Ramelteon – A Melatonin Receptor Agonist in the Treatment of Insomnia

a report by
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Insomnia is a common condition characterised by difficulty falling asleep, increased night-time wakefulness or inadequate sleep duration. Insomnia can result in daytime consequences, including tiredness, difficulty concentrating and irritability, as well as increased healthcare utilisation and reduced work productivity, lower quality of life or quality of social relationships and decrements in memory, mood or cognitive function.[1,2] Acute insomnia refers to periods of difficulty sleeping lasting one day to a few weeks, while chronic insomnia refers to sleep difficulty lasting at least three nights per week for one month or more.[2] Up to 75% of adults report symptoms of a sleep problem occurring a few nights per week or more, while approximately 10–15% have chronic insomnia.[2,3,4]

Management of insomnia includes sleep hygiene education, cognitive behavioural therapy and pharmacological therapy.[2] Pharmacological agents include benzodiazepines, non-benzodiazepine benzodiazepine receptor agonists, antihistamines, antidepressants, melatonin, herbal products and nutritional supplements.[2,5] Although highly effective at reducing sleep latency, benzodiazepine and the non-benzodiazepine benzodiazepine receptor agonists are associated with varying degrees of residual daytime sedation, abuse liability and toxicity.[6] Antidepressants and antihistamines are also effective in some patients, but have troublesome adverse effects.[1,2] Limited data also suggest that melatonin is effective in the treatment of chronic insomnia.[1] In the 2005 Sleep in America Poll, 7% of respondents reported using prescription sleep medication at least a few nights each month, 9% reported using over-the-counter sleep aids, 11% reported using alcohol, beer or wine, specifically to help them sleep, and 2% reported using melatonin for sleep.[4]

Melatonin is a neurohormone released from the pineal gland in association with the light–dark cycle that regulates sleep. The sleep-promoting and circadian effects of melatonin are attributed to interactions with two subtypes of human melatonin receptors MT_1 and MT_2.[7] A third subtype, MT_3, is a peripheral receptor.[8] The MT_1 receptor, localised in the hypothalamic suprachiasmatic nucleus, is believed to mediate circadian and reproductive effects of melatonin. The MT_2 receptor, found in the hypothalamic suprachiasmatic nucleus and the neural retina, is thought to mediate the effects of melatonin on circadian rhythms and regulate visual function. The role of the MT_3 receptor has not been defined.[9] Endogenous melatonin secretion occurs approximately two hours before an individual's habitual bedtime and is correlated with the onset of evening sleepiness. Suppression of melatonin production correlates with insomnia. Increasing plasma melatonin concentrations are associated with increased sleepiness.[7]

Ramelteon

Ramelteon (Rozerem™, Takeda) is a melatonin receptor agonist that was approved by the US Food and Drug Administration (FDA) in July 2005 for the treatment of insomnia characterised by difficulty with sleep onset.[10] It is also under evaluation for use in the treatment of circadian rhythm disorders.[9]

Pharmacology

Ramelteon is a tricyclic indan derivative that is a potent and selective human melatonin MT_1 and MT_2 receptor agonist.[9,11] Ramelteon has very low affinity for the MT_3 receptor. In comparison with melatonin, ramelteon has six-fold higher affinity for the MT_1 receptor and four-fold higher affinity for the MT_2 receptor, but 94-fold lower affinity for the MT_3 receptor.[9] The selectivity of ramelteon for MT_1 over MT_2 is more than 1,000-fold greater than that of melatonin, as melatonin has greater affinity for MT_2 receptors than MT_1 receptors.[12] Ramelteon has exhibited no measurable affinity for the gamma-aminobutyric acid (GABA) receptor complex, the benzodiazepine, cytokine, dopamine, noradrenaline, acetylcholine, neuropeptide, opiate or serotonin receptors, or ion channels and transporters.[10,13] It has exhibited low affinity for the serotonin 5-hydroxytryptamin (HT)2B receptor. Unlike melatonin, it did not exhibit activity at the serotonin 5-HT1A receptor or the dopamine D1 receptor.[13]

