Brand Names

Sonata

Indication Specific Dosing

For the treatment of insomnia

Oral dosage

Adults

10 mg PO at bedtime; a 5 mg initial dosage may be sufficient for certain individuals (debilitated, lower weight, etc.). Use lowest effective dose. Max: 20 mg/day PO at bedtime may be considered for the occasional patient who does not benefit from a lower dose. Zaleplon may be taken either at bedtime or after an attempt to fall asleep without medication, provided at least 4 or more hours of sleep time remain.

Geriatric Adults

5 mg PO at bedtime is the usual and recommended geriatric dose. Use lowest effective dose. Max: 10 mg/day; higher doses are not recommended. Zaleplon may be taken either at bedtime or after an attempt to fall asleep without medication, provided at least 4 or more hours of sleep time remain.

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. While zaleplon belongs to the nonbenzodiazepine,

benzodiazepine receptor agonist (NBRA) class, the chemical structures of the agents in this class are distinct. Cross-sensitivity to one NBRA does not imply cross-sensitivity will occur to another agent in the class.

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 zaleplon. A variety of abnormal thinking and behavioral changes have been reported to occur in association with the use of sedative/hypnotics, including zaleplon. Some of these changes included decreased inhibition (e.g., aggressiveness and extroversion that seemed out of character), bizarre behavior, agitation and depersonalization. Visual and auditory hallucinations have been reported. Amnesia and other neuropsychiatric symptoms may occur unpredictably. Some adverse effects of zaleplon appear to be dose-related; use of the lowest effective dose may mitigate these effects. Because intentional overdose is more common in people with pre-existing depression, zaleplon should be prescribed in the smallest quantity consistent with good patient management to reduce the risk of overdose.

activities requiring coordination and concentration, driving or operating machinery, drug-induced complex sleep-related behaviors

Zaleplon and other non-benzodiazepine receptor agonists (NBRAs) are contraindicated in people with a history of drug-induced complex sleep-related behaviors. Sedative-hypnotics, especially NBRAs like zaleplon, can cause complex sleep-related behaviors (e.g., sleep-driving, eating, sexual activity, or making phone calls) with no memory of these events. These effects can occur with or without concomitant use of alcohol or other CNS depressants. Rarely, serious injuries or death have occurred. Patients should discontinue zaleplon immediately and contact their healthcare provider if such episodes occur. Care teams and patients are encouraged to report adverse events to the FDA MedWatch Safety Information and Adverse Event Reporting Program. Zaleplon has rapid onset and CNS depressant effects, and should be taken immediately before bed, with at least 7 to 8 hours remaining for sleep. Patients should avoid driving or operating machinery, or engaging in activities requiring coordination and concentration the day after use. The risk for next-day impairment is increased if zaleplon is taken without adherence to recommended hours for sleep or at doses higher than recommended. Anterograde amnesia may also occur and may be increased at higher doses. Use with alcohol or other CNS depressants increases the risk of impairment and adverse effects,

and patients should avoid alcoholic beverages. Consider lower doses of zaleplon when other CNS depressants are prescribed concurrently.

respiratory insufficiency

Sedative-hypnotics have the potential to suppress respiratory drive, and caution is advised when using zaleplon in people with compromised respiratory function (respiratory insufficiency). Although studies did not reveal respiratory depressant effects at hypnotic doses of zaleplon in healthy individuals, caution is advised when considering the use of zaleplon in people with respiratory insufficiency, such as chronic obstructive pulmonary disease (COPD), sleep apnea, or individuals with concomitant opioid use.

substance abuse disorder

Zaleplon should be used with caution in people with a history of a substance abuse disorder. People with a history of addiction or abuse of drugs or alcohol are at increased risk for misuse, abuse, or addiction and should be monitored carefully when receiving zaleplon or any hypnotic. Additionally, people taking zaleplon are at risk of physical and/or psychological dependence and this risk increases with dose and duration of treatment. People with dependence on zaleplon may experience withdrawal signs and symptoms following abrupt discontinuation. To minimize these risks, zaleplon should be used at the lowest effective dose for the shortest duration of treatment possible, and reassess the patient periodically before continuing treatment for an extended period of time.

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

Zaleplon dosage reductions are recommended for people with mild to moderate hepatic impairment (Child-Pugh class A and Child-Pugh class B) due to reduced clearance in this population. Zaleplon is not recommended for use in people with severe hepatic impairment (Child-Pugh class C) or hepatic failure, as maximal concentrations and zaleplon exposure are significantly increased.

geriatric

Debilitated and geriatric adults may be more sensitive to the effects of zaleplon, including impairment of cognitive and motor function. A lower initial dosage is recommended for older adults. Because zaleplon can cause drowsiness and a decreased level of consciousness, the geriatric adult is particularly at a higher risk of falls, with the potential for subsequent severe injuries. The Beers Criteria state that zaleplon and other nonbenzodiazepine, benzodiazepine-receptor agonists (NBRAs), are potentially

inappropriate for use in geriatric adults. NBRAs may cause adverse effects similar to benzodiazepines, including falls, fractures, and delirium, which are particularly concerning in older adults. Their use is associated with increased emergency department visits, hospitalizations, and motor vehicle crashes, with minimal benefit in improving sleep latency and duration. Avoid NBRA use in individuals with dementia or cognitive impairment, or those at high risk of delirium. Additionally, avoid NBRAs in geriatric adults with a history of falls or fractures unless no safer alternatives are available. If an NBRA must be prescribed, consider reducing other CNS-active medications and employing strategies to mitigate fall risk. The U.S. Omnibus Budget Reconciliation Act (OBRA) regulates the use of sedative/hypnotic agents for residents of long-term care facilities (LTCFs); when a drug is being used to induce sleep or treat a sleep disorder, the facility should attempt periodic tapering of the medication as stated in the OBRA guidelines or provide documentation of continued medical necessity.

pregnancy

The use of zaleplon during pregnancy is not recommended due to a lack of data; in preclinical animal studies, high doses were associated with adverse effects in rats, including decreased pup growth and delayed development. Hypnotic benzodiazepine receptor agonists (HBRA) like zaleplon have been shown to cross the human placenta and rapidly clear the fetal circulation. In a small study examining data from the Swedish Medical Birth Registry, the birth outcomes for 32 infants who were exposed to zaleplon in early pregnancy were compared to nonexposed infants. In this study, the use of zaleplon was not associated with an increased risk for congenital malformations. There were 4 cases of intestinal malformations reported in infants exposed to hypnotic benzodiazepine receptor agonists (HBRAs); 2 of these cases were in infants exposed to zopiclone and 2 were exposed to zolpidem. The authors noted the presence of several potential confounders, such as exposure to other medications, smoking status, and maternal age, that may have contributed to these malformations. Published studies of other HBRAs do not indicate an increased risk of congenital malformations at typical doses. However, one study has reported neural tube defects in an infant following high-dose exposure to zolpidem in the first trimester of pregnancy. In a systematic review and meta-analysis developed to assess for risks associated with use of HBRAs in pregnancy, the authors noted that pregnancy exposure to HBRAs was not associated with an increased risk of congenital malformations but was associated with increased risks of preterm birth, low birth weight, and being small for gestational age compared to unexposed infants. Similarly, a population-based cohort study determined that HBRA use in early pregnancy may be associated with an increased risk of infants being born small for gestational age, even after controlling for numerous confounding variables. Additional studies are needed to determine the true risk and incidence of these effects.

neonates and infants exposed to this medication in utero

There is a risk of respiratory depression and sedation in neonates and infants exposed to this medication in utero during the third trimester. Monitor neonates exposed to hypnotic benzodiazepine receptor agonists in utero for signs and symptoms of respiratory depression and sedation at birth, and manage accordingly. Withdrawal symptoms may also be possible during the postnatal period. A limited number of exposed neonatal cases of moderate to severe respiratory depression requiring aspiration, artificial ventilation, or intratracheal intubation have been reported. The majority of neonates recovered within hours to a few weeks after birth once treated. Neonatal flaccidity has also been reported in newborns after maternal sedative-hypnotic use during pregnancy.

breast-feeding

Use zaleplon with caution during breast-feeding. Zaleplon is excreted in human milk, with the highest excreted amount occurring during feeding at approximately 1 hour after drug administration. Since the small amount of the drug from breast milk may result in potentially important concentrations in an infant, FDA-approved labeling recommends that zaleplon not be administered while breast-feeding. However, one small study of 5 lactating individuals indicated infant exposure through breast milk is low; the estimated dose an infant would receive is 1.28 to 1.66 mcg or 0.013% to 0.017% of the maternal 10-mg dose. Peak concentrations occurred in the milk at approximately 1.2 hours after dosing and averaged 14 mcg/mL. While the effects of zaleplon exposure on the breast-feeding infant were not evaluated, the authors noted that zaleplon disappeared from the milk rapidly and zaleplon milk concentrations were less than 5 mcg/mL at 4 hours post-dosing. Some experts consider zaleplon potentially compatible with breast-feeding due to this study. Zolpidem, a similar agent, with similarly low excretion to breast milk, is a potential alternative. If any sedative-hypnotic is used during lactation, it is recommended that the patient avoid breast-feeding at times of peak drug concentrations, and observe the child for sedation, poor feeding, and poor weight gain.

Pregnancy And Lactation

The use of zaleplon during pregnancy is not recommended due to a lack of data; in preclinical animal studies, high doses were associated with adverse effects in rats, including decreased pup growth and delayed development. Hypnotic benzodiazepine receptor agonists (HBRA) like zaleplon have been shown to cross the human placenta and rapidly clear the fetal circulation. In a small study examining data from the Swedish

Medical Birth Registry, the birth outcomes for 32 infants who were exposed to zaleplon in early pregnancy were compared to nonexposed infants. In this study, the use of zaleplon was not associated with an increased risk for congenital malformations. There were 4 cases of intestinal malformations reported in infants exposed to hypnotic benzodiazepine receptor agonists (HBRAs); 2 of these cases were in infants exposed to zopiclone and 2 were exposed to zolpidem. The authors noted the presence of several potential confounders, such as exposure to other medications, smoking status, and maternal age, that may have contributed to these malformations. Published studies of other HBRAs do not indicate an increased risk of congenital malformations at typical doses. However, one study has reported neural tube defects in an infant following high-dose exposure to zolpidem in the first trimester of pregnancy. In a systematic review and meta-analysis developed to assess for risks associated with use of HBRAs in pregnancy, the authors noted that pregnancy exposure to HBRAs was not associated with an increased risk of congenital malformations but was associated with increased risks of preterm birth, low birth weight, and being small for gestational age compared to unexposed infants. Similarly, a population-based cohort study determined that HBRA use in early pregnancy may be associated with an increased risk of infants being born small for gestational age, even after controlling for numerous confounding variables. Additional studies are needed to determine the true risk and incidence of these effects.

Interactions

Acetaminophen; Aspirin, ASA; Caffeine: (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking medications for sleep, such as zaleplon 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 medications for sleep, such as zaleplon 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) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Acetaminophen; Caffeine: (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking medications for sleep, such as zaleplon 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: (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Avoid prescribing opioid cough medications in patients taking zaleplon. Limit the use of opioid pain medications with zaleplon 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. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression. (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking medications for sleep, such as zaleplon 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) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary. (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking medications for sleep, such as zaleplon 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) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Acetaminophen; Chlorpheniramine; Dextromethorphan: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Acetaminophen; Chlorpheniramine; Dextromethorphan; Phenylephrine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Acetaminophen; Chlorpheniramine; Dextromethorphan; Pseudoephedrine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Acetaminophen; Chlorpheniramine; Phenylephrine : (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon

due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Acetaminophen; Codeine: (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Avoid prescribing opioid cough medications in patients taking zaleplon. Limit the use of opioid pain medications with zaleplon 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. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression.
Acetaminophen; Dextromethorphan; Doxylamine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Acetaminophen; diphenhydrAMINE: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Acetaminophen; HYDROcodone: (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Avoid prescribing opioid cough medications in patients taking zaleplon. Limit the use of opioid pain medications with zaleplon 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. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression.
Acetaminophen; oxyCODONE: (Moderate) Concomitant use of oxycodone with zaleplon may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If zaleplon is used concurrently with oxycodone, a reduced dosage of oxycodone and/or zaleplon is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression.
Acetaminophen; Pamabrom; Pyrilamine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose

