National PBM Drug Monograph
Ramelteon (Rozerem™)
December 2005
VHA Pharmacy Benefits Management Strategic Healthcare Group and The Medical Advisory Panel

Executive Summary:

Indications: Ramelteon received FDA approval July 22, 2005 for the treatment of insomnia characterized by difficulty with sleep onset in adult patients ≥ 18 years of age. Ramelteon, is considered a hypnotic sleep agent, rather than a sedative-hypnotic. Ramelteon is the first FDA approved prescription sleep medication that has not been designated as a controlled substance.

Pharmacology: Ramelteon is a melatonin receptor agonist with high affinities for both melatonin MT_1 and MT_2 receptors. Ramelteon has no appreciable affinity for the GABA receptor complex or for receptors that bind neuropeptides, cytokines, serotonin, dopamine, noradrenaline, acetylcholine, and opiates. Ramelteon is the first in class of melatonin agonists.

Drug Interactions: Ramelteon is metabolized primarily at CYP1A2; the CYP2C subfamily and CYP3A4 are also involved to a minor degree. The most significant drug interactions involve medications which are metabolized through these pathways such as fluvoxamine, ketoconazole, fluconazole and rifampin.

Efficacy: Published studies have demonstrated that ramelteon is safe and effective in the management of transient and chronic insomnia. In a Phase II trial in chronic insomnia employing polysomnography (PSG), ramelteon demonstrated a statistically significant decrease of 13-15 minutes in mean latency to persistent sleep (LPS) compared to placebo. Another Phase II trial in patients with transient insomnia demonstrated a statistically significant difference of 9-12 minutes in mean latency to persistent sleep (LPS) compared to placebo. However, the majority of the studies which support the safety and efficacy of this agent are not yet published.

Safety: The most common adverse events in phase 1-3 studies of ramelteon vs. placebo were headache (7% vs. 7%), somnolence (5% vs. 3%), fatigue (4% vs. 2%) and dizziness (5% vs. 3%), respectively. Five percent of the 3594 patients exposed to ramelteon in clinical studies discontinued treatment owing to an adverse event, compared to 2% of the 1370 patients on placebo. The most frequently reported adverse events leading to discontinuation in the phase 1-3 studies in subjects receiving ramelteon were somnolence (0.8%), dizziness (0.5%), nausea (0.3%), fatigue (0.3%), headache (0.3%) and insomnia (0.3%). The rates of discontinuation in patients who received placebo are not available.

Drug abuse potential: While this agent appears to have no apparent drug abuse potential, it has not been adequately studied primarily in patients with substance addiction and dependence. To date, long-term safety and efficacy trials are not available with ramelteon in individuals with known histories of benzodiazepine abuse.

Dosage and Administration: The recommended dose of ramelteon is 8 mg taken within 30 minutes of bedtime. Ramelteon should not be taken with or immediately after a high-fat meal.

Laboratory Monitoring: No laboratory monitoring is recommended per package insert. 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.

Cost: Ramelteon comes as an 8 mg, round, pale orange-yellow, film-coated tablet with "TAK" and "RAM-8" printed on one side. The cost for each dose is $1.60 (FSS price).

Introduction

Insomnia is a major health concern as it is strongly associated with psychiatric, physical, social and economic morbidity.[1,2] Studies suggest that intermittent or chronic insomnia affects 50 to 70 million Americans, representing approximately 20% of the population.[3] The Agency for Healthcare Research and Quality (AHRQ) recently published their evidence report/technology assessment on insomnia. Based on a review of high quality reports, the prevalence of insomnia in the general population ranged from 5-45%, with a median of 17.6%.[4] Several risk factors for insomnia have been identified including older age,[5] female gender,[6] divorced or separated adults, lower education, unemployment, and medical illness.[3] Ancoli-Israel et.al. reported that more than half of people who are 65 years and older complain of recurring sleep problems.[7]

There is a lack of consensus on the definition of insomnia. The International Classification of Sleep Disorders defines insomnia as difficulty in initiating and/or maintaining sleep or non-restorative sleep after a habitual sleep episode.[8] The DSM-IV criteria for primary insomnia are most frequently utilized for enrollment of qualified subjects in clinical trials of insomnia. The DSM-IV criteria[9] include:

- Difficulty initiating or maintaining sleep or nonrestorative sleep for at least 1 month;
- The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational or other important areas of functioning
- The sleeping disturbances do not occur exclusively during the course of narcolepsy breathing-related sleep disorder circadian rhythm sleep disorder or a parasomnia;
- A sleep disturbance that does not occur exclusively during the course of another mental disorder (e.g major depressive disorder generalized anxiety disorder a delirium; and the

Disturbance is not due to the direct physiological effects of a substance (e.g. a drug of abuse medication) or a general medical condition.

Ramelteon received FDA approval July 22, 2005 for the treatment of insomnia characterized by difficulty with sleep onset n adult patients ≥ 18 years of age. Ramelteon is the first in class of melatonin agonists, and is also the first FDA approved prescription sleep medication that has not been designated as a controlled substance.

Pharmacology/Pharmacokinetics

Melatonin MT_1 and MT_2 receptors are thought to be involved in the maintenance of circadian rhythm, which regulates the sleep-wake cycle. The MT_1 receptor is thought to regulate sleepiness, whereas the MT_2 receptor is thought to help the body shift easily between phases of day and night.[10,11] Ramelteon has high selectivity and affinity for melatonin MT_1 and MT_2 receptors. Ramelteon has no appreciable affinity for the GABA receptor complex or for receptors that bind neuropeptides, cytokines, serotonin, dopamine, noradrenaline, acetylcholine, and opiates.[12] The major metabolite of ramelteon, M-II, is active but has only one-tenth the binding affinity for MT_1 and one-fifth the binding affinity for MT_2 of the parent compound ramelteon. In vitro, M-II is 17-25-fold less potent than ramelteon.[15]

Table 1: Pharmacokinetic Parameters in Adults[15,17]

Absorption	Protein Binding	Half-life	Volume of Distribution	Metabolism	Excretion
0.5-1.5 hrs	70% albumin bound	Ramelteon: 1-2.6 hrs M-II (active metabolite):2-5 hrs	73.6L	CYP1A2 (major) CYP3A4 (minor) CYP2C (minor)	84% excreted in urine

Absorption: Ramelteon is rapidly absorbed, with peak median concentrations occurring at approximately 0.75 hours after fasting oral administration. Extensive first-pass metabolism provides an absolute oral bioavailability of 1.8% and a relative bioavailability of at least 84%.

