



New Drug Update

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Rozerem® (ramelteon)

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Introduction

Rozerem® (ramelteon [rah MEL tee on]) was FDA approved on July 22, 2005. Ramelteon received an indication for the treatment of insomnia due to prolonged sleep onset. Ramelteon is the first approved hypnotic that is not classified as a controlled substance. Rozerem® is currently available in an 8 mg tablet.

Therapeutic Recommendation

Ramelteon is a MT1 and MT2 melatonin receptor agonist indicated for the treatment of insomnia from prolonged sleep onset. Ramelteon is the first FDA approved treatment for insomnia that is not a controlled substance, and is approved for long term use. The drug has been compared to placebo in randomized double blind studies and has shown efficacy in reducing onset time of persistent sleep. There have been no comparative studies with other sleep agents. Side effects are mild, and consist of dizziness, nausea, headache, insomnia, and somnolence. There is no evidence of next-day residual effects after use. Ramelteon is a new approach to treating insomnia as it is the only FDA approved drug that is a melatonin ago-

nist. Ramelteon is a treatment option with low risk of side effects or dependence. Ramelteon may be very helpful in treating insomnia in the elderly due to its safe side effect profile. The use of ramelteon is not limited to short term use, making it a therapeutic option for those with chronic insomnia. Ramelteon may also be a useful agent in treating insomnia in patients with a high risk of abuse potential. Ramelteon would be an appropriate first line agent for treating insomnia in these patient populations before attempting treatment with a possibly addicting agent such as zolpidem or a benzodiazepine.

Dosing and Administration

The recommended dose of ramelteon is 8 mg taken 30 minutes before bedtime. Ramelteon should not be taken with or shortly after a fatty meal which could delay the onset of action and decrease the maximum concentration achieved. The only recommended dosage is 8 mg before bedtime, however in clinical trials 16 mg was also used.

Contraindications

Ramelteon is contraindicated in patients with a hypersensitivity to ramelteon or any components of the formulation. Ramelteon should not be used in patients with severe hepatic impairment. Ramelteon should not be used while breast feeding.

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Cost Comparison

Medication/Dose	Cost*		
	CVS	Kroger	Target
Rozerem® 8 mg bedtime	92.79	99.19	84.99
Lunesta® 2 mg bedtime	108.99	129.49	108.49
Ambien® 10 mg bedtime	97.59	125.59	105.99
Sonata® 10 mg bedtime	114.59	118.99	99.49
Restoril® 15 mg bedtime	135.99	150.29	119.49
Temazepam 15 mg bedtime	12.55	10.19	16.99
Serax® 15 mg bedtime	49.49	51.39	45.49
Oxazepam 15 mg bedtime	25.39	18.69	24.99
Ativan® 2.0 mg bedtime	73.29	70.89	67.99
Lorazepam 2.0 mg bedtime	31.49	27.29	30.99
Halcion® 0.25 mg bedtime	54.79	60.39	50.99
Triazolam 0.25 mg bedtime	21.29	18.59	20.49
Prosom® 2 mg bedtime	56.39	62.39	49.99
Estazolam 2 mg bedtime	35.29	30.89	34.49
Dalmane® 15 mg bedtime	55.89	52.59	48.49
Flurazepam 15 mg bedtime	15.79	12.69	7.99
Doral® 15 mg bedtime	119.68	139.49	118.99

*Cost to patient for typical 30-day supply

Warnings

Ramelteon has not been studied in patients with severe sleep apnea or severe COPD and it is not recommended for these populations.

Patients are advised not to consume alcohol in combination with ramelteon.

Patients should use caution when driving or operating heavy machinery after taking ramelteon.

Due to reported cognitive and behavior changes associated with the use of hypnotics, ramelteon should be used with caution in depressed patients as depression could worsen.

Special Populations

Pediatric: Ramelteon is not recommended in children under 18 as safety and effectiveness have not been established in this population.

Geriatric: Dosage adjustment is not required in the elderly. In clinical trials safety and efficacy were comparable in patients over 65 years of age to patients under 65 years.

Gender: Dosage adjustment based on gender is not needed.

Renal Impairment: No dosage adjustment is required in patients with any degree of renal impairment, or for patients who require chronic hemodialysis. No effects on C_{max} or AUC of parent drug or M-II were seen in any of the treatment groups.