adjustments may be necessary.
Adagrasib: (Moderate) Monitor for an increase in zaleplon-related adverse reactions, including excessive sedation and confusion, if coadministered with adagrasib. Routine dosage adjustments of zaleplon are not required. Zaleplon is partially metabolized by CYP3A. Adagrasib is a strong CYP3A inhibitor. Coadministration with a single dose of another strong CYP3A inhibitor increased the AUC of zaleplon by 20%.
ALFentanil: (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Limit the use of opioid pain medications with zaleplon 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. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression.
ALPRAZolam: (Major) Monitor for excessive sedation and somnolence during coadministration of zaleplon and benzodiazepines. Concurrent use may result in additive CNS depression. If used together, a reduction in the dose of one or both drugs may be needed.
Amitriptyline: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of tricyclic antidepressants and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary. Coadministration of single doses of a tricyclic antidepressant and zaleplon produced additive effects on decreased alertness and impaired psychomotor performance for 2 to 4 hours after administration.
Amobarbital: (Major) Coadministration of zaleplon and barbiturates may result in additive CNS depression. Caution should be exercised during concomitant use of anxiolytics, sedatives, and hypnotics and any barbiturate. In addition, zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inducers, such as barbiturates, may increase the clearance of zaleplon. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
Amoxapine: (Moderate) CNS depressants should be combined cautiously with amoxapine because they could cause additive depressant effects and possible respiratory depression or hypotension.
Amoxicillin; Clarithromycin; Omeprazole: (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as clarithromycin, may decrease the clearance of zaleplon. Routine dosage adjustments of zaleplon are not required. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
Apalutamide: (Moderate) Monitor for decreased efficacy of zaleplon if coadministration with apalutamide is necessary. Zaleplon is a CYP3A4 substrate and apalutamide is a

strong CYP3A4 inducer. Although CYP3A4 is normally a minor metabolizing enzyme of zaleplon, coadministration with another strong CYP3A4 inducer reduced zaleplon exposure by approximately 80%. Coadministration with apalutamide could lead to ineffectiveness of zaleplon.
Apomorphine: (Moderate) Apomorphine causes significant somnolence. Concomitant administration of apomorphine and CNS depressants could result in additive depressant effects. A reduction in the dose of one or both drugs should be considered to minimize additive sedative effects. In addition, the risk of next-day psychomotor impairment is increased during co-administration of eszopiclone and other CNS depressants, which may decrease the ability to perform tasks requiring full mental alertness such as driving.
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.
ARIPiprazole: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of atypical antipsychotics and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Asenapine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of atypical antipsychotics and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Aspirin, ASA; Butalbital; Caffeine: (Major) Coadministration of zaleplon and barbiturates may result in additive CNS depression. Caution should be exercised during concomitant use of anxiolytics, sedatives, and hypnotics and any barbiturate. In addition, zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inducers, such as barbiturates, may increase the clearance of zaleplon. Dosage adjustments should be made on an individual basis according to efficacy and tolerability. (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking medications for sleep, such as zaleplon 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 medications for sleep, such as zaleplon 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: (Moderate) Additive CNS depressant effects may be seen with combination use of orphenadrine and anxiolytics, sedatives, and hypnotics.

(Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking medications for sleep, such as zaleplon 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: (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Avoid prescribing opioid cough medications in patients taking zaleplon. Limit the use of opioid pain medications with zaleplon 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. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression. (Moderate) Carisoprodol can cause additive CNS depression if used concomitantly with other CNS depressants.
Aspirin, ASA; oxyCODONE: (Moderate) Concomitant use of oxycodone with zaleplon may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If zaleplon is used concurrently with oxycodone, a reduced dosage of oxycodone and/or zaleplon is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression.
Atazanavir: (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as atazanavir, may decrease the clearance of zaleplon. Routine dosage adjustments of zaleplon are not required. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
Atazanavir; Cobicistat: (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as atazanavir, may decrease the clearance of zaleplon. Routine dosage adjustments of zaleplon are not required. Dosage adjustments should be made on an individual basis according to efficacy and tolerability. (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as cobicistat, may decrease the clearance of zaleplon. Coadministration with a moderate CYP3A4 inhibitor increased zaleplon exposure by 20%. Routine dosage adjustments of zaleplon are not required. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
Atropine; Difenoxin: (Moderate) Concurrent administration of diphenoxylate/difenoxin with anxiolytics, sedatives, and hypnotics can potentiate the CNS-depressant effects of diphenoxylate/difenoxin. Use caution during coadministration.

atypical antipsychotic: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of atypical antipsychotics and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Azelastine: (Moderate) An enhanced CNS depressant effect may occur when azelastine is combined with CNS depressants including anxiolytics, sedatives, and hypnotics.
Azelastine; Fluticasone: (Moderate) An enhanced CNS depressant effect may occur when azelastine is combined with CNS depressants including anxiolytics, sedatives, and hypnotics.
Baclofen: (Moderate) Concurrent use of baclofen and CNS depressants such as certain sedatives or hypnotics can cause additive CNS depression. A reduction in the dose of these medications may be considered to minimize additive sedative effects, if they occur. With hypnotic medications, the risk of next-day psychomotor impairment is increased during coadministration of other CNS depressants, which may decrease the ability to perform tasks requiring full mental alertness such as driving.
Barbiturates: (Major) Coadministration of zaleplon and barbiturates may result in additive CNS depression. Caution should be exercised during concomitant use of anxiolytics, sedatives, and hypnotics and any barbiturate. In addition, zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inducers, such as barbiturates, may increase the clearance of zaleplon. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
Belladonna; Opium: (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Limit the use of opioid pain medications with zaleplon 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. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression.
Benzhydrocodone; Acetaminophen: (Major) Concomitant use of opioid agonists with zaleplon may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with zaleplon 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. If benzhydrocodone is initiated in a patient taking zaleplon, reduce initial dosage and titrate to clinical response. If zaleplon is initiated a patient taking an opioid agonist, use a lower initial dose of zaleplon and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Benzodiazepines: (Major) Monitor for excessive sedation and somnolence during coadministration of zaleplon and benzodiazepines. Concurrent use may result in

additive CNS depression. If used together, a reduction in the dose of one or both drugs may be needed.
Benztropine: (Moderate) CNS depressants, such as anxiolytics, sedatives, and hypnotics, can increase the sedative effects of benztropine.
Brexpiprazole: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of atypical antipsychotics and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Brimonidine: (Moderate) Based on the sedative effects of brimonidine in individual patients, brimonidine administration has potential to enhance the CNS depressants effects of anxiolytics, sedatives, and hypnotics.
Brimonidine; Brinzolamide: (Moderate) Based on the sedative effects of brimonidine in individual patients, brimonidine administration has potential to enhance the CNS depressants effects of anxiolytics, sedatives, and hypnotics.
Brimonidine; Timolol: (Moderate) Based on the sedative effects of brimonidine in individual patients, brimonidine administration has potential to enhance the CNS depressants effects of anxiolytics, sedatives, and hypnotics.
Brompheniramine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Brompheniramine; Dextromethorphan; Phenylephrine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Brompheniramine; Phenylephrine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Brompheniramine; Pseudoephedrine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Brompheniramine; Pseudoephedrine; Dextromethorphan: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Buprenorphine: (Major) Reserve concomitant prescribing of buprenorphine and zaleplon for use in patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for

respiratory depression and sedation. Gradually tapering a patient off other CNS depressants or decreasing to the lowest effective dose is preferred in most cases of patients being treated for opioid use disorder. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Buprenorphine; Naloxone: (Major) Reserve concomitant prescribing of buprenorphine and zaleplon for use in patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. Gradually tapering a patient off other CNS depressants or decreasing to the lowest effective dose is preferred in most cases of patients being treated for opioid use disorder. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
busPIRone: (Moderate) The combination of buspirone and other CNS depressants, such as sedative hypnotics including zaleplon, may increase the risk for drowsiness or sedation. Because the effects of the use of buspirone with most other psychotropic drugs have not been studied, the concomitant use of buspirone with other CNS-active drugs should be approached with caution.
Butalbital; Acetaminophen: (Major) Coadministration of zaleplon and barbiturates may result in additive CNS depression. Caution should be exercised during concomitant use of anxiolytics, sedatives, and hypnotics and any barbiturate. In addition, zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inducers, such as barbiturates, may increase the clearance of zaleplon. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
Butalbital; Acetaminophen; Caffeine: (Major) Coadministration of zaleplon and barbiturates may result in additive CNS depression. Caution should be exercised during concomitant use of anxiolytics, sedatives, and hypnotics and any barbiturate. In addition, zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inducers, such as barbiturates, may increase the clearance of zaleplon. Dosage adjustments should be made on an individual basis according to efficacy and tolerability. (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking medications for sleep, such as zaleplon 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) Coadministration of zaleplon and barbiturates may result in additive CNS depression. Caution should be exercised during concomitant use of anxiolytics, sedatives, and hypnotics and any barbiturate. In

addition, zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inducers, such as barbiturates, may increase the clearance of zaleplon. Dosage adjustments should be made on an individual basis according to efficacy and tolerability. (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Avoid prescribing opioid cough medications in patients taking zaleplon. Limit the use of opioid pain medications with zaleplon 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. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression. (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking medications for sleep, such as zaleplon 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) Coadministration of zaleplon and barbiturates may result in additive CNS depression. Caution should be exercised during concomitant use of anxiolytics, sedatives, and hypnotics and any barbiturate. In addition, zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inducers, such as barbiturates, may increase the clearance of zaleplon. Dosage adjustments should be made on an individual basis according to efficacy and tolerability. (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Avoid prescribing opioid cough medications in patients taking zaleplon. Limit the use of opioid pain medications with zaleplon 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. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression. (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking medications for sleep, such as zaleplon 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.

Butorphanol: (Moderate) Concomitant use of butorphanol with other central nervous system (CNS) depressants, such as zaleplon, can potentiate the effects of butorphanol and may lead to additive CNS or respiratory depression. Prior to concurrent use of

butorphanol 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. If these agents are used together, a reduced dosage of butorphanol and/or zaleplon may be necessary. Carefully monitor the patient for hypotension, CNS depression, and respiratory depression.
Caffeine: (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking medications for sleep, such as zaleplon 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 medications for sleep, such as zaleplon 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.
Calcium, Magnesium, Potassium, Sodium Oxybates: (Contraindicated) Sodium oxybate should not be used in combination with CNS depressant anxiolytics, sedatives, and hypnotics or other sedative CNS depressant drugs. Specifically, sodium oxybate use is contraindicated in patients being treated with sedative hypnotic drugs. Sodium oxybate (GHB) has the potential to impair cognitive and motor skills. For example, the concomitant use of barbiturates and benzodiazepines increases sleep duration and may contribute to rapid onset, pronounced CNS depression, respiratory depression, or coma when combined with sodium oxybate.
Cannabidiol: (Moderate) Monitor for excessive sedation and somnolence during coadministration. CNS depressants can potentiate the effects of cannabidiol.
Capsaicin; Metaxalone: (Moderate) Concomitant administration of metaxalone with other CNS depressants, such as certain sedatives and hypnotics, can potentiate the sedative effects of either agent. A reduction in the dose of these medications may be considered to minimize additive sedative effects, if they occur. With hypnotic medications, the risk of next-day psychomotor impairment is increased during co-administration of other CNS depressants, which may decrease the ability to perform tasks requiring full mental alertness such as driving.
carBAMazepine: (Moderate) Monitor for decreased efficacy when zaleplon is coadministered with carbamazepine due to decreased zaleplon exposure. Zaleplon is partially metabolized by CYP3A4; carbamazepine is a strong CYP3A4 inducer. Consider using an alternative non-CYP3A4 substrate hypnotic in patients taking strong CYP3A4 inducers. Coadministration with another strong CYP3A4 inducer reduced zaleplon exposure by approximately 80%.
Carbidopa; Levodopa: (Moderate) Advise patients of possible additive risk for somnolence during concomitant use of levodopa with sedating agents. Concomitant use

may also increase the risk for sudden sleep onset during activities of daily living, such as driving or eating; this adverse effect may occur without any warning signs. Patients should consider avoiding activities such as driving or operating machinery until the effects of this combination are known.
Carbidopa; Levodopa; Entacapone: (Major) Additive CNS depressant effects are possible during concurrent use of COMT inhibitors and zaleplon. If concurrent use is necessary, monitor for additive side effects. A reduction in the dose of one or both drugs may be needed. Patients should be advised to avoid driving or other tasks requiring mental alertness until they know how the combination affects them. (Moderate) Advise patients of possible additive risk for somnolence during concomitant use of levodopa with sedating agents. Concomitant use may also increase the risk for sudden sleep onset during activities of daily living, such as driving or eating; this adverse effect may occur without any warning signs. Patients should consider avoiding activities such as driving or operating machinery until the effects of this combination are known.
Carbinoxamine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Cariprazine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of atypical antipsychotics and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Carisoprodol: (Moderate) Carisoprodol can cause additive CNS depression if used concomitantly with other CNS depressants.
Celecoxib; Tramadol: (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Limit the use of opioid pain medications with zaleplon 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. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression.
Cenobamate: (Moderate) Monitor for excessive sedation and somnolence during coadministration of cenobamate and zaleplon. Concurrent use increases the risk for CNS depression and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Patients should be instructed to contact their provider immediately if these symptoms or behaviors occur.
Ceritinib: (Moderate) Monitor for an increase in zaleplon-related adverse reactions if coadministration with ceritinib is necessary. Zaleplon is a CYP3A4 substrate and ceritinib

