Brand Names

Aid to Sleep, Alka-Seltzer Plus Allergy, Aller-G-Time , Altaryl, Banophen , Benadryl, Benadryl Allergy, Benadryl Allergy Children's , Benadryl Allergy Dye Free, Benadryl Allergy Quick Dissolve, Benadryl Allergy Ultratab, Benadryl Children's Allergy, Benadryl Children's Allergy Fastmelt, Benadryl Children's Perfect Measure, Benadryl Itch Stopping, Ben-Tann , Children's Allergy, Children's MAXAllergy, Compoz Nighttime Sleep Aid, Dimetane, Diphedryl , DI-PHEN, Diphen AF , Diphen Elixir, Diphenhist, DiphenMax , Dytan, ElixSure Allergy, Genahist , Geri-Dryl, Hydramine, Itch Relief , M-Dryl, Nighttime Sleep Aid, Nytol, PediaCare Children's Allergy, PediaCare Nighttime Cough, PediaClear Children's Cough, PHARBEDRYL, Q-Dryl, Quenalin , Siladryl Allergy, Silphen , Simply Sleep , Sleep Tabs, Sleepinal, Sominex, Sominex Maximum Strength, Tecnu Rash Relief, Theraflu Multi-Symptom Strip, Triaminic Allergy Thin Strip, Triaminic Cough and Runny Nose Strip, Tusstat, Unisom, Uni-Tann, Valu-Dryl , Vanamine PD, Vicks Qlearquil Nighttime Allergy Relief, Vicks ZzzQuil Nighttime Sleep-Aid

Indication Specific Dosing

For the prevention and treatment of allergic or hypersensitivity reactions, including anaphylaxis, angioedema, urticaria, or pruritus; also for treating symptoms (e.g., rhinorrhea, sneezing) associated with allergic rhinitis or the common cold, and for cough caused by minor throat and bronchial irritation

For prevention and treatment of allergic or hypersensitivity reactions including allergic rhinitis, urticaria, pruritus, and angioedema, or as an adjunct to epinephrine for anaphylaxis under the supervision of a healthcare professional

Oral dosage

Adults

25 to 50 mg PO 3 to 4 times daily as needed. Max: 300 mg/day.

Infants, Children, and Adolescents

1 to 1.5 mg/kg/dose (Max: 25 to 50 mg/dose) PO 3 to 4 times daily as needed. Max: 5 mg/kg/day or 300 mg/day.

Intravenous or Intramuscular dosage

Adults

10 to 50 mg IV or IM every 4 to 6 hours, as needed. Single doses of 100 mg may be given if required. Max: 400 mg/day.

Adolescents

25 to 50 mg/dose IV or IM every 4 to 6 hours as needed (Max: 400 mg/day).

Infants and Children

1 to 2 mg/kg/dose (Max: 50 mg/dose) IV or IM every 4 to 8 hours as needed, up to 5 mg/kg/day (Max: 200 mg/day).

For non-prescription self-treatment of symptoms associated with allergic rhinitis or the common cold

Oral dosage (tablets or capsules, chewable tablets, or oral liquids, e.g., Benadryl products, non-prescription)

Adults and Adolescents

25 to 50 mg PO every 4 to 6 hours as needed. Max: 300 mg per 24 hours.

Children 6 to 12 years

12.5 to 25 mg PO every 4 to 6 hours as needed. Max: 150 mg per 24 hours.

For non-prescription self-treatment of cough caused by minor throat and bronchial irritation

Oral dosage

Adults and Adolescents

25 mg PO every 4 to 6 hours as needed. Max: 150 mg per 24 hours.

Children 6 to 12 years

12.5 mg PO every 4 to 6 hours as needed. Max: 75 mg per 24 hours.

For the treatment of motion sickness

Oral dosage

Adults and Adolescents

For nonprescription use, 25 to 50 mg PO every 4 to 6 hours as needed, not to exceed 300 mg in 24 hours.

Children 6 to 12 years

For nonprescription use, 12.5 to 25 mg PO every 4 to 6 hours as needed, not to exceed 150 mg in 24 hours.

Intravenous and intramuscular dosage

Adults and Adolescents

10 to 50 mg IV or IM initially. Usually repeated every 6 hours as needed, not to exceed 400 mg per 24 hours.

Children 6 to 12 years

1 to 1.5 mg/kg IV or IM every 6 hours as needed, not to exceed 300 mg/24 hours.

For the treatment of occasional insomnia

Oral dosage

Adults

50 mg PO at bedtime as needed. Lower dosages (e.g., 25 mg/night) may be sufficient for some adults. If insomnia persists continuously for more than 2 weeks, the patient should be evaluated. Per guidelines, not a medication of choice for insomnia.

Children and Adolescents 12 to 17 years

50 mg PO at bedtime as needed, or as directed by prescriber.

For the treatment of parkinsonism or Parkinson disease

Oral dosage

Adults

25 to 50 mg PO 3 to 4 times daily is the usual dose. Max: 300 mg/day.

Intravenous or Intramuscular dosage

Adults

10 to 50 mg IV or IM initially. Usually repeated every 6 hours as needed, not to exceed 400 mg per 24 hours.

For the treatment of drug-induced extrapyramidal symptoms

Intravenous or Intramuscular dosage

Adults

10 to 50 mg IV or IM initially. Usually repeated every 6 hours as needed, not to exceed 400 mg per 24 hours.

Infants, Children, and Adolescents

1 to 2 mg/kg/dose (Max: 50 mg/dose) IV or IM every 6 hours as needed, up to 5 mg/kg/day (Max: 300 mg/day).

Oral dosage

Adults

25 to 50 mg PO 3 to 4 times daily is the usual dose. Max: 300 mg/day.

Infants, Children, and Adolescents

1 to 1.5 mg/kg/dose (Max: 25 to 50 mg/dose) PO 3 to 4 times daily, up to 5 mg/kg/day (Max: 300 mg/day).

For temporary relief of topical pain and itching associated with: insect bites or stings, minor burns, sunburn, minor cuts or scrapes, minor skin irritation or Rhus dermatitis due to poison ivy, poison oak, and poison sumac

Topical dosage

Adults

Apply to the affected area not more than 3 to 4 times per day for up to 7 days.

Children and Adolescents 2 to 17 years

Apply to the affected area not more than 3 to 4 times per day for up to 7 days.

Topical dosage (Tecnu Ivy Complete Kit)

Adults

Apply to the affected area not more than 3 times per day for up to 7 days.

Children and Adolescents 2 to 17 years

Apply to the affected area not more than 3 times per day for up to 7 days.

For the treatment of acute peripheral vestibular nystagmus†

Oral dosage

Adults

25 to 50 mg PO every 4 to 6 hours for up to 48 hours has been recommended. It is advisable to individualize the dosage based upon clinical response and tolerability.

For the treatment of pregnancy-induced nausea/vomiting†

Oral dosage

Adults

25 to 50 mg PO every 4 to 6 hours as needed.

For the treatment of cyclic vomiting syndrome†

Intravenous dosage

Adults

50 mg IV as a single dose plus metoclopramide for nausea/vomiting or lorazepam for sedation.

Children and Adolescents

1 to 1.25 mg/kg/dose (Max: 50 mg/dose) IV every 6 hours as needed.

Oral dosage

Adults

50 mg PO as a single dose plus metoclopramide for nausea/vomiting or lorazepam for sedation. IV administration is preferred due to repeated purging.

Children and Adolescents

1 to 1.25 mg/kg/dose (Max: 50 mg/dose) PO every 6 hours as needed. IV administration is preferred due to repeated purging.

For the treatment of geographic tongue†

Oral/Topical dosage (solution)

Adults

12.5 mg PO up to 4 times daily; hold solution over tongue for 1 to 2 minutes and then swallow.

Children and Adolescents 3 to 17 years

12.5 mg PO up to 4 times daily; hold solution over tongue for 1 to 2 minutes and then swallow.

For the treatment of vertigo† and nausea† associated with Meniere disease

Oral dosage

Adults

25 to 50 mg PO every 6 hours as needed.

Intravenous or Intramuscular dosage

Adults

25 to 50 mg IV or IM every 6 hours as needed.

Contraindications And Precaution

Drug Interactions

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

asthma, chronic obstructive pulmonary disease

Use systemic dosage forms of diphenhydramine with caution in people with chronic obstructive pulmonary disease (COPD), including emphysema or chronic bronchitis. The anticholinergic activity of the first-generation H1-antagonists may result in thickened bronchial secretions in the respiratory tract, thereby aggravating COPD.
56736
56616
While there is no special precaution for people with asthma using diphenhydramine nonprescription products for allergies or insomnia at the recommended dosages, prescription-only products advise using caution in people with asthma.

Hypersensitivity

This medication is contraindicated in patients with a history of hypersensitivity to it or any of its components. Diphenhydramine is an ethanolamine class first-generation antihistamine and is contraindicated in people hypersensitive to other antihistamines of similar chemical structure.

glaucoma, increased intraocular pressure

Systemic diphenhydramine products should be used with caution in people with glaucoma, as an increase in intraocular pressure may occur from the anticholinergic actions of the medication. Older adults are more susceptible to the anticholinergic effects of diphenhydramine, including possible precipitation of undiagnosed glaucoma.
56616
Prescription products specifically precaution use of diphenhydramine in patients with narrow-angle glaucoma or increased intraocular pressure.

bladder obstruction, prostatic hypertrophy

Due to the anticholinergic effects which may aggravate urinary retention, first-generation antihistamines, such as systemic diphenhydramine products, should be used with caution in people with trouble urinating due to prostatic hypertrophy.
56616
Prescription products also precaution use of diphenhydramine in patients with bladder obstruction.

cardiovascular disease, hyperthyroidism

Oral and topical diphenhydramine nonprescription use carries no special precautions for those with heart or blood pressure conditions.
56736
Diphenhydramine rarely causes changes in heart rate or blood pressure at usual dosages. Caution is recommended with use of prescription products, which may be prescribed at higher dosages to treat more severe conditions, in people with cardiovascular disease or hypertension, or in people with hyperthyroidism.
56616

gastric outlet obstruction

Systemic diphenhydramine prescription labels contain a precaution for use for people with gastric outlet obstruction (stenosing peptic ulcer or pyloroduodenal obstruction). Diphenhydramine has anticholinergic effects that may aggravate these conditions. Nonprescription products do not have a precaution for people with these conditions.

activities requiring coordination and concentration, driving or operating machinery

Systemic diphenhydramine products can cause drowsiness. Advise individuals receiving diphenhydramine to avoid driving or operating machinery and activities requiring coordination and concentration until the effects of the drug are known. Additive drowsiness may be seen during coadministration with alcohol or other CNS depressants.
56616

children, infants, neonates, premature neonates

Systemic diphenhydramine should not be used in neonates or premature neonates/infants. Topical and systemic diphenhydramine use must be approached with caution in infants and children less than 2 years of age. Due to the risk for serious adverse reactions, the FDA recommends against administration of over the counter (OTC) cough and cold products to neonates, infants and children younger than 2 years of age. When administering OTC medications to older pediatric patients, they advise caregivers to read product labels carefully, use caution when administering multiple products to avoid duplication of ingredients, and use only measuring devices specifically designed for use with medications. Care teams should thoroughly assess the use of

similar products, both prescription and nonprescription, to avoid duplication of therapy and the potential for inadvertent overdose.

geriatric

The Beers Criteria consider treatment of an acute emergent condition, such as a severe allergic reaction, as an acceptable use of systemic diphenhydramine in the older adult when necessary. Otherwise, the Beers Criteria identify systemic first-generation antihistamines as potentially inappropriate medications (PIMs) for geriatric adults, recommending their avoidance due to their high anticholinergic properties, decreased clearance in older age, the development of tolerance when used as sleep aids, and an increased risk of anticholinergic effects and toxicity compared to younger individuals. These medications should particularly be avoided in patients with dementia or cognitive impairment (due to adverse CNS effects), those at high risk for delirium (which can worsen or trigger new-onset delirium), and men with lower urinary tract symptoms or benign prostatic hyperplasia (due to risks of urinary retention or hesitancy). Systemic antihistamines are most likely to cause dizziness, sedation, and hypotension in the older population.

measles, varicella

If a patient has varicella (chickenpox) or measles infection, the care team should be consulted before using diphenhydramine topically on the lesions to reduce itching. Topical diphenhydramine should not be applied to these lesions unless under the prescription of a health care provider. Diphenhydramine toxicity risk has been reported to be increased when it is applied topically to these infectious lesions.

pregnancy

Parenteral diphenhydramine is typically the parenteral antihistamine of choice in managing acute or severe allergic reactions during pregnancy. Oral and topical use generally pose no concerns for the usual dosages and short durations of use. Reproduction studies in rats and rabbits at doses up to 5-times the human dose and have revealed no evidence of impaired fertility or harm to the fetus. Other studies have shown no increased risk of birth defects or other pregnancy complications with diphenhydramine use. Non-pharmacologic methods (e.g., fluids and rest) are recommended to be tried first for symptomatic relief of colds or allergies during pregnancy. Alternative antihistamines may be considered. Loratadine and oral cetirizine are acceptable alternatives to first-generation antihistamines like diphenhydramine, based on their excellent safety data and recommendation in multiple guidelines for use during pregnancy. Systemic diphenhydramine has been used to treat nausea and

vomiting during pregnancy, but such use should occur under the advice and supervision of a qualified care team. ACOG guidelines allow for the use of diphenhydramine as a second-line pharmacologic option in treatment algorithms for nausea/vomiting due to pregnancy; nonpharmacologic options and pyridoxine, taken alone or in combination with doxylamine, are first-line.

breast-feeding

Oral diphenhydramine may be used with caution in breast-feeding, and single or occasional usual doses of diphenhydramine for allergies or cold symptoms, when necessary, would not be expected to cause adverse effects in breastfed infants. The prescription label of injectable diphenhydramine contraindicates use in breast-feeding due to the higher risks associated with antihistamine use in infants, particularly neonates and premature neonates, and the higher dosages often used with this dosage form. Larger doses or prolonged use may cause adverse effects in the breastfed infant or decrease the milk supply, especially if lactation is not well established. Side effects of sedating first-generation antihistamines in breastfed infants such as irritability, disturbed sleeping patterns, drowsiness, hyperexcitability, and excessive crying have been reported in a number of cases. Antihistamines can lower basal prolactin secretion and may interfere with the establishment of lactation. Consider treatment alternatives when possible. Guidelines recommend loratadine or cetirizine at the lowest dose as preferred antihistamines in breast-feeding individuals because they are safer with only low levels found in breast milk. Topical diphenhydramine use is considered compatible with breast-feeding; avoid applying to the areola or other breast areas to limit infant contact.

