Ramelteon for primary insomnia

Summary

Clinical and Patient Impact
- Ramelteon is a selective MT1/MT2 melatonin receptor agonist. Both these receptors are implicated in the effects of natural melatonin on sleep and circadian rhythms. An application for a Marketing Authorisation for the management of primary insomnia in adults has been submitted to the EMEA, and it is expected that any licence will allow for a maximum of six months of treatment. The anticipated date for EMEA approval is July 2008, and UK launch is expected in September 2008.
- Data on the efficacy of ramelteon are available from seven phase III randomised, double-blind, placebo-controlled clinical trials in patients with transient (one study) or primary insomnia (six studies), not all of which are fully published. Although there are modest, statistically significant differences for some sleep parameters, the proportion of patients who gain a worthwhile, clinically significant benefit from its use is uncertain.
- Ramelteon improves laboratory measured sleep latency and total sleep time compared with placebo by about 7.5–16 minutes and 9–19 minutes, respectively (similar to other hypnotics). However, it does not appear to improve the number of awakenings or the time of wakening from sleep onset (i.e. sleep maintenance). Patient-perceived benefits of ramelteon appear smaller than those indicated by laboratory measurements and are not consistently, statistically significant from placebo.
- Benefits of ramelteon with regard to daytime functioning, fatigue, mood and quality of life have yet to be established. There is no direct evidence that ramelteon offers any advantage over other existing therapies for insomnia, including non-pharmacological treatments, such as CBT.
- Short-term safety data suggests ramelteon is well tolerated. However in a six-month study, 32% of ramelteon recipients experienced raised prolactin levels compared with 19% on placebo. More data are required to establish the long-term adverse event profile of ramelteon.
- Studies to date show that ramelteon causes no rebound insomnia, or next-day residual effect, although it is not known if it offers advantages over existing hypnotics in these areas.
- There is limited evidence that ramelteon does not have potential for drug abuse, however, further data are required to fully assess the potential for addiction and tolerance.

NHS and Financial Impact
- One in twenty people are believed to present to healthcare professionals with insomnia-related symptoms, although it is thought that many people do not seek medical help or self-medicate with over-the-counter hypnotics.
- Ramelteon will be licensed for primary insomnia. Prescribers will need to conduct a full physical and mental assessment of patients, along with a complete drug history, to confirm this diagnosis before ramelteon is prescribed.
- It is anticipated that ramelteon will be marketed on its novel mode of action, safety data, and, differentiated from benzodiazepines and Z-drugs by its lack of abuse potential, next day residual effects and the similarity of the sleep pattern to “natural” sleep.
- Assessing the impact of ramelteon is difficult due to uncertainty of its cost, the number of patients eligible for its use (i.e. with primary insomnia) and the lack of data relative to other treatments (drug and non-drug) with regard to the important outcomes of daytime functioning and quality of life. Any shift in prescribing patterns away from the use of benzodiazepines and Z-drugs, would be expected to result in a rise in drug expenditure. Current clinical evidence of efficacy for ramelteon is insufficient to support its widespread use ahead of other treatments for insomnia.
Introduction
Insomnia is a disturbance of normal sleep patterns commonly characterised by difficulty in initiating sleep (sleep onset latency) and/or difficulty maintaining sleep (sleep maintenance) [1]. However, insomnia is highly subjective, and, although most healthy adults typically sleep between seven and nine hours per night, there is a large inter-patient variability. Insomnia can be classified as transient insomnia (lasting for <1 week), short-term insomnia (lasting for 1–4 weeks), and chronic insomnia (lasting for >4 weeks) [2].

Most cases of chronic insomnia are secondary to mental (e.g. depression, anxiety, dementia) or physical (e.g. sleep apnoea) disorders, or the direct physiological effect of substances (e.g. medications, drugs of abuse). In about 12–15% of cases of chronic insomnia, the insomnia is not caused by another condition, and is the primary complaint; this is termed primary insomnia (see Panel 1) [3]. As well as eliminating underlying mental and physical causes, diagnosis of primary insomnia requires that the sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of function.

The electrophysiological parameters of sleep (e.g. time taken to get to sleep, duration of sleep and number of awakenings) can be objectively assessed using polysomnography (PSG), which monitors sleep architecture (e.g. time in different stages of rapid-eye movement [REM] and non-REM sleep) by using electrodes applied to the scalp. However, these parameters do not fully capture the impact of the condition, and more subjective evaluations can be made using generic and disease-specific quality of life instruments and self-report measures such as sleep diaries and sleep quality indices [1].

