

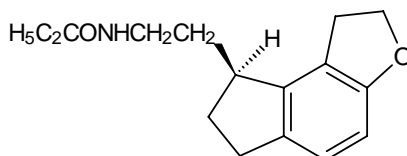
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**ROZEREM™
(ramelteon) tablets**

DESCRIPTION

ROZEREM™ (ramelteon) is an orally active hypnotic chemically designated as (*S*)-*N*-[2-(1,6,7,8-tetrahydro-2*H*-indeno-[5,4-*b*]furan-8-yl)ethyl]propionamide and containing one chiral center. The compound is produced as the (*S*)-enantiomer, with an empirical formula of C₁₆H₂₁NO₂, molecular weight of 259.34, and the following chemical structure:



Ramelteon is freely soluble in organic solvents, such as methanol, ethanol, and dimethyl sulfoxide; soluble in 1-octanol and acetonitrile; and very slightly soluble in water and in aqueous buffers from pH 3 to pH 11.

Each ROZEREM tablet includes the following inactive ingredients: lactose monohydrate, starch, hydroxypropyl cellulose, magnesium stearate, hypromellose, copovidone, titanium dioxide, yellow ferric oxide, polyethylene glycol 8000, and ink containing shellac and synthetic iron oxide black.

CLINICAL PHARMACOLOGY

Pharmacodynamics and Mechanism of Action

ROZEREM (ramelteon) is a melatonin receptor agonist with both high affinity for melatonin MT₁ and MT₂ receptors and selectivity over the MT₃ receptor. Ramelteon demonstrates full agonist activity *in vitro* in cells expressing human MT₁ or MT₂ receptors, and high selectivity for human MT₁ and MT₂ receptors compared to the MT₃ receptor.

The activity of ramelteon at the MT₁ and MT₂ receptors is believed to contribute to its sleep-promoting properties, as these receptors, acted upon by endogenous melatonin, are thought to be involved in the maintenance of the circadian rhythm underlying the normal sleep-wake cycle.

Ramelteon has no appreciable affinity for the GABA receptor complex or for receptors that bind neuropeptides, cytokines, serotonin, dopamine, noradrenaline, acetylcholine, and opiates. Ramelteon also does not interfere with the activity of a number of selected enzymes in a standard panel.

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The major metabolite of ramelteon, M-II, is active and has approximately one tenth and one fifth the binding affinity of the parent molecule for the human MT₁ and MT₂ receptors, respectively, and is 17 – 25-fold less potent than ramelteon in *in vitro* functional assays. Although the potency of M-II at MT₁ and MT₂ receptors is lower than the parent drug, M-II circulates at higher concentrations than the parent producing 20 – 100 fold greater mean systemic exposure when compared to ramelteon. M-II has weak affinity for the serotonin 5-HT_{2B} receptor, but no appreciable affinity for other receptors or enzymes. Similar to ramelteon, M-II does not interfere with the activity of a number of endogenous enzymes

All other known metabolites of ramelteon are inactive.

Pharmacokinetics

The pharmacokinetic profile of ROZEREM has been evaluated in healthy subjects as well as in subjects with hepatic or renal impairment. When administered orally to humans in doses ranging from 4 to 64 mg, ramelteon undergoes rapid, high first-pass metabolism, and exhibits linear pharmacokinetics. Maximal serum concentration (C_{max}) and area under the concentration-time curve (AUC) data show substantial intersubject variability, consistent with the high first-pass effect; the coefficient of variation for these values is approximately 100%. Several metabolites have been identified in human serum and urine.

Absorption

Ramelteon is absorbed rapidly, with median peak concentrations occurring at approximately 0.75 hour (range, 0.5 to 1.5 hours) after fasted oral administration. Although the total absorption of ramelteon is at least 84%, the absolute oral bioavailability is only 1.8% due to extensive first-pass metabolism.

Distribution

In vitro protein binding of ramelteon is approximately 82% in human serum, independent of concentration. Binding to albumin accounts for most of that binding, since 70% of the drug is bound in human serum albumin. Ramelteon is not distributed selectively to red blood cells.

Ramelteon has a mean volume of distribution after intravenous administration of 73.6 L, suggesting substantial tissue distribution.

