

PHYSICIAN'S Money Digest®

THE PRACTICAL GUIDE TO PERSONAL FINANCE

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Will Fortune Smile on

Your 2006 Stock Portfolio?



*Balance & Reason,
a Prescription for
Financial
Health*

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Will You Retire as Comfortably as You Want?

Most physicians who expect to retire comfortably are headed for a rude awakening. It's going to take a lot more money than you think to retire at the level you

had intended. Not only will living expenses cost more than you think, but your assets probably will not grow as fast as you would like.

Consider these figures. If you current-

ly require monthly living expenses of \$10,000, you will need an additional \$5000 each month in 10 years, based on a modest 3% inflation rate every year. Given an after-tax annual return of 3%

to 5%, it will take \$5 million to \$6 million in liquid assets for most doctors to retire comfortably. This amount excludes nonliquid assets that tend to be

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FIRST
IN A NOVEL
CLASS OF
SLEEP
AGENTS

NON SCHEDULED ROZEREM— ZERO

EVIDENCE OF ABUSE OR DEPENDENCE

Clinical studies show no evidence of potential abuse,* dependence, or withdrawal

- **First and only**—nonscheduled prescription insomnia medication...not a controlled substance and approved for long-term use
- **First and only**—prescription insomnia medication that targets the normal sleep-wake cycle
- **First and only**—prescription insomnia medication with no evidence of abuse potential in clinical studies
- **First and only**—prescription insomnia medication that does not act by CNS depression
- **Promote sleep with Rozerem**—patients who took Rozerem fell asleep faster than those who took placebo

Please visit www.rozerem.com

*A randomized, single-center, double-blind, dose-titration study (N=6) and a single-center, randomized, double-blind, placebo-controlled crossover study (N=14) specifically assessed the abuse liability of Rozerem in patients with a history of substance abuse.

Rozerem is indicated for the treatment of insomnia characterized by difficulty with sleep onset. Rozerem can be prescribed for long-term use. Rozerem should not be used in patients with hypersensitivity to any components of the formulation, severe hepatic impairment, or in combination with fluvoxamine. Failure of insomnia to remit after a reasonable period of time should be medically evaluated, as this may be the result of an unrecognized underlying medical disorder. Hypnotics should be administered with caution to patients exhibiting signs and symptoms of depression. Rozerem has not been studied in patients with severe sleep apnea, severe COPD, or in children or adolescents. The effects in these populations are unknown. Exercise caution if consuming alcohol in combination with Rozerem. Rozerem has been associated with decreased testosterone levels and increased prolactin levels. Health professionals should be mindful of any unexplained symptoms possibly associated with such changes in these hormone levels. Rozerem should not be taken with or immediately after a high-fat meal. Rozerem should be taken within 30 minutes before going to bed and activities confined to preparing for bed. The most common adverse events seen with Rozerem that had at least a 2% incidence difference from placebo were somnolence, dizziness, and fatigue.

Please see adjacent Brief Summary of Prescribing Information.

Rozerem[™]
ramelteon 8-mg tablets
Proven for sleep.
Nonscheduled for added safety.

Rozerem is a trademark of Takeda Pharmaceutical Company Limited and used under license by Takeda Pharmaceuticals North America, Inc.

included when calculating an individual's total net worth. Physicians must also factor additional health expenses into their future monthly income.

In addition to underestimating their monthly needs, many investors tend to overestimate their future portfolio returns, and many think their portfolio

will earn annual after-tax investment returns of 15% or more, which is unrealistic. As physician-investors near retirement, their portfolio allocations should focus on volatility rather than growth. Historically, the annual rate of return for bonds is 5% to 6%, and stocks earn 9% annually before taxes—averages that are

unlikely to change much in the future.

Very few portfolios avoid the occasional losing streak. Although an aggressive investor may make 50% in a year when the stock market only gains 8%, they may lose 50% the next year when their speculations crash. Despite this loss, the investor figures that they broke

even over the 2-year span, which is not the outcome they had hoped for, but certainly not a disaster. Yet what the investor does not realize is that the time required to make up for a single losing year is far longer than expected.