The choice of management strategy for insomnia is dependent upon the duration and nature of the presenting symptoms. Appropriate management of existing co-morbidities (e.g. nocturnal pain control) may solve sleep problems without the need for further intervention. If further action is required, counselling on good sleep hygiene is fundamental to the overall management strategy, e.g. appropriate routines to encourage good sleep, avoiding stimulants, and maintaining regular sleeping hours with a suitable environment for sleep. Other non-pharmacological interventions (e.g. cognitive behavioural therapies [CBT]) have also been shown to be effective in the management of persistent insomnia. However, although healthcare professionals can deliver appropriate advice and education, access to many non-pharmacological therapies is restricted through a combination of a lack of trained providers, cost and a poor understanding of available options [1].

When pharmacological therapy is deemed necessary, hypnotics can be prescribed. However, although they can provide relief from the symptoms of insomnia, they do not treat any underlying cause [1]. A number of hypnotic agents are currently licensed for short-term use in the treatment of insomnia, including benzodiazepines and Z-drugs (zaleplon, zolpidem and zopiclone).

Drug action
Ramelteon is a selective MT₁/MT₂ melatonin receptor agonist [5]. Both these receptors are implicated in the effects of natural melatonin on sleep and circadian rhythms. A single-dose (4–64mg) study in healthy volunteers showed that ramelteon is rapidly absorbed, reaching a mean peak concentration at less than one hour [5]. The mean elimination half-life was 0.8 to 1.9 hours, although there was wide inter-subject variability for the measures of peak and total systemic exposure. Although the total absorption of ramelteon is at least 84%, the absolute oral bioavailability is only 1.8% due to

Panel 1. DSM-IV criteria for primary insomnia [4]

- The predominant symptom is difficulty initiating or maintaining sleep or non-restorative 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 sleep disturbance does not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, or a parasomnia.
- The disturbance does not occur exclusively during the course of another mental disorder (e.g. major depressive disorder, generalised anxiety disorder, delirium).
- The disturbance is not due to the direct physiologic effects of a substance (e.g. drug of abuse, medication) or a general medical condition.
extensive first-pass metabolism [6]. However, the major metabolite of ramelteon (M-II) is also active and is reported to effectively increase the half life of ramelteon up to 5 hours [Personal communication, Takeda, September 2007].

US Prescribing Information states that ramelteon should not be used in subjects with severe hepatic impairment, and used with caution in patients with moderate impairment [6].

A single-dose study in healthy volunteers found there was a reduced clearance and higher serum levels of ramelteon in elderly subjects, although this was not associated with enhanced pharmacodynamic effects (e.g. self- and observer-rated sedation, and simple mental tests) and it was concluded that age-related dose adjustments are not required [7]. CYP1A2 is the major isozyme involved in the hepatic metabolism of ramelteon, and studies have concluded that ramelteon should not be used in combination with fluvoxamine (a strong CYP1A2 inhibitor) [6]. Ramelteon should also be used with caution in patients taking other CYP1A2 inhibiting drugs, and strong inhibitors of CYP2C9 (e.g. fluconazole) and CYP3A4 (e.g. ketoconazole). Additionally, the efficacy of ramelteon may be reduced when used in combination with strong CYP enzyme inducers such as rifampicin. Single-dose daytime co-administration of ramelteon and alcohol showed an additive effect on some measures of psychomotor performance and US Prescribing Information recommends patients are cautioned not to consume alcohol when using ramelteon [6].

Proposed indication and marketing

The proposed indication for ramelteon is the management of primary insomnia in adults and the elderly, and it is anticipated that treatment will be limited to no more than six months duration. An application for Marketing Authorisation was submitted to the European Medicines Agency (EMEA) in March 2007, via the centralised procedure. The anticipated date of EMEA approval is July 2008, with a UK launch expected to be in September 2008. Ramelteon was licensed in the USA in September 2005, where it is indicated for the treatment of insomnia (six studies). However, only three studies had been published in peer reviewed journals at the time of this review. Therefore, as well as some important clinical data, details such as randomisation and treatment allocation procedures were not always available, precluding an in-depth evaluation. There is also data available on a one-year, uncontrolled, open-label study. This section contains a brief overview of these studies, with a summary of the overall efficacy and safety of ramelteon following the safety section below. Commonly used abbreviations are shown in Panel 2.