Hepatic Impairment: Caution is advised in patients with mild to moderate hepatic impairment. In clinical trials exposure to ramelteon increased almost 4-fold in subjects with mild hepatic impairment at a 16 mg dose. Ramelteon should not be used in patients with severe hepatic failure. The manufacturer does not specify what is used to determine the degree of hepatic impairment.

Pregnancy: Ramelteon is FDA pregnancy category C. No studies have been done with pregnant humans. Ramelteon should only be used in pregnancy if the expected benefit to the mother is greater than the potential risk to the fetus.

Lactation: Ramelteon is secreted into the milk of lactating rats. It is unknown if it is excreted into human milk. The use of ramelteon is not recommended in nursing mothers.



...A Primary Care Physician's Guide to Newly Released Medications...

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Drug Interactions

Ramelteon is metabolized by the cytochrome P450 system, primarily the CYP1A2 isoenzyme. Co-administration of ramelteon with CYP1A2 inhibitors, particularly fluvoxamine, can lead to an increase in ramelteon concentration. Administration with rifampin, a CYP1A2 inducer leads to a decrease in ramelteon concentration. Ramelteon is metabolized to a minor degree by CYP2C and CYP3A4 enzymes as well. Fluconazole and ketoconazole are strong inhibitors of these enzymes respectively, and co-administration will lead to an increased ramelteon concentration. An additive effect is seen when taken with ethanol. Increased sedation may occur.

Adverse Effects

In clinical trials the adverse effects of ramelteon were mild. The most common side effects reported were somnolence, dizziness, nausea, fatigue, headache, and insomnia. The discontinuation rate as a result of these side effects was 5%, and no single side effect caused over a 0.8% discontinuation rate. In controlled trials, 2% of enrolled subjects discontinued taking the placebo due to adverse effects.

Pharmacology

Mechanism of Action: Ramelteon is a highly selective, potent MT1 and MT2 melatonin receptor agonist. The MT1 receptor is believed to regulate sleepiness, while the MT2 receptor helps the body shift between day and night by maintaining a normal circadian rhythm. Ramelteon has a greater affinity for MT1 resulting in its ability to induce sleep.

Absorption/Distribution: Ramelteon's oral absolute bioavailability is only 1.8% due to first pass metabolism. Absorption is rapid with peak concentration occurring at approximately 45 minutes. A high fat meal can decrease ramelteon's oral absorption, decreasing the C_{max} by 22% and should be avoided during or immediately before the dose. Ramelteon is 82% protein bound, most of which is bound to albumin. After intravenous administration, ramelteon has a mean volume of distribution of 73.6 L. This indicates substantial tissue distribution.

Metabolism/Excretion: Ramelteon is primarily metabolized through oxidation. The major isoenzyme in the CYP450 family involved in ramelteon's metabolism is CYP1A2. CYP3A4 and the CYP2C subfamily are involved to a smaller degree. Ramelteon has only one active metabolite, M-II. M-II has just one tenth and one fifth the binding affinity of ramelteon for the human MT1 and MT2 receptors, respectively. M-II is 17-25 times less potent than ramelteon. Ramelteon is 84% renally eliminated and 4% fecally eliminated. However, less than 0.1% was eliminated as the parent compound. Repeat once daily dosing does not lead to significant accumulation because of the short elimination t_{1/2} of 1 – 2.6 hours. Serum concentrations of ramelteon and the metabolite M-II are undetectable at 24 hours.

Patient Information

1. Take this medication within 30 minutes before going to bed.
2. It is recommended to not take this medication with or shortly after eating a high fat meal.
3. Do not drive or operate heavy machinery while taking ramelteon.
4. Side effects are generally rare and mild, but may include dizziness, nausea, headache, insomnia, and somnolence.
5. Do not take more than one 8 mg tablet a night.

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Zostavax® (Zoster Vaccine Live Oka/Merck)

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Introduction

Zostavax® [Zoster Vaccine Live (Oka/Merck)] is a live, attenuated vaccine from the Oka/Merck strain of varicella-zoster virus. Administration of the vaccine stimulates active cell-mediated immunity to disease caused by the varicella-zoster virus (VZV). The Federal Drug Administration (FDA) granted Zostavax® approval on May 25, 2006 for the prevention of herpes zoster (shingles) in individuals 60 years of age and older. It is not indicated for the treatment of herpes zoster or postherpetic neuralgia (PHN). In the Shingles Prevention Study (SPS), Zostavax® reduced the incidence of PHN by 67% and shingles by 51%. Unlike the pneumococcal and influenza vaccines which are covered under Medicare Part B, Zostavax is the first new vaccine to be covered under Medicare Part D.