Metabolism: Primarily oxidation to hydroxyl and carbonyl derivatives, with secondary metabolism producing glucuronide metabolites. CYP1A2 is the primary site of metabolism; the CYP2C subfamily and CYP3A4 are also involved to a minor degree.

Elimination: Following oral administration, 84% was excreted in the urine and 4% in the feces. Elimination is complete by 96 hours post dose.

Effect of Food: When administered with a high fat meal, the $AUC_{0\text{-}inf}$ for a single 16 mg dose of rozerem was 31% higher and the Cmax was 22% lower than when administered in the fasting state. Median Tmax was delayed by approximately 45 minutes. It is recommended that ramelteon not be taken with or immediately after a high fat meal.

Elderly: The elimination half-life in elderly patients was 2.6 hours. Compared with younger adults, the total exposure ($AUC_{0\text{-}inf}$) and Cmax of ramelteon were 97% and 86% higher, respectively, in elderly patients. Despite greater exposure and increased Cmax, no dosage adjustments for elderly patients are recommended by the manufacturer as a higher rate of adverse events was not seen in elderly patients in clinical trials at recommended doses.

FDA Approved Indication(s) and Off-label Uses[15]

Ramelteon is FDA approved for the treatment of insomnia characterized by difficulty with sleep onset. From the controlled, randomized trials currently published, ramelteon administered at bedtime decreased average latency to persistent sleep by 10-15 minutes. No off-label uses have been identified.

Current VA National Formulary Alternatives:

Drug Class	Comments
Benzodiazepines	Onset 45-60 minutes; 3-25 hours half-life
Antihistamines	Anticholinergic, rapid tolerance, not FDA approved for insomnia
Antidepressants	Not FDA approved for insomnia
Chloral Hydrate	Recent interpretive guidelines from the Centers for Medicare and Medicaid Services (CMS) discourage the use of chloral hydrate in residents of long-term care facilities.[13]

Current VA Non-Formulary Alternatives:

Drug Class	Comments
Zolpidem	Half-life: 1.4-3.8 hrs; Few residual effects and low incidence of side effects in clinical trials; drowsiness, dizziness, diarrhea, hallucinatory phenomena, other sensory distortions, Schedule IV
Zaleplon	Half-life: 1 hr; Few residual effects and low incidence of side effects in clinical trials, Schedule IV
Eszopiclone	Half-life: 6 hrs; Few residual effects and low incidence of side effects in clinical trials; unpleasant taste, dry mouth, dizziness, Schedule IV

Dosage and Administration

General Recommendations: The recommended dose of ramelteon is 8 mg taken within 30 minutes of going to bed. Doses greater than 8mg daily have not been shown to have greater effect than 8mg based on current data,[17] so doses should be limited to 8mg daily. It is recommended that ramelteon not be taken with or immediately after a high fat meal.[15]

Recommendations for Elderly Patients: Based on manufacturer data on file, ramelteon was well tolerated in elderly patients. Elderly patients have experienced a higher systemic exposure to ramelteon compared to younger subjects; however, individual variability is high. Dose adjustments are not required based on age per the manufacturer.[14] However, there remains concern for long-term use with higher drug exposure in the elderly. Per data on file, a lower dose of 4 mg appeared to be safe and effective.[17] A lower strength

may be a viable dosing option in the elderly despite 8 mg being the only marketed dose. It should be cautioned that there is the possibility that elderly patients may experience dose-related side effects not identified in short-term pre-marketing studies due to higher drug exposure.

Recommendations for Patients with Concomitant Illness

Hepatic Impairment: Ramelteon should not be used in patients with severe hepatic impairment. It should be used cautiously in patients with moderate hepatic impairment.[15,17]

Renal Impairment: Adjustment of the ramelteon dosage is not required in patients with renal impairment of any degree, including patients with severe renal impairment (CrCl of < 30 ml/min/1.73 m2) or those who require chronic hemodialysis.[15,17]

COPD: Ramelteon has demonstrated no respiratory depressant effects in subjects with mild to moderate chronic obstructive pulmonary disease. The effects of ramelteon have not been evaluated in patients with severe COPD, therefore, use in such patients is not recommended by the manufacturer at this time.[17]

Sleep Apnea: Ramelteon does not exacerbate mild to moderate obstructive sleep apnea. Ramelteon has not been studied in subjects with severe sleep apnea, therefore, use is not recommended.[17]

While ramelteon is not recommended currently in severe COPD or sleep apnea due to lack of data in these populations, clinicians may nevertheless consider it to be an attractive option in such patients since it has not demonstrated respiratory depressive effects that have been seen with GABA stimulation. Clinicians should consider the risk versus benefit of using ramelteon before using in patients with severe respiratory disease.

