Brand Names

Rozerem

Indication Specific Dosing

For the treatment of chronic or transient insomnia characterized by difficulty with sleep onset

Oral dosage

Adults

8 mg PO taken within 30 minutes of going to bed. Results from clinical trials have demonstrated efficacy for up to 6 months of use.

Contraindications And Precaution

Drug Interactions

The coadministration of certain medications may lead to harm and require avoidance or therapy modification; review all drug interactions prior to concomitant use of other medications.

Hypersensitivity

This medication is contraindicated in patients with a history of hypersensitivity to it or any of its components. Patients who develop angioedema after treatment with ramelteon should not be rechallenged with the drug.

depression, suicidal ideation

Worsening of depression and suicidal ideation, including completed suicides, have been reported during the use of hypnotics, primarily in people with pre-existing depression. Immediately evaluate patients with worsening depression, emergent suicidal ideation (suicidal thoughts or actions), or other new or worsening adverse behaviors during treatment with ramelteon.

activities requiring coordination and concentration, driving or operating machinery

Ramelteon should only be administered within 30 minutes of going to bed. People should avoid driving or operating machinery or performing other activities requiring coordination and concentration after use of ramelteon. Advise the patient to limit their activity to that necessary for going to bed. Ramelteon may also cause complex sleep-related behaviors (e.g., sleep-driving, preparing food, having sex) with no memory of the events; inform ramelteon recipients of these risks, and discontinuation of treatment should be strongly considered in any patient reporting complex sleep behaviors. The use of alcohol and other CNS depressants may increase the risk of these behaviors and cause additive sedation. Advise patients to avoid alcoholic beverages while taking ramelteon.

sleep apnea

Ramelteon has not been studied in people with severe obstructive sleep apnea (OSA) and is not recommended in this population. Ramelteon did not exacerbate mild to moderate OSA in a single-dose clinical study, and no difference was noted when compared with placebo on various apnea and hypopnea clinical indices. However, there is no available information on the respiratory effects of multiple doses of ramelteon in people with OSA and the potential for exacerbation of sleep apnea cannot be definitively known from this study. Ramelteon was also examined in adults with mild to severe chronic obstructive pulmonary disease (COPD) in a single-dose study, with no demonstrable respiratory depressant effects. There is no available information on the respiratory effects of multiple doses of ramelteon in patients with COPD. The respiratory depressant effects in people with COPD cannot be definitively known from this study.

Child-Pugh class B, Child-Pugh class C, hepatic failure

Use ramelteon with caution in people with moderate hepatic impairment (Child-Pugh class B). In clinical studies, people with mild liver impairment (Child-Pugh class A) had an almost 4-fold increase in exposure to ramelteon, while people with moderate liver impairment had more than 10-fold elevations in exposure. Ramelteon has not been studied in people with severe hepatic impairment (Child-Pugh class C) or hepatic failure and should not be used in this population.

geriatric

Ramelteon effectively reduces sleep onset in geriatric adults with sleep onset insomnia (SOI), with no significant differences in safety or efficacy compared to younger adults.

Guidelines suggest that benefits typically outweigh harms in appropriately selected patients. A single-dose study showed ramelteon does not impair balance, mobility, or memory in older adults, but the effects of multiple-night dosing have not been established. Some guidelines recommend against melatonin agonists in older adults with dementia with irregular sleep-wake rhythm disorder due to limited efficacy and potential negative effects on mood and functioning. Under the U.S. Omnibus Budget Reconciliation Act (OBRA), long-term care facilities should periodically taper sedative/hypnotics or document continued medical necessity for residents receiving sedative/hypnotic agents.

pregnancy

Available data from postmarketing reports with ramelteon use in pregnancy have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal studies, ramelteon produced evidence of developmental toxicity, including teratogenic effects, in rats at doses greater than 36-times the recommended human dose (RHD) of 8 mg/day based on body surface area (mg/m2).

people who can cause pregnancy in others, people who may become pregnant, reproductive risk

Use of ramelteon may pose a reproductive risk in people who may become pregnant and in people who can cause pregnancy in others. 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 (pediatric patients).

breast-feeding

Use ramelteon with caution during breast-feeding. Monitor infants for signs of somnolence and feeding difficulties if ramelteon is continued. A person who is breast-feeding may consider pumping and discarding breast milk during ramelteon treatment and for 25 hours (approximately 5 elimination half-lives) after ramelteon administration to minimize drug exposure to a breastfed infant. There is one case study that indicates ramelteon and its metabolite are excreted into human milk and that the infant would receive and estimated 0.24% of the maternal weight-adjusted dosage; no adverse infant effects were reported. There are no data from the manufacturer on the presence of ramelteon or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production, but the drug was excreted into the milk of lactating rats in preclinical studies. Consider the developmental and health benefits of breast-feeding

along with the clinical need for ramelteon and any potential adverse effects on the infant from ramelteon or the underlying maternal condition.

Pregnancy And Lactation

Available data from postmarketing reports with ramelteon use in pregnancy have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal studies, ramelteon produced evidence of developmental toxicity, including teratogenic effects, in rats at doses greater than 36-times the recommended human dose (RHD) of 8 mg/day based on body surface area (mg/m2).

Interactions

Acetaminophen; Aspirin, ASA; Caffeine: (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking melatonin or the melatonin analogs (ramelteon, tasimelteon) for sleep should avoid caffeine-containing medications, dietary supplements, foods, and beverages close to bedtime. Patients should be encouraged to avoid excessive total daily caffeine intake, as part of proper sleep hygiene, since caffeine intake can interfere with proper sleep.
Acetaminophen; Aspirin, ASA; Caffeine: (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking melatonin or the melatonin analogs (ramelteon, tasimelteon) for sleep should avoid caffeine-containing medications, dietary supplements, foods, and beverages close to bedtime. Patients should be encouraged to avoid excessive total daily caffeine intake, as part of proper sleep hygiene, since caffeine intake can interfere with proper sleep.
Acetaminophen; Aspirin; diphenhydrAMINE: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Acetaminophen; Caffeine: (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking melatonin or the melatonin analogs (ramelteon, tasimelteon) for sleep should avoid caffeine-containing medications, dietary supplements, foods, and beverages close to bedtime. Patients should be encouraged to avoid excessive total daily caffeine intake, as part of proper sleep hygiene, since caffeine intake can interfere with proper sleep.
Acetaminophen; Caffeine; Dihydrocodeine: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Avoid prescribing opioid cough medications in patients taking ramelteon. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment

options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression. (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking melatonin or the melatonin analogs (ramelteon, tasimelteon) for sleep should avoid caffeine-containing medications, dietary supplements, foods, and beverages close to bedtime. Patients should be encouraged to avoid excessive total daily caffeine intake, as part of proper sleep hygiene, since caffeine intake can interfere with proper sleep.
Acetaminophen; Caffeine; Pyrilamine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon. (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking melatonin or the melatonin analogs (ramelteon, tasimelteon) for sleep should avoid caffeine-containing medications, dietary supplements, foods, and beverages close to bedtime. Patients should be encouraged to avoid excessive total daily caffeine intake, as part of proper sleep hygiene, since caffeine intake can interfere with proper sleep.
Acetaminophen; Chlorpheniramine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Acetaminophen; Chlorpheniramine; Dextromethorphan: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Acetaminophen; Chlorpheniramine; Dextromethorphan; Phenylephrine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Acetaminophen; Chlorpheniramine; Dextromethorphan; Pseudoephedrine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Acetaminophen; Chlorpheniramine; Phenylephrine : (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Acetaminophen; Codeine: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Avoid prescribing opioid cough medications in patients taking ramelteon. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum

treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Acetaminophen; Dextromethorphan; Doxylamine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Acetaminophen; diphenhydrAMINE: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Acetaminophen; HYDROcodone: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Avoid prescribing opioid cough medications in patients taking ramelteon. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Acetaminophen; oxyCODONE: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Acetaminophen; Pamabrom; Pyrilamine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Adagrasib: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with adagrasib is necessary. Ramelteon is a CYP3A substrate and adagrasib is a strong CYP3A inhibitor. Coadministration with another strong CYP3A inhibitor increased ramelteon exposure by 84%.
ALFentanil: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
ALPRAZolam: (Moderate) Ramelteon is a sleep-promoting agent; therefore, additive pharmacodynamic effects are possible when combining ramelteon with benzodiazepines or other miscellaneous anxiolytics, sedatives, and hypnotics. Pharmacokinetic interactions have been observed with the use of zolpidem. Use of

ramelteon 8 mg/day for 11 days and a single dose of zolpidem 10 mg resulted in an increase in the median Tmax of zolpidem of about 20 minutes; exposure to zolpidem was unchanged. Ramelteon use with hypnotics of any kind is considered duplicative therapy and these drugs are generally not co-administered.
Amobarbital: (Major) Barbiturates can induce CYP1A2, the major metabolic pathway for ramelteon, and may eventually accelerate the clearance (and, thus, reduce the sedative properties) of ramelteon. Administration of multiple doses of a potent CYP inducer (rifampin) resulted in a mean decrease of approximately 80% in total exposure to ramelteon and its metabolite M-II. Additive CNS depression may also occur. The induction of ramelteon metabolism would likely require several days of barbiturate administration while additive drowsiness would appear immediately. Caution should be exercised during concomitant use of any CNS-depressant drugs and any barbiturate; dosage reduction of one or both agents may be necessary. If the medications must be used together, monitor for the effectiveness of ramelteon. Hypnotic barbiturates are best avoided during ramelteon therapy; the manufacturer warns against using other medications for sleep concurrently with ramelteon.
Amoxicillin; Clarithromycin; Omeprazole: (Moderate) Use caution with concurrent use of ramelteon and strong inhibitors of CYP3A4, such as clarithromycin. Because ramelteon is partially metabolized via CYP3A4, an increase in exposure of ramelteon is expected. An increase in ramelteon AUC by approximately 84% and Cmax by 36% was noted when coadministered with a strong CYP3A4 inhibitor (ketoconazole). Similar increases were noted in M-II pharmacokinetics. Patients should be monitored for increased ramelteon side effects. Also use caution with concurrent use of combinations containing clarithromycin, such as amoxicillin; clarithromycin; lansoprazole or amoxicillin; clarithromycin; omeprazole.
Anxiolytics; Sedatives; and Hypnotics: (Moderate) Ramelteon is a sleep-promoting agent; therefore, additive pharmacodynamic effects are possible when combining ramelteon with benzodiazepines or other miscellaneous anxiolytics, sedatives, and hypnotics. Pharmacokinetic interactions have been observed with the use of zolpidem. Use of ramelteon 8 mg/day for 11 days and a single dose of zolpidem 10 mg resulted in an increase in the median Tmax of zolpidem of about 20 minutes; exposure to zolpidem was unchanged. Ramelteon use with hypnotics of any kind is considered duplicative therapy and these drugs are generally not co-administered.
Apraclonidine: (Minor) No specific drug interactions were identified with systemic agents and apraclonidine during clinical trials. Theoretically, apraclonidine might potentiate the effects of CNS depressant drugs such as the anxiolytics, sedatives, and hypnotics, including barbiturates or benzodiazepines.
Aprepitant, Fosaprepitant: (Moderate) Use caution if ramelteon and aprepitant, fosaprepitant are used concurrently, and monitor for an increase in ramelteon-related adverse effects for several days after administration of a multi-day aprepitant regimen.

Ramelteon is a CYP3A4 substrate. Aprepitant, when administered as a 3-day oral regimen (125 mg/80 mg/80 mg), is a moderate CYP3A4 inhibitor and inducer and may increase plasma concentrations of ramelteon. For example, a 5-day oral aprepitant regimen increased the AUC of another CYP3A4 substrate, midazolam (single dose), by 2.3-fold on day 1 and by 3.3-fold on day 5. After a 3-day oral aprepitant regimen, the AUC of midazolam (given on days 1, 4, 8, and 15) increased by 25% on day 4, and then decreased by 19% and 4% on days 8 and 15, respectively. As a single 125 mg or 40 mg oral dose, the inhibitory effect of aprepitant on CYP3A4 is weak, with the AUC of midazolam increased by 1.5-fold and 1.2-fold, respectively. After administration, fosaprepitant is rapidly converted to aprepitant and shares many of the same drug interactions. However, as a single 150 mg intravenous dose, fosaprepitant only weakly inhibits CYP3A4 for a duration of 2 days; there is no evidence of CYP3A4 induction. Fosaprepitant 150 mg IV as a single dose increased the AUC of midazolam (given on days 1 and 4) by approximately 1.8-fold on day 1; there was no effect on day 4. Less than a 2-fold increase in the midazolam AUC is not considered clinically important. Aprepitant is also a CYP2C9 inducer and ramelteon is a CYP2C9 substrate. Administration of a CYP2C9 substrate, tolbutamide, on days 1, 4, 8, and 15 with a 3-day regimen of oral aprepitant (125 mg/80 mg/80 mg) decreased the tolbutamide AUC by 23% on day 4, 28% on day 8, and 15% on day 15. The AUC of tolbutamide was decreased by 8% on day 2, 16% on day 4, 15% on day 8, and 10% on day 15 when given prior to oral administration of aprepitant 40 mg on day 1, and on days 2, 4, 8, and 15. The effects of aprepitant on tolbutamide were not considered significant.
ARIPiprazole: (Moderate) Due to the primary CNS effects of aripiprazole, caution should be used when aripiprazole is given in combination with other centrally-acting medications including benzodiazepines and other anxiolytics, sedatives, and hypnotics.
Asenapine: (Moderate) Drugs that can cause CNS depression, if used concomitantly with asenapine, may increase adverse effects such as drowsiness, sedation, and dizziness. Caution should be used when asenapine is given in combination with anxiolytics, sedatives, and hypnotics.
Aspirin, ASA; Butalbital; Caffeine: (Major) Barbiturates can induce CYP1A2, the major metabolic pathway for ramelteon, and may eventually accelerate the clearance (and, thus, reduce the sedative properties) of ramelteon. Administration of multiple doses of a potent CYP inducer (rifampin) resulted in a mean decrease of approximately 80% in total exposure to ramelteon and its metabolite M-II. Additive CNS depression may also occur. The induction of ramelteon metabolism would likely require several days of barbiturate administration while additive drowsiness would appear immediately. Caution should be exercised during concomitant use of any CNS-depressant drugs and any barbiturate; dosage reduction of one or both agents may be necessary. If the medications must be used together, monitor for the effectiveness of ramelteon. Hypnotic barbiturates are best avoided during ramelteon therapy; the manufacturer warns against using other