Ramelteon has exhibited sleep-promoting activity in several animal models. In cats, ramelteon decreased wakefulness and increased slow wave sleep and rapid eye movement (REM) sleep, with effects persisting for six hours. Melatonin produced similar effects; however, effects only persisted for two hours after administration.[9] In monkeys, ramelteon reduced the latency to sleep onset in a dose-dependent manner. Unlike melatonin, ramelteon also increased the total duration of sleep.[14,15] In other animal models, ramelteon did not exhibit impairment of performance on learning or memory assessments (water maze and delayed matching-to-position tasks in rats), unlike diazepam and triazolam. In the conditioned place-preference test in rats, neither ramelteon nor melatonin showed evidence of rewarding properties, in contrast to diazepam, triazolam and morphine.[16]

Pharmacokinetics

Ramelteon is well absorbed orally, but undergoes extensive first-pass metabolism, resulting in an overall oral bioavailability of less than 2% (range 0.5–12%).[17,18] Following oral administration, the mean time-to-peak concentration is less than one hour.[19–21] Administration with a meal delayed the time-to-peak concentration by approximately 45 minutes and reduced the peak concentration by approximately 22%, but increased the area under the plasma concentration-time curve (AUC) by 31%.[10,22] The mean AUC and peak ramelteon concentration increased dose-proportionately over a range of doses from 4mg to 64mg.[19]

The mean elimination half-life of ramelteon is approximately 0.8 hours to 2.6 hours.[10,19–21] Ramelteon undergoes extensive first-pass metabolism to at least four metabolites, primarily via oxidation to hydroxyl and carbonyl groups, with secondary metabolism to form glucuronide conjugates. Metabolite half-lives are similar to that of the parent compound.[19–21] Cytochrome P450 (CYP)1A2 is the major isozyme involved in the hepatic metabolism, with lesser involvement of the CYP2C subfamily and CYP3A4 isozymes.[10] The primary active metabolite (M-II) has also exhibited greater selectivity for the MT_1 receptors than the MT_2 receptors, but with lower affinity for MT_1 receptors and approximately 1/50 the activity of the parent compound.[12] Systemic exposure to the M-II metabolite is 20- to 30-fold greater than that of ramelteon, while exposure to three other inactive identified metabolites is one- to four-fold greater than that of ramelteon.[10,20–23] Less than 0.1% of the dose is excreted in the urine and faeces as unchanged drug.[19,10] The majority of the dose is eliminated renally as metabolites.[20,21]

The clearance of ramelteon is reduced in elderly subjects compared with younger subjects, resulting in increased systemic exposure.[23,24] In both elderly men and elderly women, the AUC was increased, clearance reduced and half-life prolonged, in comparison with younger subjects. Overall, in the elderly subjects, the peak concentration was nearly doubled (11.6ng/ml versus 6.9ng/ml) and the half-life was increased (2.6 hours versus 1.57 hours). Pharmacokinetics of the primary active metabolite were similarly affected.[23] Despite these pharmacokinetic differences, dosage adjustments are not necessary in the elderly.[10]

In patients with mild to moderate hepatic impairment, both the peak concentration and AUC of ramelteon is increased. Dosage adjustment is not necessary because of the wide therapeutic variation and broad inter-individual variation observed with ramelteon; however, patients with moderate hepatic impairment should be dosed cautiously.[25] Ramelteon exposure was not altered in subjects with mild to moderate renal impairment and patients on haemodialysis. In patients with severe renal impairment (a creatinine clearance of less than 30ml/minute per 1.73m^2), ramelteon exposure was increased two- to four-fold, although results remained within the usual inter-individual variation. Dosage adjustment does not appear necessary in patients with renal impairment, but ramelteon should be dosed cautiously in patients with severe renal impairment not receiving haemodialysis.[26]

Clinical Efficacy

In patients with chronic insomnia, ramelteon has reduced latency to persistent sleep and increased total sleep time in several placebo-controlled studies. The dose-related efficacy and safety of ramelteon were assessed in a double-blind placebo-controlled cross-over study that enrolled 107 subjects who were 18 to 64 years of age with primary chronic insomnia (Diagnostic and Statistical Manual, Fourth Edition (DSM-IV)). Mean patient age was 37.7 years, 64.2% of patients were female, 58.5% were 39 years of age or younger and 54.7% were Caucasian.

