

# Ramelteon

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## Contents

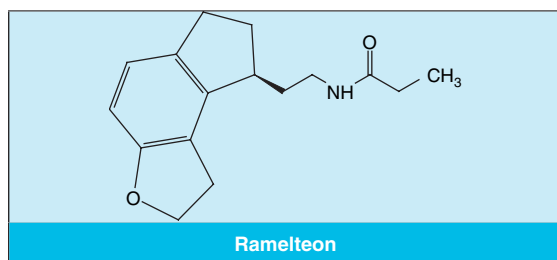
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## Abstract

- ▲ Ramelteon, approved in the US for the treatment of insomnia characterised by difficulty with sleep onset, is a highly selective agonist for the melatonin MT<sub>1</sub>/MT<sub>2</sub> receptors, which are believed to mediate the circadian rhythm in mammals.
- ▲ Ramelteon has negligible affinity for the MT<sub>3</sub> binding sites and other receptors in the brain, including the opiate, dopamine, benzodiazepine and serotonin receptors, which may explain the lack of significant adverse events and lack of abuse or dependence potential observed with ramelteon.
- ▲ In three clinical trials in patients with chronic insomnia, ramelteon 8mg was effective in reducing sleep latency, without being associated with any significant or clinically relevant residual effects. It also generally increased total sleep time and, where assessed, sleep efficiency.
- ▲ In a first-night-effect model of transient insomnia, ramelteon 8mg was significantly more effective than placebo at reducing sleep latency and increasing total sleep time.
- ▲ Ramelteon was generally well tolerated; the most commonly reported adverse events occurring in more ramelteon than placebo recipients were somnolence (5% vs 3%), fatigue (4% vs 2%) and dizziness (5% vs 3%). Adverse events were mostly mild or moderate in nature. Ramelteon has been shown to have no potential for abuse or dependence.

### Features and properties of ramelteon (Rozerem™)

Features and properties of ramelteon (Rozerem™)	
<b>Indication</b>	
Insomnia characterised by difficulty with sleep onset	
<b>Mechanism of action</b>	
Selective agonism of the melatonin MT <sub>1</sub> /MT <sub>2</sub> receptors	
<b>Dosage and administration</b>	
Dose	8mg
Route of administration	Oral
Frequency of administration	Once daily, 30 minutes prior to bedtime
<b>Pharmacokinetic profile (8mg single dose in healthy volunteers)</b>	
Area under the plasma concentration-time curve from time zero to infinity	7 ng • h/mL
Maximum plasma concentration	5.7 ng/mL
Time to maximum plasma concentration	0.75h
Elimination half-life	1.4h
<b>Adverse events</b>	
Most frequent	Somnolence, fatigue, dizziness



Insomnia can be divided into three categories: transient insomnia (lasting for <1 week), which is generally associated with an acute stressor or change in circadian patterns, as may be caused by jet lag or shift work; short-term insomnia (lasting for 1–4 weeks), which may be related to an ongoing stressor, such as bereavement, change in work circumstances or other stress; and chronic insomnia (persisting for >4 weeks), which is usually associated with underlying causative factors such as psychiatric or medical disorders, chronic drug or alcohol abuse, primary sleep disorders, poor sleep hygiene and sleep environment, or psychophysiological insomnia.<sup>[1-3]</sup> Insomnia is estimated to affect approximately one-third of the general population, with chronic insomnia thought to affect 10–15% of the population.<sup>[2]</sup>

Initial therapy for insomnia is to address the underlying cause, improve the patient's quality of life and prevent the progression from transient insomnia to chronic insomnia.<sup>[4]</sup> If insomnia cannot be adequately managed with educational and behavioural intervention, pharmacological treatment can be introduced. The most commonly prescribed agents are benzodiazepine receptor agonists, and although these drugs are effective for the treatment of insomnia, there is considerable controversy over their merit.<sup>[5]</sup> Many patients with chronic insomnia will often continue to take benzodiazepine receptor agonists, as well as such drugs as diphenhydramine and chloral hydrate, despite obtaining little subjective benefit; benzodiazepines are also associated with a higher risk of motor vehicle accidents, falls and fractures, overdose, and cogni-

tive impairment, along with the potential for abuse and dependence.<sup>[5]</sup>

