

DRUGDEX-EV 2613

MICROMEDEX

DRUGDEX® Evaluations
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RAMELTEON

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0.0] Overview

1) Class

a) This drug is a member of the following class(es):

Nonbarbiturate Hypnotic

2) Dosing Information

a) Adult

1) Insomnia

a) 8 mg ORALLY taken within 30 min of bedtime [1]

b) Pediatric

1) safety and efficacy not established in pediatric patients [1]

3) Contraindications

a) [Angioedema](#) with prior exposure [4]

b) Concomitant use with [fluvoxamine](#) [4]

4) Serious Adverse Effects

a) [Angioedema](#)

b) Depression, worsening

c) Hallucinations

d) Mania

5) Clinical Applications

a) FDA Approved Indications

1) Insomnia

1.0] Dosing Information

[Drug Properties](#)

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1.1] Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)

B) Synonyms

[Ramelteon](#)

1.2] Storage and Stability

A) Preparation

1) Oral route

a) [Ramelteon](#) should not be administered with or immediately after a high fat meal [3].

B) Oral route

1) Tablet

a) Store [ramelteon](#) tablets between 15 to 30 degrees Celsius (59 to 86 degrees Fahrenheit) and protect from moisture and humidity; keep container tightly closed [1].

1.3] Adult Dosage

1.3.1] Normal Dosage

1.3.1.A] Oral route

1.3.1.A.1] Insomnia

a) The recommended oral dose of [ramelteon](#) for the treatment of [initial insomnia](#) is 8 milligrams taken within 30 minutes of going to bed. [Ramelteon](#) should not be taken with or immediately after a high fat meal [1].

1.3.1.B) ADMINISTRATION

1) [Ramelteon](#) should not be administered with or immediately after a high fat meal [1].

1.3.2] Dosage in Renal Failure

A) No [ramelteon](#) dose adjustment is necessary in patients with [renal impairment](#), including patients with severe [renal impairment](#) ([creatinine clearance](#) less than or equal to 30 milliliters per minute per 1.73 meters squared) [1].

1.3.3] Dosage in Hepatic Insufficiency

A) While no specific ramelteon dose adjustment recommendations are available, caution should be used in patients with moderate hepatic impairment. Ramelteon should not be used in patients with severe hepatic impairment (Child-Pugh Class C) [1].

B) Ramelteon exposure increased almost 4-fold in subjects with mild hepatic impairment who received ramelteon 16 milligrams per day for 7 days compared to healthy controls. Exposure to ramelteon increased more than 10-fold in subjects with moderate hepatic impairment compared to controls. Ramelteon pharmacokinetics have not been studied in patients with severe hepatic impairment [1].

1.4] Pediatric Dosage

1.4.1] Normal Dosage

A) The safety and efficacy of ramelteon has not been established in pediatric patients [1].

1.4.3] Dosage in Hepatic Insufficiency

A) should be used with caution in patients with moderate hepatic impairment and should not be used in patients with severe hepatic impairment (Child-Pugh Class C)

2.0] Pharmacokinetics

Drug Concentration Levels

ADME

2.2] Drug Concentration Levels

A) Time to Peak Concentration

1) Insomnia, oral: 0.75 hour [1].

a) Following the fasted, oral administration of ramelteon, median peak plasma concentration occurs at 0.75 hour (range, 0.5 to 1.5 hours) [1].

b) Elderly patients

1) Insomnia: 11.6 ng/mL [1].

a) Following the administration of a 16 milligram dose of ramelteon to elderly subjects aged 63 to 79 years (n=24), the mean area under the curve (AUC) was 18.7 nanograms x hour/milliliter (SD, 19.4) and the mean maximum concentration was 11.6 nanograms/milliliter (SD, 13.8). The AUC and maximum concentration of ramelteon increased by 97% and 86%, respectively, as compared with younger adults. The AUC and maximum concentration of M-II, the major metabolite of ramelteon, were 30% and 13% higher, respectively, as compared with younger subjects[1].

B) Area Under the Curve

1) Elderly patients

a) Following the administration of a 16 milligram dose of [ramelteon](#) to elderly subjects aged 63 to 79 years (n=24), the mean area under the curve (AUC) was 18.7 nanograms x hour/milliliter (SD, 19.4) and the mean maximum concentration was 11.6 nanograms/milliliter (SD, 13.8). The AUC and maximum concentration of [ramelteon](#) increased by 97% and 86%, respectively, as compared with younger adults. The AUC and maximum concentration of M-II, the major metabolite of [ramelteon](#), were 30% and 13% higher, respectively, as compared with younger subjects[1].

2.3] ADME

2.3.1] Absorption

A) Bioavailability

1) Oral, 1.8%

a) The total absorption of [ramelteon](#) is at least 84% following fasted oral administration; however, due to extensive first-pass metabolism, absolute oral bioavailability is only 1.8% [1].

b) Hepatic Impairment

1) Ramelteon exposure increased almost 4-fold in subjects with mild hepatic impairment who received ramelteon 16 milligrams per day for 7 days compared to healthy controls. Exposure to ramelteon increased more than 10-fold in subjects with moderate hepatic impairment compared to controls. Exposure to the major metabolite of ramelteon, M-II, was marginally increased in subjects with mild to moderate hepatic impairment as compared with healthy controls. Ramelteon pharmacokinetics have not been studied in patients with severe hepatic impairment [1].

B) Effects of Food

1) Following the administration of a single 16 milligram dose of [ramelteon](#) with a high-fat meal, the area under the curve was 31% higher and the maximum concentration was 22% lower than when administration occurred during a fasted state. When [ramelteon](#) was given with food, the time to peak concentration was delayed by approximately 45 minutes. Similar effects of food were observed for the AUC values of the principle metabolite M-II. Taking [ramelteon](#) with or immediately after a high fat meal is not recommended [1].

2.3.2] Distribution

A) Distribution Sites

1) Protein Binding

a) 82% [1].

1) Ramelteon protein binding is approximately 82% in human serum, independent of concentration. Seventy percent of the drug is bound in human serum albumin [1].

B) Distribution Kinetics

1) Volume of Distribution

a) intravenous: 73.6 L [1].

1) Following intravenous administration of ramelteon, the mean volume of distribution is 73.6 liters [1].

2.3.3] Metabolism

A) Metabolism Sites and Kinetics

1) Liver [1].

a) Primary metabolism of ramelteon consists of oxidation to hydroxyl and carbonyl derivatives; secondary metabolism produces glucuronide conjugates. The major isozyme involved in the hepatic metabolism of ramelteon is CYP1A2; the CYP2C subfamily and CYP3A4 isozymes are also involved to a minor degree [1].