Metabolism

Metabolism of ramelteon consists primarily of oxidation to hydroxyl and carbonyl derivatives, with secondary metabolism producing glucuronide conjugates. CYP1A2 is the major isozyme involved in the hepatic metabolism of ramelteon; the CYP2C subfamily and CYP3A4 isozymes are also involved to a minor degree.

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The rank order of the principal metabolites by prevalence in human serum is M-II, M-IV, M-I, and M-III. These metabolites are formed rapidly and exhibit a monophasic decline and rapid elimination. The overall mean systemic exposure of M-II is approximately 20- to 100 -fold higher than parent drug.

Elimination

Following oral administration of radiolabeled ramelteon, 84% of total radioactivity was excreted in urine and approximately 4% in feces, resulting in a mean recovery of 88%. Less than 0.1% of the dose was excreted in urine and feces as the parent compound. Elimination was essentially complete by 96 hours post-dose.

Repeated once daily dosing with ROZEREM does not result in significant accumulation owing to the short elimination half-life of ramelteon (on average, approximately 1- 2.6 hours).

The half-life of M-II is 2 to 5 hours and independent of dose. Serum concentrations of the parent drug and its metabolites in humans are at or below the lower limits of quantitation within 24 hours.

Effect of Food

When administered with a high-fat meal, the AUC_{0-inf} for a single 16-mg dose of ROZEREM was 31% higher and the C_{max} was 22% lower than when given in a fasted state. Median T_{max} was delayed by approximately 45 minutes when ROZEREM was administered with food. Effects of food on the AUC values for M-II were similar. It is therefore recommended that ROZEREM not be taken with or immediately after a high fat meal (see **DOSAGE AND ADMINISTRATION**).

Special Populations

Age: In a group of 24 elderly subjects aged 63 to 79 years administered with a single ROZEREM 16-mg dose, the mean C_{max} and AUC_{0-inf} values were 11.6 ng/mL (SD, 13.8) and 18.7 ng·hr/mL (SD, 19.4), respectively. The elimination half-life was 2.6 hour (SD, 1.1). Compared with younger adults, the total exposure (AUC_{0-inf}) and C_{max} of ramelteon were 97% and 86% higher, respectively, in elderly subjects. The AUC_{0-inf} and C_{max} of M-II were increased by 30% and 13%, respectively, in elderly subjects.

Gender: There are no clinically meaningful gender-related differences in the pharmacokinetics of ROZEREM or its metabolites.

Hepatic Impairment: Exposure to ROZEREM was increased almost 4-fold in subjects with mild hepatic impairment after 7 days of dosing with 16 mg/day; exposure was further increased (more than 10-fold) in subjects with moderate hepatic impairment. Exposure to M-II was only marginally increased in mildly and moderately impaired subjects relative to healthy

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matched controls. The pharmacokinetics of ROZEREM have not been evaluated in subjects with severe hepatic impairment (Child-Pugh Class C). ROZEREM should be used with caution in patients with moderate hepatic impairment (see **WARNINGS**).

Renal Impairment: The pharmacokinetic characteristics of ROZEREM were studied after administering a 16-mg dose to subjects with mild, moderate, or severe renal impairment based on pre-dose creatinine clearance (53 to 95, 35 to 49, or 15 to 30 mL/min/1.73 m², respectively), and in subjects who required chronic hemodialysis. Wide inter-subject variability was seen in ROZEREM exposure parameters. However, no effects on C_{max} or AUC_{0-t} of parent drug or M-II were seen in any of the treatment groups; the incidence of adverse events was similar across groups. These results are consistent with the negligible renal clearance of ramelteon, which is principally eliminated via hepatic metabolism. No adjustment of ROZEREM dosage is required in patients with renal impairment, including patients with severe renal impairment (creatinine clearance of ≤ 30 mL/min/1.73 m²) and patients who require chronic hemodialysis.

Chronic Obstructive Pulmonary Disease: The effects of ROZEREM were evaluated after administering a 16-mg dose or placebo in a crossover design to subjects with mild to moderate chronic obstructive pulmonary disease. Treatment with ROZEREM 16 mg for one night showed no difference compared with placebo on mean arterial oxygen saturation during sleep for the entire night, for each stage of sleep, or for each hour of sleep, and no significant difference in the Apnea/Hypopnea index. While ROZEREM did not show a respiratory depressant effect in this study of patients with chronic obstructive pulmonary disease, the effect of ROZEREM in patients with severe COPD (e.g., those with elevated pCO₂ levels or those needing nocturnal oxygen therapy) has not been studied.