In mammals, melatonin is responsible for modulating the circadian rhythm.<sup>[6]</sup> Environmental light/dark signals are transferred from the retina to the suprachiasmatic nucleus in the hypothalamus, which upon activation stimulates melatonin release from the pineal gland into the circulation.<sup>[7]</sup> Melatonin receptors were originally categorised as either ML<sub>1</sub> (high affinity) or ML<sub>2</sub> (low affinity) receptors.<sup>[8]</sup> However, there are at least three ML<sub>1</sub> receptor subtypes, of which the MT<sub>1</sub> and MT<sub>2</sub> subtypes appear to play a key role in the regulation of the circadian rhythm.<sup>[9]</sup> The ML<sub>2</sub> receptor (now called MT<sub>3</sub>), however, is not thought to be involved in the effects of melatonin on the circadian rhythm or sleep.<sup>[8,9]</sup> Supplemental melatonin is used for the treatment of a variety of sleep disorders, but its clinical usefulness is limited by a short half-life (20–30 minutes) and a lack of specificity for the MT<sub>1</sub>/MT<sub>2</sub> receptors;<sup>[6]</sup> furthermore, there is little evidence for its efficacy in the treatment of insomnia.<sup>[3]</sup>

Ramelteon (Rozerem™)<sup>1</sup> is a selective MT<sub>1</sub>/MT<sub>2</sub> receptor agonist, and is the first drug in a new class of insomnia therapies. This review summarises the pharmacology, efficacy and tolerability of ramelteon in the treatment of patients with insomnia, with the focus on the US FDA-approved dose of 8mg.

## 1. Pharmacodynamic Profile

### Receptor Binding

- *In vitro* studies using human MT<sub>1</sub> and MT<sub>2</sub> receptors expressed in Chinese hamster ovary cells and MT<sub>3</sub> binding sites from hamster brain, showed that ramelteon had a dissociation constant (K<sub>i</sub>) of 14.0 and 112 pmol/L for the MT<sub>1</sub> and MT<sub>2</sub> receptors, compared with 2650 nmol/L for the MT<sub>3</sub> binding sites.<sup>[10]</sup> This compares with a K<sub>i</sub> of 0.0807 and 0.383 nmol/L for the MT<sub>1</sub> and MT<sub>2</sub> receptors, respectively, and 24.1 nmol/L for the MT<sub>3</sub> binding sites for melatonin; the selectivity for MT<sub>1</sub>/MT<sub>2</sub>

**1** The use of trade names is for product identification purposes only and does not imply endorsement.

over  $MT_3$  is more than 300-fold greater for ramelteon than for melatonin.<sup>[10]</sup>

- The  $K_i$  of the active ramelteon metabolite, M-II, was 109 pmol/L for the human  $MT_1$  receptor and >9000 nmol/L for the  $MT_3$  binding sites.<sup>[11]</sup> Forskolin-stimulated cyclic AMP production in Chinese hamster ovary cells expressing human  $MT_1$  receptors was inhibited by both ramelteon and M-II at picomolar concentrations (50% inhibition at 10.8 and 159 pmol/L, respectively).<sup>[11]</sup>

- Ramelteon has no measurable affinity for any of a large number of ligand binding sites, including the opiate, dopamine, benzodiazepine and serotonin receptors.<sup>[12]</sup> Whereas melatonin shows a weak affinity for the dopamine  $D_1$  and serotonin 5-HT $_{1A}$  receptors, M-II shows weak affinity for only the 5-HT $_{2B}$  receptor ( $K_i$  1.75 nmol/L).<sup>[12]</sup>

#### Animal Studies

- Orally administered ramelteon 0.03 and 0.3 mg/kg in young adult female macaques shortened the latency to sleep onset and increased total duration of sleep.<sup>[13]</sup> By contrast, melatonin 0.3 mg/kg, but not 1 and 3 mg/kg, reduced the latency to sleep onset, and zolpidem 1, 3, 10 and 30 mg/kg had no significant effect on latency to sleep onset; neither melatonin nor zolpidem had an effect on total sleep duration. Ramelteon and melatonin had no effect on behaviour of the freely moving monkeys, whereas zolpidem 30 mg/kg was associated with sedation and muscle relaxation.<sup>[13]</sup>