Table 2: Efficacy Measures Used in Ramelteon Clinical Trials[17]

Objective Measurements by PSG	**Subjective Measurements** (from post-sleep questionnaires and sleep diaries)
Latency to Persistent Sleep (LPS): time required to initially fall asleep and defined as the onset of first 10 minutes of continuous sleep	**Subjective Sleep Latency (sSL)—**patient reported time period measured from "lights out," or bedtime, to the beginning of sleep
Total Sleep Time (TST): sum of all minutes in all stages of sleep	**Subjective Total Sleep Time (sTST)—**patient reported amount of actual sleep time in a sleep period.
Sleep Efficiency: TST/total time in bed x 100, expressed as %	**Sleep Quality—**the reported quality of the sleep
Wake After Sleep Onset (WASO): total amount of minutes spent awake after sleep onset	**Subjective Wake After Sleep Onset (sWASO)—**patient reported time spent awake from sleep onset to final awakening
Number of Awakenings (NAW): number of times a subject returns to the awake state during the night	**Subjective Number of Awakenings (sNAW)—**patient reported number of awakenings
	Ease of Falling Back to Sleep
	Physician-rated Clinical Global Impression (CGI)- a three-item scale used to assess Severity of Illness; Global Improvement; Efficacy Index.[15]

Summary of Efficacy Findings

Ramelteon efficacy is supported by 5 Phase III, randomized, double-blind, placebo-controlled, muticenter clinical trials in patients with transient or chronic insomnia. No phase III trials are published in peer-reviewed journals at the time of this review. Two phase III studies, were conducted in elderly populations.[17]

Transient Insomnia:

Roth et al[16] conducted a Phase II, multicenter, randomized, double-blind, placebo-controlled, single dose, parallel-group study conducted in a sleep laboratory. The study investigated the safety and hypnotic efficacy of ramelteon after single-dose administration of 16 mg or 64 mg compared with placebo in healthy subjects unfamiliar with a sleep laboratory environment. The primary efficacy endpoint was

PSG-recorded mean LPS, with secondary measures of vital signs, laboratory tests, 12-lead ECG, and physical examination. Significant differences ($p<0.001$) in mean LPS were seen with both strengths of ramelteon vs. placebo (ramelteon 16 mg 14.1 ± 15.1 minutes, ramelteon 64 mg 15.5 ± 15.4 minutes , placebo, 24.6 ± 21.9). There were no differences in residual effects as measured by the Digit Symbol Substitution Test (DSST) scores in each of the three groups. The 64-mg group reported small but statistically significant declines in subjective level of alertness and ability to concentrate, as compared to the placebo group. The 16-mg group was not significantly different from the placebo group on these measures. Both dosages of ramelteon were associated with a statistically significant decrease in mean LPS and significant increases in mean TST and therefore, better sleep efficiency compared to placebo. The differences in WASO, awakenings after persistent sleep and number of awakenings lasting longer than 2 minutes did not differ among the treatment groups vs. placebo. There were also no statistically significant differences among the three groups for percentage of TST spent in any sleep stage. The subjective number of awakenings and subjective ease of falling back to sleep did not differ from placebo for either group. (See appendix A for additional details).

Zammit et al.[17] evaluated 289 healthy subjects in a Phase III trial conducted in a sleep laboratory with PSG. Subjects received ramelteon 8 mg, 16 mg, or placebo 30 min before bedtime. Preliminary results from data on file with Takeda report a significant difference in LPS vs. placebo with the 8mg, but not with the 16mg dose.[17] Total sleep time (TST) was significantly increased in both treatment groups vs. placebo.[17]

Chronic Insomnia:

Erman et al[18] conducted a Phase II, multicenter, randomized, double-blind, placebo-controlled, 5-period crossover study conducted in a sleep laboratory. Men and women 18-64 yrs. of age with DSM-IV defined chronic insomnia for ≥ 3 months were administered ramelteon at doses of 4, 8, 16, and 32 mg compared to placebo. The study consisted of five 2-day treatment periods for each dose and placebo, with a 5- to 12- day washout period between each treatment. The primary efficacy endpoint was mean latency to persistent sleep (LPS), with secondary objective measures including TST, WASO and percentage of sleep time in each stage. Subjective efficacy measures of sleep latency, total sleep time and sleep quality were also examined. All tested doses resulted in statistically significant reductions in mean LPS (ramelteon 4 mg, 8 mg, 16 mg, 32 mg vs placebo; 24 min, 24.3 min, 24 min, 22.9 min, vs. 37.7 min, respectively ($p < 0.001$)). This reduction in LPS with ramelteon compared to placebo ranged from 13-15 minutes. In addition, all ramelteon doses resulted in statistically significant increases in TST (ramelteon 4 mg, 8 mg, 16 mg, 32 mg vs. placebo; 411 min, 412.9 min, 411.2 min, 418.2 min vs. 400.2 min, respectively ($p = 0.001$)). No statistically significant differences in WASO were seen. According to patient reports, ramelteon did not greatly impact perceived sleep latency or TST. There were no differences on next-day performance or alertness measures, and the incidences of adverse events were similar in both groups. (See appendix A for additional details).

Preliminary data on file from a Phase III trial in adults with chronic insomnia show a statistically significant decrease in LPS versus placebo (11-16 minutes). Preliminary Phase III data has not demonstrated statistically significant differences in subjective sleep measures.[17]

Chronic Insomnia in Elderly Patients:

Current data on file from a Phase III study in patients 65 years and older with primary insomnia for at least 3 months resulted in a decrease in LPS and an increase in TST with 4mg or 8mg compared to placebo. A decrease in subjective sleep latency was reported with active treatment; however, no differences were reported in other subjective sleep measures for any treatment group compared to placebo.[17]

The available abstracts for the studies in elderly patients reveal little information regarding concurrent medications and disease states in their subjects. The lack of information does not allow one to determine if the elderly subjects in the studies are similar to the elderly patients in a VA system in terms of

comorbidities and medication burden. The studies may lack external validity and should be cautiously applied to VA patients until more data is available for analysis.

Clinical Significance of Efficacy Measures: While there were statistically significant PSG-recorded decreases in mean LPS and increases in mean TST, the lack of available published data on subjective efficacy measures limits the ability to determine the overall improvement in quality of life experienced by patients taking ramelteon. In addition, available published studies are limited to short duration. Published studies examining clinically significant outcomes over a longer period of time in patients with chronic insomnia are needed to determine the value of ramelteon in the clinical setting.