Table 2. Commonly used abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>PSG</td>
<td>Polysomnography</td>
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<tr>
<td>LPS</td>
<td>Latency to persistent sleep</td>
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<tr>
<td>TST</td>
<td>Total sleep time</td>
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<tr>
<td>CBT</td>
<td>Cognitive behavioural therapy</td>
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<tr>
<td>NAW</td>
<td>Night-time awakenings</td>
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<tr>
<td>WASO</td>
<td>Wake-up time after sleep onset</td>
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<td>CGI</td>
<td>Clinical Global Impression</td>
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Transient insomnia

In a US, randomised, parallel-group study, 289 healthy adults (mean age 28.8 years) received ramelteon 8mg, 16mg, or placebo, 30 minutes before bedtime [8] (Abstract). PSG-measured latency to persistent sleep (LPS) was statistically significantly reduced with the 8mg dose compared with placebo (12.2 vs. 19.7 minutes, P=0.004). Total sleep time (TST) was significantly increased from 420 minutes with placebo to 437 minutes with ramelteon 8mg (P=0.009) and 433 minutes with ramelteon 16mg (P=0.043). Ramelteon had no statistically significant effect on sleep architecture [8].

Chronic (primary) insomnia

Although not explicitly stated in the reports of all of the following studies (A to F), the inclusion and exclusion criteria were such that most patients included essentially met the DSM-IV diagnostic criteria for primary insomnia (see Panel 1). All of the studies were carried out in the US, with the exception of studies E and F, which included patients from Europe to support the EMEA application.

Panel A. A 3-way, randomised, crossover study assessed the efficacy of ramelteon 4mg, 8mg, and placebo in 100 elderly patients (>65 years, mean age 71 years, 63% female) [9]. The study drug was taken 30 minutes before habitual bedtime, and the two treatment phases were separated by washout periods of 5 to 12 days.

The primary efficacy measure was mean LPS for each 2-night treatment period. Compared with placebo (38.4 minutes), statistically significant reductions in LPS were
seen for ramelteon 4mg (28.7 minutes; P<0.001) and 8mg (30.8 minutes; P=0.005). Significant differences were also seen for some secondary outcomes. For example, compared with placebo (350 minutes), TST was statistically significantly increased in patients receiving ramelteon 4mg (359 minutes; P=0.036) and 8mg (362 minutes; P=0.007). Ramelteon 4mg (but not 8mg) showed statistically significantly more night-time awakenings (NAW) than placebo (10.9 vs. 10.1; P=0.016). No significant differences in wake-up time after sleep onset (WASO) were seen between treatment groups. Small statistically significant changes in sleep architecture between ramelteon and placebo were seen, but were not considered to have any clinical implications. Although a statistically significant reduction in subjective sleep latency (post-sleep questionnaire) was found for the 4mg dose compared with placebo (48.2 vs. 58.2 minutes, P=0.037), no significant differences were found for the 8mg dose, or for both doses with regard to other subjective sleep measures (TST and sleep quality) [9].

Study B. An unpublished, double-blind, randomised, outpatient study compared 35 nights of treatment with ramelteon 8mg, 16mg or placebo in 848 patients (aged 18 to 64 years). A 7-night, single-blind, placebo run-out phase was used to assess rebound insomnia and withdrawal symptoms. Efficacy data was collected via subjective daily sleep diaries, and weekly clinic visits [Personal communication, Takeda, June 2007].

The study failed to show a significant difference between groups in its primary endpoint of subjective sleep latency. Changes recorded for ramelteon 8mg, 16mg, and placebo, respectively, were from 85.2, 92.5 and 85.5 minutes at baseline to 74.8, 77.2 and 74.4 minutes at week-1 (primary endpoint), and 64.1, 65.2 and 66.5 minutes at week-5 [10]. Results for secondary endpoints did not demonstrate a consistent ability of either ramelteon dose to be distinguished from placebo at any specified time point.

Study C. A randomised, double-blind, placebo-controlled, 35-night study compared ramelteon 8mg or 16mg in 405 adults (mean age 39 years) [11] (Abstract). Patients were evaluated in a sleep laboratory on nights 1–2 (week-1), 15–16 (week-3), 29–30 (week-5), and 36–37 using PSG, and a post-sleep questionnaire. Placebo was given on nights 36 to 37 to evaluate rebound insomnia and withdrawal effects.

Statistically significant reductions in PSG-measured LPS (primary endpoint) were observed with ramelteon 8mg and 16mg vs. placebo at week-1 (32.2 and 28.9 vs. 47.9 minutes; both P<0.001), and maintained at weeks 3 and 5. Ramelteon (both doses) resulted in statistically significant improvements in PSG-measured TST (394 and 398 vs. 375 minutes; both P<0.001), and sleep efficiency (82.3% and 83.4% vs. 78.3%; both P<0.001) at week-1. However at 3 and 5 weeks there were no significant differences in PSG-measured TST, except for the 16mg dose at 3 weeks (394 vs. 382 minutes; P=0.047). There were no significant differences in WASO and NAW between groups. No evidence of rebound insomnia was found. Statistically significant improvements in subjective sleep latency and TST were found for the 8mg dose at all time points. However, improvements in these measures at week-1 with the 16mg dose were not maintained through week-5. Subjective awake time was only significantly different from placebo (both doses) at week-1, and there were no significant differences in subjective sleep quality. Ramelteon had no clinically meaningful effects on sleep architecture, next morning psychomotor tasks, alertness, or ability to concentrate. No rebound or withdrawal effects were observed [11].