- Ramelteon 0.001–0.1 mg/kg had a sleep-promoting effect in freely moving cats, which lasted for 6 hours following administration, compared with only 2 hours following melatonin 0.01–1 mg/kg.<sup>[14]</sup>

- In rats, neither ramelteon 3–30 mg/kg nor melatonin 3–100 mg/kg had an effect on learning or memory.<sup>[15]</sup>

- Diazepam induced a dose-dependent impairment of the rota-rod performance, whereas ramelteon, melatonin and *N*-acetyl-5-hydroxytryptamine (an  $MT_3$  binding site ligand) did not. Furthermore, the diazepam-induced impairment was exacerbated by melatonin and *N*-acetyl-5-hydroxytryptamine, but not by ramelteon.<sup>[15]</sup>

- Neither melatonin nor ramelteon had any rewarding properties, implying that neither drug has any potential for abuse.<sup>[15]</sup>

#### Human Studies

- Sleep latency in 106 patients with chronic insomnia was significantly shorter with ramelteon 4, 8, 16, or 32mg than with placebo, administered on two consecutive nights in a randomised, double-blind, crossover, polysomnography study (22.9–24.3 vs 37.7 minutes; all  $p < 0.001$ ). Ramelteon also increased total sleep time and sleep efficiency.<sup>[16]</sup> There were no significant between-group differences in awake time after onset of persistent sleep, subjective total sleep time or sleep quality.<sup>[16]</sup> Ramelteon was associated with a slightly lower percentage of total time in non-REM stage 3/4 sleep than placebo.<sup>[16]</sup> There were no significant between-group differences in post-sleep mood and feeling, digit symbol substitution test (DSST) scores, memory recall tests, or subjective levels of alertness and ability to concentrate.

- Latency to persistent sleep was significantly shorter among recipients of a single dose of ramelteon 16 or 64mg than in placebo recipients (14.1 and 15.5 min vs 24.6 min; both  $p < 0.001$ ) in a randomised, double-blind, first-night-effect model of transient insomnia that enrolled healthy volunteers naive to a sleep laboratory ( $n = 375$ ).<sup>[17]</sup> Mean total sleep time, assessed using polysomnography, was significantly longer with ramelteon 16 and 64mg than with placebo (425.4 and 422.4 min vs 411.3 min; both  $p < 0.05$ ).<sup>[17]</sup> No residual sedation on DSST was evident in either ramelteon group, although volunteers receiving the higher dose reported a significant reduction in subjective levels of alertness ( $p = 0.02$ ) and ability to concentrate ( $p = 0.043$ ) compared with placebo recipients.<sup>[17]</sup>

- Ramelteon 16mg had no effect on observer-rated sedation, self-rated sedation or DSST scores among young males or females (aged 18–34 years) or elderly males (aged 63–79 years) in a randomised, double-blind, placebo-controlled, crossover study in healthy volunteers ( $n = 44$ ).<sup>[18]</sup> However, compared with placebo, ramelteon was

associated with a significant increase in self-rated sedation ( $p < 0.05$ ) and a significant decrease in DSST score ( $p < 0.05$ ) in elderly females.<sup>[18]</sup> Results of information acquisition and recall tests did not differ between ramelteon or placebo recipients in any age group.<sup>[18]</sup>

- The effect of ramelteon 16 mg/day for 6 months on 12 different endocrine laboratory parameters was studied in patients with chronic insomnia. Ramelteon had no effect on the thyroid or adrenal axes, but did have an effect on mean prolactin levels in women.<sup>[19,20]</sup> Mean serum prolactin levels increased by 34% in female ramelteon recipients, compared with a 4% decrease in female placebo recipients ( $p = 0.003$ ).<sup>[19]</sup>