Safety Measures Used in Ramelteon Clinical Trials[17]

Safety Assessments	Comments
Spontaneously Reported Adverse Events	Defined as unintended change in structure or function of the body which may or may be considered drug-related.
Serious Adverse Event	Defined as any event that was fatal, life-threatening, disabling or incapacitating, resulting in hospitalization, associated with congenital abnormality, or important medical events requiring intervention
Vital Signs/Physical Exam	
Laboratory Tests/12-lead Electrocardiogram (ECG)	
Residual Pharmacologic Effects	Measured via Digit Symbol Substitution Test (DSST), Visual Analog Scale (VAS), Memory Recall Test, Subjective Level of Alertness and/or Subjective Ability to Concentrate.
Rebound Insomnia	Measured via changes in sleep latency post discontinuation of a drug
Withdrawal	Measured via Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ)

Adverse Events (Safety Data)[15.17]

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%

Discontinuation Rates[14,15,17]

Five percent of subjects exposed to ramelteon during phase I-III clinical studies discontinued treatment subsequent to an adverse effect, compared with 2% of the 1370 subjects receiving placebo.

The most intolerable adverse events with ramelteon and their discontinuation rates are:

- Gastrointestinal: nausea (0.3%)
- Neurologic: dizziness (0.5%), fatigue (0.3%), insomnia (0.3%), somnolence (0.8%), headache (0.3%)

Rates of discontinuation for specific side effects are not available for placebo.

Endocrine side effects were evaluated over a six-month period in 122 subjects with chronic insomnia treated with ramelteon 16mg or placebo[12]. There were elevations in mean serum prolactin levels from baseline for women in the ramelteon group compared to placebo (4.9 mcg/L (34% increase) vs -0.6 mcg/L (4% decrease) p=0.003). Subject-reported menstrual patterns were similar between groups. There were no differences treatment and placebo were observed in men.

In a 12-month open-label study, 2 patients had abnormal cortisol levels and abnormal ACTH stimulation tests. A 29-yr-old female patient was also diagnosed with a prolactinoma. The relationship of these events to ramelteon is not known.

The adverse events reported in trials were infrequent and classified as mild-to-moderate. However, since ramelteon exerts its pharmacological effects by mimicking melatonin, there is concern as to whether ramelteon will exert similar adverse events that have been reported with long-term use of melatonin. Current data reflects similar reports of drowsiness, headache, nausea, dizziness and mild depression associated with both ramelteon and melatonin.[19] Adverse events associated with melatonin but not reported in ramelteon studies include increased irritability and anxiety, lowering of core body temperature, enhancement of immune system functioning and inhibition of ovarian function. The adverse events anticipated from ramelteon should not be based solely from those reported in clinical studies, but also from those encountered with melatonin use. Post-marketing data is needed to determine the safety of long-term use of ramelteon.

Drug abuse potential: One trial assessed the drug abuse potential of ramelteon compared to triazolam in 14 patients with known history of sedative drug abuse. Doses of ramelteon up to 20x the therapeutic dose, resulted in no abuse potential or behavioral impairment compared to triazolam.[17, 20]

Precautions[15,17]

- Ramelteon has not been studied in subjects with severe hepatic impairment, severe sleep apnea, or severe COPD, therefore, use is not recommended in such patients.
- Adolescents or children; reproductive development may be affected (effect is not known)
- Concurrent use of alcohol
- Concurrent use of fluvoxamine
- Depressed patients; worsening of depression or suicidal ideation may occur
- Following ingestion of ramelteon, patients should limit their activities to bedtime preparation
- Hazardous activities such as operation of motor vehicles or heavy machinery should be avoided
- Underlying physical or psychiatric disorders; worsening of insomnia, failure of insomnia to remit, or emergence of new behavioral or cognitive abnormalities may indicate the presence of a primary medical and/or psychiatric illness

Laboratory Monitoring[15]

No ongoing laboratory 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.

Contraindications[15]
Hypersensitivity to ramelteon or any excipients in the ramelteon formulation.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for trade name Rozerem:

Potential name confusion: Remeron® (mirtazapine): Remeron is indicated for use in depression, and is sometimes used off-label for insomnia. Rozerem is only available in 8 mg whereas Remeron comes in doses of 15, 30 and 45 mg.
Potential Severity: Minor
Probability: Occasional

Potential name confusion: Reminyl (4mg, 8mg, 12 mg)
Potential Severity: Minor
Probability: Uncommon

Potential name confusion: Razadyne (8mg, 16mg, 24mg)
Potential Severity: Minor
Probability: Frequent

Potential name confusion: Romazicon (0.1mg/ml injection)
Potential Severity: Minor
Probability: Uncommon

LA/SA for generic name ramelteon:

Potential name confusion: Ramipril (Altace®): Ramipril is a non-formulary ACE inhibitor available in doses of 1.25 mg and 2.5 mg.
Potential Severity: Minor-Moderate
Probability: Infrequent

Drug Interactions[15,17]

Ramelteon is metabolized primarily at CYP1A2; the CYP2C subfamily and CYP3A4 are also involved to a minor degree. The most significant drug interactions involve medications which are metabolized through these pathways.

Medications which inhibit CYP3A4 (ketoconazole):

Ketoconazole, a potent CYP3A4 inhibitor, may increase ramelteon plasma concentrations when used concurrently. Subjects of a study were administered ketoconazole 200 mg twice daily for four days, then administered a single dose of ramelteon 16 mg. The ramelteon AUC and Cmax increased 84% and 36%, respectively, compared to ramelteon alone. Similar results were observed with the M-II metabolite pharmacokinetic parameters. Use caution with the concomitant use of ramelteon and potent CYP3A4 inhibitors such as ketoconazole. If used concomitantly, monitor for signs and symptoms of ramelteon toxicity including somnolence, dizziness, fatigue, nausea, headache and insomnia.