is a strong CYP3A4 inhibitor.
Cetirizine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of cetirizine and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Cetirizine; Pseudoephedrine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of cetirizine and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Chlophedianol; Dexbrompheniramine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Chlophedianol; Dexchlorpheniramine; Pseudoephedrine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Chloramphenicol: (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as chloramphenicol, may decrease the clearance of zaleplon. Routine dosage adjustments of zaleplon are not required. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
Chlorcyclizine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
chlordiazePOXIDE: (Major) Monitor for excessive sedation and somnolence during coadministration of zaleplon and benzodiazepines. Concurrent use may result in additive CNS depression. If used together, a reduction in the dose of one or both drugs may be needed.
chlordiazePOXIDE; Amitriptyline: (Major) Monitor for excessive sedation and somnolence during coadministration of zaleplon and benzodiazepines. Concurrent use may result in additive CNS depression. If used together, a reduction in the dose of one or both drugs may be needed. (Moderate) Monitor for unusual drowsiness and sedation during coadministration of tricyclic antidepressants and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary. Coadministration of single doses of a tricyclic antidepressant and zaleplon produced additive effects on decreased alertness and impaired psychomotor performance for 2 to 4 hours after administration.
chlordiazePOXIDE; Clidinium: (Major) Monitor for excessive sedation and somnolence during coadministration of zaleplon and benzodiazepines. Concurrent use may result in additive CNS depression. If used together, a reduction in the dose of one or both drugs

may be needed.
Chlorpheniramine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Chlorpheniramine; Codeine: (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Avoid prescribing opioid cough medications in patients taking zaleplon. Limit the use of opioid pain medications with zaleplon 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. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression. (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Chlorpheniramine; Dextromethorphan: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Chlorpheniramine; Dextromethorphan; Phenylephrine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Chlorpheniramine; Dextromethorphan; Pseudoephedrine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Chlorpheniramine; HYDROcodone: (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Avoid prescribing opioid cough medications in patients taking zaleplon. Limit the use of opioid pain medications with zaleplon 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. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression. (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS

depression and next-day psychomotor impairment; dose adjustments may be necessary.
Chlorpheniramine; Ibuprofen; Pseudoephedrine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Chlorpheniramine; Phenylephrine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Chlorpheniramine; Pseudoephedrine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
chlorproMAZINE: (Moderate) Phenothiazines are CNS depressant drugs that may have cumulative effects when administered with other CNS depressant drugs and they should be used cautiously with anxiolytic, sedative, and hypnotics. Caution should be exercised during simultaneous use of these agents due to potential excessive CNS effects or additive hypotension. Additionally, sleep-related behaviors, such as sleep-driving, are more likely to occur during concurrent use of hypnotics and other CNS depressants than with use of a hypnotic alone.
Chlorzoxazone: (Moderate) Concurrent use of chlorzoxazone and CNS depressants such as certain sedatives or hypnotics can cause additive CNS depression. A reduction in the dose of these medications may be considered to minimize additive sedative effects, if they occur. With hypnotic medications, the risk of next-day psychomotor impairment is increased during co-administration of other CNS depressants, which may decrease the ability to perform tasks requiring full mental alertness such as driving.
Cimetidine: (Major) Reduce the initial dose of zaleplon to 5 mg in patients receiving concomitant cimetidine therapy. Concomitant administration of cimetidine 800 mg with zaleplon 10 mg resulted in an 85% increase in the Cmax and AUC of zaleplon. Cimetidine inhibits both aldehyde oxidase and CYP3A4, the primary and secondary enzymes, respectively, responsible for zaleplon metabolism.
Clarithromycin: (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as clarithromycin, may decrease the clearance of zaleplon. Routine dosage adjustments of zaleplon are not required. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
Clemastine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.

cloBAZam: (Moderate) Concomitant administration of clobazam with other CNS depressant drugs including sedatives and hypnotics, can potentiate the CNS effects (i.e., increased sedation or respiratory depression) of either agent.
clomiPRAMINE: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of tricyclic antidepressants and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary. Coadministration of single doses of a tricyclic antidepressant and zaleplon produced additive effects on decreased alertness and impaired psychomotor performance for 2 to 4 hours after administration.
clonazePAM: (Major) Monitor for excessive sedation and somnolence during coadministration of zaleplon and benzodiazepines. Concurrent use may result in additive CNS depression. If used together, a reduction in the dose of one or both drugs may be needed.
Clorazepate: (Major) Monitor for excessive sedation and somnolence during coadministration of zaleplon and benzodiazepines. Concurrent use may result in additive CNS depression. If used together, a reduction in the dose of one or both drugs may be needed.
cloZAPine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of atypical antipsychotics and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Cobicistat: (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as cobicistat, may decrease the clearance of zaleplon. Coadministration with a moderate CYP3A4 inhibitor increased zaleplon exposure by 20%. Routine dosage adjustments of zaleplon are not required. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
Codeine: (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Avoid prescribing opioid cough medications in patients taking zaleplon. Limit the use of opioid pain medications with zaleplon 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. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression.
Codeine; Dexbrompheniramine: (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Avoid prescribing opioid cough medications in patients taking zaleplon. Limit the use of opioid pain medications with zaleplon 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. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression. (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Codeine; guaiFENesin: (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Avoid prescribing opioid cough medications in patients taking zaleplon. Limit the use of opioid pain medications with zaleplon 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. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression.
Codeine; guaiFENesin; Pseudoephedrine: (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Avoid prescribing opioid cough medications in patients taking zaleplon. Limit the use of opioid pain medications with zaleplon 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. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression.
Codeine; Phenylephrine; Promethazine: (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Avoid prescribing opioid cough medications in patients taking zaleplon. Limit the use of opioid pain medications with zaleplon 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. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression. (Moderate) Phenothiazines are CNS depressant drugs that may have cumulative effects when administered with other CNS depressant drugs and they should be used cautiously with anxiolytic, sedative, and hypnotics. Caution should be exercised during simultaneous use of these agents due to potential excessive CNS effects or

additive hypotension. Additionally, sleep-related behaviors, such as sleep-driving, are more likely to occur during concurrent use of hypnotics and other CNS depressants than with use of a hypnotic alone.
Codeine; Promethazine: (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Avoid prescribing opioid cough medications in patients taking zaleplon. Limit the use of opioid pain medications with zaleplon 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. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression. (Moderate) Phenothiazines are CNS depressant drugs that may have cumulative effects when administered with other CNS depressant drugs and they should be used cautiously with anxiolytic, sedative, and hypnotics. Caution should be exercised during simultaneous use of these agents due to potential excessive CNS effects or additive hypotension. Additionally, sleep-related behaviors, such as sleep-driving, are more likely to occur during concurrent use of hypnotics and other CNS depressants than with use of a hypnotic alone.
COMT inhibitors: (Major) Additive CNS depressant effects are possible during concurrent use of COMT inhibitors and zaleplon. If concurrent use is necessary, monitor for additive side effects. A reduction in the dose of one or both drugs may be needed. 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.
Cyproheptadine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Dantrolene: (Moderate) Simultaneous use of dantrolene and other CNS depressants, such as anxiolytics, sedatives, and hypnotics, can increase CNS depression (e.g., drowsiness). A reduction in the dose of these medications may be considered to minimize additive sedative effects, if they occur. With hypnotic medications, the risk of next-day psychomotor impairment is increased during co-administration of other CNS depressants, which may decrease the ability to perform tasks requiring full mental alertness such as driving.

Daridorexant: (Major) Use of daridorexant with other sedatives and hypnotics should generally be avoided due to duplication of treatments and due to the additive CNS depressant and complex sleep-related behaviors that may occur. While anxiolytic medications may be used concurrently with daridorexant, a reduction in dose of one or both agents may be needed.
Darunavir: (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as darunavir, may decrease the clearance of zaleplon. Routine dosage adjustments of zaleplon are not required. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
Darunavir; Cobicistat: (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as cobicistat, may decrease the clearance of zaleplon. Coadministration with a moderate CYP3A4 inhibitor increased zaleplon exposure by 20%. Routine dosage adjustments of zaleplon are not required. Dosage adjustments should be made on an individual basis according to efficacy and tolerability. (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as darunavir, may decrease the clearance of zaleplon. Routine dosage adjustments of zaleplon are not required. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
Darunavir; Cobicistat; Emtricitabine; Tenofovir alafenamide: (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as cobicistat, may decrease the clearance of zaleplon. Coadministration with a moderate CYP3A4 inhibitor increased zaleplon exposure by 20%. Routine dosage adjustments of zaleplon are not required. Dosage adjustments should be made on an individual basis according to efficacy and tolerability. (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as darunavir, may decrease the clearance of zaleplon. Routine dosage adjustments of zaleplon are not required. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
Desipramine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of tricyclic antidepressants and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary. Coadministration of single doses of a tricyclic antidepressant and zaleplon produced additive effects on decreased alertness and impaired psychomotor performance for 2 to 4 hours after administration.
Deutetrabenazine: (Moderate) Advise patients that concurrent use of deutetrabenazine and drugs that can cause CNS depression, such as zaleplon, may have additive effects and worsen drowsiness or sedation.
Dexbrompheniramine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be

necessary.
Dexbrompheniramine; Dextromethorphan; Phenylephrine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Dexbrompheniramine; Pseudoephedrine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Dexchlorpheniramine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Dexchlorpheniramine; Dextromethorphan; Pseudoephedrine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
dexmedeTOMIDine: (Moderate) Co-administration of dexmedetomidine with anxiolytics, sedatives, and hypnotics is likely to lead to an enhancement of CNS depression.
Dextromethorphan; diphenhydrAMINE; Phenylephrine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
diazePAM: (Major) Monitor for excessive sedation and somnolence during coadministration of zaleplon and benzodiazepines. Concurrent use may result in additive CNS depression. If used together, a reduction in the dose of one or both drugs may be needed.
Dicyclomine: (Moderate) Dicyclomine can cause drowsiness, so it should be used cautiously in patients receiving CNS depressants like anxiolytics, sedatives, and hypnotics.
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.
dimenhyDRINATE: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
diphenhydrAMINE: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be

necessary.
diphenhydrAMINE; Ibuprofen: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
diphenhydrAMINE; Naproxen: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
diphenhydrAMINE; Phenylephrine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Diphenoxylate; Atropine: (Moderate) Concurrent administration of diphenoxylate/difenoxin with anxiolytics, sedatives, and hypnotics can potentiate the CNS-depressant effects of diphenoxylate/difenoxin. Use caution during coadministration.
Doxepin: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of tricyclic antidepressants and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary. Coadministration of single doses of a tricyclic antidepressant and zaleplon produced additive effects on decreased alertness and impaired psychomotor performance for 2 to 4 hours after administration.
Doxylamine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Doxylamine; Pyridoxine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
droNABinol: (Moderate) Concomitant use of dronabinol with other CNS depressants, such as zaleplon, can potentiate the effects of dronabinol on respiratory depression.
droPERidol: (Moderate) Central nervous system (CNS) depressants like zaleplon have additive or potentiating effects with droperidol. Following administration of droperidol, the dose of the other CNS depressant should be reduced.
Elvitegravir; Cobicistat; Emtricitabine; Tenofovir Alafenamide: (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as cobicistat, may decrease the clearance of zaleplon. Coadministration with a moderate CYP3A4 inhibitor increased zaleplon exposure by 20%. Routine dosage adjustments of

zaleplon are not required. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
Elvitegravir; Cobicistat; Emtricitabine; Tenofovir Disoproxil Fumarate: (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as cobicistat, may decrease the clearance of zaleplon. Coadministration with a moderate CYP3A4 inhibitor increased zaleplon exposure by 20%. Routine dosage adjustments of zaleplon are not required. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
Encorafenib: (Moderate) Monitor for decreased efficacy when zaleplon is coadministered with encorafenib due to decreased zaleplon exposure. Zaleplon is partially metabolized by CYP3A; encorafenib is a strong CYP3A inducer. Consider using an alternative non-CYP3A substrate hypnotic in patients taking strong CYP3A inducers. Coadministration with another strong CYP3A inducer reduced zaleplon exposure by approximately 80%.
Entacapone: (Major) Additive CNS depressant effects are possible during concurrent use of COMT inhibitors and zaleplon. If concurrent use is necessary, monitor for additive side effects. A reduction in the dose of one or both drugs may be needed. Patients should be advised to avoid driving or other tasks requiring mental alertness until they know how the combination affects them.
Enzalutamide: (Major) Consider an alternative to enzalutamide if treatment with zaleplon is necessary due to decreased plasma concentrations of zaleplon. Zaleplon is a CYP3A4 substrate and enzalutamide is a strong CYP3A4 inducer. Although CYP3A4 is normally a minor metabolizing enzyme of zaleplon, coadministration with another strong CYP3A4 inducer reduced zaleplon exposure by approximately 80%.
Ergotamine; Caffeine: (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking medications for sleep, such as zaleplon 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) Monitor for an increase in zaleplon-related adverse effects if concomitant use with erythromycin is necessary. Concomitant use has been observed to increase zaleplon concentrations which may increase the risk for adverse effects. Coadministration of single oral doses of erythromycin 800 mg and zaleplon 10 mg resulted in a 34% increase in zaleplon peak concentrations and a 20% increase in zaleplon exposure. Zaleplon is a CYP3A substrate and erythromycin is a CYP3A inhibitor.
Esketamine: (Major) Use of zaleplon during treatment with esketamine may increase sedation and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Instruct patients to contact their provider immediately if these symptoms or behaviors occur and not to drive or engage in other activities requiring alertness until the next day after a restful sleep.