- Although mean serum prolactin levels stayed within the normal reference range in female ramelteon recipients throughout the 6-month study, 14 of 34 women had normal baseline prolactin levels that increased to above the upper limit of normal at some point during the 6-month study, compared with 4 of 35 female placebo recipients;<sup>[20]</sup> no significant between-group difference was seen in males. Additionally, mean free and total testosterone levels were not significantly different between ramelteon and placebo patients (male or female) except for an increase in free testosterone at month 1.<sup>[20]</sup>

## 2. Pharmacokinetic Profile

### Absorption and Distribution

- Although ramelteon is rapidly and extensively absorbed following oral administration, the absolute bioavailability following a single oral 16mg dose is <2% because of extensive first-pass metabolism.<sup>[21,22]</sup>

- In a dose-escalation study, ramelteon area under the plasma concentration-time curve from time zero to infinity ( $AUC_{\infty}$ ) and maximum plasma concentration ( $C_{max}$ ) values were dose proportional in 60 volunteers.<sup>[23]</sup>  $AUC_{\infty}$  values for ramelteon 4, 8, 16, 32 and 64mg were 1.7, 7.0, 9.9, 22.5 and 36.1 ng • h/mL.<sup>[23]</sup> The corresponding  $C_{max}$  values were 1.1, 5.7, 6.9, 17.4 and 25.9 ng/mL.<sup>[23]</sup> Time to  $C_{max}$  values remained relatively constant at each dose

level: 0.78, 0.75, 0.79, 0.88 and 0.94 hours for ramelteon 4, 8, 16, 32 and 64mg.<sup>[23]</sup>

- Systemic exposure to ramelteon is greater in the elderly than in younger adults. Following a single dose of ramelteon 16mg, the mean  $C_{max}$  and  $AUC_{\infty}$  values in elderly volunteers (aged 63–79 years) were 11.6 ng/mL and 18.7 ng • h/mL; these values were 86% and 97% higher than those in the younger volunteers (aged 18–34 years).<sup>[19,24]</sup> The age effects on exposure to the major active ramelteon metabolite M-II were less pronounced;  $C_{max}$  and  $AUC_{\infty}$  values for M-II were 13% and 30% higher in the elderly than in younger recipients.<sup>[19,24]</sup>

### Metabolism and Excretion

- Following oral administration, ramelteon undergoes extensive first-pass hepatic metabolism and has an elimination half-life ( $t_{1/2}$ ) of 1.2 hours.<sup>[22]</sup> There are four main metabolites, M-I, M-II, M-III and M-IV, with M-II being the major active moiety; indeed, the systemic exposure of M-II is 20- to 100-fold greater than that of ramelteon, whereas the exposures of M-I, M-III and M-IV are 1- to 4-fold greater.<sup>[19,22]</sup> The  $t_{1/2}$  values of the four metabolites ranged from 1 to 3 hours.<sup>[22]</sup>

- The primary metabolic pathway is oxidation to hydroxyl and carbonyl groups, with secondary metabolism to glucuronide conjugates.<sup>[22]</sup> The predominant isozyme involved in hepatic metabolism of ramelteon is cytochrome P450 (CYP) 1A2, although isozymes of the CYP2C subfamily and CYP3A4 are also involved to a minor degree.<sup>[19]</sup> Following administration of a single oral dose of [<sup>14</sup>C]ramelteon in healthy males, 84% of the total radioactivity was recovered in the urine, with 4% eliminated via the faeces.<sup>[22]</sup> Negligible urinary excretion (<2%) of unmetabolised ramelteon occurs.<sup>[23]</sup>

- In a dose-escalation study,<sup>[23]</sup> the mean  $t_{1/2}$  was somewhat dose dependent, at 0.83, 1.36, 1.28, 1.59 and 1.9 hours for ramelteon 4, 8, 16, 32 and 64mg, respectively.