Medications which inhibit CYP2C9 (fluconazole):
Fluconazole, a potent CYP2C9 and less potent CYP3A4 inhibitor, may increase ramelteon plasma concentrations when used concurrently. When coadministered with fluconazole, after a single dose of ramelteon 16 mg, the AUC and Cmax of ramelteon increased approximately 150%, compared to

ramelteon alone. Similar results were observed with the M-II metabolite pharmacokinetic parameters. Use caution with the concomitant use of ramelteon and potent CYP inhibitors such as fluconazole. If used concomitantly, monitor for signs and symptoms of ramelteon toxicity including somnolence, dizziness, fatigue, nausea, headache and insomnia.

Medications which inhibit CYP1A2 (fluvoxamine):

Fluvoxamine, a potent CYP1A2 inhibitor, significantly increases ramelteon plasma concentrations when used concurrently. When a single dose of ramelteon 16 mg was coadministered to subjects who received fluvoxamine 100 mg twice daily for 3 days prior, the ramelteon area under the concentration-time curve (AUC) and maximum concentration (Cmax) increased approximately 190-fold and 70-fold, respectively. Concurrent use of ramelteon and fluvoxamine is not recommended. If concomitant use cannot be avoided, monitor for signs and symptoms of ramelteon toxicity including somnolence, dizziness, fatigue, nausea, headache and insomnia.

Potent inhibitors of CYP450 (rifampin):

Rifampin is a potent inducer of cytochrome P450 metabolism and may significantly reduce ramelteon bioavailability when used concurrently. When subjects were administered rifampin 600 mg once daily for 11 days and a single dose of ramelteon 32 mg, the total exposure (both AUC and Cmax) to ramelteon and it's metabolite M-II decreased a mean of approximately 80% (range 40% to 90%). Ramelteon efficacy may be significantly reduced when used concurrently with potent CYP1A2, CYP2C and CYP3A4 inducers. Concomitant use of ramelteon during rifampin therapy may result in decreased efficacy of ramelteon due to rifampin induction of ramelteon metabolism via CYP2C and CYP3A4 isoenzymes. If used concomitantly, monitor patients for lack of ramelteon efficacy.

Alcohol

With single-dose daytime administration of ramelteon 32 mg (4 times the recommended dose) and alcohol (0.6 g/kg), an additive effect was seen on some measures of psychomotor performance. Because alcohol itself impairs performance and ramelteon is intended for sleep, patients should exercise caution when using ramelteon with alcohol.

Drug-Lab Interactions[17]

Ramelteon 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 using two standard urine drug screening methods.

Acquisition Costs

Comparison of the Acquisition Costs of Ramelteon vs. other Insomnia Treatments

Drug	Dose	Cost per tablet/capsule*
Ramelteon (Rozerem™)†	8 mg	$1.60
Zolpidem (Ambien™)∞	5 mg, 10 mg	$1.26, $1.85
Zaleplon (Sonata™)∞	5 mg, 10 mg	$1.28, $1.59
Eszopiclone (Lunesta™)∞	1 mg, 2 mg, 3 mg	$1.50**, $1.50**, $1.50**
Temazepam	15 mg, 30 mg	$0.05, $0.06
Lorazepam	0.5 mg, 1 mg, 2 mg	$0.03, $0.04, $0.07
Diazepam	5 mg, 10 mg	$0.02, $0.06
Trazodone	50 mg, 100 mg	$0.02, $0.04
Mirtazapine	15 mg, 30 mg, 45 mg	$0.13, $0.21, $0.29
Doxepin	25 mg, 50 mg	$0.03, $0.04
Cyproheptadine	4 mg, 8 mg	$0.04 (comes only in 4mg)

***Lowest FSS pricing as of 1/06- rounded to the nearest cent; **FSSR price**
∞Not on National VA formulary; †-pending formulary status

Pharmacoeconomic Analysis:[17]

A budget impact model has been designed by Takeda evaluating the impact ramelteon is likely to have on a plan's drug budget and total medical treatment costs among an enrolled population. The model was based on a retrospective pre-post study design to estimate the treatment costs for insomnia prior to and after the introduction of ramelteon and designed with three main inputs: health-plan related inputs (base case estimated for plan population of 1,000,000 enrollees (50.8% women), overall prevalence of insomnia (10% with 50% of those patients actually treated for insomnia), drug-treatment related inputs (base case assumed a 1.9% market share for ramelteon in the first year for treated insomnia patients) and resource-related inputs (base case used wholesale acquisition drug costs (WAC) and estimated number and costs associated with provider visits according to national surveys). The key assumptions to the model include prevalence of insomnia for one year and drug therapies immediately available for use.

The base case results estimated that the total annual budget is estimated to increase by approximately $134,000 with an incremental per member per month (PMPM) cost of $0.02. The best-base and worse-case scenarios were estimated using one-way sensitivity analysis with a relative change of ± 50% for each of the following parameters: unit cost of ramelteon, percentage of insomnia patients treated, percent of ramelteon use, and average number of prescriptions per year. The best-case scenario decreased the incremental PMPM from the best case value of $0.02 to $0.01 using the assumptions that the unit cost was $1.13, 25% of patients with insomnia are actually treated, an average of three prescriptions are filled yearly and a ramelteon market share level of 1%. In contrast, the worst-case scenario results increased the PMPM cost to $0.13 with the assumptions that the unit cost was $3.38, 75% of patients with insomnia were actually treated, nine prescriptions were filled yearly and ramelteon market share increased to 2.9%.

This model has several limitations in its applicability in a VA setting. The predicted market share of 1.9% in the first year is likely an appropriate estimation. However, the base case analysis included a patient population consisting of 50% female patients and an age distribution of only 6% for patients over the age of 65. Clearly, this is not reflective of the VA population and carries important implications given that insomnia is seen more frequently in females than males and has a high prevalence rate in the elderly. The average drug acquisition cost in the model and current VA pricing are similar ($2.25 vs. $2.14), but the Federal Supply Schedule price for the product will likely be significantly lower. Accurate VA pricing and data inputs more reflective of a male elderly population are required to determine whether the VA system results for the model would lie more toward the best or worse case scenario values.