In order to reach the comfortable retirement you want, you must form a team of competent advisors. An investment advisor will help construct various retirement scenarios, determine necessary annual contributions, and manage assets within your personal risk tolerance. While there is no one right investment advisor for everyone, you certainly want to know that you, your advisor, and the other members of your team are all on the same page. Advisors with large amounts of money under their management can seem like a safe choice, but the more money a manager takes in, the harder it is to deliver performance above broad market returns. While typically not a physician's first consideration in choosing an investment advisor, a record of avoiding large losses may be the most important aspect of an advisor's resume.

Investors must always keep in mind that without safeguarding their investible asset base, there is no opportunity for future returns. In most years, it's better to have a 15% return with only 30% of your capital at risk rather than risking 100% of your capital with a 20% return. That's because if a natural disaster, act of terrorism, currency devaluation, interest rate or inflation spike, or any other event causes a market tremor, the portfolio with the least capital at risk is best insulated.

Seek out ways to introduce undervalued assets and additional income into your retirement plan. Many physicians own their practice's building with a low cost basis, which can be purchased and incorporated into their retirement plan. This strategy shelters the income as well as the proceeds if the building is sold. Often, debt on various assets can be financed by a pension plan, which generates tax-free interest that is nonetheless deductible. If you and your advisory team review your assets and come up with a feasible retirement plan, the future you want will be possible. ■

Steven Holt Abernathy is principal and chairman of The Abernathy Group in New York, NY. The organization provides wealth management and financial services to medical professionals. It has been ranked the top money manager in the nation 8 times in the past 12 years by Nelson's. Mr. Abernathy welcomes questions or comments at 212-293-3469 or sabernathy@abbygroup.com. For more information, visit www.abernathyfinancial.com.



Rozerem
gabapentin

Brief Summary of Prescribing Information

05-1144

Rozerem™
 (gabapentin) Tablets

INDICATIONS AND USAGE
 Rozerem is indicated for the treatment of insomnia characterized by difficulty with sleep onset.

CONTRAINDICATIONS
 Rozerem is contraindicated in patients with a hypersensitivity to gabapentin or any components of the Rozerem formulation.

WARNINGS
 Sleep stage disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after a reasonable period of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia, or the emergence of new cognitive or behavioral abnormalities, may be the result of an unrecognized underlying psychiatric or physical disorder and requires further evaluation of the patient. As with other hypnotics, exacerbation of insomnia and emergence of cognitive and behavioral abnormalities were seen with Rozerem during the clinical development program.

Rozerem should not be used by patients with severe hepatic impairment.

Rozerem should not be used in combination with fluvoxamine (see **PRECAUTIONS: Drug Interactions**).

A variety of cognitive and behavior changes have been reported to occur in association with the use of Rozerem. In primarily depressed patients, worsening of depression, including suicidal ideation, has been reported in association with the use of Rozerem.

Patients should avoid engaging in hazardous activities that require concentration (such as operating a motor vehicle or heavy machinery) after taking Rozerem.

After taking Rozerem, patients should confine their activities to those necessary to ensure their bed.

PRECAUTIONS

General
 Rozerem has not been studied in subjects with severe sleep apnea or severe COPD and is not recommended for use in those populations. Patients should be advised to exercise caution if they consume alcohol in combination with Rozerem.

Use in Adolescents and Children
 Rozerem has been associated with an effect on reproductive hormones in adults, e.g. decreased testosterone levels and increased prolactin levels. It is not known what effect chronic or even short-term use of Rozerem may have on the reproductive axis in developing humans (see **Preclinical Use**).

Information for Patients
 Patients should be advised to take Rozerem within 30 minutes prior to going to bed and should confine their activities to those necessary to prepare for bed.

Patients should be advised to avoid engaging in hazardous activities (such as operating a motor vehicle or heavy machinery) after taking Rozerem.

Patients should be advised that they should not take Rozerem with or immediately after a high fat meal.

Patients should be advised to consult their health care provider if they experience worsening of insomnia or any new behavioral signs or symptoms of concern.