B) Metabolites

1) M-II, active [1].

2) M-IV, M-I, and M-III, inactive [1].

a) M-II is the major, active metabolite of ramelteon. The rank order of principle metabolites by prevalence in human serum is M-II, M-IV, M-I, and M-III. Although M-II is approximately 17 to 25-fold less potent than ramelteon, it has an overall mean systemic exposure that is approximately 20 to 100 times higher than its parent compound [1].

2.3.4] Excretion

A) Kidney

1) Renal Excretion (%)

a) 84% [1].

1) Eighty-four percent of an oral, radiolabeled dose is recovered in the urine within 96 hours of administration; less than 0.1% of the dose is excreted as parent compound [1].

B) Feces

1) 4% [1].

a) Four percent of an oral, radiolabeled dose is recovered in the feces within 96 hours of administration; less than 0.1% of the dose is excreted as parent compound [1].

2.3.5] Elimination Half-life

A) Parent Compound

1) approximately 1 to 2.6 hours [1].

B)) Metabolites

1)) M-II, 2 to 5 hours (independent of dose) [1].

2.3.6] Extracorporeal Elimination

A)) Hemodialysis

1)) Dialyzable: No[1]

a)) **Hemodialysis** is not effective for the reduction of exposure to **ramelteon** [1].

3.0] Cautions

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

[Teratogenicity/Effects in Pregnancy/Breastfeeding](#)

[Drug Interactions](#)

3.1] Contraindications

A)) **Angioedema** with prior exposure [4]

B)) Concomitant use with **fluvoxamine** [4]

3.2] Precautions

A)) Concomitant Use: Alcohol may produce additive effects; avoid use [4]

B)) Hepatic: Severe **hepatic impairment**; use not recommended [4]

C)) Immunologic: **Angioedema** has been reported and can be fatal in some cases, permanently discontinue, do not rechallenge [4]

D)) Psychiatric: Worsening of insomnia, failure of insomnia to remit after 7 to 10 days, or emergence of new behavioral abnormalities may indicate an unrecognized underlying psychiatric disorder; baseline evaluation and continued monitoring recommended [4]

E)) Psychiatric: Worsening of depression, **suicidal ideation**, and completed suicides have been reported [4]

F)) Psychiatric: Hallucinations, agitation, mania, amnesia, anxiety, and other neuropsychiatric events have been reported [4]

G)) Psychiatric: Complex behaviors with subsequent amnesia (eg, sleep driving, preparing food, making phone calls, or having sex) may occur; increased risk with concomitant use of alcohol or other CNS depressants; discontinue use if suspected [4]

H)) Reproductive: Decreased **testosterone** and increased prolactin levels have been reported; monitoring recommended in symptomatic patients [4]

I)) Respiratory: **Sleep apnea**; use not recommended [4]

3.3] Adverse Reactions

3.3.4] Gastrointestinal Effects

3.3.4.A] Nausea

1)) Incidence: 3% [5]

2)) During clinical trials, nausea was observed in 3% of subjects following the use of **ramelteon** 8 milligrams during clinical trials (n=1405) [5].

3.3.6] Hepatic Effects

3.3.6.A] Autoimmune hepatitis

1]) Adult Case Reports

a]) A 50-year-old man with a history of depression and chronic alcohol consumption developed autoimmune hepatitis, ultimately resulting in death, with symptoms developing 1 month following initiation of ramelteon 8 mg/day for the treatment of insomnia. Current medications included stable doses of alprazolam and escitalopram. He presented with jaundice of skin, scleral icterus, mild hepatomegaly, and a distended, soft abdomen with fluid wave. Laboratory testing revealed elevated liver functions tests, IgA 749 mg/dL, IgG 1710 mg/dL, and normal IgM and albumin levels. Ultrasound revealed hepatosplenomegaly, liver nodularity consistent with cirrhosis, and abdominal ascites. Signs of alcoholic hepatitis were absent. Autoimmune hepatitis was confirmed by transjugular liver biopsy. Despite mild improvements in liver function tests 3 weeks following discontinuation of ramelteon and treatment with prednisone, the patient developed bacterial peritonitis and expired due to systemic inflammatory response syndrome with an underlying cause of death of autoimmune hepatitis [6].

3.3.9] Neurologic Effects

3.3.9.A] Amnesia

1]) Amnesia may occur in patients following the use of ramelteon [5].

3.3.9.B] Decreased mental alertness

1]) Patients who are prescribed ramelteon should be advised to use caution while operating machinery, including automobiles, until the effects of the drug are known [5].

3.3.9.C] Dizziness

1]) Incidence: 4% [5]

2]) During clinical trials, dizziness was reported in 4% of subjects exposed to ramelteon 8 milligrams during clinical trials (n=1405) [5].

3.3.9.D] Fatigue

1]) Incidence: 3%[5]

2]) Fatigue was reported in 3% of subjects exposed to ramelteon 8 milligrams during clinical trials (n=1405) [5].

3.3.9.E] Insomnia, exacerbated

1]) Incidence: 3% [5]

2]) Three percent of subjects reported exacerbation of insomnia following the use of ramelteon 8 milligrams during clinical trials (n=1405) [5].

3.3.9.F] Somnolence

1]) Incidence: 3%[5]

2]) Somnolence was observed in 3% of subjects following the use of ramelteon 8 milligrams during clinical trials (n=1405) [1].

3.3.12] Psychiatric Effects

3.3.12.A] Agitation

1) Agitation has been reported in patients following the use of [ramelteon](#) [5].

3.3.12.B] Anxiety

1) Anxiety may occur in patients following the use of [ramelteon](#) [5].

3.3.12.C] Complex mannerisms - behavior

1) Complex behaviors including sleep driving, preparing and eating food, making phone calls, or having sexual intercourse while not fully awake and subsequently not remembering the performance of these activities has occurred following administration of sedative-hypnotics. These behaviors have occurred in sedative-hypnotic-naïve and sedative-hypnotic-experienced patients. Although, determination of causality (ie, drug-induced, spontaneous in origin, result of an underlying psychiatric or physical disorder) can not be made with certainty in most cases, any new behaviors should be immediately and carefully assessed. In cases of sleep-driving, strongly consider discontinuation of [ramelteon](#) due to the risk to the patient and others [5].

3.3.12.D] Depression, worsening

1) Worsening depression has been reported in patients following use of hypnotics, and may occur with [ramelteon](#) [5].

3.3.12.E] Hallucinations

1) Hallucinations have been reported in patients following the use of [ramelteon](#) [5].

3.3.12.F] Mania

1) Mania has been reported in patients following the use of [ramelteon](#) [5].