Estazolam: (Major) Monitor for excessive sedation and somnolence during coadministration of zaleplon and benzodiazepines. Concurrent use may result in additive CNS depression. If used together, a reduction in the dose of one or both drugs may be needed.
Ethanol: (Major) Advise patients not to use zaleplon if they drank alcohol that evening or before bed. There are additive effects of alcohol with zaleplon, leading to additive CNS depression and psychomotor impairment. Zaleplon potentiated the CNS-impairing effects of alcohol 0.75 g/kg on balance testing and reaction time for 1 hour after alcohol administration and on the digit symbol substitution test (DSST), symbol copying test, and the variability component of the divided attention test for 2.5 hours after alcohol administration. The potentiation resuls from a CNS pharmacodynamic interaction; zaleplon did not affect the pharmacokinetics of alcohol.
Etomidate: (Moderate) Coadministration of zaleplon and general anesthetics may result in additive CNS depressant effects. In premarketing studies, zaleplon potentiated the CNS effects of ethanol, imipramine, and thioridazine for at least 2 to 4 hours. A similar interaction may occur with zaleplon and other CNS depressants including general anesthetics. If concurrent use is necessary, monitor for additive side effects. A temporary dose reduction of zaleplon should be considered following administration of general anesthetics. The risk of next-day psychomotor impairment is increased during co-administration, which may decrease the ability to perform tasks requiring full mental alertness such as driving.
Fenfluramine: (Moderate) Monitor for excessive sedation and somnolence during coadministration of fenfluramine and zaleplon. Concurrent use increases the risk for CNS depression and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake).
fentaNYL: (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation and somnolence. Limit the use of opioid pain medications with zaleplon 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.
Flumazenil: (Major) Flumazenil, a benzodiazepine antagonist, can reverse the sedative/hypnotic effects of zaleplon. Flumazenil and zaleplon are pharmacological opposites.
fluPHENAZine: (Moderate) Phenothiazines are CNS depressant drugs that may have cumulative effects when administered with other CNS depressant drugs and they should be used cautiously with anxiolytic, sedative, and hypnotics. Caution should be exercised during simultaneous use of these agents due to potential excessive CNS effects or additive hypotension. Additionally, sleep-related behaviors, such as sleep-driving, are more likely to occur during concurrent use of hypnotics and other CNS depressants than

with use of a hypnotic alone.
Flurazepam: (Major) Monitor for excessive sedation and somnolence during coadministration of zaleplon and benzodiazepines. Concurrent use may result in additive CNS depression. If used together, a reduction in the dose of one or both drugs may be needed.
Food: (Major) Administration with or immediately after heavy, high-fat food slows the absorption of zaleplon. This is expected to reduce the effect of zaleplon on sleep latency.
(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.
Fosamprenavir: (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as fosamprenavir, may decrease the clearance of zaleplon. Routine dosage adjustments of zaleplon are not required. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
Foscarbidopa; Foslevodopa: (Moderate) Advise patients of possible additive risk for somnolence during concomitant use of levodopa with sedating agents. Concomitant use may also increase the risk for sudden sleep onset during activities of daily living, such as driving or eating; this adverse effect may occur without any warning signs. Patients should consider avoiding activities such as driving or operating machinery until the effects of this combination are known.
Fosphenytoin: (Moderate) Monitor for decreased efficacy when zaleplon is coadministered with fosphenytoin due to decreased zaleplon exposure. Zaleplon is partially metabolized by CYP3A; phenytoin is a strong CYP3A inducer. Consider using an alternative non-CYP3A substrate hypnotic in patients taking strong CYP3A inducers. Coadministration with another strong CYP3A inducer reduced zaleplon exposure by approximately 80%.
Gabapentin: (Major) Initiate gabapentin at the lowest recommended dose and monitor patients for symptoms of sedation and somnolence during coadministration of gabapentin and zaleplon. Concomitant use of gabapentin with zaleplon may cause additive CNS depression and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Educate patients about the risks and symptoms of excessive CNS depression. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur.
General anesthetics: (Moderate) Coadministration of zaleplon and general anesthetics may result in additive CNS depressant effects. In premarketing studies, zaleplon potentiated the CNS effects of ethanol, imipramine, and thioridazine for at least 2 to 4 hours. A similar interaction may occur with zaleplon and other CNS depressants including general anesthetics. If concurrent use is necessary, monitor for additive side effects. A temporary dose reduction of zaleplon should be considered following administration of general anesthetics. The risk of next-day psychomotor impairment is increased during co-administration, which may decrease the ability to perform tasks

requiring full mental alertness such as driving.
Grapefruit juice: (Moderate) Grapefruit and grapefruit juice should be avoided if possible in patients taking zaleplon. Because zaleplon is partially metabolized by CYP3A4, an interaction is possible with CYP3A4 inhibitors such as grapefruit juice. Grapefruit and grapefruit juice inhibit CYP3A4 metabolism in gut enterocytes, and therefore may cause increased systemic concentrations of zaleplon potentially resulting in somnolence, ataxia, sleep-related behaviors, or other adverse CNS effects.
Haloperidol: (Moderate) Haloperidol can potentiate the actions of other CNS depressants such as anxiolytics, sedatives, and hypnotics, and they should be used cautiously in combination.
Homatropine; HYDROcodone: (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Avoid prescribing opioid cough medications in patients taking zaleplon. Limit the use of opioid pain medications with zaleplon 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. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression.
HYDROcodone: (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Avoid prescribing opioid cough medications in patients taking zaleplon. Limit the use of opioid pain medications with zaleplon 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. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression.
HYDROcodone; Ibuprofen: (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Avoid prescribing opioid cough medications in patients taking zaleplon. Limit the use of opioid pain medications with zaleplon 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. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression.
HYDROmorphone: (Moderate) Concomitant use of hydromorphone with zaleplon can potentiate the effects of hydromorphone and may lead to additive CNS or respiratory depression, profound sedation, or coma. Prior to concurrent use, assess the level of

tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If hydromorphone is used concurrently with zaleplon, a reduced dosage of hydromorphone and/or zaleplon is recommended; start with one-third to one-half of the estimated hydromorphone starting dose when using hydromorphone extended-release tablets. Carefully monitor the patient for hypotension, CNS depression, and respiratory depression. Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.
hydrOXYzine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Idelalisib: (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as idelalisib, may decrease the clearance of zaleplon. Routine dosage adjustments of zaleplon are not required. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
Iloperidone: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of atypical antipsychotics and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Imipramine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of tricyclic antidepressants and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary. Coadministration of single doses of a tricyclic antidepressant and zaleplon produced additive effects on decreased alertness and impaired psychomotor performance for 2 to 4 hours after administration.
Isocarboxazid: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of anxiolytics, sedatives, and hypnotics and monoamine oxidase inhibitors (MAOIs) due to the risk for additive CNS depression.
Isoflurane: (Moderate) Coadministration of zaleplon and general anesthetics may result in additive CNS depressant effects. In premarketing studies, zaleplon potentiated the CNS effects of ethanol, imipramine, and thioridazine for at least 2 to 4 hours. A similar interaction may occur with zaleplon and other CNS depressants including general anesthetics. If concurrent use is necessary, monitor for additive side effects. A temporary dose reduction of zaleplon should be considered following administration of general anesthetics. The risk of next-day psychomotor impairment is increased during co-administration, which may decrease the ability to perform tasks requiring full mental alertness such as driving.
Itraconazole: (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as itraconazole, may decrease the clearance of

zaleplon. Routine dosage adjustments of zaleplon are not required. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
Ketamine: (Moderate) Coadministration of zaleplon and general anesthetics may result in additive CNS depressant effects. In premarketing studies, zaleplon potentiated the CNS effects of ethanol, imipramine, and thioridazine for at least 2 to 4 hours. A similar interaction may occur with zaleplon and other CNS depressants including general anesthetics. If concurrent use is necessary, monitor for additive side effects. A temporary dose reduction of zaleplon should be considered following administration of general anesthetics. The risk of next-day psychomotor impairment is increased during co-administration, which may decrease the ability to perform tasks requiring full mental alertness such as driving.
Ketoconazole: (Moderate) Monitor for an increase in zaleplon-related adverse reactions, including excessive sedation and confusion, if coadministered with ketoconazole. Routine dosage adjustments of zaleplon are not required. CYP3A4 is a minor metabolic pathway for zaleplon elimination as sum of desethylzaleplon (formed via CYP3A4) and its metabolites (5-oxo-desethylzaleplon and 5-oxo-desethylzaleplon glucuronide) account for only 9% of the urinary recovery of a zaleplon dose. Use of a strong, selective CYP3A4 inhibitor produced a 34% increase in zaleplon's Cmax and a 20% increase in the exposure. Other strong selective CYP3A4 inhibitors such as ketoconazole can be expected to have similar effects.
Lansoprazole; Amoxicillin; Clarithromycin: (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as clarithromycin, may decrease the clearance of zaleplon. Routine dosage adjustments of zaleplon are not required. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
Lasmiditan: (Moderate) Monitor for excessive sedation and somnolence during coadministration of lasmiditan and zaleplon. Concurrent use increases the risk for CNS depression and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Patients should be instructed to contact their provider immediately if these symptoms or behaviors occur.
Lemborexant: (Moderate) Use of lemborexant with other sedatives and hypnotics should generally be avoided due to duplication of treatments and due to the additive CNS depressant and complex sleep-related behaviors that may occur. While anxiolytic medications may be used concurrently with lemborexant, a reduction in dose of one or both agents may be needed.
Levocetirizine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of cetirizine and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Levodopa: (Moderate) Advise patients of possible additive risk for somnolence during concomitant use of levodopa with sedating agents. Concomitant use may also increase

the risk for sudden sleep onset during activities of daily living, such as driving or eating; this adverse effect may occur without any warning signs. Patients should consider avoiding activities such as driving or operating machinery until the effects of this combination are known.
Levoketoconazole: (Moderate) Monitor for an increase in zaleplon-related adverse reactions, including excessive sedation and confusion, if coadministered with ketoconazole. Routine dosage adjustments of zaleplon are not required. CYP3A4 is a minor metabolic pathway for zaleplon elimination as sum of desethylzaleplon (formed via CYP3A4) and its metabolites (5-oxo-desethylzaleplon and 5-oxo-desethylzaleplon glucuronide) account for only 9% of the urinary recovery of a zaleplon dose. Use of a strong, selective CYP3A4 inhibitor produced a 34% increase in zaleplon's Cmax and a 20% increase in the exposure. Other strong selective CYP3A4 inhibitors such as ketoconazole can be expected to have similar effects.
Levorphanol: (Moderate) Concomitant use of levorphanol with zaleplon can potentiate the effects of levorphanol on respiration, blood pressure, and alertness. Severe hypotension, respiratory depression, profound sedation, or coma may occur. Prior to concurrent use, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. When concomitant treatment with levorphanol with another CNS depressant is necessary, reduce the dose of 1 or both drugs. The initial dose of levorphanol should be reduced by approximately 50% or more when levorphanol is used with another drug that may depress respiration.
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 additive sedation during coadministration of lofexidine and anxiolytics, sedatives, and hypnotics. Lofexidine can potentiate the effects of CNS depressants. Patients should be advised to avoid driving or performing any other tasks requiring mental alertness until the effects of the combination are known.
Lonafarnib: (Moderate) Monitor for an increase in zaleplon-related adverse reactions, including excessive sedation and confusion, if coadministered with lonafarnib. Routine dosage adjustments of zaleplon are not required. Zaleplon is partially metabolized by CYP3A4 and lonafarnib is a strong CYP3A4 inhibitor. Coadministration with a single dose of another strong CYP3A4 inhibitor increased the AUC of zaleplon by 20%.
Lopinavir; Ritonavir: (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as ritonavir, may decrease the clearance of zaleplon. Routine dosage adjustments of zaleplon are not required. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
LORazepam: (Major) Monitor for excessive sedation and somnolence during coadministration of zaleplon and benzodiazepines. Concurrent use may result in