- Compared with young males, elderly males had reduced clearance of ramelteon following administration of a single 16mg dose (757 vs 381 mL/min/kg;  $p < 0.05$ ).<sup>[24]</sup> Similarly, clearance was reduced in

elderly females compared with that in young females (387 vs 1009 mL/min/kg;  $p < 0.05$ ).<sup>[24]</sup> The ramelteon  $t_{1/2}$  was also longer in elderly males and females (1.6 and 2.2 hours) compared with that in younger males and females (1.2 and 1.3 hours).<sup>[19,24]</sup>

### Potential Drug Interactions

- Because ramelteon is metabolised predominantly by CYP1A2, but also by CYP3A4 and isozymes of the CYP2C subfamily to a minor degree, there is the potential for pharmacokinetic interactions between ramelteon and CYP inhibitors or inducers.<sup>[19]</sup>

- Indeed, coadministration of ramelteon with fluvoxamine, a potent CYP1A2 inhibitor, resulted in a 190-fold increase in the  $AUC_{\infty}$  for ramelteon.<sup>[19]</sup> Conversely, coadministration of ramelteon with rifampicin (rifampin), a CYP inducer, resulted in an 80% reduction in the  $AUC_{\infty}$  for ramelteon and M-II.<sup>[19]</sup> The  $AUC_{\infty}$  of ramelteon was  $\approx 84\%$  and  $150\%$  higher after concomitant administration of ramelteon with ketoconazole, a CYP3A4 inhibitor, or fluconazole, a CYP2C9 inhibitor, respectively.<sup>[19]</sup>

- However, coadministration of ramelteon with omeprazole (CYP1A2 inducer/CYP2C19 inhibitor),<sup>[25]</sup> fluoxetine (CYP2D6 inhibitor),<sup>[26]</sup> theophylline (CYP1A2 substrate)<sup>[19]</sup> or dextromethorphan (CYP2D6 substrate)<sup>[19]</sup> had no clinically significant effect on exposure to ramelteon. Similarly, ramelteon had no clinically significant effect on AUC or  $C_{max}$  values for omeprazole, dextromethorphan, theophylline, midazolam (CYP3A4 substrate), digoxin (P-glycoprotein substrate) or warfarin (CYP2C9/1A2 substrate).<sup>[19,25,26]</sup>

- Although a pharmacokinetic interaction between ramelteon and alcohol has not been demonstrated, ramelteon has been reported to have additive effects with alcohol on some measures of psychomotor performances, such as the DSST, the psychomotor vigilance task and visual analogue scale for sedation.<sup>[19]</sup>

### 3. Therapeutic Efficacy

The efficacy of ramelteon in the treatment of chronic ( $>3$  months) primary insomnia has been

compared with that of placebo in a randomised, double-blind, crossover study in elderly patients (aged  $\geq 65$  years; mean age 70.7 years;  $n = 100$ ),<sup>[27]</sup> and in two randomised, double-blind, parallel-group trials: one in adult patients 18–64 years of age (mean age 39.3;  $n = 405$ )<sup>[28]</sup> and a second in elderly patients (aged  $\geq 65$  years; mean age 72.4 years;  $n = 829$ ).<sup>[29]</sup> In each study, DSM-IV-TR<sup>[30]</sup> criteria were used to define insomnia. The large study ( $n = 829$ ) in elderly patients was conducted on an out-patient basis.<sup>[29]</sup> The sleep-promoting effect of ramelteon has also been evaluated in a first-night-effect model of transient insomnia in a randomised, double-blind, crossover study ( $n = 289$ ).<sup>[31]</sup> This study enrolled healthy volunteers naive to a sleep laboratory.<sup>[31]</sup> Data from these studies have been obtained from abstracts,<sup>[27-29,31]</sup> posters,<sup>[28]</sup> and/or the FDA medical review on ramelteon.<sup>[20]</sup>

Patients with chronic insomnia in the parallel-group studies received ramelteon 8 or 16mg or placebo each night for 5 weeks (in adults aged 18–64 years)<sup>[28]</sup> or ramelteon 4 or 8mg or placebo each night for 5 weeks (in elderly patients aged  $\geq 65$  years).<sup>[29]</sup> Elderly patients in the crossover study received ramelteon 4 or 8mg or placebo, administered 30 minutes prior to bedtime on two consecutive nights with a 5- to 12-day washout period between treatments.<sup>[27]</sup> Adult volunteers in the transient insomnia study received ramelteon 8 or 16mg or placebo 30 minutes before bedtime for one night.<sup>[31]</sup>

The approved dosage of ramelteon in the US is 8 mg/day;<sup>[19]</sup> as such, this section will focus on the 8mg dosage.