3.3.12.G] Suicidal

1) Suicide has been reported in patients following use of hypnotics, and may occur with [ramelteon](#) [5].

3.3.12.H] Suicidal thoughts

1) Suicidal thoughts have been reported in patients following use of hypnotics, and may occur with [ramelteon](#) [5].

3.3.14] Reproductive Effects

3.3.14.A] Decreased [testosterone](#) level

1) Decreased [testosterone](#) levels have been reported in patients following the use of [ramelteon](#) [5].

3.3.14.B] Increased prolactin level

1) Increased prolactin levels have been reported in patients following the use of [ramelteon](#) [5].

2) A randomized, double-blinded, placebo-controlled, multicenter study of 52 male and 69 female subjects (aged 18 to 45 years; mean 34.3 years) with [chronic insomnia](#), [ramelteon](#) 16 mg showed a mild, brief

increase in prolactin levels among women only compared to placebo, but no clinical symptoms were reported. Three weeks prior to the start of the study, medical history, sleep history, vital signs, laboratory tests (thyroid, adrenal, and reproductive hormones) and ECG were assessed. Subjects were randomly assigned to [ramelteon](#) 16 mg or placebo nightly for 6 months. Premenopausal women were to maintain a menstrual diary. After a 2-week washout following the study, final hormonal concentrations were obtained, physical exams, adverse effects, and menstrual diaries were assessed. Tests showed no significant increase in thyroid, reproductive hormones, or adrenal functions. Although prolactin concentrations were increased by 4.9 micrograms/L in the [ramelteon](#) arm (n=34) compared with a reduction of 0.6 micrograms/L in the placebo arm (n=35) among women (p=0.003) overall, there were no reported clinical effects. The detectable increases were statistically significant at month 1 (p=0.004), month 2 (p=0.018) and month 4 (p=0.007). In contrast, the overall increase in prolactin concentrations among men was relatively small in magnitude and similar between the [ramelteon](#) (n=22) and placebo (n=30) arms (1.2 micrograms/L vs 0.2 micrograms/mL; p=0.414) [7].

3.3.16] Other

3.3.16.A] [Angioedema](#)

1)] Incidence: rare [5]

2)] [Angioedema of the tongue](#), glottis, or larynx has been reported in patients following the use of [ramelteon](#) [5].

3.4] [Teratogenicity/Effects in Pregnancy/Breastfeeding](#)

A)] [Teratogenicity/Effects in Pregnancy](#)

1)] U.S. Food and Drug Administration's Pregnancy Category: Category C (All Trimesters)

a)] Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential [risk to the fetus](#).

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2)] Crosses Placenta: Unknown

3)] Clinical Management

a)] Well-controlled studies in pregnant women are absent. The manufacturer recommends that [ramelteon](#) should be administered during pregnancy only if its potential benefit outweighs the potential [risk to the fetus](#) [1].

4)] Literature Reports

a)] Studies conducted in rats have shown [ramelteon](#) to be a developmental teratogen when administered in doses 197 times greater than the maximum recommended human dose (MRHD) on a mg/m(2) basis. In this study, the no-effect level for [teratogenicity](#) was 40 mg/kg/day (1892-times greater than the therapeutic response to [ramelteon](#) at the MRHD based on an area-under-the-curve comparison). Studies conducted in pregnant rabbits demonstrated maternal toxicity at 300 mg/kg/day but fetal [teratogenic effects](#) were absent at any dose level. [Ramelteon](#) has not been studied in pregnant women [1].

B)) Breastfeeding

1)) Micromedex Lactation Rating: Infant risk cannot be ruled out.

a)) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

2)) Clinical Management

a)) It is unknown whether [ramelteon](#) is excreted in human milk. The manufacturer recommends that [ramelteon](#) should not be used in nursing women [1].

3)) Literature Reports

a)) [Ramelteon](#) is excreted in the milk of lactating rats. In studies conducted in rats, the no-effect level for pre- and postnatal development was 30 mg/kg/day (39 times greater than the MRHD on a mg/m(2) basis). There are no adequate clinical studies in nursing women and it is unknown whether [ramelteon](#) is excreted in human milk [1].

3.5) Drug Interactions

3.5.1) Drug-Drug Combinations

3.5.1.A) [Alfentanil](#)

- 1)) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2)) Summary: The concomitant use of [alfentanil](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[28].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Reserve concomitant use of [alfentanil](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[28].
- 7)) Probable Mechanism: additive CNS depression

3.5.1.B) [Bromazepam](#)

- 1)) Interaction Effect: increased risk of respiratory or cardiovascular depression
- 2)) Summary: Concomitant use of bromazepam with another CNS depressant should be avoided due to increased risk for respiratory or cardiovascular depression and profound sedation[24].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical

6) Clinical Management: Concomitant use of bromazepam, which is a CNS depressant, with another CNS depressant may result in respiratory or cardiovascular depression and profound sedation. Due to the added CNS depressant effects, avoid use of bromazepam and other CNS depressants[24].

7) Probable Mechanism: additive CNS depression

3.5.1.C] Bromopride

1) Interaction Effect: potentiation of sedative effects

2) Summary: Potentiation of sedative effects may occur with concomitant use of bromopride and sedatives. Avoid concomitant use[39].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of bromopride with sedatives. Additive sedation may occur with concomitant use[39].

7) Probable Mechanism: unknown

3.5.1.D] Buprenorphine

1) Interaction Effect: increased risk of [respiratory depression](#)

2) Summary: Coadministration of [buprenorphine](#) and a CNS depressant may result in additive CNS depression and an increased risk of [respiratory depression](#). If concomitant use is required, consider reducing the dose of one or both agents[14][15] and monitor for signs of [respiratory depression](#), sedation, and hypotension [14].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [buprenorphine](#) and a CNS depressant may result in additive CNS depression and an increased risk of [respiratory depression](#). If concomitant use is required, consider reducing the dose of one or both agents[14][15] and monitor for signs of [respiratory depression](#), sedation, and hypotension [14].

7) Probable Mechanism: additive [respiratory depression](#)

3.5.1.E] Butorphanol

1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)

2) Summary: The concomitant use of [butorphanol](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[28].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Reserve concomitant use of [butorphanol](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[28].

