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REVIEWED
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CLASSES

Anticonvulsants, Benzodiazepines
Anxiolytics, Benzodiazepines
Benzodiazepine Sedative/Hypnotics

BOXED WARNING

Alcoholism, chronic obstructive pulmonary disease (COPD), CNS depression, coadministration with other CNS depressants, congenital heart disease, ethanol intoxication, pulmonary disease, pulmonary hypertension, respiratory depression, respiratory insufficiency, sleep apnea, status asthmaticus

As with other benzodiazepines, lorazepam should be used with extreme caution in patients with pulmonary disease and in patients with respiratory insufficiency resulting from chronic obstructive pulmonary disease (COPD), status asthmaticus, abnormal airway anatomy, cyanotic congenital heart disease, or pulmonary hypertension. Additionally, avoid coadministration with other CNS depressants, especially opioids, when possible, as this significantly increases the risk for profound sedation, respiratory depression, low blood pressure, and death. Reserve concomitant use of these drugs for patients in whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations possible and monitor patients closely for signs and symptoms of respiratory depression and sedation. Lorazepam injection is contraindicated in patients with sleep apnea syndrome or severe respiratory insufficiency who are not receiving mechanical ventilation. Lorazepam can cause respiratory depression, apnea, airway obstruction, and oxygen desaturation; it is more likely to cause adverse respiratory effects when administered to patients with pulmonary conditions, significant CNS depression, or ethanol intoxication. Avoid use of lorazepam in patients with active alcoholism. In addition, hypercarbia and hypoxia can occur after lorazepam administration and may pose a significant risk to patients with congenital heart disease or pulmonary hypertension. Carefully monitor respiratory status and oxygen saturation in at risk patients.

DEA CLASS

Rx, schedule IV

DESCRIPTION

Oral and parenteral benzodiazepine; glucuronidated to inactive metabolites; used for anxiety disorders, acute ethanol withdrawal, preoperative sedation and amnesia; replaced diazepam as the preferred parenteral drug for status epilepticus due to longer persistence in the CNS.

COMMON BRAND NAMES

Ativan

HOW SUPPLIED

Ativan/Lorazepam Intramuscular Inj Sol: 1mL, 2mg, 4mg
Ativan/Lorazepam Intravenous Inj Sol: 1mL, 2mg, 4mg
Ativan/Lorazepam Oral Tab: 0.5mg, 1mg, 2mg
Lorazepam Oral Sol: 1mL, 2mg

DOSAGE & INDICATIONS

For the short-term management of anxiety.

Oral dosage

Adults

Initially, 2 to 3 mg/day PO given in 2 to 3 divided doses. In debilitated adults give 1 to 2 mg/day PO in 2 to 3 divided doses initially. Increase gradually as needed and tolerated. The usual dosage is 2 to 6 mg/day PO. Range: 1 to 10 mg/day PO. When a higher dosage is needed, the evening dose should be increased before the daytime doses. Efficacy of long-term use (more than 4 months) for anxiety disorders has not been evaluated.

Geriatric Adults

Initially, 1 to 2 mg/day PO given in 2 to 3 divided doses, then increase gradually as needed and tolerated. The usual dosage is 2 to 6 mg/day PO. Use smallest effective dose in order to reduce the risk of ataxia or oversedation. The federal Omnibus Budget Reconciliation Act (OBRA) regulates the use of anxiolytics in long-term care facility (LTCF) residents. Max: 2 mg/day PO in residents meeting the criteria for treatment, except when documentation is provided showing that higher doses are necessary to maintain or improve the resident's functional status. In addition, the facility should attempt periodic tapering of the medication or provide documentation of medical necessity in accordance with OBRA guidelines.

Children and Adolescents 12 years and older

Initially, 2 to 3 mg/day PO given in 2 to 3 divided doses. In debilitated patients give 1 to 2 mg/day PO in 2 to 3 divided doses initially. Increase gradually as needed and tolerated. The usual dosage is 2 to 6 mg/day PO. Range: 1 to 10 mg/day PO. When a higher dosage is

needed, the evening dose should be increased before the daytime doses. Efficacy of long-term use (more than 4 months) for anxiety disorders has not been evaluated.

Children† 11 years and younger

Dosage not available for anxiety disorders; however, lorazepam 0.025 to 0.05 mg/kg/dose PO as needed (no more frequently than every 4 hours) has been used in burn patients with anxiety related to being in the hospital, dressing changes, etc. In older pediatric patients, the daily dosage for anxiety disorders is typically divided into 2 to 3 doses and should not exceed 10 mg/day in those 12 years and older.

For the short-term treatment of insomnia due to anxiety or transient situational stress.

Oral dosage

Adults, Adolescents, and Children 12 years and older

2 to 4 mg PO at bedtime as needed. Efficacy of long-term use (more than 4 months) has not been evaluated.

Geriatric Adults

Initially, use a low dosage (i.e., 1 to 2 mg PO) and titrate slowly in the geriatric patient. Usual adult dose range is 2 to 4 mg PO at bedtime as needed; use for more than 4 months has not been evaluated. The federal Omnibus Budget Reconciliation Act (OBRA) regulates the use of sedative/hypnotics in long-term care facility (LTCF) residents. In residents meeting the criteria for treatment, the dose of lorazepam should not exceed 1 mg/day PO, except when documentation is provided showing that higher doses are necessary to maintain or improve the resident's functional status. All sleep medications should be used in accordance with approved product labeling. If the sleep agent is used routinely and is beyond the manufacturer's recommendations for duration of use, the facility should attempt a quarterly taper, unless clinically contraindicated as defined in the OBRA guidelines.

For procedural sedation or preoperative sedation induction.

For operative amnesia induction in adult patients.

Intravenous dosage

Adults

Up to 0.05 mg/kg IV during surgery or the procedure; maximum dose is 4 mg IV.

For preoperative sedation induction and/or relief of preoperative anxiety in adult patients.

Intravenous or Intramuscular dosage

Adults

0.044 mg/kg IV 15—20 minutes prior to surgery or the procedure; maximum dose is 2 mg IV. Alternatively, 0.05 mg/kg IM administered two hours prior to surgery or the procedure; maximum dose is 4 mg IM.

For amnesia induction† and anxiety relief in pediatric patients.

Oral dosage

Infants, Children, and Adolescents

0.05 mg/kg PO as a single dose 45 to 90 minutes prior to procedure. Dose range: 0.02 to 0.09 mg/kg/dose. Max: 4 mg/dose.

Intravenous or Intramuscular dosage

Infants†, Children†, and Adolescents†

0.05 mg/kg IV or IM as a single dose prior to procedure. Dose range: 0.02 to 0.1 mg/kg/dose. Lorazepam 2 mg IV will sedate most adult patients. Max: 4 mg/dose. For optimum lack of recall, administer IV dose 15 to 20 minutes prior to procedure and IM dose 2 hours prior to procedure.

For the treatment of status epilepticus.

NOTE: The intramuscular route is not preferred for the treatment of status epilepticus because therapeutic concentrations may not be achieved as quickly compared to using the intravenous route. However, if an intravenous port is not available, the intramuscular route may be useful.

Intravenous dosage (preferred) or Intramuscular dosage

Adults

4 mg IV given slowly at a rate of 2 mg/minute. A second 4 mg dose may be given in 10—15 minutes if needed. Experience with further doses of lorazepam is limited.

Infants†, Children†, and Adolescents†

0.05 to 0.1 mg/kg IV (Max: 4 mg/dose) as a single dose administered slowly over 1 to 2 minutes. Max rate: 2 mg/minute. May repeat dose in 10 to 15 minutes if needed.

Neonates†

0.05 to 0.1 mg/kg IV as a single dose administered slowly over 2 to 5 minutes. May repeat dose in 10 to 15 minutes if needed.

For sedation maintenance† in mechanically-ventilated patients, to alleviate agitation† and/or anxiety.

Intermittent Intravenous dosage

Adults

0.044 mg/kg (e.g., 2—4 mg) IV every 2—4 hours, as needed; however, the required dosage is highly variable and should be titrated to desired degree of sedation. A single dose should not exceed 4 mg IV.

Neonates, Infants, Children, and Adolescents

0.05 mg/kg/dose IV every 2 to 8 hours as needed. Dose range: 0.025 to 0.1 mg/kg/dose. Max initial dose: 2 mg/dose. Due to a prolonged half-life, neonates and infants may require doses at less frequent intervals (e.g., every 6 to 8 hours) compared to children and adolescents.

Continuous IV Infusion† dosage

Adults

The usual dosage range is 0.5—8 mg/hour (or 0.01—0.1 mg/kg/hour); titrated to effect. The required dosage is highly variable and should be titrated to desired degree of sedation. A loading dose (i.e., 2—4 mg IV) is generally required.

For the treatment of alcohol withdrawal†.

For acute alcohol-related seizure prophylaxis†.

Intravenous dosage

Adults

One study has reported that a single dose of lorazepam 2 mg IV given within 6 hours of a witnessed ethanol-related seizure may significantly reduce the recurrence of a second seizure, and decrease the need for hospitalization.

For the treatment and prevention of the symptoms of alcohol withdrawal†.

Intravenous, Intramuscular, or Oral dosage

Adults

Initially 1—2 mg IV, IM, or PO every 8 hours. Titrate dose for desired clinical response. Maximum single dose is 4 mg. Decrease the dose after 1—2 days of therapy as clinically indicated and tolerated. NOTE: Dosing is highly variable in this condition. Cases have been reported where some patients required massive doses of benzodiazepines during the acute phase of ethanol withdrawal. Intravenous diazepam doses of 270 mg over 45 minutes and 2335 mg over a period of 4 days have been reported.

For chemotherapy-induced nausea/vomiting prophylaxis† as an adjunct to antiemetics.

Intravenous dosage

Adults

Doses of 0.025 mg/kg IV have been reported to be effective in reducing emesis and anxiety due to chemotherapy with minimal adverse effects. Alternatively, 1.5 mg/m2 (Usual Max: 3 mg) IV can be given 45 minutes prior to initiation of chemotherapy. Dosage generally produces some amnesia of short-term memory.

Children and Adolescents

0.04 to 0.05 mg/kg IV as a single dose administered 30 minutes prior to chemotherapy. Infuse over 15 to 20 minutes. Max: 4 mg/dose. Alternatively, 0.025 to 0.05 mg/kg/dose IV every 6 hours as needed for management of anticipatory or breakthrough nausea/vomiting. Max: 4 mg/dose.

Oral dosage

Children and Adolescents

Limited data available; 0.025 to 0.05 mg/kg/dose PO every 6 hours as needed for management of anticipatory nausea/vomiting. Max: 4 mg/dose. May start 12 to 24 hours prior to chemotherapy.

†Indicates off-label use

MAXIMUM DOSAGE

Adults

10 mg/day PO; maximum IM and IV dose highly variable dependent upon indication.

Geriatric

10 mg/day PO; maximum IM and IV dose highly variable depending upon indication.

Adolescents

10 mg/day PO for anxiety disorders; 4 mg/day PO for insomnia. Safety and efficacy of parenteral lorazepam have not been established. Specific maximum dosage information not available; the dose required is dependent on route of administration, indication, and clinical response.

Children

12 years: 10 mg/day PO for anxiety disorders; 4 mg/day PO for insomnia. Safety and efficacy of parenteral lorazepam have not been established. Specific maximum dosage information not available; the dose required is dependent on route of administration, indication, and clinical response
1 to 11 years: Safety and efficacy have not been established. Specific maximum dosage information not available; the dose required is dependent on route of administration, indication, and clinical response.

Infants

Safety and efficacy have not been established. Specific maximum dosage information not available; the dose required is dependent on route of administration, indication, and clinical response.

Neonates

Safety and efficacy have not been established. Specific maximum dosage information not available; the dose required is dependent on route of administration, indication, and clinical response.

DOSING CONSIDERATIONS

Hepatic Impairment

Lorazepam dosage should be modified based on clinical response and degree of hepatic impairment; a smaller dosage may be sufficient for patients with severe insufficiency. No quantitative recommendations are available.

Renal Impairment

Lorazepam dosage should be modified depending on clinical response and degree of renal impairment. No quantitative recommendations are available. Patients with renal impairment receiving high doses of intravenous lorazepam may be more likely to develop propylene glycol toxicity.