The primary endpoint in all studies was latency to persistent sleep. In the 5-week studies, the primary endpoint (sleep latency) was measured either by the patient using a sleep diary on nights 1–7<sup>[29]</sup> or by polysomnography in the sleep laboratory on nights 1 and 2.<sup>[28]</sup> Subsequent measures of sleep latency were also obtained and evaluated at weeks 3 and 5.<sup>[28,29]</sup> Sleep latency in the other two studies was measured by polysomnography, on nights 1 and 2 in the crossover study in the elderly<sup>[27]</sup> and night 1 in the transient insomnia study.<sup>[31]</sup>

Secondary endpoints included polysomnographically measured total sleep time and sleep efficiency,<sup>[28]</sup> and subjectively measured sleep latency<sup>[27,28]</sup> and total sleep time.<sup>[27-29]</sup> Post-sleep residual effects were also reported, measured using the DSST, memory recall tests, questionnaires to determine levels of alertness and ability to concentrate, memory tests for immediate and delayed recall, and visual analogue scales for mood and feeling (see section 4 for discussion of these results).<sup>[27,28,31]</sup> Patients in the 5-week studies also completed the Benzodiazepine Withdrawal Symptoms Questionnaire, in order to assess any withdrawal effects (see section 4).<sup>[28,29]</sup>

### Chronic Insomnia

- Sleep latency was significantly reduced with ramelteon compared with placebo in patients with chronic insomnia in all three studies.<sup>[27-29]</sup>

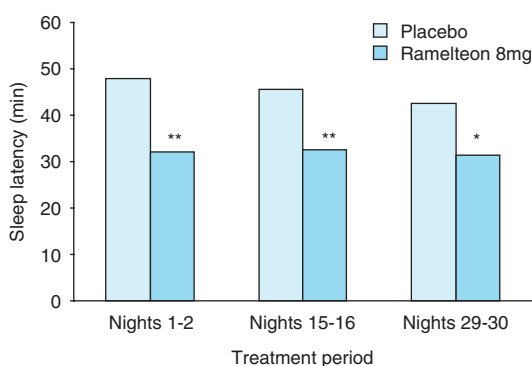
- Over a treatment period of 5 weeks, sleep latency was significantly reduced with ramelteon 8 mg/day at weeks 1, 3 and 5 in adults aged 18–64 years (figure 1), as measured by polysomnography. Total sleep time was also significantly increased with ramelteon compared with placebo at week 1; increases from baseline in total sleep time of approximately 44 and 32 minutes were observed with ramelteon 8mg and placebo ( $p \leq 0.001$  vs placebo; values estimated from a graph).<sup>[28]</sup> However, at weeks 3 and 5 there were no statistically significant differences between ramelteon and placebo.<sup>[28]</sup>

- Sleep efficiency was also significantly increased with ramelteon. Sleep efficiency increased from 73% to 82.5% with ramelteon at week 1, compared with an increase from 71.5% to 78.5% with placebo ( $p < 0.001$  vs placebo; values estimated from a graph). In line with the total sleep time results, there was no significant difference between ramelteon 8mg and placebo at weeks 3 and 5.<sup>[28]</sup>