Pregnancy And Lactation

Parenteral diphenhydramine is typically the parenteral antihistamine of choice in managing acute or severe allergic reactions during pregnancy. Oral and topical use generally pose no concerns for the usual dosages and short durations of use. Reproduction studies in rats and rabbits at doses up to 5-times the human dose and have revealed no evidence of impaired fertility or harm to the fetus. Other studies have shown no increased risk of birth defects or other pregnancy complications with diphenhydramine use. Non-pharmacologic methods (e.g., fluids and rest) are recommended to be tried first for symptomatic relief of colds or allergies during pregnancy. Alternative antihistamines may be considered. Loratadine and oral cetirizine are acceptable alternatives to first-generation antihistamines like diphenhydramine, based on their excellent safety data and recommendation in multiple guidelines for use during pregnancy. Systemic diphenhydramine has been used to treat nausea and

vomiting during pregnancy, but such use should occur under the advice and supervision of a qualified care team. ACOG guidelines allow for the use of diphenhydramine as a second-line pharmacologic option in treatment algorithms for nausea/vomiting due to pregnancy; nonpharmacologic options and pyridoxine, taken alone or in combination with doxylamine, are first-line.

Interactions

Acetaminophen; Caffeine; Dihydrocodeine: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus. Acetaminophen; Codeine: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus. Acetaminophen; HYDROcodone: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus. Acetaminophen; oxyCODONE: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus. ALFentanil: (Major) Reserve concomitant use of opioids and diphenhydramine for

patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
Alosetron: (Moderate) Alosetron, if combined with drugs that possess anticholinergic properties like sedating H1 blockers, may seriously worsen constipation, leading to events such as GI obstruction/impaction or paralytic ileus.
ALPRAZolam: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Amantadine: (Moderate) Medications with significant anticholinergic activity may potentiate the anticholinergic effects of amantadine, and may increase the risk of antimuscarinic-related side effects. Additive drowsiness may also occur.
Amikacin: (Minor) Diphenhydramine may mask vestibular symptoms (e.g., dizziness, tinnitus, or vertigo) that are associated with ototoxicity induced by aminoglycosides. Antiemetics block the histamine or acetylcholine response that causes nausea due to vestibular emetic stimuli such as motion.
Aminoglycosides: (Minor) Diphenhydramine may mask vestibular symptoms (e.g., dizziness, tinnitus, or vertigo) that are associated with ototoxicity induced by aminoglycosides. Antiemetics block the histamine or acetylcholine response that causes nausea due to vestibular emetic stimuli such as motion.
Amitriptyline: (Moderate) Monitor for unusual drowsiness and sedation, urinary retention, and reduced gastric motility during coadministration of diphenhydramine and tricyclic antidepressants. Concomitant use may result in additive CNS depression or anticholinergic effects.
Amivantamab; Hyaluronidase: (Minor) H1-blockers (antihistamines), when given in large systemic doses, may render tissues partially resistant to the action of hyaluronidase. Patients receiving these medications may require larger amounts of hyaluronidase for equivalent dispersing effect.
Amobarbital: (Major) Because diphenhydramine can cause pronounced sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as barbiturates.
Amoxapine: (Moderate) Additive anticholinergic effects may be seen when amoxapine is used concomitantly with drugs are known to possess relatively significant antimuscarinic properties, including sedating H1-blockers. Antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature Additive sedation may also occur.

Amphetamine: (Moderate) Amphetamines may pharmacodynamically counteract the sedative properties of some antihistamines, such as the sedating H1-blockers (i.e., diphenhydramine). This effect may be clinically important if a patient is receiving an antihistamine agent for treatment of insomnia. Alternatively, if a patient is receiving an amphetamine for treatment of narcolepsy, the combination with a sedating antihistamine may reverse the action of the amphetamine.
Amphetamine; Dextroamphetamine Salts: (Moderate) Amphetamines may pharmacodynamically counteract the sedative properties of some antihistamines, such as the sedating H1-blockers (i.e., diphenhydramine). This effect may be clinically important if a patient is receiving an antihistamine agent for treatment of insomnia. Alternatively, if a patient is receiving an amphetamine for treatment of narcolepsy, the combination with a sedating antihistamine may reverse the action of the amphetamine.
Amphetamine; Dextroamphetamine: (Moderate) Amphetamines may pharmacodynamically counteract the sedative properties of some antihistamines, such as the sedating H1-blockers (i.e., diphenhydramine). This effect may be clinically important if a patient is receiving an antihistamine agent for treatment of insomnia. Alternatively, if a patient is receiving an amphetamine for treatment of narcolepsy, the combination with a sedating antihistamine may reverse the action of the amphetamine.
Apomorphine: (Moderate) Apomorphine causes significant somnolence. Concomitant administration of apomorphine and diphenhydramine could result in additive depressant effects. Careful monitoring is recommended during combined use. A dose reduction of one or both drugs may be warranted.
Apraclonidine: (Minor) No specific drug interactions were identified with systemic agents and apraclonidine during clinical trials. Theoretically, apraclonidine might potentiate the effects of CNS depressant drugs such as the anxiolytics, sedatives, and hypnotics, including barbiturates or benzodiazepines.
Aprepitant, Fosaprepitant: (Minor) Use caution if diphenhydramine and aprepitant are used concurrently and monitor for a possible decrease in the efficacy of diphenhydramine. After administration, fosaprepitant is rapidly converted to aprepitant and shares the same drug interactions. Diphenhydramine is a CYP2C9 substrate and aprepitant is a CYP2C9 inducer. Administration of a CYP2C9 substrate, tolbutamide, on days 1, 4, 8, and 15 with a 3-day regimen of oral aprepitant (125 mg/80 mg/80 mg) decreased the tolbutamide AUC by 23% on day 4, 28% on day 8, and 15% on day 15. The AUC of tolbutamide was decreased by 8% on day 2, 16% on day 4, 15% on day 8, and 10% on day 15 when given prior to oral administration of aprepitant 40 mg on day 1, and on days 2, 4, 8, and 15. The effects of aprepitant on tolbutamide were not considered significant. When a 3-day regimen of aprepitant (125 mg/80 mg/80 mg) given to healthy patients on stabilized chronic warfarin therapy (another CYP2C9 substrate), a 34% decrease in S-warfarin trough concentrations was noted, accompanied by a 14% decrease in the INR at five days after completion of aprepitant.

ARIPiprazole: (Moderate) Monitor for aripiprazole-related adverse reactions during concomitant use of diphenhydramine. Patients receiving both a CYP3A inhibitor plus diphenhydramine may require an aripiprazole dosage adjustment. Dosing recommendations vary based on aripiprazole dosage form and CYP3A inhibitor strength. See prescribing information for details. Concomitant use may increase aripiprazole exposure and risk for side effects. Aripiprazole is a CYP2D6 and CYP3A substrate; diphenhydramine is a moderate CYP2D6 inhibitor.
Artemether; Lumefantrine: (Moderate) Lumefantrine is an inhibitor and diphenhydramine is a substrate/inhibitor of the CYP2D6 isoenzyme; therefore, coadministration may lead to increased diphenhydramine concentrations. Concomitant use warrants caution due to the potential for increased side effects.
Articaine; EPINEPHrine: (Moderate) Diphenhydramine may potentiate the arrhythmogenic effects of epinephrine.
Asenapine: (Moderate) Using drugs that can cause CNS depression, such as sedating H1-blockers, concomitantly with asenapine may increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, and dizziness.
Aspirin, ASA; Butalbital; Caffeine: (Major) Because diphenhydramine can cause pronounced sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as barbiturates.
Aspirin, ASA; Caffeine; Orphenadrine: (Moderate) Additive anticholinergic effects may be seen when drugs with anticholinergic properties, like sedating H1-blockers and orphenadrine, are used concomitantly. Adverse effects may be seen not only on GI smooth muscle, but also on bladder function, the CNS, the eye, and temperature regulation. Additive drowsiness may also occur.
Aspirin, ASA; Carisoprodol; Codeine: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
(Moderate) Carisoprodol is metabolized to meprobamate, a significant CNS depressant. Carisoprodol can cause additive CNS depression if used concomitantly with other CNS depressants. Additive effects of sedation and dizziness, which can impair the ability to undertake tasks requiring mental alertness, may occur if carisoprodol is taken with sedating H1-blockers. Utilize appropriate caution if carisoprodol is coadministered with another CNS depressant.
Aspirin, ASA; oxyCODONE: (Major) Reserve concomitant use of opioids and

diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
Atazanavir; Cobicistat: (Moderate) Caution is warranted when cobicistat is administered with diphenhydramine as there is a potential for elevated diphenhydramine and cobicistat concentrations. Diphenhydramine is a substrate/inhibitor of CYP2D6 and a substrate of CYP2C9. Cobicistat is an substrate/inhibitor of CYP2D6.
Atezolizumab; Hyaluronidase: (Minor) H1-blockers (antihistamines), when given in large systemic doses, may render tissues partially resistant to the action of hyaluronidase. Patients receiving these medications may require larger amounts of hyaluronidase for equivalent dispersing effect.
Atropine: (Moderate) Monitor for unusual drowsiness or excess sedation and for signs or symptoms of anticholinergic toxicity during concomitant sedating H1-blocker and atropine use. Concomitant use may result in additive CNS depression or anticholinergic adverse effects.
Atropine; Difenoxin: (Moderate) An enhanced CNS depressant effect may occur when diphenoxylate/difenoxin is combined with other CNS depressants.
Diphenoxylate/difenoxin decreases GI motility. Other drugs that also decrease GI motility, such as sedating H1 blockers, may produce additive effects with diphenoxylate/difenoxin if used concomitantly. (Moderate) Monitor for unusual drowsiness or excess sedation and for signs or symptoms of anticholinergic toxicity during concomitant sedating H1-blocker and atropine use. Concomitant use may result in additive CNS depression or anticholinergic adverse effects.
Azelastine: (Major) Avoid concomitant use of azelastine and sedating H1-blockers due to risk for additive CNS depression.
Azelastine; Fluticasone: (Major) Avoid concomitant use of azelastine and sedating H1-blockers due to risk for additive CNS depression.
Baclofen: (Moderate) An enhanced CNS depressant effect may occur when sedating H1-blockers are combined with other CNS depressants including skeletal muscle relaxants, such as baclofen.
Barbiturates: (Major) Because diphenhydramine can cause pronounced sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as barbiturates.
Belladonna; Opium: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory

depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
(Moderate) Monitor for signs or symptoms of anticholinergic toxicity during concomitant sedating H1-blocker and belladonna use. Concomitant use may result in additive anticholinergic adverse effects.
Benzgalantamine: (Moderate) Concurrent use of sedating H1-blockers and galantamine should be avoided if possible. Galantamine inhibits acetylcholinesterase, the enzyme responsible for the degradation of acetylcholine, and improves the availability of acetylcholine. Sedating H1-blockers may exhibit significant anticholinergic activity, thereby interfering with the therapeutic effect of galantamine.
Benzhydrocodone; Acetaminophen: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
Benzodiazepines: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Benzoic Acid; Hyoscyamine; Methenamine; Methylene Blue; Phenyl Salicylate: (Moderate) Monitor for signs or symptoms of anticholinergic toxicity during concomitant sedating H1-blocker and hyoscyamine use. Concomitant use may result in additive anticholinergic adverse effects.
Benzphetamine: (Moderate) Amphetamines may pharmacodynamically counteract the sedative properties of some antihistamines, such as the sedating H1-blockers. This effect may be clinically important if a patient is receiving an antihistamine agent for treatment of insomnia. Alternatively, if a patient is receiving an amphetamine for treatment of narcolepsy, the combination with a sedating antihistamine may reverse the action of the amphetamine.
Benztropine: (Moderate) Monitor for signs or symptoms of anticholinergic toxicity during concomitant sedating H1-blocker and benztropine use. Concomitant use may result in additive anticholinergic adverse effects.
Bethanechol: (Moderate) Drugs that possess antimuscarinic properties, such as diphenhydramine, are pharmacologic opposites of bethanechol. These agents should not be used with bethanechol except when the specific intent is to counteract excessive

actions of one or the other.
Budesonide; Glycopyrrolate; Formoterol: (Moderate) Monitor for signs or symptoms of anticholinergic toxicity during concomitant sedating H1-blocker and glycopyrrolate use. Concomitant use may result in additive anticholinergic adverse effects.
BUPivacaine; EPINEPHrine: (Moderate) Diphenhydramine may potentiate the arrhythmogenic effects of epinephrine.
Buprenorphine: (Major) Reserve concomitant prescribing of buprenorphine and diphenhydramine for use in patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. Gradually tapering a patient off other CNS depressants or decreasing to the lowest effective dose is preferred in most cases of patients being treated for opioid use disorder. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose. Also monitor for signs of urinary retention or reduced gastric motility during concomitant use. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
Buprenorphine; Naloxone: (Major) Reserve concomitant prescribing of buprenorphine and diphenhydramine for use in patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. Gradually tapering a patient off other CNS depressants or decreasing to the lowest effective dose is preferred in most cases of patients being treated for opioid use disorder. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose. Also monitor for signs of urinary retention or reduced gastric motility during concomitant use. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
Butalbital; Acetaminophen: (Major) Because diphenhydramine can cause pronounced sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as barbiturates.
Butalbital; Acetaminophen; Caffeine: (Major) Because diphenhydramine can cause pronounced sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as barbiturates.
Butalbital; Acetaminophen; Caffeine; Codeine: (Major) Because diphenhydramine can cause pronounced sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as barbiturates. (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and

durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
Butalbital; Aspirin; Caffeine; Codeine: (Major) Because diphenhydramine can cause pronounced sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as barbiturates. (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
Butorphanol: (Moderate) Concomitant use of butorphanol with sedating H1-blockers can potentiate the effects of butorphanol on CNS and/or respiratory depression. Use together with caution. If a CNS depressant needs to be used with butorphanol, use the smallest effective dose and the longest dosing frequency of butorphanol.
Cannabidiol: (Moderate) Monitor for excessive sedation and somnolence during coadministration of cannabidiol and sedating H1-blockers. CNS depressants can potentiate the effects of cannabidiol.
Capsaicin; Metaxalone: (Moderate) Concomitant administration of metaxalone with other CNS depressants can potentiate the sedative effects of either agent.
Carbidopa; Levodopa; Entacapone: (Moderate) COMT inhibitors should be given cautiously with other agents that cause CNS depression, including sedating H1-blockers, due to the possibility of additive sedation. COMT inhibitors have also been associated with sudden sleep onset during activities of daily living such as driving, which has resulted in accidents in some cases. Prescribers should re-assess patients for drowsiness or sleepiness regularly throughout treatment, especially since events may occur well after the start of treatment. Patients should be advised to avoid driving or other tasks requiring mental alertness until they know how the combination affects them.
Cariprazine: (Moderate) Due to the CNS effects of cariprazine, caution should be used when cariprazine is given in combination with other centrally-acting medications including benzodiazepines and other anxiolytics, sedatives, and hypnotics like diphenhydramine.
Carisoprodol: (Moderate) Carisoprodol is metabolized to meprobamate, a significant