ADMINISTRATION

Oral Administration

Tablets and oral solution concentrate are available to be administered orally. In some countries, a sublingual† dosage form is available; some published literature describes the effective sublingual administration† of available oral tablets, particularly in pre-operative use; chronic use of this administration route is not well-supported.

Oral Liquid Formulations

Oral solution concentrate: The dose of the oral concentrate solution should be added to 30 ml or more of liquid (e.g., water, juices, carbonated, soda-like beverages) or to semi-solid foods (e.g., applesauce, pudding) prior to administration.

Injectable Administration

For intravenous or intramuscular administration only. Do not administer lorazepam injection by intra-arterial injection since arteriospasm can occur which may cause tissue damage and/or gangrene.
Visually inspect parenteral products for particulate matter and discoloration prior to administration whenever solution and container permit.

Intravenous Administration

IV injection:
Dilute the parenteral injection with an equal volume of a compatible diluent such as NS, sterile water for injection, or D5W. Prefilled syringes (Tubex) may be diluted by extruding all of the air from the half-filled syringe and slowly aspirating an equal volume of diluent; pull the plunger back slightly to allow space for mixing. Mix the contents of the syringe thoroughly by gently inverting the syringe repeatedly until a homogenous solution is obtained; do not shake vigorously. Alternatively, withdraw the desired dose from a vial of lorazepam injection into an empty syringe and then follow the procedure above for mixing the prefilled syringe.
Following dilution, inject directly into a vein or into the tubing of a freely-flowing compatible IV infusion. Rate of injection should not exceed 2 mg/minute. Direct IV injection should be made with repeated aspiration to ensure that none of the drug is injected intra-arterially and that perivascular extravasation does not occur.

Continuous IV infusion†:
When PVC containers are used to administer lorazepam, significant drug losses (up to 29% within 24 hours) occur due to sorption. PVC administration sets can also be expected to contribute to sorption losses. Use of glass or polyolefin containers is recommended.
Dilute lorazepam injection with a compatible diluent such as D5W (preferred) to a final concentration of up to 0.2 mg/ml. Lorazepam crystalline particle formation may occur when IV solution concentrations are > 0.08 mg/ml; however, manufacturers data and limited reports suggest that concentrations of 1 mg/ml are stable for up to 24 hours and may be used in fluid-restricted patients. Solutions should not be used if they appear discolored or contain a precipitate.

Intramuscular Administration

No dilution necessary.
Inject deeply into a large muscle mass. Aspirate prior to injection to avoid injection into a blood vessel.

STORAGE

Generic:
- Discard opened bottle after 90 days
- Protect from light
- Store between 36 to 46 degrees F

Ativan:
- Store at controlled room temperature (between 68 and 77 degrees F)

CONTRAINDICATIONS / PRECAUTIONS

Benzodiazepine hypersensitivity, benzyl alcohol hypersensitivity

Lorazepam is contraindicated in any patient with a known lorazepam or benzodiazepine hypersensitivity. Lorazepam injection is contraindicated in patients who are hypersensitive to other ingredients in these products (i.e., propylene glycol or polyethylene glycol). Too much propylene glycol can cause central nervous system toxicity such as seizures and intraventricular hemorrhage, unresponsiveness, tachypnea, tachycardia, and diaphoresis. Some formulations of lorazepam injection also contain benzyl alcohol and are contraindicated in patients with known benzyl alcohol hypersensitivity. Of note, normal therapeutic lorazepam injectable doses contain very small amounts of propylene glycol, polyethylene glycol, and benzyl alcohol.

Bipolar disorder, depression, mania, psychosis, suicidal ideation

Lorazepam is not recommended for use in patients with primary depressive disorder, as preexisting depression may emerge or worsen during the use of benzodiazepines. If lorazepam is used in patients with depression, ensure adequate antidepressant therapy and monitor closely for worsening symptoms. Administer lorazepam cautiously to patients with a history of suicidal ideation; do not prescribe large quantities for patients with known suicidal ideation or a history of suicide attempt. Though FDA-approved oral product labeling specifically recommends against the use of lorazepam in psychosis, benzodiazepines are commonly used in clinical practice for the acute management of psychosis and mania, as well as in the treatment of extrapyramidal symptoms associated with antipsychotics. Benzodiazepines may cause disinhibition and paradoxical stimulation (e.g., agitation, mania), both of which are more common in children. In addition, paradoxical reactions are more common in patients with psychiatric and/or personality disorders, particularly in patients with histories of anger and aggression. Hence, benzodiazepines should be used with caution in patients with a history of autism, bipolar disorder, or psychosis.

Status epilepticus

The use of injectable benzodiazepines, like lorazepam, in status epilepticus is often implemented as an adjunct to other supportive therapies. In status epilepticus, ventilatory support and other life-saving measures should be readily available. Additional seizure maintenance medication should be ordered if required. The sedative effects of injectable benzodiazepines may add to the CNS depressive state seen in the postictal stage. Ventilatory support should also be available for the preanesthetic use of injectable benzodiazepines.

Intraarterial administration

Injectable lorazepam is contraindicated for intraarterial administration due to the possibility of arteriospasm and resultant gangrene that may require amputation.

Alcoholism, chronic obstructive pulmonary disease (COPD), CNS depression, coadministration with other CNS depressants, congenital heart disease, ethanol intoxication, pulmonary disease, pulmonary hypertension, respiratory depression, respiratory insufficiency, sleep apnea, status asthmaticus

As with other benzodiazepines, lorazepam should be used with extreme caution in patients with pulmonary disease and in patients with respiratory insufficiency resulting from chronic obstructive pulmonary disease (COPD), status asthmaticus, abnormal airway anatomy, cyanotic congenital heart disease, or pulmonary hypertension. Additionally, avoid coadministration with other CNS depressants, especially opioids, when possible, as this significantly increases the risk for profound sedation, respiratory depression, low blood pressure, and death. Reserve concomitant use of these drugs for patients in whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations possible and monitor patients closely for signs and symptoms of respiratory depression and sedation. Lorazepam injection is contraindicated in patients with sleep apnea syndrome or severe respiratory insufficiency who are not receiving mechanical ventilation. Lorazepam can cause respiratory depression, apnea, airway obstruction, and oxygen desaturation; it is more likely to cause adverse respiratory effects when administered to patients with pulmonary conditions, significant CNS depression, or ethanol intoxication. Avoid use of lorazepam in patients with active alcoholism. In addition, hypercarbia and hypoxia can occur after lorazepam administration and may pose a significant risk to patients with congenital heart disease or pulmonary hypertension. Carefully monitor respiratory status and oxygen saturation in at risk patients.

Driving or operating machinery

Particular caution is required in determining the amount of time needed after outpatient procedures or surgery before it is safe for any patient to ambulate. No patient should get out of bed unassisted within 8 hours of lorazepam injection. In addition, patients should not attempt driving or operating machinery until 24 to 48 hours after surgery or until the central nervous system depressant effects have subsided, whichever is longer. The caregivers of ambulatory patients on oral therapy should be cautioned to monitor the patient carefully until it is clear how lorazepam may affect the patient.

Closed-angle glaucoma

Injectable and oral lorazepam formulations are contraindicated in patients with acute closed-angle glaucoma. The mechanistic rational for this contraindication has been questioned, as benzodiazepines do not have antimuscarinic activity and do not raise intraocular pressure. Benzodiazepines may be used in patients with open-angle glaucoma who are receiving appropriate therapy.

Hepatic disease, hepatic encephalopathy, renal failure, renal impairment

Benzodiazepines should be administered cautiously to patients with renal impairment or renal failure, hepatic disease or hepatic encephalopathy; liver and renal function should be monitored regularly during prolonged therapy. As with all benzodiazepines, the use of lorazepam may worsen hepatic encephalopathy and should be used cautiously in severe hepatic impairment. Because lorazepam undergoes conjugative metabolism as opposed to oxidative metabolism, it is relatively safer to use in patients with hepatic dysfunction with careful clinical monitoring versus other benzodiazepines.

Abrupt discontinuation, benzodiazepine dependence, seizure disorder, substance abuse

Lorazepam can cause physical and psychological dependence, and should be used with extreme caution in patients with known, suspected or a history of substance abuse. Generally, benzodiazepines should be prescribed for short periods (2 to 4 weeks) with continued reevaluation of the need for treatment. Tolerance (or tachyphylaxis) may develop to the sedative effects of benzodiazepines. Patients should be questioned about the need for escalating doses, and the clinician may need to intervene to prevent further tolerance or increased risk for addiction. Abrupt discontinuation of lorazepam after prolonged use should be avoided. Abrupt discontinuation of benzodiazepine therapy has been reported to cause withdrawal symptoms, especially following high dose or prolonged therapy. However, benzodiazepine dependence can occur following administration of therapeutic doses for as few as 1 to 2 weeks, and withdrawal symptoms may be seen following the discontinuation of therapy. Benzodiazepine withdrawal can be more intense with short-acting benzodiazepines such as lorazepam. Patients with a history of a seizure disorder or who are taking other drugs that lower the seizure threshold (i.e., tricyclic antidepressants, phenothiazines) should not be withdrawn abruptly from benzodiazepines due to the risk of precipitating a seizure. Benzodiazepines should be withdrawn slowly, using a gradual dosage-tapering schedule. During withdrawal, the greatest risk of seizure appears to be during the first 24 to 72 hours.

Neuromuscular disease, Parkinson's disease

Lorazepam should be used with caution in patients with a neuromuscular disease, such as muscular dystrophy, myotonia, or myasthenia gravis as these conditions can be exacerbated. Patients with late stage Parkinson's disease may experience worsening of their psychosis or impaired cognition with administration of benzodiazepines. Benzodiazepines may also cause incoordination or paradoxical reactions that may worsen symptoms of Parkinson's disease.

GI disease

Lorazepam has not been shown to be effective for comorbid conditions associated with anxiety (i.e., cardiovascular or gastrointestinal disorders). Esophageal dilation has been shown to occur in rats with high doses (6 mg/kg/day) and prolonged therapy (more than 1 year) of lorazepam. The effect was reversible only if therapy was stopped within 2 months of observation. Although the clinical significance is not known, patients utilizing lorazepam for prolonged periods should have frequent evaluation for symptoms of upper GI disease.

Dementia, geriatric

Clinical studies of lorazepam generally were not adequate to determine whether geriatric subjects respond differently than younger adults, however, adult patients over 50 years of age may experience a greater incidence of central nervous system (CNS) depression and more respiratory depression, particularly with preanesthetic use. Age does not appear to have a clinically significant effect on lorazepam kinetics alone. Clinical circumstances, some of which may be more common in the geriatric adult, such as hepatic or renal impairment, should be considered. In general, dose selection for the geriatric patient should be cautious, usually starting at the low end of the dosing range. According to the Beers Criteria, benzodiazepines are considered potentially inappropriate medications (PIMs) for use in geriatric patients and avoidance is generally recommended, although some agents from this class may be appropriate for seizure disorders, rapid eye movement sleep disorders, benzodiazepine withdrawal, severe generalized anxiety disorder, peri-procedural anesthesia, and end of life care. Older adults have an increased sensitivity to benzodiazepines. In general, all benzodiazepines increase the risk of cognitive impairment, delirium, falls, fractures, and motor vehicle accidents in older adults. The Panel recommends avoiding benzodiazepines in geriatric patients with the following disease states or symptoms due to the potential for exacerbation of the condition or increased risk of adverse effects: delirium (possible new-onset or worsening delirium), dementia (adverse CNS effects), and history of falls/fractures (ataxia, impaired psychomotor function, syncope, and additional falls). If a benzodiazepine must be used in a patient with a history of falls or fractures, consider reducing use of other CNS-active medications that increase the risk of falls and fractures and implement other strategies to reduce fall risk. The federal Omnibus Budget Reconciliation Act (OBRA) regulates medication use in residents of long-term care facilities (LTCFs). Specific criteria for anxiolytics must be met, including 1) limiting use to indications specified in the OBRA guidelines (e.g., generalized anxiety disorder, panic disorder, significant anxiety to a situational trigger, alcohol withdrawal) which meet the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for the indication, and 2) evidence exists that other possible reasons for the individual's distress have been considered, and 3) use results in maintenance or improvement in mental, physical, and psychosocial well-being as reflected on the Minimum Data Set (MDS) or other assessment tool. Anxiolytics should be used for delirium, dementia, or other cognitive disorders only when there are associated behaviors that are 1) quantitatively and objectively documented, and 2) are persistent, and 3) are not due to preventable or correctable reasons, and 4) constitute clinically significant distress or dysfunction to the LTCF resident or represent a danger to the resident or

