INTRODUCTION

Over the past decade, drug companies have focused much of their attention on addressing the problem of insomnia. This effort should come as no surprise—in 2005, the National Sleep Foundation, part of the National Institutes of Health, estimated that more than half (54%) of all Americans were reporting symptoms of insomnia a few nights a week, and one third (33%) were reporting symptoms nearly every night. Epidemiologists have suggested that 10% to 20% of people in the U.S. and in Western Europe experience chronic insomnia. These statistics clearly demonstrate a need for sleep medications and an opportunity for the pharmaceutical industry to develop new and improved sleep aids with hopes of promising revenues while improving outcomes in patient health care and quality of life.

Most medications available for insomnia focus on modulation of the GABA-ergic system. Because of the properties of most currently prescribed medications, which act primarily by enhancing the neurotransmitter gamma-aminobutyric acid (GABA) at its receptors through binding to benzodiazepine (BZD) receptors as allosteric modulators, they are classified as controlled substances and carry some risk for dependence or abuse. These sleep-promoting agents include the older benzodiazepines: flurazepam (Dalmane, ICN), temazepam (Restoril, Malinchrodt), triazolam (Halcion, Pfizer), estazolam (ProSom, Abbott), and quazepam (Doral, Wallace) as well as newer agents, the non-benzodiazepines. The non-benzodiazepines selectively act on the BZD receptors and include zolpidem (Ambien, Sanofi-Aventis), zaleplon (Sonata, King/Wyeth), and eszopiclone (Lunesta, Sepracor).

The newer medications are fairly well tolerated, and their risk for abuse or dependence is lower than that of the older BZDs. Older sedative medications, like the BZDs, are still very effective but carry a higher risk for abuse and dependence when used over the long term. Barbiturates commonly have a high potential for abuse, dependence, and toxicity; generally, they are no longer recommended for sleep.

In addition to the problems of abuse and dependence, drugs that act by modulating GABA are especially complicated in elderly people. According to the updated Beers criteria for potentially inappropriate medications used in older adults, benzodiazepines are of great concern. They have been reported to cause prolonged sedation; an increased risk of falls, possibly leading to fractures; cognitive impairment; dizziness; and depression. These drugs are not usually recommended for patients 65 years of age or older unless they are considered absolutely necessary.

Similarly, barbiturates are contraindicated for insomnia in the elderly and carry an increased risk of side effects and toxicity. Even non-benzodiazepines, although much safer than barbiturates and benzodiazepines, can cause confusion and increased falls in older adults.

These concerns of drug abuse, dependence, and problematic side effects highlight the need and opportunities for the development of innovative therapies for insomnia. One agent, approved by the Food and Drug Administration (FDA) in 2005, is ramelteon (Rozerem, Takeda Pharmaceuticals). Ramelteon is the first FDA-approved medication that acts on melatonin receptors. As a result of this mechanism of action, the dependence and abuse potential are eliminated; therefore, ramelteon does not need to be restricted as a controlled substance. In addition, dose reductions are not required in the elderly. This drug may even be beneficial in blind or neurologically compromised patients for whom other insomnia treatments are ineffective or contraindicated.

CHEMICAL AND PHYSICAL PROPERTIES

Ramelteon is a melatonin receptor agonist. According to the manufacturer, its molecular structure is composed of a substituted tetrahydroindeno[1,2-b]fur derivative containing a propionamide moiety with one chiral center, and the compound is produced as the (S) enantiomer. It is freely soluble in organic solvents and is considered very slightly soluble in water or aqueous buffers with a pH between 3 and 11.

Ramelteon is available as a round, pale orange-yellow, film-coated 8-mg tablet. It should be stored between 15° and 30°C (59° and 86°F) and protected from moisture and humidity to avoid degradation of the contents.

MECHANISM OF ACTION

Normally, the pineal gland secretes melatonin at night to initiate sleep onset and to sustain night-time sleep. This action occurs because of melatonin’s inhibition of the neuronal firing rate that maintains wakefulness involved in the circadian rhythm of humans.
As a melatonin agonist, ramelteon mimics the actions of melatonin to trigger sleep onset. It weakly binds to the melatonin-3 receptor (MT3) and has high selectivity as an agonist for MT1 and MT2 receptors in the suprachiasmatic nucleus. Its high affinity for MT1 and MT2 is thought to exert its sleep-promoting properties in a fashion similar to how endogenous melatonin acts in maintaining a normal sleep–wake cycle. The MT1 receptor is believed to regulate sleepiness, whereas the MT2 receptor is probably involved in the adjustment of circadian rhythms.