Study D. A randomised, double-blind, placebo-controlled study of 829 elderly patients (mean age 72.4, 59% female) with chronic insomnia compared ramelteon 4mg, 8mg, or placebo taken every night for 35 days. The study included a 7-night, single-blind, placebo run-out period to evaluate possible rebound insomnia and withdrawal effects [12].

128 (15.4%) patients discontinued double-blind treatment prematurely (relatively even across treatment groups). It is unclear if data from these patients were excluded from the efficacy analyses. There were statistically significant reductions in the primary endpoint of subjective sleep latency with ramelteon 4mg and 8mg compared with placebo at week-1 (70.2 minutes for both doses vs. 78.5 minutes for placebo; both P=0.008). Statistically significant differences were also found at weeks 3 and 5 for the 8mg dose, but were only found at week-5 for the 4mg dose. Although there was a statistically significant increase in subjective TST for ramelteon 4mg vs. placebo at week-1 (325 vs. 314 minutes; P=0.004) and week-3 (336 vs. 324 minutes; P=0.007); there was no significant difference between the 8mg dose and placebo at any time. No significant differences between groups were identified for other subjective patient-recorded measures (sleep quality, NAW, ease of falling back to sleep) or investigator assessed clinical global impression (CGI) at any time-points. There was no evidence of rebound insomnia or withdrawal effects following treatment discontinuation [12].

Study E. A randomised, double-blind, study in adults (mean age 42 years) examined the effect of peak plasma levels of ramelteon 8mg on balance platform stability compared with placebo, with zopiclone used as a reference treatment [13] (Poster). [Personal communication, Takeda, May 2007]. This study was undertaken because the extent of drug-induced postural sway is purported to be linked to likelihood of nocturnal falls in the elderly – an important consideration for all hypnotic medication. Following a 14-night, single-blind, placebo run-in, 275 adults received placebo, ramelteon 8mg, or zopiclone 7.5mg for 28 nights. After 14 nights, patients were admitted to a sleep laboratory. A balance platform task was performed at 1.5 hours before dosing and again after waking them 1.5 to 2 hours post-dose (about the peak plasma drug level). 260 adults completed these tests. Compared with placebo, ramelteon did not
significantly affect body sway, whereas zopiclone did. The mean post-dose log centres of pressure (COPs) recorded on the balance platform with eyes open (primary endpoint) were 1.617cm$^2$ for placebo, 1.497cm$^2$ for ramelteon ($P=0.532$ vs. placebo), and 3.539cm$^2$ for zopiclone ($P<0.001$ vs. placebo) [13]. The study was not designed to directly compare the two active drugs.

These results are consistent with a smaller single-blind, randomised, single-dose, crossover study of ramelteon 8mg, zolpidem 10mg and placebo in 33 elderly patients with primary insomnia. No significant differences were seen between ramelteon and placebo in balance, mobility and memory on waking the patients two hours after dosing, whereas zolpidem significantly decreased performance on each of these measures [14] (Poster). However, it should be noted that in this study the dose of zopiclone was higher than the recommended UK dose.

**Study F.** A randomised, placebo-controlled study in 451 adults with chronic insomnia evaluated the efficacy, safety, and potential for residual effects of ramelteon when administered for 6 months [15] (Poster), [Personal communication, Takeda, May 2007]. Patients received a night-time dose of ramelteon 8mg or placebo with assessments performed at baseline, at week-1, and then at 1, 3, 5 and 6 months. The primary efficacy endpoint was the mean LPS of 2-night PSG.

Ramelteon produced a consistently reduced PSG-measured LPS (by about 7 to 15 minutes throughout) compared with placebo ($P<0.05$) at all time points. A statistically significantly greater increase of PSG-measured TST was observed with ramelteon compared with placebo at week-1 (381 vs. 366 minutes; $P<0.001$) [15]. Subjectively assessed sleep onset time was about 6 to 14 minutes shorter than placebo throughout, but was only significantly different at week-1, and after 1 and 5 months. There were no significant differences between ramelteon and placebo at any time point on the following measures: subjective TST, subjective number of awakenings, sleep quality, and restorative nature of sleep. No significant difference in subjective awake time was observed between ramelteon and placebo at any time point except after 6 months (ramelteon: 90.9 minutes, placebo: 79.5 minutes; $P=0.036$) [15].