others. There are exceptions that may warrant the use of an anxiolytic such as a long-acting benzodiazepine for withdrawal from a short-acting benzodiazepine, use for neuromuscular syndromes (e.g., tardive dyskinesia, restless legs syndrome, seizure disorder, cerebral palsy), or end of life care. The need for indefinite continuation of lorazepam (e.g., seizure disorder) should be based on confirmation of the condition being treated and its potential cause(s). When lorazepam is used as a sedative, factors potentially causing insomnia should be evaluated before medication initiation (e.g., sleep environment, inadequate physical activity, provision of care disruptions, caffeine or medications, pain and discomfort, or other underlying conditions that cause insomnia). Initiation of sleep induction or maintenance medication should be preceded or accompanied by non-pharmacologic interventions and maximized treatment of underlying conditions (if applicable). All sleep medications should be used in accordance with approved product labeling. The use of sedating medications for individuals with diagnosed sleep apnea requires careful assessment, documented clinical rationale, and close monitoring. Exceptions to the OBRA provisions include: single dose sedative use for a dental or medical procedure or short-term sedative use during initiation of treatment for depression, pain, or other comorbid condition until symptoms improve or the underlying causative factor can be identified and/or effectively treated. It should be noted that benzodiazepines may increase the risk of confusion, sedation, and falls. OBRA provides dosing guidance for lorazepam as an anxiolytic and a sedative. When a medication is used to induce sleep, treat a sleep disorder, manage behavior, stabilize mood, or treat a psychiatric disorder, the facility should attempt periodic tapering of the medication or provide documentation of medical necessity in accordance with OBRA guidelines.

Labor, obstetric delivery, pregnancy

Benzodiazepines may cause harm to the fetus when administered to pregnant women. An increased risk of congenital malformations during the first trimester of pregnancy has been suggested in several studies involving minor tranquilizers, including benzodiazepines. When benzodiazepines are administered late in pregnancy, they are easily transferred to the fetus where they have the potential to accumulate, causing 2 major neonatal syndromes: a neonatal abstinence syndrome (NAS) and floppy infant syndrome (FIS). Symptoms of NAS from case reports include tremors, irritability, hyperactivity, hypertonicity, tachypnea, vigorous sucking, poor weight gain, loose stools, and vomiting. FIS symptoms include hypotonia, inactivity, weak cry, lethargy, sucking difficulties, low Apgar score, hypothermia, apnea, cyanosis, hyperbilirubinemia, and central nervous system (CNS) depression. FIS typically occurs after chronic fetal exposure to long-acting benzodiazepines (e.g., chlordiazepoxide), or when benzodiazepines are administered shortly before delivery, resulting in newborn toxicity of variable severity and duration. FIS primarily occurs within the first few hours after labor and may last for up to 14 days. Therefore, benzodiazepines are not recommended for use in obstetrical procedures, labor, or obstetric delivery, including cesarean section. The incidence, time to onset, and duration of NAS or FIS symptoms is multi-factorial (e.g., duration of use, drug lipophilicity, placental disposition, degree of accumulation in neonatal tissues). It should be noted that in some case series and studies conducted on specific benzodiazepines, including lorazepam, there was no evidence of neonatal toxicity or withdrawal syndromes in newborns exposed in utero. Nevertheless, if a benzodiazepine is required during pregnancy, avoid first trimester administration if possible, consider short-acting agents (e.g., lorazepam, oxazepam), limit treatment to the shortest possible duration and lowest effective dose, and discontinue the drug well before delivery. According to FDA-approved labeling for lorazepam injection, the drug should not be given to a pregnant woman except in serious or life-threatening situations (e.g., status epilepticus) where safer drugs cannot be used or are ineffective. The possibility that a woman of childbearing potential may be pregnant at the time of treatment initiation should be considered. Patients who become pregnant or intend to become pregnant while taking lorazepam should be advised to discuss the possibility of discontinuing the drug with their physician. Repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures during the third trimester of pregnancy may have negative effects on fetal brain development. Consider the benefits of appropriate anesthesia in pregnant women against the potential risks, especially for procedures that may last more than 3 hours or if multiple procedures are required prior to delivery. It may be appropriate to delay certain procedures if doing so will not jeopardize the health of the child and/or mother. No specific anesthetic or sedation drug has been shown to be safer than another. Human studies suggest that a single short exposure to a general anesthetic in young pediatric patients is unlikely to have negative effects on behavior and learning; however, further research is needed to fully characterize how anesthetic exposure affects brain development.

Breast-feeding

Lorazepam should generally not be administered to breast-feeding mothers. Lorazepam is excreted into human breast milk in low levels. In a study of 4 lactating women, concentrations of free lorazepam in breast milk 4 hours after a single 3.5 mg oral dose were found to be 8 to 9 ng/mL, which accounted for 14.8% to 25.7% of the mother's plasma concentration. In a separate case, a woman taking lorazepam 2.5 mg PO twice daily for the first 5 days postpartum had milk concentrations of free and conjugated lorazepam of 12 and 35 mcg/L, respectively, at an unspecified time on day 5, and her infant showed no signs of sedation. In a retrospective cohort study of breast-feeding mothers using a benzodiazepine (n = 124), sedation was not reported in any infant exposed to lorazepam through breast milk (52% of participants). According to a evidence-based analysis designed to provide information about breast-fed infant drug exposure concentrations and adverse events, the amount of sedative or hypnotic exposure in the breast-fed infant is not very high; however, caution is recommended since neonatal metabolism of benzodiazepines occurs more slowly than in adults, and when used chronically, accumulation may occur in the infant producing sedation, nausea, poor feeding, or other adverse effects, particularly with long-acting benzodiazepines (e.g., diazepam, chlordiazepoxide). If a benzodiazepine must be used, a short-acting agent such as oxazepam or lorazepam should be selected, and administered at the minimum dosage and duration required for symptom relief. The infant should be monitored regularly, and if sedation, nausea, reduced suckling, or other signs of toxicity are observed, either breast-feeding or the benzodiazepine should be discontinued.

Children, infants, neonates, premature neonates

Both oral and injectable lorazepam solutions contain propylene glycol and polyethylene glycol. Lorazepam injection also contains benzyl alcohol as a preservative. Pediatric patients, in particular premature neonates and term neonates, may be more sensitive to these compounds. Lorazepam injection is contraindicated in premature neonates due to its benzyl alcohol content. Although normal therapeutic doses of lorazepam contain very small amounts of propylene glycol, polyethylene glycol, and benzyl alcohol, the clinician should be aware of the toxic potential, especially if other drugs containing the compounds are administered. Excessive propylene glycol can cause lactic acidosis, hyperosmolality, tachypnea, tachycardia, diaphoresis, and central nervous system toxicity (e.g., seizures, intraventricular hemorrhage). Excessive amounts of benzyl alcohol in neonates have been associated with hypotension, metabolic acidosis, and kernicterus. A "gasping syndrome" characterized by CNS depression, metabolic acidosis, and gasping respirations has been associated with benzyl alcohol dosages more than 99 mg/kg/day in neonates. However, the minimum amount of benzyl alcohol at which toxicity may occur is unknown and premature and low-birth-weight neonates may be more likely to develop toxicity. Repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in neonates, infants, and children younger than 3 years, including in utero exposure during the third trimester, may have negative effects on brain development. Consider the benefits of appropriate anesthesia in young children against the potential risks, especially for procedures that may last more than 3 hours or if multiple procedures are required during the first 3 years of life. It may be appropriate to delay certain procedures if doing so will not jeopardize the health of the child. No specific anesthetic or sedation drug has been shown to be safer than another. Human studies suggest that a single short exposure to a general anesthetic in young pediatric patients is unlikely to have negative effects on behavior and learning; however, further research is needed to fully characterize how anesthetic exposure affects brain development. Infants and children are also more susceptible to the therapeutic effects of benzodiazepines. Although commonly used off-label in the pediatric population, safe and effective use of oral and parenteral lorazepam has not been established in pediatric patients younger than 12 years and 18 years, respectively.

ADVERSE REACTIONS

Severe

coma / Early / 0-1.2
seizures / Delayed / 0-1.0
apnea / Delayed / 1.0

suicidal ideation / Delayed / Incidence not known
muscle paralysis / Delayed / Incidence not known
GI bleeding / Delayed / Incidence not known
hearing loss / Delayed / Incidence not known
heart failure / Delayed / Incidence not known
respiratory arrest / Rapid / Incidence not known
cardiac arrest / Early / Incidence not known
pneumothorax / Early / Incidence not known
pulmonary hypertension / Delayed / Incidence not known
pulmonary edema / Early / Incidence not known
pericardial effusion / Delayed / Incidence not known
bradycardia / Rapid / Incidence not known
teratogenesis / Delayed / Incidence not known
neuroleptic malignant syndrome / Delayed / Incidence not known
pancytopenia / Delayed / Incidence not known
lactic acidosis / Delayed / Incidence not known
SIADH / Delayed / Incidence not known
coagulopathy / Delayed / Incidence not known
agranulocytosis / Delayed / Incidence not known
anaphylactoid reactions / Rapid / Incidence not known

Moderate

hypotension / Rapid / 0.1-2.4
erythema / Early / 2.0-2.4
delirium / Early / 1.3-1.3
depression / Delayed / 1.3-1.3
confusion / Early / 0.1-1.3
hypoventilation / Rapid / 0-1.2
ataxia / Delayed / 0.1-1.0
hallucinations / Early / 0.1-1.0
elevated hepatic enzymes / Delayed / 0-1.0
metabolic acidosis / Delayed / 0-1.0
cystitis / Delayed / 0-1.0
hypertension / Early / 0.1-0.1
tolerance / Delayed / Incidence not known
psychological dependence / Delayed / Incidence not known
physiological dependence / Delayed / Incidence not known
amnesia / Delayed / Incidence not known
memory impairment / Delayed / Incidence not known
mania / Early / Incidence not known
psychosis / Early / Incidence not known
hyperreflexia / Delayed / Incidence not known
euphoria / Early / Incidence not known
hostility / Early / Incidence not known
dysarthria / Delayed / Incidence not known
impotence (erectile dysfunction) / Delayed / Incidence not known
constipation / Delayed / Incidence not known
urinary incontinence / Early / Incidence not known
hyperbilirubinemia / Delayed / Incidence not known
blurred vision / Early / Incidence not known
jaundice / Delayed / Incidence not known
hypoxia / Early / Incidence not known
respiratory depression / Rapid / Incidence not known
sinus tachycardia / Rapid / Incidence not known
withdrawal / Early / Incidence not known
myoclonia / Delayed / Incidence not known
hyponatremia / Delayed / Incidence not known
thrombocytopenia / Delayed / Incidence not known

Mild

injection site reaction / Rapid / 0.5-17.0
drowsiness / Early / 1.5-15.9
dizziness / Early / 6.9-6.9
weakness / Early / 4.2-4.2
restlessness / Early / 1.3-1.3
headache / Early / 0.1-1.2
tremor / Early / 0.1-1.0
agitation / Early / 0.1-1.0
nausea / Early / 0-1.0
vomiting / Early / 0-1.0
hypersalivation / Early / 0.1-1.0
hyperventilation / Early / 0-1.0
chills / Rapid / 0-1.0
infection / Delayed / 0-1.0
insomnia / Early / Incidence not known
nightmares / Early / Incidence not known
anxiety / Delayed / Incidence not known
hyperactivity / Early / Incidence not known
irritability / Delayed / Incidence not known
asthenia / Delayed / Incidence not known
fatigue / Early / Incidence not known
vertigo / Early / Incidence not known
libido increase / Delayed / Incidence not known
diarrhea / Early / Incidence not known
diplopia / Early / Incidence not known

orgasm dysfunction / Delayed / Incidence not known
libido decrease / Delayed / Incidence not known
diaphoresis / Early / Incidence not known
hypothermia / Delayed / Incidence not known
alopecia / Delayed / Incidence not known
rash / Early / Incidence not known