medications for sleep concurrently with ramelteon. (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking melatonin or the melatonin analogs (ramelteon, tasimelteon) for sleep should avoid caffeine-containing medications, dietary supplements, foods, and beverages close to bedtime. Patients should be encouraged to avoid excessive total daily caffeine intake, as part of proper sleep hygiene, since caffeine intake can interfere with proper sleep.
Aspirin, ASA; Caffeine: (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking melatonin or the melatonin analogs (ramelteon, tasimelteon) for sleep should avoid caffeine-containing medications, dietary supplements, foods, and beverages close to bedtime. Patients should be encouraged to avoid excessive total daily caffeine intake, as part of proper sleep hygiene, since caffeine intake can interfere with proper sleep.
Aspirin, ASA; Caffeine; Orphenadrine: (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking melatonin or the melatonin analogs (ramelteon, tasimelteon) for sleep should avoid caffeine-containing medications, dietary supplements, foods, and beverages close to bedtime. Patients should be encouraged to avoid excessive total daily caffeine intake, as part of proper sleep hygiene, since caffeine intake can interfere with proper sleep.
Aspirin, ASA; Carisoprodol; Codeine: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Avoid prescribing opioid cough medications in patients taking ramelteon. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Aspirin, ASA; oxyCODONE: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Atazanavir: (Moderate) The serum concentrations of ramelteon may increase when ramelteon is administered with strong CYP3A4 inhibitors like the anti-retroviral protease inhibitors. Because there is the potential for multiple CYPP450 enzyme inhibition interactions between protease inhibitors and ramelteon, caution should be used if these 2 drugs are coadministered. The patient should be monitored closely for toxicity even though ramelteon has a wide therapeutic index.
Atazanavir; Cobicistat: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with cobicistat is necessary. Ramelteon is a CYP3A4 substrate and cobicistat is a strong CYP3A4 inhibitor. Coadministration with another

strong CYP3A4 inhibitor increased ramelteon exposure by 84%. (Moderate) The serum concentrations of ramelteon may increase when ramelteon is administered with strong CYP3A4 inhibitors like the anti-retroviral protease inhibitors. Because there is the potential for multiple CYPP450 enzyme inhibition interactions between protease inhibitors and ramelteon, caution should be used if these 2 drugs are coadministered. The patient should be monitored closely for toxicity even though ramelteon has a wide therapeutic index.
Barbiturates: (Major) Barbiturates can induce CYP1A2, the major metabolic pathway for ramelteon, and may eventually accelerate the clearance (and, thus, reduce the sedative properties) of ramelteon. Administration of multiple doses of a potent CYP inducer (rifampin) resulted in a mean decrease of approximately 80% in total exposure to ramelteon and its metabolite M-II. Additive CNS depression may also occur. The induction of ramelteon metabolism would likely require several days of barbiturate administration while additive drowsiness would appear immediately. Caution should be exercised during concomitant use of any CNS-depressant drugs and any barbiturate; dosage reduction of one or both agents may be necessary. If the medications must be used together, monitor for the effectiveness of ramelteon. Hypnotic barbiturates are best avoided during ramelteon therapy; the manufacturer warns against using other medications for sleep concurrently with ramelteon.
Belladonna; Opium: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Benzhydrocodone; Acetaminophen: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Benzodiazepines: (Moderate) Ramelteon is a sleep-promoting agent; therefore, additive pharmacodynamic effects are possible when combining ramelteon with benzodiazepines or other miscellaneous anxiolytics, sedatives, and hypnotics. Pharmacokinetic interactions have been observed with the use of zolpidem. Use of ramelteon 8 mg/day for 11 days and a single dose of zolpidem 10 mg resulted in an increase in the median Tmax of zolpidem of about 20 minutes; exposure to zolpidem was unchanged. Ramelteon use with hypnotics of any kind is considered duplicative therapy and these drugs are generally not co-administered.
Bismuth Subcitrate Potassium; metroNIDAZOLE; Tetracycline: (Moderate)

Coadministration of ramelteon with inhibitors of CYP2C9, such as metronidazole, may lead to increases in the serum concentrations of ramelteon.
Bismuth Subsalicylate; metroNIDAZOLE; Tetracycline: (Moderate) Coadministration of ramelteon with inhibitors of CYP2C9, such as metronidazole, may lead to increases in the serum concentrations of ramelteon.
Brompheniramine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Brompheniramine; Dextromethorphan; Phenylephrine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Brompheniramine; Phenylephrine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Brompheniramine; Pseudoephedrine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Brompheniramine; Pseudoephedrine; Dextromethorphan: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Buprenorphine: (Moderate) If concurrent use of ramelteon and buprenorphine is necessary, consider a dose reduction of one or both drugs because of the potential for additive pharmacological effects. Hypotension, profound sedation, coma, respiratory depression, or death may occur during co-administration of buprenorphine and other CNS depressants. Prior to concurrent use of buprenorphine in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Evaluate the patient's use of alcohol or illicit drugs. It is recommended that the injectable buprenorphine dose be halved for patients who receive other drugs with CNS depressant effects; for the buprenorphine transdermal patch, start with the 5 mcg/hour patch. Monitor patients for sedation or respiratory depression.
Buprenorphine; Naloxone: (Moderate) If concurrent use of ramelteon and buprenorphine is necessary, consider a dose reduction of one or both drugs because of the potential for additive pharmacological effects. Hypotension, profound sedation, coma, respiratory depression, or death may occur during co-administration of buprenorphine and other CNS depressants. Prior to concurrent use of buprenorphine in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment.

Evaluate the patient's use of alcohol or illicit drugs. It is recommended that the injectable buprenorphine dose be halved for patients who receive other drugs with CNS depressant effects; for the buprenorphine transdermal patch, start with the 5 mcg/hour patch. Monitor patients for sedation or respiratory depression.
busPIRone: (Moderate) Due to pharmacodynamic additive effects, also use caution when combining ramelteon with buspirone.
Butalbital; Acetaminophen: (Major) Barbiturates can induce CYP1A2, the major metabolic pathway for ramelteon, and may eventually accelerate the clearance (and, thus, reduce the sedative properties) of ramelteon. Administration of multiple doses of a potent CYP inducer (rifampin) resulted in a mean decrease of approximately 80% in total exposure to ramelteon and its metabolite M-II. Additive CNS depression may also occur. The induction of ramelteon metabolism would likely require several days of barbiturate administration while additive drowsiness would appear immediately. Caution should be exercised during concomitant use of any CNS-depressant drugs and any barbiturate; dosage reduction of one or both agents may be necessary. If the medications must be used together, monitor for the effectiveness of ramelteon. Hypnotic barbiturates are best avoided during ramelteon therapy; the manufacturer warns against using other medications for sleep concurrently with ramelteon.
Butalbital; Acetaminophen; Caffeine: (Major) Barbiturates can induce CYP1A2, the major metabolic pathway for ramelteon, and may eventually accelerate the clearance (and, thus, reduce the sedative properties) of ramelteon. Administration of multiple doses of a potent CYP inducer (rifampin) resulted in a mean decrease of approximately 80% in total exposure to ramelteon and its metabolite M-II. Additive CNS depression may also occur. The induction of ramelteon metabolism would likely require several days of barbiturate administration while additive drowsiness would appear immediately. Caution should be exercised during concomitant use of any CNS-depressant drugs and any barbiturate; dosage reduction of one or both agents may be necessary. If the medications must be used together, monitor for the effectiveness of ramelteon. Hypnotic barbiturates are best avoided during ramelteon therapy; the manufacturer warns against using other medications for sleep concurrently with ramelteon. (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking melatonin or the melatonin analogs (ramelteon, tasimelteon) for sleep should avoid caffeine-containing medications, dietary supplements, foods, and beverages close to bedtime. Patients should be encouraged to avoid excessive total daily caffeine intake, as part of proper sleep hygiene, since caffeine intake can interfere with proper sleep.
Butalbital; Acetaminophen; Caffeine; Codeine: (Major) Barbiturates can induce CYP1A2, the major metabolic pathway for ramelteon, and may eventually accelerate the clearance (and, thus, reduce the sedative properties) of ramelteon. Administration of multiple doses of a potent CYP inducer (rifampin) resulted in a mean decrease of approximately 80% in total exposure to ramelteon and its metabolite M-II. Additive CNS

depression may also occur. The induction of ramelteon metabolism would likely require several days of barbiturate administration while additive drowsiness would appear immediately. Caution should be exercised during concomitant use of any CNS-depressant drugs and any barbiturate; dosage reduction of one or both agents may be necessary. If the medications must be used together, monitor for the effectiveness of ramelteon. Hypnotic barbiturates are best avoided during ramelteon therapy; the manufacturer warns against using other medications for sleep concurrently with ramelteon. (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Avoid prescribing opioid cough medications in patients taking ramelteon. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression. (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking melatonin or the melatonin analogs (ramelteon, tasimelteon) for sleep should avoid caffeine-containing medications, dietary supplements, foods, and beverages close to bedtime. Patients should be encouraged to avoid excessive total daily caffeine intake, as part of proper sleep hygiene, since caffeine intake can interfere with proper sleep.
Butalbital; Aspirin; Caffeine; Codeine: (Major) Barbiturates can induce CYP1A2, the major metabolic pathway for ramelteon, and may eventually accelerate the clearance (and, thus, reduce the sedative properties) of ramelteon. Administration of multiple doses of a potent CYP inducer (rifampin) resulted in a mean decrease of approximately 80% in total exposure to ramelteon and its metabolite M-II. Additive CNS depression may also occur. The induction of ramelteon metabolism would likely require several days of barbiturate administration while additive drowsiness would appear immediately. Caution should be exercised during concomitant use of any CNS-depressant drugs and any barbiturate; dosage reduction of one or both agents may be necessary. If the medications must be used together, monitor for the effectiveness of ramelteon. Hypnotic barbiturates are best avoided during ramelteon therapy; the manufacturer warns against using other medications for sleep concurrently with ramelteon. (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Avoid prescribing opioid cough medications in patients taking ramelteon. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression. (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking melatonin or the melatonin analogs (ramelteon, tasimelteon) for sleep should avoid caffeine-containing medications, dietary supplements, foods, and beverages close to bedtime. Patients should be

encouraged to avoid excessive total daily caffeine intake, as part of proper sleep hygiene, since caffeine intake can interfere with proper sleep.
Cabergoline: (Moderate) Cabergoline should not be coadministered with ramelteon, if possible. The prolactin-lowering effect of cabergoline may be diminished by medications that increase prolactin levels such as ramelteon.
Caffeine: (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking melatonin or the melatonin analogs (ramelteon, tasimelteon) for sleep should avoid caffeine-containing medications, dietary supplements, foods, and beverages close to bedtime. Patients should be encouraged to avoid excessive total daily caffeine intake, as part of proper sleep hygiene, since caffeine intake can interfere with proper sleep.
Caffeine; Sodium Benzoate: (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking melatonin or the melatonin analogs (ramelteon, tasimelteon) for sleep should avoid caffeine-containing medications, dietary supplements, foods, and beverages close to bedtime. Patients should be encouraged to avoid excessive total daily caffeine intake, as part of proper sleep hygiene, since caffeine intake can interfere with proper sleep.
Cannabidiol: (Moderate) Monitor for excessive sedation and somnolence during coadministration of cannabidiol and ramelteon. CNS depressants can potentiate the effects of cannabidiol.
Capmatinib: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with capmatinib is necessary, as concurrent use may increase ramelteon exposure.. Ramelteon is a CYP1A2 substrate and capmatinib is a moderate CYP1A2 inhibitor.
carBAMazepine: (Moderate) Efficacy of ramelteon may be reduced when it is used in combination with strong CYP1A2 enzyme inducers such as carbamazepine.
Carbidopa; Levodopa; Entacapone: (Moderate) COMT inhibitors should be given cautiously with other agents that cause CNS depression, including ramelteon, due to the possibility of additive sedation. COMT inhibitors have also been associated with sudden sleep onset during activities of daily living such as driving, which has resulted in accidents in some cases. Prescribers should re-assess patients for drowsiness or sleepiness regularly throughout treatment, especially since events may occur well after the start of treatment. Patients should be advised to avoid driving or other tasks requiring mental alertness until they know how the combination affects them.
Carbinoxamine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Cariprazine: (Moderate) Due to the CNS effects of cariprazine, caution should be used when cariprazine is given in combination with other centrally-acting medications including benzodiazepines and other anxiolytics, sedatives, and hypnotics like ramelteon.