7) Probable Mechanism: additive CNS depression

3.5.1.F] Carbinoxamine

- 1) Interaction Effect: additive CNS effects
- 2) Summary: Avoid concurrent use of [carbinoxamine](#) and CNS depressants, including alcohol, tranquilizers, or sedatives, as this may cause additive CNS effects[25][26]. Counsel patients on the risk of additive CNS cognitive and motor effects if coadministration of [carbinoxamine](#) and a CNS depressant is required.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [carbinoxamine](#) with CNS depressants, including alcohol, tranquilizers, or sedatives, may have additive effects and is therefore not recommended[25][26]. Counsel patients on the risk of additive CNS cognitive and motor effects if coadministration of [carbinoxamine](#) and a CNS depressant is required.
- 7) Probable Mechanism: additive effects on the CNS

3.5.1.G] Codeine

- 1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2) Summary: The concomitant use of [codeine](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation. Avoid concomitant use of [codeine cough](#) medications with CNS depressants[28].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Reserve concomitant use of [codeine](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation. Avoid concomitant use of [codeine cough](#) medications with CNS depressants[28].
- 7) Probable Mechanism: additive CNS depression

3.5.1.H] Dihydrocodeine

- 1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2) Summary: The concomitant use of [dihydrocodeine](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation. Avoid concomitant use of [dihydrocodeine cough](#) medications with CNS depressants[28].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Reserve concomitant use of [dihydrocodeine](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring

for [respiratory depression](#) and sedation. Avoid concomitant use of [dihydrocodeine cough](#) medications with CNS depressants[28].

7) Probable Mechanism: additive CNS depression

3.5.1.I] [Donepezil](#)

1) Interaction Effect: increased [ramelteon](#) exposure

2) Summary: Concomitant use of [donepezil](#) and [ramelteon](#) increased [ramelteon](#) exposure. When a single 8-mg dose of [ramelteon](#) was administered to patients who had already been receiving [donepezil](#) 10 mg once daily for 26 days, there were mean increases in [ramelteon](#) AUC and Cmax of approximately 100% and 87%, respectively, compared with [donepezil](#) therapy alone; there was no change in M-II metabolite exposure. Therefore, patients should be closely monitored when [donepezil](#) and [ramelteon](#) are coadministered[4].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Concomitant use of [donepezil](#) and [ramelteon](#) resulted in increased [ramelteon](#) Cmax and AUC. Therefore, closely monitor the patient when [donepezil](#) and [ramelteon](#) are coadministered[4].

7) Probable Mechanism: unknown

3.5.1.J] [Doxepin](#)

1) Interaction Effect: increased [ramelteon](#) exposure

2) Summary: Concomitant use of [doxepin](#) and [ramelteon](#) increased [ramelteon](#) exposure. When a single 8-mg dose of [ramelteon](#) was administered to patients who had already been receiving [doxepin](#) 10 mg once daily for 23 days, there were mean increases in [ramelteon](#) AUC and Cmax of approximately 66% and 69%, respectively, compared with [doxepin](#) therapy alone; there was no change in M-II exposure. Therefore, patients should be closely monitored when [doxepin](#) and [ramelteon](#) are coadministered[4].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Concomitant use of [doxepin](#) and [ramelteon](#) resulted in increased [ramelteon](#) Cmax and AUC. Therefore, closely monitor the patient when [doxepin](#) and [ramelteon](#) are coadministered[4].

7) Probable Mechanism: unknown

3.5.1.K] [Doxylamine](#)

1) Interaction Effect: increased risk of CNS depression

2) Summary: Coadministration of [doxylamine](#) and a CNS depressant is not recommended due to the potential for additive CNS depression[17][18]. If concomitant use is required, consider monitoring and dose reduction of one or both agents.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [doxylamine](#) and a CNS depressant is not recommended due to the potential for additive CNS depression[17][18]. If concomitant use is required, consider monitoring and dose reduction of one or both agents.

7) Probable Mechanism: additive CNS depression

3.5.1.L] Fentanyl

- 1) Interaction Effect: increased risk of CNS depression
- 2) Summary: Coadministration of [fentanyl](#), a CNS depressant, with other CNS depressants may cause additive CNS depression including [respiratory depression](#), hypotension, and profound sedation, which could potentially lead to coma or death[34]. Severe hypotension has been reported with coadministration of [fentanyl](#) and [midazolam](#) in neonates, including those maintained on an infusion of either drug who subsequently received rapid injections of either [fentanyl](#) or [midazolam](#) [35]. Due to the risk of additive CNS effects, use caution, monitor patients closely, and reduce the dose of one or both when these agents are administered concomitantly [34].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [fentanyl](#), which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Due to the added CNS depressant effects, exercise caution if coadministration of [fentanyl](#) and another CNS depressant is required. Carefully monitor patients receiving concomitant [fentanyl](#) and other CNS depressants and adjust dosage of one or both agents[34].
- 7) Probable Mechanism: additive CNS depression

3.5.1.M] Flibanserin

- 1) Interaction Effect: additive CNS depression
- 2) Summary: The concomitant use of flibanserin with CNS depressants may increase the risk of CNS depression (eg, somnolence and sedation) compared with the use of flibanserin alone. Advise the patient of the risks of CNS depressant use while using flibanserin[23].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of flibanserin with CNS depressants may increase the risk of CNS depression (eg, somnolence and sedation) compared with the use of flibanserin alone. Advise the patient of the risks of CNS depressant use while using flibanserin[23].
- 7) Probable Mechanism: additive CNS depression

3.5.1.N] Fluconazole

- 1) Interaction Effect: increased exposure to [ramelteon](#) with increased risk of side effects
- 2) Summary: [Fluconazole](#), a potent CYP2C9 and less potent CYP3A4 inhibitor, may increase [ramelteon](#) plasma concentrations when used concurrently. When coadministered with [fluconazole](#), after a single dose of [ramelteon](#) 16 mg, the AUC and Cmax of [ramelteon](#) increased approximately 150%, compared to [ramelteon](#) alone. Similar results were observed with the M-II metabolite pharmacokinetic parameters. Use caution with the concomitant use of [ramelteon](#) and potent CYP inhibitors such as [fluconazole](#)[1].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Caution is warranted with the concurrent use of [ramelteon](#) and [fluconazole](#) due to [fluconazole](#) inhibition of [ramelteon](#) metabolism. If used concomitantly, monitor for signs and symptoms of [ramelteon](#) toxicity including somnolence, dizziness, fatigue, nausea, headache and insomnia.
- 7) Probable Mechanism: [fluconazole](#) inhibition of CYP2C9 and CYP3A4-mediated [ramelteon](#) metabolism

3.5.1.O] Fluvoxamine

- 1) Interaction Effect: increased [ramelteon](#) plasma concentrations with increased risk of side effects
- 2) Summary: Concurrent administration of [fluvoxamine](#) and [ramelteon](#) is contraindicated due to significantly increased [ramelteon](#) plasma concentrations with concurrent [fluvoxamine](#) use[30][5].
- 3) Severity: contraindicated
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Concurrent administration of [fluvoxamine](#) and [ramelteon](#) is contraindicated[30][5].
- 7) Probable Mechanism: inhibition of CYP1A2-mediated [ramelteon](#) metabolism by [fluvoxamine](#)
- 8) Literature Reports

a) [Fluvoxamine](#), a strong CYP1A2 inhibitor, significantly increases [ramelteon](#) plasma concentrations when used concurrently. When a single dose of [ramelteon](#) 16 mg was coadministered to subjects who received [fluvoxamine](#) 100 mg twice daily for 3 days prior, the [ramelteon](#) AUC and Cmax increased approximately 190-fold and 70-fold, respectively [30][5].