DRUG INTERACTIONS

Acetaminophen; Aspirin, ASA; Caffeine: (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Acetaminophen; Butalbital: (Moderate) Additive CNS and/or respiratory depression may occur with concurrent use.
Acetaminophen; Butalbital; Caffeine: (Moderate) Additive CNS and/or respiratory depression may occur with concurrent use. (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Acetaminophen; Butalbital; Caffeine; Codeine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines. (Moderate) Additive CNS and/or respiratory depression may occur with concurrent use. (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Acetaminophen; Caffeine; Dihydrocodeine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines. (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Acetaminophen; Caffeine; Magnesium Salicylate; Phenyltoloxamine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Acetaminophen; Caffeine; Phenyltoloxamine; Salicylamide: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Acetaminophen; Chlorpheniramine; Dextromethorphan; Phenylephrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Acetaminophen; Chlorpheniramine; Dextromethorphan; Pseudoephedrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Acetaminophen; Codeine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines.
Acetaminophen; Dextromethorphan; Doxylamine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Acetaminophen; Dextromethorphan; Guaifenesin; Phenylephrine: (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Acetaminophen; Dextromethorphan; Phenylephrine: (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Acetaminophen; Dichloralphenazone; Isometheptene: (Moderate) The CNS depressant effects of dichloralphenazone can be potentiated by benzodiazepines.
Acetaminophen; Diphenhydramine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Acetaminophen; Guaifenesin; Phenylephrine: (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Acetaminophen; Hydrocodone: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines.
Acetaminophen; Oxycodone: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 oxycodone is initiated in a patient taking a benzodiazepine, reduce dosages and titrate to clinical response. For acetaminophen; oxycodone extended-release tablets, start with 1 tablet PO every 12 hours, and for other oxycodone products, use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Acetaminophen; Pentazocine: (Major) Concomitant use of mixed opiate agonists/antagonists with benzodiazepines may cause respiratory

depression, hypotension, profound sedation, and death. Limit the use of mixed opiate agonists/antagonists with benzodiazepines 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 a mixed opiate agonist/antagonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the mixed opiate agonist/antagonist and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking a mixed opiate agonist/antagonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Acetaminophen; Propoxyphene: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. The dose of any opiate agonist administered with parenteral diazepam should be reduced by at least one-third.
Acetaminophen; Tramadol: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Acrivastine; Pseudoephedrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Aldesleukin, IL-2: (Moderate) Aldesleukin, IL-2 may affect CNS function significantly. Therefore, psychotropic pharmacodynamic interactions could occur following concomitant administration of drugs with significant CNS activity. Use with caution.
Alfentanil: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Alprazolam: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs can potentiate the CNS effects of either agent.
Amobarbital: (Moderate) Additive CNS and/or respiratory depression may occur with concurrent use.
Amoxapine: (Moderate) Amoxapine may enhance the response to the effects of benzodiazepines and other CNS depressants. Patients should be warned of the possibility of drowsiness that may impair performance of potentially hazardous tasks such as driving an automobile or operating machinery.
Amphetamine; Dextroamphetamine Salts: (Major) Patients who are taking anticonvulsants for epilepsy/seizure control should use dextroamphetamine with caution. Amphetamines may decrease the seizure threshold and may increase the risk of seizures.
Apomorphine: (Moderate) Apomorphine causes significant somnolence. Concomitant administration of apomorphine and CNS depressants could result in additive depressant effects.
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) Due to the primary CNS effects of aripiprazole, caution should be used when aripiprazole is given in combination with other centrally-acting medications including benzodiazepines and other anxiolytics, sedatives, and hypnotics. The intensity of sedation and orthostatic hypotension is greater during concurrent use of lorazepam and oral aripiprazole and during use of a parenteral benzodiazepine and intramuscular (IM) aripiprazole compared to aripiprazole alone; therefore, patients receiving a benzodiazepine with oral or parenteral aripiprazole should be monitored for sedation and blood pressure and the dose should be adjusted accordingly. Data from the manufacturer indicate there are no clinically significant pharmacokinetic changes when aripiprazole is given with lorazepam.
Asenapine: (Moderate) Drugs that can cause CNS depression, if used concomitantly with asenapine, may increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, and dizziness. Caution should be used when asenapine is given in combination with other centrally-acting medications including anxiolytics, sedatives, and hypnotics (including barbiturates), buprenorphine, buprenorphine; naloxone, butorphanol, dronabinol, THC, nabilone, nalbuphine, opiate agonists, pentazocine, acetaminophen; pentazocine, aspirin, ASA; pentazocine, and pentazocine; naloxone.
Aspirin, ASA; Butalbital; Caffeine: (Moderate) Additive CNS and/or respiratory depression may occur with concurrent use. (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Aspirin, ASA; Butalbital; Caffeine; Codeine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines. (Moderate) Additive CNS and/or respiratory depression may occur with concurrent use. (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Aspirin, ASA; Caffeine; Dihydrocodeine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines. (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Aspirin, ASA; Carisoprodol; Codeine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines.
Aspirin, ASA; Oxycodone: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 oxycodone is initiated in a patient taking a benzodiazepine, reduce dosages and titrate to clinical response. For acetaminophen; oxycodone extended-release tablets, start with 1 tablet PO every 12 hours, and for other oxycodone products, use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Atracurium: (Moderate) Concurrent use of benzodiazepines and other CNS active medications including neuromuscular blockers, can potentiate the CNS effects of either agent. Lower doses of one or both agents may be required. The severity of this interaction may be increased when additional CNS depressants are given.

Atropine; Difenoxin: (Moderate) Concomitant administration of benzodiazepines with CNS-depressant drugs, such as diphenoxylate/difenoxin, can potentiate the CNS effects of either agent.
Atropine; Diphenoxylate: (Moderate) Concomitant administration of benzodiazepines with CNS-depressant drugs, such as diphenoxylate/difenoxin, can potentiate the CNS effects of either agent.
Atropine; Hyoscyamine; Phenobarbital; Scopolamine: (Moderate) Additive CNS and/or respiratory depression may occur with concurrent use. (Moderate) Scopolamine may cause dizziness and drowsiness. Concurrent use of scopolamine and CNS depressants can adversely increase the risk of CNS depression.
Azelastine: (Moderate) An enhanced CNS depressant effect may occur when azelastine is combined with CNS depressants including benzodiazepines.
Azelastine; Fluticasone: (Moderate) An enhanced CNS depressant effect may occur when azelastine is combined with CNS depressants including benzodiazepines.
Barbiturates: (Moderate) Additive CNS and/or respiratory depression may occur with concurrent use.
Belladonna Alkaloids; Ergotamine; Phenobarbital: (Moderate) Additive CNS and/or respiratory depression may occur with concurrent use.
Belladonna; Opium: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Benztropine: (Moderate) CNS depressants, such as anxiolytics, sedatives, and hypnotics, can increase the sedative effects of benztropine.
Brimonidine: (Moderate) Based on the sedative effects of brimonidine in individual patients, brimonidine administration has potential to enhance the CNS depressants effects of the anxiolytics, sedatives, and hypnotics including benzodiazepines.
Brimonidine; Brinzolamide: (Moderate) Based on the sedative effects of brimonidine in individual patients, brimonidine administration has potential to enhance the CNS depressants effects of the anxiolytics, sedatives, and hypnotics including benzodiazepines.
Brimonidine; Timolol: (Moderate) Based on the sedative effects of brimonidine in individual patients, brimonidine administration has potential to enhance the CNS depressants effects of the anxiolytics, sedatives, and hypnotics including benzodiazepines.
Brompheniramine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Brompheniramine; Carbetapentane; Phenylephrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including benzodiazepines. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Brompheniramine; Dextromethorphan; Guaifenesin: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Brompheniramine; Guaifenesin; Hydrocodone: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines. (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Brompheniramine; Hydrocodone; Pseudoephedrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines. (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Brompheniramine; Pseudoephedrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Buprenorphine: (Major) Concomitant use of mixed opiate agonists/antagonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of mixed opiate agonists/antagonists with benzodiazepines 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 a mixed opiate agonist/antagonist is initiated for pain in a patient taking a benzodiazepine, use a lower initial dose of the mixed opiate agonist/antagonist and titrate to clinical response. Reduce injectable buprenorphine dose by 1/2, and for the buprenorphine transdermal patch, start therapy with the 5 mcg/hour patch. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking a mixed opiate agonist/antagonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. In patients treated with buprenorphine for opioid use disorder, cessation of benzodiazepines or other CNS depressants is preferred in most cases. Consider alternatives to benzodiazepines for conditions such as anxiety or insomnia in patients receiving buprenorphine maintenance treatment. Educate patients about the risks and symptoms of respiratory depression and sedation.
Buprenorphine; Naloxone: (Major) Concomitant use of mixed opiate agonists/antagonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of mixed opiate agonists/antagonists with benzodiazepines 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 a mixed opiate agonist/antagonist is initiated for pain in a patient taking a benzodiazepine, use a lower initial dose of the mixed opiate agonist/antagonist and titrate to clinical response. Reduce injectable buprenorphine dose by 1/2, and for the buprenorphine transdermal patch, start therapy with the 5 mcg/hour patch. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking a mixed opiate agonist/antagonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. In patients treated with buprenorphine for opioid use disorder, cessation of benzodiazepines or other CNS depressants is preferred in most cases. Consider alternatives to benzodiazepines for conditions such as anxiety or insomnia in patients receiving buprenorphine maintenance treatment. Educate patients about the risks and symptoms of respiratory depression and sedation.
Buspirone: (Moderate) It is common for patients to overlap anxiety treatment when switching from benzodiazepines to buspirone. Buspirone has a slow onset of action and the drug will not block the withdrawal syndrome often seen with cessation of benzodiazepine therapy in those with benzodiazepine dependence. Therefore, before starting therapy with buspirone, withdraw patients gradually from the benzodiazepine. Alternatively, conversion to buspirone therapy may require treatment overlap to allow for the downward titration of the benzodiazepine while buspirone takes effect. It should be noted that the combination of buspirone and benzodiazepines can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent.
Butabarbital: (Moderate) Additive CNS and/or respiratory depression may occur with concurrent use.
Butorphanol: (Major) Concomitant use of mixed opiate agonists/antagonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of mixed opiate agonists/antagonists with benzodiazepines 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 a mixed opiate agonist/antagonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the mixed opiate agonist/antagonist and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking a mixed opiate agonist/antagonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Caffeine: (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Caffeine; Ergotamine: (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Carbamazepine: (Moderate) As carbamazepine is known to induce CYP1A2 and CYP3A4, serum concentrations of lorazepam may be decreased because of CYP enzyme induction. Increased dosages of lorazepam may be needed.
Carbetapentane; Chlorpheniramine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including benzodiazepines.
Carbetapentane; Chlorpheniramine; Phenylephrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including benzodiazepines. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Carbetapentane; Diphenhydramine; Phenylephrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including benzodiazepines. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Carbetapentane; Guaifenesin: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including benzodiazepines.
Carbetapentane; Guaifenesin; Phenylephrine: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including benzodiazepines. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Carbetapentane; Phenylephrine: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including benzodiazepines. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Carbetapentane; Phenylephrine; Pyrilamine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including benzodiazepines. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Carbetapentane; Pseudoephedrine: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including benzodiazepines.
Carbetapentane; Pyrilamine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including benzodiazepines.
Carbinoxamine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Carbinoxamine; Dextromethorphan; Pseudoephedrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Carbinoxamine; Hydrocodone; Phenylephrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines. (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Carbinoxamine; Hydrocodone; Pseudoephedrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines. (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Carbinoxamine; Phenylephrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Carbinoxamine; Pseudoephedrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Cariprazine: (Moderate) Due to the CNS effects of cariprazine, caution should be used when cariprazine is given in combination with other centrally-acting medications including benzodiazepines and other anxiolytics, sedatives, and hypnotics.
Cetirizine: (Moderate) Additive drowsiness may occur if cetirizine/levocetirizine is administered with other drugs that depress the CNS, including benzodiazepines.
Cetirizine; Pseudoephedrine: (Moderate) Additive drowsiness may occur if cetirizine/levocetirizine is administered with other drugs that depress the CNS, including benzodiazepines.
Chlophedianol; Dexchlorpheniramine; Pseudoephedrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Chlophedianol; Guaifenesin; Phenylephrine: (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Chlorcyclizine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Chlorpheniramine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.