CNS depressant. Carisoprodol can cause additive CNS depression if used concomitantly with other CNS depressants. Additive effects of sedation and dizziness, which can impair the ability to undertake tasks requiring mental alertness, may occur if carisoprodol is taken with sedating H1-blockers. Utilize appropriate caution if carisoprodol is coadministered with another CNS depressant.
Celecoxib; Tramadol: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
Cenobamate: (Moderate) Monitor for excessive sedation and somnolence during coadministration of cenobamate and sedating H1-blockers. Concurrent use may result in additive CNS depression.
Cetirizine: (Moderate) Monitor for unusual drowsiness and sedation, urinary retention, and reduced gastric motility during coadministration of cetirizine and sedating H1-blockers. Concomitant use may result in additive CNS depression or anticholinergic effects.
Cetirizine; Pseudoephedrine: (Moderate) Monitor for unusual drowsiness and sedation, urinary retention, and reduced gastric motility during coadministration of cetirizine and sedating H1-blockers. Concomitant use may result in additive CNS depression or anticholinergic effects.
chlordiazePOXIDE: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
chlordiazePOXIDE; Amitriptyline: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) Monitor for unusual drowsiness and sedation, urinary retention, and reduced gastric motility during coadministration of diphenhydramine and tricyclic antidepressants. Concomitant use may result in additive CNS depression or anticholinergic effects.
chlordiazePOXIDE; Clidinium: (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) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider

prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
Chlorpheniramine; HYDROcodone: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
chlorproMAZINE: (Moderate) Additive anticholinergic and sedative effects may be seen when chlorpromazine is used with first generation antihistamines, such as diphenhydramine. Patients should be informed to read non-prescription allergy, sleep, and cough and cold product labels carefully for additional interacting antihistamines.
Chlorzoxazone: (Moderate) Additive CNS depression is possible if chlorzoxazone is used concomitantly with other CNS depressants including sedating H1-blockers. Additive effects of sedation and dizziness can occur, which can impair the ability to undertake tasks requiring mental alertness. Dosage adjustments of one or both medications may be necessary.
cloBAZam: (Moderate) Clobazam, a benzodiazepine, may cause drowsiness or other CNS effects. Additive drowsiness may occur when clobazam is combined with CNS depressants such as sedating H1-blockers. In addition, caution is recommended when administering clobazam with medications extensively metabolized by CYP2D6 such as diphenhydramine because clobazam has been shown to inhibit CYP2D6 in vivo and may increase concentrations of drugs metabolized by this enzyme.
clomiPRAMINE: (Moderate) Monitor for unusual drowsiness and sedation, urinary retention, and reduced gastric motility during coadministration of diphenhydramine and tricyclic antidepressants. Concomitant use may result in additive CNS depression or anticholinergic effects.
clonazePAM: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Clorazepate: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
cloZAPine: (Moderate) Clozapine exhibits clinically significant anticholinergic effects and sedation that may be additive with other medications that may cause anticholinergic effects and sedation, including antihistamines such as diphenhydramine. Patients should be informed to read non-prescription cough and cold product labels carefully for additional interacting antihistamines and to avoid tasks requiring mental alertness until

they are aware of the effects of the combination.
Cobicistat: (Moderate) Caution is warranted when cobicistat is administered with diphenhydramine as there is a potential for elevated diphenhydramine and cobicistat concentrations. Diphenhydramine is a substrate/inhibitor of CYP2D6 and a substrate of CYP2C9. Cobicistat is an substrate/inhibitor of CYP2D6.
Codeine: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
Codeine; Dexbrompheniramine: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
Codeine; guaiFENesin: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
Codeine; guaiFENesin; Pseudoephedrine: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
Codeine; Phenylephrine; Promethazine: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for

respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus. (Moderate) Monitor for unusual drowsiness and sedation, urinary retention, and reduced gastric motility during coadministration of diphenhydramine and promethazine. Concomitant use may result in additive CNS depression or anticholinergic effects.
Codeine; Promethazine: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus. (Moderate) Monitor for unusual drowsiness and sedation, urinary retention, and reduced gastric motility during coadministration of diphenhydramine and promethazine. Concomitant use may result in additive CNS depression or anticholinergic effects.
COMT inhibitors: (Moderate) COMT inhibitors should be given cautiously with other agents that cause CNS depression, including sedating H1-blockers, due to the possibility of additive sedation. COMT inhibitors have also been associated with sudden sleep onset during activities of daily living such as driving, which has resulted in accidents in some cases. Prescribers should re-assess patients for drowsiness or sleepiness regularly throughout treatment, especially since events may occur well after the start of treatment. Patients should be advised to avoid driving or other tasks requiring mental alertness until they know how the combination affects them.
Cyclobenzaprine: (Moderate) Monitor for unusual drowsiness and sedation, urinary retention, and reduced gastric motility during coadministration of cyclobenzaprine and diphenhydramine. Concomitant use may result in additive CNS depression or anticholinergic effects.
Dantrolene: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect (e.g., drowsiness) may occur when dantrolene is combined with other CNS depressants.
Daratumumab; Hyaluronidase: (Minor) H1-blockers (antihistamines), when given in large systemic doses, may render tissues partially resistant to the action of hyaluronidase. Patients receiving these medications may require larger amounts of hyaluronidase for equivalent dispersing effect.

Darunavir; Cobicistat: (Moderate) Caution is warranted when cobicistat is administered with diphenhydramine as there is a potential for elevated diphenhydramine and cobicistat concentrations. Diphenhydramine is a substrate/inhibitor of CYP2D6 and a substrate of CYP2C9. Cobicistat is an substrate/inhibitor of CYP2D6.
Darunavir; Cobicistat; Emtricitabine; Tenofovir alafenamide: (Moderate) Caution is warranted when cobicistat is administered with diphenhydramine as there is a potential for elevated diphenhydramine and cobicistat concentrations. Diphenhydramine is a substrate/inhibitor of CYP2D6 and a substrate of CYP2C9. Cobicistat is an substrate/inhibitor of CYP2D6.
Desflurane: (Minor) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when they are combined with general anesthetics.
Desipramine: (Moderate) Monitor for unusual drowsiness and sedation, urinary retention, and reduced gastric motility during coadministration of diphenhydramine and tricyclic antidepressants. Concomitant use may result in additive CNS depression or anticholinergic effects.
Desloratadine: (Minor) Although desloratadine is considered a 'non-sedating' antihistamine, dose-related sedation has been noted. For this reason, it would be prudent to monitor for drowsiness during concurrent use of desloratadine with CNS depressants such as other H1-blockers.
Desloratadine; Pseudoephedrine: (Minor) Although desloratadine is considered a 'non-sedating' antihistamine, dose-related sedation has been noted. For this reason, it would be prudent to monitor for drowsiness during concurrent use of desloratadine with CNS depressants such as other H1-blockers.
Deutetrabenazine: (Moderate) Advise patients that concurrent use of deutetrabenazine and drugs that can cause CNS depression, such as diphenhydramine, may have additive effects and worsen drowsiness or sedation.
dexmedeTOMIDine: (Moderate) Consider a dosage reduction for dexmedetomidine or the sedating antihistamine during concomitant use due to the risk of additive CNS effects.
Dextroamphetamine: (Moderate) Amphetamines may pharmacodynamically counteract the sedative properties of some antihistamines, such as the sedating H1-blockers (i.e., diphenhydramine). This effect may be clinically important if a patient is receiving an antihistamine agent for treatment of insomnia. Alternatively, if a patient is receiving an amphetamine for treatment of narcolepsy, the combination with a sedating antihistamine may reverse the action of the amphetamine.
Dextromethorphan; quiNIDine: (Moderate) Caution is recommended when administering quinidine with medications extensively metabolized by CYP2D6 such as diphenhydramine because quinidine inhibits CYP2D6 and may increase concentrations of drugs metabolized by this enzyme.
diazePAM: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased

sedation or respiratory depression) of either agent. Use caution with this combination.
Dicyclomine: (Moderate) Monitor for signs or symptoms of anticholinergic toxicity during concomitant sedating H1-blocker and dicyclomine use. Concomitant use may result in additive anticholinergic adverse effects.
Diphenoxylate; Atropine: (Moderate) An enhanced CNS depressant effect may occur when diphenoxylate/difenoxin is combined with other CNS depressants. Diphenoxylate/difenoxin decreases GI motility. Other drugs that also decrease GI motility, such as sedating H1 blockers, may produce additive effects with diphenoxylate/difenoxin if used concomitantly. (Moderate) Monitor for unusual drowsiness or excess sedation and for signs or symptoms of anticholinergic toxicity during concomitant sedating H1-blocker and atropine use. Concomitant use may result in additive CNS depression or anticholinergic adverse effects.
Disopyramide: (Moderate) The anticholinergic effects of sedating H1-blockers, such as diphenhydramine, may be enhanced when combined with other drugs with moderate to significant anticholinergic effects including disopyramide. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation.
Donepezil: (Moderate) Concurrent use of sedating H1-blockers and donepezil should be avoided if possible. Donepezil inhibits acetylcholinesterase, the enzyme responsible for the degradation of acetylcholine, and improves the availability of acetylcholine. Sedating H1-blockers may exhibit significant anticholinergic activity, thereby interfering with the therapeutic effect of donepezil.
Donepezil; Memantine: (Moderate) Concurrent use of sedating H1-blockers and donepezil should be avoided if possible. Donepezil inhibits acetylcholinesterase, the enzyme responsible for the degradation of acetylcholine, and improves the availability of acetylcholine. Sedating H1-blockers may exhibit significant anticholinergic activity, thereby interfering with the therapeutic effect of donepezil.
Doxepin: (Moderate) Monitor for unusual drowsiness and sedation, urinary retention, and reduced gastric motility during coadministration of diphenhydramine and tricyclic antidepressants. Concomitant use may result in additive CNS depression or anticholinergic effects.
Doxercalciferol: (Moderate) Doxercalciferol is converted in the liver to its active metabolites. Although not specifically studied, cytochrome P450 enzyme inhibitors including diphenhydramine may inhibit the 25-hydroxylation of doxercalciferol, thereby decreasing the formation of the active metabolite and thus, decreasing efficacy. Patients should be monitored for a decrease in efficacy if products containing diphenhydramine are coadministered with doxercalciferol.
DOXOrubicin Liposomal: (Minor) Diphenhydramine is a CYP2D6 inhibitor and doxorubicin is a major substrate of CYP2D6. However, these drugs are often used together in treatment.

DOXOrubicin: (Minor) Diphenhydramine is a CYP2D6 inhibitor and doxorubicin is a major substrate of CYP2D6. However, these drugs are often used together in treatment.
droNABinol: (Moderate) Use caution if coadministration of dronabinol with antihistamines is necessary. Concurrent use of dronabinol, THC with antihistamines may result in additive drowsiness, hypertension, tachycardia, and possibly cardiotoxicity.
Dronedarone: (Moderate) Dronedarone is an inhibitor of CYP2D6. Diphenhydramine is a substrate for CYP2D6. The concomitant administration of dronedarone and CYP2D6 substrates may result in increased exposure of the substrate and should, therefore, be undertaken with caution.
droPERidol: (Moderate) Sedating H1-blockers have additive or potentiating sedative and other CNS effects with droperidol. Following administration of droperidol, lower doses of the other CNS depressant may need to be used.
Dutasteride; Tamsulosin: (Moderate) Use caution if coadministration of diphenhydramine with tamsulosin is necessary, especially at a tamsulosin dose higher than 0.4 mg, as the systemic exposure of tamsulosin may be increased resulting in increased treatment-related adverse reactions including hypotension, dizziness, and vertigo. Tamsulosin is a CYP2D6 substrate and diphenhydramine is a moderate CYP2D6 inhibitor.
Efgartigimod Alfa; Hyaluronidase: (Minor) H1-blockers (antihistamines), when given in large systemic doses, may render tissues partially resistant to the action of hyaluronidase. Patients receiving these medications may require larger amounts of hyaluronidase for equivalent dispersing effect.
Elexacaftor; tezacaftor; ivacaftor: (Minor) Increased monitoring is recommended if ivacaftor is administered concurrently with CYP2C9 substrates, such as diphenhydramine. In vitro studies showed ivacaftor to be a weak inhibitor of CYP2C9. Co-administration may lead to increased exposure to CYP2C9 substrates; however, the clinical impact of this has not yet been determined.
Eliglustat: (Major) In extensive or intermediate CYP2D6 metabolizers (EMs or IMs), coadministration of scheduled diphenhydramine and eliglustat requires dosage reduction of eliglustat to 84 mg PO once daily during the course of antihistamine treatment; however coadministration of eliglustat with both diphenhydramine and a strong or moderate CYP3A inhibitor is contraindicated. It is unclear whether a single dose of diphenhydramine warrants modification of eliglustat therapy. Diphenhydramine is a substrate and moderate inhibitor of CYP2D6; eliglustat is a substrate and inhibitor of CYP2D6 and a CYP3A substrate. Coadministration of eliglustat with CYP2D6 inhibitors, such as diphenhydramine, may increase eliglustat exposure and the risk of serious adverse events (e.g., QT prolongation and cardiac arrhythmias); the effects of a single diphenhydramine dose are unknown. In addition, coadministration of eliglustat with CYP2D6 substrates (e.g., diphenhydramine) may result in increased concentrations of the concomitant drug; monitor patients closely for anticholinergic adverse events.