Therapeutic Recommendations

Herpes zoster is caused by the varicella-zoster virus, which is the same virus that causes chickenpox. After a person has had chickenpox, the virus lays dormant in the dorsal root or cranial sensory ganglia. The cause of reactivation is not fully understood, but it may be due to stress, a weakened immune system, or increasing age. Herpes zoster (also known as "shingles") usually presents as a painful, unilateral, vesicular eruption that occurs in a dermatomal distribution. PHN is a chronic pain syndrome that typically persists in the same dermatomal distribution where the eruption occurred, and may last for months or years. The pain associated with PHN can be disabling, and treatment strategies for acute shingles eruptions and PHN have typically focused on reducing both the occurrence of PHN and the duration or severity of the PHN itself. Com-

plications occur in almost 50% of older adults with shingles, making PHN a significant clinical problem.

Results from the Shingles Prevention Study demonstrated that Zostavax® reduced morbidity from herpes zoster and postherpetic neuralgia in adults at least 60 years of age. The study enrolled 38,546 adults that were at least 60 years old, and either had a past history of chickenpox or had been living in the United States for at least 30 years. A total of 957 cases of herpes zoster were confirmed: 315 among vaccine recipients (none of the zoster virus isolates were felt to be the vaccine strain) and 642 among placebo recipients (5.42 cases vs. 11.12 cases per 1000 person-years, respectively; $p < 0.001$). Vaccine efficacy with respect to the incidence of herpes zoster was 51.3% (95% confidence interval, 44.2 to 57.6). A total of 107 cases of postherpetic neuralgia were confirmed: 27 among vaccine recipients and 80 among placebo recipients (0.46 case vs. 1.38 cases per 1000 person-years, respectively; $p < 0.001$). Vaccine efficacy with respect to the incidence of postherpetic neuralgia was 66.5% (95% confidence interval, 47.5 to 79.2). It is worth noting that in this study, the primary effect of the vaccine in reducing incidence and severity of PHN was in the primary reduction of cases of shingles. Also, the vaccine effectiveness was much higher in the age group 60-69 than in the over 70 age group (63.9% vs. 37.6% reductions respectively, $P < 0.001$).

Clinical studies have demonstrated Zostavax® efficacy for 4 years, but the duration of prophylaxis has not been established. The need for revaccination has not been determined to date. The use of Zostavax® in individuals 50 to 59 years of age is currently being evaluated to determine if both safety and efficacy exist in this population as well.

Dosing and Administration

Zostavax® is administered as a single dose subcutaneous injection. It is supplied as a lyophilized powder that must be reconstituted using a sterile, preservative-free diluent that is supplied with the product. Before reconstitution, the vial should be stored in the freezer. Each 0.65-mL dose contains a minimum of 19,400 plaque-forming units of the Oka/Merck strain of VZV when reconstituted. The vaccine must be administered within 30 minutes after reconstitution to prevent loss of potency.

Cost

The cost of a single-dose vial of vaccine with sterile diluent is approximately \$150. A news release by Merck stated that the vaccine would be available free of charge for low-income, uninsured adults through a new patient assistance program. Also, some Medicare Part D plans are covering this vaccine.

Warnings/Precautions

Individuals who are immunosuppressed may be at greater risk of experiencing a more extensive vaccine-associated rash or disseminated disease when vaccinated with a live, attenuated vaccine.

There is a theoretical risk of transmitting the vaccine virus to close contacts that are varicella-susceptible (individuals who haven't had chickenpox). Although there is very limited data that suggest it may be safe to administer Zostavax® to older adult patients without definite prior primary varicella infections, it may be appropriate to consider antibody testing in those older adult patients when the available history is limited. Similarly, and in large part because the history of childhood infections can be especially difficult to obtain for older adult patients, the vaccine is approved for those adults over age 60 who have histories of previous zoster eruptions.

