RAMELTEON: A Novel Hypnotic Indicated for the Treatment of Insomnia

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ABSTRACT

Ramelteon is a hypnotic with a novel mechanism of action and is the only melatonin agonist currently indicated for the treatment of insomnia. This drug acts at the MT_1 and MT_2 receptors to promote sleep and exert an effect on circadian rhythms. Unlike traditional hypnotics, ramelteon demonstrates no affinity for any CNS receptors commonly associated with sedation (GABA, dopamine, opiate, serotonin). Perhaps due to this unique mechanism of action, ramelteon has demonstrated a low potential for abuse in clinical trials involving both insomnia patients and individuals with a history of substance abuse. It is the only insomnia therapeutic that is not classified as a scheduled drug by the US Drug Enforcement Agency (DEA). However, it has been shown in multiple studies to demonstrate a moderate, statistically significant improvement in reducing the time to sleep onset in both adult and elderly insomnia patients in studies lasting up to one year. Generally, treatment with ramelteon is well tolerated and produces few adverse effects.

INTRODUCTION

Insomnia is defined as difficulty in initiating or maintaining sleep, or non-restorative sleep, which commonly is associated with distress or impairment in daytime functioning. Individual experiences of insomnia

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range from transient and mild to chronic and severe. Prevalence estimates in the general population vary widely depending on the criteria used. Studies using liberal criteria have shown that between 36 to 56 percent of the population experiences some symptoms of the disorder, while more restrictive surveys have found that 8 to 13 percent of the general population would meet the *Diagnostic and Statistical Manual of Mental Disorders, Text Revision, Fourth Edition* (DSM-TR-IV) criteria for insomnia.[1–4]

Research in the field of sleep medicine has shown that there is an association between insomnia and a number of psychiatric and medical conditions. Coronary artery disease and hypertension appear to be linked to insomnia[5,6] and a particularly strong, bidirectional connection has been found between insomnia and both depression and anxiety.[2,7–9] While the root causes of this disorder are only partially understood, certain risk factors, (i.e., age, female gender, psychiatric or physical illness, and some types of shift work) appear to increase an individual's risk for developing chronic insomnia.[1,2,8,10–12]

TREATMENT OPTIONS

The number of treatment options for insomnia has increased markedly in recent years. The benzodiazepine receptor agonists (BZRAs), including benzodiazepines and the non-benzodiazepines, are the leading class of insomnia therapeutics. These compounds act at the GABA receptor complex in order to induce sedation. Benzodiazepines used in the management of sleep include triazolam, temazepam, estazolam, quazepam, and flurazepam. The non-benzodiazepines include zolpidem, zolpidem CR, zaleplon, and eszopiclone. While both types of BZRAs act via a similar mechanism of action, the non-benzodiazepines exert a greater separation of hypnotic, sedative, and amnesiac effects from anxiolytic, myorelaxant, and respiratory depressant activity by binding more selectively to a subset of the GABA receptor complex.[13–15]

Although the preponderance of evidence has shown that BZRAs are safe and effective for most individuals, some concerns regarding their use have been raised. Triazolam was originally prescribed at what is now understood to be a supratherapeutic dose, leading to a variety of serious side effects,[16] and several BZRAs have been shown to present the risk for abuse and dependence in at-risk subpopulations including drug-abusers.[17] Most recently, reports in the lay press seem to indicate that in rare cases, often involving misuse or concurrent use of alcohol, BZRAs may be associated with sleep eating and sleep driving behaviors.[18]

Due to these lingering safety concerns and the common presentation of comorbid insomnia and depression, low-dose antidepressants are widely prescribed to treat insomnia on an off-label basis. Unfortunately, the clinical evidence supporting this treatment course is limited, especially in patients with mood disorders.[19–21] Trazodone has been shown to improve some sleep parameters for up to two weeks,[22,23] but evidence of its efficacy in primary insomnia does not warrant its common use. There also is modest evidence for the use of doxepin (20–25mg),[24,25] while other frequently used sedating antidepressants (e.g., mirtazapine, amitriptyline) have been practically unstudied in chronic insomnia.