Elvitegravir; Cobicistat; Emtricitabine; Tenofovir Alafenamide: (Moderate) Caution is warranted when cobicistat is administered with diphenhydramine as there is a potential for elevated diphenhydramine and cobicistat concentrations. Diphenhydramine is a substrate/inhibitor of CYP2D6 and a substrate of CYP2C9. Cobicistat is an substrate/inhibitor of CYP2D6. (Moderate) Caution is warranted when elvitegravir is administered with diphenhydramine as there is a potential for decreased diphenhydramine concentrations. Diphenhydramine is a substrate of CYP2C9, while elvitegravir is a CYP2C9 inducer.
Elvitegravir; Cobicistat; Emtricitabine; Tenofovir Disoproxil Fumarate: (Moderate) Caution is warranted when cobicistat is administered with diphenhydramine as there is a potential for elevated diphenhydramine and cobicistat concentrations. Diphenhydramine is a substrate/inhibitor of CYP2D6 and a substrate of CYP2C9. Cobicistat is an substrate/inhibitor of CYP2D6. (Moderate) Caution is warranted when elvitegravir is administered with diphenhydramine as there is a potential for decreased diphenhydramine concentrations. Diphenhydramine is a substrate of CYP2C9, while elvitegravir is a CYP2C9 inducer.
Entacapone: (Moderate) COMT inhibitors should be given cautiously with other agents that cause CNS depression, including sedating H1-blockers, due to the possibility of additive sedation. COMT inhibitors have also been associated with sudden sleep onset during activities of daily living such as driving, which has resulted in accidents in some cases. Prescribers should re-assess patients for drowsiness or sleepiness regularly throughout treatment, especially since events may occur well after the start of treatment. Patients should be advised to avoid driving or other tasks requiring mental alertness until they know how the combination affects them.
EPINEPHrine: (Moderate) Diphenhydramine may potentiate the arrhythmogenic effects of epinephrine.
Esketamine: (Moderate) Closely monitor patients receiving esketamine and diphenhydramine for sedation and other CNS depressant effects. Instruct patients who receive a dose of esketamine not to drive or engage in other activities requiring alertness until the next day after a restful sleep.
Estazolam: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Eszopiclone: (Moderate) A reduction in the dose of eszopiclone and concomitantly administered CNS depressants, such as sedating H1-blockers, should be considered to minimize additive sedative effects. In addition, the risk of next-day psychomotor impairment is increased during co-administration of eszopiclone and other CNS depressants, which may decrease the ability to perform tasks requiring full mental alertness such as driving.
Ethanol: (Major) Advise patients to avoid alcohol consumption while taking CNS depressants. Alcohol consumption may result in additive CNS depression.

Etomidate: (Minor) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when they are combined with general anesthetics.
Fenfluramine: (Moderate) Monitor for excessive sedation and somnolence during coadministration of fenfluramine and diphenhydramine. Concurrent use may result in additive CNS depression.
Fenofibric Acid: (Minor) At therapeutic concentrations, fenofibric acid is a weak inhibitor of CYP2C19 and a mild-to-moderate inhibitor of CYP2C9. Concomitant use of fenofibric acid with CYP2C19 and CYP2C9 substrates, such as diphenhydramine, has not been formally studied. Fenofibric acid may theoretically increase plasma concentrations of CYP2C19 and CYP2C9 substrates and could lead to toxicity for drugs that have a narrow therapeutic range. Monitor the therapeutic effect of diphenhydramine during coadministration with fenofibric acid.
fentaNYL: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
flavoxATE: (Moderate) Monitor for signs or symptoms of anticholinergic toxicity during concomitant sedating H1-blocker and flavoxate use. Concomitant use may result in additive anticholinergic adverse effects.
Flibanserin: (Moderate) The concomitant use of flibanserin with CNS depressants, such as sedating H1-blockers, may increase the risk of CNS depression (e.g., dizziness, somnolence) compared to the use of flibanserin alone. Patients should avoid activities requiring full alertness (e.g., operating machinery or driving) until at least 6 hours after each dose and until they know how flibanserin affects them.
fluPHENAZine: (Moderate) Additive sedative effects may be seen when fluphenazine is used with first generation antihistamines, such as diphenhydramine. Patients should be informed to read non-prescription allergy, sleep, and cough and cold product labels carefully for additional interacting antihistamines.
Flurazepam: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Food: (Major) Advise patients to avoid cannabis use while taking CNS depressants due to the risk for additive CNS depression and potential for other cognitive adverse reactions.
Gabapentin: (Moderate) Monitor for excessive sedation and somnolence during coadministration of diphenhydramine and gabapentin. Concurrent use may result in additive CNS depression.
Galantamine: (Moderate) Concurrent use of sedating H1-blockers and galantamine

should be avoided if possible. Galantamine inhibits acetylcholinesterase, the enzyme responsible for the degradation of acetylcholine, and improves the availability of acetylcholine. Sedating H1-blockers may exhibit significant anticholinergic activity, thereby interfering with the therapeutic effect of galantamine.
Gentamicin: (Minor) Diphenhydramine may mask vestibular symptoms (e.g., dizziness, tinnitus, or vertigo) that are associated with ototoxicity induced by aminoglycosides. Antiemetics block the histamine or acetylcholine response that causes nausea due to vestibular emetic stimuli such as motion.
Glycopyrrolate: (Moderate) Monitor for signs or symptoms of anticholinergic toxicity during concomitant sedating H1-blocker and glycopyrrolate use. Concomitant use may result in additive anticholinergic adverse effects.
Glycopyrrolate; Formoterol: (Moderate) Monitor for signs or symptoms of anticholinergic toxicity during concomitant sedating H1-blocker and glycopyrrolate use. Concomitant use may result in additive anticholinergic adverse effects.
Halogenated Anesthetics: (Minor) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when they are combined with general anesthetics.
Haloperidol: (Moderate) Haloperidol can potentiate the actions of other CNS depressants such as diphenhydramine, a sedating H1-blocker. Additive anticholinergic effects may occur. Clinicians should note that antimuscarinic effects may be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. Additive drowsiness or CNS effects may also occur.
Heparin: (Minor) Antihistamines may partially counteract the anticoagulant actions of heparin, according to the product labels. However, this interaction is not likely of clinical significance since heparin therapy is adjusted to the partial thromboplastin time (aPTT) and other clinical parameters of the patient.
Homatropine; HYDROcodone: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus. (Moderate) Monitor for signs or symptoms of anticholinergic toxicity during concomitant sedating H1-blocker and homatropine use. Concomitant use may result in additive anticholinergic adverse effects.
Hyaluronidase, Recombinant; Immune Globulin: (Minor) H1-blockers (antihistamines), when given in large systemic doses, may render tissues partially resistant to the action of hyaluronidase. Patients receiving these medications may require larger amounts of

hyaluronidase for equivalent dispersing effect.
Hyaluronidase: (Minor) H1-blockers (antihistamines), when given in large systemic doses, may render tissues partially resistant to the action of hyaluronidase. Patients receiving these medications may require larger amounts of hyaluronidase for equivalent dispersing effect.
HYDROcodone: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
HYDROcodone; Ibuprofen: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
HYDROmorphone: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
Hyoscyamine: (Moderate) Monitor for signs or symptoms of anticholinergic toxicity during concomitant sedating H1-blocker and hyoscyamine use. Concomitant use may result in additive anticholinergic adverse effects.
Hyoscyamine; Methenamine; Methylene Blue; Phenyl Salicylate; Sodium Biphosphate: (Moderate) Monitor for signs or symptoms of anticholinergic toxicity during concomitant sedating H1-blocker and hyoscyamine use. Concomitant use may result in additive anticholinergic adverse effects.
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, such as sedating H1-

blockers.
Imipramine: (Moderate) Monitor for unusual drowsiness and sedation, urinary retention, and reduced gastric motility during coadministration of diphenhydramine and tricyclic antidepressants. Concomitant use may result in additive CNS depression or anticholinergic effects.
Indacaterol; Glycopyrrolate: (Moderate) Monitor for signs or symptoms of anticholinergic toxicity during concomitant sedating H1-blocker and glycopyrrolate use. Concomitant use may result in additive anticholinergic adverse effects.
Isocarboxazid: (Contraindicated) Concomitant use of monoamine oxidase inhibitors and sedating H1-blockers is contraindicated due to increased anticholinergic effects.
Isoflurane: (Minor) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when they are combined with general anesthetics.
Isoproterenol: (Moderate) Monitor hemodynamic parameters during concomitant isoproterenol and diphenhydramine use; dosage adjustments may be necessary. Diphenhydramine may potentiate the effects of isoproterenol.
Ivacaftor: (Minor) Increased monitoring is recommended if ivacaftor is administered concurrently with CYP2C9 substrates, such as diphenhydramine. In vitro studies showed ivacaftor to be a weak inhibitor of CYP2C9. Co-administration may lead to increased exposure to CYP2C9 substrates; however, the clinical impact of this has not yet been determined.
Ketamine: (Minor) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when they are combined with general anesthetics.
Lasmiditan: (Moderate) Monitor for excessive sedation and somnolence during coadministration of lasmiditan and sedating H1-blockers. Concurrent use may result in additive CNS depression.
Lemborexant: (Moderate) Monitor for excessive sedation and somnolence during coadministration of lemborexant and sedating antihistamines (H1-blockers). Dosage adjustments of lemborexant and sedating H1-blockers may be necessary when administered together because of potentially additive CNS effects. The risk of next-day impairment, including impaired driving, is increased if lemborexant is taken with other CNS depressants. Patients should generally avoid nonprescription antihistamine products that are marketed as sleep-aids concurrently with lemborexant.
Levocetirizine: (Moderate) Monitor for unusual drowsiness and sedation, urinary retention, and reduced gastric motility during coadministration of cetirizine and sedating H1-blockers. Concomitant use may result in additive CNS depression or anticholinergic effects.
Levorphanol: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone

for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
Lidocaine; EPINEPHrine: (Moderate) Diphenhydramine may potentiate the arrhythmogenic effects of epinephrine.
Lofexidine: (Major) Monitor for excessive sedation during coadministration of diphenhydramine and lofexidine due to the potential for additive CNS depressant effects. Patients should be advised to avoid driving or performing any other tasks requiring mental alertness until the effects of the combination are known.
Lopinavir; Ritonavir: (Moderate) Concurrent administration of diphenhydramine with ritonavir may result in elevated plasma concentrations of diphenhydramine. Diphenhydramine is a CYP2D6 substrate, and ritonavir is a CYP2D6 inhibitor. Caution and close monitoring are advised if these drugs are administered together.
Loratadine: (Minor) Although loratadine is considered a 'non-sedating' antihistamine, dose-related sedation has been noted. For this reason, it would be prudent to monitor for drowsiness during concurrent use of loratadine with CNS depressants such as other H1-blockers.
Loratadine; Pseudoephedrine: (Minor) Although loratadine is considered a 'non-sedating' antihistamine, dose-related sedation has been noted. For this reason, it would be prudent to monitor for drowsiness during concurrent use of loratadine with CNS depressants such as other H1-blockers.
LORazepam: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Loxapine: (Moderate) Sedating H1-blockers are associated with anticholinergic effects and sedation; therefore, additive effects may be seen during concurrent use with other drugs having anticholinergic activity and CNS depressant properties such as traditional antipsychotic agents, including loxapine. Clinicians should note that antimuscarinic effects may be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. Additive drowsiness or other CNS effects may also occur.
Lumacaftor; Ivacaftor: (Minor) Concomitant use of diphenhydramine and lumacaftor; ivacaftor may alter diphenhydramine exposure; monitor for diphenhydramine efficacy and adverse events. Diphenhydramine is partially metabolized by CYP2C9 and CYP2C19. In vitro data suggest that lumacaftor; ivacaftor may induce CYP2C19 and induce and/or inhibit CYP2C9. Although induction of diphenhydramine through the CYP2C19 pathway may lead to decreased drug efficacy, the net effect of lumacaftor; ivacaftor on CYP2C9-mediated metabolism is not clear. (Minor) Increased monitoring is recommended if ivacaftor is administered concurrently with CYP2C9 substrates, such as diphenhydramine. In vitro studies showed ivacaftor to be a weak inhibitor of CYP2C9.