This analysis was conducted using placebo trials and not against other active and acceptable agents so the relevance of this analysis is unknown.

Conclusions

Ramelteon, an MT_1/MT_2 receptor agonist is the first prescription hypnotic that is not designated as a controlled substance. While the agent appears to have no apparent drug abuse potential, to date, it has not been adequately studied in patients with known histories of substance addiction and dependence. Long-term safety and efficacy trials are not available with ramelteon in individuals with histories of benzodiazepine abuse. A number of clinical trials have been conducted with ramelteon in transient and chronic insomnia, though only two trials are available in full text at the present time. Trials have consistently reported a significant decrease in mean LPS; however, consistent improvements in subjective sleep measures have not been reported. Ramelteon appears to only have a hypnotic effect in which there is sleep induction but no confirmed maintenance of sleep. Benzodiazepines and other sedative-hypnotics provide both induction and maintenance of sleep. Ramelteon cannot be considered as an alternative option to benzodiazepines and other sedative-hypnotics for sleep maintenance. Ramelteon may be effective for those who have trouble falling asleep, but further peer-reviewed published data is needed to determine its clinical value and place in therapy.

Appendix A: Clinical Trials

Single dose Transient Insomnia Model in Healthy Non-elderly Adults

Trial /Design	Primary Objective/Endpoints	Methods	Inclusion/Exclusion	Results	Adverse Events/Withdrawals
Trial: Roth et al[20] Design: Phase II, multicenter, randomized, double-blind, placebo-controlled, single dose, parallel-group study conducted in a sleep laboratory.	Primary Objective: Safety and hypnotic efficacy of ramelteon in a sleep laboratory after single-dose administration of ramelteon (16 mg or 64 mg) compared with placebo in subjects unfamiliar with a sleep laboratory environment. Primary safety and efficacy endpoints: PSG-recorded mean LPS, vital signs, laboratory tests, 12-lead ECG, and physical examination before leaving laboratory.	Duration: One night Treatment: Subjects were stratified into two groups according to usual reported sleep duration (6.5 to <7.5 hrs or 7.5 to 8.5 hrs) and then randomly assigned with double-blind procedures a 16 mg group, 64 mg group or placebo with a single administration 30 minutes before bedtime. Monitoring: PSG recordings every eight hours with a post-sleep questionnaire and DSST test thirty minutes post-PSG.	Inclusion criteria: Men and women 35-60 yrs. of age; a reported usual total sleep duration of 6.5 to 8.5 hrs; a usual sleep latency of 30 minutes or less, and a habitual bedtime between 8:30 PM and midnight; be within 20% of their ideal body weight and in overall good health. Exclusion criteria: Had previously slept in a sleep laboratory; Epworth Sleepiness Scale score >10; changed sleep schedules within the preceding 3 months, or any physical or psychiatric disorder that may have been associated with a sleep disturbance.	Baseline: Placebo group: Mean age: 44.0 ± 7.1, 62% female, 84% Caucasian, 78% ≤ 50 yrs; Ramelteon 16 mg group: Mean age: 44.7 ± 6.6, 65% female, 87% white, 83% ≤ 50 yrs; Ramelteon 64 mg group: Mean age 43.9 ± 7.0, 56% female, 85% white, 79% ≤ 50 yrs.	There were no discontinuations in the study because of adverse events, abnormal laboratory test, vital sign measurement, electrocardiographic finding, or physical examination finding.

Parameters	**Placebo**	**Ramelteon 16 mg**	**Ramelteon 64 mg**	**P-value**
Latency to persistent sleep	24.6 ± 21.9	14.1 ± 15.1	15.5 ± 15.4	< .001
Total Sleep Time	441.3 ± 41.7	425.4 ± 37.6	422.4 ± 34.8	.008
Wake time after sleep onset	42.1 ± 33.3	37.4 ± 28.1	39.5 ± 25.7	.436
Mean number of awakenings	6.7 ± 3.69	6.8 ± 4.01	7.0 ± 3.98	.793
TST in stage 1 sleep, %	12.6 ± 6.2	11.7 ± 5.5	12.8 ± 6.1	.282
TST in stage 2 sleep, %	58.0 ± 8.9	59.3 ± 9.2	58.9 ± 8.2	.426
TST in stage 3/4 sleep, %	9.8 ± 9.1	8.7 ± 9.0	8.2 ± 7.5	.280
TST in REM sleep, %	19.6 ± 5.7	20.3 ± 6.3	20.0 ± 6.0	.648
Subjective sleep latency, min	31.2 ± 26.8	22.2 ± 24.1	25.4 ± 28.3	.022
Subjective TST, min	410.6 ± 56.0	427.8 ± 57.4	419.9 ± 56.7	.060
Subjective sleep quality	3.3 ± 1.0	3.1 ± 1.2	3.5 ± 1.1	.012
Subjective number awakenings	3.2 ± 2.20	3.1 ± 1.97	3.5 ± 2.74	.441

Adverse Events	Placebo, n=123	Ramelteon 16 mg, n=126	Ramelteon 64 mg, n=126
Total Subjects with any adverse event	21 (17.1)	20 (15.9)	22 (17.5)
Headache NOS	2 (1.6)	9 (7.1)	8 (6.3)
Fatigue	0 (0.0)	3 (2.4)	5 (4.0)
Somnolence	3 (2.4)	6 (4.8)	3 (2.4)
Nausea	0 (0.0)	3 (2.4)	2 (1.6)
Dizziness (except vertigo)	1 (0.8)	3 (2.4)	1 (0.8)

				Subjective ease of falling back to sleep, % responding yes	23.2%	22.2%	30.4%	.349	

Study Conclusions:
Safety: There were no differences in mean DSST scores in each of the three groups. The 64-mg group reported small but statistically significant declines in subjective level of alertness and ability to concentrate, as compared to the placebo group. The 16-mg group was not significantly different from the placebo group on any of these measures.
Efficacy: Both dosage levels of ramelteon were associated with a statistically significant decrease in mean LPS and significant increases in mean TST and therefore, sleep efficiency. The differences in WASO, awakenings after persistent sleep, number of awakenings lasting longer than 2 minutes did not differ statistically between the two groups. There were also no statistically significant differences among the three groups for percentage of TST spent in any sleep stage. The subjective number of awakenings and subjective ease of falling back to sleep did not differ from placebo for either group.