Enrolled patients had a diagnosis of primary insomnia for at least three months, with a polysomnography (PSG)-defined mean latency to persistent sleep of more than 20 minutes and a mean wake time longer than 60 minutes on two consecutive nights in a sleep laboratory. At screening, mean latency to persistent sleep was 75.2 minutes, mean total sleep time was 347.9 minutes and mean wake time after sleep onset was 63

Table 1: Dose-finding Cross-over Study with Ramelteon in Patients with Chronic Insomnia[27]

	Ramelteon				Placebo
Parameter	**4mg (n=103)**	**8mg (n=103)**	**16mg (n=106)**	**32mg (n=103)**	**– (n=103)**
Latency to persistent sleep (min)[a]	24[b]	24.3[b]	24[b]	22.9[b]	37.7
Total sleep time (minutes)[a]	411[c]	412.9[d]	411.2[c]	418.2[b]	400.2
Sleep efficiency (total sleep time/total time in bed)	85.7%	86%	85.7%	87.1%	83.5%

a. Least square means. b. p<0.001 versus placebo. c. p<0.05 versus placebo. d. p<0.01 versus placebo.

Table 2: Polysomnograph Assessment of Sleep Latency, Total Sleep Time and Sleep Efficiency with Ramelteon versus Placebo[28]

Parameter	**Ramelteon 8mg**	**Ramelteon 16mg**	**Placebo**	**p Value[a]**
Nights one to two				
Mean latency to persistent sleep (minutes)	32.2	28.9	47.9	p<0.001
Total sleep time (minutes)	394.2	397.6	375.2	p<0.001
Sleep efficiency	82.3%	83.4%	78.3%	p<0.001
Nights 15 to 16				
Mean latency to persistent sleep (minutes)	32.6	27.9	45.5	p<0.001
Nights 29 to 30				
Mean latency to persistent sleep (minutes)	31.5	29.5	42.5	p=0.003

a. Ramelteon 8mg and 16mg versus placebo.

minutes. Each subject was randomised to receive five treatments (ramelteon 4mg, 8mg, 16mg and 32mg, and placebo) with a five- or 12-day wash-out between each treatment. Each treatment was administered 30 minutes prior to habitual bedtime on two consecutive nights. PSG was performed for eight hours, followed, upon awakening, by visual analogue scale (VAS), digit-symbol substitution test (DSST), memory recall tests and post-sleep questionnaires to assess next-day performance and alertness. Results are summarised in *Table 1*.

The latency to persistent sleep was reduced for every ramelteon dose, compared with placebo (p<0.001). Total sleep time and sleep efficiency were increased with each ramelteon dose, compared with placebo. With the ramelteon 16mg dose, subjects also reported shorter subjective sleep latency compared with placebo (p=0.015). There were no differences between groups in wake time after onset of persistent sleep, subjective total sleep time, subjective sleep quality, VAS, DSST, memory recall tests or post-sleep subjective level of alertness or ability to concentrate. The only change in sleep stage was a shorter period of time in non-REM stage 3/4 sleep with ramelteon at each dose (difference from placebo: -1.3% to -2.1%).[27]

Ramelteon was also assessed in a randomised double-blind study enrolling 405 subjects who were 18 to 64 years of age (mean age 39.3 years) with chronic primary insomnia. Patients received a single nightly dose of ramelteon 8mg or 16mg, or placebo for 35 days. PSG was performed on the first two nights in each of weeks 1, 3 and 5 of treatment. Both ramelteon doses were associated with a reduction in average latency to persistent sleep at each time point. Results are summarised in *Table 2*. At week 1, ramelteon 8mg was associated with more fatigue than placebo. At week 3, patients treated with ramelteon 8mg had a lower mean score for immediate recall (7.5 out of 16 words), compared with placebo (8.2 words), and a mean VAS score indicating more sluggishness (27mm on a 100mm VAS), compared with placebo (22mm). At week 5, there was no difference between ramelteon and placebo on measures of next-morning residual effects.[10,28]

Ramelteon was also compared with placebo in a randomised double-blind study enrolling 829 elderly patients with chronic primary insomnia. Mean age was 72.4 years, 341 patients were men and 488 women. After a seven-day placebo lead-in period, patients were randomised to receive ramelteon 4mg or 8mg, or placebo nightly for five weeks, followed by a seven-day placebo period. The primary study end-point was patient-reported sleep latency. Patients reported a reduction in sleep latency at week 1 with the 4mg dose (70.2 minutes versus 78.5 minutes; p=0.008) and 8mg dose (70.2 minutes versus 78.5 minutes; p=0.008). Patients reported that total sleep time was also increased at week 1 with the 4mg dose (324.6 minutes versus