Celecoxib; Tramadol: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Cenobamate: (Moderate) Monitor for excessive sedation and somnolence during coadministration of cenobamate and ramelteon. Concurrent use may result in additive CNS depression.
Ceritinib: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with ceritinib is necessary. Ramelteon is a CYP3A4 and CYP2C9 substrate. Ceritinib is a strong CYP3A4 inhibitor and a weak CYP2C9 inhibitor. Coadministration with another strong CYP3A4 inhibitor increased ramelteon exposure by 84%.
Cetirizine: (Moderate) Concurrent use of cetirizine/levocetirizine with ramelton should generally be avoided. Coadministration may increase the risk of CNS depressant-related side effects. If concurrent use is necessary, monitor for excessive sedation and somnolence.
Cetirizine; Pseudoephedrine: (Moderate) Concurrent use of cetirizine/levocetirizine with ramelton should generally be avoided. Coadministration may increase the risk of CNS depressant-related side effects. If concurrent use is necessary, monitor for excessive sedation and somnolence.
Chlophedianol; Dexbrompheniramine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Chlophedianol; Dexchlorpheniramine; Pseudoephedrine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Chloramphenicol: (Moderate) The AUC and Cmax of ramelteon may be increased by strong CYP3A4 inhibitors such as chloramphenicol.
Chlorcyclizine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
chlordiazePOXIDE: (Moderate) Ramelteon is a sleep-promoting agent; therefore, additive pharmacodynamic effects are possible when combining ramelteon with benzodiazepines or other miscellaneous anxiolytics, sedatives, and hypnotics. Pharmacokinetic interactions have been observed with the use of zolpidem. Use of ramelteon 8 mg/day for 11 days and a single dose of zolpidem 10 mg resulted in an increase in the median Tmax of zolpidem of about 20 minutes; exposure to zolpidem

was unchanged. Ramelteon use with hypnotics of any kind is considered duplicative therapy and these drugs are generally not co-administered.
chlordiazePOXIDE; Amitriptyline: (Moderate) Ramelteon is a sleep-promoting agent; therefore, additive pharmacodynamic effects are possible when combining ramelteon with benzodiazepines or other miscellaneous anxiolytics, sedatives, and hypnotics. Pharmacokinetic interactions have been observed with the use of zolpidem. Use of ramelteon 8 mg/day for 11 days and a single dose of zolpidem 10 mg resulted in an increase in the median Tmax of zolpidem of about 20 minutes; exposure to zolpidem was unchanged. Ramelteon use with hypnotics of any kind is considered duplicative therapy and these drugs are generally not co-administered.
chlordiazePOXIDE; Clidinium: (Moderate) Ramelteon is a sleep-promoting agent; therefore, additive pharmacodynamic effects are possible when combining ramelteon with benzodiazepines or other miscellaneous anxiolytics, sedatives, and hypnotics. Pharmacokinetic interactions have been observed with the use of zolpidem. Use of ramelteon 8 mg/day for 11 days and a single dose of zolpidem 10 mg resulted in an increase in the median Tmax of zolpidem of about 20 minutes; exposure to zolpidem was unchanged. Ramelteon use with hypnotics of any kind is considered duplicative therapy and these drugs are generally not co-administered.
Chlorpheniramine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Chlorpheniramine; Codeine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon. (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Avoid prescribing opioid cough medications in patients taking ramelteon. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Chlorpheniramine; Dextromethorphan: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Chlorpheniramine; Dextromethorphan; Phenylephrine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Chlorpheniramine; Dextromethorphan; Pseudoephedrine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is

combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Chlorpheniramine; HYDROcodone: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon. (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Avoid prescribing opioid cough medications in patients taking ramelteon. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Chlorpheniramine; Ibuprofen; Pseudoephedrine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Chlorpheniramine; Phenylephrine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Chlorpheniramine; Pseudoephedrine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Cimetidine: (Major) Caution is recommended during concurrent use of ramelteon and cimetidine. Because ramelteon is metabolized via CYP3A4 and CYP1A2, use with CYP3A4 and CYP1A2 inhibitors, such as cimetidine, may increase exposure to ramelteon and the potential for adverse reactions. Other CYP1A2 inhibitors have been shown to have significant interactions with ramelteon, leading to elevated AUC of ramelteon > 190-fold and Cmax > 70 fold. If cimetidine must be administered with ramelteon, monitor the patient closely for toxicity due to elevated ramelteon serum concentrations. Alternatives to cimetidine may be considered, such as famotidine or nizatidine.
Ciprofloxacin: (Major) Ramelteon should be administered with caution to patients taking CYP1A2 inhibitors, such as systemic ciprofloxacin. Strong CYP1A2 inhibitors have been shown to have significant interactions with ramelteon, leading to elevated AUC of ramelteon > 190-fold and Cmax > 70-fold. If ciprofloxacin must be administered with ramelteon, monitor the patient closely for toxicity due to elevated ramelteon serum concentrations. Consider if an alternative fluoroquinolone with no CYP1A2 inhibition, like levofloxacin, could be utilized, or, if ramelteon therapy could be temporarily halted during use of ciprofloxacin. Non-systemic ciprofloxacin formulas, like ear drops, do not interact.
Clarithromycin: (Moderate) Use caution with concurrent use of ramelteon and strong

inhibitors of CYP3A4, such as clarithromycin. Because ramelteon is partially metabolized via CYP3A4, an increase in exposure of ramelteon is expected. An increase in ramelteon AUC by approximately 84% and Cmax by 36% was noted when coadministered with a strong CYP3A4 inhibitor (ketoconazole). Similar increases were noted in M-II pharmacokinetics. Patients should be monitored for increased ramelteon side effects. Also use caution with concurrent use of combinations containing clarithromycin, such as amoxicillin; clarithromycin; lansoprazole or amoxicillin; clarithromycin; omeprazole.
Clemastine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
clonazePAM: (Moderate) Ramelteon is a sleep-promoting agent; therefore, additive pharmacodynamic effects are possible when combining ramelteon with benzodiazepines or other miscellaneous anxiolytics, sedatives, and hypnotics. Pharmacokinetic interactions have been observed with the use of zolpidem. Use of ramelteon 8 mg/day for 11 days and a single dose of zolpidem 10 mg resulted in an increase in the median Tmax of zolpidem of about 20 minutes; exposure to zolpidem was unchanged. Ramelteon use with hypnotics of any kind is considered duplicative therapy and these drugs are generally not co-administered.
Clorazepate: (Moderate) Ramelteon is a sleep-promoting agent; therefore, additive pharmacodynamic effects are possible when combining ramelteon with benzodiazepines or other miscellaneous anxiolytics, sedatives, and hypnotics. Pharmacokinetic interactions have been observed with the use of zolpidem. Use of ramelteon 8 mg/day for 11 days and a single dose of zolpidem 10 mg resulted in an increase in the median Tmax of zolpidem of about 20 minutes; exposure to zolpidem was unchanged. Ramelteon use with hypnotics of any kind is considered duplicative therapy and these drugs are generally not co-administered.
Cobicistat: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with cobicistat is necessary. Ramelteon is a CYP3A4 substrate and cobicistat is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor increased ramelteon exposure by 84%.
Codeine: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Avoid prescribing opioid cough medications in patients taking ramelteon. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Codeine; Dexbrompheniramine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.

(Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Avoid prescribing opioid cough medications in patients taking ramelteon. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Codeine; guaiFENesin: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Avoid prescribing opioid cough medications in patients taking ramelteon. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Codeine; guaiFENesin; Pseudoephedrine: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Avoid prescribing opioid cough medications in patients taking ramelteon. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Codeine; Phenylephrine; Promethazine: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Avoid prescribing opioid cough medications in patients taking ramelteon. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Codeine; Promethazine: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Avoid prescribing opioid cough medications in patients taking ramelteon. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
COMT inhibitors: (Moderate) COMT inhibitors should be given cautiously with other agents that cause CNS depression, including ramelteon, due to the possibility of additive sedation. COMT inhibitors have also been associated with sudden sleep onset during activities of daily living such as driving, which has resulted in accidents in some cases. Prescribers should re-assess patients for drowsiness or sleepiness regularly throughout

treatment, especially since events may occur well after the start of treatment. Patients should be advised to avoid driving or other tasks requiring mental alertness until they know how the combination affects them.
Cyclobenzaprine: (Moderate) Cyclobenzaprine may cause additive CNS depression if used concomitantly with other CNS depressants, such as anxiolytics, sedatives, and hypnotics. Combination therapy can cause additive effects of sedation and dizziness, which can impair the patient's ability to undertake tasks requiring mental alertness. Dosage adjustments of either or both medications may be necessary.
cycloSPORINE: (Moderate) Coadministration of ramelteon with inhibitors of CYP3A4, such as cyclosporine, may lead to increases in the serum concentrations of ramelteon.
Cyproheptadine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Darunavir: (Moderate) The serum concentrations of ramelteon may increase when ramelteon is administered with strong CYP3A4 inhibitors like the anti-retroviral protease inhibitors. Because there is the potential for multiple CYPP450 enzyme inhibition interactions between protease inhibitors and ramelteon, caution should be used if these 2 drugs are coadministered. The patient should be monitored closely for toxicity even though ramelteon has a wide therapeutic index.
Darunavir; Cobicistat: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with cobicistat is necessary. Ramelteon is a CYP3A4 substrate and cobicistat is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor increased ramelteon exposure by 84%. (Moderate) The serum concentrations of ramelteon may increase when ramelteon is administered with strong CYP3A4 inhibitors like the anti-retroviral protease inhibitors. Because there is the potential for multiple CYPP450 enzyme inhibition interactions between protease inhibitors and ramelteon, caution should be used if these 2 drugs are coadministered. The patient should be monitored closely for toxicity even though ramelteon has a wide therapeutic index.
Darunavir; Cobicistat; Emtricitabine; Tenofovir alafenamide: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with cobicistat is necessary. Ramelteon is a CYP3A4 substrate and cobicistat is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor increased ramelteon exposure by 84%. (Moderate) The serum concentrations of ramelteon may increase when ramelteon is administered with strong CYP3A4 inhibitors like the anti-retroviral protease inhibitors. Because there is the potential for multiple CYPP450 enzyme inhibition interactions between protease inhibitors and ramelteon, caution should be used if these 2 drugs are coadministered. The patient should be monitored closely for toxicity even though ramelteon has a wide therapeutic index.
Degarelix: (Major) Avoid coadministration of degarelix with ramelteon due to the risk of

reduced efficacy of degarelix. Ramelteon can cause hyperprolactinemia, which reduces the number of pituitary gonadotropin releasing hormone (GnRH) receptors; degarelix is a GnRH analog.
Desogestrel: Ethinyl Estradiol; Ferrous Bisglycinate: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with ethinyl estradiol is necessary. Ramelteon is a CYP1A2 substrate and ethinyl estradiol is a moderate CYP1A2 inhibitor.
Desogestrel; Ethinyl Estradiol: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with ethinyl estradiol is necessary. Ramelteon is a CYP1A2 substrate and ethinyl estradiol is a moderate CYP1A2 inhibitor.
Deutetrabenazine: (Moderate) Advise patients that concurrent use of deutetrabenazine and drugs that can cause CNS depression, such as ramelteon, may have additive effects and worsen drowsiness or sedation.
Dexbrompheniramine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Dexbrompheniramine; Dextromethorphan; Phenylephrine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Dexbrompheniramine; Pseudoephedrine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Dexchlorpheniramine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Dexchlorpheniramine; Dextromethorphan; Pseudoephedrine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Dextromethorphan; diphenhydrAMINE; Phenylephrine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
diazePAM: (Moderate) Ramelteon is a sleep-promoting agent; therefore, additive pharmacodynamic effects are possible when combining ramelteon with benzodiazepines or other miscellaneous anxiolytics, sedatives, and hypnotics. Pharmacokinetic interactions have been observed with the use of zolpidem. Use of ramelteon 8 mg/day for 11 days and a single dose of zolpidem 10 mg resulted in an

increase in the median Tmax of zolpidem of about 20 minutes; exposure to zolpidem was unchanged. Ramelteon use with hypnotics of any kind is considered duplicative therapy and these drugs are generally not co-administered.
Difelikefalin: (Moderate) Monitor for dizziness, somnolence, mental status changes, and gait disturbances if concomitant use of difelikefalin with CNS depressants is necessary. Concomitant use may increase the risk for these adverse reactions.
dilTIAZem: (Moderate) Coadministration of ramelteon with inhibitors of CYP3A4, such as diltiazem, may lead to increases in the serum concentrations of ramelteon.
dimenhyDRINATE: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
diphenhydrAMINE: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
diphenhydrAMINE; Ibuprofen: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
diphenhydrAMINE; Naproxen: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
diphenhydrAMINE; Phenylephrine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Disulfiram: (Moderate) Coadministration of ramelteon with inhibitors of CYP2C9, such as disulfiram, may lead to increases in the serum concentrations of ramelteon.
Donepezil: (Moderate) Concurrent use of donepezil and ramelteon results in increased ramelteon exposure. If these agents are used together, monitor the patient closely for adverse effects. Use of donepezil 10 mg/day for 26 days and ramelteon as a single 8 mg dose resulted in increased mean AUC and Cmax of ramelteon of approximately 100% and 87%, respectively. No change was observed with regard to the active metabolite, M-II. Clinically meaningful changes in peak and total exposure of donepezil have not been observed.
Donepezil; Memantine: (Moderate) Concurrent use of donepezil and ramelteon results in increased ramelteon exposure. If these agents are used together, monitor the patient closely for adverse effects. Use of donepezil 10 mg/day for 26 days and ramelteon as a single 8 mg dose resulted in increased mean AUC and Cmax of ramelteon of approximately 100% and 87%, respectively. No change was observed with regard to the active metabolite, M-II. Clinically meaningful changes in peak and total exposure of donepezil have not been observed.
Doxepin: (Moderate) Concurrent use of doxepin and ramelteon results in increased

