, which may be related to lack of apparent abuse liability
- Only approved hypnotic agent that is not scheduled and is considered to have no abuse liability
- No evidence that ramelteon worsens apnea/hypopnea index in COPD or in obstructive sleep apnea, but not recommended in severe cases
✿ May be preferred over benzodiazepines because of its rapid onset of action, short duration of effect, and safety profile
- Rebound insomnia does not appear to be common
- May have fewer carryover side effects than some other sedative hypnotics
Suggested Reading