3.5.1.P] Fospropofol

- 1) Interaction Effect: additive cardiorespiratory effects
- 2) Summary: Concomitant use of fospropofol and [ramelteon](#) may result in additive cardiorespiratory effects due to the sedative action of both drugs[29]. Monitoring the patient for adverse effects may be warranted and possible dose adjustments may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Consider monitoring the patient for cardiorespiratory depression when fospropofol and [ramelteon](#) are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression

3.5.1.Q] Hydrocodone

- 1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2) Summary: Use caution with the concomitant use of [hydrocodone](#) and a CNS depressant as this may result in additive CNS effects and increase the risk of [respiratory depression](#), profound sedation, coma, and/or death. If combination therapy is required, reduce the initial [hydrocodone](#) dose by 20% to 30% and consider using a lower dose of the concomitant CNS depressant. Monitor patients for signs of [respiratory depression](#), sedation, or hypotension[38]. Avoid concomitant use of [hydrocodone cough](#) medications with CNS depressants [28].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [hydrocodone](#) and a CNS depressant may result in additive CNS effects and increase the risk of [respiratory depression](#), profound sedation, coma, and/or death. If combination therapy is required, reduce the initial [hydrocodone](#) dose by 20% to 30% and use a lower dose of the concomitant CNS depressant. Monitor patients for signs of [respiratory depression](#),

sedation, or hypotension[38]. Avoid concomitant use of [hydrocodone cough](#) medications with CNS depressants [28].

7J) Probable Mechanism: additive CNS depression

3.5.1.RJ [Hydromorphone](#)

1J) Interaction Effect: an increase in CNS or [respiratory depression](#)

2J) Summary: The concomitant use of [HYDROmorphone](#) and other CNS depressants, such as sedatives and hypnotics, may result in additive CNS depressant effects, including [respiratory depression](#), hypotension, profound sedation, and coma. When administering [HYDROmorphone](#) and a sedative or hypnotic together, dose reduction of one or both of the medications should be considered[41].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [HYDROmorphone](#) and other CNS depressants, such as sedatives or hypnotics, may result in [respiratory depression](#), hypotension, profound sedation, and coma. When concomitant use is required, dose reduction of one or both medications should be considered[41].

7J) Probable Mechanism: additive CNS depression

3.5.1.SJ [Ketoconazole](#)

1J) Interaction Effect: increased exposure to [ramelteon](#) with increased risk of side effects

2J) Summary: [Ketoconazole](#), a potent CYP3A4 inhibitor, may increase [ramelteon](#) plasma concentrations when used concurrently. Subjects of a study were administered [ketoconazole](#) 200 mg twice daily for four days, then administered a single dose of [ramelteon](#) 16 mg. The [ramelteon](#) AUC and Cmax increased 84% and 36%, respectively, compared to [ramelteon](#) alone. Similar results were observed with the M-II metabolite pharmacokinetic parameters. Use caution with the concomitant use of [ramelteon](#) and potent CYP3A4 inhibitors such as [ketoconazole](#)[1].

3J) Severity: moderate

4J) Onset: delayed

5J) Substantiation: probable

6J) Clinical Management: Caution is warranted with the concurrent use of [ramelteon](#) and [ketoconazole](#) due to [ketoconazole](#) inhibition of [ramelteon](#) metabolism. If used concomitantly, monitor for signs and symptoms of [ramelteon](#) toxicity including somnolence, dizziness, fatigue, nausea, headache and insomnia.

7J) Probable Mechanism: [ketoconazole](#) inhibition of CYP3A4-mediated [ramelteon](#) metabolism

3.5.1.TJ [Loxapine](#)

1J) Interaction Effect: potentiation of impaired cognitive function and motor skills and an increased risk of [respiratory depression](#), hypotension, oversedation, and syncope

2J) Summary: Concomitant use of [loxapine](#), a CNS depressant, and other CNS depressants may potentiate impaired cognitive function and motor skills and increase the risk of [respiratory depression](#), hypotension, oversedation, and syncope. If [loxapine](#) and other CNS depressants are used concurrently, consider a dose reduction of the CNS depressant[36] and use with caution [37].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [loxapine](#) and other CNS depressants may potentiate impaired cognitive function and motor skills and increase the risk of [respiratory depression](#), hypotension, oversedation, and syncope. If [loxapine](#) and CNS depressants are used concurrently, consider a dose reduction of the CNS depressant[36] and use with caution [37].

7J) Probable Mechanism: additive CNS depression

3.5.1.U] Meclizine

1J) Interaction Effect: an increase in CNS or [respiratory depression](#)

2J) Summary: Concomitant use of [meclizine](#) and CNS depressants, including alcohol, tranquilizers, or sedatives may potentiate CNS depression cognitive and motor effects. Avoid concurrent use of alcohol while taking [meclizine](#)[31][32][33] and counsel patients on the risk of additive CNS cognitive and motor effects if coadministration of [meclizine](#) and a CNS depressant is required.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [meclizine](#) with CNS depressants, including alcohol, tranquilizers, or sedatives, may potentiate CNS depression. Avoid concurrent use of alcohol with [meclizine](#)[31][32][33] and counsel patients on the risk of additive CNS cognitive and motor effects if coadministration of [meclizine](#) and a CNS depressant is required.

7J) Probable Mechanism: additive CNS depression

3.5.1.V] Meperidine

1J) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)

2J) Summary: The concomitant use of [meperidine](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[28].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Reserve concomitant use of [meperidine](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[28].