Zostavax® should not be administered to individuals with a history of anaphylactic reaction to topically or systemically administered neomycin.

This vaccination should not be given to children, pregnant women, or women who may become pregnant within 3 months of receiving the vaccine.

Zostavax® is not interchangeable with Varivax®, the vaccination against primary varicella infection (chickenpox) for individuals 12 months of age and older. In fact, the dose of Zostavax is approximately 14 times more plaque forming units than Varivax, primarily because it is felt that larger doses are needed to achieve the desired increase in cell-mediated immunity.

Avoid administration to individuals with acute febrile illness (e.g. fever > 101.3°F).

This vaccine is not currently approved for use in individuals who are less than 60 years of age.

Contraindications

Zostavax® is contraindicated in individuals with an allergy to any of its ingredients (including gelatin and neomycin), a history of primary or acquired immunodeficiency, have active untreated tuberculosis, are on

immunosuppressive therapy (including prednisone taken at doses equivalent to either 2 mg/kg of body weight or a total of 20 mg/day for 2 weeks or longer), or who are or may be pregnant.

Special Populations

Renal Impairment: No adjustment is required.

Hepatic Impairment: No adjustment is required.

Geriatrics: This is the target population for Zostavax® use. The median age of subjects in the largest clinical study of Zostavax® was 69 years of age.

Pediatrics: Zostavax® should not be used in children. This vaccine is not interchangeable with Varivax®, the vaccination against varicella in individuals 12 months of age and older.

Pregnancy and Lactation: Zostavax® is pregnancy category C. It should not be used in pregnant females, and pregnancy should be avoided for 3 months following administration. Caution is advised if Zostavax® is administered to a nursing woman. It is not known if the vaccine is excreted into breast milk.

Drug Interactions

Concurrent administration of Zostavax® and other vaccines, and concurrent administration of Zostavax® with antiviral medications known to be effective against VZV have not been evaluated. Concurrent administration with immunosuppressant drugs may result in decreased vaccine effect and increased risk of varicella disease. Individuals who have received 20 mg/day or more of prednisone or other high dose steroids for 2 weeks or longer should delay vaccination for 3 months after discontinuation of the steroid. Decreased vaccine effect may also be seen if given within 5 months of immune globulins.

Adverse Reactions

The most common side effects observed during clinical studies were redness, pain, swelling, itching, warmth, and bruising at the injection site, and headache. Subjects vaccinated with Zostavax® experienced a significantly greater incidence of vaccine-related injection-site adverse effects (48%) versus subjects who received placebo (17%). Incidence of headache was 1.4% for the Zostavax® group versus 0.8% in the placebo group.

Pharmacology

Mechanism of Action: The mechanism by which Zostavax® protects against herpes zoster and its complications is thought to be by boosting VZV-specific cell mediated immunity. VZV-specific immunity is believed to progressively decline with age, leading to an increased risk of developing herpes zoster.

Duration of Effect: Clinical studies have demonstrated its efficacy for 4 years, but the duration of prophylaxis has not been established. The need for revaccination has not been determined.

Patient Information

1. Zostavax® is a vaccine to help prevent herpes zoster (shingles) in adults 60 years of age or older who have had chickenpox or the vaccine for chickenpox.
2. This vaccine cannot be used to treat herpes zoster once you have it.
3. Zostavax® reduces the risk of developing herpes zoster by about 50%.
4. If you do get herpes zoster after receiving Zostavax®, the vaccine may prevent or reduce the nerve pain that can follow shingles.
5. The most common side effects of Zostavax® are injection-site reactions such as redness, pain, swelling, itching, warmth, and bruising. Headache is another common adverse effect from the injection.
6. Inform your physician or healthcare provider if you have any of these conditions: cancer, fe-

ver or infection, herpes zoster or shingles, TB (tuberculosis), HIV infection or AIDS, immune system problems, an allergy to neomycin, gelatin, or other components of the vaccine, if you are currently taking prednisone or other medications that affect the immune system, or if you are pregnant, trying to become pregnant, or are breast-feeding.

7. Inform your physician or healthcare provider if you may be in close contact with someone who may be pregnant and has not had chickenpox or received the chickenpox vaccine, or someone with a weakened immune system.
8. This vaccination will be administered by your physician or healthcare provider as an injection under the skin on your upper arm.

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