The binding affinity of ramelteon to these receptors is three to 16 times that of melatonin. This property is thought to exert an increased potency when compared with that of melatonin. However, no comparison study has been performed to determine whether the recommended dose of ramelteon (8 mg) exerts any advantage over standard doses of melatonin (0.3 mg), including long-term usage.

### PHARMACOKINETICS

#### Absorption and Distribution

Ramelteon is rapidly absorbed after oral administration. Administration of ramelteon after a high-fat meal results in a 31% increase in the area-under-the-curve (AUC) concentration and in a 22% decrease in peak concentration (Cmax). The median time of maximum concentration (Tmax) is delayed by 45 minutes after administration with food (Table 1).

The Cmax is approximately 0.5 to 1.5 hours after fasting with oral administration. The drug has extensive first-pass metabolism, with an absolute oral bioavailability of 1.8%. Plasma protein-binding ability is moderate at 82% in human serum, with the majority of binding to serum albumin accounting for 70%. Thus, the drug is not highly protein-bound. No drug–drug interactions caused by this mechanism have been reported.

The mean volume of distribution of ramelteon after intravenous (IV) administration is 73.6 liters, which suggests substantial distribution to the tissues.

#### Metabolism and Elimination

Ramelteon is metabolized primarily via the hepatic system. It is oxidized to hydroxyl and carbonyl derivatives, with secondary metabolism producing glucuronide conjugates. Cytochrome CYP 1A2 is the major isoenzyme involved; the CYP 2C9 and CYP 3A4 isoenzymes have a minor role.

Ramelteon has an active major metabolite, M-II. M-II has a much lower binding affinity than the parent molecule for MT1 and MT2 receptors. Thus, it is much less potent than the parent drug, but it circulates at higher concentrations to exhibit a greater systemic exposure than the parent molecule. It also has weak affinity for the serotonin receptor 5-HT2B.

After oral administration, 84% of the drug is excreted in the urine and 4% is eliminated in the feces. Less than 0.1% is excreted as the parent compound. The elimination half-life of the parent drug is approximately 1 to 2.6 hours, a relatively short duration. The active metabolite’s elimination half-life is slightly longer, at two to five hours.

#### Table 1  Pharmacokinetic Properties of Ramelteon

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral bioavailability</td>
<td>Less than 2% (extensive first-pass hepatic metabolism)</td>
</tr>
<tr>
<td>Tmax</td>
<td>0.5–1.5 hours (delayed by 45 minutes if taken with food)</td>
</tr>
<tr>
<td>Mean half-life</td>
<td>1.0 to 2.6 hours</td>
</tr>
<tr>
<td>Protein binding</td>
<td>82%</td>
</tr>
<tr>
<td>Primary metabolic pathway</td>
<td>CYP 1A2</td>
</tr>
<tr>
<td>Secondary metabolic pathways</td>
<td>CYP 3A4, CYP 2C subfamily</td>
</tr>
<tr>
<td>Excretion</td>
<td>Less than 1% renally eliminated unchanged</td>
</tr>
</tbody>
</table>

CYP = cytochrome; Tmax = time to maximum concentration.

#### DOSAGE

##### Adults

The recommended dose of ramelteon is 8 mg, taken within 30 minutes of bedtime. Ramelteon should not be taken with, or immediately after, a high-fat meal because of the delay in absorption.

##### Elderly Patients

No overall differences in safety or efficacy were observed between elderly and younger adult subjects. In a phase 3 study of elderly patients with chronic insomnia conducted by Roth and colleagues, patients aged 65 to 83 years demonstrated no significant adverse events and no evidence of next-morning psychomotor or memory impairment.

Dosing of ramelteon in this phase 3 study ranged from 4 mg to 8 mg daily.

##### Hepatically Impaired Patients

In patients with mild hepatic impairment, their exposure to ramelteon was increased by four-fold in comparison with normal subjects. The manufacturer recommends use with caution in patients with mild-to-moderate hepatic impairment. The pharmacokinetic properties of ramelteon have not been evaluated in patients with severe hepatic impairment, and the use of this agent should be avoided in this group.

##### Renally Impaired Patients

Because ramelteon is eliminated primarily via hepatic metabolism, no adjustment of the drug is required for patients with renal impairment (a creatinine clearance of 30 mL/minute per 1.73 m² or less) or for patients who require chronic hemodialysis.

##### Pregnant and Lactating Patients

Ramelteon has been classified as a Pregnancy Category C drug. No studies have been performed in pregnant or lactating women. This agent was a developmental teratogen in rats when it was given in doses near 200 times the recommended human dosage.