ramelteon exposure. If these agents are used together, monitor the patient closely for adverse effects. Use of doxepin 10 mg/day for 23 days and ramelteon as a single 8 mg dose resulted in increased mean AUC and Cmax of ramelteon of approximately 66% and 69%, respectively. No change was observed with regard to the active metabolite, M-II. Clinically meaningful changes in peak and total exposure of doxepin have not been observed.
Doxylamine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Doxylamine; Pyridoxine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Dronedarone: (Moderate) Dronedarone is metabolized by and is an inhibitor of CYP3A. Ramelteon is a substrate for CYP3A4. The concomitant administration of dronedarone and CYP3A substrates may result in increased exposure of the substrate and should, therefore, be undertaken with caution.
droPERidol: (Moderate) Due to pharmacodynamic additive effects, also use caution when combining ramelteon with droperidol.
Drospirenone; Ethinyl Estradiol: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with ethinyl estradiol is necessary. Ramelteon is a CYP1A2 substrate and ethinyl estradiol is a moderate CYP1A2 inhibitor.
Drospirenone; Ethinyl Estradiol; Levomefolate: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with ethinyl estradiol is necessary. Ramelteon is a CYP1A2 substrate and ethinyl estradiol is a moderate CYP1A2 inhibitor.
Elbasvir; Grazoprevir: (Moderate) Administering ramelteon with elbasvir; grazoprevir may result in elevated ramelteon plasma concentrations. Ramelteon is a substrate of CYP3A; grazoprevir is a weak CYP3A inhibitor. If these drugs are used together, closely monitor for signs of adverse events.
Elexacaftor; tezacaftor; ivacaftor: (Minor) Increased monitoring is recommended if ivacaftor is administered concurrently with CYP2C9 substrates, such as ramelteon. Ivacaftor is an inhibitor of CYP3A and a weak inhibitor of CYP2C9; ramelteon is partially metabolized by CYP3A and CYP2C9. Co-administration of ivacaftor with CYP3A and CYP2C9 substrates, such as ramelteon, can theoretically increase ramelteon exposure leading to increased or prolonged therapeutic effects and adverse events; however, the clinical impact of this has not yet been determined.
Elvitegravir; Cobicistat; Emtricitabine; Tenofovir Alafenamide: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with cobicistat is necessary. Ramelteon is a CYP3A4 substrate and cobicistat is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor increased ramelteon exposure

by 84%.
Elvitegravir; Cobicistat; Emtricitabine; Tenofovir Disoproxil Fumarate: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with cobicistat is necessary. Ramelteon is a CYP3A4 substrate and cobicistat is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor increased ramelteon exposure by 84%.
Enasidenib: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with enasidenib is necessary. Ramelteon is a CYP1A2 substrate and enasidenib is a strong CYP1A2 inhibitor. Coadministration with another strong CYP1A2 inhibitor increased ramelteon exposure by 190-fold.
Encorafenib: (Moderate) Monitor for a decrease in the efficacy of ramelteon if coadministration with encorafenib is necessary. Ramelteon is a CYP3A substrate; encorafenib is a strong CYP3A inducer. Coadministration with another strong CYP3A inducer decreased total exposure to ramelteon and metabolite M-II by approximately 80%.
Entacapone: (Moderate) COMT inhibitors should be given cautiously with other agents that cause CNS depression, including ramelteon, due to the possibility of additive sedation. COMT inhibitors have also been associated with sudden sleep onset during activities of daily living such as driving, which has resulted in accidents in some cases. Prescribers should re-assess patients for drowsiness or sleepiness regularly throughout treatment, especially since events may occur well after the start of treatment. Patients should be advised to avoid driving or other tasks requiring mental alertness until they know how the combination affects them.
Enzalutamide: (Moderate) Monitor for a decrease in the efficacy of ramelteon if coadministration with enzalutamide is necessary. Ramelteon is a CYP3A4 and CYP2C9 substrate. Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 inducer. Coadministration with another strong CYP3A4 and moderate CYP2C9 inducer decreased total exposure to ramelteon and metabolite M-II by approximately 80%.
Ergotamine; Caffeine: (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking melatonin or the melatonin analogs (ramelteon, tasimelteon) for sleep should avoid caffeine-containing medications, dietary supplements, foods, and beverages close to bedtime. Patients should be encouraged to avoid excessive total daily caffeine intake, as part of proper sleep hygiene, since caffeine intake can interfere with proper sleep.
Erythromycin: (Moderate) Coadministration of ramelteon with inhibitors of CYP3A4, such as erythromycin, may lead to increases in the serum concentrations of ramelteon.
Esketamine: (Moderate) Closely monitor patients receiving esketamine and ramelteon for sedation and other CNS depressant effects. Instruct patients who receive a dose of esketamine not to drive or engage in other activities requiring alertness until the next day after a restful sleep.

Estazolam: (Moderate) Ramelteon is a sleep-promoting agent; therefore, additive pharmacodynamic effects are possible when combining ramelteon with benzodiazepines or other miscellaneous anxiolytics, sedatives, and hypnotics. Pharmacokinetic interactions have been observed with the use of zolpidem. Use of ramelteon 8 mg/day for 11 days and a single dose of zolpidem 10 mg resulted in an increase in the median Tmax of zolpidem of about 20 minutes; exposure to zolpidem was unchanged. Ramelteon use with hypnotics of any kind is considered duplicative therapy and these drugs are generally not co-administered.
Eszopiclone: (Moderate) Ramelteon is a sleep-promoting agent; therefore, additive pharmacodynamic effects are possible when combining ramelteon with benzodiazepines or other miscellaneous anxiolytics, sedatives, and hypnotics. Pharmacokinetic interactions have been observed with the use of zolpidem. Use of ramelteon 8 mg/day for 11 days and a single dose of zolpidem 10 mg resulted in an increase in the median Tmax of zolpidem of about 20 minutes; exposure to zolpidem was unchanged. Ramelteon use with hypnotics of any kind is considered duplicative therapy and these drugs are generally not co-administered.
Ethanol: (Major) Advise patients to avoid alcohol consumption while taking CNS depressants. Alcohol consumption may result in additive CNS depression.
Ethinyl Estradiol; Norelgestromin: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with ethinyl estradiol is necessary. Ramelteon is a CYP1A2 substrate and ethinyl estradiol is a moderate CYP1A2 inhibitor.
Ethinyl Estradiol; Norethindrone Acetate: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with ethinyl estradiol is necessary. Ramelteon is a CYP1A2 substrate and ethinyl estradiol is a moderate CYP1A2 inhibitor.
Ethinyl Estradiol; Norgestrel: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with ethinyl estradiol is necessary. Ramelteon is a CYP1A2 substrate and ethinyl estradiol is a moderate CYP1A2 inhibitor.
Ethynodiol Diacetate; Ethinyl Estradiol: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with ethinyl estradiol is necessary. Ramelteon is a CYP1A2 substrate and ethinyl estradiol is a moderate CYP1A2 inhibitor.
Etonogestrel; Ethinyl Estradiol: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with ethinyl estradiol is necessary. Ramelteon is a CYP1A2 substrate and ethinyl estradiol is a moderate CYP1A2 inhibitor.
Fenfluramine: (Moderate) Monitor for excessive sedation and somnolence during coadministration of fenfluramine and ramelteon. Concurrent use may result in additive CNS depression.
Fenofibric Acid: (Minor) At therapeutic concentrations, fenofibric acid is a mild-to-moderate inhibitor of CYP2C9. Concomitant use of fenofibric acid with CYP2C9 substrates, such as ramelteon, has not been formally studied. Fenofibric acid may

theoretically increase plasma concentrations of CYP2C9 substrates and could lead to toxicity for drugs that have a narrow therapeutic range. Monitor the therapeutic effect of ramelteon during coadministration with fenofibric acid.
fentaNYL: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Fexinidazole: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with fexinidazole is necessary. Ramelteon is a CYP1A2 substrate and fexinidazole is a moderate CYP1A2 inhibitor.
Fluconazole: (Moderate) The AUC and Cmax of ramelteon after a single 16 mg dose was increased by approximately 150% when administered with fluconazole (a CYP2C9 inhibitor). Ramelteon should be administered with caution in subjects taking CYP2C9 inhibitors such as fluconazole. The patient should be monitored closely for toxicity from ramelteon.
Flurazepam: (Moderate) Ramelteon is a sleep-promoting agent; therefore, additive pharmacodynamic effects are possible when combining ramelteon with benzodiazepines or other miscellaneous anxiolytics, sedatives, and hypnotics. Pharmacokinetic interactions have been observed with the use of zolpidem. Use of ramelteon 8 mg/day for 11 days and a single dose of zolpidem 10 mg resulted in an increase in the median Tmax of zolpidem of about 20 minutes; exposure to zolpidem was unchanged. Ramelteon use with hypnotics of any kind is considered duplicative therapy and these drugs are generally not co-administered.
fluvoxaMINE: (Contraindicated) Ramelteon is contraindicated for use in combination with fluvoxamine, a strong CYP1A2 inhibitor; CYP1A2 is the major isozyme involved in the hepatic metabolism of ramelteon. When fluvoxamine 100 mg twice daily was administered for 3 days prior to single-dose co-administration of ramelteon 16 mg and fluvoxamine, the AUC for ramelteon increased roughly 190-fold, and the Cmax increased approximately 70-fold, compared to ramelteon administered alone.
Food: (Major) Advise patients to avoid cannabis use while taking CNS depressants due to the risk for additive CNS depression and potential for other cognitive adverse reactions. (Major) Patients should avoid taking ramelteon with or immediately after a meal with high fat food, as the sleep promoting effects of ramelteon may be altered. After administration with a high fat meal, the systemic exposure of ramelteon was 31% higher, the maximum serum concentration (Cmax) was 22% lower, and the median time to the maximum serum concentration (Tmax) was 45 minutes longer as compared with the fasted state. Similar effects were noted with the pharmacokinetics of the active metabolite, M-II. In addition, ramelteon should likely not be taken with grapefruit juice;

grapefruit juice might increase the risk for ramelteon side effects. Ramelteon is a high extraction ratio drug, and grapefruit inhibits enteric CYP3A4 activity.
Fosamprenavir: (Moderate) The serum concentrations of ramelteon may increase when ramelteon is administered with strong CYP3A4 inhibitors like the anti-retroviral protease inhibitors. Because there is the potential for multiple CYPP450 enzyme inhibition interactions between protease inhibitors and ramelteon, caution should be used if these 2 drugs are coadministered. The patient should be monitored closely for toxicity even though ramelteon has a wide therapeutic index.
Gabapentin: (Moderate) Monitor for excessive sedation and somnolence during coadministration of ramelteon and gabapentin. Concurrent use may result in additive CNS depression.
Givosiran: (Major) Avoid concomitant use of givosiran and ramelteon due to the risk of increased ramelteon-related adverse reactions. If use is necessary, consider decreasing the ramelteon dose. Ramelteon is a sensitive CYP1A2 substrate. Givosiran may moderately reduce hepatic CYP1A2 enzyme activity because of its pharmacological effects on the hepatic heme biosynthesis pathway.
Goserelin: (Major) Avoid coadministration of goserelin with ramelteon due to the risk of reduced efficacy of goserelin. Ramelteon can cause hyperprolactinemia, which reduces the number of pituitary gonadotropin releasing hormone (GnRH) receptors; goserelin is a GnRH analog.
Grapefruit juice: (Major) Ramelteon should not taken with grapefruit or grapefruit juice. Ramelteon is a high extraction ratio drug, and grapefruit inhibits enteric CYP3A4 activity.
Haloperidol: (Moderate) An enhanced CNS depressant effect may occur when haloperidol is combined with other CNS depressants including hypnotic drugs such as ramelteon.
Histrelin: (Major) Avoid coadministration of histrelin with ramelteon due to the risk of reduced efficacy of histrelin. Ramelteon can cause hyperprolactinemia, which reduces the number of pituitary gonadotropin releasing hormone (GnRH) receptors; histrelin is a GnRH analog.
Homatropine; HYDROcodone: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Avoid prescribing opioid cough medications in patients taking ramelteon. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
HYDROcodone: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Avoid prescribing opioid cough medications in patients taking ramelteon. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use

is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
HYDROcodone; Ibuprofen: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Avoid prescribing opioid cough medications in patients taking ramelteon. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
HYDROmorphone: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
hydrOXYzine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Idelalisib: (Major) Avoid concomitant use of idelalisib, a strong CYP3A inhibitor, with ramelteon, a CYP3A substrate, as ramelteon toxicities may be significantly increased. The AUC of a sensitive CYP3A substrate was increased 5.4-fold when coadministered with idelalisib.
Imatinib: (Moderate) Coadministration of ramelteon with inhibitors of CYP3A4, such as imatinib, may lead to increases in the serum concentrations of ramelteon.
Isavuconazonium: (Moderate) Concomitant use of isavuconazonium with ramelteon may result in increased serum concentrations of ramelteon. Ramelteon is a substrate of the hepatic isoenzyme CYP3A4; isavuconazole, the active moiety of isavuconazonium, is a moderate inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are used together.
Isocarboxazid: (Moderate) The CNS depressant effects of MAOIs can be potentiated with concomitant administration of other drugs known to cause CNS depression including ramelteon.
Itraconazole: (Moderate) Monitor for adverse reactions related to ramelteon if coadministration of itraconazole is necessary. A reduced dose of ramelteon may be necessary. Ramelteon is a CYP3A4 substrate; itraconazole is a strong CYP3A4 inhibitor. Coadministration of another strong CYP3A4 inhibitor increased the AUC and Cmax of ramelteon by approximately 84% and 36%.
Ivacaftor: (Minor) Increased monitoring is recommended if ivacaftor is administered concurrently with CYP2C9 substrates, such as ramelteon. Ivacaftor is an inhibitor of