313.9 minutes; p=0.004) and the 8mg dose (321.1 minutes versus 313.9 minutes; p=0.055). In the combined ramelteon groups, reductions in sleep latency compared with placebo were observed for week 1 (p=0.009), week 3 (p=0.013) and week 5 (p<0.001). Neither rebound insomnia nor withdrawal effects were observed upon discontinuation of ramelteon.[29,30]

Another randomised double-blind placebo-controlled study assessed the effects of a single dose of ramelteon in a first-night model of transient insomnia. Healthy adults aged 35 to 60 years (n=375; 228 women) who were naïve to a sleep laboratory were randomised to receive placebo (123 subjects), ramelteon 16mg (126 subjects) or ramelteon 64mg (126 subjects) approximately 30 minutes before their habitual bedtimes. Patients were monitored by PSG for eight hours, followed, upon awakening, by the DSST and subjective measures of alertness and ability to concentrate. The mean latency to persistent sleep was 14.1 minutes in the ramelteon 16mg group and 15.5 minutes in the ramelteon 64mg group, compared with 24.6 minutes in the placebo group (p<0.001 for both ramelteon doses versus placebo). Mean total sleep time was 425.4 minutes in the 16mg group and 422.4 minutes in the 64mg group, compared with 411.3 minutes in the placebo group (p<0.05 for both ramelteon doses versus placebo). Wake after sleep onset and time spent in each sleep stage were not different from placebo with either dose of ramelteon.

No evidence of residual sedation was observed in either ramelteon group, although subjects in the 64mg group reported reductions in subjective assessments of alertness and ability to concentrate, compared with the placebo group.[31]

In 60 healthy subjects aged 35 to 65 years receiving one of five doses of ramelteon (4mg, 8mg, 16mg, 32mg or 64mg; eight subjects per dose group) or placebo (20 subjects) as a single oral dose, mean DSST and VAS scores for alertness, measured one, two, three, four, six and eight hours post-dose, were similar across dose groups and did not differ from placebo.[32] In another randomised double-blind cross-over study in healthy subjects aged 18 to 34 years, a single dose of ramelteon 16mg and placebo in the morning on two occasions separated by at least one week produced no differences in younger men, younger women or elderly men for observer-rated sedation, self-rated sedation or DSST scores. For elderly women, observer-rated sedation did not differ between ramelteon and placebo; however, self-rated sedation was increased and DSST scores were reduced with ramelteon (p<0.05).[24,33]

Table 3: Adverse Reactions (≥3%) with Ramelteon and Placebo in Phase I to III Studies[10]

Adverse Reaction	Placebo (n=1,370)	Ramelteon 8mg (n=1,250)
Headache	7%	7%
Dizziness	3%	5%
Somnolence	3%	5%
Fatigue	2%	4%
Insomnia exacerbated	2%	3%
Nausea	2%	3%
Upper respiratory tract infection	2%	3%

Patient Considerations

Cautions

Ramelteon is contraindicated in patients with a known hypersensitivity to ramelteon or any of the product ingredients.[10] In addition, ramelteon should not be used by patients with severe hepatic impairment or in combination with fluvoxamine.[10]

As with other sleep-promoting agents, patients should avoid engaging in hazardous activities that require concentration after taking ramelteon.[10]

Respiratory depression was not observed following a single dose of ramelteon 16mg in subjects with mild to moderate chronic obstructive pulmonary disease (COPD).[34] In subjects with mild to moderate obstructive sleep apnoea, single-dose administration of ramelteon 16mg at night did not exacerbate sleep apnoea. Mean oxygen saturation was higher during REM sleep with ramelteon than with placebo.[35] Ramelteon has not been studied in patients with severe COPD or severe sleep apnoea, and use is not recommended in such patients.[10]

In an abuse liability study including 14 subjects with a history of sedative/hypnotic or anxiolytic abuse, ramelteon 16mg to 160mg was compared with triazolam 0.25mg to 0.75mg and placebo. Ramelteon exhibited responses in standard tests of abuse potential similar to those of placebo at doses up to 20 times the recommended therapeutic dose, while triazolam exhibited a dose-response effect on the subjective and behavioural measures.[36] No rewarding effects or physical dependence was observed in monkeys.[37–39] After chronic administration, withdrawal signs have not been observed in animals or humans.[10]