Chlorpheniramine; Codeine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines. (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Chlorpheniramine; Dextromethorphan: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Chlorpheniramine; Dextromethorphan; Phenylephrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Chlorpheniramine; Dihydrocodeine; Phenylephrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines. (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Chlorpheniramine; Dihydrocodeine; Pseudoephedrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines. (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Chlorpheniramine; Guaifenesin; Hydrocodone; Pseudoephedrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines. (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Chlorpheniramine; Hydrocodone: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines. (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Chlorpheniramine; Hydrocodone; Phenylephrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines. (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Chlorpheniramine; Hydrocodone; Pseudoephedrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines. (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Chlorpheniramine; Phenylephrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Chlorpheniramine; Pseudoephedrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Chlorthalidone; Clonidine: (Moderate) Clonidine has CNS depressive effects and can potentiate the actions of other CNS depressants including benzodiazepines.
Cisapride: (Moderate) Cisapride may enhance the sedative effects of benzodiazepines. Patients should not drive or operate heavy machinery until they know how the combination affects them. Patient counseling is important, as cisapride alone does not cause drowsiness or affect psychomotor function.
Cisatracurium: (Moderate) Concurrent use of benzodiazepines and other CNS active medications including neuromuscular blockers, can potentiate the CNS effects of either agent. Lower doses of one or both agents may be required. The severity of this interaction may be increased when additional CNS depressants are given.
Clemastine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Clobazam: (Moderate) Use clobazam with other benzodiazepines with caution due to the potential for increased risk of drowsiness and sedation.
Clonidine: (Moderate) Clonidine has CNS depressive effects and can potentiate the actions of other CNS depressants including benzodiazepines.

Clozapine: (Moderate) If concurrent therapy with clozapine and a benzodiazepine is necessary, it is advisable to begin with the lowest possible benzodiazepine dose and closely monitor the patient, particularly at initiation of treatment and following dose increases. Although the combination has been used safely, adverse reactions such as confusion, ataxia, somnolence, delirium, collapse, cardiac arrest, respiratory arrest, and death have occurred rarely in patients receiving clozapine concurrently or following benzodiazepine therapy. Several benzodiazepines, including clonazepam, oxazepam, flurazepam, diazepam, clobazam, flunitrazepam, and lorazepam have been implicated in these reactions. At least one case of sudden death was reported following intravenous administration of lorazepam to a patient receiving clozapine.
Codeine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines.
Codeine; Guaifenesin: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines.
Codeine; Phenylephrine; Promethazine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines. (Moderate) Because promethazine causes pronounced sedation, an enhanced CNS depressant effect or additive drowsiness may occur when it is combined with other CNS depressants including benzodiazepines. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Codeine; Promethazine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines. (Moderate) Because promethazine causes pronounced sedation, an enhanced CNS depressant effect or additive drowsiness may occur when it is combined with other CNS depressants including benzodiazepines.
Colesevelam: (Moderate) Colesevelam may decrease the absorption of anticonvulsants. To minimize potential for interactions, consider administering oral anticonvulsants at least 1 hour before or at least 4 hours after colesevelam.
COMT inhibitors: (Moderate) Concomitant administration of benzodiazepines with CNS-depressant drugs, including COMT inhibitors, can potentiate the CNS effects of either agent.
Cyclizine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Cyproheptadine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Desflurane: (Moderate) Concurrent use with benzodiazepines can decrease the minimum alveolar concentration (MAC) of desflurane needed to produce anesthesia.
Deutetrabenazine: (Moderate) Advise patients that concurrent use of deutetrabenazine and drugs that can cause CNS depression, such as lorazepam, may have additive effects and worsen drowsiness or sedation.
Dexchlorpheniramine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Dexchlorpheniramine; Dextromethorphan; Pseudoephedrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Dexmedetomidine: (Moderate) Co-administration of dexmedetomidine with benzodiazepines is likely to lead to an enhancement of CNS depression.
Dextromethorphan; Diphenhydramine; Phenylephrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Dextromethorphan; Guaifenesin; Phenylephrine: (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Dextromethorphan; Promethazine: (Moderate) Because promethazine causes pronounced sedation, an enhanced CNS depressant effect or additive drowsiness may occur when it is combined with other CNS depressants including benzodiazepines.
Dichlorphenamide: (Moderate) Use dichlorphenamide and lorazepam together with caution. Metabolic acidosis is associated with the use of dichlorphenamide and has been reported rarely with the use of lorazepam injection for the treatment of status epilepticus. Concurrent use may increase the severity of metabolic acidosis. Measure sodium bicarbonate concentrations at baseline and periodically during dichlorphenamide treatment. If metabolic acidosis occurs or persists, consider reducing the dose or discontinuing dichlorphenamide therapy.
Dicyclomine: (Moderate) Dicyclomine can cause drowsiness, so it should be used cautiously in patients receiving CNS depressants like benzodiazepines.
Dihydrocodeine; Guaifenesin; Pseudoephedrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines.
Dimenhydrinate: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Diphenhydramine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Diphenhydramine; Hydrocodone; Phenylephrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is

prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines. (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Diphenhydramine; Ibuprofen: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Diphenhydramine; Naproxen: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Diphenhydramine; Phenylephrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Doxacurium: (Moderate) Concurrent use of benzodiazepines and other CNS active medications including neuromuscular blockers, can potentiate the CNS effects of either agent. Lower doses of one or both agents may be required. The severity of this interaction may be increased when additional CNS depressants are given.
Doxylamine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Doxylamine; Pyridoxine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Dronabinol: (Moderate) Use caution if the use of benzodiazepines are necessary with dronabinol, and monitor for additive dizziness, confusion, somnolence, and other CNS effects.
Droperidol: (Major) Droperidol administration is associated with an established risk for QT prolongation and torsades de pointes. In December 2001, the FDA issued a black box warning regarding the use of droperidol and its association with QT prolongation and potential for cardiac arrhythmias based on post-marketing surveillance data. Risk factors for the development of prolonged QT syndrome may include the use of benzodiazepines. Also, droperidol and benzodiazepines can both cause CNS depression. If used with a benzodiazepine, droperidol should be initiated at a low dose and adjusted upward, with caution, as needed to achieve the desired effect.
Drospirenone; Ethinyl Estradiol: (Minor) Ethinyl estradiol may enhance the metabolism of lorazepam. It appears glucuronide conjugation of lorazepam is increased in the presence of combined hormonal oral contraceptives; the clinical significance of this interaction is not determined.
Drospirenone; Ethinyl Estradiol; Levomefolate: (Minor) Ethinyl estradiol may enhance the metabolism of lorazepam. It appears glucuronide conjugation of lorazepam is increased in the presence of combined hormonal oral contraceptives; the clinical significance of this interaction is not determined.
Enflurane: (Moderate) Concomitant administration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent.
Eszopiclone: (Moderate) Concomitant administration of benzodiazepines with eszopiclone can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. The concurrent use of eszopiclone with other anxiolytics, sedatives, and hypnotics at bedtime or in the middle of the night is not recommended. 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. If used together, a reduction in the dose of one or both drugs may be needed.
Ethanol: (Major) Alcohol is associated with CNS depression. The combined use of alcohol and CNS depressants can lead to additive CNS depression, which could be dangerous in tasks requiring mental alertness and fatal in overdose. Alcohol taken with other CNS depressants can lead to additive respiratory depression, hypotension, profound sedation, or coma. Consider the patient's use of alcohol or illicit drugs when prescribing CNS depressant medications. In many cases, the patient should receive a lower dose of the CNS depressant initially if the patient is not likely to be compliant with avoiding alcohol.
Ethinyl Estradiol: (Minor) Ethinyl estradiol may enhance the metabolism of lorazepam. It appears glucuronide conjugation of lorazepam is increased in the presence of combined hormonal oral contraceptives; the clinical significance of this interaction is not determined.
Ethinyl Estradiol; Desogestrel: (Minor) Ethinyl estradiol may enhance the metabolism of lorazepam. It appears glucuronide conjugation of lorazepam is increased in the presence of combined hormonal oral contraceptives; the clinical significance of this interaction is not determined.
Ethinyl Estradiol; Ethynodiol Diacetate: (Minor) Ethinyl estradiol may enhance the metabolism of lorazepam. It appears glucuronide conjugation of lorazepam is increased in the presence of combined hormonal oral contraceptives; the clinical significance of this interaction is not determined.
Ethinyl Estradiol; Etonogestrel: (Minor) Ethinyl estradiol may enhance the metabolism of lorazepam. It appears glucuronide conjugation of lorazepam is increased in the presence of combined hormonal oral contraceptives; the clinical significance of this interaction is not determined.
Ethinyl Estradiol; Levonorgestrel: (Minor) Ethinyl estradiol may enhance the metabolism of lorazepam. It appears glucuronide conjugation of lorazepam is increased in the presence of combined hormonal oral contraceptives; the clinical significance of this interaction is not determined.
Ethinyl Estradiol; Levonorgestrel; Ferrous bisglycinate: (Minor) Ethinyl estradiol may enhance the metabolism of lorazepam. It appears glucuronide conjugation of lorazepam is increased in the presence of combined hormonal oral contraceptives; the clinical significance of this interaction is not determined.
Ethinyl Estradiol; Levonorgestrel; Folic Acid; Levomefolate: (Minor) Ethinyl estradiol may enhance the metabolism of lorazepam. It appears glucuronide conjugation of lorazepam is increased in the presence of combined hormonal oral contraceptives; the clinical significance of this interaction is not determined.
Ethinyl Estradiol; Norelgestromin: (Minor) Ethinyl estradiol may enhance the metabolism of lorazepam. It appears glucuronide conjugation of lorazepam is increased in the presence of combined hormonal oral contraceptives; the clinical significance of this interaction is not determined.
Ethinyl Estradiol; Norethindrone Acetate: (Minor) Ethinyl estradiol may enhance the metabolism of lorazepam. It appears glucuronide conjugation of lorazepam is increased in the presence of combined hormonal oral contraceptives; the clinical significance of this interaction is not determined.
Ethinyl Estradiol; Norethindrone Acetate; Ferrous fumarate: (Minor) Ethinyl estradiol may enhance the metabolism of lorazepam. It appears glucuronide conjugation of lorazepam is increased in the presence of combined hormonal oral contraceptives; the clinical significance of this interaction is not determined.
Ethinyl Estradiol; Norethindrone: (Minor) Ethinyl estradiol may enhance the metabolism of lorazepam. It appears glucuronide conjugation of lorazepam is increased in the presence of combined hormonal oral contraceptives; the clinical significance of this interaction is not determined.
Ethinyl Estradiol; Norethindrone; Ferrous fumarate: (Minor) Ethinyl estradiol may enhance the metabolism of lorazepam. It appears glucuronide conjugation of lorazepam is increased in the presence of combined hormonal oral contraceptives; the clinical significance of this interaction is not determined.
Ethinyl Estradiol; Norgestimate: (Minor) Ethinyl estradiol may enhance the metabolism of lorazepam. It appears glucuronide conjugation of lorazepam is increased in the presence of combined hormonal oral contraceptives; the clinical significance of this interaction is not determined.
Ethinyl Estradiol; Norgestrel: (Minor) Ethinyl estradiol may enhance the metabolism of lorazepam. It appears glucuronide conjugation of lorazepam is increased in the presence of combined hormonal oral contraceptives; the clinical significance of this interaction is not determined.
Ethotoin: (Moderate) Hydantoin anticonvulsants can theoretically add to the CNS depressant effects of other CNS depressants including the benzodiazepines.
Etomidate: (Moderate) Concomitant administration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent.
Fentanyl: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the

benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Flumazenil: (Major) Flumazenil competes with benzodiazepines for binding at the GABA/benzodiazepine-receptor complex, the specific binding site of benzodiazepines. Because binding at the receptor is competitive and flumazenil has a much shorter duration of action than do most benzodiazepines, it is possible for the effects of flumazenil to dissipate sooner than the effects of the benzodiazepine. Flumazenil does not affect the pharmacokinetics of the benzodiazepines. Abrupt awakening can cause dysphoria, agitation, and possibly increased adverse effects. If administered to patients who have received a benzodiazepine chronically, abrupt interruption of benzodiazepine agonism by flumazenil can induce benzodiazepine withdrawal including seizures. Flumazenil has minimal effects on benzodiazepine-induced respiratory depression; suitable ventilatory support should be available, especially in treating acute benzodiazepine overdose. Flumazenil does not reverse the actions of barbiturates, opiate agonists, or tricyclic antidepressants.
Fluoxetine; Olanzapine: (Major) Concurrent use of intramuscular olanzapine and parenteral benzodiazepines is not recommended due to the potential for adverse effects from the combination including excess sedation and/or cardiorespiratory depression. Although oral formulations of olanzapine and benzodiazepines may be used together, additive effects on respiratory depression and/or CNS depression are possible. Drugs that can cause CNS depression, if used concomitantly with olanzapine, can increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, dizziness, and orthostatic hypotension. Besides ethanol, clinicians should use other anxiolytics, sedatives, and hypnotics cautiously with olanzapine.
Food: (Major) Coadministration of marijuana with benzodiazepines may result in an exaggerated sedative effect. Instruct patients receiving these medications concurrently not to drive or operate machinery.
Fosphenytoin: (Moderate) Hydantoin anticonvulsants can theoretically add to the CNS depressant effects of other CNS depressants including the benzodiazepines.
Fospropofol: (Moderate) Concomitant administration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent.
General anesthetics: (Moderate) Concomitant administration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent.
Green Tea: (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products, such as green tea, prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Guaifenesin; Hydrocodone: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines.
Guaifenesin; Hydrocodone; Pseudoephedrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines.
Guaifenesin; Phenylephrine: (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Guanabenz: (Moderate) Guanabenz is associated with sedative effects. Guanabenz can potentiate the effects of CNS depressants such as benzodiazepines, when administered concomitantly.
Guanfacine: (Moderate) Guanfacine has been associated with sedative effects and can potentiate the actions of other CNS depressants including benzodiazepines.
Guarana: (Minor) Caffeine, an active constituent of guarana, is a CNS stimulant associated with heightened attentiveness and insomnia, and is used to treat or prevent drowsiness or fatigue; patients taking benzodiazepines for insomnia should not use guarana-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine or zolpidem.
Haloperidol: (Moderate) Haloperidol can potentiate the actions of other CNS depressants, such as benzodiazepines, Caution should be exercised with simultaneous use of these agents due to potential excessive CNS effects.
Halothane: (Moderate) Concomitant administration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent.
Homatropine; Hydrocodone: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines.
Hydantoins: (Moderate) Hydantoin anticonvulsants can theoretically add to the CNS depressant effects of other CNS depressants including the benzodiazepines.
Hydrochlorothiazide, HCTZ; Methyldopa: (Moderate) Methyldopa is associated with sedative effects. Methyldopa can potentiate the effects of CNS depressants such as barbiturates, benzodiazepines, opiate agonists, or phenothiazines when administered concomitantly.
Hydrocodone: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines.
Hydrocodone; Ibuprofen: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines.
Hydrocodone; Phenylephrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines. (Moderate) The

therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Hydrocodone; Potassium Guaiacolsulfonate: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines.
Hydrocodone; Potassium Guaiacolsulfonate; Pseudoephedrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines.
Hydrocodone; Pseudoephedrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines.
Hydromorphone: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 hydromorphone is initiated in a patient taking a benzodiazepine, reduce the initial dosage of hydromorphone and titrate to clinical response; for hydromorphone extended-release tablets, use 1/3 to 1/2 of the estimated hydromorphone starting dose. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Hydroxychloroquine: (Moderate) Caution is warranted with the coadministration of hydroxychloroquine and antiepileptic drugs, such as lorazepam. Hydroxychloroquine can lower the seizure threshold; therefore, the activity of antiepileptic drugs may be impaired with concomitant use.
Hydroxyzine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Ibuprofen; Oxycodone: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 oxycodone is initiated in a patient taking a benzodiazepine, reduce dosages and titrate to clinical response. For acetaminophen; oxycodone extended-release tablets, start with 1 tablet PO every 12 hours, and for other oxycodone products, use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Iloperidone: (Moderate) Drugs that can cause CNS depression, if used concomitantly with iloperidone, may increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, and dizziness. Caution should be used when iloperidone is given in combination with other centrally-acting medications including anxiolytics, sedatives, and hypnotics.
Iohexol: (Moderate) The use of intrathecal radiopaque contrast agents is associated with a risk of seizures. Patients should be instructed to continue using benzodiazepines during procedures or exams that require the use of intrathecal radiopaque contrast agents as abrupt discontinuation of benzodiazepines may also increase seizure risk.
Iopamidol: (Moderate) The use of intrathecal radiopaque contrast agents is associated with a risk of seizures. Patients should be instructed to continue using benzodiazepines during procedures or exams that require the use of intrathecal radiopaque contrast agents as abrupt discontinuation of benzodiazepines may also increase seizure risk.
Isoflurane: (Moderate) Concomitant administration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent.
Kava Kava, Piper methysticum: (Major) The German Commission E warns that any substances that act on the CNS, including psychotropic agents, may interact with kava kava. While the interactions can be pharmacodynamic in nature, kava kava has been reported to inhibit many CYP isozymes (i.e., CYP1A2, 2C9, 2C19, 2D6, 3A4, and 4A9/11) and important pharmacokinetic interactions with agents that undergo oxidative metabolism (e.g., selected benzodiazepines) are also possible. Patients on benzodiazepine therapy should avoid concomitant administration of kava kava. Patients should discuss the use of herbal supplements with their health care professional prior to consuming kava kava and should not abruptly stop taking their prescribed medications.
Ketamine: (Moderate) Concomitant administration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent.
Levocetirizine: (Moderate) Additive drowsiness may occur if cetirizine/levocetirizine is administered with other drugs that depress the CNS, including benzodiazepines.
Levomethadyl: (Moderate) Concomitant administration of benzodiazepines with CNS-depressant drugs, including opiate agonists, can potentiate the CNS effects of either agent.
Levomilnacipran: (Moderate) Concurrent use of many CNS active drugs, including benzodiazepines, with levomilnacipran has not been evaluated by the manufacturer. Therefore, caution is advisable when combining anxiolytics, sedatives, and hypnotics or other psychoactive medications with levomilnacipran.
Levorphanol: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 levorphanol is initiated in a patient taking a benzodiazepine, reduce the initial dose of levorphanol by approximately 50% or more. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Lisdexamfetamine: (Major) Patients who are taking anticonvulsants for epilepsy/seizure control should use lisdexamfetamine with caution. Amphetamines may decrease the seizure threshold and may increase the risk of seizures. If seizures occur, amphetamine discontinuation may be necessary.
Lithium: (Moderate) Because lithium has the potential to impair cognitive and motor skills, caution is advisable during concurrent use of other medications with centrally-acting effects including anxiolytics, sedatives, and hypnotics.
Lofexidine: (Moderate) Monitor for excessive hypotension and sedation during coadministration of lofexidine and benzodiazepines. Lofexidine can potentiate the effects of CNS depressants such as benzodiazepines.
Loxapine: (Moderate) The combination of loxapine and lorazepam has been associated with acute respiratory depression, stupor, and/or

hypotension in several patients. Lorazepam, and possibly other benzodiazepines, should be used cautiously in patients receiving loxapine.
Lurasidone: (Moderate) Due to the CNS effects of lurasidone, caution should be used when lurasidone is given in combination with other centrally acting medications such as anxiolytics, sedatives, and hypnotics, including benzodiazepines. In one study, co-administration of lurasidone and midazolam increased the Cmax and AUC of midazolam by about 21% and 44%, respectively, compared to midazolam alone; however, dosage adjustment of midazolam based upon pharmacokinetic parameters is not required during concurrent use of lurasidone.
Magnesium Salts: (Minor) Because of the CNS-depressant effects of magnesium sulfate, additive central-depressant effects can occur following concurrent administration with CNS depressants such as benzodiazepines. Caution should be exercised when using these agents concurrently.
Maprotiline: (Moderate) Benzodiazepines or other CNS depressants should be combined cautiously with maprotiline because they could cause additive depressant effects and possible respiratory depression or hypotension. The combination of benzodiazepines and maprotiline is commonly used clinically and is considered to be safe as long as patients are monitored for excessive adverse effects from either agent. Maprotiline may lower the seizure threshold, so when benzodiazepines are used for anticonvulsant effects the patient should be monitored for desired clinical outcomes.
Meclizine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Mefloquine: (Moderate) Coadministration of mefloquine and anticonvulsants may result in lower than expected anticonvulsant concentrations and loss of seizure control. Monitoring of the anticonvulsant serum concentration is recommended. Dosage adjustments may be required during and after therapy with mefloquine.
Melatonin: (Major) Use caution when combining melatonin with the benzodiazepines; when the benzodiazepine is used for sleep, co-use of melatonin should be avoided. In animal studies, melatonin has been shown to increase benzodiazepine binding to receptor sites. In one case report, a benzodiazepine-dependent woman with an 11 year history of insomnia weaned and discontinued her benzodiazepine prescription within a few days without rebound insomnia or apparent benzodiazepine withdrawal when melatonin was given. In another case report, the ingestion of excessive melatonin along with normal doses of chlordiazepoxide and an antidepressant resulted in lethargy and short-term amnestic responses. Both cases suggest additive pharmacodynamic effects. 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 opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Meperidine; Promethazine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. (Moderate) Because promethazine causes pronounced sedation, an enhanced CNS depressant effect or additive drowsiness may occur when it is combined with other CNS depressants including benzodiazepines.
Mephobarbital: (Moderate) Additive CNS and/or respiratory depression may occur with concurrent use.
Meprobamate: (Moderate) Concomitant administration of benzodiazepines with meprobamate can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. If used together, a reduction in the dose of one or both drugs may be needed.
Methadone: (Major) Concurrent use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective dose and minimum duration possible. If methadone is initiated for pain in an opioid-naive patient taking a benzodiazepine, use an initial methadone dose of 2.5 mg PO every 12 hours. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial benzodiazepine dose and titrate to response. In patients treated with methadone for opioid use disorder, cessation of benzodiazepines or other CNS depressants is preferred in most cases. Consider alternatives to benzodiazepines for conditions such as anxiety or insomnia during methadone maintenance treatment. Educate patients about the risks and symptoms of respiratory depression and sedation.
Methocarbamol: (Moderate) Concurrent use of benzodiazepines and other CNS active medications including skeletal muscle relaxants, can potentiate the CNS effects of either agent. Lower doses of one or both agents may be required. The severity of this interaction may be increased when additional CNS depressants are given.
Methohexital: (Moderate) Additive CNS and/or respiratory depression may occur with concurrent use.
Methscopolamine: (Moderate) CNS depression can be increased when methscopolamine is combined with other CNS depressants such as any anxiolytics, sedatives, and hypnotics.
Methyldopa: (Moderate) Methyldopa is associated with sedative effects. Methyldopa can potentiate the effects of CNS depressants such as barbiturates, benzodiazepines, opiate agonists, or phenothiazines when administered concomitantly.
Metoclopramide: (Minor) Combined use of metoclopramide and other CNS depressants, such as anxiolytics, sedatives, and hypnotics, can increase possible sedation.
Metyrapone: (Moderate) Metyrapone may cause dizziness and/or drowsiness. Other drugs that may also cause drowsiness, such as benzodiazepines, should be used with caution. Additive drowsiness and/or dizziness is possible.
Metyrosine: (Moderate) The concomitant administration of metyrosine with benzodiazepines can result in additive sedative effects.
Milnacipran: (Moderate) Concurrent use of many CNS-active drugs with milnacipran or levomilnacipran has not been evaluated by the manufacturer. Therefore, caution is advisable when combining anxiolytics, sedatives, and hypnotics or other psychoactive medications with these medications.
Minocycline: (Minor) Injectable minocycline contains magnesium sulfate heptahydrate. Because of the CNS-depressant effects of magnesium sulfate, additive central-depressant effects can occur following concurrent administration with CNS depressants such as benzodiazepines. Caution should be exercised when using these agents concurrently.
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 benzodiazepines.
Mivacurium: (Moderate) Concurrent use of benzodiazepines and other CNS active medications including neuromuscular blockers, can potentiate the CNS effects of either agent. Lower doses of one or both agents may be required. The severity of this interaction may be increased when additional CNS depressants are given.
Molindone: (Moderate) Consistent with the pharmacology of molindone, additive effects may occur with other CNS active drugs such as anticonvulsants. In addition, seizures have been reported during the use of molindone, which is of particular significance in patients with a seizure disorder receiving anticonvulsants. Adequate dosages of anticonvulsants should be continued when molindone is added; patients should be monitored for clinical evidence of loss of seizure control or the need for dosage adjustments of either molindone or the anticonvulsant.
Monoamine oxidase inhibitors: (Moderate) The CNS-depressant effects of MAOIs can be potentiated with concomitant administration of other drugs known to cause CNS depression including benzodiazepines. MAOIs can cause a variable change in seizure patterns, so careful monitoring of the patient with epilepsy is required when benzodiazepines are used in the treatment of epilepsy.
Morphine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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