CYP3A and a weak inhibitor of CYP2C9; ramelteon is partially metabolized by CYP3A and CYP2C9. Co-administration of ivacaftor with CYP3A and CYP2C9 substrates, such as ramelteon, can theoretically increase ramelteon exposure leading to increased or prolonged therapeutic effects and adverse events; however, the clinical impact of this has not yet been determined.
Ketoconazole: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with ketoconazole is necessary. Ramelteon is a CYP3A4 substrate and ketoconazole is a strong CYP3A4 inhibitor. Coadministration with ketoconazole increased ramelteon exposure by 84%.
Lansoprazole; Amoxicillin; Clarithromycin: (Moderate) Use caution with concurrent use of ramelteon and strong inhibitors of CYP3A4, such as clarithromycin. Because ramelteon is partially metabolized via CYP3A4, an increase in exposure of ramelteon is expected. An increase in ramelteon AUC by approximately 84% and Cmax by 36% was noted when coadministered with a strong CYP3A4 inhibitor (ketoconazole). Similar increases were noted in M-II pharmacokinetics. Patients should be monitored for increased ramelteon side effects. Also use caution with concurrent use of combinations containing clarithromycin, such as amoxicillin; clarithromycin; lansoprazole or amoxicillin; clarithromycin; omeprazole.
Lasmiditan: (Moderate) Monitor for excessive sedation and somnolence during coadministration of lasmiditan and ramelteon. Concurrent use may result in additive CNS depression.
Leflunomide: (Moderate) Coadministration of ramelteon with inhibitors of CYP2C9, such as leflunomide, may lead to increases in the serum concentrations of ramelteon.
Lemborexant: (Major) The use of lemborexant with other hypnotic drugs, such as ramelteon, is not recommended. Additive sedative, CNS depressant effects, impairment, and effects on mood and behaviors, including sleep-related behaviors, may occur.
Letermovir: (Moderate) Plasma concentrations of ramelteon could be increased when administered concurrently with letermovir. The magnitude of this interaction may be increased in patients who are also receiving cyclosporine. If these drugs are given together, closely monitor for reduced ramelteon efficacy and ramelteon-related adverse events. Ramelteon is a substrate of CYP3A4. Letermovir a moderate inhibitor of CYP3A4. When given with cyclosporine, the combined effect of letermovir and cyclosporine on CYP3A4 substrates may be similar to a strong CYP3A4 inhibitor. In a drug interaction study, administration of ramelteon with another strong CYP3A4 inhibitor increased the exposure and maximum plasma concentration of ramelteon by approximately 84% and 36%, respectively.
Leuprolide: (Major) Avoid coadministration of leuprolide with ramelteon due to the risk of reduced efficacy of leuprolide. Ramelteon can cause hyperprolactinemia, which reduces the number of pituitary gonadotropin releasing hormone (GnRH) receptors; leuprolide is a GnRH analog.

Leuprolide; Norethindrone: (Major) Avoid coadministration of leuprolide with ramelteon due to the risk of reduced efficacy of leuprolide. Ramelteon can cause hyperprolactinemia, which reduces the number of pituitary gonadotropin releasing hormone (GnRH) receptors; leuprolide is a GnRH analog.
Levocetirizine: (Moderate) Concurrent use of cetirizine/levocetirizine with ramelton should generally be avoided. Coadministration may increase the risk of CNS depressant-related side effects. If concurrent use is necessary, monitor for excessive sedation and somnolence.
Levoketoconazole: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with ketoconazole is necessary. Ramelteon is a CYP3A4 substrate and ketoconazole is a strong CYP3A4 inhibitor. Coadministration with ketoconazole increased ramelteon exposure by 84%.
Levonorgestrel; Ethinyl Estradiol: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with ethinyl estradiol is necessary. Ramelteon is a CYP1A2 substrate and ethinyl estradiol is a moderate CYP1A2 inhibitor.
Levonorgestrel; Ethinyl Estradiol; Ferrous Bisglycinate: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with ethinyl estradiol is necessary. Ramelteon is a CYP1A2 substrate and ethinyl estradiol is a moderate CYP1A2 inhibitor.
Levonorgestrel; Ethinyl Estradiol; Ferrous Fumarate: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with ethinyl estradiol is necessary. Ramelteon is a CYP1A2 substrate and ethinyl estradiol is a moderate CYP1A2 inhibitor.
Levorphanol: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Lithium: (Moderate) Because lithium has the potential to impair cognitive and motor skills, caution is advisable during concurrent use of other medications with centrally-acting effects including anxiolytics, sedatives, and hypnotics.
Lofexidine: (Moderate) Monitor for excessive sedation during coadministration of lofexidine and ramelteon. Lofexidine can potentiate the effects of CNS depressants.
Lonafarnib: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with lonafarnib is necessary. Ramelteon is a CYP3A4 substrate and lonafarnib is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor increased ramelteon exposure by 84%.
Lopinavir; Ritonavir: (Moderate) The serum concentrations of ramelteon may increase when ramelteon is administered with strong CYP3A4 inhibitors like the anti-retroviral

protease inhibitors. Because there is the potential for multiple CYPP450 enzyme inhibition interactions between protease inhibitors and ramelteon, caution should be used if these 2 drugs are coadministered. The patient should be monitored closely for toxicity even though ramelteon has a wide therapeutic index.
LORazepam: (Moderate) Ramelteon is a sleep-promoting agent; therefore, additive pharmacodynamic effects are possible when combining ramelteon with benzodiazepines or other miscellaneous anxiolytics, sedatives, and hypnotics. Pharmacokinetic interactions have been observed with the use of zolpidem. Use of ramelteon 8 mg/day for 11 days and a single dose of zolpidem 10 mg resulted in an increase in the median Tmax of zolpidem of about 20 minutes; exposure to zolpidem was unchanged. Ramelteon use with hypnotics of any kind is considered duplicative therapy and these drugs are generally not co-administered.
Lumacaftor; Ivacaftor: (Minor) Concomitant use of ramelteon and lumacaftor; ivacaftor may alter ramelteon exposure; caution and close monitoring are advised if these drugs are used together. Ramelteon is a minor substrate of CYP3A4 and CYP2C9. Lumacaftor is a strong CYP3A inducer; in vitro data also suggest that lumacaftor; ivacaftor may induce and and/or inhibit CYP2C9. Although induction of ramelteon through the secondary CYP3A pathway may lead to decreases in drug efficacy, the net effect of lumacaftor; ivacaftor on CYP2C9-mediated metabolism is not clear. (Minor) Increased monitoring is recommended if ivacaftor is administered concurrently with CYP2C9 substrates, such as ramelteon. Ivacaftor is an inhibitor of CYP3A and a weak inhibitor of CYP2C9; ramelteon is partially metabolized by CYP3A and CYP2C9. Co-administration of ivacaftor with CYP3A and CYP2C9 substrates, such as ramelteon, can theoretically increase ramelteon exposure leading to increased or prolonged therapeutic effects and adverse events; however, the clinical impact of this has not yet been determined.
Lumacaftor; Ivacaftor: (Minor) Concomitant use of ramelteon and lumacaftor; ivacaftor may alter ramelteon exposure; caution and close monitoring are advised if these drugs are used together. Ramelteon is a minor substrate of CYP3A4 and CYP2C9. Lumacaftor is a strong CYP3A inducer; in vitro data also suggest that lumacaftor; ivacaftor may induce and and/or inhibit CYP2C9. Although induction of ramelteon through the secondary CYP3A pathway may lead to decreases in drug efficacy, the net effect of lumacaftor; ivacaftor on CYP2C9-mediated metabolism is not clear.
Lumateperone: (Moderate) Monitor for excessive sedation and somnolence during coadministration of lumateperone and ramelteon. Concurrent use may result in additive CNS depression.
Lurasidone: (Moderate) Due to the CNS effects of lurasidone, caution should be used when lurasidone is given in combination with other centrally acting medications such as anxiolytics, sedatives, and hypnotics.
Meclizine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including

anxiolytics, sedatives, and hypnotics, such as ramelteon.
Melatonin: (Major) Because of pharmacologic similarities in action as melatonin-receptor agonists, melatonin should not be coadministered with ramelteon. The actions would be expected to be duplicative, and might result in additive side effects, such as somnolence, headache, unusual behaviors or moods, memory impairment, or balance and coordination issues. In a clinical trial, there was clear evidence for a transitory pharmacodynamic interaction between melatonin and another hypnotic agent one hour following co-dosing. Concomitant administration resulted in increased impairment of attention, memory and coordination compared to the hypnotic agent alone. Use of more than one agent for hypnotic purposes may increase the risk for over-sedation, CNS effects, or sleep-related behaviors. Be alert for unusual changes in moods or behaviors. Patients should be advised to avoid dietary supplements containing melatonin.
Meperidine: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Meprobamate: (Moderate) Ramelteon is a sleep-promoting agent; therefore, additive pharmacodynamic effects are possible when combining ramelteon with benzodiazepines or other miscellaneous anxiolytics, sedatives, and hypnotics. Pharmacokinetic interactions have been observed with the use of zolpidem. Use of ramelteon 8 mg/day for 11 days and a single dose of zolpidem 10 mg resulted in an increase in the median Tmax of zolpidem of about 20 minutes; exposure to zolpidem was unchanged. Ramelteon use with hypnotics of any kind is considered duplicative therapy and these drugs are generally not co-administered.
Methadone: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Methohexital: (Major) Barbiturates can induce CYP1A2, the major metabolic pathway for ramelteon, and may eventually accelerate the clearance (and, thus, reduce the sedative properties) of ramelteon. Administration of multiple doses of a potent CYP inducer (rifampin) resulted in a mean decrease of approximately 80% in total exposure to ramelteon and its metabolite M-II. Additive CNS depression may also occur. The induction of ramelteon metabolism would likely require several days of barbiturate administration while additive drowsiness would appear immediately. Caution should be exercised during concomitant use of any CNS-depressant drugs and any barbiturate;

dosage reduction of one or both agents may be necessary. If the medications must be used together, monitor for the effectiveness of ramelteon. Hypnotic barbiturates are best avoided during ramelteon therapy; the manufacturer warns against using other medications for sleep concurrently with ramelteon.
Metoclopramide: (Minor) Combined use of metoclopramide and other CNS depressants, such as anxiolytics, sedatives, and hypnotics, can increase possible sedation.
metroNIDAZOLE: (Moderate) Coadministration of ramelteon with inhibitors of CYP2C9, such as metronidazole, may lead to increases in the serum concentrations of ramelteon.
Mexiletine: (Major) Coadministration of ramelteon with inhibitors of CYP1A2, such as mexiletine, may lead to increases in the serum concentrations of ramelteon.
Midazolam: (Moderate) Ramelteon is a sleep-promoting agent; therefore, additive pharmacodynamic effects are possible when combining ramelteon with benzodiazepines or other miscellaneous anxiolytics, sedatives, and hypnotics. Pharmacokinetic interactions have been observed with the use of zolpidem. Use of ramelteon 8 mg/day for 11 days and a single dose of zolpidem 10 mg resulted in an increase in the median Tmax of zolpidem of about 20 minutes; exposure to zolpidem was unchanged. Ramelteon use with hypnotics of any kind is considered duplicative therapy and these drugs are generally not co-administered.
miFEPRIStone: (Moderate) Ramelteon should be administered with caution in subjects taking strong CYP3A4 inhibitors. Because ramelteon is partially metabolized via CYP3A4, an increase in exposure of ramelteon is expected. An increase in ramelteon AUC by approximately 84% and Cmax by 36% was noted when coadministered with a strong CYP3A4 inhibitor (ketoconazole). Similar increases were noted in M-II pharmacokinetics. Patients should be monitored for increased ramelteon side effects. Examples of CYP3A4 inhibitors include: chloramphenicol, conivaptan, cyclosporine, dalfopristin; quinupristin, delavirdine, diltiazem, erythromycin, ethinyl estradiol, imatinib, STI-571, itraconazole, systemic miconazole, mifepristone, troleandomycin, verapamil, voriconazole, and zafirlukast. This list is not inclusive of all CYP3A4 inhibitors. Imatinib, voriconazole, and zafirlukast are also CYP2C9 inhibitors, and when administered with ramelteon may result in multiple hepatic enzyme inhibition interactions, although the significance of these interactions has not been studied. The patient should be monitored closely for ramelteon-associated toxicity.
Mitotane: (Major) Use caution if mitotane and ramelteon are used concomitantly, and monitor for decreased efficacy of ramelteon and a possible change in dosage requirements. Mitotane is a strong CYP3A4 inducer and ramelteon is a CYP3A4 substrate; coadministration may result in decreased plasma concentrations of ramelteon. Administration of another strong CYP inducer, rifampin, for 11 days resulted in a mean decrease of approximately 80% (40% to 90%) in total exposure to ramelteon and metabolite M-II, (both AUC and Cmax) after a single 32 mg dose of ramelteon.
Monoamine oxidase inhibitors: (Moderate) The CNS depressant effects of MAOIs can be