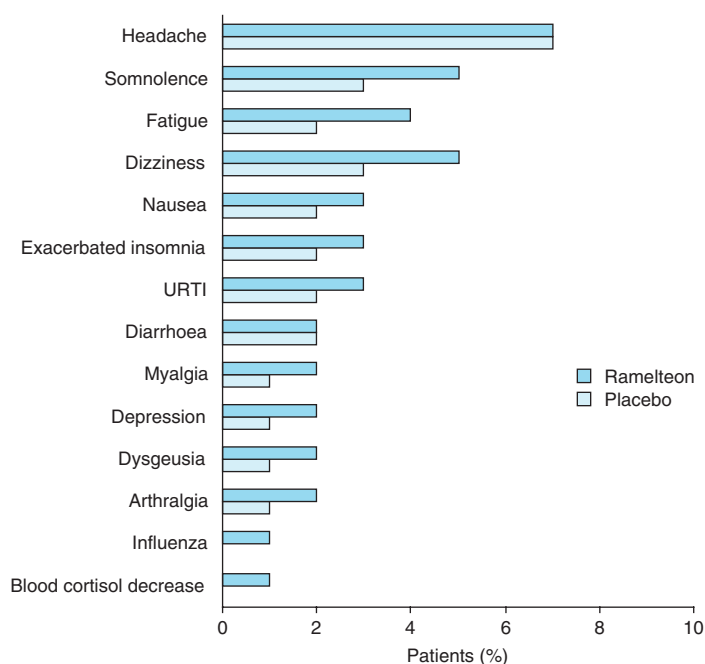
- A significant reduction in subjective sleep latency with ramelteon 8mg versus placebo at weeks 1, 3 and 5 (all  $p < 0.001$ ) was revealed in an analysis of the sleep laboratory post-sleep questionnaire, as was a significant increase in subjective total sleep time with ramelteon 8mg at weeks 1, 3 and 5 (all  $p \leq 0.05$ ).<sup>[28]</sup>

- Elderly patients with chronic insomnia experienced a significant reduction in sleep latency with ramelteon 8mg compared with placebo, as measured by polysomnography in the crossover trial (30.8 vs 38.4 min;  $p = 0.005$ ).<sup>[27]</sup> Total sleep time also significantly favoured ramelteon recipients (362.0 vs 350.4 min;  $p = 0.007$ ). By contrast, significant differences between ramelteon 8mg and placebo in subjectively measured sleep latency or total sleep time were not evident.

- In the outpatient trial in elderly patients, subjective sleep latency was significantly shorter at week 1 in ramelteon 8mg recipients than in placebo recipients (70.2 minutes vs 78.5 minutes;  $p = 0.008$ ), as well as at week 3 (by 9.2 minutes;  $p = 0.003$ ) and week 5 (by 12.8 minutes;  $p < 0.001$ ).<sup>[20,29]</sup> However, there was no significant difference between ramelteon 8mg and placebo for subjectively measured total sleep time (313.9 vs 321.1 minutes;  $p = 0.055$ ). When data from both ramelteon dosage groups were combined (ramelteon 4 and 8mg), statistically significant differences in total sleep time were apparent in favour of ramelteon at week 1 ( $p = 0.009$ ), 3 ( $p = 0.013$ ) and 5 ( $p < 0.001$ ). There were no significant differences between ramelteon and placebo in terms of sleep quality, number of night-time awakenings, and ease of falling back to sleep.<sup>[29]</sup>



**Fig. 1.** Efficacy of ramelteon in adults aged 18–64 years with chronic insomnia. Mean sleep latency measured on days 1 and 2 (primary endpoint), 15 and 16, and 29 and 30 of treatment with ramelteon 8mg ( $n = 139$ ) or placebo ( $n = 131$ ) once daily each night for 35 nights in a randomised, double-blind trial.<sup>[28]</sup> Sleep latency in patients was evaluated by polysomnography in a sleep laboratory. \*  $p = 0.003$ , \*\*  $p < 0.001$  vs placebo.



**Fig. 2.** Tolerability of ramelteon. The incidence of treatment-emergent adverse events in phase I–III clinical trials in which patients received ramelteon 8mg or placebo, as reported in the manufacturer’s prescribing information<sup>[19]</sup> and the US FDA medical review.<sup>[20]</sup> The majority of patients with chronic insomnia or healthy volunteers in these studies received ramelteon 8 mg/day for 7–35 days, although approximately 20% had data extending to 6 months of treatment; the mean duration of treatment was 51 days. **URTI** = upper respiratory tract infection.