Sleep Apnea: The effects of ROZEREM were evaluated after administering a 16-mg dose or placebo in a crossover design to subjects with mild to moderate obstructive sleep apnea. Treatment with ROZEREM 16 mg for one night showed no difference compared with placebo on the Apnea/Hypopnea Index (the primary outcome variable), apnea index, hypopnea index, central apnea index, mixed apnea index, and obstructive apnea index. Mean SaO₂ during the REM stage of sleep was statistically significantly higher for ROZEREM than for placebo. No differences from placebo were detected in all other secondary outcome variables. These results indicate that ROZEREM does not exacerbate mild to moderate obstructive sleep apnea. ROZEREM has not been studied in subjects with severe obstructive sleep apnea; use of ROZEREM is not recommended in such patients.

Results of drug-drug interaction trials are discussed under **PRECAUTIONS**.

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CLINICAL TRIALS

Controlled Trials Supporting Efficacy

Chronic Insomnia

ROZEREM was studied in two randomized, double-blind trials in subjects with chronic insomnia employing polysomnography (PSG).

One study enrolled younger adults (aged 18 to 64 years, inclusive) with chronic insomnia and employed a parallel design in which the subjects received a single, nightly dose of ROZEREM 8 mg or 16 mg or matching placebo for 35 days. PSG was performed on the first two nights in each of Weeks 1, 3, and 5 of treatment. Both doses of ROZEREM reduced the average latency to persistent sleep at each of the time points when compared to placebo.

The second study employing PSG was a three-period crossover trial performed in subjects aged 65 years and older with a history of chronic insomnia. Subjects received ROZEREM 4 mg or 8 mg or placebo and underwent PSG assessment in a sleep laboratory for two consecutive nights in each of the three study periods. Both doses of ROZEREM reduced latency to persistent sleep compared to placebo.

A randomized, double-blind, parallel group study was conducted in outpatients aged 65 years and older with chronic insomnia and employed subjective measures of efficacy (sleep diaries). Subjects received ROZEREM 4 mg or 8 mg or placebo for 35 nights. Both doses of ROZEREM reduced patient-reported sleep latency compared to placebo. A similarly designed study performed in younger adults (aged 18-64 years) using 8 and 16mg of ramelteon did not replicate this finding of reduced patient-reported sleep latency compared to placebo.

Transient Insomnia

In a randomized, double-blind, parallel-group trial using a first-night-effect model, healthy adults received placebo or ROZEREM 8 mg or 16 mg before spending one night in a sleep laboratory and being evaluated with PSG. The 8-mg dose demonstrated a decrease in mean latency to persistent sleep as compared to placebo.

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Studies Pertinent to Safety Concerns for Sleep-Promoting Agents

Results from Human Laboratory Abuse Liability Studies

A human laboratory abuse potential study was performed in 14 subjects with a history of sedative/hypnotic or anxiolytic drug abuse. Subjects received single oral doses of ROZEREM (16, 80, or 160mg.), triazolam (0.25, 0.50, or 0.75mg.) or placebo. All subjects received each of the 7 treatments separated by a wash-out period and underwent multiple standard tests of abuse potential. No differences in subjective responses indicative of abuse potential were found between ROZEREM and placebo at doses up to 20 times the recommended therapeutic dose. The positive control drug, triazolam, consistently showed a dose-response effect on these subjective measures, as demonstrated by the differences from placebo in peak effect and overall 24-hour effect.

Residual Pharmacological Effects in Insomnia Trials

In order to evaluate potential next-day residual effects, the following scales were used: a Memory Recall Test, a Word List Memory Test, a Visual Analog Mood and Feeling Scale, the Digit-Symbol Substitution Test, and a post-sleep questionnaire to assess alertness and ability to concentrate.

There was no evidence of next-day residual effect seen after 2 nights of ramelteon use during the crossover studies.