Patients should consult their health care provider if they experience one of the following: cessation of menses or galactorrhea in females, decreased libido, or problems with fertility.

Laboratory Tests
 No standard monitoring is required.

For patients presenting with unexplained anemia, galactorrhea, decreased libido, or problems with fertility, assessment of prolactin levels and testosterone levels should be considered as appropriate.

Drug Interactions
 Rozerem has a highly variable linear-subject pharmacokinetic profile (approximately 100% coefficient of variation in C_{max} and AUC). As noted above, CYP1A2 is the major isozyme involved in the metabolism of Rozerem. The CYP2C8 isozyme and CYP2A6 isozymes are also involved to a minor degree.

Effects of Other Drugs on Rozerem Metabolism
 Fluvoxamine (strong CYP1A2 inhibitor): When fluvoxamine 100 mg twice daily was administered for 3 days prior to single-dose oral administration of Rozerem 16 mg and fluvoxamine, the AUC_{0-24} for Rozerem increased approximately 150-fold, and the C_{max} increased approximately 70-fold, compared to Rozerem administered alone. Rozerem should not be used in combination with fluvoxamine (see **WARNINGS**). Other less potent CYP1A2 inhibitors have not been adequately studied. Rozerem should be administered with caution to patients taking strong CYP1A2 inhibitors.

Rifampin (strong CYP enzyme inducer): Administration of rifampin 600 mg once daily for 11 days resulted in a mean decrease of approximately 80% (40% to 90%) in total exposure to Rozerem and metabolite M-II, (both AUC_{0-24} and C_{max}) after a single 32 mg dose of Rozerem. Efficacy may be reduced when Rozerem is used in combination with strong CYP enzyme inducers such as rifampin.

Ketozazole (strong CYP2A6 inhibitor): The AUC_{0-24} and C_{max} of Rozerem increased by approximately 94% and 50%, respectively, when a single 16 mg dose of Rozerem was administered on the fourth day of ketozazole 200 mg twice daily administration, compared to administration of Rozerem alone. Similar increases were seen in M-II pharmacokinetic variables. Rozerem should be administered with caution in subjects taking strong CYP2A6 inhibitors such as ketozazole.

Fluoxetine (strong CYP2D6 inhibitor): The total and peak systemic exposure (AUC_{0-24} and C_{max}) of Rozerem after a single 16 mg dose of Rozerem was increased by approximately 150% when administered with fluoxetine. Similar increases were seen in M-II exposure. Rozerem should be administered with caution in subjects taking strong CYP2D6 inhibitors such as fluoxetine.

Interaction studies of concomitant administration of Rozerem with fluoxetine (CYP2D6 inhibitor), omperazole (CYP1A2 inhibitor/CYP2C8 inhibitor), theophylline (CYP1A2 substrate), and dextromethorphan (CYP2D6 substrate) did not produce clinically meaningful changes in either peak or total exposure to Rozerem or the M-II metabolite.

Effects of Rozerem on Metabolism of Other Drugs
 Concomitant administration of Rozerem with omperazole (CYP2C8 substrate), dextromethorphan (CYP2D6 substrate), midazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate), digoxin (p-glycoprotein substrate), and warfarin (CYP2C9/CYP2C19 substrate) did not produce clinically meaningful changes in peak and total exposures to these drugs.

Effect of Alcohol on Rozerem
 Alcohol (with single-dose, daytime co-administration of Rozerem 32 mg and alcohol (0.5 g/kg), there were no clinically meaningful or statistically sig-

nificant effects on peak or total exposure to Rozerem. However, an additive effect was seen on some measures of cognitive performance (i.e., the Digit Symbol Substitution Test, the Psychomotor Vigilance Test, and a Visual Analog Scale of sedation) at some post-dose time points. No additive effect was seen on the Delayed Word Recognition Test. Because alcohol by itself impairs performance, and the intended effect of Rozerem is to promote sleep, patients should be cautioned not to consume alcohol while using Rozerem.