Co-administration may lead to increased exposure to CYP2C9 substrates; however, the clinical impact of this has not yet been determined.
Lumacaftor; Ivacaftor: (Minor) Concomitant use of diphenhydramine and lumacaftor; ivacaftor may alter diphenhydramine exposure; monitor for diphenhydramine efficacy and adverse events. Diphenhydramine is partially metabolized by CYP2C9 and CYP2C19. In vitro data suggest that lumacaftor; ivacaftor may induce CYP2C19 and induce and/or inhibit CYP2C9. Although induction of diphenhydramine through the CYP2C19 pathway may lead to decreased drug efficacy, the net effect of lumacaftor; ivacaftor on CYP2C9-mediated metabolism is not clear.
Lumateperone: (Moderate) Monitor for excessive sedation and somnolence during coadministration of lumateperone and diphenhydramine. Concurrent use may result in additive CNS depression.
Lurasidone: (Moderate) Due to the CNS effects of lurasidone, caution should be used when lurasidone is given in combination with other centrally acting medications.
Sedating H1-blockers are associated with sedation; therefore, additive effects may be seen during concurrent use with other drugs having CNS depressant properties such as antipsychotics. Additive drowsiness or other CNS effects may occur.
Maprotiline: (Moderate) Additive anticholinergic effects may be seen when maprotiline is used concomitantly with other commonly used drugs with moderate to significant anticholinergic effects, such as diphenhydramine, a sedating H1-blocker.
Meclizine: (Major) The anticholinergic and sedative effects of meclizine may be enhanced when combined with other drugs with antimuscarinic activity, including other sedating antihistamines (H1-blockers). Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation.
Melatonin: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of melatonin and sedating H1-blockers due to the risk for additive CNS depression.
Meperidine: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
Meprobamate: (Moderate) The CNS-depressant effects of meprobamate can be potentiated with concomitant administration of other drugs known to cause CNS depression including sedating H1-blockers.
Metaxalone: (Moderate) Concomitant administration of metaxalone with other CNS

depressants can potentiate the sedative effects of either agent.
Methadone: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
Methamphetamine: (Moderate) Amphetamines may pharmacodynamically counteract the sedative properties of sedating H1-blockers. This effect may be clinically important if a patient is receiving an antihistamine agent for treatment of insomnia. Alternatively, if a patient is receiving an amphetamine for treatment of narcolepsy, the combination with a sedating antihistamine may reverse the action of the amphetamine. Coadminister with caution and monitor for altered response to drug therapy.
Methenamine; Sodium Acid Phosphate; Methylene Blue; Hyoscyamine: (Moderate) Monitor for signs or symptoms of anticholinergic toxicity during concomitant sedating H1-blocker and hyoscyamine use. Concomitant use may result in additive anticholinergic adverse effects.
Methocarbamol: (Moderate) Methocarbamol may cause additive CNS depression if used concomitantly with other CNS depressants such as sedating H1-blockers. Combination therapy can cause additive effects of sedation and dizziness, which can impair the patient's ability to undertake tasks requiring mental alertness. Dosage adjustments of either or both medications may be necessary.
Methohexital: (Major) Because diphenhydramine can cause pronounced sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as barbiturates.
Methscopolamine: (Moderate) Monitor for signs or symptoms of anticholinergic toxicity during concomitant sedating H1-blocker and methscopolamine use. Concomitant use may result in additive anticholinergic adverse effects.
Metoclopramide: (Minor) Combined use of metoclopramide and other CNS depressants, such as anxiolytics, sedatives, and hypnotics, can increase possible sedation.
Metoprolol: (Moderate) Monitor for metoprolol-related adverse reactions, including bradycardia and hypotension, during coadministration with diphenhydramine. Concomitant use may increase metoprolol serum concentrations which would decrease the cardioselectivity of metoprolol. Metoprolol is a CYP2D6 substrate and diphenhydramine is a CYP2D6 inhibitor.
Metoprolol; hydroCHLOROthiazide, HCTZ: (Moderate) Monitor for metoprolol-related adverse reactions, including bradycardia and hypotension, during coadministration with diphenhydramine. Concomitant use may increase metoprolol serum concentrations

which would decrease the cardioselectivity of metoprolol. Metoprolol is a CYP2D6 substrate and diphenhydramine is a CYP2D6 inhibitor.
metyraPONE: (Moderate) Metyrapone may cause dizziness and/or drowsiness. Other drugs that may also cause drowsiness, such as sedating H1-blockers, should be used with caution. Additive drowsiness and/or dizziness is possible.
metyroSINE: (Moderate) The concomitant administration of metyrosine with sedating H1-blockers can result in additive sedative effects.
Midazolam: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
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 sedating H1-blockers. Caution should be exercised when using these agents concurrently.
Mirabegron: (Moderate) Mirabegron is a moderate CYP2D6 inhibitor. Exposure of drugs metabolized by CYP2D6 isoenzymes such as diphenhydramine may be increased when co-administered with mirabegron. Diphenhydramine is primarily metabolized by CYP2D6. Therefore, appropriate monitoring and dose adjustment may be necessary.
Mirtazapine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of diphenhydramine and mirtazapine due to the risk for additive CNS depression.
Mitotane: (Moderate) Mitotane can cause sedation, lethargy, vertigo, and other CNS side effects. Concomitant administration of mitotane and CNS depressants, including sedating h1-blockers, may cause additive CNS effects.
Molindone: (Moderate) An enhanced CNS depressant effect may occur when sedating h1-blockers are combined with other CNS depressants including molindone.
Monoamine oxidase inhibitors: (Contraindicated) Concomitant use of monoamine oxidase inhibitors and sedating H1-blockers is contraindicated due to increased anticholinergic effects.
Morphine: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
Nalbuphine: (Moderate) Concomitant use of nalbuphine with other CNS depressants, such as sedating H1-blockers, can potentiate the effects of nalbuphine on respiratory depression, CNS depression, and sedation.

Nebivolol: (Moderate) Monitor for increased toxicity as well as increased therapeutic effect of nebivolol if coadministered with diphenhydramine; adjust the nebivolol dose according to blood pressure response. Concomitant use may increase the exposure of nebivolol. Nebivolol is a CYP2D6 substrate and diphenhydramine is a moderate CYP2D6 inhibitor.
Nefazodone: (Moderate) An enhanced CNS depressant effect may occur when sedating H1-blockers are combined with other CNS depressants including nefazodone.
Neostigmine; Glycopyrrolate: (Moderate) Monitor for signs or symptoms of anticholinergic toxicity during concomitant sedating H1-blocker and glycopyrrolate use. Concomitant use may result in additive anticholinergic adverse effects.
Nirmatrelvir; Ritonavir: (Moderate) Concurrent administration of diphenhydramine with ritonavir may result in elevated plasma concentrations of diphenhydramine. Diphenhydramine is a CYP2D6 substrate, and ritonavir is a CYP2D6 inhibitor. Caution and close monitoring are advised if these drugs are administered together.
Nivolumab; Hyaluronidase: (Minor) H1-blockers (antihistamines), when given in large systemic doses, may render tissues partially resistant to the action of hyaluronidase. Patients receiving these medications may require larger amounts of hyaluronidase for equivalent dispersing effect.
Nortriptyline: (Moderate) Monitor for unusual drowsiness and sedation, urinary retention, and reduced gastric motility during coadministration of diphenhydramine and tricyclic antidepressants. Concomitant use may result in additive CNS depression or anticholinergic effects.
Ocrelizumab; Hyaluronidase: (Minor) H1-blockers (antihistamines), when given in large systemic doses, may render tissues partially resistant to the action of hyaluronidase. Patients receiving these medications may require larger amounts of hyaluronidase for equivalent dispersing effect.
OLANZapine: (Moderate) Olanzapine exhibits anticholinergic effects that may be clinically significant. Clinicians should keep this in mind when using antimuscarinics and other medications with anticholinergic activity in combination with olanzapine. Some medications exhibit additive anticholinergic effects include sedating H1-blockers. Olanzapine may also cause additive sedation with many of these drugs.
OLANZapine; FLUoxetine: (Moderate) Olanzapine exhibits anticholinergic effects that may be clinically significant. Clinicians should keep this in mind when using antimuscarinics and other medications with anticholinergic activity in combination with olanzapine. Some medications exhibit additive anticholinergic effects include sedating H1-blockers. Olanzapine may also cause additive sedation with many of these drugs.
OLANZapine; Samidorphan: (Moderate) Olanzapine exhibits anticholinergic effects that may be clinically significant. Clinicians should keep this in mind when using antimuscarinics and other medications with anticholinergic activity in combination with olanzapine. Some medications exhibit additive anticholinergic effects include sedating

H1-blockers. Olanzapine may also cause additive sedation with many of these drugs.
Oliceridine: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
Opiate Agonists: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
Opicapone: (Moderate) COMT inhibitors should be given cautiously with other agents that cause CNS depression, including sedating H1-blockers, due to the possibility of additive sedation. COMT inhibitors have also been associated with sudden sleep onset during activities of daily living such as driving, which has resulted in accidents in some cases. Prescribers should re-assess patients for drowsiness or sleepiness regularly throughout treatment, especially since events may occur well after the start of treatment. Patients should be advised to avoid driving or other tasks requiring mental alertness until they know how the combination affects them.
Oritavancin: (Moderate) Diphenhydramine is metabolized by CYP2C9, CYP2C19 and CYP2D6; oritavancin is a weak inducer of CYP2D6 and a weak CYP2C9 and CYP2C19 inhibitor. Coadministration may result in altered diphenhydramine plasma concentrations. If these drugs are administered concurrently, monitor for diphenydramine toxicity, such as drowsiness, or decreased effectiveness.
Orphenadrine: (Moderate) Additive anticholinergic effects may be seen when drugs with anticholinergic properties, like sedating H1-blockers and orphenadrine, are used concomitantly. Adverse effects may be seen not only on GI smooth muscle, but also on bladder function, the CNS, the eye, and temperature regulation. Additive drowsiness may also occur.
Oxazepam: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
oxyBUTYnin: (Moderate) Monitor for signs or symptoms of anticholinergic toxicity during concomitant sedating H1-blocker and oxybutynin use. Concomitant use may result in additive anticholinergic adverse effects.

oxyCODONE: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
oxyMORphone: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
Paliperidone: (Moderate) Coadministration of drugs with CNS depressant effects, including paliperidone and diphenhydramine, can increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, and dizziness. Monitor for signs and symptoms of CNS depression and advise patients to avoid driving or engaging in other activities requiring mental alertness until they know how this combination affects them.
Papaverine: (Moderate) Concurrent use of papaverine with potent CNS depressants such as diphenhydramine could lead to enhanced sedation.
Paromomycin: (Minor) Diphenhydramine may mask vestibular symptoms (e.g., dizziness, tinnitus, or vertigo) that are associated with ototoxicity induced by aminoglycosides. Antiemetics block the histamine or acetylcholine response that causes nausea due to vestibular emetic stimuli such as motion.
PARoxetine: (Moderate) Monitor for an increase in paroxetine-related adverse reactions, including serotonin syndrome, if concomitant use with diphenhydramine is necessary. Concomitant use may increase paroxetine exposure and risk for additive anticholinergic adverse effects. Paroxetine is a CYP2D6 substrate and diphenhydramine is a moderate CYP2D6 inhibitor.
Peginterferon Alfa-2b: (Moderate) Monitor for adverse effects associated with increased exposure to diphenhydramine if peginterferon alfa-2b is coadministered. Peginterferon alfa-2b is a CYP1A2 and CYP2D6 inhibitor, while diphenhydramine is a CYP1A2 and CYP2D6 substrate.
Pembrolizumab; berahyaluronidase alfa: (Minor) H1-blockers (antihistamines), when given in large systemic doses, may render tissues partially resistant to the action of hyaluronidase. Patients receiving these medications may require larger amounts of

hyaluronidase for equivalent dispersing effect.
Pentazocine; Naloxone: (Moderate) Use pentazocine with caution in any patient receiving medication with CNS depressant and/or anticholinergic activity. Coadministration of pentazocine with sedating H1-blockers may result in additive respiratory and CNS depression and anticholinergic effects, such as urinary retention and constipation.
PENTobarbital: (Major) Because diphenhydramine can cause pronounced sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as barbiturates.
Perampanel: (Moderate) Co-administration of perampanel with CNS depressants, including ethanol, may increase CNS depression. The combination of perampanel (particularly at high doses) with ethanol has led to decreased mental alertness and ability to perform complex tasks (such as driving), as well as increased levels of anger, confusion, and depression; similar reactions should be expected with concomitant use of other CNS depressants, such as sedating H1-blockers.
Perphenazine: (Moderate) Additive anticholinergic and sedative effects may be seen when perphenazine is used with first generation antihistamines, such as diphenhydramine. Patients should be informed to read non-prescription allergy, sleep, and cough and cold product labels carefully for additional interacting antihistamines.
Perphenazine; Amitriptyline: (Moderate) Additive anticholinergic and sedative effects may be seen when perphenazine is used with first generation antihistamines, such as diphenhydramine. Patients should be informed to read non-prescription allergy, sleep, and cough and cold product labels carefully for additional interacting antihistamines. (Moderate) Monitor for unusual drowsiness and sedation, urinary retention, and reduced gastric motility during coadministration of diphenhydramine and tricyclic antidepressants. Concomitant use may result in additive CNS depression or anticholinergic effects.
Pertuzumab; Trastuzumab; Hyaluronidase: (Minor) H1-blockers (antihistamines), when given in large systemic doses, may render tissues partially resistant to the action of hyaluronidase. Patients receiving these medications may require larger amounts of hyaluronidase for equivalent dispersing effect.
Phenelzine: (Contraindicated) Concomitant use of monoamine oxidase inhibitors and sedating H1-blockers is contraindicated due to increased anticholinergic effects.
PHENobarbital: (Major) Because diphenhydramine can cause pronounced sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as barbiturates.
PHENobarbital; Hyoscyamine; Atropine; Scopolamine: (Major) Because diphenhydramine can cause pronounced sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as barbiturates. (Moderate) Monitor for signs or