**Study G.** In an open-label study, 1213 adults with chronic insomnia received ramelteon nightly for a year followed by a 3-day single-blind placebo run-out [16]. Subjects aged 65 years or older (mean 72 years) received ramelteon 8mg (n=248); those aged 18 to 64 years (mean 46 years) received ramelteon 16mg (n=965). Efficacy was evaluated by subject-maintained daily sleep diaries and CGI assessments performed by the investigator. Continued improvements from baseline in sleep latency and TST were reported in both groups throughout the treatment period with no notable changes during a 3-day placebo-run out phase. For example, sleep latency dropped to less than 50 minutes after 6 months (a 35-minute improvement). At 6 months and 1 year, CGI indices showed an improved insomnia condition, a sustained decrease in severity of illness, and a moderate therapeutic effect from baseline. Little useful evidence on the efficacy of ramelteon relative to other treatments (including no treatment) is provided by this study because of its open-label nature and lack of controls (placebo or active) [16].

**Safety**

Safety data from the studies discussed above are limited, and the following information is taken from US Prescribing Information, which describes data relating to exposure to ramelteon in 4251 subjects, including 346 exposed for 6 months or longer, and 473 subjects for 1 year [6]. Six percent of patients exposed to ramelteon in clinical studies discontinued treatment due to an adverse event compared with 2% receiving placebo. The most frequent adverse events leading to discontinuation in patients receiving ramelteon were somnolence (0.8%), dizziness (0.5%), nausea (0.3%), fatigue (0.3%), headache (0.3%), and insomnia (0.3%). The most commonly observed adverse events in Phase I–III trials for placebo (n=1370) and ramelteon 8mg (n=1250), respectively, were headache (7% vs. 7%), somnolence (3% vs. 5%), fatigue (2% vs. 4%), dizziness (3% vs. 5%), nausea (2% vs. 3%), and exacerbated insomnia (2% vs. 3%).

In a 12-month, open-label study, adverse events in adults (including elderly patients) were primarily mild or moderate. There were 2 patients who were noted to have abnormal morning cortisol levels, and subsequent abnormal ACTH stimulation tests, and 1 female patient was also diagnosed with a prolactinoma. The relationship of these events to ramelteon therapy is not clear. US prescribing information states that as ramelteon has been associated with an effect on reproductive hormones in adults, e.g. decreased testosterone levels and increased prolactin levels, it is not known what effect chronic or even chronic intermittent use of ramelteon may have on the reproductive axis in developing humans. For patients presenting with unexplained amenorrhoea, galactorrhoea, decreased libido, or problems with fertility, assessment of prolactin levels and testosterone levels should be considered as appropriate [6].

A 6-month study comparing ramelteon 16mg and placebo in 122 patients with chronic insomnia evaluated effects on thyroid axis, adrenal axis and reproductive axis [6]. No significant abnormalities were seen in either the thyroid or the adrenal axes, although abnormalities were noted within the reproductive axis. Overall, the mean serum prolactin level change from baseline was 4.9 µg/L (34% increase) for women in the ramelteon group compared with −0.6 µg/L (4% decrease) for women in the placebo group ($P=0.003$). No differences were seen in men. Thirty-two percent of patients who were treated with ramelteon in this study (women and men) had prolactin levels that increased from normal baseline levels compared with 19% of patients who were treated with placebo. However, subject-reported menstrual patterns were similar between the two groups [6].
Ramelteon

Studies to date have shown that ramelteon has no significant impact on next-day residual effect measures including the digit symbol substitution test, memory tests, and visual analog scales for mood and feeling [8,9,15,17]. However, US prescribing information includes a caution to avoid engaging in hazardous activities that require concentration (such as driving) after taking ramelteon [6]. Studies indicate that there are no statistically significant differences between ramelteon and placebo for rebound insomnia or withdrawal effects [11,12,15].

A single-dose, double-blind, crossover study has assessed the abuse liability of ramelteon in 14 adults with histories of sedative abuse [17]. Subjects each received ramelteon (16, 80, or 160mg), triazolam (0.25, 0.5, or 0.75mg) and placebo, and were assessed by subject-rated measures including items relevant to potential for abuse (e.g. drug liking, street value, and pharmacological classification). Compared with placebo, ramelteon showed no significant effects indicative of potential for abuse at doses up to 160mg, whereas triazolam resulted in significant differences in the direction of greater drug strength, and potential for abuse [17]. Although this study suggests that ramelteon may not have potential for abuse, further data are required to evaluate its potential to cause physical or psychological dependence, and whether or not tolerance develops with its use. No cases of ramelteon overdose have been reported [6].