Quality Assessment (Fair): not generalizable to VA population
Phase II trial
Mean age of 44 years, majority female patients
Multiple exclusions, most significant being that patients have not had prior sleep disturbances
No investigation on effects of concurrent medication use
Co-morbidities not reported
Inclusion criteria was not based on DSM-IV criteria for primary insomnia but rather enrolled healthy subjects

The study was sponsored by Takeda.

Short-term treatment of Chronic Insomnia in a nonelderly population

Trial /Design	Primary Objective/Endpoints	Methods	Inclusion/Exclusion	Results
Trial: Erman et al[22] Design: Thirteen center, randomized, double-blind, placebo-controlled, five-period crossover study conducted in sleep laboratory	Primary Objective: Safety, efficacy, and dose response of ramelteon at doses 4, 8, 16, and 32 mg compared to placebo in subjects with chronic primary insomnia as defined by DSM-IV (as evidenced by mean LPS measured during a 2-night PSG screening in a sleep center). Endpoints:	Duration: 5 periods of 2 nights each, with a 5-day or 12-day washout period in between treatments. Treatment: A total of 107 patients, aged 18-64 years, were randomized into a dosing schedule that	Inclusion Criteria: Men and non-pregnant, non-lactating women 18-64 yrs of age with DSM-IV defined chronic insomnia for ≥ 3 months; sSL > 30 min; sTST < 6.5 hours per night; daytime complaint(s) associated with disturbed sleep; mean latency to sleep ≥ 20 min on two consecutive	Baseline Population: Mean age: 37.7 yrs.; 64.2% women, 54.7% Caucasian, 22.6% Hispanic, African-American 21.7% and 0.9% Asian. Baseline Objective Sleep Measures : At screening, mean LPS for all patients was 75.2 min, mean TST was 347.9 min, and mean WASO was 63.0 min. Table 1: PSG and subjective sleep measures

Parameters	Ramelteon 4 mg (n=103)	Ramelteon 8 mg (n=103)	Ramelteon 16 mg (n=103)	Ramelteon 32 mg (n=103)	Placebo	P-value
Objective LPS (LS mean), min	24.0	24.3	24.0	22.9	37.7	P < 0.001
Difference from placebo (95%CI)	-13.7(-20.4, -7.0)	-13.4(-20.0, -6.7)	-13.7(-20.4, -7.0)	-14.8(-21.5, -8.1)		
Subjective Sleep Latency (min)	50.9	46.7	43.9	46.5	57.0	P = 0.040
Difference from placebo (95%Cl)	-6.2(-17.4, 5.0)	-10.4(-21.6, 0.8)	-13.1(-24.3, -1.9)	-10.5(-21.7, 0.7)		
PSG total sleep time (TST), min	411.0	412.9	411.2	418.2	400.2	P=0.001
Difference from placebo (95%CI)	10.7 (0.4, 21.0)	12.6(2.4, 22.9)	10.9(0.7, 21.1)	17.9(7.7, 28.2)		
Subjective total sleep time (TST), min	364.1	370.4	370.9	372.8	360.6	P=0.282
Difference from placebo	3.5(-12.4, 19.3)	9.8(-6.1, 25.7)	10.2(-5.6, 26.1)	12.2(-3.7, 28.1)		

	Primary objective (assessed by PSG): 1.) Latency to persistent sleep (LPS), the first epoch of the first consecutive 30-s epoch not scored as awake. Secondary objective (assessed by PSG): 1.) total sleep time, TST 2.) WASO, total amount of time spent awake after the onset of persistent sleep 3.) Sleep architecture percentage of sleep time in each stage. Patient-reported sleep latency, total sleep time, and sleep quality.	included 4, 8, 16 and 32 mg of TAK-375 and placebo. Patients received all five treatments, with a 5- to12-day washout period between treatments. Monitoring: Each night PSG monitoring was performed for 8 hours and upon awakening, visual analog scale (VAS) for mood and feeling, digit symbol substitution test (DSST), memory recall tests, and post-sleep questionnaires were completed.	PSG screening nights with no night < 15 minutes; a mean awake time after sleep onset (WASO) ≥ 60 minutes for two consecutive PSG screening nights with no night <45 minutes; a habitual bedtime between 8:30 PM and midnight; and a body weight within 20% of the ideal. Exclusion Criteria: *Patients whose histories included a potential medical or psychiatric condition (depression, anxiety, seizure disorders, drug addiction, sleep apnea, noctural myoclonus, mental retardation, history of alcohol abuse within past two years, tobacco use within the past 90 days, or psychotropic drug use. *Use of St. John's Wort or melatonin *Consumption of grapefruit or grapefruit juice within 3 weeks prior to the study *Shift workers who	

(95%CI)						
Subjective sleep quality	3.6	3.7	3.7	3.7	3.8	P=0.525
Difference from placebo (95%CI)	-0.2(-0.4, 0.1)	-0.1(-0.4, 0.1)	-0.1(-0.3, 0.2)	-0.1(-0.3, 0.2)		
PSG WASO (min)	48.8	47.0	48.3	43.0	45.5	P=0.470
Difference from placebo (95%CI)	3.3(-5.4, 11.9)	1.6(-7.1, 10.2)	2.8(-5.8, 11.4)	-2.5(-11.2, 6.1)		

According to patient reports, ramelteon did not greatly impact perceived sleep latency or TST and subjective sleep quality did not differ from placebo for any treatment group.