symptoms of anticholinergic toxicity during concomitant sedating H1-blocker and hyoscyamine use. Concomitant use may result in additive anticholinergic adverse effects. (Moderate) Monitor for unusual drowsiness or excess sedation and for signs or symptoms of anticholinergic toxicity during concomitant sedating H1-blocker and atropine use. Concomitant use may result in additive CNS depression or anticholinergic adverse effects. (Moderate) Monitor for unusual drowsiness or excess sedation and for signs or symptoms of anticholinergic toxicity during concomitant sedating H1-blocker and scopolamine use. Concomitant use may result in additive CNS depression or anticholinergic adverse effects.
Phentermine; Topiramate: (Moderate) Monitor for increased CNS effects if topiramate is coadministered with diphenhydramine. Although not specifically studied, coadministration of CNS depressant drugs with topiramate may potentiate CNS depression, such as dizziness or cognitive adverse reactions, or other centrally mediated effects of these agents.
Pimozide: (Moderate) Due to the effects of pimozide on cognition, it should be used cautiously with other CNS depressants including sedating antihistamines. Sedating H1-blockers are associated with anticholinergic effects and sedation; therefore, additive effects may be seen during concurrent use with pimozide. Additive drowsiness or other CNS effects may occur.
Pitolisant: (Major) Avoid coadministration of pitolisant with diphenhydramine as the effect of pitolisant may be decreased. Pitolisant increases histamine concentrations in the brain; therefore, H1-receptor antagonists like diphenhydramine, may reduce pitolisant efficacy.
Plazomicin: (Minor) Diphenhydramine may mask vestibular symptoms (e.g., dizziness, tinnitus, or vertigo) that are associated with ototoxicity induced by aminoglycosides. Antiemetics block the histamine or acetylcholine response that causes nausea due to vestibular emetic stimuli such as motion.
Pramipexole: (Moderate) Concomitant use of pramipexole with other CNS depressants, such as sedating H1-blockers, can potentiate the sedation effects of pramipexole.
Pregabalin: (Moderate) Monitor for excessive sedation and somnolence during coadministration of diphenhydramine and pregabalin. Concurrent use may result in additive CNS depression.
Prilocaine; EPINEPHrine: (Moderate) Diphenhydramine may potentiate the arrhythmogenic effects of epinephrine.
Primidone: (Major) Because diphenhydramine can cause pronounced sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as barbiturates.
Procarbazine: (Moderate) Use procarbazine and sedating H1-blockers together with caution; additive central nervous system depression may occur.
Prochlorperazine: (Moderate) Additive anticholinergic and sedative effects may be seen

when Prochlorperazine is used with first generation antihistamines, such as diphenhydramine. Patients should be informed to read non-prescription allergy, sleep, and cough and cold product labels carefully for additional interacting antihistamines.
Promethazine: (Moderate) Monitor for unusual drowsiness and sedation, urinary retention, and reduced gastric motility during coadministration of diphenhydramine and promethazine. Concomitant use may result in additive CNS depression or anticholinergic effects.
Promethazine; Dextromethorphan: (Moderate) Monitor for unusual drowsiness and sedation, urinary retention, and reduced gastric motility during coadministration of diphenhydramine and promethazine. Concomitant use may result in additive CNS depression or anticholinergic effects.
Promethazine; Phenylephrine: (Moderate) Monitor for unusual drowsiness and sedation, urinary retention, and reduced gastric motility during coadministration of diphenhydramine and promethazine. Concomitant use may result in additive CNS depression or anticholinergic effects.
Propantheline: (Moderate) Monitor for signs or symptoms of anticholinergic toxicity during concomitant sedating H1-blocker and propantheline use. Concomitant use may result in additive anticholinergic adverse effects.
Propofol: (Minor) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when they are combined with general anesthetics.
Protriptyline: (Moderate) Monitor for unusual drowsiness and sedation, urinary retention, and reduced gastric motility during coadministration of diphenhydramine and tricyclic antidepressants. Concomitant use may result in additive CNS depression or anticholinergic effects.
Quazepam: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
QUEtiapine: (Moderate) Monitor for unusual drowsiness and sedation, urinary retention, and reduced gastric motility during coadministration of diphenhydramine and quetiapine. Concomitant use may result in additive CNS depression or anticholinergic effects.
quiNIDine: (Moderate) Caution is recommended when administering quinidine with medications extensively metabolized by CYP2D6 such as diphenhydramine because quinidine inhibits CYP2D6 and may increase concentrations of drugs metabolized by this enzyme.
Ramelteon: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as ramelteon.
Rasagiline: (Moderate) Concurrent use of monoamine oxidase inhibitors (MAOIs) and sedating H1-blockers (sedating antihistamines) may result in additive sedation, anticholinergic effects, or hypotensive reactions. Rasagiline may be less likely to produce

these interactions than other MAOIs, due to MAO-B selectivity. However, consider alternatives therapy to antihistamines where possible. If alternative combinations are not available, these medications may be used together with close monitoring. Many non-prescription products for coughs, colds, allergy, hay fever or insomnia contain sedating antihistamines. Patients receiving rasagiline should be counseled that it is essential to consult their healthcare provider or pharmacist prior to the use of any non-prescription products. Patients should also be advised against driving or engaging in other activities requiring mental alertness until they know how this combination affects them.
Remifentanil: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
Remimazolam: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
risperiDONE: (Moderate) Due to the primary CNS effects of risperidone, caution is advisable when risperidone is given with other centrally acting medications including sedating H1-blockers such as diphenhydramine. This combination is commonly used in clinical practice; however, additive drowsiness or other CNS effects may occur. Patients should be informed of the risk of driving or performing other tasks requiring mental alertness until the effects of these medicines are known.
Ritonavir: (Moderate) Concurrent administration of diphenhydramine with ritonavir may result in elevated plasma concentrations of diphenhydramine. Diphenhydramine is a CYP2D6 substrate, and ritonavir is a CYP2D6 inhibitor. Caution and close monitoring are advised if these drugs are administered together.
riTUXimab; Hyaluronidase: (Minor) H1-blockers (antihistamines), when given in large systemic doses, may render tissues partially resistant to the action of hyaluronidase. Patients receiving these medications may require larger amounts of hyaluronidase for equivalent dispersing effect.
Rivastigmine: (Moderate) Concurrent use of sedating H1-blockers and rivastigmine should be avoided if possible. Rivastigmine inhibits acetylcholinesterase, the enzyme responsible for the degradation of acetylcholine, and improves the availability of acetylcholine. Sedating H1-blockers may exhibit significant anticholinergic activity, thereby interfering with the therapeutic effect of rivastigmine.
Rolapitant: (Major) Use caution if diphenhydramine and rolapitant are used

concurrently, and monitor for diphenhydramine-related adverse effects. Consider if another antihistamine would be a better choice for treatment. Diphenhydramine is a CYP2D6 substrate and rolapitant is a moderate CYP2D6 inhibitor; the inhibitory effect of rolapitant is expected to persist beyond 28 days for an unknown duration. Exposure to another CYP2D6 substrate, following a single dose of rolapitant increased about 3-fold on Days 8 and Day 22. The inhibition of CYP2D6 persisted on Day 28 with a 2.3-fold increase in the CYP2D6 substrate concentrations, the last time point measured.
rOPINIRole: (Moderate) Concomitant use of ropinirole with other CNS depressants, such as sedating H1-blockers, can potentiate the sedation effects of ropinirole.
Rotigotine: (Major) Concomitant use of rotigotine with other CNS depressants, such as diphenhydramine, can potentiate the sedation 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 other sedating medications, such as sedating H1-blockers.
Scopolamine: (Moderate) Monitor for unusual drowsiness or excess sedation and for signs or symptoms of anticholinergic toxicity during concomitant sedating H1-blocker and scopolamine use. Concomitant use may result in additive CNS depression or anticholinergic adverse effects.
Secobarbital: (Major) Because diphenhydramine can cause pronounced sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as barbiturates.
Selegiline: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of diphenhydramine and selegiline due to the risk for additive CNS depression.
Sevoflurane: (Minor) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when they are combined with general anesthetics.
Sincalide: (Moderate) Sincalide-induced gallbladder ejection fraction may be affected by concurrent medications, including H1-blockers. False study results are possible; thorough patient history is important in the interpretation of procedure results.
Solifenacin: (Moderate) Additive anticholinergic effects may be seen when drugs with antimuscarinic properties like solifenacin are used concomitantly with other antimuscarinics, such as diphenhydramine.
Stiripentol: (Moderate) Monitor for excessive sedation and somnolence during coadministration of stiripentol and diphenhydramine. CNS depressants can potentiate the effects of stiripentol.
Streptomycin: (Minor) Diphenhydramine may mask vestibular symptoms (e.g., dizziness, tinnitus, or vertigo) that are associated with ototoxicity induced by aminoglycosides.

Antiemetics block the histamine or acetylcholine response that causes nausea due to vestibular emetic stimuli such as motion.
SUFentanil: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
Suvorexant: (Moderate) Monitor for excessive sedation and somnolence during coadministration of suvorexant and sedating antihistamines (H1-blockers). Dosage adjustments of suvorexant and sedating H1-blockers may be necessary when administered together because of potentially additive CNS effects. The risk of next-day impairment, including impaired driving, is increased if suvorexant is taken with other CNS depressants. Patients should generally avoid nonprescription antihistamine products that are marketed as sleep-aids concurrently with suvorexant.
Tamsulosin: (Moderate) Use caution if coadministration of diphenhydramine with tamsulosin is necessary, especially at a tamsulosin dose higher than 0.4 mg, as the systemic exposure of tamsulosin may be increased resulting in increased treatment-related adverse reactions including hypotension, dizziness, and vertigo. Tamsulosin is a CYP2D6 substrate and diphenhydramine is a moderate CYP2D6 inhibitor.
Tapentadol: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
Tasimelteon: (Moderate) Because sedating H1-blockers cause sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics, such as tasimelteon.
Temazepam: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Tetrabenazine: (Moderate) Concurrent use of tetrabenazine and drugs that can cause CNS depression, such as diphenhydramine, can increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, dizziness, and orthostatic hypotension.

Tezacaftor; Ivacaftor: (Minor) Increased monitoring is recommended if ivacaftor is administered concurrently with CYP2C9 substrates, such as diphenhydramine. In vitro studies showed ivacaftor to be a weak inhibitor of CYP2C9. Co-administration may lead to increased exposure to CYP2C9 substrates; however, the clinical impact of this has not yet been determined.
Thalidomide: (Major) Avoid the concomitant use of thalidomide with opiate agonists; antihistamines; antipsychotics; anxiolytics, sedatives, and hypnotics; and other central nervous system depressants due to the potential for additive sedative effects.
Thioridazine: (Contraindicated) Diphenhydramine is a moderate inhibitor of CYP2D6 and the use of thioridazine concomitantly with CYP2D6 inhibitors is contraindicated due to the possible risk of QT prolongation and subsequent arrhythmias, or other serious side effects, occurring from elevated serum concentrations of thioridazine. Also, additive anticholinergic and sedative effects may be seen when thioridazine is used with first generation antihistamines, such as diphenhydramine. Consider if an alternative to diphenhydramine would be appropriate for the patient's condition.
Thiothixene: (Moderate) Additive anticholinergic effects may be seen when antipsychotics, such as thiothixene, are used concomitantly with other drugs such as sedating H1-blockers. Additive drowsiness or other CNS effects may also occur.
tiZANidine: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of diphenhydramine and tizanidine due to the risk for additive CNS depression.
Tobramycin: (Minor) Diphenhydramine may mask vestibular symptoms (e.g., dizziness, tinnitus, or vertigo) that are associated with ototoxicity induced by aminoglycosides. Antiemetics block the histamine or acetylcholine response that causes nausea due to vestibular emetic stimuli such as motion.
Tolcapone: (Moderate) COMT inhibitors should be given cautiously with other agents that cause CNS depression, including sedating H1-blockers, due to the possibility of additive sedation. COMT inhibitors have also been associated with sudden sleep onset during activities of daily living such as driving, which has resulted in accidents in some cases. Prescribers should re-assess patients for drowsiness or sleepiness regularly throughout treatment, especially since events may occur well after the start of treatment. Patients should be advised to avoid driving or other tasks requiring mental alertness until they know how the combination affects them.
Topiramate: (Moderate) Monitor for increased CNS effects if topiramate is coadministered with diphenhydramine. Although not specifically studied, coadministration of CNS depressant drugs with topiramate may potentiate CNS depression, such as dizziness or cognitive adverse reactions, or other centrally mediated effects of these agents.
traMADol: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and

durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
Tramadol; Acetaminophen: (Major) Reserve concomitant use of opioids and diphenhydramine for patients in whom alternate treatment options are inadequate. Limit dosages and durations to the minimum required and monitor patients closely for respiratory depression and sedation. If concomitant use is necessary, consider prescribing naloxone for the emergency treatment of opioid overdose and monitor for signs of urinary retention or reduced gastric motility. Concomitant use can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death as well as urinary retention and/or severe constipation, which may lead to paralytic ileus.
Tranylcypromine: (Contraindicated) Concomitant use of monoamine oxidase inhibitors and sedating H1-blockers is contraindicated due to increased anticholinergic effects.
Trastuzumab; Hyaluronidase: (Minor) H1-blockers (antihistamines), when given in large systemic doses, may render tissues partially resistant to the action of hyaluronidase. Patients receiving these medications may require larger amounts of hyaluronidase for equivalent dispersing effect.
traZODone: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of diphenhydramine and trazodone due to the risk for additive CNS depression.
Triazolam: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Tricyclic antidepressants: (Moderate) Monitor for unusual drowsiness and sedation, urinary retention, and reduced gastric motility during coadministration of diphenhydramine and tricyclic antidepressants. Concomitant use may result in additive CNS depression or anticholinergic effects.
Trifluoperazine: (Moderate) Additive anticholinergic and sedative effects may be seen when Trifluoperazine is used with first generation antihistamines, such as diphenhydramine. Patients should be informed to read non-prescription allergy, sleep, and cough and cold product labels carefully for additional interacting antihistamines.
Trihexyphenidyl: (Moderate) Monitor for signs or symptoms of anticholinergic toxicity during concomitant sedating H1-blocker and trihexyphenidyl use. Concomitant use may result in additive anticholinergic adverse effects.
Trimethobenzamide: (Moderate) The concurrent use of trimethobenzamide with other medications that cause CNS depression, like the sedating h1-blockers, may potentiate the effects of either trimethobenzamide or the sedating h1-blocker.
Trimipramine: (Moderate) Monitor for unusual drowsiness and sedation, urinary

retention, and reduced gastric motility during coadministration of diphenhydramine and tricyclic antidepressants. Concomitant use may result in additive CNS depression or anticholinergic effects.
Trospium: (Moderate) Additive anticholinergic effects may be seen when trospium is used concomitantly with drugs that are known to possess relatively significant antimuscarinic properties, including sedating H1-blockers. Clinicians should note that additive antimuscarinic effects may be seen not only on GI smooth muscle, but also on bladder function and temperature regulation. While CNS-related side effects such as drowsiness and blurred vision are not typically noted with trospium, they may occur in some patients.
Vemurafenib: (Moderate) Concomitant use of vemurafenib and diphenhydramine may result in increased diphenhydramine concentrations. Vemurafenib is a CYP1A2, CYP2C9, and CYP2D6 inhibitor and diphenhydramine is a substrate of these isoenzymes. Patients should be monitored for toxicity and sedation.
Vigabatrin: (Moderate) Vigabatrin may cause somnolence and fatigue. Drugs that can cause CNS depression, if used concomitantly with vigabatrin, may increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, and dizziness. Caution should be used when vigabatrin is given with sedating H1-blockers.
Vilazodone: (Moderate) Due to the CNS effects of vilazodone, caution should be used when vilazodone is given in combination with other centrally acting medications such as anxiolytics, sedatives, and hypnotics. Also, Cyproheptadine is an antagonist of serotonin in the CNS, a property which may oppose some of the pharmacologic effects of vilazodone. Cyproheptadine has been used for the management of orgasm dysfunction caused by the serotonergic antidepressants and for the adjunctive treatment of serotonin syndrome; however, a reversal of antidepressant effects may occur when cyproheptadine is given in a routine manner along with the antidepressant. Clinically, cyproheptadine reportedly has interfered with the antidepressant and anti-bulimia actions of fluoxetine, but more data are needed to confirm a direct drug-drug interaction.
Xanomeline; Trospium: (Moderate) Additive anticholinergic effects may be seen when trospium is used concomitantly with drugs that are known to possess relatively significant antimuscarinic properties, including sedating H1-blockers. Clinicians should note that additive antimuscarinic effects may be seen not only on GI smooth muscle, but also on bladder function and temperature regulation. While CNS-related side effects such as drowsiness and blurred vision are not typically noted with trospium, they may occur in some patients.
Zaleplon: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zaleplon due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary.