The most recently approved class of insomnia therapeutics is the melatonin agonist. Although several melatonin agonists are in various stages of development, ramelteon is first member of this class to be approved for the treatment of insomnia in the US market.

CLINICAL PHARMACOLOGY

Ramelteon is chemically described as (*S*)-*N*-[2-(1,6,7,8-tetrahydro-2*H*-indeno-[5,4-*b*]furan-8-yl)ethyl]propionamide and its chemical structure is $C_{16}H_{21}NO_2$.

Unlike the BZRAs, which modulate the GABA receptor complex, ramelteon acts on melatonin receptors, which are known to be involved in the modulation of the normal sleep-wake cycle. The suprachiasmatic nucleus (SCN) controls circadian rhythms of sleep and wakefulness, and is the location of most of the melatonin receptors. Ramelteon binds to the MT_1 and MT_2 melatonin receptors in the SCN, inhibiting neuronal firing and thereby enabling the homeostatic mechanism to promote sleep.[26] The affinity of ramelteon for the MT_1 and MT_2 receptors is 3 to 16 times higher than that of endogenous melatonin. Furthermore, ramelteon has no affinity for dopamine, opiate, serotonin or GABA receptors, thus narrowly confining its activity to the melatonin receptor complex.

In healthy adults, ramelteon is rapidly absorbed and eliminated and displays linear pharmacokinetics over a dose range of 4 to 64mg.[27,28] Peak concentration is reached

Ramelteon has demonstrated a low potential for abuse in clinical trials involving both insomnia patients and individuals with a history of substance abuse. It is the only insomnia therapeutic that is not classified as a scheduled drug by the US Drug Enforcement Agency (DEA).

approximately 45 minutes post-dose and the elimination half-life ($T_{1/2}$) is 1 to 2.6 hours. Total exposure ($AUC_{0\text{-inf}}$) and the time of maximal plasma drug concentration (T_{max}) both increase, while the maximal concentration (C_{max}) decreases if ramelteon is administered with a high fat meal. Co-administration of ethanol and ramelteon increases subjects' exposure to ramelteon, although not to a clinically significant level, but it does not produce significant changes in the pharmacokinetics of ethanol itself.[28] The total absorption of ramelteon is 84 percent. However, extensive first-pass metabolization limits absolute oral bioavailability to approximately two percent. Ramelteon is primarily metabolized via the CYP1A2 pathway and principally eliminated in urine (84%). Due to the compound's short half-life, repeated once-daily dosing does not appear to result in accumulation.

Unlike with the BZRAs, age and gender do not appear to impact ramelteon's sedative properties.[29] In one study, a 16mg dose of ramelteon resulted in significantly higher values for $AUC_{0\text{-inf}}$ and C_{max}, and significantly longer $T_{1/2}$ in elderly versus adult subjects. However, the clinical relevance of this difference appeared to be of minimal or no significance. No meaningful PK gender differences were observed.

Relative to healthy controls, mild to moderate renal impairment is not associated with any marked changes in ramelteon exposure.[30] However, mild to moderate hepatic impairment is associated with statistically significant increases in systemic exposure to ramelteon.[31] These increases (4-fold and 10-fold, respectively, after 7 days of dosing with 16mg) were not deemed clinically relevant in light of the wide inter-subject variability in ramelteon AUC seen throughout this product's clinical development.

Respiratory depressant effects are a concern with many hypnotics. Two at-risk populations, patients with obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD), were observed following dosing with 16mg ramelteon or placebo. In an evaluation with 26 mild to moderate OSA patients, the apnea-hypopnea index and arterial oxygen saturation level (SaO2) were similar across the groups treated with ramelteon and placebo.[32] A different study involving 26 mild to moderate COPD patients also found comparable SaO2 levels and the apnea-hypopnea indexes for both treatment conditions.[33] The results from both studies imply that ramelteon is unlikely to produce respiratory depressant effects or to exacerbate sleep apnea in at-risk patients.