#### Transient Insomnia

- Sleep latency was significantly reduced, and total sleep time was significantly increased, with ramelteon 8mg compared with placebo in a first-night-effect model of transient insomnia. In healthy volunteers naive to a sleep laboratory, polysomnographically measured sleep latency was significantly shorter in ramelteon recipients than in placebo recipients (12.2 vs 19.7 min;  $p = 0.004$ ), and total sleep time was significantly longer (436.8 vs 419.7 min;  $p = 0.009$ ).<sup>[31]</sup>

#### 4. Tolerability

- Ramelteon was generally well tolerated in patients with chronic or transient insomnia in the clinical trials presented in section 3,<sup>[28,29,31,32]</sup> although only limited tolerability data were reported.
- According to the manufacturer’s prescribing information,<sup>[19]</sup> among 3594 subjects who have received any dosage of ramelteon in phase I–III stud-

ies, 5% discontinued because of adverse events, compared with 2% of placebo recipients; these adverse events included somnolence (0.8%), dizziness (0.5%), nausea (0.3%), fatigue (0.3%), headache (0.3%) and insomnia (0.3%).

- The most commonly reported adverse events occurring in ramelteon 8mg ( $n = 1370$ ) and placebo ( $n = 1250$ ) recipients during phase I–III trials, as reported in the manufacturer’s prescribing information<sup>[19]</sup> and the FDA medical review,<sup>[20]</sup> are presented in figure 2.<sup>[19]</sup> Among patients who received ramelteon 8mg in these studies, 3.8% discontinued because of adverse events.<sup>[20]</sup>

#### Abuse Potential and Behavioural Effects

The abuse potential and behavioural effects of ramelteon have been evaluated in a randomised, double-blind, placebo-controlled, crossover study in 14 experienced drug users. Volunteers with a history of nonmedical sedative-hypnotic use were told they

may receive drugs from a variety of classes, including sedatives, opiates, stimulants or placebo. After a single-blind alprazolam challenge to ensure the volunteers preferred alprazolam to placebo, the volunteers received ramelteon 16, 80 or 160mg, triazolam 0.25, 0.5 or 0.75mg or placebo in randomised, cross-over fashion.<sup>[33]</sup> Subjective, objective and performance measurements were recorded 0.5 hours predose and for up to 24 hours postdose.

- Ramelteon was not associated with any potential for abuse or behavioural impairment at doses up to 20-times those indicated for clinical use.<sup>[33]</sup> Retrospective evaluation of the previous day's drug effect at 24 hours post administration showed there were no significant differences between ramelteon 16, 80 or 160mg and placebo for the primary outcome measures of 'drug liking', 'drug strength', 'good effects' and 'street value'.<sup>[33]</sup> By contrast, triazolam was associated with significant increases on all these measures. Additionally, ramelteon had no effect on any behavioural and cognitive performance tests, whereas triazolam showed dose-related effects on all measures.<sup>[33]</sup>

- In the phase III trials discussed in section 3, ramelteon 8mg was not associated with any clinically relevant residual effects, as assessed using DSST, memory tests for immediate and delayed recall, visual analogue scale for mood and feeling, and post-sleep questionnaire items for level of alertness and ability to concentrate.<sup>[27,28,31]</sup> Furthermore, no rebound insomnia or withdrawal effects were reported following 5 weeks of treatment.<sup>[28,29]</sup>

- Because of the lack of potential for abuse or dependence, ramelteon is not scheduled under the US Controlled Substances Act.<sup>[19]</sup>

## 5. Dosage and Administration

The recommended dosage of ramelteon in the US for the treatment of insomnia is 8mg orally once daily, taken within 30 minutes of going to bed.<sup>[19]</sup> Ramelteon should not be taken with or immediately after a high-fat meal, and should not be taken in combination with fluvoxamine; care should be taken if the patient is also receiving other CYP1A2 inhibitors (section 2). Ramelteon should not be used in

patients with severe hepatic impairment and used with caution in those with moderate hepatic impairment.<sup>[19]</sup> The manufacturer's prescribing information should be consulted for other warnings, precautions and contraindications.

## 6. Ramelteon: Current Status

Ramelteon is approved in the US for the treatment of insomnia characterised by difficulty with sleep onset. Ramelteon has demonstrated efficacy in the management of chronic insomnia in terms of sleep latency, total sleep time and sleep efficiency. Ramelteon is generally well tolerated, with an incidence of adverse events similar to that of placebo. Furthermore, ramelteon has been shown to have no potential for abuse or dependence and, thus, is not scheduled under the Controlled Substances Act.

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