Adverse Effects

The most frequently reported adverse reactions in ramelteon clinical trials have included headache, somnolence, fatigue, nausea, dizziness and

insomnia.[10,19,23,27] Adverse reactions have generally been reported to be similar in ramelteon- and placebo-treatment groups (see *Table 3*).[10,27] Adverse effects did not appear dose-related in a cross-over study assessing doses from 4mg to 32mg.[27]

Monitoring

Patients should be monitored for effects on sleep and continued efficacy. Routine laboratory monitoring is not necessary; however, in patients with unexplained amenorrhea, galactorrhea or decreased libido, or problems with fertility, prolactin levels and testosterone levels should be assessed.[10] Nightly administration of ramelteon 16mg had no effect on thyroid hormones or adrenal hormones, but it has been associated with increases in serum prolactin and reductions in testosterone.[10,40]

Drug Interactions

Ramelteon is primarily metabolised via CYP1A2 and, to a lesser extent, via the CYP2C subfamily and CYP3A4.[10] Ramelteon does not appear to be an inhibitor or inducer of CYP1A2, CYP3A4, CYP2C9 or CYP2D6.[41–44]

With administration of fluvoxamine (a strong CYP1A2 inhibitor) 100mg twice daily for three days prior to a single dose of ramelteon 16mg, the AUC for ramelteon was increased approximately 190-fold and the peak concentration was increased approximately 70-fold, compared with ramelteon alone. As mentioned above, ramelteon should not be used in combination with fluvoxamine. Caution is advised when ramelteon is administered in conjunction with other CYP1A2 inhibitors.[10]

Administration of rifampin (a strong CYP inducer) 600mg once daily for 11 days resulted in a mean reduction of approximately 80% in total exposure to ramelteon and the M-II metabolite after a single ramelteon 32mg dose. Ramelteon efficacy may be reduced when it is administered in combination with a strong CYP inducer.[10]

Administration with fluconazole (a strong CYP2C9 inhibitor) resulted in a 152% increase in the ramelteon AUC, while administration with ketoconazole (a strong CYP3A4 inhibitor) resulted in an 84% increase in the ramelteon AUC.[45] Ramelteon should be used with caution in patients receiving strong CYP2C9 or CYP3A4 inhibitors.[10]

Co-administration with fluoxetine (a CYP2D6 inhibitor) resulted in an approximately 50% increase in the AUC and peak concentration of ramelteon, as well as increases in levels of the M-II ramelteon metabolite.[46] Co-administration with theophylline (a CYP1A2 substrate) has also resulted in a 40% increase in the ramelteon AUC and peak concentration.[42] Despite these increases, routine dosage adjustments for ramelteon have not been recommended when it is administered together with either fluoxetine or theophylline.[10,42,46]

Co-administration of ramelteon with omeprazole resulted in a modest reduction in ramelteon concentrations, but does not require dosage modification.[47] Ramelteon did not alter the pharmacokinetics of dextromethorphan (a CYP2D6 substrate), digoxin (a p-glycoprotein substrate), midazolam (a CYP3A4 substrate) or its primary metabolite, omeprazole (a CYP2C19 substrate), theophylline or warfarin (a CYP2C9/CYP1A2 substrate).[41–44,47] Dextromethorphan and omeprazole had no effect on the pharmacokinetics of ramelteon or its primary M-II metabolite.[10,43]

No pharmacokinetic interaction was observed with co-administration of alcohol with ramelteon, but an additive effect was seen on some measures of psychomotor performance (DSST, Psychomotor Vigilance Task Test and VAS sedation).[10]

Dosing

The recommended dose of ramelteon is 8mg taken within 30 minutes before going to bed. Ramelteon should not be taken with or immediately after a high-fat meal. No dosage adjustments are necessary in the elderly or patients with renal impairment. As mentioned above, ramelteon should be used with caution in patients with moderate hepatic impairment and avoided in patients with severe hepatic impairment.[10]

Summary

Ramelteon is the first FDA-approved melatonin receptor agonist. Ramelteon reduces the time-to-sleep onset and increases total sleep duration; however, comparative studies with other sleep agents, including melatonin, are necessary to determine comparative efficacy and the place of ramelteon in therapy. Efficacy in placebo-controlled study has been observed in both acute and chronic insomnia.

Similar to eszopiclone, long-term studies have been conducted and recommended use is not limited to 30 days. Ramelteon was well tolerated in clinical studies, with little residual sedation, and has not been associated with physical dependence or abuse liability. ■

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