additive CNS depression. If used together, a reduction in the dose of one or both drugs may be needed.
Loxapine: (Moderate) In premarketing studies, zaleplon potentiated the CNS effects of ethanol, imipramine, and thioridazine for at least 2 to 4 hours. Other antipsychotics may also have additive CNS effects with zaleplon.
Lumacaftor; Ivacaftor: (Moderate) Monitor for decreased efficacy of zaleplon if coadministration with lumacaftor; ivacaftor is necessary. Zaleplon is a CYP3A4 substrate and lumacaftor; ivacaftor is a strong CYP3A4 inducer. Although CYP3A4 is normally a minor metabolizing enzyme of zaleplon, coadministration with another strong CYP3A4 inducer reduced zaleplon exposure by approximately 80%. Coadministration with lumacaftor; ivacaftor could lead to ineffectiveness of zaleplon.
Lumacaftor; Ivacaftor: (Moderate) Monitor for decreased efficacy of zaleplon if coadministration with lumacaftor; ivacaftor is necessary. Zaleplon is a CYP3A4 substrate and lumacaftor; ivacaftor is a strong CYP3A4 inducer. Although CYP3A4 is normally a minor metabolizing enzyme of zaleplon, coadministration with another strong CYP3A4 inducer reduced zaleplon exposure by approximately 80%. Coadministration with lumacaftor; ivacaftor could lead to ineffectiveness of zaleplon.
Lumateperone: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of atypical antipsychotics and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Lurasidone: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of atypical antipsychotics and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Maprotiline: (Moderate) CNS depressants should be combined cautiously with maprotiline because they could cause additive depressant effects and possible respiratory depression or hypotension.
Meclizine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Melatonin: (Major) Pharmacodynamic interactions often occur when sedative agents are used together. Until more data are available, avoid combining melatonin with other hypnotics, including zaleplon. 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 reporting unusual sleep-related behaviors likely should discontinue melatonin use.
Meperidine: (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Limit the use of opioid pain medications with zaleplon 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. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression.
Metaxalone: (Moderate) Concomitant administration of metaxalone with other CNS depressants, such as certain sedatives and hypnotics, can potentiate the sedative effects of either agent. A reduction in the dose of these medications may be considered to minimize additive sedative effects, if they occur. With hypnotic medications, the risk of next-day psychomotor impairment is increased during co-administration of other CNS depressants, which may decrease the ability to perform tasks requiring full mental alertness such as driving.
Methadone: (Moderate) Concomitant use of methadone with zaleplon can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also consider a using a lower dose of zaleplon. Monitor patients for sedation and respiratory depression.
Methocarbamol: (Moderate) Methocarbamol may cause additive CNS depression if used concomitantly with other CNS depressants. Dosage reduction of one or both agents may be necessary.
Methohexital: (Major) Coadministration of zaleplon and barbiturates may result in additive CNS depression. Caution should be exercised during concomitant use of anxiolytics, sedatives, and hypnotics and any barbiturate. In addition, zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inducers, such as barbiturates, may increase the clearance of zaleplon. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
Methscopolamine: (Moderate) CNS depression can be increased when methscopolamine is combined with other CNS depressants such as any anxiolytics, sedatives, and hypnotics.
Metoclopramide: (Minor) Combined use of metoclopramide and other CNS depressants, such as anxiolytics, sedatives, and hypnotics, can increase possible sedation.
Midazolam: (Major) Monitor for excessive sedation and somnolence during

coadministration of zaleplon and benzodiazepines. Concurrent use may result in additive CNS depression. If used together, a reduction in the dose of one or both drugs may be needed.
miFEPRIStone: (Moderate) Monitor for an increase in zaleplon-related adverse reactions, including excessive sedation and confusion, if coadministered with mifepristone. Routine dosage adjustments of zaleplon are not required. The clinical significance of this interaction with the short-term use of mifepristone for termination of pregnancy is unknown. Zaleplon is partially metabolized by CYP3A. Mifepristone is a strong CYP3A inhibitor. Coadministration with a single dose of another strong CYP3A inhibitor increased the AUC of zaleplon by 20%.
Mirtazapine: (Moderate) Consistent with the pharmacology of mirtazapine and the drug's side effect profile, additive effects may occur with other CNS-active agents, including anxiolytics, sedatives, and hypnotics.
Mitotane: (Moderate) Monitor for decreased efficacy of zaleplon if coadministration with mitotane is necessary. Zaleplon is a CYP3A4 substrate and mitotane is a strong CYP3A4 inducer. Although CYP3A4 is normally a minor metabolizing enzyme of zaleplon, coadministration with another strong CYP3A4 inducer reduced zaleplon exposure by approximately 80%. Coadministration with mitotane could lead to ineffectiveness of zaleplon.
Molindone: (Moderate) Consistent with the pharmacology of molindone, additive central nervous system (CNS) effects may occur with other CNS active drugs such as zaleplon. Caution is advisable during concurrent use.
Monoamine oxidase inhibitors: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of anxiolytics, sedatives, and hypnotics and monoamine oxidase inhibitors (MAOIs) due to the risk for additive CNS depression.
Morphine: (Moderate) Concomitant use of morphine with zaleplon can potentiate the effects of morphine on respiration, blood pressure, and alertness. Prior to concurrent use, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If zaleplon is used concurrently with morphine, a reduced dosage of morphine and/or the zaleplon is recommended; for extended-release products, start with the lowest possible dose of morphine (i.e., 15 mg PO every 12 hours, extended-release tablets; 30 mg or less PO every 24 hours; extended-release capsules). Monitor patients for sedation and respiratory depression.
Nalbuphine: (Moderate) Concomitant use of nalbuphine with other CNS depressants, such as zaleplon, can potentiate the effects of nalbuphine on respiratory depression, CNS depression, and sedation.
Nefazodone: (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as nefazodone, may decrease the clearance of zaleplon. Routine dosage adjustments of zaleplon are not required. Dosage adjustments

should be made on an individual basis according to efficacy and tolerability.
Nelfinavir: (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as nelfinavir, may decrease the clearance of zaleplon. Routine dosage adjustments of zaleplon are not required. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
Nirmatrelvir; Ritonavir: (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as ritonavir, may decrease the clearance of zaleplon. Routine dosage adjustments of zaleplon are not required. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
Nortriptyline: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of tricyclic antidepressants and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary. Coadministration of single doses of a tricyclic antidepressant and zaleplon produced additive effects on decreased alertness and impaired psychomotor performance for 2 to 4 hours after administration.
OLANZapine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of atypical antipsychotics and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
OLANZapine; FLUoxetine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of atypical antipsychotics and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
OLANZapine; Samidorphan: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of atypical antipsychotics and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Oliceridine: (Major) Concomitant use of oliceridine with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Limit the use of oliceridine with zaleplon 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.
Opicapone: (Major) Additive CNS depressant effects are possible during concurrent use of COMT inhibitors and zaleplon. If concurrent use is necessary, monitor for additive side effects. A reduction in the dose of one or both drugs may be needed. Patients should be advised to avoid driving or other tasks requiring mental alertness until they know how the combination affects them.
Orphenadrine: (Moderate) Additive CNS depressant effects may be seen with combination use of orphenadrine and anxiolytics, sedatives, and hypnotics.

Oxazepam: (Major) Monitor for excessive sedation and somnolence during coadministration of zaleplon and benzodiazepines. Concurrent use may result in additive CNS depression. If used together, a reduction in the dose of one or both drugs may be needed.
oxyCODONE: (Moderate) Concomitant use of oxycodone with zaleplon may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If zaleplon is used concurrently with oxycodone, a reduced dosage of oxycodone and/or zaleplon is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression.
oxyMORphone: (Moderate) Concomitant use of oxymorphone with zaleplon may produce additive CNS depressant effects. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If zaleplon is used concurrently with oxymorphone, a reduced dosage of oxymorphone (1/3 to 1/2 of the usual dose) and/or zaleplon is recommended. If the extended-release oxymorphone tablets are used concurrently with a CNS depressant, it is recommended to use an initial dosage of 5 mg PO every 12 hours. Monitor for sedation or respiratory depression.
Paliperidone: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of atypical antipsychotics and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Papaverine: (Moderate) Papaverine is a benzylisoquinoline alkaloid of opium and may have synergistic effects with potent CNS depressants such as anxiolytics, sedatives, and hypnotics, which could lead to enhanced sedation.
Pentazocine; Naloxone: (Moderate) Concomitant use of pentazocine with zaleplon can potentiate respiratory depression, CNS depression, and sedation. Pentazocine should be used cautiously in any patient receiving zaleplon. If concurrent use is necessary, a dose reduction of one or both medications may be required.
PENTobarbital: (Major) Coadministration of zaleplon and barbiturates may result in additive CNS depression. Caution should be exercised during concomitant use of anxiolytics, sedatives, and hypnotics and any barbiturate. In addition, zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inducers, such as barbiturates, may increase the clearance of zaleplon. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
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 zaleplon.
Perphenazine: (Moderate) Phenothiazines are CNS depressant drugs that may have cumulative effects when administered with other CNS depressant drugs and they should be used cautiously with anxiolytic, sedative, and hypnotics. Caution should be exercised during simultaneous use of these agents due to potential excessive CNS effects or additive hypotension. Additionally, sleep-related behaviors, such as sleep-driving, are more likely to occur during concurrent use of hypnotics and other CNS depressants than with use of a hypnotic alone.
Perphenazine; Amitriptyline: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of tricyclic antidepressants and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary. Coadministration of single doses of a tricyclic antidepressant and zaleplon produced additive effects on decreased alertness and impaired psychomotor performance for 2 to 4 hours after administration. (Moderate) Phenothiazines are CNS depressant drugs that may have cumulative effects when administered with other CNS depressant drugs and they should be used cautiously with anxiolytic, sedative, and hypnotics. Caution should be exercised during simultaneous use of these agents due to potential excessive CNS effects or additive hypotension. Additionally, sleep-related behaviors, such as sleep-driving, are more likely to occur during concurrent use of hypnotics and other CNS depressants than with use of a hypnotic alone.
Phenelzine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of anxiolytics, sedatives, and hypnotics and monoamine oxidase inhibitors (MAOIs) due to the risk for additive CNS depression.
PHENobarbital: (Major) Coadministration of zaleplon and barbiturates may result in additive CNS depression. Caution should be exercised during concomitant use of anxiolytics, sedatives, and hypnotics and any barbiturate. In addition, zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inducers, such as barbiturates, may increase the clearance of zaleplon. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
PHENobarbital; Hyoscyamine; Atropine; Scopolamine: (Major) Coadministration of zaleplon and barbiturates may result in additive CNS depression. Caution should be exercised during concomitant use of anxiolytics, sedatives, and hypnotics and any barbiturate. In addition, zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inducers, such as barbiturates, may increase the clearance of zaleplon. Dosage adjustments should be made on an individual basis according to efficacy and tolerability. (Moderate) Scopolamine may cause dizziness and drowsiness. Concurrent

use of scopolamine and CNS depressants can adversely increase the risk of CNS depression.
Phenothiazines: (Moderate) Phenothiazines are CNS depressant drugs that may have cumulative effects when administered with other CNS depressant drugs and they should be used cautiously with anxiolytic, sedative, and hypnotics. Caution should be exercised during simultaneous use of these agents due to potential excessive CNS effects or additive hypotension. Additionally, sleep-related behaviors, such as sleep-driving, are more likely to occur during concurrent use of hypnotics and other CNS depressants than with use of a hypnotic alone.
Phentermine; Topiramate: (Moderate) Although not specifically studied, coadministration of CNS depressant drugs (e.g., anxiolytics, sedatives, and hypnotics) 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.
Phenytoin: (Moderate) Monitor for decreased efficacy when zaleplon is coadministered with phenytoin due to decreased zaleplon exposure. Zaleplon is partially metabolized by CYP3A; phenytoin is a strong CYP3A inducer. Consider using an alternative non-CYP3A substrate hypnotic in patients taking strong CYP3A inducers. Coadministration with another strong CYP3A inducer reduced zaleplon exposure by approximately 80%.
Pimozide: (Moderate) Due to the effects of pimozide on cognition, it should be used cautiously with other CNS depressants including sedatives and hypnotics like zaleplon. In premarketing studies, zaleplon potentiated the CNS effects of ethanol, imipramine, and thioridazine for at least 2 to 4 hours and may result in similar interactions with other antipsychotics, including pimozide.
Posaconazole: (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as posaconazole, may decrease the clearance of zaleplon. Routine dosage adjustments of zaleplon are not required. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
Pramipexole: (Moderate) The use of zaleplon in combination with pramipexole may increase the risk of clinically significant sedation via a pharmacodynamic interaction.
Pregabalin: (Major) Initiate pregabalin at the lowest recommended dose and monitor patients for symptoms of sedation and somnolence during coadministration of pregabalin and zaleplon. Concomitant use of pregabalin with zaleplon may cause additive CNS depression and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Educate patients about the risks and symptoms of excessive CNS depression. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur.
Primidone: (Major) Coadministration of zaleplon and barbiturates may result in additive CNS depression. Caution should be exercised during concomitant use of anxiolytics, sedatives, and hypnotics and any barbiturate. In addition, zaleplon is partially