potentiated with concomitant administration of other drugs known to cause CNS depression including ramelteon.
Morphine: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Nelfinavir: (Moderate) The serum concentrations of ramelteon may increase when ramelteon is administered with strong CYP3A4 inhibitors like the anti-retroviral protease inhibitors. Because there is the potential for multiple CYPP450 enzyme inhibition interactions between protease inhibitors and ramelteon, caution should be used if these 2 drugs are coadministered. The patient should be monitored closely for toxicity even though ramelteon has a wide therapeutic index.
Nirmatrelvir; Ritonavir: (Moderate) The serum concentrations of ramelteon may increase when ramelteon is administered with strong CYP3A4 inhibitors like the anti-retroviral protease inhibitors. Because there is the potential for multiple CYPP450 enzyme inhibition interactions between protease inhibitors and ramelteon, caution should be used if these 2 drugs are coadministered. The patient should be monitored closely for toxicity even though ramelteon has a wide therapeutic index.
Norethindrone Acetate; Ethinyl Estradiol; Ferrous fumarate: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with ethinyl estradiol is necessary. Ramelteon is a CYP1A2 substrate and ethinyl estradiol is a moderate CYP1A2 inhibitor.
Norethindrone; Ethinyl Estradiol: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with ethinyl estradiol is necessary. Ramelteon is a CYP1A2 substrate and ethinyl estradiol is a moderate CYP1A2 inhibitor.
Norethindrone; Ethinyl Estradiol; Ferrous fumarate: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with ethinyl estradiol is necessary. Ramelteon is a CYP1A2 substrate and ethinyl estradiol is a moderate CYP1A2 inhibitor.
Norgestimate; Ethinyl Estradiol: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with ethinyl estradiol is necessary. Ramelteon is a CYP1A2 substrate and ethinyl estradiol is a moderate CYP1A2 inhibitor.
OLANZapine: (Moderate) Additive effects are possible when olanzapine is combined with other drugs which cause respiratory depression and/or CNS depression including ramelteon.
OLANZapine; FLUoxetine: (Moderate) Additive effects are possible when olanzapine is combined with other drugs which cause respiratory depression and/or CNS depression including ramelteon.

OLANZapine; Samidorphan: (Moderate) Additive effects are possible when olanzapine is combined with other drugs which cause respiratory depression and/or CNS depression including ramelteon.
Oliceridine: (Moderate) Concomitant use of oliceridine with ramelteon may cause excessive sedation and somnolence. Limit the use of oliceridine with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect.
Omeprazole; Amoxicillin; Rifabutin: (Moderate) Administration of rifabutin, a CYP1A2 enzyme inducer, may theoretically result in decreased exposure to ramelteon. Monitor the patient closely if rifabutin therapy is initiated or stopped in patients receiving ramelteon.
Opicapone: (Moderate) COMT inhibitors should be given cautiously with other agents that cause CNS depression, including ramelteon, due to the possibility of additive sedation. COMT inhibitors have also been associated with sudden sleep onset during activities of daily living such as driving, which has resulted in accidents in some cases. Prescribers should re-assess patients for drowsiness or sleepiness regularly throughout treatment, especially since events may occur well after the start of treatment. Patients should be advised to avoid driving or other tasks requiring mental alertness until they know how the combination affects them.
Oritavancin: (Moderate) Coadministration of oritavancin and ramelteon may result in increases or decreases in ramelteon exposure and may increase side effects or decrease efficacy of ramelteon. Ramelteon is metabolized by CYP3A4 and CYP2C9. Oritavancin weakly induces CYP3A4, while weakly inhibiting CYP2C9. If these drugs are administered concurrently, monitor the patient for signs of toxicity or lack of efficacy.
Osilodrostat: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with osilodrostat is necessary. Ramelteon is a CYP1A2 substrate and osilodrostat is a moderate CYP1A2 inhibitor.
Oxazepam: (Moderate) Ramelteon is a sleep-promoting agent; therefore, additive pharmacodynamic effects are possible when combining ramelteon with benzodiazepines or other miscellaneous anxiolytics, sedatives, and hypnotics. Pharmacokinetic interactions have been observed with the use of zolpidem. Use of ramelteon 8 mg/day for 11 days and a single dose of zolpidem 10 mg resulted in an increase in the median Tmax of zolpidem of about 20 minutes; exposure to zolpidem was unchanged. Ramelteon use with hypnotics of any kind is considered duplicative therapy and these drugs are generally not co-administered.
oxyCODONE: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment

durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
oxyMORphone: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
PAZOPanib: (Moderate) Pazopanib is a weak inhibitor of CYP3A4. Coadministration of pazopanib and ramelteon, a CYP3A4 substrate, may cause an increase in systemic concentrations of ramelteon. Use caution when administering these drugs concomitantly.
PENTobarbital: (Major) Barbiturates can induce CYP1A2, the major metabolic pathway for ramelteon, and may eventually accelerate the clearance (and, thus, reduce the sedative properties) of ramelteon. Administration of multiple doses of a potent CYP inducer (rifampin) resulted in a mean decrease of approximately 80% in total exposure to ramelteon and its metabolite M-II. Additive CNS depression may also occur. The induction of ramelteon metabolism would likely require several days of barbiturate administration while additive drowsiness would appear immediately. Caution should be exercised during concomitant use of any CNS-depressant drugs and any barbiturate; dosage reduction of one or both agents may be necessary. If the medications must be used together, monitor for the effectiveness of ramelteon. Hypnotic barbiturates are best avoided during ramelteon therapy; the manufacturer warns against using other medications for sleep concurrently with ramelteon.
Perampanel: (Moderate) Co-administration of perampanel with CNS depressants, including ethanol, may increase CNS depression. The combination of perampanel (particularly at high doses) with ethanol has led to decreased mental alertness and ability to perform complex tasks (such as driving), as well as increased levels of anger, confusion, and depression; similar reactions should be expected with concomitant use of other CNS depressants, such as ramelteon.
Phenelzine: (Moderate) The CNS depressant effects of MAOIs can be potentiated with concomitant administration of other drugs known to cause CNS depression including ramelteon.
Phenicol Derivatives: (Moderate) The AUC and Cmax of ramelteon may be increased by strong CYP3A4 inhibitors such as chloramphenicol.
PHENobarbital: (Major) Barbiturates can induce CYP1A2, the major metabolic pathway for ramelteon, and may eventually accelerate the clearance (and, thus, reduce the sedative properties) of ramelteon. Administration of multiple doses of a potent CYP inducer (rifampin) resulted in a mean decrease of approximately 80% in total exposure to ramelteon and its metabolite M-II. Additive CNS depression may also occur. The

induction of ramelteon metabolism would likely require several days of barbiturate administration while additive drowsiness would appear immediately. Caution should be exercised during concomitant use of any CNS-depressant drugs and any barbiturate; dosage reduction of one or both agents may be necessary. If the medications must be used together, monitor for the effectiveness of ramelteon. Hypnotic barbiturates are best avoided during ramelteon therapy; the manufacturer warns against using other medications for sleep concurrently with ramelteon.
PHENobarbital; Hyoscyamine; Atropine; Scopolamine: (Major) Barbiturates can induce CYP1A2, the major metabolic pathway for ramelteon, and may eventually accelerate the clearance (and, thus, reduce the sedative properties) of ramelteon. Administration of multiple doses of a potent CYP inducer (rifampin) resulted in a mean decrease of approximately 80% in total exposure to ramelteon and its metabolite M-II. Additive CNS depression may also occur. The induction of ramelteon metabolism would likely require several days of barbiturate administration while additive drowsiness would appear immediately. Caution should be exercised during concomitant use of any CNS-depressant drugs and any barbiturate; dosage reduction of one or both agents may be necessary. If the medications must be used together, monitor for the effectiveness of ramelteon. Hypnotic barbiturates are best avoided during ramelteon therapy; the manufacturer warns against using other medications for sleep concurrently with ramelteon.
Phentermine; Topiramate: (Major) Although not specifically studied, coadministration of CNS depressant drugs with topiramate may potentiate CNS depression such as dizziness or cognitive adverse reactions, or other centrally mediated effects of these agents. Monitor for increased CNS effects if coadministering.
Posaconazole: (Moderate) Posaconazole and ramelteon should be coadministered with caution due to an increased potential for ramelteon-related adverse events. Posaconazole is a potent inhibitor of CYP3A4, an isoenzyme partially responsible for the metabolism of ramelteon. These drugs used in combination may result in elevated ramelteon plasma concentrations, causing an increased risk for ramelteon-related adverse events.
Pregabalin: (Moderate) Monitor for excessive sedation and somnolence during coadministration of ramelteon and pregabalin. Concurrent use may result in additive CNS depression.
Primidone: (Major) Barbiturates can induce CYP1A2, the major metabolic pathway for ramelteon, and may eventually accelerate the clearance (and, thus, reduce the sedative properties) of ramelteon. Administration of multiple doses of a potent CYP inducer (rifampin) resulted in a mean decrease of approximately 80% in total exposure to ramelteon and its metabolite M-II. Additive CNS depression may also occur. The induction of ramelteon metabolism would likely require several days of barbiturate administration while additive drowsiness would appear immediately. Caution should be

exercised during concomitant use of any CNS-depressant drugs and any barbiturate; dosage reduction of one or both agents may be necessary. If the medications must be used together, monitor for the effectiveness of ramelteon. Hypnotic barbiturates are best avoided during ramelteon therapy; the manufacturer warns against using other medications for sleep concurrently with ramelteon.
Protease inhibitors: (Moderate) The serum concentrations of ramelteon may increase when ramelteon is administered with strong CYP3A4 inhibitors like the anti-retroviral protease inhibitors. Because there is the potential for multiple CYPP450 enzyme inhibition interactions between protease inhibitors and ramelteon, caution should be used if these 2 drugs are coadministered. The patient should be monitored closely for toxicity even though ramelteon has a wide therapeutic index.
Pseudoephedrine; Triprolidine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Quazepam: (Moderate) Ramelteon is a sleep-promoting agent; therefore, additive pharmacodynamic effects are possible when combining ramelteon with benzodiazepines or other miscellaneous anxiolytics, sedatives, and hypnotics. Pharmacokinetic interactions have been observed with the use of zolpidem. Use of ramelteon 8 mg/day for 11 days and a single dose of zolpidem 10 mg resulted in an increase in the median Tmax of zolpidem of about 20 minutes; exposure to zolpidem was unchanged. Ramelteon use with hypnotics of any kind is considered duplicative therapy and these drugs are generally not co-administered.
Rasagiline: (Moderate) The CNS-depressant effects of MAOIs can be potentiated with concomitant administration of other drugs known to cause CNS depression including anxiolytics, sedatives, and hypnotics, including ramelteon, a melatonin-receptor agonist used to induce sleep. Use these drugs cautiously with MAOIs; warn patients to not drive or perform other hazardous activities until they know how a particular drug combination affects them. In some cases, the dosages of the CNS depressants may need to be reduced.
Remifentanil: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Remimazolam: (Moderate) Ramelteon is a sleep-promoting agent; therefore, additive pharmacodynamic effects are possible when combining ramelteon with benzodiazepines or other miscellaneous anxiolytics, sedatives, and hypnotics. Pharmacokinetic interactions have been observed with the use of zolpidem. Use of ramelteon 8 mg/day for 11 days and a single dose of zolpidem 10 mg resulted in an

increase in the median Tmax of zolpidem of about 20 minutes; exposure to zolpidem was unchanged. Ramelteon use with hypnotics of any kind is considered duplicative therapy and these drugs are generally not co-administered.
Ribociclib: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with ribociclib is necessary. Ramelteon is a CYP3A4 substrate and ribociclib is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor increased ramelteon exposure by 84%.
Ribociclib; Letrozole: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with ribociclib is necessary. Ramelteon is a CYP3A4 substrate and ribociclib is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor increased ramelteon exposure by 84%.
Rifabutin: (Moderate) Administration of rifabutin, a CYP1A2 enzyme inducer, may theoretically result in decreased exposure to ramelteon. Monitor the patient closely if rifabutin therapy is initiated or stopped in patients receiving ramelteon.
rifAMPin: (Moderate) Administration of rifampin, a potent CYP1A2 enzyme inducer, may result in a decrease in total exposure to ramelteon. Efficacy may be reduced when ramelteon is used in combination with strong CYP1A2 enzyme inducers such as rifampin.
Rifapentine: (Moderate) Monitor for a decrease in the efficacy of ramelteon if coadministration with rifapentine is necessary. Ramelteon is a CYP3A4 substrate; rifapentine is a strong CYP3A4 inducer. Coadministration with another strong CYP3A4 inducer decreased total exposure to ramelteon and metabolite M-II by approximately 80%.
Ritlecitinib: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with ritlecitinib is necessary. Ramelteon is a CYP1A2 substrate and ritlecitinib is a moderate CYP1A2 inhibitor.
Ritonavir: (Moderate) The serum concentrations of ramelteon may increase when ramelteon is administered with strong CYP3A4 inhibitors like the anti-retroviral protease inhibitors. Because there is the potential for multiple CYPP450 enzyme inhibition interactions between protease inhibitors and ramelteon, caution should be used if these 2 drugs are coadministered. The patient should be monitored closely for toxicity even though ramelteon has a wide therapeutic index.
Rotigotine: (Moderate) Concomitant use of rotigotine with other CNS depressants, such as ramelteon, can potentiate the sedation effects of rotigotine.
Rucaparib: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with rucaparib is necessary. Ramelteon is a CYP1A2 substrate and rucaparib is a moderate CYP1A2 inhibitor.
Safinamide: (Moderate) Dopaminergic medications, including safinamide, may cause a sudden onset of somnolence which sometimes has resulted in motor vehicle accidents. Patients may not perceive warning signs, such as excessive drowsiness, or they may