7J) Probable Mechanism: additive CNS depression

3.5.1.W] Methadone

1J) Interaction Effect: increased risk of CNS depression

2J) Summary: Concomitant use of [methadone](#), which is a CNS depressant, with another CNS depressant may result in additive effects including [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. If [methadone](#) is coadministered with a CNS depressant, initiate the dose of [methadone](#) at 2.5 mg every 12 hours, and consider lowering the dose of the concomitant CNS depressant. Monitor for signs and symptoms of [respiratory depression](#), hypotension, and sedation[13].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [methadone](#), which is a CNS depressant, with another CNS depressant may result in additive effects including [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of

tolerance to CNS depressants. If [methadone](#) is coadministered with a CNS depressant, initiate the dose of [methadone](#) at 2.5 mg every 12 hours, and consider lowering the dose of the concomitant CNS depressant. Monitor for signs and symptoms of [respiratory depression](#), hypotension, and sedation[13].

7J) Probable Mechanism: additive CNS depression effects

3.5.1.X] [Morphine](#)

1J) Interaction Effect: increased risk of CNS depression

2J) Summary: Concomitant use of [morphine](#), which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. Carefully monitor patients receiving concomitant [morphine](#) and other CNS depressants for hypotension, [respiratory depression](#) and sedation, initiate [morphine](#) at the lowest dose (ie, 30 mg every 24 hours or 15 mg every 12 hours), and reduce the dose of 1 or both drugs[19][20][21].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [morphine](#), which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. Carefully monitor patients for hypotension, [respiratory depression](#) or sedation, initiate [morphine](#) at the lowest dose (ie, 30 mg every 24 hours or 15 mg every 12 hours), and reduce the dose of 1 or both drugs[19][20][21].

7J) Probable Mechanism: additive CNS depression effects

3.5.1.Y] [Morphine Sulfate Liposome](#)

1J) Interaction Effect: increased risk of CNS depression

2J) Summary: Concomitant use of [morphine](#), which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. Carefully monitor patients receiving concomitant [morphine](#) and other CNS depressants for hypotension, [respiratory depression](#) and sedation, initiate [morphine](#) at the lowest dose (ie, 30 mg every 24 hours or 15 mg every 12 hours), and reduce the dose of 1 or both drugs[19][20][21].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [morphine](#), which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. Carefully monitor patients for hypotension, [respiratory depression](#) or sedation, initiate [morphine](#) at the lowest dose (ie, 30 mg every 24 hours or 15 mg every 12 hours), and reduce the dose of 1 or both drugs[19][20][21].

7J) Probable Mechanism: additive CNS depression effects

3.5.1.Z] [Oxycodone](#)

1J) Interaction Effect: an increase in CNS or [respiratory depression](#)

2J) Summary: Concomitant use of [oxycodone](#) with other CNS depressants, such as sedatives or hypnotics, may result in [respiratory depression](#), hypotension, profound sedation, coma or death. If combined use is necessary, monitor the patient and reduce the dose of one or both medications. Initiate [oxycodone](#)

controlled-release formulations at one-third to one-half of the usual dosage[10][11] and initiate extended-release [oxycodone](#) hydrochloride/[acetaminophen](#) at one-half the usual dose [12].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [oxycodone](#) with other CNS depressants, such as sedatives or hypnotics, may result in [respiratory depression](#), hypotension, profound sedation, coma or death. If combined use is necessary, monitor the patient and reduce the dose of one or both medications. Initiate [oxycodone](#) controlled-release formulations at one-third to one-half of the usual dosage[10][11] and initiate extended-release [oxycodone](#) hydrochloride/[acetaminophen](#) at one-half the usual dose [12].

7) Probable Mechanism: additive CNS depression

3.5.1.AA] [Oxymorphone](#)

1) Interaction Effect: increased risk of [respiratory depression](#), profound sedation, coma, and death

2) Summary: Coadministration of [oxymorphone](#) and a CNS depressant may result in additive respiratory and CNS depressant effects and an increased risk of [respiratory depression](#), profound sedation, coma, and death. If concurrent use is clinically necessary, initiate [oxymorphone](#) at a dose of 5 mg every 12 hours. Monitor patients for sedation, hypotension, and [respiratory depression](#), and consider reducing the CNS depressant dose[16].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [oxymorphone](#) and a CNS depressant may result in additive respiratory and CNS depressant effects. If concurrent use is clinically necessary, initiate [oxymorphone](#) at a dose of 5 mg every 12 hours. Monitor patients for sedation and [respiratory depression](#), sedation, and hypotension, and consider reducing the CNS depressant dose[16].

7) Probable Mechanism: additive respiratory and CNS depressant effects

3.5.1.AB] [Pentazocine](#)

1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)

2) Summary: The concomitant use of [pentazocine](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[28].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Reserve concomitant use of [pentazocine](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[28].

7) Probable Mechanism: additive CNS depression

3.5.1.AC] [Periciazine](#)

1) Interaction Effect: risk of enhanced CNS depression

2) Summary: Concomitant use of periciazine with other phenothiazine derivatives or CNS depressants may enhance the CNS depressive effects of both agents. If coadministered, reduce the dose of the phenothiazine derivative or CNS depressant by at least 50% while periciazine is being gradually initiated[8] [9].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of periciazine with other phenothiazine derivatives or CNS depressants may enhance the CNS depressive effects of both agents. If coadministered, reduce the dose of the phenothiazine derivative or CNS depressant by at least 50% while periciazine is being gradually initiated[8][9].

7) Probable Mechanism: additive CNS depression

3.5.1.AD] Propofol

1) Interaction Effect: additive cardiorespiratory effects

2) Summary: Concomitant use of fospropofol and [ramelteon](#) may result in additive cardiorespiratory effects due to the sedative action of both drugs[29]. Monitoring the patient for adverse effects may be warranted and possible dose adjustments may be necessary.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Consider monitoring the patient for cardiorespiratory depression when fospropofol and [ramelteon](#) are used in combination. A reduction in dose of one or both drugs may be necessary.

7) Probable Mechanism: CNS depression

3.5.1.AE] Remifentanyl

1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)

2) Summary: The concomitant use of [remifentanyl](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[28].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Reserve concomitant use of [remifentanyl](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[28].

7) Probable Mechanism: additive CNS depression

3.5.1.AF] Rifampin

1) Interaction Effect: decreased bioavailability of [ramelteon](#)

2) Summary: [Rifampin](#) is a potent inducer of cytochrome P450 metabolism and may significantly reduce [ramelteon](#) bioavailability when used concurrently. When subjects were administered [rifampin](#) 600 mg once daily for 11 days and a single dose of [ramelteon](#) 32 mg, the total exposure (both AUC and Cmax)

to [ramelteon](#) and its metabolite M-II decreased a mean of approximately 80% (range 40% to 90%). [Ramelteon](#) efficacy may be significantly reduced when used concurrently with potent CYP1A2, CYP2C and CYP3A4 inducers[1].