In a 35-night, double-blind, placebo-controlled, parallel-group study in adults with chronic insomnia, measures of residual effects were performed at three time points. Overall, the magnitudes of any observed differences were small. At Week 1, patients who received 8 mg of ROZEREM had a mean VAS score (46 mm on a 100 mm scale) indicating more fatigue in comparison to patients who received placebo (42 mm). At Week 3, patients who received 8 mg of ROZEREM had a lower mean score for immediate recall (7.5 out of 16 words) compared to patients who received placebo (8.2 words); and the ROZEREM-treated patients had a mean VAS score indicating more sluggishness (27 mm on a 100 mm VAS) in comparison to the placebo-treated patients (22 mm). Neither ROZEREM dose had next-morning residual effects that were different from placebo at Week 5.

Rebound Insomnia/Withdrawal

Potential rebound insomnia and withdrawal effects were assessed in three long-term insomnia studies in which subjects received ROZEREM for 35 days. These studies included a total of 2082 subjects, of whom 829 were elderly.

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Tyrer Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ): The BWSQ is a self-report questionnaire that solicits specific information on 20 symptoms commonly experienced during withdrawal from benzodiazepine receptor agonists. In two of the three 35-day insomnia studies, the questionnaire was administered one week after completion of treatment; in the third study, the questionnaire was administered on Days 1 and 2 after completion.

In all three studies, subjects receiving ROZEREM 4 mg, 8 mg, or 16 mg daily reported BWSQ scores similar to those of subjects receiving placebo.

Rebound Insomnia: Rebound insomnia was assessed in three of the long-term studies by continuing to measure sleep latency after abrupt treatment discontinuation. One of these studies employed PSG in younger adult subjects receiving ROZEREM 8 mg or 16 mg; the other two studies employed subjective measures of sleep-onset insomnia in elderly subjects receiving ROZEREM 4 mg or 8 mg, and in younger adult subjects receiving ROZEREM 8 mg or 16 mg. In each of these studies, there was no evidence that ROZEREM caused rebound insomnia at any time during the post-treatment period at any of the three doses.

Special Studies to Evaluate Effects on Endocrine Function

Two controlled studies evaluated the effects of ROZEREM on endocrine function.

In the first trial, ROZEREM 16 mg once daily or placebo was administered to 99 healthy volunteer subjects for 4 weeks. This study evaluated the thyroid axis, adrenal axis and reproductive axis. No clinically significant endocrinopathies were demonstrated in this study. However, the study was limited in its ability to detect such abnormalities due to its limited duration.

In the second trial, ROZEREM 16 mg once daily or placebo was administered to 122 subjects with chronic insomnia for 6 months. This study evaluated the thyroid axis, adrenal axis and reproductive axis. There were no significant abnormalities seen in either the thyroid or the adrenal axes. Abnormalities were, however, noted within the reproductive axis. Overall, the mean serum prolactin level change from baseline was 4.9 µg/L (34 % increase) for women in the ROZEREM group compared with -0.6 µg/L (4% decrease) for women in the placebo group (p=0.003). No differences between active- and placebo-treated groups occurred among men. Thirty-two percent of all patients who were treated with ramelteon in this study (women and men) had prolactin levels which increased from normal baseline levels compared to nineteen percent of patients who were treated with placebo. Subject-reported menstrual patterns were similar between the two treatment groups.

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In a 12-month, open-label study in adult and elderly patients, there were two patients who were noted to have abnormal morning cortisol levels, and subsequent abnormal ACTH stimulation tests. A 29 year old female patient was also diagnosed with a prolactinoma. The relationship of these events to ROZEREM therapy is not clear.

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 ramelteon or any components of the ROZEREM formulation.

WARNINGS

Since sleep 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 hypnotics. In primarily depressed patients, worsening of depression, including suicidal ideation, has been reported in association with the use of hypnotics.

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 prepare for bed.

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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 chronic intermittent use of ROZEREM may have on the reproductive axis in developing humans. (see **Pediatric 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 amenorrhea, galactorrhea, decreased libido, or problems with fertility, assessment of prolactin levels, and testosterone levels should be considered as appropriate.