report feeling alert immediately prior to the event. Because of possible additive effects, advise patients about the potential for increased somnolence during concurrent use of safinamide with other sedating medications, such as Ramelteon.
Saquinavir: (Moderate) The serum concentrations of ramelteon may increase when ramelteon is administered with strong CYP3A4 inhibitors like the anti-retroviral protease inhibitors. Because there is the potential for multiple CYPP450 enzyme inhibition interactions between protease inhibitors and ramelteon, caution should be used if these 2 drugs are coadministered. The patient should be monitored closely for toxicity even though ramelteon has a wide therapeutic index.
Secobarbital: (Major) Barbiturates can induce CYP1A2, the major metabolic pathway for ramelteon, and may eventually accelerate the clearance (and, thus, reduce the sedative properties) of ramelteon. Administration of multiple doses of a potent CYP inducer (rifampin) resulted in a mean decrease of approximately 80% in total exposure to ramelteon and its metabolite M-II. Additive CNS depression may also occur. The induction of ramelteon metabolism would likely require several days of barbiturate administration while additive drowsiness would appear immediately. Caution should be exercised during concomitant use of any CNS-depressant drugs and any barbiturate; dosage reduction of one or both agents may be necessary. If the medications must be used together, monitor for the effectiveness of ramelteon. Hypnotic barbiturates are best avoided during ramelteon therapy; the manufacturer warns against using other medications for sleep concurrently with ramelteon.
Sedating H1-blockers: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Segesterone Acetate; Ethinyl Estradiol: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with ethinyl estradiol is necessary. Ramelteon is a CYP1A2 substrate and ethinyl estradiol is a moderate CYP1A2 inhibitor.
Selegiline: (Moderate) Monitor for excessive sedation and somnolence during coadministration of selegiline and ramelteon. Concurrent use may result in additive CNS depression.
Stiripentol: (Moderate) Consider a dose adjustment of ramelteon when coadministered with stiripentol. Coadministration may alter plasma concentrations of ramelteon resulting in an increased risk of adverse reactions and/or decreased efficacy. Additive somnolence and sedation may occur. Ramelteon is a sensitive CYP1A2 substrate. In vitro data predicts inhibition or induction of CYP1A2 by stiripentol potentially resulting in clinically significant interactions.
SUFentanil: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment

durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Sulfamethoxazole; Trimethoprim, SMX-TMP, Cotrimoxazole: (Moderate) Ramelteon should be administered with caution to patients taking CYP2C9 inhibitors, such as sulfamethoxazole. The AUC and Cmax of ramelteon have been elevated > 150% when administered with other CYP2C9 inhibitors. The patient should be monitored closely for toxicity even though ramelteon has a wide therapeutic index.
Suvorexant: (Major) The use of suvorexant with other hypnotic drugs, such as ramelteon, is not recommended. Additive sedative, CNS depressant effects, impairment, and effects on mood and behaviors, including sleep-related behaviors, may occur.
Tapentadol: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Tasimelteon: (Contraindicated) Because of pharmacologic similarities in action as melatonin-receptor agonists, ramelteon should not be coadministered with tasimelteon. The actions would be expected to be duplicative, and might result in additive side effects, such as somnolence, headache, unusual behaviors or moods, memory impairment, or balance and coordination issues.
Temazepam: (Moderate) Ramelteon is a sleep-promoting agent; therefore, additive pharmacodynamic effects are possible when combining ramelteon with benzodiazepines or other miscellaneous anxiolytics, sedatives, and hypnotics. Pharmacokinetic interactions have been observed with the use of zolpidem. Use of ramelteon 8 mg/day for 11 days and a single dose of zolpidem 10 mg resulted in an increase in the median Tmax of zolpidem of about 20 minutes; exposure to zolpidem was unchanged. Ramelteon use with hypnotics of any kind is considered duplicative therapy and these drugs are generally not co-administered.
Tezacaftor; Ivacaftor: (Minor) Increased monitoring is recommended if ivacaftor is administered concurrently with CYP2C9 substrates, such as ramelteon. Ivacaftor is an inhibitor of CYP3A and a weak inhibitor of CYP2C9; ramelteon is partially metabolized by CYP3A and CYP2C9. Co-administration of ivacaftor with CYP3A and CYP2C9 substrates, such as ramelteon, can theoretically increase ramelteon exposure leading to increased or prolonged therapeutic effects and adverse events; however, the clinical impact of this has not yet been determined.
Thalidomide: (Major) Avoid the concomitant use of thalidomide with anxiolytics, sedatives, and hypnotics due to the potential for additive sedative effects.
Tipranavir: (Moderate) The serum concentrations of ramelteon may increase when ramelteon is administered with strong CYP3A4 inhibitors like the anti-retroviral protease

inhibitors. Because there is the potential for multiple CYPP450 enzyme inhibition interactions between protease inhibitors and ramelteon, caution should be used if these 2 drugs are coadministered. The patient should be monitored closely for toxicity even though ramelteon has a wide therapeutic index.
tiZANidine: (Moderate) Concurrent use of tizanidine and CNS depressants like ramelteon can cause additive CNS depression.
Tolcapone: (Moderate) COMT inhibitors should be given cautiously with other agents that cause CNS depression, including ramelteon, due to the possibility of additive sedation. COMT inhibitors have also been associated with sudden sleep onset during activities of daily living such as driving, which has resulted in accidents in some cases. Prescribers should re-assess patients for drowsiness or sleepiness regularly throughout treatment, especially since events may occur well after the start of treatment. Patients should be advised to avoid driving or other tasks requiring mental alertness until they know how the combination affects them.
Topiramate: (Major) Although not specifically studied, coadministration of CNS depressant drugs with topiramate may potentiate CNS depression such as dizziness or cognitive adverse reactions, or other centrally mediated effects of these agents. Monitor for increased CNS effects if coadministering.
traMADol: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Tramadol; Acetaminophen: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Trandolapril; Verapamil: (Moderate) Coadministration of ramelteon with inhibitors of CYP3A4, such as verapamil, may lead to increases in the serum concentrations of ramelteon.
Tranylcypromine: (Moderate) The CNS depressant effects of MAOIs can be potentiated with concomitant administration of other drugs known to cause CNS depression including ramelteon.
traZODone: (Moderate) CNS depressants should be used cautiously in patients receiving trazodone because of additive CNS depressant effects, including possible respiratory depression or hypotension. A dose reduction of one or both drugs may be warranted.
Triazolam: (Moderate) Ramelteon is a sleep-promoting agent; therefore, additive

pharmacodynamic effects are possible when combining ramelteon with benzodiazepines or other miscellaneous anxiolytics, sedatives, and hypnotics. Pharmacokinetic interactions have been observed with the use of zolpidem. Use of ramelteon 8 mg/day for 11 days and a single dose of zolpidem 10 mg resulted in an increase in the median Tmax of zolpidem of about 20 minutes; exposure to zolpidem was unchanged. Ramelteon use with hypnotics of any kind is considered duplicative therapy and these drugs are generally not co-administered.
Triprolidine: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Triptorelin: (Major) Avoid coadministration of triptorelin with ramelteon due to the risk of reduced efficacy of triptorelin. Ramelteon can cause hyperprolactinemia, which reduces the number of pituitary gonadotropin releasing hormone (GnRH) receptors; triptorelin is a GnRH analog.
Tucatinib: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with tucatinib is necessary. Ramelteon is a CYP3A4 substrate and tucatinib is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor increased ramelteon exposure by 84%.
Valerian, Valeriana officinalis: (Major) In general, patients taking ramelteon should avoid use of valerian; the manufacturer advises avoidance of other medications that can have additive sedative effects. It is not known if ramelteon interacts with valerian, Valeriana officinalis; however, additive pharmacodynamic effects mgiht occur. Any substances that act on the CNS may theoretically interact with valerian. The valerian derivative, dihydrovaltrate, binds at barbiturate binding sites; valerenic acid has been shown to inhibit enzyme-induced breakdown of GABA in the brain; the non-volatile monoterpenes (valepotriates) have sedative activity.
Vemurafenib: (Moderate) Concomitant use of vemurafenib and ramelteon may result in altered concentrations of ramelteon. Vemurafenib is an inhibitor of CYP2C9 and CYP1A2 and an inducer of CYP3A4. Ramelteon is a substrate of CYP2C9, CYP1A2, and CYP3A4. Use caution and monitor patients for toxicity and efficacy.
Verapamil: (Moderate) Coadministration of ramelteon with inhibitors of CYP3A4, such as verapamil, may lead to increases in the serum concentrations of ramelteon.
Vigabatrin: (Moderate) Vigabatrin may cause somnolence and fatigue. Drugs that can cause CNS depression, if used concomitantly with vigabatrin, may increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, and dizziness. Caution should be used when vigabatrin is given with ramelteon.
Vilazodone: (Moderate) Due to the CNS effects of vilazodone, caution should be used when vilazodone is given in combination with other centrally acting medications such as anxiolytics, sedatives, and hypnotics.
Viloxazine: (Contraindicated) Concomitant use of viloxazine and ramelteon is

contraindicated due to the increased risk for ramelteon-related adverse effects and exposure. Ramelteon is a CYP1A2 substrate and viloxazine is a strong CYP1A2 inhibitor. Coadministration with another strong CYP1A2 inhibitor increased ramelteon exposure by 190-fold.
Vonoprazan; Amoxicillin; Clarithromycin: (Moderate) Use caution with concurrent use of ramelteon and strong inhibitors of CYP3A4, such as clarithromycin. Because ramelteon is partially metabolized via CYP3A4, an increase in exposure of ramelteon is expected. An increase in ramelteon AUC by approximately 84% and Cmax by 36% was noted when coadministered with a strong CYP3A4 inhibitor (ketoconazole). Similar increases were noted in M-II pharmacokinetics. Patients should be monitored for increased ramelteon side effects. Also use caution with concurrent use of combinations containing clarithromycin, such as amoxicillin; clarithromycin; lansoprazole or amoxicillin; clarithromycin; omeprazole.
Voriconazole: (Moderate) Monitor for an increase in ramelteon-related adverse reactions if coadministration with voriconazole is necessary. Ramelteon is a CYP3A4 substrate and voriconazole is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor increased ramelteon exposure by 84%.
Zafirlukast: (Moderate) Coadministration of ramelteon with inhibitors of CYP3A4, such as zafirlukast, may lead to increases in the serum concentrations of ramelteon.
Zaleplon: (Moderate) Ramelteon is a sleep-promoting agent; therefore, additive pharmacodynamic effects are possible when combining ramelteon with benzodiazepines or other miscellaneous anxiolytics, sedatives, and hypnotics. Pharmacokinetic interactions have been observed with the use of zolpidem. Use of ramelteon 8 mg/day for 11 days and a single dose of zolpidem 10 mg resulted in an increase in the median Tmax of zolpidem of about 20 minutes; exposure to zolpidem was unchanged. Ramelteon use with hypnotics of any kind is considered duplicative therapy and these drugs are generally not co-administered.
Zolpidem: (Moderate) Ramelteon is a sleep-promoting agent; therefore, additive pharmacodynamic effects are possible when combining ramelteon with benzodiazepines or other miscellaneous anxiolytics, sedatives, and hypnotics. Pharmacokinetic interactions have been observed with the use of zolpidem. Use of ramelteon 8 mg/day for 11 days and a single dose of zolpidem 10 mg resulted in an increase in the median Tmax of zolpidem of about 20 minutes; exposure to zolpidem was unchanged. Ramelteon use with hypnotics of any kind is considered duplicative therapy and these drugs are generally not co-administered.
Zuranolone: (Major) Avoid the use of multiple sedating agents due to the risk for additive CNS depression. If use is necessary, consider a downward dosage adjustment of either or both medications, especially in patients with additional risk factors for sedation-related harm.