3) Severity: minor

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Concomitant use of [ramelteon](#) during [rifampin](#) therapy may result in decreased efficacy of [ramelteon](#) due to [rifampin](#) induction of [ramelteon](#) metabolism via CYP2C and CYP3A4 isoenzymes. If used concomitantly, monitor patients for lack of [ramelteon](#) efficacy.

7) Probable Mechanism: [rifampin](#) induced cytochrome P450 metabolism of [ramelteon](#)

3.5.1.AG] [Sodium Oxybate](#)

1) Interaction Effect: increased CNS depression

2) Summary: Concomitant use of [sodium oxybate](#) and certain sedative hypnotics is contraindicated because of the risk for additive CNS depression[22].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [sodium oxybate](#) and certain sedative hypnotics is contraindicated[22].

7) Probable Mechanism: additive CNS depression

3.5.1.AH] [Sufentanil](#)

1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)

2) Summary: The concomitant use of [sufentanil](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[28].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Reserve concomitant use of [sufentanil](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[28].

7) Probable Mechanism: additive CNS depression

3.5.1.AI] [Suvorexant](#)

1) Interaction Effect: additive sedative effects

2) Summary: Avoid concomitant use of suvorexant and this drug as potentiation of sedative effects may occur[27].

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of suvorexant and this drug is not recommended as potentiation of sedative effects may occur[27].

7J) Probable Mechanism: additive CNS depression

3.5.1.AJ] Tapentadol

1J) Interaction Effect: an increase in CNS and [respiratory depression](#)

2J) Summary: The concomitant use of tapentadol with other CNS depressants, including sedatives, may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[28].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Reserve concomitant use of tapentadol with other CNS depressants, including sedatives, to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[28].

7J) Probable Mechanism: additive CNS depression

3.5.1.AK] Tramadol

1J) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)

2J) Summary: The concomitant use of [tramadol](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[28].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Reserve concomitant use of [tramadol](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[28].

7J) Probable Mechanism: additive CNS depression

3.5.1.AL] Zolpidem

1J) Interaction Effect: an increase in CNS depressant effects

2J) Summary: The concomitant use of [zolpidem](#) with drugs that have sedative or hypnotic properties at bedtime or in the middle of the night is not recommended. Any drug with CNS-depressant effects could potentially enhance the CNS-depressant effects of [zolpidem](#). Additionally the risk of complex behaviors such as sleep-driving (driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) is increased with concomitant use. Dosage adjustments of [zolpidem](#) and other concomitant CNS-depressants may be necessary when coadministered because of the potentially additive effects[40].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [zolpidem](#) with drugs that have sedative or hypnotic properties at bedtime or in the middle of the night is not recommended. Any drug with CNS-depressant

effects could potentially enhance the CNS-depressant effects of [zolpidem](#). Additionally the risk of complex behaviors such as sleep-driving (driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) is increased with concomitant use. Dosage adjustments of [zolpidem](#) and other concomitant CNS-depressants may be necessary when coadministered because of the potentially additive effects[40].

7J) Probable Mechanism: additive effects

3.5.2] Drug-Food Combinations

3.5.2.A] Ethanol

1J) Interaction Effect: an increased risk of CNS effects

2J) Summary: Concomitant use of [ramelteon](#) and ethanol may increase impairment of mental or motor skills. Patients should be cautioned against alcohol consumption while taking [ramelteon](#)[5].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Patients receiving [ramelteon](#) should be advised to avoid the use of alcohol[5].

7J) Probable Mechanism: additive CNS depression

4.0] Clinical Applications

[Monitoring Parameters](#)

[Patient Instructions](#)

[Place In Therapy](#)

[Mechanism of Action / Pharmacology](#)

[Therapeutic Uses](#)

4.1] Monitoring Parameters

AJ) Therapeutic

1J) Physical Findings

aJ) Improvement in the quality, onset, and duration of sleep.

BJ) Toxic

1J) Laboratory Parameters

aJ) Prolactin and [testosterone](#) levels should be assessed in patients who develop unexplained [amenorrhea](#), [galactorrhea](#), decreased libido, or fertility problems [1].

4.2] Patient Instructions

AJ) [Ramelteon](#) (By mouth)

[Ramelteon](#)

Treats insomnia (trouble falling asleep).

When This Medicine Should Not Be Used:

You should not use this medicine if you have had an [allergic reaction](#) to [ramelteon](#), if you are also using [fluvoxamine](#) ([Luvox®](#)), or if you have severe liver disease.

How to Use This Medicine:

Tablet

Your doctor will tell you how much medicine to use. Do not use more than directed.

It is best to take this medicine no more than 30 minutes before you go to bed. After you take the medicine, do not engage in any other activity except getting ready for bed.

Do not take this medicine with or right after a high-fat meal.

Swallow the tablet whole. Do not break, crush, or chew it.

This medicine should come with a Medication Guide. Ask your pharmacist for a copy if you do not have one.

If a Dose is Missed:

If you forget to take your medicine at bedtime and you cannot sleep, take it as soon as you remember the missed dose. If it is almost time for you to awaken, skip the missed dose and wait until the next night to take your medicine. Do not take extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any outdated medicine or medicine no longer needed.

Keep all medicine out of the reach of children. Never share your medicine with anyone.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Make sure your doctor knows if you are also using [donepezil \(Aricept®\)](#), [doxepin \(Sinequan®\)](#), [fluconazole \(Diflucan®\)](#), [ketoconazole \(Nizoral®\)](#), or [rifampin \(Rifadin®, Rimactane®\)](#).

Tell your doctor if you use anything else that makes you sleepy. Some examples are allergy medicine, narcotic pain medicine, and alcohol.

Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant or breastfeeding, or if you have liver disease, [sleep apnea](#), or a breathing disorder such as COPD ([chronic obstructive pulmonary disease](#)). Tell your doctor if you have a history of depression or mental illness, or if you have ever had thoughts of hurting yourself.

This medicine may cause a serious type of [allergic reaction](#) called [anaphylaxis](#). [Anaphylaxis](#) can be life-threatening and requires immediate medical attention. Stop taking this medicine and call your doctor right away if you have itching, hives, trouble breathing, or any swelling of your hands, face, mouth, or tongue when you take this medicine.

You might have mood or behavior changes with this medicine, such as feeling sad or hopeless, or getting upset easily. You could feel nervous or hostile. Some people become violent and want to hurt themselves or others. You might have too much energy, or see or hear unusual things. Call your doctor right away if you have any strange feelings, thoughts, or behaviors.

This medicine may cause sleep-related behaviors such as driving a car (sleep-driving), walking (sleep-walking), having sex, making phone calls, or preparing and eating food while you are asleep or not fully awake. If these unwanted effects occur, tell your doctor right away.