Ramelteon is also secreted into the milk of lactating rats. The potential risks and benefits of using this medication in pregnant and lactating women should be carefully considered.

##### Pediatric Populations

In two small studies, ramelteon was...
shown to increase prolactin levels in adults, thus possibly playing a role in altering the reproductive axis in developing children or adolescents. Because of potential adverse effects and a lack of available studies, this drug is not indicated for use in pediatric patients.11

**INDICATIONS**

Ramelteon is indicated for the treatment of insomnia characterized by difficulty with sleep onset. The drug can be prescribed for long-term use.11

**CONTRAINDICATIONS AND PRECAUTIONS**

Ramelteon should not be used in patients with hypersensitivity to any components of the formulation or in patients with severe hepatic impairment. It should not be used in combination with fluvoxamine maleate (Luvox, Solvay), and it should not be taken with alcohol.

Ramelteon has not been studied in patients with severe sleep apnea or severe chronic obstructive lung disease or in pediatric patients.11

**ADVERSE DRUG EFFECTS**

The adverse drug events (ADEs) associated with ramelteon appear to be minor and similar to those of placebo. Of the 3,594 subjects evaluated in the phase 1 to phase 3 studies of ramelteon, the most frequent ADEs leading to discontinuation were somnolence (0.8%), dizziness (0.5%), nausea (0.3%), fatigue (0.3%), headache (0.3%), and insomnia (0.3%). Of those patients receiving ramelteon 8 mg in studies, only 3.8% discontinued therapy because of ADEs.17

No significant changes in laboratory values, electrocardiograms (ECG), or blood and urine analyses have been reported in clinical trials. The drug has been associated with effects on the reproductive system in adults. Patients experiencing unexplained amenorrhea, galactorrhea, decreased libido, or problems with fertility should be assessed for alterations in testosterone levels or increased prolactin.11,21

**ABUSE POTENTIAL**

When compared with triazolam (Halcion) and placebo in a small sample of 14 subjects who were evaluated for abuse liability, ramelteon demonstrated no abuse potential. No evidence of abuse was demonstrated even at doses up to 20 times the usual treatment dose. These results were vastly different from the abuse potential demonstrated by triazolam at treatment doses and doses up to three times higher than usual.18

**DRUG INTERACTIONS**

The cytochrome CYP 1A2 isoenzyme is the major enzyme involved in the metabolism of ramelteon. The use of ramelteon is contraindicated with fluvoxamine (Luvox), which is a strong inhibitor of the CYP 1A2 isoenzyme. Ramelteon should be administered with caution to patients taking other CYP 1A2 inhibitors. The CYP 2C9 and CYP 3A4 isoenzymes are also involved with the drug’s metabolism to a minor degree. Health care providers should use caution when prescribing ramelteon in conjunction with strong inhibitors of these isoenzymes as well.11

**CLINICAL EFFICACY**

Studies in animals have consistently shown that ramelteon has a sleep-promoting action; it does not appear to cause learning, memory, or motor function impairment or to provide “reward” properties.19–21 Thus far, ramelteon does not tend to be associated with benzodiazepine-like abuse or dependence in long-term studies lasting over one year of administration in human and animal models.14,19,21,22

Erman et al.23 Erman and colleagues conducted a multicenter, double-blind, randomized, placebo-controlled crossover study to evaluate the dose-related efficacy, safety, and dose response of ramelteon. They enrolled 107 patients, 18 to 64 years of age, with chronic primary insomnia, according to criteria from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV).

Patients had presented with insomnia complaints for at least three months, as confirmed with a polysomnograph. The inclusion criteria consisted of a mean latency to persistent sleep of more than 20 minutes, and mean wake-up time of more than 60 minutes in a sleep laboratory on two consecutive nights. Latency can be defined as the amount of time it takes for an awake person to fall asleep.

Each patient was randomly assigned to a dosing sequence that included 4, 8, 16, and 32 mg of ramelteon and placebo. Patients served as their own controls and received all five treatments with washout periods of five to 12 days between treatments.

The medication was administered 30 minutes before the patient’s habitual bedtime, followed by eight hours of polysomnographic monitoring.

To determine the patients’ alertness and ability to concentrate, the investigators assessed residual effects using next day Visual Analogue Scale (VAS) scores to measure mood and feeling as well as a post-sleep questionnaire. They also measured a Digit Symbol Substitution Test (DSST) and a word list memory test involving immediate and delayed recall. In the DSST, the patient is given a key and must fill in a symbol corresponding to a number within 90 or 120 seconds. The score is the number of correctly completed symbols.