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Drug Interactions

ROZEREM has a highly variable inter-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 CYP2C subfamily and CYP3A4 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 co-administration of ROZEREM 16 mg and fluvoxamine, the $AUC_{0-\infty}$ for ramelteon increased approximately 190-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 less 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 ramelteon and metabolite M-II, (both $AUC_{0-\infty}$ and C_{\max}) after a single 32mg dose of ROZEREM. Efficacy may be reduced when ROZEREM is used in combination with strong CYP enzyme inducers such as rifampin.

Ketoconazole (strong CYP3A4 inhibitor): The $AUC_{0-\infty}$ and C_{\max} of ramelteon increased by approximately 84% and 36%, respectively, when a single 16mg dose of ROZEREM was administered on the fourth day of ketoconazole 200mg 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 CYP3A4 inhibitors such as ketoconazole.

Fluconazole (strong CYP2C9 inhibitor): The total and peak systemic exposure ($AUC_{0-\infty}$ and C_{\max}) of ramelteon after a single 16mg dose of ROZEREM was increased by approximately 150% when administered with fluconazole. Similar increases were also seen in M-II exposure. ROZEREM should be administered with caution in subjects taking strong CYP2C9 inhibitors such as fluconazole.

Interaction studies of concomitant administration of ROZEREM with fluoxetine (CYP2D6 inhibitor), omeprazole (CYP1A2 inducer/CYP2C19 inhibitor), theophylline (CYP1A2 substrate), and dextromethorphan (CYP2D6 substrate) did not produce clinically meaningful changes in either peak or total exposures to ramelteon or the M-II metabolite.

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Effects of ROZEREM™ on Metabolism of Other Drugs

Concomitant administration of ROZEREM with omeprazole (CYP2C19 substrate), dextromethorphan (CYP2D6 substrate), midazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate), digoxin (p-glycoprotein substrate), and warfarin (CYP2C9 [S]/CYP1A2 [R] 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 32mg and alcohol (0.6 g/kg), there were no clinically meaningful or statistically significant effects on peak or total exposure to ROZEREM. However, an additive effect was seen on some measures of psychomotor performance (i.e., the Digit Symbol Substitution Test, the Psychomotor Vigilance Task 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 when 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 ramelteon does not cause false-positive results for benzodiazepines, opiates, barbiturates, cocaine, cannabinoids, or amphetamines in two standard urine drug screening methods *in vitro*.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

In a two-year carcinogenicity study, B6C3F₁ mice were administered ramelteon at doses of 0, 30, 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 carcinoma at the 1000 mg/kg/day dose level. The no-effect level for hepatic tumors in male mice was 30 mg/kg/day (103-times and 3-times the therapeutic exposure to ramelteon 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 (827-times and 12-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

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In a two-year carcinogenicity study conducted in the Sprague-Dawley rat, male and female rats were administered ramelteon at doses of 0, 15, 60, 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 testis at dose levels \geq 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 \geq 60 mg/kg/day and hepatic carcinoma 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 (1,429-times and 12-times the therapeutic exposure to ramelteon 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 ramelteon 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 reductions in circulating testosterone levels 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 ramelteon administration at 250 and 1000 mg/kg/day for 4 weeks was associated with a reduction in plasma testosterone levels. In the same study, luteinizing hormone levels were elevated over a 24 hour period after the last ramelteon treatment; however, the durability of this luteinizing hormone finding and its support for the proposed mechanistic explanation was not clearly established.

Although the rodent tumors observed following ramelteon treatment occurred at plasma levels of ramelteon and M-II in excess of mean clinical plasma concentrations at the MRHD, the relevance of both rodent hepatic tumors and benign rat Leydig cell tumors to humans is not known.

Mutagenesis

Ramelteon was not genotoxic in the following: *in vitro* bacterial reverse mutation (Ames) assay; *in vitro* mammalian cell gene mutation assay using the mouse lymphoma TK^{+/-} cell line; *in vivo/in vitro* unscheduled DNA synthesis assay in rat hepatocytes; and in *in vivo* micronucleus assays conducted in mouse and rat. Ramelteon was positive in the chromosomal aberration assay in Chinese hamster lung cells in the presence of S9 metabolic activation.