Adverse Reaction

dizziness, drowsiness, fatigue, headache, insomnia

Central nervous system (CNS) effects are the most frequent of the adverse reactions associated with the use of ramelteon. During placebo-controlled clinical trials of patients with chronic insomnia, the following CNS effects occurred more frequently in the ramelteon group than the placebo group: drowsiness (3% vs 2%), fatigue (3% vs 2%), dizziness (4% vs 3%), and exacerbated insomnia (3% vs 2%). Drowsiness, dizziness, fatigue, headache, and insomnia were among the most frequent causes of treatment discontinuation (incidence <= 1%). In an 8 mg single-dose study in elderly subjects with insomnia (n=33), nighttime dosing did not impair middle of the night balance, mobility, or memory functions compared to placebo. However, further study in this patient population is needed, including the effects of multiple dosing. Rebound insomnia, withdrawal effects, and next-day residual effect (i.e., hangover effect) due to ramelteon have been evaluated in several human clinical trials (n=2082). To assess rebound insomnia, ramelteon use (4, 8, or 16 mg PO) was abruptly discontinued after 35 days. There was no evidence of rebound insomnia at any of the doses studied in elderly or younger subjects. Next-day residual effects of a ramelteon 8 mg PO dose were evaluated at weeks 1, 3, and 5 in a 35-day double-blind, parallel group study. Several standardized tools were used for evaluation. Slight differences in fatigue, recall, and sluggishness scores were noted during the first and third weeks, but they were not considered clinically significant. Next morning residual effects were not different from placebo at week five. Next morning residual effects were also not noted after 2 nights of ramelteon use in crossover studies. In single-dose studies, ramelteon (single PO doses of 16, 80, or 160 mg) did not exhibit subjective responses indicative of the potential for abuse. Triazolam, the control drug, did exhibit a dose-response effect on those subjective measures compared to placebo (i.e., peak effect, overall 24-hour effect).

nausea

During placebo-controlled clinical trials of patients with chronic insomnia, nausea occurred more frequently in patients receiving ramelteon than placebo (3% vs 2%). Nausea was also among the most frequent causes of treatment discontinuation during clinical trials (incidence < = 1%).

adrenocortical insufficiency

In a one year open-label study of adult and elderly patients, two patients were noted to have decreased morning cortisol concentrations (adrenocortical insufficiency) and

subsequent abnormal ACTH stimulation tests. The relationship between ramelteon and changes in adrenal functioning is not clear.

agitation, depression, hallucinations, mania, suicidal ideation

Psychiatric effects which have been reported during use of ramelteon include hallucinations, agitation, mania, depression and unspecified bizarre behavior. Suicidal ideation and completed suicides have been reported in depressed patients in association with other sedative/hypnotics. Amnesia, anxiety, or other effects are possible. Caution is advisable during use of ramelteon in patients with schizophrenia, bipolar disorder, or major depression.

hyperprolactinemia

Ramelteon has been associated with an effect on reproductive hormones in adults (e.g., decreased testosterone levels and increased prolactin concentrations). It is not known what effect chronic or even chronic intermittent use of ramelteon has on the reproductive axis in developing humans. In a 6-month chronic insomnia trial in patients (n=122) receiving ramelteon orally at 16 mg/day or placebo, the mean serum prolactin change from baseline was statistically elevated by 34% (4.9 mcg/L for ramelteon) vs. a 4% decrease (-0.6 mcg/L for placebo) in women only. However, 32% of all patients receiving ramelteon (men and women) had prolactin elevations from a normal baseline value vs. 19% with placebo. Menstrual patterns were similar between the 2 groups. In a 12 month, open-label study in adult and geriatric patients, one female (29 years old) ramelteon recipient was diagnosed with prolactinoma; the relationship of ramelteon therapy to prolactinoma is not clear. For ramelteon recipients presenting with unexplained menstrual irregularity, decreased libido, infertility, or other potential hyperprolactinemia or testosterone-related symptoms, consider assessment of prolactin and/or testosterone concentrations. When ramelteon (doses of 6 to 600 mg/kg/day) was administered orally to male and female rats in animal reproductive studies, alterations in estrus cyclicity and decreased numbers of corpora lutea, implantations, and live embryos were observed at doses greater than 20 mg/kg/day. The no-effect dose is approximately 24-times the usual human dose of 8 mg/day based on mg/m2. Oral administration of ramelteon (up to 600 mg/kg/day) to male rats had no effects on sperm quality or reproductive performance.

complex sleep-related behaviors, somnambulism

Sedative-hypnotic medications have the potential to cause complex sleep-related behaviors such as sleep-driving, a state of driving after ingestion of a sedative-hypnotic while not fully awake and having no memory of the event. Other sleep-related behaviors

may include sleep-walking (somnambulism) or making phone calls or eating while asleep. Sleep-related behaviors have been reported with the use of ramelteon. The use of alcohol and other CNS depressants may increase the risk of such behaviors. The exact incidences among various sedative products are unknown; however, patients should be informed of the risks prior to receiving any medication from this class, including ramelteon.

anaphylactoid reactions, angioedema

Anaphylactoid reactions (e.g., angioedema) may occur with sedative-hypnotics, such as ramelteon, and may become evident as early as the initial dose. Rare cases of angioedema involving the tongue, glottis, or larynx have been reported in patients after taking initial or subsequent doses of ramelteon. Airway obstruction resulting from angioedema of the tongue, glottis, or larynx may be fatal. Other symptoms suggestive of anaphylaxis may include dyspnea, throat closing, and nausea/vomiting. Patients should be instructed on the appropriate action in the event of an allergic reaction. Treatment should not be reinitiated in patients who experience ramelteon-induced angioedema.

hepatitis

A case of autoimmune hepatitis has been reported in the literature due to ramelteon, a melatonin agonist.

Description

Ramelteon is a selective melatonin receptor agonist used for the treatment of chronic or transient insomnia characterized by difficulty with sleep onset, targeting specific melatonin receptors which are believed to be involved in the regulation of the circadian rhythm. In contrast to traditional hypnotics such as benzodiazepines which have abuse potential and may cause next-day impairment, ramelteon does not appear to have abuse potential and available data have shown no consistent evidence of next-day residual impairment. Similar to other sedatives, ramelteon has been associated with sleep-related behaviors such as engaging in activities of daily living while not fully awake and having no memory of the event. The use of alcohol and other CNS depressants may increase the risk of these behaviors. Through a systematic review and using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) process, the task force of the American Academy of Sleep Medicine found that there is weak evidence of efficacy of ramelteon in the treatment of sleep onset insomnia, with limited or no consistent evidence of adverse events in excess of placebo. Therefore, the benefits were deemed to marginally outweigh harms. The task force further determined that due to the efficacy of ramelteon for sleep onset and its relatively benign side effect profile, a

majority of patients would be likely to use ramelteon compared to no treatment. Ramelteon was approved by the FDA in 2005 for the treatment of insomnia.

Mechanism Of Action

Mechanism of Action: Ramelteon is the first in a new class of agents termed melatonin receptor agonists. Melatonin receptors belong to the 7 transmembrane G protein-coupled receptor family. The 3 subtypes of mammalian melatonin receptors that have been identified are MT1, MT2, and MT3. Ramelteon selectively targets the melatonin receptors MT1 and MT2, which are located in the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN functions as the body's internal clock and regulates the 24-hour sleep-wake cycle. The MT1 and MT2 receptors are believed to be involved in the promotion of sleep and the maintenance of the normal circadian rhythm (shift between day and night), respectively, when acted upon by endogenous melatonin. The activation of the MT1 and MT2 receptor sites is associated with the inhibition of adenylate cyclase and the resultant decrease in cAMP accumulation. Ramelteon has 3—16 times higher affinity for human MT1 and MT2 receptors than melatonin. Compared to exogenous melatonin, ramelteon may preferentially select MT1 over MT2 and, therefore, may be more suitable therapy for sleep-onset insomnia. Although the results from animal studies suggest that the MT1 and MT2 receptors have distinct functional roles in the SCN, there may be some overlap in function. In animal and human clinical trials, ramelteon appears to be modestly effective in both shortening the the delay to sleep onset and increasing the total amount of sleep time. MT3 receptors appear to be a form of quinone reductase. The importance of melatonin-binding to the MT3 receptor is not well-defined; ramelteon has limited affinity for this site.Unlike the benzodiazepines, ramelteon has not been shown to decrease rapid eye movement (REM) sleep. In animal studies, ramelteon has not been shown to exhibit the reward properties of benzodiazepines or morphine, which suggests that MT1 and MT2 receptor agonists have minimal abuse potential. Ramelteon has shown no affinity for the GABA-receptor complex, which is the primary target area for many of the current hypnotics on the market including the benzodiazepines and the newer agents zolpidem and zaleplon. Ramelteon also shows very low affinity for MT3 binding site, as well as receptors that bind neuropeptides, cytokines, serotonin, dopamine, noradrenaline, acetylcholine, and opiates.

Pharmacokinetics

Ramelteon is administered orally. In vitro protein binding of ramelteon is roughly 82% with binding primarily to albumin. Ramelteon is not distributed selectively to red blood cells; however, the drug has a mean volume of distribution of 73.6 L after IV

administration, which suggests substantial tissue distribution. Metabolized occurs primarily by oxidation and secondarily to form glucuronide conjugates. Ramelteon metabolites (M-I, M-II, M-III, and M-IV) are rapidly formed and eliminated (half-life of 1—3 h). M-II is the only major active metabolite; M-II has approximately one tenth and one fifth the binding affinity of the parent molecule for the human MT1 and MT2 receptors, respectively. The M-II metabolite is 17—25 fold less potent than ramelteon in in vitro functional assays. Although the potency of M-II at MT1 and MT2 receptors is lower than the parent drug, M-II circulates at higher concentrations than the parent producing 20—100 fold greater mean systemic exposure when compared to ramelteon. M-II has weak affinity for the serotonin 5-HT2B receptor but no appreciable affinity for other receptors or enzymes. Similar to ramelteon, M-II does not interfere with the activity of a number of endogenous enzymes. CYP1A2 is the major isozyme involved in the hepatic metabolism of ramelteon (see Drug Interactions); the CYP2C subfamily and CYP3A4 isozymes are involved to a minor degree. Drug elimination is 84% renal and 4% fecal; the metabolites account for the majority of the dose eliminated. Less than 0.1% of a ramelteon dose is eliminated unchanged. Repeat once daily dosing does not result in significant accumulation due to the short elimination half-life ranging from 1—2.6 hours. The half-life of the major metabolite, M-II, ranges from 2—5 hours and is independent of dose. Serum concentrations of ramelteon and the M-II metabolite are essentially undetectable at 24 hours.

Affected cytochrome P450 isoenzymes and drug transporters: CYP1A2, CYP2C9, CYP3A4 Cytochrome P450 (CYP) 1A2 is the major isozyme involved in the hepatic metabolism of ramelteon; the CYP2C subfamily and CYP3A4 isozymes are also involved to a minor degree. In vitro studies have been undertaken to evaluate the effect of CYP inducers or inhibitors when ramelteon is acting as a substrate. Interaction studies with fluoxetine (CYP2D6 inhibitor), omeprazole (a CYP1A2 inducer and CYP2C19 inhibitor), theophylline (CYP1A2 substrate), and dextromethorphan (CYP2D6 substrate) have not revealed clinically meaningful changes in either peak (Cmax) or total (AUC) exposures to ramelteon or the M-II metabolite. Additionally, ramelteon has been evaluated for its effect as an inducer or inhibitor on different substrates. It did not cause clinically meaningful changes in either the peak or total exposure of omeprazole (CYP2C19 substrate), dextromethorphan (CYP2D6 substrate), midazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate), digoxin (p-glycoprotein substrate), warfarin (CYP2C9 (S)/CYP1A2 (R) substrate), venlafaxine, sertraline, escitalopram, or gabapentin. It appears unlikely that ramelteon would act as an inducer or inhibitor of CYP hepatic enzymes; however, more study is needed.

Route-Specific Pharmacokinetics

- **Oral Route**

Following oral administration, ramelteon (16 mg PO) is rapidly absorbed (tmax = 0.3 h) and exhibits linear pharmacokinetics. Median peak concentrations occur at roughly 0.75 hour (range 0.5—1.5 hours) after fasted oral administration. A high fat meal can alter the oral absorption of ramelteon and should be avoided during or immediately before the ramelteon dose. Although the total absorption of ramelteon is at least 84%, the absolute oral bioavailability following a single oral dose is low (1.8%) due to extensive first-pass metabolism. Extensive first-pass metabolism is evidenced by low concentrations of the unchanged compound in both urine and plasma. Maximal serum concentration (Cmax) and area under the concentration-time curve (AUC) data show substantial intersubject variability, which is consistent with the high first-pass effect; the coefficient of variation for these values is approximately 100%.

- **Intravenous Route**

Although not clinically administered via IV injection, ramelteon has a mean volume of distribution after IV administration of 73.6 L, which suggests substantial tissue distribution.

- **Hepatic Impairment**

In patients with mild or moderate hepatic impairment, systemic exposure to ramelteon is elevated 4- or 10-fold, respectively. The pharmacokinetics of ramelteon have not been evaluated in subjects with severe hepatic impairment (see Dosing). Ramelteon use should be avoided in patients with severe liver disease (Child-Pugh Class C).

- **Renal Impairment**

The pharmacokinetic parameters of ramelteon are not clinically altered in patients with renal impairment or those on chronic hemodialysis. These results are consistent with the negligible renal clearance of the parent drug, ramelteon. Dose adjustments of ramelteon are not suggested in patients with any degree of renal impairment.

- **Geriatric**

Systemic exposure to ramelteon is higher in elderly individuals, although the clinical significance of this effect is not known. Compared with younger adults, the total exposure (AUC) and Cmax of ramelteon are 97% and 86% higher, respectively. The AUC and Cmax of M-II were increased by 30% and 13%, respectively, in elderly subjects. However, dose adjustments based on age alone have not been recommended.

Administration

For storage information, see the specific product information within the How Supplied section.

Oral Administration

Do not take ramelteon with or immediately after a high-fat meal; doing so would slow absorption and is expected to reduce the effect on sleep latency.
Administer within 30 minutes of going to bed. Once administered, activities should be limited to those necessary to get ready for bed.

Maximum Dosage Limits

- **Adults**
  8 mg/day PO.
- **Elderly**
  8 mg/day PO.
- **Adolescents**
  Safety and efficacy have not been established.
- **Children**
  Safety and efficacy have not been established.

Dosage Forms

- Ramelteon 8mg Oral tablet
- Rozerem 8mg Tablet

Dosage Adjustment Guidelines

Hepatic Impairment

Use of ramelteon is not recommended in patients with severe hepatic impairment (Child-Pugh Class C). Ramelteon should be used with caution in patients with mild or moderate liver disease; although specific dosage adjustment recommendations are not available.

Renal Impairment

No dose adjustment is required in patients with any degree of renal impairment.

Intermittent hemodialysis
Supplemental dosing is not required following hemodialysis.

Continuous hemodialysis (CAVHD, CVVHD)
Supplemental dosing is not required following hemodialysis.