Polysomnographic assessment demonstrated statistically significant reductions in latency to persistent sleep and increases in total sleep time for all tested doses of ramelteon, compared with placebo (P < 0.001). Total sleep time and sleep efficiency improved with each increase in ramelteon dosage in comparison with placebo:

- With the 8-mg group of patients, the reduced latency to persistent sleep was 24.3 minutes; with placebo, it was 37.7 minutes (P < 0.001).
- With the 8-mg group, the total sleep time was 412.9 minutes; with placebo, it was 400.2 minutes (P < 0.01).

The researchers observed a decrease of approximately 1.3% to 2.1% in slow-wave sleep (stages 3 and 4 of the sleep cycle) in the treated patients. Patients receiving placebo did not demonstrate any changes in sleep stages. No differences were apparent in the ramelteon or placebo groups among the dosage sequences administered in awake time after the onset of persistent sleep, subjective total sleep time, quality of sleep, VAS scores, DSST scores, memory test scores, or in post-sleep levels of alertness or concentration.

There were no next-day residual effects or differences in the number or type of ADEs seen at any dose, compared
with placebo. The most commonly reported ADEs were mild and included headache, somnolence, and sore throat.

Overall, the drug was well tolerated and demonstrated statistically significant reductions in latency to persistent sleep and increases in total sleep time in patients with chronic primary insomnia.

Roth et al.16

A double-blind study by Roth and colleagues evaluated the efficacy of ramelteon in treating transient insomnia in healthy adults ranging from 35 to 60 years of age. Subjects received 16 mg, 64 mg, or placebo 30 minutes before bedtime. The study enrolled 375 patients from 14 sleep research centers in the U.S. The investigators used the “first night effect” model, which is characteristic of transient insomnia; this refers to insomnia that often occurs when someone is assessed in a sleep laboratory.

To be eligible for enrollment, participants had to report a customary total sleep duration of 6.5 to 8.5 hours, a usual sleep latency of 30 minutes or less, and a habitual bedtime between 8:30 p.m. and midnight. They also had to be within 20% of their ideal body weight and in good overall health, as determined by a medical history, a physical examination, clinical laboratory values, and a 12-lead ECG.

Patients were excluded from the study if they were pregnant or nursing, had an Epworth Sleepiness Scale score above 10, had changed their sleep schedule within the past three months, had flown across three or more time zones within the past seven days, had signs and symptoms of a primary sleep disorder, or had any physical or psychiatric disorder that could be associated with a disturbance in sleep.

All prescription medications and over-the-counter medications were discontinued for an equivalent of five half-lives before ramelteon or placebo was given.

Subjects were placed into two groups according to their reported sleep duration: 6.5 to 7.5 hours or 7.5 to 8.5 hours. They were then randomly assigned to one of three groups: ramelteon 64 mg (n = 126), ramelteon 16 mg (n = 126), or placebo (n = 123).

The subjects were instructed to refrain from alcohol and products containing caffeine for the six hours before their arrival at the sleep laboratory. They were to arrive 1.5 to 2 hours before their normal bedtime.

Polysonmographic readings began 30 minutes before sleep and continued for eight hours. Thirty minutes after the readings were terminated, the subjects completed a post-sleep questionnaire that included subjective information regarding sleep latency, total sleep time, number of awakenings, and sleep quality. A DSST was also administered.

The primary efficacy outcome measure was mean latency to persistent sleep. Secondary outcome measures included total sleep time, wake-up time after sleep onset, the percentage of sleep time in each sleep stage, and the number of awakenings.

All 375 subjects enrolled completed the study. There were no significant differences among the three treatment groups in terms of race, sex, or age. Both dosage levels of ramelteon resulted in statistically significant decreases in mean latency to persistent sleep as follows: 24.6 minutes to persistent sleep with placebo, 14.1 minutes with a ramelteon dose of 16 mg, and 15.5 minutes with 64 mg (P < 0.001).

Total sleep times were 411.3 minutes with placebo, 425.4 minutes with ramelteon 16 mg, and 422.4 minutes with a dose of 64 mg (P < 0.05).

Differences in wake-up times after sleep with ramelteon and placebo were not statistically significant. The subjective number of awakenings and the subjective ease of falling back to sleep did not differ with ramelteon or placebo.

No serious ADEs were reported, and increased dosages of the study drug did not show an increased number of ADEs. Of the 375 participants, 63 reported at least one ADE as follows: in 21 patients taking placebo, in 20 patients taking ramelteon 16 mg, and in 22 patients taking ramelteon 64 mg.