The interactions between ramelteon and a number of frequently prescribed medications have been characterized in healthy adults. Co-administration of fluvoxamine (100mg, twice daily for 3-day run-in period), a strong CYP1A2 inhibitor, and ramelteon (16mg, single dose) increased the AUC of ramelteon by 190-fold and C_{max} by 70-fold.[28] Fluvoxamine is the only drug that is specifically contraindicated by the ramelteon labeling, and caution is urged for co-administration with other CYP1A2 inhibitors. Rifampin, a strong CYP inducer, was shown to significantly reduce ramelteon exposure to such a degree that ramelteon may be not be an appropriate hypnotic for subjects receiving this medication.[28] Fluconazole (strong CYP2C9 inhibitor), ketoconazole (strong CYP3A4 inhibitor), and donepezil (CYP2D6/CYP3A4 substrate) all significantly increased systemic exposure to ramelteon (by 85%, 150%, and 100%, respectively), suggesting caution for co-administration.[28,34–36] Co-administration of ramelteon and theophylline (CYP1A2 substrate), fluoxetine (CYP2D6 substrate), omeprazole (CYP1A2 inducer/CYP2C19 inhibitor), and dextromethorphan (CYP2D6 substrate)[37–40] did not produce clinically meaningful changes in subject exposure to ramelteon. Interaction studies with midazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate), dextromethorphan (CYP2D6 substrate), digoxin (p-glycoprotein substrate), warfarin (CYP2C9 [S]/CYP1A2 [R] substrate), and omeprazole (CYP1A2 inducer/CYP2C19 inhibitor)[28,37,38,40–42] found no significant changes in pharmacokinetics when co-administered with ramelteon.

> Due to [ramelteon]'s short half-life, repeated once-daily dosing does not appear to result in accumulation.

RAMELTEON EFFICACY IN CLINICAL TRIALS

Insomnia is frequently categorized as either transient or chronic. Transient insomnia may occur on one or several days. To be considered chronic, insomnia must typically occur several nights a week over a period of months. The 'first night effect' (i.e., sleep disruption resulting from spending one night in an unfamiliar setting) often is used to evaluate a hypnotic's impact in transient insomnia. In one trial, healthy adult volunteers (*N*=375) received either ramelteon 16mg, 64mg or placebo 30 minutes prior to bedtime and then underwent a single night of polysomnography recording (PSG).[43] Both dose groups saw significant improvements in objectively measured Latency to Persistent Sleep (LPS) and Total Sleep Time (TST). Subjects in the 16mg condition also reported significant improvements in subjective Sleep Latency (sSL). No change was seen relative to placebo in PSG measured Wake time After Sleep Onset (WASO) and both the objective Number of Awakenings

(NAW) and subjective NAW (sNAW).

Ramelteon's short-term effects in chronic insomnia have been evaluated in two 2-night cross-over studies. Adult subjects meeting the DSM-IV-TR criteria for chronic insomnia for at least three months (*N*=107) participated in a dose response study evaluating the impact of ramelteon 4, 8, 16, and 32mg relative to placebo.[44] PSG recordings found significant improvements in LPS and TST relative to placebo at each dose level. sSL and subjective TST (sTST) showed numerical improvements relative to placebo but, with the exception of sSL at 16mg, did not reach statistical significance. The second two-night study was a three-period cross-over trial involving placebo and ramelteon 4 and 8mg in elderly subjects diagnosed with chronic insomnia (*N*=100).[45] PSG measured LPS, TST, and sleep efficiency all were significantly improved with both doses compared to placebo. In addition, a post-sleep questionnaire found significant improvements in sSL at the 4mg dose, but not with the higher dose level. No other subjective sleep assessments reached statistical significance.

The effect of long-term nightly dosing with ramelteon also has been examined. A 35-night study in adults diagnosed with chronic insomnia (*N*=405) compared ramelteon 8 and 16mg with placebo.[46] LPS was significantly improved with both doses at all measurement points throughout the study. Both doses also produced significant improvements in TST and sleep efficiency at the first assessment (Nights 1 and 2). Subjective patient assessments of sleep parameters were supportive of the objective PSG data.