Table 2: Latency to REM and total sleep time spent in each sleep stage:

Parameters	Ramelteon 4 mg (n=103)	Ramelteon 8 mg (n=103)	Ramelteon 16 mg (n=103)	Ramelteon 32 mg (n=103)	Placebo	P-value
Latency to REM, min	79.7	75.2	78.0	79.1	79.7	P < 0.05
Difference from placebo (95%CI)	-13.7(-20.4, -7.0)	-13.4(-20.0, -6.7)	-13.7(-20.4, -7.0)	-1.6(-10.9, -7.6)		
Stage 1, %	11.4	11.5	11.7	12.0	11.1	P < 0.05
Difference from placebo (95%Cl)	0.4(-0.6, 1.3)	0.4(-0.5, 1.4)	0.6(-0.3, 1.6)	0.9(0.0, 1.9)		
Stage 2, %	55.0	54.3	54.3	54.1	53.3	P < 0.05
Difference from placebo (95%CI)	1.7 (0.2,3.1)	1.0(-0.5, 2.4)	1.0(-0.5, 2.4)	0.8(-0.7, 2.3)		
Stage 3/4, %	13.6	13.0	13.4	12.8	14.9	P < 0.05
Difference from placebo (95%CI)	-1.3(-2.5, -0.2)	-1.9(-3.0, -0.7)	-1.4(-2.6, -0.3)	-2.1(-3.3, -1.0)		
REM, %	48.8	47.0	48.3	43.0	20.9	P < 0.05
Difference from placebo (95%CI)	-0.7(-1.9, 0.5)	0.1(-1.1, 1.3)	2.8(-5.8, 11.4)	-0.5(-1.6, 0.7)		

The statistically significant decrease in Stage ¾ sleep for each ramelteon dose compared to placebo appears to primarily be a consequence of an increase in amount of total sleep desired combined with small reduction in minutes of stage ¾.
Percentage of time spent in stage ¾: total min in stage ¾/total min in TST *100; an increase in TST will decrease the percentage time in stage ¾ sleep.

Table 3: Next-day performance and alertness
There were no statiscally significant differences between placebo and any ramelteon dose group on next-day performance and alertness measures, regardless of dose.

Parameters	Ramelteon 4 mg (n=103)	Ramelteon 8 mg (n=103)	Ramelteon 16 mg (n=103)	Ramelteon 32 mg (n=103)	Placebo, (N=103)
DSST	47.3	46.5	47.7	47.5	47.4
Memory test-immediate recall	8.0	7.9	7.7	8.0	8.0
Memory test-delayed recall	4.9	5.0	5.4	5.1	4.9
Level of alertness	3.6	3.5	3.6	3.5	3.6
Ability to concentrate	3.6	3.5	3.5	3.5	3.6

			had flown across ≥3 time zones within 7 days prior to the screening *History of hypersensitivity to ramelteon or related compounds.	

Adverse Events/Withdrawals

Fifty-six patients experienced an adverse event; twenty-nine experienced mild adverse events and twenty-two patients experienced moderate adverse events. The incidence of adverse events ranged from 8.4 to10.7% among the ramelteon dose groups and 8.7% in the placebo group.

Six severe adverse events did occur: atrioventricular block (placebo), lung cancer and syncope (placebo), headache (placebo), sinus headache (4 mg ramelteon; possible related to study drug), and contact dermatitis (8 mg ramelteon; considered not related to study drug). No subject discontinued the study due to an adverse event.

Summary of most frequently reported adverse events:

Parameters	**Ramelteon 4 mg (n=103)**	**Ramelteon 8 mg (n=103)**	**Ramelteon 16 mg (n=103)**	**Ramelteon 32 mg (n=103)**	**Placebo, (N=103)**
All adverse events	25.2	18.3	19.6	21.4	19.4
Headache NOS	2.8	4.8	4.7	5.8	4.9
Somnolence	0.0	1.9	3.7	1.9	1.0
Pharyngolaryngeal pain	3.9	0.0	0.0	3.9	1.0
Nasopharyngitis	1.0	0.0	1.9	1.0	2.9
Nausea	2.9	1.0	0.9	1.0	1.9
Dyspepsia	1.0	0.0	0.9	2.9	0.0
Influenza	1.0	1.0	0.0	0.0	12.9
Abdominal pain, upper	1.0	1.0	0.9	0.0	1.0
Dysmenorrhea	1.9	1.0	0.0	1.0	0.0
Dry mouth	1.9	0.0	0.0	0.0	1.0
Fatigue	0.0	1.0	0.9	1.9	0.0

Conclusions: There was a statistically significant difference in mean LPS and TST, but WASO was not affected. Sleep architecture and next-day performance were also not affected. Adverse events were mild-to-moderate in severity with no discontinuations.

Quality Assessment (fair): although not generalizable to a VA population:

- Mean age of 37.7 years, 64.2% women, 35.8% men
- Study was powered to detect differences in objective measures, but not powered to detect differences in subjective effects.
- Multiple exclusions; effects on jet lag could not be determined due to exclusionary criteria
- Comorbidities were not reported
- Ramelteon reduced LPS by 13-15 min, will within the range seen with commonly prescribed sedative-hypnotics (e.g. zolpidem and zaleplon) of 8-17 min reduction in LPS compared to placebo.
- There was a lack of treatment effect on WASO, both in patients with high and low baseline WASO values.
- Ramelteon does not appear to alter sleep architecture as there were no apparent differences among the treatments for latency to REM or percentage of time spent in REM, stage 1, or stage 2 sleep.

The study was sponsored by Takeda.

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