metabolized by CYP3A4, and concurrent use of strong CYP3A4 inducers, such as barbiturates, may increase the clearance of zaleplon. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
Prochlorperazine: (Moderate) Phenothiazines are CNS depressant drugs that may have cumulative effects when administered with other CNS depressant drugs and they should be used cautiously with anxiolytic, sedative, and hypnotics. Caution should be exercised during simultaneous use of these agents due to potential excessive CNS effects or additive hypotension. Additionally, sleep-related behaviors, such as sleep-driving, are more likely to occur during concurrent use of hypnotics and other CNS depressants than with use of a hypnotic alone.
Promethazine: (Moderate) Phenothiazines are CNS depressant drugs that may have cumulative effects when administered with other CNS depressant drugs and they should be used cautiously with anxiolytic, sedative, and hypnotics. Caution should be exercised during simultaneous use of these agents due to potential excessive CNS effects or additive hypotension. Additionally, sleep-related behaviors, such as sleep-driving, are more likely to occur during concurrent use of hypnotics and other CNS depressants than with use of a hypnotic alone.
Promethazine; Dextromethorphan: (Moderate) Phenothiazines are CNS depressant drugs that may have cumulative effects when administered with other CNS depressant drugs and they should be used cautiously with anxiolytic, sedative, and hypnotics. Caution should be exercised during simultaneous use of these agents due to potential excessive CNS effects or additive hypotension. Additionally, sleep-related behaviors, such as sleep-driving, are more likely to occur during concurrent use of hypnotics and other CNS depressants than with use of a hypnotic alone.
Promethazine; Phenylephrine: (Moderate) Phenothiazines are CNS depressant drugs that may have cumulative effects when administered with other CNS depressant drugs and they should be used cautiously with anxiolytic, sedative, and hypnotics. Caution should be exercised during simultaneous use of these agents due to potential excessive CNS effects or additive hypotension. Additionally, sleep-related behaviors, such as sleep-driving, are more likely to occur during concurrent use of hypnotics and other CNS depressants than with use of a hypnotic alone.
Propofol: (Moderate) Coadministration of zaleplon and general anesthetics may result in additive CNS depressant effects. In premarketing studies, zaleplon potentiated the CNS effects of ethanol, imipramine, and thioridazine for at least 2 to 4 hours. A similar interaction may occur with zaleplon and other CNS depressants including general anesthetics. If concurrent use is necessary, monitor for additive side effects. A temporary dose reduction of zaleplon should be considered following administration of general anesthetics. The risk of next-day psychomotor impairment is increased during co-administration, which may decrease the ability to perform tasks requiring full mental alertness such as driving.

Protriptyline: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of tricyclic antidepressants and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary. Coadministration of single doses of a tricyclic antidepressant and zaleplon produced additive effects on decreased alertness and impaired psychomotor performance for 2 to 4 hours after administration.
Pseudoephedrine; Triprolidine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Quazepam: (Major) Monitor for excessive sedation and somnolence during coadministration of zaleplon and benzodiazepines. Concurrent use may result in additive CNS depression. If used together, a reduction in the dose of one or both drugs may be needed.
QUEtiapine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of atypical antipsychotics and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Ramelteon: (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 buprenorphine, butorphanol, dronabinol, THC, nabilone, nalbuphine, and anxiolytics, sedatives, and hypnotics. 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: (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Limit the use of opioid pain medications with zaleplon 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. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors

occur. Educate patients about the risks and symptoms of excessive CNS depression.
Remimazolam: (Major) Monitor for excessive sedation and somnolence during coadministration of zaleplon and benzodiazepines. Concurrent use may result in additive CNS depression. If used together, a reduction in the dose of one or both drugs may be needed.
Ribociclib: (Moderate) Monitor for an increase in zaleplon-related adverse reactions if coadministration with ribociclib is necessary. Zaleplon is a CYP3A4 substrate and ribociclib is a strong CYP3A4 inhibitor. Coadministration with a moderate CYP3A4 inhibitor increased zaleplon exposure by 20%.
Ribociclib; Letrozole: (Moderate) Monitor for an increase in zaleplon-related adverse reactions if coadministration with ribociclib is necessary. Zaleplon is a CYP3A4 substrate and ribociclib is a strong CYP3A4 inhibitor. Coadministration with a moderate CYP3A4 inhibitor increased zaleplon exposure by 20%.
rifAMPin: (Moderate) Monitor for decreased efficacy of zaleplon if coadministration with rifampin is necessary. Zaleplon is a partial CYP3A4 substrate and rifampin is a strong CYP3A4 inducer. Although CYP3A4 is normally a minor metabolizing enzyme of zaleplon, multiple-dose administration of rifampin (600 mg every 24 hours for 14 days) reduced zaleplon Cmax and AUC by approximately 80%.
Rifapentine: (Moderate) Monitor for decreased efficacy when zaleplon is coadministered with rifapentine due to decreased zaleplon exposure. Zaleplon is partially metabolized by CYP3A4; rifapentine is a strong CYP3A4 inducer. Consider using an alternative non-CYP3A4 substrate hypnotic in patients taking strong CYP3A4 inducers. Coadministration with another strong CYP3A4 inducer reduced zaleplon exposure by approximately 80%.
risperiDONE: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of atypical antipsychotics and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Ritonavir: (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as ritonavir, may decrease the clearance of zaleplon. Routine dosage adjustments of zaleplon are not required. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
rOPINIRole: (Moderate) Concomitant use of ropinirole with other CNS depressants, such as zaleplon, can potentiate the sedation effects of ropinirole.
Rotigotine: (Moderate) A reduction in the dose of anxiolytics, sedatives, hypnotics and concomitantly administered dopamine agonists with sedative properties (e.g., ropinirole, pramipexole, rotigotine, apomorphine) should be considered to minimize additive sedative effects. In addition, the risk of next-day psychomotor impairment is increased during co-administration, which may decrease the ability to perform tasks requiring full mental alertness such as driving.
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 anxiolytics, sedatives, and hypnotics.
Saquinavir: (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as saquinavir, may decrease the clearance of zaleplon. Routine dosage adjustments of zaleplon are not required. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
Scopolamine: (Moderate) Scopolamine may cause dizziness and drowsiness. Concurrent use of scopolamine and CNS depressants can adversely increase the risk of CNS depression.
Secobarbital: (Major) Coadministration of zaleplon and barbiturates may result in additive CNS depression. Caution should be exercised during concomitant use of anxiolytics, sedatives, and hypnotics and any barbiturate. In addition, zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inducers, such as barbiturates, may increase the clearance of zaleplon. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
Sedating H1-blockers: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Selegiline: (Moderate) Monitor for excessive sedation and somnolence during coadministration of selegiline with anxiolytics, sedatives, and hypnotics. Concurrent use may result in additive CNS depression.
Sevoflurane: (Moderate) Coadministration of zaleplon and general anesthetics may result in additive CNS depressant effects. In premarketing studies, zaleplon potentiated the CNS effects of ethanol, imipramine, and thioridazine for at least 2 to 4 hours. A similar interaction may occur with zaleplon and other CNS depressants including general anesthetics. If concurrent use is necessary, monitor for additive side effects. A temporary dose reduction of zaleplon should be considered following administration of general anesthetics. The risk of next-day psychomotor impairment is increased during co-administration, which may decrease the ability to perform tasks requiring full mental alertness such as driving.
Sodium Oxybate: (Contraindicated) Sodium oxybate should not be used in combination with CNS depressant anxiolytics, sedatives, and hypnotics or other sedative CNS depressant drugs. Specifically, sodium oxybate use is contraindicated in patients being treated with sedative hypnotic drugs. Sodium oxybate (GHB) has the potential to impair cognitive and motor skills. For example, the concomitant use of barbiturates and

benzodiazepines increases sleep duration and may contribute to rapid onset, pronounced CNS depression, respiratory depression, or coma when combined with sodium oxybate.
St. John's Wort, Hypericum perforatum: (Moderate) Monitor for decreased efficacy/ineffectiveness of zaleplon if coadministration with St. John's Wort is necessary. Zaleplon is a CYP3A4 substrate and St. John's Wort is a strong CYP3A4 inducer. Although CYP3A4 is normally a minor metabolizing enzyme of zaleplon, coadministration with another strong CYP3A4 inducer reduced zaleplon exposure by approximately 80%. An alternative non-CYP3A4 substrate hypnotic agent may be considered in patients taking strong CYP3A4 inducers.
Stiripentol: (Moderate) Monitor for excessive sedation and somnolence during coadministration of stiripentol and zaleplon. CNS depressants can potentiate the effects of stiripentol.
SUFentanil: (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Limit the use of opioid pain medications with zaleplon 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. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression.
Suvorexant: (Moderate) Use of suvorexant with other sedatives and hypnotics should generally be avoided due to duplication of treatments and due to the additive CNS depressant and complex sleep-related behaviors that may occur. While anxiolytic medications may be used concurrently with suvorexant, a reduction in dose of one or both of these agents may be needed.
Tapentadol: (Major) Concomitant use of opioid agonists with other CNS depressants may cause excessive sedation and somnolence. Limit the use of opioid pain medications with anotehr CNS depressant 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.
Temazepam: (Major) Monitor for excessive sedation and somnolence during coadministration of zaleplon and benzodiazepines. Concurrent use may result in additive CNS depression. If used together, a reduction in the dose of one or both drugs may be needed.
Tetrabenazine: (Moderate) Concurrent use of tetrabenazine and drugs that can cause CNS depression, such as anxiolytics, sedatives, and hypnotics, can increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, dizziness, and orthostatic hypotension.

Thalidomide: (Major) The use of anxiolytics, sedatives, or hypnotics concomitantly with thalidomide may cause an additive sedative effect and should be avoided. Thalidomide frequently causes drowsiness and somnolence. Dose reductions may be required. Patients should be instructed to avoid situations where drowsiness may be a problem and not to take other medications that may cause drowsiness without adequate medical advice. Advise patients as to the possible impairment of mental and/or physical abilities required for the performance of hazardous tasks, such as driving a car or operating other complex or dangerous machinery.
Thioridazine: (Moderate) Phenothiazines are CNS depressant drugs that may have cumulative effects when administered with other CNS depressant drugs and they should be used cautiously with anxiolytic, sedative, and hypnotics. Caution should be exercised during simultaneous use of these agents due to potential excessive CNS effects or additive hypotension. Additionally, sleep-related behaviors, such as sleep-driving, are more likely to occur during concurrent use of hypnotics and other CNS depressants than with use of a hypnotic alone.
Thiothixene: (Moderate) Coadministration of zaleplon and antipsychotics like thiothixene can result in additive CNS depressant effects. In premarketing studies, zaleplon potentiated the CNS effects of ethanol, imipramine, and thioridazine for at least 2 to 4 hours. A similar interaction may occur with other antipsychotics.
Tipranavir: (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as tipranavir, may decrease the clearance of zaleplon. Routine dosage adjustments of zaleplon are not required. Dosage adjustments should be made on an individual basis according to efficacy and tolerability.
tiZANidine: (Moderate) Monitor for excessive sedation and somnolence during coadministration of tizanidine with anxiolytics, sedatives, and hypnotics. Concurrent use may result in additive CNS depression. A reduction in the dose of these medications may be considered to minimize additive sedative effects, if they occur. With hypnotic medications, the risk of next-day psychomotor impairment is increased during co-administration of other CNS depressants, which may decrease the ability to perform tasks requiring full mental alertness such as driving.
Tolcapone: (Major) Additive CNS depressant effects are possible during concurrent use of COMT inhibitors and zaleplon. If concurrent use is necessary, monitor for additive side effects. A reduction in the dose of one or both drugs may be needed. Patients should be advised to avoid driving or other tasks requiring mental alertness until they know how the combination affects them.
Topiramate: (Moderate) Although not specifically studied, coadministration of CNS depressant drugs (e.g., anxiolytics, sedatives, and hypnotics) 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: (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Limit the use of opioid pain medications with zaleplon 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. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression.
Tramadol; Acetaminophen: (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Limit the use of opioid pain medications with zaleplon 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. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression.
Tranylcypromine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of anxiolytics, sedatives, and hypnotics and monoamine oxidase inhibitors (MAOIs) due to the risk for additive CNS depression.
traZODone: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of zaleplon and other CNS depressants, such as trazodone, due to the risk for additive CNS depression and next-day psychomotor impairment; dosage adjustments may be necessary.
Triazolam: (Major) Monitor for excessive sedation and somnolence during coadministration of zaleplon and benzodiazepines. Concurrent use may result in additive CNS depression. If used together, a reduction in the dose of one or both drugs may be needed.
Tricyclic antidepressants: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of tricyclic antidepressants and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary. Coadministration of single doses of a tricyclic antidepressant and zaleplon produced additive effects on decreased alertness and impaired psychomotor performance for 2 to 4 hours after administration.
Trifluoperazine: (Moderate) Phenothiazines are CNS depressant drugs that may have cumulative effects when administered with other CNS depressant drugs and they should be used cautiously with anxiolytic, sedative, and hypnotics. Caution should be exercised during simultaneous use of these agents due to potential excessive CNS effects or additive hypotension. Additionally, sleep-related behaviors, such as sleep-driving, are more likely to occur during concurrent use of hypnotics and other CNS depressants than