Elderly subjects with insomnia (*N*=829) participated in another 35-night study that compared ramelteon 4 and 8mg with placebo.[47] Patient reported sleep data were collected using sleep diaries and indicated that sSL was significantly improved over all measurement points during the course of the study. Improvements were statistically significant at Week 1 (4, 8mg), Week 3 (8mg) and Week 5 (4, 8mg). Improvements seen in sTST reached significance at Weeks 1 and 3 for the 4mg-dose group. No significant differences were observed between active treatment and placebo on other subjective measures (NAW, sleep quality).

Finally, both adult (*N*=965) and elderly subjects (*N*=248) with chronic insomnia were included in a year-long trial of nightly ramelteon administration.[48] Elderly subjects age 65 and older received ramelteon 8mg, while adults (age 18–64) received ramelteon 16mg. sSL improved for both subject groups beginning and Month 1 and continuing to steadily become more improved through Month 12 assessments. Similar progressive improvements were seen in sTST, again beginning at Month 1 and continuing through Month 12. At Month 6 and Month 12 in both treatment groups, a Clinical Global Impression (CGI) assessment found an improvement in insomnia condition, a moderate and sustained improvement in severity of illness and a modest therapeutic effect.

SAFETY AND TOLERABILITY IN CLINICAL TRIALS

Ramelteon's safety was evaluated in all of the trials described above. Adverse events were generally mild to moderate and occurred at low frequency in both ramelteon and placebo treated groups. The most frequently reported adverse events in the year-long ramelteon study were nasopharyngitis (10.5% in the 8mg group, 14.9% in the 16mg group), somnolence (9.5%, 8.1%), upper respiratory tract infection (7.6%, 11.1%), and sinusitis (1.9%, 7.8%).[48]

No next-day residual effects were observed following either short-term or long-term dosing. In the transient insomnia study evaluating a single dose of ramelteon (16 or 64mg), next-day residuals were evaluated via the Digit Symbol Substitution Test (DSST) and subject assessments of alertness and ability to concentrate.[43] Ramelteon 16mg was indistinguishable from placebo while small but statistically significant declines were seen in the subjective assessments at the 64mg dose level. The two-night study of ramelteon 4 to 32mg found no next-day residual effects at any dose level as measured by the DSST, an immediate and delayed memory recall evaluation, and subject reports of level of alertness and ability to concentrate.[44] In the two-night study of 4 and 8mg in elderly subjects, no next-morning effects were seen with either dose as evaluated by the DSST, memory recall tests (immediate and delayed), visual analog scale (VAS) of feeling and mood, and subject assessments of alertness and ability to concentrate.[45]

The effect of ramelteon on middle of the night balance near peak plasma concentration was examined in two recent studies. In one trial, adults with chronic insomnia (*N*=275) were randomized to placebo, ramelteon 8mg or zopiclone 7.5mg for a 28-day double-blind treatment period.[50] On Night 14, subjects performed a balance assessment 1.5 hours prior to bedtime. Subjects were then administered their nightly dose of test article, went to bed, and were awakened 1.5 to 2 hours later to repeat the balance test. While the effect of zopiclone was pronounced, ramelteon's effect on body sway was no different than that of placebo. The second balance study was a single night balance comparison of ramelteon 8mg with zolpidem 10mg and placebo in elderly subjects with insomnia (*N*=33).[49] A balance test was performed during the day, subjects were dosed with double-blind study medication at bedtime, and then awakened two hours post-dose in order to repeat the balance assessment. Standing balance, turning speed, and stability were similar for ramelteon and placebo, while significant decrements were seen in all measures with zolpidem. There is concern that commonly prescribed insomnia medications may increase the risk of falls, especially in the elderly. The results from these studies seem to suggest that ramelteon may be free of this particular concern.

ABUSE POTENTIAL

Although safe for most patients, hypnotics present a small, but important, risk for misuse and physical dependence in a subset of the general population. Generally, abuse of these drugs is rare and largely limited to individuals with a co-existing drug or alcohol abuse problem.[51,52] Even so, a clinician's choice of a hypnotic for any given patient must take into account the potential for this risk.