Ziconotide: (Moderate) Sedating H1-blockers are CNS depressant medications that may increase drowsiness, dizziness, and confusion that are associated with ziconotide.
Ziprasidone: (Moderate) Sedating H1-blockers are associated with sedation; therefore, additive effects may be seen during concurrent use with other drugs having CNS depressant properties such as antipsychotics. Additive drowsiness or other CNS effects may occur with ziprasidone.
Zolpidem: (Moderate) Monitor for unusual drowsiness and sedation during coadministration of sedating H1-blockers and zolpidem due to the risk for additive CNS depression and next-day psychomotor impairment; dose adjustments may be necessary. Limit the dose of Intermezzo sublingual tablets to 1.75 mg/day.
Zuranolone: (Major) Avoid the use of multiple sedating agents due to the risk for additive CNS depression. If use is necessary, consider a downward dosage adjustment of either or both medications, especially in patients with additional risk factors for sedation-related harm.

Adverse Reaction

asthenia, confusion, dizziness, drowsiness, euphoria, fatigue, headache, neuritis, paresthesias, psychomotor impairment, tinnitus, tremor, vertigo

CNS depression manifested as drowsiness (sedation) and/or dizziness can occur during therapy with diphenhydramine. Other less frequently occurring CNS effects of sedating antihistamines include disturbed coordination, fatigue, confusion, nervousness, tremor, euphoria, paresthesias, vertigo, tinnitus, acute labyrinthitis, and neuritis. In a randomized, double-blind study, 610 patients with moderate-to-severe seasonal allergic rhinitis received diphenhydramine (50 mg PO 3 times daily), desloratadine (5 mg PO once daily), or placebo for 1 week. Somnolence occurred more frequently with diphenhydramine (22.1%) compared to desloratadine (4.5%) and placebo (3.4%). Other adverse events reported for diphenhydramine were asthenia (4.4%), headache (2.5%), and dizziness (2.5%). Psychomotor impairment is also possible. In a double-blind study to assess driving performance, diphenhydramine was associated with significantly poorer driving coherence (i.e., the ability to maintain appropriate velocity based on a lead car that varied its speed) compared to ethanol, fexofenadine, or placebo. The study also showed that patients receiving diphenhydramine were more likely to cross the center line of the road than those receiving fexofenadine or placebo. There is considerable individual patient response to sedative effects, so patients should be warned of the possible impairment of mental acuity. First-generation sedating antihistamines are most likely to cause dizziness and sedation in elderly patients. If

sedation persists or is severe, a dosage reduction or switching to a non-sedating antihistamine may be advisable, depending on the indication for use.

agitation, excitability, insomnia, irritability, restlessness, seizures

Diphenhydramine can cause CNS stimulation (paradoxical excitation); this excitability is more likely to occur in children. CNS stimulatory symptoms may include agitation, nervousness, restlessness, insomnia, increased heart rate, irritability, muscle spasms, and in severe cases, seizures.

anorexia, constipation, diarrhea, dyspepsia, nausea, vomiting, xerostomia

The anticholinergic effects of first-generation sedating antihistamines are widely known to cause such effects as dry mouth (xerostomia). Other GI effects include dyspepsia (epigastric distress), anorexia, nausea, vomiting, diarrhea, and constipation .56616
Xerostomia is a common adverse effect; in a randomized, double-blind study, xerostomia occurred more frequently in patients receiving diphenhydramine (4.9%) compared to desloratadine (1.5%) and placebo (less than 1%). Higher incidences of dry mouth are often reported in trials where parenteral doses are administered for various indications.

blurred vision, diplopia, mydriasis, xerophthalmia

Diphenhydramine possesses a significant degree of anticholinergic and nervous system effects, which can result in ocular effects such as xerophthalmia, blurred vision, diplopia, and mydriasis.

menstrual irregularity, urinary retention

Diphenhydramine has been associated with genitourinary effects such as a change in urinary frequency, difficult urination, urinary retention, and early menses (menstrual irregularity). Urinary retention is usually associated with anticholinergic actions of sedating antihistamines.

nasal congestion, nasal dryness, wheezing

Diphenhydramine possesses a significant degree of anticholinergic effects, which can result in thickening of bronchial secretions. Chest or throat tightness, wheezing, nasal dryness, and nasal congestion have also been reported rarely.

anaphylactic shock, atopic dermatitis, chills, contact dermatitis, hyperhidrosis, photosensitivity, rash, urticaria

Dermatological, general, and/or allergic adverse effects of systemic use of diphenhydramine may include urticaria, drug rash, anaphylactic shock, photosensitivity, excessive perspiration (hyperhidrosis), chills, and dryness of the mouth, nose, and throat. Topical application of diphenhydramine can cause an allergic-type contact dermatitis through a T-cell mediated response; a hypersensitivity reaction through hapten formation has also been noted. Allergic atopic dermatitis can occur after systemic use, but it is most commonly the result of topical use of the drug; cases are thought to be infrequent. Once allergic contact dermatitis has occurred and is confirmed, cross-sensitivity between topically and orally administered diphenhydramine may be seen.

agranulocytosis, hemolytic anemia, thrombocytopenia

Hematologic adverse events that may rarely occur with diphenhydramine use include hemolytic anemia, thrombocytopenia, and agranulocytosis.

coma, flushing, hypotension, palpitations, sinus tachycardia

Cardiovascular effects of systemic diphenhydramine and other first-generation sedating antihistamines are rare at usual dosages and with proper use but can include hypotension, headache, palpitations, sinus tachycardia, and extrasystoles. High doses, inadvertent exposures or overdoses increase the risk for systemic toxicity, which may include cardiovascular events and excessive CNS stimulation, including seizures/convulsions, coma, and death. Atropine-like signs and symptoms, dry mouth (xerostomia); fixed, dilated pupils (mydriasis); flushing, and gastrointestinal symptoms may also occur. Serious adverse events, including death, have been reported after the ingestion of large oral doses of diphenhydramine during the "Benadryl Challenge", a social media "challenge" aimed at young people. Accidental oral ingestion of topical products may also cause systemic toxicity as these are more concentrated than oral products. For example, a 2% topical formulation equals diphenhydramine 100 mg/5 mL, whereas oral liquid preparations typically contain diphenhydramine 12.5 mg/5 mL. Similarities in topical gel and oral liquid product packaging may contribute to consumer confusion and improper administration and use.

Description

Diphenhydramine is an oral, topical, and parenteral first-generation, sedating antihistamine (H1-blocker) of the ethanolamine class. Ethanolamine class antihistamines

have significant antimuscarinic activity and produce marked sedation in most patients. Topical formulas are used to relieve pain and itching associated with insect bites, minor burns or cuts, skin irritations or rashes such as poison ivy, oak or sumac. Diphenhydramine is often used systemically to treat symptoms associated with allergic reactions and in pre-medication regimens prior to the use of medications or treatments associated with infusion-related reactions. Oral formulations are often used to treat minor allergic reactions, seasonal allergies, and some symptoms associated with the common cold. Because of its anticholinergic properties, diphenhydramine is effective in the relief of nausea, vomiting, and vertigo associated with motion sickness. Due to its ability to induce drowsiness, it is also promoted as a non-prescription (OTC) treatment for sleep. Diphenhydramine is also used to treat drug-induced extrapyramidal symptoms as well as to treat mild symptoms of Parkinson's disease. Diphenhydramine has the potential for abuse; patients taking higher than recommended doses may experience adverse events. Serious adverse events, including death, have been reported after the ingestion of large oral doses of diphenhydramine during the "Benadryl Challenge", a social media "challenge" aimed at young people. Taking larger than recommended systemic doses can cause serious heart problems, seizures, coma, and death. Diphenhydramine was originally approved by the FDA in 1946 as a prescription-only drug, but the oral and topical formulations were later changed to non-prescription (OTC) status.

Mechanism Of Action

Diphenhydramine does not prevent the release of histamine, as do cromolyn and nedocromil, but rather competes with free histamine for binding at H1-receptor sites. Diphenhydramine competitively antagonizes the effects of histamine on H1-receptors in the GI tract, uterus, large blood vessels, and bronchial muscle. Blockade of H1-receptors also suppresses the formation of edema, flare, and pruritus that result from histaminic activity.

H1-antagonists possess anticholinergic properties in varying degrees; ethanolamine derivatives have greater anticholinergic activity than do other antihistamines, which probably accounts for the antidyskinetic action of diphenhydramine. This anticholinergic action appears to be due to a central antimuscarinic effect, which also may be responsible for its antiemetic effects, although the exact mechanism is unknown. Diphenhydramine has a direct suppressive action on the cough center and causes sedation via CNS depression. Topical diphenhydramine provides local relief from insect bites, minor burns, sunburn, or minor abrasions, possibly due to an anesthetic effect resulting from decreased permeability of nerve cell membranes to sodium ions (preventing the transmission of nerve impulses). Following prolonged use of

diphenhydramine, tolerance can occur, but this may be beneficial because of reduced sedative effects.

Pharmacokinetics

Diphenhydramine may be administered orally, topically, intravenously, or intramuscularly. Less soluble H1-antagonists have a slower onset of action and are less likely to cause toxicity. The duration of action ranges from 4—6 hours. The maximum sedative effect of the drug occurs between 1—3 hours. Diphenhydramine is highly protein-bound. It is widely distributed in body tissues and fluids, and it crosses the placenta and is excreted into breast milk.

Metabolism occurs in the liver to produce diphenylmethoxyacetic acid, which then becomes conjugated; other metabolites are also formed. Plasma half-life is between 2—8 hours. Most unchanged drug and metabolites are excreted renally within 24—48 hours of a dose.

Affected cytochrome P450 isoenzymes: CYP2D6, CYP1A2, CYP2C9, CYP2C19
In vitro and in vivo studies indicate that diphenhydramine is a substrate and inhibitor of CYP2D6 isoenzymes. To a lesser extent, it is also metabolized by CYP1A2, CYP2C9, and CYP2C19 isoenzymes.

Route-Specific Pharmacokinetics

- **Oral Route**

H1-antagonists are well absorbed from the GI tract, but they have variable solubility, which ultimately affects the onset of action. Onset of action following oral administration of diphenhydramine occurs in 15—30 minutes, with peak concentrations occurring in about 2—4 hours.

- **Intramuscular Route**

The onset of antiextrapyramidal effects following an intramuscular injection is 15—30 minutes.

Administration

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

Oral Administration

May administer without regard to meals.
If taken as a nighttime sleep aid, administer the dosage at bedtime as directed on the product label.

Oral Solid Formulations

Film-coated tablets, capsules, or liquid gel capsules:
Swallow with a sip of water or other liquid.

Chewable tablets:
Tablet should be chewed well before swallowing.

Orally disintegrating tablets (ODTs):
Allow tablet to dissolve in the mouth. Alternatively, the patient may chew tablets before swallowing.
Tablets dissolve with or without water.

Oral Liquid Formulations

Oral solution or syrup:
Use a calibrated oral measuring device to measure and ensure accurate dosage.

Injectable Administration

Diphenhydramine is administered intravenously or intramuscularly. Do not use subcutaneously or perivascularly. Because of the risk of local necrosis, diphenhydramine injection should not be used as a local anesthetic.
Visually inspect parenteral products for particulate matter and discoloration prior to administration whenever solution and container permit.

Intravenous Administration

The maximum intravenous infusion rate is 25 mg/minute.

Intramuscular Administration

Inject deeply into a large muscle mass (e.g., upper outer quadrant of gluteal muscle).

Topical Administration

Cream/Ointment/Lotion Formulations

Topical cream, topical solution, or topical gel:
External use only. Do NOT administer orally or apply to mucous membranes.
Apply gently to affected area.

Use only as directed on product labeling. Not to be applied to lesions associated with varicella (e.g., chickenpox) or measles infection.
Inadvertent oral ingestion may cause serious toxicity. To decrease the likelihood of an administration route error, store topical preparations separately from oral products and advise patients to do the same

Tecnu Ivy Complete Kit
Cleanse the affected area of skin with soap or Poison Ivy Scrub and warm water for at least 15 seconds.
Dry affected area.
Apply diphenhydramine gel to the affected area.
The area may be covered with a bandage. If using a bandage, let the area dry first.

Maximum Dosage Limits

Maximum doses are indication-specific; do not exceed product labeling. The following are general guidelines:

- **Adults**
  300 mg/day PO; 400 mg/day IV or IM.
- **Geriatric**
  300 mg/day PO; 400 mg/day IV or IM.
- **Adolescents**
  300 mg/day PO; 400 mg/day IV or IM.
- **Children**
  5 mg/kg/24 hours PO,IV, or IM, not to exceed 300 mg/day. OTC use in children 2 to 5 years is not recommended unless under supervision of their care team.
- **Infants**
  5 mg/kg/24 hours IV or IM. Safety and efficacy have not been established for oral formulations. OTC use is not recommended.
- **Neonates**
  Contraindicated.