Headache, the most common ADE, occurred in two patients taking placebo, in nine patients taking 16 mg, and in eight patients taking 64 mg. Less common ADEs were fatigue, nausea, somnolence, and dizziness. Assessment of vital signs, laboratory values, and ECGs between the two treated groups revealed no statistically significant differences.

The study authors concluded that ramelteon’s mechanism of action might offer a novel way to treat insomnia. They noted a flat dose–response curve from the four-fold increase in the ramelteon dose, resulting in a 1.5-minute difference on the primary outcome measure (latency to persistent sleep). In terms of this response, ramelteon did not appear to produce dose-dependent sedation; it affected only sleep promotion.

The investigators suggest the need for further studies of patients with chronic insomnia, because the data in the current study might portray unrealistic results from healthy patients in a simulated environment.

Roth et al.24

Roth and associates conducted a randomized, double-blind phase 3 study to determine the efficacy of ramelteon in promoting sleep in 829 elderly patients with a diagnosis of chronic insomnia, as defined by DSM-IV criteria, for at least three months. Patients received placebo, ramelteon 4 mg, or ramelteon 8 mg for five weeks. Sleep was assessed with polysonmography as well as with a post-sleep questionnaire. The primary endpoint was the mean latency time to sleep.

A statistically significant difference was noted between sleep latency times of those subjects taking placebo and subjects receiving ramelteon 4 mg and 8 mg. The approximate reduction in sleep latency between active treatment and placebo was eight minutes at week one (70.2 minutes in the ramelteon groups vs. 78.5 minutes with placebo; P = 0.008). The reduction continued to improve through to week five (57.7 minutes in the ramelteon groups vs. 70.6 minutes with placebo; P < 0.001).

At the first week, total sleep times were improved (i.e., increased) with each dose of ramelteon, compared with placebo: 324.6 minutes with 4 mg vs. 313.9 minutes with placebo (P = 0.004) and 321.1 minutes with 8 mg vs. 313.9 minutes with placebo (P = 0.055). There was no evidence of significant rebound or withdrawal effects after ramelteon therapy was discontinued.

ADEs were reported to be mild and similar to those experienced by the placebo treatment group. The investigators concluded that ramelteon promoted sleep in elderly patients with chronic insomnia, as determined by statistically
significant decreases in sleep latency over a period of five weeks.

**ACQUISITION COSTS**

The average wholesale price (AWP) of a one-month supply (30 8-mg tablets) of ramelteon (Rozerem) is $96.67. This price may vary among different health care systems. The AWPs of the other leading agents indicated for insomnia for a 30-day supply (30 tablets) are as follows:

- zolpidem tartrate (Ambien) 10 mg, $135.79
- zolpidem (Genpharm, Inc.), 10 mg, $115.49 (generic equivalent)
- zaleplon (Sonata) 10 mg, $111.20
- eszopiclone (Lunesta) 2 mg, $126.77

Although the AWP of ramelteon is lower than that of some of the other insomnia agents, a comparison of prices may be irrelevant because of ramelteon’s novel mechanism of action. The statistically significant improvement in sleep, in terms of decreased latency and increased total sleep time, averaged 10 to 15 minutes between treatment and placebo. The cost of $2.00 to $3.00 per day for a 15-minute difference in sleep onset and total sleep time might be an important consideration for some patients and an easy choice for others.

**CONCLUSION**

Ramelteon appears to have advantages over previous medications for treating insomnia. It is the first non-scheduled prescription drug indicated for insomnia. It is also noteworthy that no study has been completed or reported comparing the efficacy of melatonin versus ramelteon, and it is therefore possible that one agent might not offer any clinical advantage over the other.

The studies that are available to assess the efficacy of ramelteon also show a desirable side-effect profile. The absence of tolerance, dependence, and toxicity help to prevent ADEs associated with other medications for insomnia. A low incidence of side effects makes it especially favorable for elderly people. The rapid onset of action of ramelteon suggests that it should have a place for the treatment of primary or transient insomnia as a safe alternative to other available medications.

True insomnia is rare. Physicians and pharmacists should carefully evaluate all patients and their presenting symptoms before recommending any hypnotic agent, because insomnia can be a sign of another pre-existing condition that, if addressed, might help resolve the secondary insomnia.

For patients whose transient or chronic insomnia is refractory to non-pharmacological interventions and is not secondary to an underlying medical or psychiatric condition, ramelteon may be an alternative treatment option to be considered and utilized.

**REFERENCES**


Vol. 32 No. 8 • August 2007 • P&T • 431