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Separate studies indicated that the concentration of the M-II metabolite formed by the rat liver S9 fraction used in the *in vitro* genetic toxicology studies described above, exceeded the concentration of ramelteon; therefore, the genotoxic potential of the M-II metabolite was also assessed in these studies.

Impairment of Fertility

Ramelteon was administered to male and female Sprague-Dawley rats in an initial fertility and early embryonic development study at dose levels of 6, 60, or 600 mg/kg/day. No effects on male or female mating or fertility were observed with a ramelteon 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 ≥ 60 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 ramelteon 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 ramelteon at 20, 60 or 200 mg/kg/day for the same study duration, females demonstrated irregular estrus cycles with doses ≥ 60 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 studies.

Pregnancy: Pregnancy Category C

Ramelteon has been shown to be a developmental teratogen in the rat when given in doses 197 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. Ramelteon should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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The effects of ramelteon on embryo-fetal development were assessed in both the rat and rabbit. Pregnant rats were administered ramelteon by oral gavage at doses of 0, 10, 40, 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 scapula). At 600 mg/kg/day, reductions in fetal body weights and malformations including cysts on the external genitalia were additionally observed. The no-effect level for teratogenicity in this study was 40 mg/kg/day (1,892-times and 45-times higher than the therapeutic exposure to ramelteon and the active metabolite M-II, respectively, at the MRHD based on an area-under-the-curve [AUC] comparison). Pregnant rabbits were administered ramelteon 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. Although maternal toxicity was apparent with a ramelteon 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 (11,862-times and 99-times higher than the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

The effects of ramelteon on pre- and post-natal development in the rat were studied by administration of ramelteon 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 adrenal gland weight. Reduced body weight during the post-weaning period was also noticed in the offspring of the groups given 100 mg/kg/day and 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 alteration of emotional response. These delays are often observed in the presence of reduced offspring body 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 (39-times higher than the MRHD on a mg/m² basis).

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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

Ramelteon 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, 199 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 3594 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 (0.8%), dizziness (0.5%), nausea (0.3%), fatigue (0.3%), headache (0.3%), and insomnia (0.3%).

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ROZEREM Most Commonly Observed Adverse Events in Phase 1-3 trials

Table 1 displays the incidence of adverse events during the Phase 1 through 3 trials.

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 may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Table 1. Incidence (% of subjects) of Treatment-Emergent Adverse Events in Phase 1-3 Studies

MedDRA Preferred Term	Placebo (n=1370)	Ramelteon
		8 mg (n=1250)
Headache NOS	7%	7%
Somnolence	3%	5%
Fatigue	2%	4%
Dizziness	3%	5%
Nausea	2%	3%
Insomnia exacerbated	2%	3%
Upper respiratory tract infection NOS	2%	3%
Diarrhea NOS	2%	2%
Myalgia	1%	2%
Depression	1%	2%
Dysgeusia	1%	2%
Arthralgia	1%	2%
Influenza	0	1%
Blood Cortisol Decreased	0	1%

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**, for the results of human laboratory abuse potential trials with ROZEREM.

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

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

OVERDOSAGE

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.

Poison Control Center

As with the management of all overdose, 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.

DOSAGE AND ADMINISTRATION

The recommended dose of ROZEREM™ is 8 mg taken within 30 minutes of going to bed. It is recommended that ROZEREM not be taken with or immediately after a high fat meal.

ROZEREM should not be used in subjects with severe hepatic impairment. ROZEREM should be used with caution in patients with moderate hepatic impairment.

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ROZEREM should not be used in combination with fluvoxamine.
ROZEREM should be used with caution in patients taking other CYP1A2 inhibiting drugs (see **PRECAUTIONS: Drug Interactions**).

HOW SUPPLIED

ROZEREM is available as round, pale orange-yellow, film-coated, 8 mg tablets, with “TAK” and “RAM-8” printed on one side, in the following quantities:

NDC 64764-805-30	Bottle of 30
NDC 64764-805-10	Bottle of 100
NDC 64764-805-50	Bottle of 500

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP controlled room temperature]. Keep container tightly closed and protected from moisture and humidity.