Summary of Efficacy and Safety

Currently, controlled trial data are limited, relatively short-term, and there is a lack of direct comparative efficacy studies compared with established therapies for insomnia. A large placebo response was seen in all the studies for both objective and subjective sleep measures, and suggests that for the majority of patients with primary insomnia drug treatment may not be necessary. Simple sleep hygiene measures (see MeReC Briefing 2001 Good Sleep Guide, available at www.npc.nhs.uk/MeReC_Briefings/2001/good_sleep_guide.pdf) may be all that is necessary. There is no evidence of any benefit for ramelteon over non-drug interventions. CBT is an effective treatment for sleep disorders that can reduce hypnotic consumption at a reasonable cost among long-term hypnotic users with chronic sleep difficulties [18].

Results from available studies show that ramelteon provides statistically significant improvements over placebo in laboratory assessed sleep latency and total time asleep. However, the absolute improvement for ramelteon 4mg and 8mg (proposed licensed doses in UK) over placebo appear very modest, ranging from 7.5 to 16 minutes for LPS, and 9 to 19 minutes for TST. How meaningful these differences are to individual patients is uncertain. Nevertheless, the differences in laboratory-assessed sleep latency are similar to those of other hypnotics. A systematic review of randomised controlled trials identified PSG-measured reductions in sleep latency relative to placebo of 10.0 minutes (95%CI 3.4 to 16.6) for benzodiazepines and 12.8 minutes (95%CI 8.8 to 16.9) for non-benzodiazepines [19].

Ramelteon does not appear to significantly improve laboratory-assessed sleep maintenance, the number of awakenings, or time to waking from sleep onset.

In several studies, the differences between ramelteon and placebo for subjective sleep parameters (including latency to sleep, total time asleep and sleep quality) were smaller than those of objective laboratory measures, and in many cases not statistically significant. Whilst these outcomes were often secondary endpoints, the lack of a clear patient-perceived advantage for ramelteon over placebo questions the clinical significance of any laboratory-measured improvements seen.

The effects that have been demonstrated for ramelteon pertain mainly to sleep induction but not maintenance, whereas benzodiazepines and other sedative hypnotics provide both induction and maintenance of sleep. Ramelteon, therefore, may not help many patients whose main complaint is that of not getting back to sleep after they wake up.

When considering the benefits of ramelteon, it is important to consider the extent of the improvement in efficacy outcomes that are of most importance to patients and balance these against the potential for adverse effects. The clinical significance depends not just on changes in sleep parameters, but also (and possibly more importantly) the effect on daytime functioning, fatigue, mood and quality of life [20]. To date, evidence to suggest that ramelteon provides benefits in these measures is sparse. Additionally, there are still questions over the optimum dose of ramelteon. A randomised, double blind, placebo controlled, crossover, dose-response study of patients (n=107) with primary insomnia suggests little difference between 4mg and 32mg doses with regard to PSG-measured or subjective sleep latency [21].

The rigorous exclusion criteria applied in all studies, effectively limiting the population studied to those with primary insomnia, means that there are no data for the use of ramelteon in the majority of patients with chronic insomnia, whose sleep problems arise from or are concomitant with a psychiatric or medical illness [1].

The Medicines and Older People section of the National Service Framework (NSF) for Older People states that patients taking hypnotics are more liable to fall during the night, and this has been shown for short-acting as well as long-acting drugs [22]. Additionally, NICE guidance on falls states that older people on psychotropic medications should be reviewed and psychotropics discontinued if possible to reduce their risk of falling [23]. Unpublished data show that at peak drug concentrations ramelteon recipients had comparable body sway to placebo, whereas zopiclone caused a statistically significant increase in this measure [13]. However, this study was not conducted in an elderly population (mean age 42 years) and it remains to be seen whether the advantage of ramelteon on the surrogate endpoint of body sway translates into a clinically meaningful
reduction in fall rate in the elderly population versus existing therapies. Further studies with clinically relevant outcomes are required to demonstrate this.

Relatively short-term studies suggest ramelteon produces no rebound insomnia, withdrawal and next morning residual effects. Limited data also suggests a lack of abuse potential in known substance misusers but this does not necessarily preclude dependence.