with use of a hypnotic alone.
Trihexyphenidyl: (Moderate) CNS depressants, such as anxiolytics, sedatives, and hypnotics, can increase the sedative effects of trihexyphenidyl.
Trimethobenzamide: (Moderate) The concurrent use of trimethobenzamide with other medications that cause CNS depression, like anxiolytics, sedatives and hypnotics, may potentiate the effects of either trimethobenzamide or the anxiolytics, sedatives and hypnotics.
Trimipramine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of tricyclic antidepressants and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary. Coadministration of single doses of a tricyclic antidepressant and zaleplon produced additive effects on decreased alertness and impaired psychomotor performance for 2 to 4 hours after administration.
Triprolidine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
Tucatinib: (Moderate) Monitor for an increase in zaleplon-related adverse reactions if coadministration with tucatinib is necessary. Concurrent use may increase zaleplon exposure. Zaleplon is a CYP3A4 substrate and tucatinib is a strong CYP3A4 inhibitor.
Valerian, Valeriana officinalis: (Major) Patients who are taking sedative/hypnotic drugs should generally avoid concomitant administration of valerian. Any substances that act on the CNS, including sedatives and hypnotics, may theoretically interact with valerian, Valeriana officinalis. 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. These interactions are probably pharmacodynamic in nature. There is a possibility of interaction with valerian at normal prescription dosages of sedatives and hypnotics.
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 anxiolytics, sedatives, and hypnotics.
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.
Vonoprazan; Amoxicillin; Clarithromycin: (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as clarithromycin, may decrease the clearance of zaleplon. Routine dosage adjustments of zaleplon are not required. Dosage adjustments should be made on an individual basis according to

efficacy and tolerability.
Voriconazole: (Moderate) Monitor for an increase in zaleplon-related adverse reactions if coadministration with voriconazole is necessary. Dosage adjustments should be made on an individual basis according to efficacy and tolerability. Zaleplon is a CYP3A4 substrate and voriconazole is a strong CYP3A4 inhibitor. Coadministration with a moderate CYP3A4 inhibitor increased zaleplon exposure by 20%.
Ziconotide: (Moderate) Due to potentially additive effects, dosage adjustments may be necessary if ziconotide is used with a drug that has CNS depressant effects such as anxiolytics, sedatives, and hypnotics. Coadministration of CNS depressants may increase drowsiness, dizziness, and confusion that are associated with ziconotide. Patients taking sedatives with ziconotide may be at higher risk of depressed levels of consciousness. If altered consciousness occurs, consideration of sedative cessation is warranted in addition to ziconotide discontinuation.
Ziprasidone: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of atypical antipsychotics and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.
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

abdominal pain, anorexia, appetite stimulation, cheilitis, cholelithiasis, colitis, constipation, dyspepsia, dysphagia, elevated hepatic enzymes, eructation, esophagitis, flatulence, gastritis, GI obstruction, gingivitis, glossitis, hypersalivation, melena, nausea, oral ulceration, peptic ulcer, stomatitis, teeth grinding (bruxism), tongue discoloration, xerostomia

Zaleplon has been associated with gastrointestinal adverse reactions. During clinical trials in which patients received zaleplon (5 mg, 10 mg, or 20 mg) or placebo for 28 or 35 nights, the following gastrointestinal (GI) effects were reported in the active treatment groups versus the placebo groups, respectively: abdominal pain (6% vs 3%), anorexia (2% or less vs less than 1%), colitis (1% or less vs 0%), and nausea (6% to 8% vs 7%). During other pre-marketing evaluation of zaleplon, the following adverse GI effects were reported in at least 1% of patients: constipation, xerostomia, and dyspepsia. Adverse GI effects reported in 0.1% to 1% of patients included eructation, esophagitis, flatulence, gastritis, gastroenteritis, gingivitis, glossitis, appetite stimulation, melena, oral ulceration,

rectal hemorrhage, and stomatitis. Rarely reported effects (less than 0.1%) included aphthous stomatitis, biliary pain, teeth grinding (bruxism), cardiospasm, cheilitis, cholelithiasis, peptic ulcer, dysphagia, enteritis, gum hemorrhage, hypersalivation, GI obstruction, elevated hepatic enzymes, tongue discoloration, tongue swelling, and ulcerative stomatitis.

asthenia, back pain, edema, fever, malaise

During clinical trials in which patients received zaleplon (5 mg, 10 mg, or 20 mg) or placebo for 28 or 35 nights, the following adverse general effects were reported in the active treatment groups versus the placebo groups, respectively: asthenia (5% to 7% vs 5%) and malaise (2% or less vs less than 1%). During other pre-marketing evaluation of zaleplon, the following adverse general effects were reported in at least 1% of patients: back pain and fever. Adverse effects reported in 0.1% to 1% of patients included chills, face edema, generalized edema, and hangover effect.

abnormal dreams, agitation, amnesia, anxiety, ataxia, confusion, depression, dizziness, drowsiness, dysarthria, dystonic reaction, emotional lability, euphoria, hallucinations, headache, hostility, hyperesthesia, hyperkinesis, hyperreflexia, hypertonia, hyporeflexia, hypotonia, impaired cognition, libido decrease, memory impairment, myoclonia, neuropathic pain, nightmares, nystagmus, paresthesias, psychomotor impairment, ptosis, tremor, trismus, vertigo

A variety of centrally-mediated (CNS) effects have been reported during the use of sedative/hypnotics, including abnormal thinking and behavioral changes similar to those produced by alcohol or other CNS depressants. During clinical trials in which patients received zaleplon (5 mg, 10 mg, or 20 mg) or placebo for 28 or 35 nights, the following CNS and psychiatric effects were reported more frequently in the active treatment groups than the placebo groups: headache (30% to 42%), amnesia (2% to 4%), confusion (1% or less), depersonalization (2% or less), dizziness (7% to 9%), hallucinations (1% or less), hypertonia (1% or less), hyperesthesia (2% or less), paresthesias (3%), drowsiness (5% to 6%), tremor (2%), and vertigo (1% or less). Because zaleplon can cause drowsiness and a decreased level of consciousness (impaired cognition), there is a higher risk of falls, particularly in the elderly, with the potential for subsequent severe injuries. During other premarketing evaluations of zaleplon, the following adverse CNS effects were reported in at least 1% of patients: anxiety, depression, nervousness, and abnormal thinking/difficulty concentrating. Adverse CNS effects reported in 0.1% to 1% of patients included abnormal gait, agitation, apathy, ataxia, circumoral paresthesias, emotional lability, euphoria, hyperkinesis, hypotonia, incoordination, insomnia, libido decrease, neuropathic pain, and nystagmus. Rarely reported effects (less than 0.1%) included CNS

stimulation, delusions, dysarthria, dystonic reaction, facial paralysis, hostility, hypokinesia, myoclonia, neuropathy, psychomotor impairment, ptosis, hyporeflexia, hyperreflexia, stupor, and trismus. Abnormal dreams and nightmares have been reported during postmarketing use. Studies examining the effect of single doses of zaleplon 10 mg or 20 mg on short-term memory impairment showed that the effects were most noticeable at 1 hour, with a tendency for the effect to be greater with zaleplon 20 mg. Consistent with the rapid clearance of the drug, memory impairment was no longer present as early as 2 hours after dosing in one study, and in none of the studies after 3 to 4 hours. The sedative and psychomotor impairment effects of zaleplon were observed similarly, with zaleplon 20 mg showing a greater effect. Because the elderly may be more sensitive to the CNS effects of zaleplon, a lower dose is recommended in this patient population.

complex sleep-related behaviors, somnambulism

Sedative-hypnotics can cause complex sleep-related behaviors such as phone calls, sexual activity, preparing and eating food, or driving while not fully awake and in some cases having no memory of the event. These behaviors appear to be more frequent with nonbenzodiazepine benzodiazepine-receptor agonists (NBRAs), such as zaleplon, than other sedative-hypnotics and may occur with or without the concomitant use of alcohol or other CNS depressants. Although rare, serious injuries or death have occurred in patients with and without a history of such behaviors, even at the lowest recommended doses; the behaviors can occur after just one dose. Sleep-talking and sleep-walking (somnambulism) were reported in less than 0.1% of patients during premarketing evaluation of zaleplon. Patients should be informed of the risks before receiving zaleplon, including instructions to discontinue the medication if they experience a sleep-related episode and to contact their health care provider immediately. Health care professionals and patients are encouraged to report adverse events or side effects related to the use of NBRAs to the FDA MedWatch Safety Information and Adverse Event Reporting Program.

blepharitis, cataracts, conjunctivitis, corneal erosion, diplopia, dysgeusia, hearing loss, hyperacusis, ocular hemorrhage, ocular pain, otalgia, parosmia, photophobia, retinal detachment, tinnitus, visual impairment, xerophthalmia

During clinical trials in which patients received zaleplon (5 mg, 10 mg, or 20 mg) or placebo for 28 or 35 nights, the following adverse effects affecting the special senses were reported in the active treatment groups versus the placebo groups, respectively: visual impairment (2% or less vs less than 1%), otalgia (1% or less vs 0%), ocular pain (3% to 4% vs 2%), hyperacusis (1% to 2% vs less than 1%), and parosmia (2% or less vs less

than 1%). During other pre-marketing evaluation of zaleplon, adverse effects affecting the special senses that were reported in at least 1% of patients included conjunctivitis and dysgeusia. Infrequently reported effects (0.1% to 1%) included diplopia, photophobia, tinnitus, watery eyes, and xerophthalmia. Rare (less than 0.1%) reactions included abnormality of accommodation, blepharitis, cataracts, corneal erosion, deafness (hearing loss), glaucoma, labyrinthitis, retinal detachment, taste loss, ocular hemorrhage, and visual field defect.

acne vulgaris, alopecia, anaphylactoid reactions, angioedema, atopic dermatitis, contact dermatitis, hyperhidrosis, maculopapular rash, photosensitivity, pruritus, psoriasis, rash, skin discoloration, urticaria, xerosis

During clinical trials in which patients received zaleplon (5 mg, 10 mg, or 20 mg) or placebo for 28 or 35 nights, photosensitivity was reported in 1% or less of patients in the active treatment groups and less than 1% of patients in the placebo groups. During other pre-marketing evaluation of zaleplon, dermatologic and/or allergic effects including pruritus and rash (unspecified) were reported in at least 1% of patients. Infrequently reported dermatologic effects (0.1% to 1%) included acne vulgaris, alopecia, contact dermatitis, xerosis, atopic dermatitis, maculopapular rash, skin hypertrophy, hyperhidrosis, urticaria, and vesiculobullous rash. Rare (less than 0.1%) reactions included melanosis, psoriasis, pustular rash, and skin discoloration. Anaphylactoid reactions (e.g., angioedema) may occur with sedative-hypnotics, and may become evident as early as the initial dose. Airway obstruction resulting from angioedema of the tongue, glottis, or larynx may be fatal. Other symptoms suggestive of anaphylaxis include shortness of breath, bronchial spasm, skin eruptions, low blood pressure, and circulatory collapse. Some formulations of zaleplon contain FD&C Yellow Number 5 (tartrazine) which may cause allergic-type reactions in certain susceptible persons. Anaphylactic and anaphylactoid reactions have been reported during post-market use of zaleplon. Patients should be instructed on the appropriate action in the event of an allergic reaction. Treatment with zaleplon should not be reinitiated in patients who experience angioedema.

apnea, bronchospasm, dyspnea, epistaxis, hiccups, hyperventilation, laryngitis, pleural effusion