Rx only

Manufactured by:

Takeda Pharmaceutical Company, Ltd.
540-8645 Osaka, Japan

Manufactured in:

Takeda Ireland Ltd.
Kilruddery, County Wicklow, Republic of Ireland

Marketed by:

Takeda Pharmaceuticals America, Inc.
475 Half Day Road
Lincolnshire, IL 60069

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

Rozerem™ 8 mg Sample Carton




(b) (4)










FINAL PROOF Date: 7/22/2005

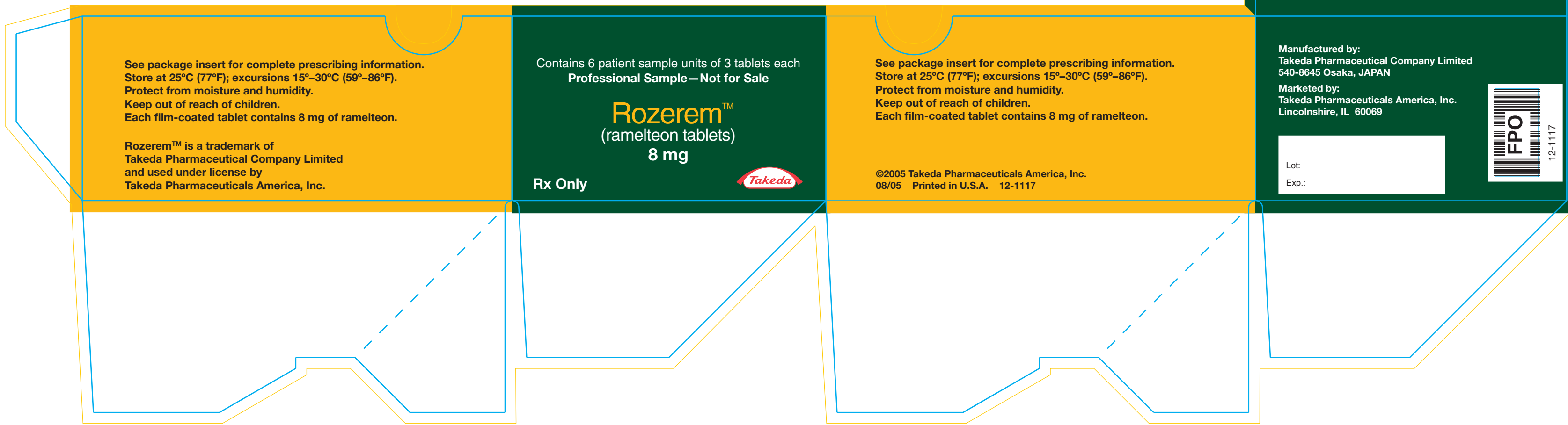
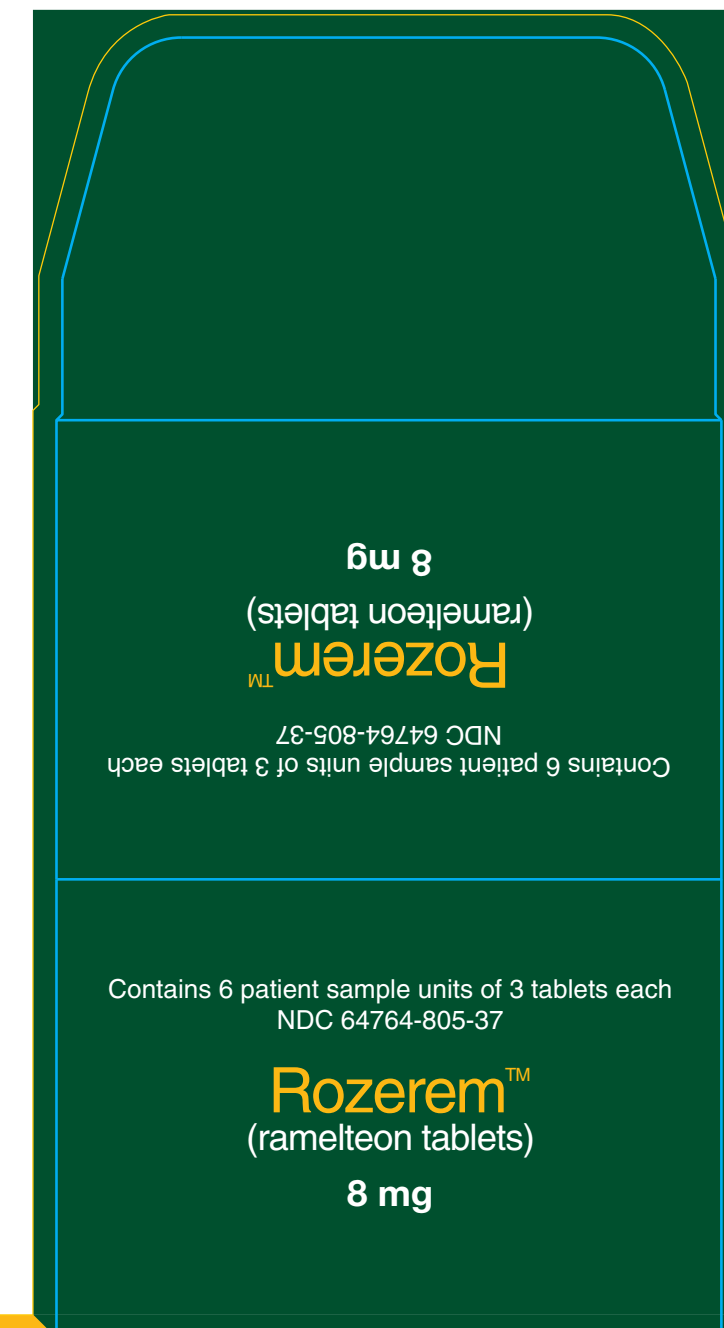
Rozerem™ 8 mg Sample Carton Size: 2.00" X .703" X 3.4375"
(50.8 mm X 17.86 mm X 87.31 mm)