The long-term adverse event profile of ramelteon has not been established. Most clinical reports of its use suggest that adverse effects are mild to moderate. However, in a six month study, 32% of ramelteon recipients experienced raised prolactin levels. This effect warrants further study as prolonged hyperprolactinaemia could lead to hypogonadism, infertility, decreased libido, and osteoporosis.

**Treatment alternatives**

No medicines are currently licensed in the UK for the long-term treatment of chronic insomnia, primary or otherwise. Hypnotics (shorter-acting benzodiazepines, Z-drugs) can be considered for short-term use in patients with chronic insomnia strictly in accordance with their licence. They should only be used to treat insomnia when it is severe, disabling, or subjecting the individual to extreme distress.

Before prescribing hypnotics, the underlying cause of the insomnia should be established, and where possible the underlying cause should be treated. NICE guidance recommends that doctors should consider using non-medicine treatments initially, and if this approach fails, a hypnotic medicine may be considered as an appropriate way to treat severe insomnia that is interfering with normal daily life [1]. If a Z-drug or a shorter-acting benzodiazepine is considered appropriate, then it is recommended that the drug with the lowest purchase cost should be prescribed, and that switching from one of these hypnotics to another should only occur if a patient experiences adverse effects considered to be directly related to a specific agent. Patients who have not responded to one of these hypnotic drugs should not be prescribed any of the others.

Drugs licensed for treating insomnia include the benzodiazepines (lorazepam, lormetazepam, nitrazepam, temazepam), Z-drugs (zaleplon, zolpidem, zopiclone), chloral derivatives (chloral hydrate, triclofos), clomethiazole, and promethazine. Usual dosages, licensed indications and approximate costs for the two most commonly prescribed hypnotics are given in the table below. Patients may also use non-licensed medicines, e.g. antihistamines, or alcohol without consulting their doctor. Prolonged-release melatonin (Circadin®) is expected to be launched in the UK in 2008 [24], and probably ahead of ramelteon. Unlike the proposed indication of ramelteon, the licence limits its use to short-term treatment of primary insomnia in patients who are aged 55 years or older. Its costs are unknown presently.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual dose</th>
<th>Licensed indication</th>
<th>Approx. cost for 28-days*</th>
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</thead>
<tbody>
<tr>
<td>Temazepam</td>
<td>10–20mg</td>
<td>Short-term treatment of sleep disturbances considered severe or disabling or where insomnia is subjecting the individual to extreme distress.</td>
<td>£0.63–£1.12, £1.42–£2.36³</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>3.75–7.5mg</td>
<td>Short-term treatment of insomnia, including difficulties in falling asleep, nocturnal awakening and early awakening, transient, situational or chronic insomnia, and insomnia secondary to psychiatric disturbances, in situations where the insomnia is debilitating or is causing severe distress for the patient.</td>
<td>£2.93–£2.94</td>
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</table>

*Drug Tariff, September 2007  
³Original pack dispensing

**Current drug usage**

In the financial year 2006/2007, 4.8 million items for benzodiazepine hypnotics (temazepam, nitrazepam, lormetazepam, loprazolam) and 4.8 million items for Z-drugs were dispensed at a cost of £11.4 million and £13.4 million, respectively [25].

**Estimated NHS impact**

It has been estimated that the prevalence of insomnia varies from 10–38%, with the variation attributed to different definitions, classification systems and diagnostic criteria [1]. A recent systematic review of the epidemiological literature suggested that, while 30–48% of people reported the presence of insomnia symptoms, and 8–18% reported dissatisfaction with sleep quality or quantity, only 6% met the criteria for a diagnosis of insomnia. Although one in twenty people are believed to present to healthcare professionals with insomnia-related symptoms, it is thought that many people with insomnia do not seek medical help [1].

It is important to note that ramelteon will be licensed for the treatment of primary insomnia only (estimated to account for 12-15% of patients with chronic insomnia [3]), and should therefore only be prescribed for patients after a full physical and mental assessment, along with a full medication history, in order to ascertain a correct diagnosis. However, in practice, distinguishing between primary insomnia and chronic insomnia secondary to other conditions may be difficult. For example, although insomnia is a common symptom of psychiatric disorders, such as depression, chronic unremitting insomnia may predispose to their development [3].

It is anticipated that ramelteon will be marketed on its novel mode of action (with long-term treatment being necessary to gain control of the wake sleep cycle), its good tolerability, and differentiated from benzodiazepines and Z-drugs by producing a more normal, natural sleep pattern, no or reduced residual (hang-over) effects, and having less potential for abuse. Ramelteon will compete with prolonged-release melatonin (Circadin®) for the treatment of primary insomnia, which, though limited to short-term use, is also likely to be marketed as having a new mechanism of action different from the other approved medicines, i.e. mimicking the
physiological profile of the body’s own melatonin secretion, and not having the drawback of dependency and residual drowsiness associated with the sedative hypnotics [24].