morphine is initiated in a patient taking a benzodiazepine, reduce initial dosages and titrate to clinical response. For extended-release tablets, start with morphine 15 mg PO every 12 hours, and for extended-release capsules, start with 30 mg PO every 24 hours or less. Use an initial morphine; naltrexone dose of 20 mg/0.8 mg PO every 24 hours. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Morphine; Naltrexone: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 morphine is initiated in a patient taking a benzodiazepine, reduce initial dosages and titrate to clinical response. For extended-release tablets, start with morphine 15 mg PO every 12 hours, and for extended-release capsules, start with 30 mg PO every 24 hours or less. Use an initial morphine; naltrexone dose of 20 mg/0.8 mg PO every 24 hours. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Nabilone: (Moderate) Concomitant use of nabilone with other CNS depressants can potentiate the effects of nabilone on respiratory depression.

Nalbuphine: (Major) Concomitant use of mixed opiate agonists/antagonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of mixed opiate agonists/antagonists with benzodiazepines 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 a mixed opiate agonist/antagonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the mixed opiate agonist/antagonist and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking a mixed opiate agonist/antagonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Neuromuscular blockers: (Moderate) Concurrent use of benzodiazepines and other CNS active medications including neuromuscular blockers, can potentiate the CNS effects of either agent. Lower doses of one or both agents may be required. The severity of this interaction may be increased when additional CNS depressants are given.

Nitroglycerin: (Minor) Nitroglycerin can cause hypotension. This action may be additive with other agents that can cause hypotension such as benzodiazepines. Patients should be monitored more closely for hypotension if nitroglycerin is used concurrently with benzodiazepines.

Olanzapine: (Major) Concurrent use of intramuscular olanzapine and parenteral benzodiazepines is not recommended due to the potential for adverse effects from the combination including excess sedation and/or cardiorespiratory depression. Although oral formulations of olanzapine and benzodiazepines may be used together, additive effects on respiratory depression and/or CNS depression are possible. Drugs that can cause CNS depression, if used concomitantly with olanzapine, can increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, dizziness, and orthostatic hypotension. Besides ethanol, clinicians should use other anxiolytics, sedatives, and hypnotics cautiously with olanzapine.

Oxybutynin: (Moderate) Additive CNS depression may occur when oxybutynin is used concomitantly with other CNS-depressant drugs, including anxiolytics, sedatives, and hypnotics.

Oxycodone: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 oxycodone is initiated in a patient taking a benzodiazepine, reduce dosages and titrate to clinical response. For acetaminophen; oxycodone extended-release tablets, start with 1 tablet PO every 12 hours, and for other oxycodone products, use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Oxymorphone: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 oxymorphone is initiated in a patient taking a benzodiazepine, use an initial dose of oxymorphone at 1/3 to 1/2 the usual dosage and titrate to clinical response. If the extended-release oxymorphone tablets are used concurrently with a CNS depressant, use an initial dosage of 5 mg PO every 12 hours. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Paliperidone: (Moderate) Drugs that can cause CNS depression, if used concomitantly with paliperidone, can increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, and dizziness. Caution should be used when paliperidone is given in combination with other centrally-acting medications including anxiolytics, sedatives, and hypnotics, buprenorphine, butorphanol, dronabinol, THC, ethanol, nabilone, nalbuphine, opiate agonists, and pentazocine.

Pancuronium: (Moderate) Concurrent use of benzodiazepines and other CNS active medications including neuromuscular blockers, can potentiate the CNS effects of either agent. Lower doses of one or both agents may be required. The severity of this interaction may be increased when additional CNS depressants are given.

Papaverine: (Moderate) Concurrent use of papaverine with potent CNS depressants such as benzodiazepines could lead to enhanced sedation.

Pemoline: (Major) A reduction in seizure threshold has been reported following concomitant administration of pemoline with anticonvulsant agents. Dosage adjustments of anticonvulsants may be necessary during simultaneous use of these drugs.

Pentazocine: (Major) Concomitant use of mixed opiate agonists/antagonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of mixed opiate agonists/antagonists with benzodiazepines 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 a mixed opiate agonist/antagonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the mixed opiate agonist/antagonist and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking a mixed opiate agonist/antagonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Pentazocine; Naloxone: (Major) Concomitant use of mixed opiate agonists/antagonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of mixed opiate agonists/antagonists with benzodiazepines 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 a mixed opiate agonist/antagonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the mixed opiate agonist/antagonist and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking a mixed opiate agonist/antagonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Pentobarbital: (Moderate) Additive CNS and/or respiratory depression may occur with concurrent use.

Perampanel: (Moderate) Patients taking benzodiazepines with perampanel may experience increased CNS depression. Monitor patients for adverse effects; dose adjustment of either drug may be necessary. Use of midazolam in healthy subjects who received perampanel 6 mg once daily for 20 days decreased the AUC and Cmax of midazolam by 13% and 15%, respectively, possibly due to weak induction of CYP3A4 by perampanel; the specific clinical significance of this interaction is unknown.

Phenobarbital: (Moderate) Additive CNS and/or respiratory depression may occur with concurrent use.

Phenothiazines: (Moderate) Phenothiazines are CNS depressant drugs that may have cumulative effects when administered concurrently and they should be used cautiously with anxiolytic, sedative, and hypnotic type drugs, such as the benzodiazepines. 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 other CNS depressants than with sedatives alone. Monitor for additive effects, unusual moods or behaviors, and warn about the potential effects to driving and other activities.

Phentermine; Topiramate: (Moderate) Topiramate has the potential to cause CNS depression as well as other cognitive and/or neuropsychiatric adverse reactions. The CNS depressant effects of topiramate can be potentiated pharmacodynamically by concurrent use of CNS depressant

agents such as the benzodiazepines. Concurrent use of topiramate and benzodiazepines associated with thrombocytopenia (e.g., clonazepam, lorazepam, and clobazam), may also increase the risk of bleeding; monitor patients appropriately during benzodiazepine therapy.
Phenylephrine: (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Phenylephrine; Promethazine: (Moderate) Because promethazine causes pronounced sedation, an enhanced CNS depressant effect or additive drowsiness may occur when it is combined with other CNS depressants including benzodiazepines. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Phenytoin: (Moderate) Hydantoin anticonvulsants can theoretically add to the CNS depressant effects of other CNS depressants including the benzodiazepines.
Pimozide: (Moderate) Due to the effects of pimozide on cognition, it should be used cautiously with other CNS depressants including benzodiazepines.
Pramipexole: (Major) Concomitant administration of benzodiazepines with CNS-depressant drugs, including pramipexole, can potentiate the CNS effects.
Prasterone, Dehydroepiandrosterone, DHEA (Dietary Supplements): (Major) Prasterone, dehydroepiandrosterone, DHEA may inhibit the metabolism of benzodiazepines (e.g., alprazolam, estazolam, midazolam) which undergo CYP3A4-mediated metabolism. In one study of elderly volunteers, half of the patients received DHEA 200 mg/day PO for 2 weeks, followed by a single dose of triazolam 0.25 mg. Triazolam clearance was reduced by close to 30% in the DHEA-pretreated patients vs. the control group; however, the effect of DHEA on CYP3A4 metabolism appeared to vary widely among subjects. While more study is needed, benzodiazepine-induced CNS sedation and other adverse effects might be increased in some individuals if DHEA is co-administered.
Prasterone, Dehydroepiandrosterone, DHEA (FDA-approved): (Major) Prasterone, dehydroepiandrosterone, DHEA may inhibit the metabolism of benzodiazepines (e.g., alprazolam, estazolam, midazolam) which undergo CYP3A4-mediated metabolism. In one study of elderly volunteers, half of the patients received DHEA 200 mg/day PO for 2 weeks, followed by a single dose of triazolam 0.25 mg. Triazolam clearance was reduced by close to 30% in the DHEA-pretreated patients vs. the control group; however, the effect of DHEA on CYP3A4 metabolism appeared to vary widely among subjects. While more study is needed, benzodiazepine-induced CNS sedation and other adverse effects might be increased in some individuals if DHEA is co-administered.
Pregabalin: (Moderate) Pregabalin can potentiate the CNS-depressant action of other drugs such as benzodiazepines. Caution should be exercised during simultaneous use of these agents due to potential excessive CNS effects or additive hypotension.
Primidone: (Moderate) Additive CNS and/or respiratory depression may occur with concurrent use.
Probenecid: (Moderate) Probenecid may inhibit the metabolism of the benzodiazepines, including those which are metabolized by conjugation (e.g., lorazepam) or oxidation (e.g., midazolam). Probenecid has been shown to decrease lorazepam clearance by about 50% and increase its elimination half-life. In addition, pretreatment with probenecid shortened the induction time (85 vs. 109 seconds) of midazolam in presurgical patients. Patients receiving alprazolam therapy should be monitored for signs of altered benzodiazepine response when probenecid is initiated or discontinued.
Procarbazine: (Minor) CNS depressants benzodiazepines can potentiate the CNS depression caused by procarbazine therapy, so these drugs should be used together cautiously.
Promethazine: (Moderate) Because promethazine causes pronounced sedation, an enhanced CNS depressant effect or additive drowsiness may occur when it is combined with other CNS depressants including benzodiazepines.
Propofol: (Moderate) Concomitant administration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent.
Propoxyphene: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. The dose of any opiate agonist administered with parenteral diazepam should be reduced by at least one-third.
Pyrimethamine: (Moderate) Mild hepatotoxicity has been reported when pyrimethamine was coadministered with lorazepam.
Pyrimethamine; Sulfadoxine: (Moderate) Mild hepatotoxicity has been reported when pyrimethamine was coadministered with lorazepam.
Quetiapine: (Moderate) Quetiapine decreases lorazepam clearance by about 20%. Patients should be monitored for a potential increase in the pharmacologic effect of lorazepam when coadministered with quetiapine. Somnolence is a commonly reported adverse effect of quetiapine; coadministration of quetiapine with lorazepam may result in additive sedative effects.
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.
Rapacuronium: (Moderate) Concurrent use of benzodiazepines and other CNS active medications including neuromuscular blockers, can potentiate the CNS effects of either agent. Lower doses of one or both agents may be required. The severity of this interaction may be increased when additional CNS depressants are given.
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 opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Benzodiazepine doses may need to be reduced up to 75% during coadministration with remifentanil. Educate patients about the risks and symptoms of respiratory depression and sedation.
Risperidone: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including anxiolytics, sedatives, and hypnotics.
Rocuronium: (Moderate) Concurrent use of benzodiazepines and other CNS active medications including neuromuscular blockers, can potentiate the CNS effects of either agent. Lower doses of one or both agents may be required. The severity of this interaction may be increased when additional CNS depressants are given.
Ropinirole: (Moderate) Concomitant use of ropinirole with other CNS depressants can potentiate the sedation effects of ropinirole.
Rotigotine: (Major) Concomitant use of rotigotine with other CNS depressants, such as benzodiazepines, can potentiate the sedative effects of rotigotine.
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 benzodiazepines.
Scopolamine: (Moderate) Scopolamine may cause dizziness and drowsiness. Concurrent use of scopolamine and CNS depressants can adversely increase the risk of CNS depression.
Secobarbital: (Moderate) Additive CNS and/or respiratory depression may occur with concurrent use.
Sedating H1-blockers: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Sevoflurane: (Moderate) Concomitant administration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent.