Item No.: 09-1114 P/N.:

New Proof Required OK With Changes 
COMMERCIAL QA OPERATIONS

(b) (4)

FINAL PROOF		Date: 7/22/2005
Rozerem™ 8 mg Sample Tray		Size: 4.875" x 3.5625" x 2.09375" (123.83 mm x 90.49 mm x 53.18 mm)
Item No.: 12-1117	P/N.:	 COMMERCIAL QA OPERATIONS
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 DRAFT COPY	 DIE LINE	 VARNISH
 PMS 185C	 PMS 3435C	 PMS 130C




Rozerem™ 8 mg/500 Count Label



Affix Approval Label Here

(b) (4)


FINAL PROOF		Date: 7/22/2005
Rozerem™ 8 mg/500 Count		Size: 4.00" x 1.75" (101.6 mm x 44.45 mm)
Item No.: 07-1118	P/N.:	
<input type="checkbox"/> New Proof Required	<input type="checkbox"/> OK With Changes	 COMMERCIAL QA OPERATIONS



Rozerem™ 8 mg/100 Count Label



Affix Approval Label Here

FINAL PROOF		Date: 7/22/2005
Rozerem™ 8 mg/100 Count		Size: 3.50" x 1.625" (88.9 mm x 41.275 mm)
Item No.: 07-1115	P/N.:	 COMMERCIAL QA OPERATIONS
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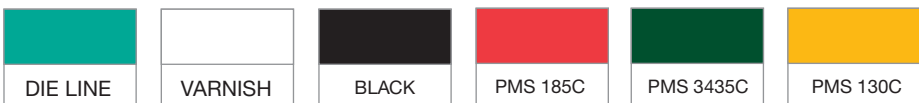
Rozerem™ 8 mg/30 Count Label



Affix Approval Label Here

(b) (4)

FINAL PROOF		Date: 7/22/2005
Rozerem™ 8 mg/30 Count		Size: 3.50" x 1.625" (88.9 mm x 41.275 mm)
Item No.: 07-1112	P/N.:	
<input type="checkbox"/> New Proof Required	<input type="checkbox"/> OK With Changes	 COMMERCIAL QA OPERATIONS




Rozerem™ 8 mg/30 Count Sample Label



Affix Approval Label Here

(b) (4)

FINAL PROOF		Date: 7/22/2005
Rozerem™ 8 mg/30 Count Sample Label		Size: 3.50" x 1.625" (88.9 mm x 41.275 mm)
Item No.: 07-1148	P/N.:	 COMMERCIAL QA OPERATIONS
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