During clinical trials in which patients received zaleplon (5 mg, 10 mg, or 20 mg) or placebo for 28 or 35 nights, epistaxis was reported in 1% or less of patients in the active treatment groups and less than 1% of patients in the placebo groups. During other pre-marketing evaluation of zaleplon, bronchitis was reported in at least 1% of patients. Infrequently reported respiratory effects (0.1% to 1%) included asthma (bronchospasm),

dyspnea, laryngitis, pneumonia, snoring, and voice alteration. Rare (less than 0.1%) reactions included apnea, hiccups, hyperventilation, pleural effusion, and increased sputum.

respiratory depression

Signs and symptoms of zaleplon overdose can be expected to present as exaggerations of its pharmacological effects. Overdose is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion, and lethargy; in more serious cases, symptoms may include ataxia, hypotonia, low blood pressure, respiratory depression, rarely coma, and very rarely death. Most fatal outcomes following overdose have involved ingestion of additional CNS depressants. General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Animal studies suggest that flumazenil is an antagonist to zaleplon. However, there is no pre-marketing clinical experience with the use of flumazenil as an antidote to a zaleplon overdose.

arthralgia, arthropathy, myalgia, myasthenia, osteoporosis

During pre-marketing evaluation of zaleplon, adverse musculoskeletal effects that were reported in at least 1% of patients included arthralgia, arthritis, and myalgia. Infrequently reported musculoskeletal effects (0.1% to 1%) included arthrosis, bursitis, arthropathy (joint pain, stiffness, or swelling), myasthenia, tenosynovitis, and neck rigidity. Rare (less than 0.1%) reactions included myositis and osteoporosis.

cystitis, dysmenorrhea, dysuria, hematuria, impotence (erectile dysfunction), increased urinary frequency, leukorrhea, mastalgia, menorrhagia, menstrual irregularity, nephrolithiasis, proteinuria, urinary incontinence, urinary retention, urinary urgency, vaginal bleeding, vaginitis

During clinical trials in which patients received zaleplon (5 mg, 10 mg, or 20 mg) or placebo for 28 or 35 nights, dysmenorrhea was reported in 3% to 4% of patients in the active treatment groups and 2% of patients in the placebo groups. During other pre-marketing evaluation of zaleplon, infrequently reported genitourinary or reproductive effects (0.1% to 1%) included bladder pain, mastalgia, cystitis, decreased urine stream, dysuria, hematuria, impotence (erectile dysfunction), nephrolithiasis, kidney pain, menorrhagia, metrorrhagia, increased urinary frequency, urinary incontinence, urinary urgency, and vaginitis. Rare (less than 0.1%) reactions included proteinuria, delayed menstruation (menstrual irregularity), leukorrhea, menopause, urethritis, urinary retention, and vaginal bleeding (hemorrhage).

gout, hyperbilirubinemia, hypercholesterolemia, hyperglycemia, hyperuricemia, hypoglycemia, lactose intolerance, peripheral edema, weight gain, weight loss

During clinical trials in which patients received zaleplon (5 mg, 10 mg, or 20 mg) or placebo for 28 or 35 nights, peripheral edema was reported in 1% of patients in the active treatment groups and less than 1% of patients in the placebo groups. During other pre-marketing evaluation of zaleplon, infrequently reported metabolic or nutritional effects (0.1% to 1%) included edema, gout, hypercholesterolemia, thirst, and weight gain. Rare (less than 0.1%) reactions included hyperbilirubinemia, hyperglycemia, hyperuricemia, hypoglycemia, hypoglycemic reaction, ketosis, lactose intolerance, and weight loss.

angina, bradycardia, bundle-branch block, chest pain (unspecified), cyanosis, hypertension, hypotension, orthostatic hypotension, palpitations, pericardial effusion, peripheral vasodilation, pulmonary embolism, sinus tachycardia, syncope, ventricular tachycardia

During pre-marketing evaluation of zaleplon, chest pain (unspecified) was reported in at least 1% of patients. The following adverse cardiovascular effects were reported in 0.1% to 1% of patients: angina, bundle-branch block, substernal chest pain, hypertension, hypotension, palpitations, syncope, sinus tachycardia, peripheral vasodilation, and ventricular extrasystoles. Rare (less than 0.1%) cardiovascular or cerebrovascular reactions included bigeminy, cerebral ischemia, cyanosis, pericardial effusion, orthostatic hypotension, pulmonary embolism, sinus bradycardia, thrombophlebitis, and ventricular tachycardia.

diabetes mellitus, goiter, hypothyroidism

During pre-marketing evaluation of zaleplon, endocrine effects including diabetes mellitus, goiter, and hypothyroidism were reported in less than 0.1% of patients.

anemia, ecchymosis, eosinophilia, leukocytosis, lymphadenopathy, lymphocytosis, purpura

During pre-marketing evaluation of zaleplon, infrequently reported hematologic effects (0.1% to 1%) included anemia, ecchymosis, and lymphadenopathy. Rare (less than 0.1%) hematologic reactions included eosinophilia, leukocytosis, lymphocytosis, and purpura.

insomnia, physiological dependence, seizures

Premarketing studies showed that zaleplon was not associated with a withdrawal syndrome following chronic dosing. Most patients experienced rebound insomnia on the first night following withdrawal of zaleplon; insomnia appeared to be resolved by the second night. It has not been determined whether zaleplon is associated with physiological dependence. Available data cannot provide a reliable estimate of the incidence of dependence during treatment at recommended doses. Other sedative/hypnotics have been associated with various signs and symptoms following abrupt discontinuation, ranging from mild dysphoria and insomnia to a withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremulousness, and seizures. Seizures have been observed in two patients, one of which had a prior seizure, in clinical trials with zaleplon. Seizures and death have been seen following the withdrawal of zaleplon from animals at doses many times higher than those proposed for human use.

Description

Zaleplon is a short-acting, non-benzodiazepine sedative-hypnotic approved for the short-term treatment of insomnia. It belongs to a class of drugs known as pyrazolopyrimidines. Zaleplon possesses anticonvulsant, anxiolytic, hypnotic, and myorelaxant properties. It has been shown to decrease the time to sleep onset for up to 35 days in clinical trials without tolerance and has minimal withdrawal-emergent adverse effects. Zaleplon also has a short terminal elimination half-life, making it less likely to cause next-day impairment compared to other sedative-hypnotics. As with all medications in this class, zaleplon has a boxed warning for an increased risk of complex sleep behaviors, which may include sleep-walking, sleep-driving, and engaging in other activities while not fully awake. Zaleplon also has CNS-depressant effects and should only be taken when there is enough time for a full night's rest to avoid next day sedation. Patients should be made aware of these risks prior to starting treatment with zaleplon.

Mechanism Of Action

Zaleplon is an agonist at type 1 benzodiazepine (BZ1 or omega1) receptors on the GABA-A/chloride-ion channel complex within the CNS. Specifically, it has been shown that zaleplon binds selectively to the brain omega1 receptor situated on the alpha subunit of the GABA-A receptor complex. Nonspecific subunit modulation of this complex is also hypothesized to be responsible for some pharmacological properties of benzodiazepines, including sedative, anticonvulsant, anxiolytic, and myorelaxant effects. However, zaleplon demonstrates higher affinity for the alpha1 subunit and lower affinity

for alpha2 and alpha3 subunits, making it more selective for sedative and hypnotic effects while also showing less activity as an anxiolytic than benzodiazepines.

Pharmacokinetics

Zaleplon is administered orally. Zaleplon is lipophilic and is distributed substantially into extravascular tissues. The in vitro plasma protein binding of zaleplon is approximately 60%; the drug is not sensitive to alterations in protein binding. The blood to plasma ratio for zaleplon is approximately 1 which indicates that the drug is uniformly distributed throughout the blood with no extensive distribution into red blood cells. Zaleplon is primarily metabolized by aldehyde oxidase to form 5-oxo-zaleplon. To a lesser extent, zaleplon is metabolized by CYP3A4 to form desethylzaleplon, which is quickly converted to 5-oxo-desethylzaleplon. All metabolites are inactive. Based on radiolabeled studies, approximately 70% of an administered dose is recovered in urine within 48 hours (71% recovered within 6 days), mostly as zaleplon metabolites and their glucuronides. An additional 17% is recovered in feces within 6 days, almost all as 5-oxo-zaleplon. The terminal-phase elimination half-life of zaleplon is 1 hour.

Affected cytochrome P450 (CYP450) isoenzymes, other enzymes, and drug transporters: Aldehyde oxidase, CYP3A4
Aldehyde oxidase (in vitro) and CYP3A4 (in vitro and in vivo) are the primary and secondary enzymes, respectively, responsible for zaleplon metabolism. Cimetidine, an aldehyde oxidase inhibitor and CYP3A inhibitor, will reduce the metabolism of zaleplon. CYP3A4, by itself, is a minor elimination pathway of zaleplon. However, the Cmax and AUC of zaleplon were reduced by 80% during coadministration of rifampin, a strong CYP3A4 inducer. Coadministration of zaleplon and a single dose of a moderate CYP3A4 inhibitor produced a 34% increase in Cmax and 20% increase in AUC of zaleplon. Routine dosage adjustments are not required, although patients should be monitored for a decrease in efficacy or an increase in adverse effects during concurrent use of zaleplon and potent CYP3A4 inducers or potent CYP3A4 inhibitors, respectively.

Route-Specific Pharmacokinetics

- **Oral Route**

Following oral administration, the drug is rapidly and almost completely absorbed. The oral bioavailability is approximately 30% because of extensive first-pass metabolism. The onset of action is approximately 30 minutes and the duration of action is about 4 hours. Peak zaleplon serum concentrations occur in about 1 hour. Heavy, high-fat meals prolong the absorption of zaleplon compared to the fasted state. Tmax is delayed by approximately 2 hours and Cmax is reduced by about 35%. The AUC and elimination of zaleplon are not significantly affected. Accumulation of the drug does not occur with

once-daily dosing and its pharmacokinetics are dose proportional in the therapeutic range. Initial dosage adjustment is recommended for those with hepatic disease, who are taking drugs that decrease zaleplon metabolism, for the elderly, and for debilitated adults.

- **Hepatic Impairment**

Compared to healthy subjects, the oral clearance of zaleplon is reduced by 70% and 87% in patients with compensated and decompensated cirrhosis, respectively, leading to marked increases in mean Cmax and AUC (up to 4-fold and 7-fold in compensated and decompensated cirrhotic patients, respectively). Initial dosage adjustment is recommended for those with hepatic disease.

- **Renal Impairment**

Because renal excretion of unchanged zaleplon accounts for less than 1% of the administered dose, the pharmacokinetics of zaleplon are not altered in patients with renal insufficiency. In patients with mild to moderate renal impairment, dosage adjustment is not needed. However, zaleplon has not been studied clinically in patients with severe renal impairment.

- **Geriatric**

The pharmacokinetics of zaleplon have been investigated in 3 studies with geriatric men and women ranging in age from 65 to 85 years. The pharmacokinetics in elderly subjects, including those over 75 years of age, are not significantly different from those in young healthy adult subjects. However, clinical response is altered. Elderly patients typically respond to lower zaleplon dosages (e.g., 5 mg) vs. younger adults, indicated greater sensitivity to the drug. Initial dosage adjustment of zaleplon is recommended for the elderly and for debilitated adults.

- **Ethnic Differences**

In Japanese adults (and possibly other Asian populations), the Cmax and AUC of zaleplon were increased 37% and 64%, respectively. This is likely due to differences in body weight or may represent differences in enzyme activities resulting from differences in diet, environment, or other factors.

Administration

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

Oral Administration

Administer immediately before bedtime or after the patient has gone to bed and has experienced difficulty falling asleep, as long as at least 4 hours of sleep time remain.

Administration with or immediately after a heavy, high-fat meal slows absorption and is expected to reduce effects on sleep latency.

Maximum Dosage Limits

- **Adults**
  20 mg/day PO at bedtime. Debilitated adult patients may require 10 mg/day PO.
- **Geriatric**
  10 mg/day PO at bedtime.
- **Adolescents**
  Safety and efficacy have not been established.
- **Children**
  Safety and efficacy have not been established.
- **Infants**
  Not indicated.

Dosage Forms

- Zaleplon 10mg Oral capsule
- Zaleplon 5mg Oral capsule

Dosage Adjustment Guidelines

Hepatic Impairment

Mild to moderate hepatic impairment (e.g., Child Pugh A or B): Use an initial dose of 5 mg PO at bedtime for mild to moderate hepatic impairment due to reduced clearance. Severe hepatic impairment (i.e., Child Pugh C): Zaleplon is not recommended. Marked increases in maximal concentrations and exposure occur (up to 4-fold and 7-fold in compensated and decompensated cirrhotic patients, respectively).

Renal Impairment

No dosage adjustment is necessary in patients with mild to moderate renal impairment. Zaleplon has not been adequately studied in patients with severe renal impairment. Renal excretion of unchanged zaleplon accounts for less than 1% of the administered dose and zaleplon pharmacokinetics are not altered in patients with renal insufficiency.