Ramelteon is the only compound approved for insomnia therapy that has demonstrated no abuse potential in either pre-clinical animal models or in clinical evaluation in humans.[52] Due to this unique characteristic, it is the only insomnia therapeutic that is not classified as a scheduled drug by the US Drug Enforcement Agency (DEA).

Rhesus monkeys have commonly been used to demonstrate the addictive properties of various medications, and were used in a similar evaluation of ramelteon's potential for abuse. Four rhesus monkeys were trained to reliably discriminate between vehicle and a benzodiazepine.[53] Their response after receiving ramelteon (up to 10.0mg/kg) indicated that they did not substitute it for the benzodiazepine. The results from a different experiment involving rhesus monkeys dependent on a benzodiazepine indicated that ramelteon (up to 10.0mg/kg) did not attenuate the discriminative stimulus effects of benzodiazepine agonists.[53] Four rhesus monkeys received ramelteon for one year, with periodic treatment interruptions to allow for the evaluation of withdrawal effects.[54] Over this period, no behavioral effects were seen either with ramelteon treatment or its discontinuation, suggesting that it is unlikely to produce physical dependence. A final intravenous self-administration experiment in rhesus monkeys found that ramelteon did not produce positive reinforcing effects, again suggesting a low potential for abuse.[55]

Human studies have supported the results from the preclinical animal studies. Adults with a history of sedative abuse (N=14) participated in a study evaluating ramelteon's behavioral effects and abuse potential.[56] Subjects received once-daily doses of ramelteon (16, 80, 160mg), triazolam (0.25, 0.5, 0.75mg) or placebo. Outcome measures were evaluated 30 minutes prior to drug administration and were repeated up to 24 hours post-administration. Ramelteon showed no significant effect on any of the subjective-rated measures including those related to potential for abuse (drug liking, street value). Furthermore, 79 percent of participants identified the highest dose of ramelteon as placebo. Investigators found no difference between placebo and any dose of ramelteon on any observer-rated assessments of sedation and impairment, Word Recall/Recognition Task, Enter and Recall Task, Balance Task, DSST and Circular Lights performance. In contrast and consistent with its well established profile as a sedative drug, triazolam showed dose-related effects on a wide range of subject-rated, observer-rated and motor and cognitive performance measures.

Similarly, studies involving adults with no history of substance abuse, have found no evidence of dependence development. No rebound insomnia or withdrawal effects were observed during a two-night placebo run-out period at the conclusion of the 35-night study of ramelteon 8 and 16mg.[46] Finally, the 35-night study of ramelteon 4 and 8mg in elderly subjects produced no evidence of rebound insomnia during a one-week placebo run-out period.[47] In fact, relative to baseline values, improvements in sleep latency were maintained for the first one or two nights of the placebo run-out in both the active treatment groups. The Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) found no evidence of withdrawal symptoms in either group treated with ramelteon.

The clinical studies conducted during the development program of this therapeutic found a low frequency of adverse events, which were generally mild to moderate in severity and negligible with regard to their impact on next-day functioning.

SUMMARY

Ramelteon is the first of a novel class of therapeutics, the melatonin agonists, to be approved for the treatment of insomnia. Unlike other sedative-hypnotics, which act on the benzodiazepine receptors, ramelteon acts on melatonin receptors MT1 and MT2, promoting sleep and affecting circadian mechanisms. Ramelteon has a fast onset of action, is rapidly eliminated, and presents a safe pharmacological profile at up to eight times the therapeutic dose level. Ramelteon has been shown to successfully reduce PSG measured Latency to Persistent Sleep in short- and long-term studies lasting up to a year in both adults and elderly insomnia patients. Although less consistent, improvements were also demonstrated in subjective Sleep Latency and both objective and subjective Total Sleep Time.

Ramelteon appears to be safe. The clinical studies conducted during the development program of this therapeutic found a low frequency of adverse events, which were generally mild to moderate in severity and negligible with regard to their impact on next-day functioning. Recent studies of ramelteon's effect on middle-of-the-night balance found it

to be similar to that of placebo. Finally, ramelteon appears have a low abuse potential, presenting an important differentiation for the subset of insomnia patients with an elevated risk for addiction to traditional hypnotics.

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