Drug/ Laboratory Test Interactions
 Rozerem is not known to interfere with commonly used clinical laboratory tests. In addition, in vitro data indicate that Rozerem does not cause false-positive results for benzodiazepines, opiates, barbiturates, cocaine, cannabinoids, or amphetamines in two standard urine drug screening methods (i.e., with).

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Carcinogenesis
 In a two-year carcinogenicity study, B6C3F₁ mice were administered Rozerem at doses of 0, 10, 100, 300, or 1000 mg/kg/day by oral gavage. Male mice exhibited a dose-related increase in the incidence of hepatic tumors at dose levels ≥100 mg/kg/day including hepatic adenoma, hepatic carcinoma, and hepatoblastoma. Female mice developed a dose-related increase in the incidence of hepatic adenomas at dose levels ≥300 mg/kg/day and hepatic tumors in male mice were 30 mg/kg/day (103-times and 3-times the therapeutic exposure to Rozerem and the active metabolite M-II, respectively, at the maximum recommended human dose [MRHD] based on an area-under-the-curve [AUC] comparison). The no-effect level for hepatic tumors in female mice was 100 mg/kg/day (327-times and 12-times the therapeutic exposure to Rozerem and M-II, respectively, at the MRHD based on AUC).

In a two-year carcinogenicity study conducted in the Sprague-Dawley rat, male animals were administered Rozerem at doses of 0, 10, 100, 300, 1000, 250 or 1000 mg/kg/day by oral gavage. Male rats exhibited a dose-related increase in the incidence of hepatic adenoma and benign Leydig cell tumors of the testes at dose levels ≥250 mg/kg/day and hepatic carcinoma at the 1000 mg/kg/day dose level. Female rats exhibited a dose-related increase in the incidence of hepatic adenoma at dose levels ≥50 mg/kg/day and hepatic carcinomas at the 1000 mg/kg/day dose level. The no-effect level for hepatic tumors and benign Leydig cell tumors in male rats was 60 mg/kg/day (1.629-times and 12-times the therapeutic exposure to Rozerem and M-II, respectively, at the MRHD based on AUC). The no-effect level for hepatic tumors in female rats was 15 mg/kg/day (472-times and 16-times the therapeutic exposure to Rozerem and M-II, respectively, at the MRHD based on AUC).

The development of hepatic tumors in rodents following chronic treatment with non-genotoxic compounds may be secondary to microsomal enzyme induction, a mechanism for tumor generation not thought to occur in humans. Leydig cell tumor development following treatment with non-genotoxic compounds in rodents has been linked to circulating androgenic substances with compensatory increases in luteinizing hormone release, which is a known proliferative stimulus to Leydig cells in the rat testis. Rat Leydig cells are more sensitive to the stimulatory effects of luteinizing hormone than human Leydig cells. In mechanistic studies conducted in the rat, daily Rozerem administration at 250 and 1000 mg/kg/day for 4 weeks was associated with a reduction in plasma luteinizing hormone levels. In the same study, luteinizing hormone levels were elevated over a 24 hour period after the last Rozerem treatment; however, the durability of the luteinizing hormone response and its support for the proposed mechanistic explanation was not clearly established.

Although the rodent tumors observed following Rozerem treatment occurred at a mechanism for tumor generation not thought to occur in humans, Rozerem is not genotoxic in the following: *in vitro* bacterial reverse mutation (Ames) assay, *in vitro* mammalian cell gene mutation assay using the *hprt* locus in Chinese hamster ovary cells, *in vivo* unscheduled DNA synthesis assay in rat hepatocytes, and *in vivo* micronucleus assays conducted in mouse and rat. Rozerem was positive in the chromosomal aberration assay in Chinese hamster lung cells in the presence of 50 metabolite exposure. Separate studies indicated that the concentration of the M-II metabolite formed by the rat liver 50 fraction used in the *in vivo* genotoxicology studies was similar to that observed with the concentrated Rozerem treatment. The genotoxic potential of the M-II metabolite was also assessed in these studies.