Sincalide: (Moderate) Sincalide-induced gallbladder ejection fraction may be affected by benzodiazepines. False study results are possible in patients with drug-induced hyper- or hypo-responsiveness; thorough patient history is important in the interpretation of procedure results.
Skeletal Muscle Relaxants: (Moderate) Concomitant use of skeletal muscle relaxants with benzodiazepines can result in additive CNS depression. The severity of this interaction may be increased when additional CNS depressants are given.
Sodium Oxybate: (Severe) 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.
Succinylcholine: (Moderate) Concurrent use of benzodiazepines and other CNS active medications including neuromuscular blockers, can potentiate the CNS effects of either agent. Lower doses of one or both agents may be required. The severity of this interaction may be increased when additional CNS depressants are given.
Sufentanil: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Suvorexant: (Moderate) CNS depressant drugs may have cumulative effects when administered concurrently and they should be used cautiously with suvorexant. A reduction in dose of the CNS depressant may be needed in some cases. These agents include the benzodiazepines.
Tapentadol: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 tapentadol is initiated in a patient taking a benzodiazepine, a reduced initial dosage of tapentadol is recommended. If the extended-release tapentadol tablets are used concurrently with a benzodiazepine, use an initial tapentadol dose of 50 mg PO every 12 hours. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Teduglutide: (Moderate) Teduglutide may increase absorption of benzodiazepines or other psychotropic agents because of it's pharmacodynamic effect of improving intestinal absorption. In studies with teduglutide, one of the subjects was receiving concomitant treatment with prazepam and experienced dramatic deterioration in mental status progressing to coma during her first week of teduglutide therapy. Upon admission to the ICU, her benzodiazepine level was reported as >300 mcg/L. Both drugs were discontinued, and the coma resolved 5 days later. Careful monitoring and possible dose adjustment of the psychotropic agent is recommended.
Tetrabenazine: (Moderate) Concurrent use of tetrabenazine and drugs that can cause CNS depression, such as benzodiazepines, can increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, dizziness, and orthostatic hypotension.
Thalidomide: (Major) The use of benzodiazepine anxiolytics, sedatives, or hypnotics 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.
Theophylline, Aminophylline: (Moderate) Aminophylline has been reported to counteract the pharmacodynamic effects of diazepam. A proposed mechanism is competitive binding of aminophylline to adenosine receptors in the brain. Whether a similar interaction occurs with other benzodiazepines is not known. If aminophylline therapy is initiated or discontinued, monitor the clinical response to benzodiazepines. (Moderate) Theophylline has been reported to counteract the pharmacodynamic effects of diazepam. A proposed mechanism is competitive binding of theophylline to adenosine receptors in the brain. Whether a similar interaction occurs with other benzodiazepines is not known. If theophylline therapy is initiated or discontinued, monitor the clinical response to benzodiazepines.
Thiopental: (Moderate) Additive CNS and/or respiratory depression may occur with concurrent use.
Thiothixene: (Moderate) Thiothixene can potentiate the CNS-depressant action of other drugs such as benzodiazepines. Caution should be exercised during simultaneous use of these agents due to potential excessive CNS effects or additive hypotension.
Tiagabine: (Moderate) Because of the possible additive effects of drugs that depress the central nervous system, benzodiazepines should be used with caution in patients receiving tiagabine.
Tizanidine: (Moderate) Concurrent use of tizanidine and CNS depressants like the benzodiazepines can cause additive CNS depression. The severity of this interaction may be increased when additional CNS depressants are given.
Topiramate: (Moderate) Topiramate has the potential to cause CNS depression as well as other cognitive and/or neuropsychiatric adverse reactions. The CNS depressant effects of topiramate can be potentiated pharmacodynamically by concurrent use of CNS depressant agents such as the benzodiazepines. Concurrent use of topiramate and benzodiazepines associated with thrombocytopenia (e.g., clonazepam, lorazepam, and clobazam), may also increase the risk of bleeding; monitor patients appropriately during benzodiazepine therapy.
Tramadol: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines 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 an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Trazodone: (Moderate) Trazodone can lower the seizure threshold of anticonvulsants, although the overall risk is low at therapeutic doses. Patients may require increased concentrations of anticonvulsants to achieve equivalent effects if trazodone is added. CNS depressants should be used cautiously in patients receiving trazodone because of additive CNS-depressant effects, including possible respiratory depression or hypotension.
Tricyclic antidepressants: (Moderate) Concomitant administration of benzodiazepines with CNS-depressant drugs, such as tricyclic antidepressants, can potentiate the CNS effects of either agent. Tricyclic antidepressants may also lower the seizure threshold leading to pharmacodynamic interactions with anticonvulsant benzodiazepines (i.e., clobazam, clonazepam, diazepam, and lorazepam). The plasma concentrations of imipramine and desipramine may increase an average of 31% and 20%, respectively, when administered concurrently with alprazolam. The significance of this interaction has not been described; therefore, patients should be monitored closely for symptoms of tricyclic toxicity during coadministration of these agents with alprazolam.
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 the benzodiazepines, may potentiate the effects of either trimethobenzamide or the benzodiazepine.
Triprolidine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Tubocurarine: (Moderate) Concurrent use of benzodiazepines and other CNS active medications including neuromuscular blockers, can potentiate the CNS effects of either agent. Lower doses of one or both agents may be required. The severity of this interaction may be increased when additional CNS depressants are given.
Valerian, Valeriana officinalis: (Major) Any substances that act on the CNS, including psychoactive drugs and drugs used as anesthetic adjuvants (e.g., barbiturates, benzodiazepines), 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 anxiolytics, sedatives, and hypnotics (including barbiturates and benzodiazepines). Patients who are taking barbiturates or other sedative/hypnotic drugs should avoid concomitant administration of valerian. Patients taking medications such as tricyclic

antidepressants, lithium, MAOIs, skeletal muscle relaxants, SSRIs and serotonin norepinephrine reuptake inhibitors (e.g., duloxetine, venlafaxine) should discuss the use of herbal supplements with their health care professional prior to consuming valerian; combinations should be approached with caution in the absence of clinical data. Patients should not abruptly stop taking their prescribed psychoactive medications.
Valproic Acid, Divalproex Sodium: (Moderate) Valproic acid, divalproex sodium has been reported to increase lorazepam peak plasma concentrations and the AUC by 8% and 20%, respectively. In this study, concurrent valproic therapy did not alter sedation scores. This interaction is attributed to inhibition of hepatic glucuronidation of lorazepam by valproate.
Vancomycin: (Moderate) The concurrent administration of vancomycin and anesthetics has been associated with erythema, histamine-like flushing, and anaphylactoid reactions.
Vecuronium: (Moderate) Concurrent use of benzodiazepines and other CNS active medications including neuromuscular blockers, can potentiate the CNS effects of either agent. Lower doses of one or both agents may be required. The severity of this interaction may be increased when additional CNS depressants are given.
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 in combination with benzodiazepines.
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 the benzodiazepines.
Zaleplon: (Moderate) In premarketing studies, zaleplon potentiated the CNS effects of ethanol, imipramine, and thioridazine for at least 2 to 4 hours. Other drugs that may have additive CNS effects with zaleplon but have not been studied include benzodiazepines. If used together, a reduction in the dose of one or both drugs may be needed.
Ziprasidone: (Moderate) Ziprasidone has the potential to impair cognitive and motor skills. Additive CNS depressant effects are possible when ziprasidone is used concurrently with any CNS depressant.
Zolpidem: (Moderate) Concomitant administration of benzodiazepines with zolpidem can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. If used together, a reduction in the dose of one or both drugs may be needed. For Intermezzo brand of sublingual zolpidem tablets, reduce the dose to 1.75 mg/night. Concurrent use of zolpidem with other sedative-hypnotics, including other zolpidem products, at bedtime or the middle of the night is not recommended. In addition, sleep-related behaviors, such as sleep-driving, are more likely to occur during concurrent use of zolpidem and other CNS depressants than with zolpidem alone.

PREGNANCY AND LACTATION

Pregnancy

Benzodiazepines may cause harm to the fetus when administered to pregnant women. An increased risk of congenital malformations during the first trimester of pregnancy has been suggested in several studies involving minor tranquilizers, including benzodiazepines. When benzodiazepines are administered late in pregnancy, they are easily transferred to the fetus where they have the potential to accumulate, causing 2 major neonatal syndromes: a neonatal abstinence syndrome (NAS) and floppy infant syndrome (FIS). Symptoms of NAS from case reports include tremors, irritability, hyperactivity, hypertonicity, tachypnea, vigorous sucking, poor weight gain, loose stools, and vomiting. FIS symptoms include hypotonia, inactivity, weak cry, lethargy, sucking difficulties, low Apgar score, hypothermia, apnea, cyanosis, hyperbilirubinemia, and central nervous system (CNS) depression. FIS typically occurs after chronic fetal exposure to long-acting benzodiazepines (e.g., chlordiazepoxide), or when benzodiazepines are administered shortly before delivery, resulting in newborn toxicity of variable severity and duration. FIS primarily occurs within the first few hours after labor and may last for up to 14 days. Therefore, benzodiazepines are not recommended for use in obstetrical procedures, labor, or obstetric delivery, including cesarean section. The incidence, time to onset, and duration of NAS or FIS symptoms is multi-factorial (e.g., duration of use, drug lipophilicity, placental disposition, degree of accumulation in neonatal tissues). It should be noted that in some case series and studies conducted on specific benzodiazepines, including lorazepam, there was no evidence of neonatal toxicity or withdrawal syndromes in newborns exposed in utero. Nevertheless, if a benzodiazepine is required during pregnancy, avoid first trimester administration if possible, consider short-acting agents (e.g., lorazepam, oxazepam), limit treatment to the shortest possible duration and lowest effective dose, and discontinue the drug well before delivery. According to FDA-approved labeling for lorazepam injection, the drug should not be given to a pregnant woman except in serious or life-threatening situations (e.g., status epilepticus) where safer drugs cannot be used or are ineffective. The possibility that a woman of childbearing potential may be pregnant at the time of treatment initiation should be considered. Patients who become pregnant or intend to become pregnant while taking lorazepam should be advised to discuss the possibility of discontinuing the drug with their physician. Repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures during the third trimester of pregnancy may have negative effects on fetal brain development. Consider the benefits of appropriate anesthesia in pregnant women against the potential risks, especially for procedures that may last more than 3 hours or if multiple procedures are required prior to delivery. It may be appropriate to delay certain procedures if doing so will not jeopardize the health of the child and/or mother. No specific anesthetic or sedation drug has been shown to be safer than another. Human studies suggest that a single short exposure to a general anesthetic in young pediatric patients is unlikely to have negative effects on behavior and learning; however, further research is needed to fully characterize how anesthetic exposure affects brain development.

MECHANISM OF ACTION

Mechanism of Action: Benzodiazepines act at the level of the limbic, thalamic, and hypothalamic regions of the CNS, and can produce any level of CNS depression required including sedation, hypnosis, skeletal muscle relaxation, anticonvulsant activity, and coma. The action of these drugs is mediated through the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Central benzodiazepine receptors interact allosterically with GABA receptors, potentiating the effects of GABA and thereby increasing the inhibition of the ascending reticular activating system. Benzodiazepines block the cortical and limbic arousal that occurs following stimulation of the reticular pathways.As an anticonvulsant, lorazepam has become the preferred parenteral benzodiazepine. Although lorazepam has a shorter elimination half-life than diazepam, lorazepam persists in the CNS longer than diazepam.

PHARMACOKINETICS

Lorazepam is administered orally and parenterally. The drug has also been given sublingually; although, specific sublingual dosage forms are not available in the United States. Lorazepam is widely distributed throughout the body tissues. Approximately 91% of lorazepam present in the blood is protein-bound. Lorazepam has been reported to cross the placental barrier and has been detected in human breast milk.

Lorazepam is glucuronidated by the liver to lorazepam glucuronide, an inactive metabolite. The half-life of lorazepam is approximately 12 hours in adults. The metabolites of lorazepam are excreted in the urine.

Oral Route

Lorazepam is absorbed rapidly following an oral dose.