About 10 million items of hypnotic medications are prescribed each year at a total cost of about £25 million pounds. Additionally, up to 40% of people with insomnia self-medicate with hypnotics that are available without prescription from pharmacies (for example, sedative antihistamines) [1]. Assessing the impact of ramelteon is difficult to assess due to uncertainty regarding the number of patients eligible for its use (i.e. with primary insomnia) and the lack of data relative to other treatments (drug and non-drug) on meaningful benefits with regard to daytime functioning and quality of life. It is also not known how the launch of prolonged-release melatonin (Circadin®) will impact on the use of ramelteon.

Ramelteon, unlike other hypnotics, may be licensed for long-term use (up to six months). If such a licence is approved, then the course prescribed for a patient is likely to be longer than that usually prescribed for other hypnotics. As the cost of ramelteon (£10–20 for 30 days) is also considerably higher than currently available hypnotics, its widespread use could have a significant impact on prescribing costs for insomnia.

Current evidence is insufficient to support the widespread use of ramelteon. It is possible that ramelteon may have a role as an alternative to the inappropriate long-term or repetitive use of benzodiazepines and Z-drugs in certain circumstances, i.e. where drug treatments are considered necessary and other interventions are either ineffective, contraindicated or, in the case of non-drug treatments, not readily available. Further research in these areas is required.

It is important to ensure that the uptake of new drugs is based on published robust evidence and not on prescriber perception. However, a recent study, which determined primary care physicians’ perceptions of the benefits and risks of benzodiazepine and Z-drug use, showed that this is not always the case [26]. While NICE concluded that there is a lack of compelling evidence to distinguish between the Z-drugs and the shorter-acting benzodiazepine hypnotics, the majority of practitioners questioned believed that Z-drugs were more effective and safer than benzodiazepines [26]. Prescribing data for England appears to confirm the findings of this study, as in 2006 more prescriptions were dispensed in primary care for zopiclone than temazepam [25].

Ramelteon is in Phase II studies for the management of circadian rhythm sleep disorders [Personal communication, Takeda, May 2007]. It is also being studied in patients with sleep apnoea and COPD — conditions in which other hypnotics are contraindicated or need to be used with caution because of potential respiratory depression. Other entities in at least Phase III development for the treatment of insomnia include low-dose doxepin, eplivanserin, esmirtazapine, eszopiclone, and indiplon [27].

Points to consider in determining the place in therapy of ramelteon in the treatment of chronic insomnia

- Where drugs are necessary, the shorter-acting benzodiazepines (e.g. temazepam) and the Z-drugs are safe and effective at licensed doses for short-term treatment of insomnia for people who are acutely distressed. NICE recommends that the cheapest agent be used [1].
- The proposed licence is for primary insomnia. There are no published data assessing the use of ramelteon in patients with a significant concomitant psychological and/or medical illness, which represent the majority of patients with chronic insomnia. In order to assist in diagnosis, a comprehensive physical and mental assessment, along with a complete medication history, may be helpful.
- Ramelteon produces modest, statistically significant improvements in objective, laboratory-measured sleep latency time and the total sleep time. These effects are similar to those of benzodiazepines and Z-drugs. However, unlike the sedative hypnotics, ramelteon appears not to offer any advantage over placebo with regard to the number of awakenings, or in the time of wakening from sleep onset (i.e. sleep maintenance).
- Patient-perceived (subjective) benefits of ramelteon are smaller than those indicated by laboratory measurements, and in many cases not statistically significant. Unless patients perceive a benefit from the use of ramelteon they may not continue to use it.
- Ramelteon appears not to exhibit next-day residual effects, although there is no direct evidence of a benefit compared with other hypnotics.
- In laboratory studies, ramelteon improves balance upon awakening during the night compared with Z-drugs. However, it is not known whether this translates into a significant benefit in terms of falls and fractures in the elderly.
- Benefits of ramelteon with regard to daytime functioning, fatigue, mood and quality of life have not been established.
- There is limited data suggesting that ramelteon does not have potential for drug abuse. However, further data are required to fully assess the potential for dependence and tolerance.
- More data are required to establish the long-term adverse event profile of ramelteon.
- Published comparative studies are required to directly assess any efficacy and safety differences vs. existing therapies including behavioural interventions, such as CBT.
References


27. AdisInsight R&D website. Available at URL: http://bi.adisinsight.com [subscription necessary]. Accessed on 18.06.07