Impairment of Fertility
 Rozerem was administered to male and female Sprague-Dawley rats in an initial fertility and early embryonic development study at dose levels of 0, 50, or 600 mg/kg/day. No effects on male or female mating or fertility were observed with a Rozerem dose up to 600 mg/kg/day (786-times higher than the MRHD on a mg/m² basis). Irregular estrus cycles, reduction in the number of implants, and reduction in the number of live embryos were noted with dosing females at ≥50 mg/kg/day (79-times higher than the MRHD on a mg/m² basis). A reduction in the number of corpora lutea occurred at the 600 mg/kg/day dose level. Administration of Rozerem up to 600 mg/kg/day to male rats for 7 weeks had no effect on sperm quality and when the treated male rats were mated with untreated female rats there was no effect on implants or embryos. In a repeat of this study using oral administration of Rozerem at 20, 60 or 200 mg/kg/day for the same study duration, females demonstrated irregular estrus cycles with doses ≥200 mg/kg/day, but no effects were seen on implantation or embryo viability. The no-effect dose for fertility endpoints was 20 mg/kg/day in females (26-times the MRHD on a mg/m² basis) and 600 mg/kg/day in males (786-times higher than the MRHD on a mg/m² basis) when considering all endpoints.

Pregnancy, Pregnancy Category C
 Rozerem has been shown to be a developmental teratogen in the rat when given in doses 187 times higher than the maximum recommended human dose (MRHD) on a mg/m² basis. There are no adequate and well-controlled studies in pregnant women. Rozerem should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The effects of Rozerem on embryo-fetal development were assessed in both the rat and rabbit. Pregnant rats were administered Rozerem by oral gavage at doses of 0, 10, 100, 150, or 600 mg/kg/day during gestation days 6-17, which is the period of organogenesis in this species. Evidence of maternal toxicity and fetal teratogenicity was observed at doses greater than or equal to 150 mg/kg/day. Maternal toxicity was chiefly characterized by decreased body weight and, at 600 mg/kg/day, ataxia and decreased spontaneous movement. At maternally toxic doses (150 mg/kg/day or greater), the fetuses demonstrated visceral malformations consisting of diaphragmatic hernia and minor anatomical variations of the skeleton (irregularly shaped scapulae). At 600 mg/kg/day, reductions in total body weights and malformations including cysts on the external genitalia were additionally observed. The no-effect level for teratogenicity in this study was 60 mg/kg/day (1,800-times and 45-times higher than the therapeutic exposure to Rozerem and the active metabolite M-II, respectively, at the MRHD based on an area-under-the-curve [AUC] comparison). Pregnant rabbits were administered Rozerem by oral gavage at doses of 0, 12, 60, or 300 mg/kg/day during gestation days 6-18, which is the period of organogenesis in this species. Evidence of maternal toxicity was observed with a Rozerem dose of 300 mg/kg/day, no evidence of fetal effects or teratogenicity was associated with any dose level. The no-effect level for teratogenicity was, therefore, 300 mg/kg/day (11,802-times and 69-times

higher than the therapeutic exposure to Rozerem and M-II, respectively, at the MRHD based on AUC).

The effects of Rozerem on pre- and post-natal development in the rat were studied by administration of Rozerem to the pregnant rat by oral gavage at doses of 0, 30, 100, or 300 mg/kg/day from day 6 of gestation through parturition to postnatal (lactation) day 21, at which time offspring were weaned. Maternal toxicity was noted at doses of 100 mg/kg/day or greater and consisted of reduced body weight gain and increased prepartum weight. Reduced body weight during the post-weaning period was also noted in the offspring of the groups given 100 mg/kg/day or higher. Offspring in the 300 mg/kg/day group demonstrated physical and developmental delays including delayed eruption of the lower incisors, a delayed acquisition of the righting reflex, and an abatement of emotional response. These delays are often observed in the presence of reduced offspring weight but may still be indicative of developmental delay. An apparent decrease in the viability of offspring in the 300 mg/kg/day group was likely due to altered maternal behavior and function observed at this dose level. Offspring of the 300 mg/kg/day group also showed evidence of diaphragmatic hernia, a finding observed in the embryo-fetal development study previously described. There were no effects on the reproductive capacity of offspring and the resulting progeny were not different from those of vehicle-treated offspring. The no-effect level for pre- and postnatal development in this study was 30 mg/kg/day (93-times higher than the MRHD on a mg/m² basis).