This medicine may cause some hormone changes. Talk to your doctor if you have any of these symptoms: a decreased interest in sex; problems getting pregnant; an irregular or change in menstrual periods; or discharge from the nipples (in women).

This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert.

Call your doctor if your symptoms do not improve or if they get worse.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
 Changes in behavior or thoughts of hurting yourself or others.
 Changes in menstrual periods.
 Discharge from the nipples in women.
 Feeling depressed, anxious, or agitated.
 Loss of interest in sex.
 Seeing, hearing, or feeling things that are not there.
 Unusual thoughts or behavior.
 Unusual tiredness or weakness.
 Worsening of insomnia (trouble sleeping).

If you notice these less serious side effects, talk with your doctor:

Dizziness or drowsiness.
 Headaches.
 Nausea.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3] Place In Therapy

A) **Ramelteon** is a **melatonin** receptor agonist developed for the treatment of insomnia distinguished by difficulty with onset of sleep. The drug works in a manner similar to endogenous **melatonin** in helping to support the circadian rhythm which underlies the normal sleep cycle. **Ramelteon** offers several advantages over other hypnotics in that it is not a controlled substance, which may be more appealing to prescribers; and it does not appear to produce residual effects, rebound insomnia, or symptoms of withdrawal with prolonged use. **Ramelteon** therapy may also be prescribed for long-term use; this is an advantage over other hypnotics, such as **zolpidem**, in which therapy should be limited to 7 to 10 days. Additional clinical studies are required to clearly establish the safety profile and place in therapy for **ramelteon** [1].

4.4] Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) **Ramelteon** is a **melatonin** receptor agonist which has a high affinity for **melatonin** MT-1 and MT-2 receptors and selectivity over the MT-3 receptor. The sleep-promoting properties of **ramelteon** are believed to be due its activity at the MT-1 and MT-2 receptors because these receptors, when acted upon by endogenous **melatonin**, are thought to be involved in the maintenance of the circadian rhythm which supports the normal sleep-wake cycle. **Ramelteon** has no discernible affinity for the **GABA** receptor complex or for receptors that bind cytokines, neuropeptides, **dopamine**, serotonin, noradrenaline, **acetylcholine**, and opiates. In addition, it does not impede the activity of numerous selected enzymes in a standard panel [1].

4.5] Therapeutic Uses

4.5.1] FDA Uses

4.5.1.A] Insomnia

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; **Pediatric, no**

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

2) Summary:

[Ramelteon](#) is effective for the treatment of chronic [2][1] and transient insomnia [1] characterized by difficulty with sleep onset

Decreases mean latency to persistent sleep [2][1]

3) Adult:

a) In a multicenter, double-blind, randomized, placebo-controlled, five-period crossover study, [ramelteon](#) was effective in reducing the latency to persistent sleep (LPS) and increasing total sleep time (TST) among patients with chronic [primary insomnia](#). Patients (n=107; mean age, 37.7 years) diagnosed with [primary insomnia](#) for at least 3 months were randomized to one of five dosing sequences consisting of [ramelteon](#) 4 milligrams (mg), 8 mg, 16 mg, 32 mg, and placebo administered 30 minutes prior to habitual bedtimes. Each patient served as his own control and underwent five 2-day treatment periods. There was a 5- to 12-day washout period between treatments. At baseline, the mean LPS for all participants was 75.2 minutes, the mean TST was 347.9 minutes, and the mean wake time after sleep onset (WASO) was 63 minutes. Relative to placebo, [ramelteon](#) 4 mg, 8 mg, 16 mg, and 32 mg reduced the mean LPS (primary efficacy outcome) by 13.7, 13.4, 13.7, and 14.8 minutes (p less than 0.001), and increased the mean TST by 10.7, 12.6, 10.9 and 17.9 minutes (p less than 0.05) on polysomnographic (PSG) recording. However, the WASO did not differ among the active treatment and placebo groups. Patients with a higher LPS and lower TST at baseline experienced a greater margin of LPS and TST improvement from [ramelteon](#) relative to patients with less severe insomnia. The next-day performance and alertness, as well as ability to concentrate, were not affected and did not differ between the active treatment and placebo groups. The most frequently-reported adverse effects (incidence greater than 2%) were headache, somnolence, and pharyngolaryngeal pain, and the incidences were not dose-independent [2].

b) [Ramelteon](#) decreased average latency to persistent sleep in adult patients (age 18 to 64 years) with [chronic insomnia](#) in a randomized, double-blind, placebo-controlled clinical trial. Patients received oral [ramelteon](#) (8 milligrams (mg) or 16 mg) or placebo once nightly for 35 nights. Latency to persistent sleep was measured using [polysomnography](#) on the first 2 nights of treatment weeks 1, 3, and 5. [Ramelteon](#), at either the 8 mg or 16 mg dose, reduced the average latency to persistent sleep at all time points. After completion of treatment, patient-reported withdrawal symptoms were assessed using the Tyrer Benzodiazepine Withdrawal Symptom Questionnaire; these scores did not differ between the [ramelteon](#) and placebo groups. In addition, no significant rebound insomnia or residual pharmacological effects were reported during the posttreatment period [1].

c) A randomized, double-blind, clinical trial demonstrated that [ramelteon](#) decreased average latency to persistent sleep in elderly patients (age 65 years and older) with [chronic insomnia](#). Patients received oral [ramelteon](#) (4 milligrams (mg) or 8 mg) or placebo in this three-period crossover trial. Latency to persistent sleep was measured using [polysomnography](#) in a sleep laboratory for 2 consecutive nights in each of the study periods. [Ramelteon](#), at either the 4 mg or 8

mg dose, decreased the average latency to persistent sleep compared to placebo. No residual effect of ramelteon on the day following treatment was reported [1].

d) Using sleep diaries, a subjective measure of effectiveness, ramelteon effectively reduced patient-reported sleep latency in elderly patients (age 65 years and older), but not in younger adult patients (age 18 to 64 years). For these two randomized, double-blind, placebo-controlled trials, patients received oral ramelteon (4 milligrams (mg) or 8 mg in elderly patients, 8 mg or 16 mg in younger adults) or placebo once nightly for 35 nights. For the ramelteon groups, patient-reported sleep latency improved in the elderly patients, but did not differ from placebo in the younger adult patients. After completion of treatment, patient-reported withdrawal symptoms were assessed using the Tyrer Benzodiazepine Withdrawal Symptom Questionnaire; these scores did not differ between the ramelteon and placebo groups. In addition, no significant rebound insomnia or residual pharmacological effects were reported during the posttreatment period [1].

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