Labor and Delivery
 The potential effects of Rozerem on the duration of labor and/or delivery, for either the mother or the fetus, have not been studied. Rozerem has no established use in labor and delivery.

Nursing Mothers
 Rozerem is secreted into the milk of lactating rats. It is not known whether this drug is excreted in human milk. No clinical studies in nursing mothers have been performed. The use of Rozerem in nursing mothers is not recommended.

Pediatric Use
 Safety and effectiveness of Rozerem in pediatric patients have not been established. Further study is needed prior to determining that this product may be used safely in pre-pubescent and pubescent patients.

Geriatric Use
 A total of 654 subjects in double-blind, placebo-controlled, efficacy trials who received Rozerem were at least 65 years of age, of these, 169 were 75 years of age or older. No overall differences in safety or efficacy were observed between elderly and younger adult subjects.

ADVERSE REACTIONS
Overview
 The data described in this section reflect exposure to Rozerem in 4251 subjects, including 346 exposed for 6 months or longer, and 473 subjects for one year.

Adverse Reactions Resulting in Discontinuation of Treatment
 Five percent of the 3504 individual subjects exposed to Rozerem in clinical studies discontinued treatment owing to an adverse event, compared with 2% of the 1370 subjects receiving placebo. The most frequent adverse events leading to discontinuation in subjects receiving Rozerem were somnolence (0.9%), dizziness (0.5%), nausea (0.3%), fatigue (0.3%), headache (0.3%), and insomnia (0.3%).

Rozerem Most Commonly Observed Adverse Events in Phase 1-3 trials
 The incidence of adverse events during the Phase 1 through 3 trials (1% placebo, n=1370; 1% Rozerem 16 mg, n=1250) were: headache NDS (7%, 7%), somnolence (3%, 3%), fatigue (2%, 4%), dizziness (2%, 2%), nausea (2%, 2%), respiratory tract infection (2%, 2%), upper respiratory tract infection NDS (2%, 2%), diarrhea NDS (2%, 2%), myalgia (1%, 2%), diplopia (1%, 1%), constipation (1%, 2%), dry mouth (1%, 2%), influenza (0, 1%), blood cortisol decreased (0, 1%).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of other drugs, and they may not reflect the rates observed in practice. The adverse reaction information from clinical trials lists, however, provides a basis for comparing the adverse events that appear to be related to drug use for approximating rates.

DRUG ABUSE AND DEPENDENCE
 Rozerem is not a controlled substance.

Human Data See the **CLINICAL TRIALS** section. **Studies Pertinent to Safety Concerns for Sleep-Promoting Agents in the Complete Prescribing Information**

Animal Data Rozerem did not produce any signals from animal behavioral studies indicating that the drug produces rewarding effects. Monkeys did not self-administer Rozerem and the drug did not induce a conditioned place preference in rats. There was no generalization between Rozerem and diazepam. Rozerem did not affect rotarod performance, an indicator of motor function, and it did not potentiate the ability of diazepam to interfere with rotarod performance.

Discontinuation of Rozerem in animals or in humans after chronic administration did not produce withdrawal signs. Rozerem does not appear to produce physical dependence.

OVERDOSE
Signs and Symptoms
 No cases of Rozerem overdose have been reported during clinical development.

Rozerem was administered in single doses up to 160 mg in an abuse liability trial. No safety or tolerability concerns were seen.

Recommended Treatment
 General symptomatic and supportive measures should be used, along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate vital signs should be monitored, and general supportive measures employed.

Hemodialysis does not effectively reduce exposure to Rozerem. Therefore, the use of dialysis in the treatment of overdose is not appropriate.

Patient Care Center
 As with the management of all overdoses, the possibility of multiple drug ingestion should be considered. The physician may contact a poison control center for current information on the management of overdose.

Rx only
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References: 1. Rozerem package insert, Takeda Pharmaceuticals America, Inc. 2. Data on file, Takeda Pharmaceuticals North America, Inc.