Dosage Forms

- Aleve PM 220mg-25mg Caplet
- Aleve PM Soft Grip 220mg-25mg Caplet
- Aller-G-Time 25mg Caplet

- Anti-Itch 2%-0.1%Topical Cream
- AURODRYL Children's Allergy Dye-Free 12.5mg/5mL Solution (Bubblegum)
- BANOPHEN 25mg Capsule
- BANOPHEN 25mg Capsule
- BANOPHEN 25mg Minitabs Tablet
- Banophen 50mg Capsule
- Banophen 50mg Capsule
- Banophen Anti-Itch Extra Strength 2%-0.1% Topical Cream
- Benadryl Allergy 25mg Liqui-gel Capsule
- Benadryl Allergy Extra Strength 50mg Tablet
- Benadryl Allergy Extra Strength 50mg Tablet
- Benadryl Allergy Plus Congestion 25mg-10mg Tablet
- Benadryl Allergy Ultratab 25mg Tablet
- Benadryl Allergy Ultratab 25mg Tablet
- Benadryl Children's Allergy 12.5mg Chewable Tablet (Grape)
- Benadryl Children's Allergy 12.5mg/5mL Solution
- Benadryl Children's Allergy Plus Congestion 12.5mg-5mg/5mL Solution (Grape)
- Benadryl Extra Strength 2%-0.1% Topical Cream
- Benadryl Extra Strength Itch Relief Stick
- Benadryl Extra Strength Spray
- Benadryl Itch Stopping Extra Strength 2% Topical Gel
- Benadryl Original Strength 1%-0.1% Topical Cream
- Buckley's Bedtime 12.5mg-22mg/5ml Suspension
- Children's Allergy 12.5mg/5mL Solution (Bubblegum)
- Children's Allergy Relief Dye Free 12.5mg/5mL Solution (Cherry)
- Children's MAXAllergy Relief Dye Free 12.5mg/5mL Solution (Bubblegum)
- Contrast Allergy PreMed Pack
- CVS Adult Allergy Relief 50mg/20mL Maximum Strength Liquid (Cherry)
- CVS Adult Allergy Relief 50mg/20mL Maximum Strength Liquid (Grape)
- CVS Allergy 25mg Capsule
- CVS Allergy 25mg Softgel
- CVS Allergy 25mg Tablet
- CVS Allergy Relief 25mg Capsule
- CVS Allergy Relief 25mg Chewable Tablet
- CVS Allergy Relief 25mg Rapid Melt Tablet (Grape)
- CVS Allergy Relief 25mg Tablet
- CVS Allergy-D 25mg-10mg Tablet
- CVS Children's Allergy Plus Congestion 12.5mg-5mg/5mL Solution (Grape)
- CVS Children's Allergy Relief 12.5mg Rapid Melt Tablet (Grape)
- CVS Children's Allergy Relief 12.5mg/5mL Solution (Cherry)

- CVS Children's Allergy Relief Dye-Free 12.5mg Rapid Melt Tablet (Bubblegum)
- CVS Children's Allergy Single Dose 12.5mg/5ml Solution (Cherry)
- CVS Children's Cold & Cough Nighttime 6.25mg-2.5mg/5ml Solution (Grape)
- CVS Instant Itch Relief Extra Strength Spray
- CVS Itch Relief 1%-0.1% Topical Cream
- CVS Itch Relief Extra Strength 2% Topical Gel
- CVS Itch Relief Extra Strength 2%-0.1% Topical Cream
- CVS Itch Relief Extra Strength Spray
- CVS Nighttime Sleep Aid 25mg Caplet
- CVS Nighttime Sleep Aid 25mg Mini-Caplet
- CVS Nighttime Sleep Aid 25mg Softgel
- CVS Nighttime Sleep Aid Maximum Strength 50mg Softgel
- CVS Nighttime Sleep Melts 25mg Tablet (Cherry)
- CVS Nighttime Sleep Melts 25mg Tablet (Grape)
- CVS Nighttime Sleep-Aid 25mg Mini-Caplet
- CVS Nighttime Sleep-Aid 25mg Mini-Capsule
- CVS Nighttime Sleep-Aid 50mg Effervescent Tablet
- CVS Nighttime Sleep-Aid 50mg Softgel
- CVS Nighttime Sleep-Aid Solution (Berry)
- CVS Nighttime Sleep-Aid Solution Twin Pack (Berry)
- CVS Sleep-Aid 25mg Tablet
- DI-PHEN 12.5mg/5mL Solution
- Dimetane Allergy Relief 25mg Softgel
- Dimetane Allergy Relief 50mg Softgel
- Dimetapp Children's Cold & Congestion Nighttime 6.25mg-2.5mg/5ml Solution (Grape)
- DIPHEN ELIXIR 12.5mg/5mL Solution
- Diphenhydramine Hydrochloride 12.5mg Soft chew
- Diphenhydramine Hydrochloride 12.5mg/5mL Oral solution
- Diphenhydramine Hydrochloride 2%, Zinc Acetate 0.1% Topical cream
- Diphenhydramine Hydrochloride 25mg Oral capsule
- Diphenhydramine Hydrochloride 25mg Oral tablet
- Diphenhydramine Hydrochloride 25mg, Naproxen Sodium 220mg Oral tablet
- Diphenhydramine Hydrochloride 25mg/10mL Oral solution
- Diphenhydramine Hydrochloride 50mg Oral capsule
- Diphenhydramine Hydrochloride 50mg/1mL Solution for injection
- Diphenhydramine Hydrochloride Bulk powder
- Doans PM 580mg-25mg Extra Strength Caplet
- Dormin The Original Night-Time Sleep Aid 25mg Capsule
- ElixSure Allergy 12.5mg/5ml Solution

- Equaline Allergy Relief 25mg Tablet
- Equaline Children's Allergy 12.5mg Chewable Tablet (Grape)
- Equaline Nighttime Sleep Aid 25mg Caplet
- Equaline Nighttime Sleep-Aid 25mg Softgel
- Equate Allergy Relief 25mg Capsule
- Equate Allergy Relief 25mg Tablet
- Equate Allergy Relief 25mg Tablet
- Equate Allergy Relief 25mg Tablet (Twin Pack)
- Equate Anti-Itch Extra Strength Continuous 2%-0.1% Spray
- Equate Children's Allergy 12.5mg Chewable Tablet (Cherry)
- Equate Children's Allergy Relief 12.5mg/5mL Solution (Cherry)
- First-Mouthwash 0.1g/0.8g BLM Compounding Kit
- First-Mouthwash 0.2g/1.6g BLM Compounding Kit
- Foster & Thrive Allergy Relief 25mg Capsule
- Foster & Thrive Allergy Relief 25mg Minitab
- Foster & Thrive Allergy Relief 25mg Minitab
- Foster & Thrive Allergy Relief 25mg Tablet
- Foster & Thrive Anti-Itch Extra Strength 2%-0.1% Topical Cream
- Foster & Thrive Children's Allergy Relief 12.5mg/5mL Solution (Cherry)
- Foster & Thrive Nighttime Sleep Aid 25mg Caplet
- Genahist Capsule
- Geri-Dryl Allergy Relief 12.5mg/5mL Solution
- Geri-Dryl Allergy Relief 25mg Capsule
- GERI-DRYL Allergy Relief 25mg Tablet
- GNP Allergy 25mg Capsule
- GNP Allergy 25mg Tablet
- GNP Allergy Antihistamine 50mg/20mL Maximum Strength Liquid (Cherry)
- GNP Allergy Antihistamine 50mg/20mL Maximum Strength Liquid (Cherry)
- GNP Allergy Relief 25mg Capsule
- GNP Allergy Relief 25mg Liquid Filled Softgel
- GNP Allergy Relief 25mg Minitab
- GNP Allergy Relief 25mg Softgel
- GNP Anti-Itch 2%-0.1% Topical Cream
- GNP Anti-Itch Extra Strength 2%-0.1% Topical Cream
- GNP Children's Allergy 12.5mg/5mL Liquid (Bubble Gum)
- GNP Children's Allergy 12.5mg/5mL Solution (Bubble Gum)
- GNP Children's Allergy 12.5mg/5mL Solution (Cherry)
- GNP Children's Allergy Plus Congestion 12.5mg-5mg/5mL Solution
- GNP Children's Allergy Relief Dye Free 12.5mg/5mL Solution (Bubble Gum)
- GNP ClearTime Nighttime Allergy Relief 25mg Caplet

- GNP Itch Relief Extra Strength 2%-0.1% Topical Spray
- GNP Itch Relief Extra Strength Spray
- GNP Nighttime Sleep Aid 25mg Mini-Caplet
- GNP Nighttime Sleep Aid 50mg/30mL Solution (Berry)
- GNP Nighttime Sleep-Aid Maximum Strength 50mg Softgel
- GNP Sleep Aid 25mg Mini Caplet
- GNP Sleep Time Nighttime Sleep-Aid Softgel
- GNP Sleep Time Nighttime Sleep-Aid Solution (Berry)
- GoodSense Allergy Relief 25mg Tablet
- GoodSense Children's Allergy Relief Liquid
- GoodSense Diphedryl 25mg Capsule
- GoodSense Diphedryl 25mg Tablet
- GoodSense Diphenhydramine Hydrochloride 25mg Tablet
- GoodSense Itch Relief Cream 2%-0.1% Topical Cream
- GoodSense Nighttime Sleep Aid 25mg Mini-Caplet
- Goodsense Nighttime Sleep Aid Maximum Strength 50mg Softgel
- GoodSense Sleep Time Nighttime Sleep-Aid Solution (Berry)
- HEALTH STAR NightTime Sleep-Aid 25mg Caplet
- HEB Antihistamine Allergy 25mg Tablet
- Itch Relief 2% Topical Cream
- Itch Relief 2% Topical Cream
- KinderMed Kid's Allergy 12.5mg/5mL Solution (Cherry)
- KinderMed Kid's Nighttime Cold & Cough 6.25mg-2.5mg/5mL Solution (Cherry)
- Kroger Allergy 25mg Tablet
- Leader Allergy 25mg Capsule
- Leader Allergy 25mg Tablet
- Leader Allergy Relief 25mg Liquid Filled Capsule
- Leader Allergy Relief 25mg Softgel
- Leader Allergy Relief 25mg Tablet
- Leader Anti-Itch 2%-0.1% Topical Cream
- Leader Children's Allergy Liquid (Cherry)
- Leader Children's Allergy Relief 12.5mg/5mL Solution (Cherry)
- Leader Itch Relief Extra Strength Spray
- Leader Nighttime Sleep Aid 25mg Softgel
- Leader Nighttime Sleep-Aid 50mg Softgel
- Leader Nighttime Sleep-Aid 50mg/30mL Solution (Berry)
- Leader Nighttime Sleep-Aid Maximum Strength 50mg Softgel
- Leader Sleep Aid 25mg Nighttime Caplet
- Leader Sleep Aid 50mg/30mL Solution (Berry)
- Leader Sleep-Aid 25mg Liquid Filled Capsule

- Leader Sleep-Aid Nighttime Softgel
- M-Dryl 12.5mg/5mL Oral Solution (Cherry)
- M-Dryl 12.5mg/5mL Solution
- Medique Diphen 25mg Caplet
- Member's Mark Aller-Ben 25mg Tablet
- NARAMIN 12.5mg/5mL Oral Solution (Cherry)
- Nytol Quickcaps 25mg Caplet
- PediaClear Children's Cough 6.25mg/mL Liquid
- PHARBEDRYL 25mg Capsule
- PHARBEDRYL 25mg Capsule
- PHARBEDRYL 50mg Capsule
- Picnic Allergy 25mg Tablet
- Premier Value Allergy Extra Strength 2%-0.1% with Aloe Topical Cream
- Premier Value Allergy Relief 25mg Capsule
- Premier Value Allergy Relief Maximum Strength 2% Topical Gel
- Premier Value Allergy Relief Maximum Strength 2%-0.1% Topical Spray
- Premier Value Children's Allergy 12.5mg/5ml Liquid (Bubble Gum)
- Premier Value Children's Allergy Liquid (Bubblegum)
- Premier Value Children's Allergy Liquid (Cherry)
- Premier Value Children's Complete Allergy 12.5mg Rapid Melt Tablet (Cherry)
- Premier Value Children's Complete Allergy 12.5mg Rapid Melt Tablet (Grape)
- Premier Value Complete Allergy 25mg Tablet
- Premier Value Complete Allergy 25mg Tablet (Coated Mint)
- Premier Value Complete Allergy Medicine 25mg Capsule
- Premier Value Complete Allergy Softgel
- Premier Value Night Time Cough & Cold Relief Solution (Grape)
- Premier Value Nighttime Sleep Aid 25mg Tablet
- Premier Value Nighttime Sleep Aid Maximum Strength 50mg Softgel
- Premier Value Nighttime Sleep-Aid Liquid (Berry)
- Premier Value Nyt-Time Sleep Caps 25mg Caplet
- Premier Value Rest Simply 25mg Caplet
- Premier Value Sleep Aid 25mg Caplet
- Publix Allergy 25mg Capsule
- Publix Allergy 25mg Tablet
- Publix Children's Allergy 12.5mg/5ml Liquid
- Quality Choice Allergy Relief 25mg Capsule
- Quality Choice Allergy Relief 25mg Softgel
- Quality Choice Allergy Relief 25mg Tablet
- Quality Choice Anti-Itch Extra Strength 2%-0.1% Topical Cream
- Quality Choice Children's Allergy 12.5mg/5mL Solution (Bubblegum)

- Quality Choice Children's Allergy 12.5mg/5mL Solution (Cherry)
- Quality Choice Children's Allergy Dye Free 12.5mg/5mL Solution (Bubblegum)
- Quality Choice EZ Nite Sleep 50mg/30mL Liquid (Berry)
- Quality Choice Itch Relief Extra Strength 2%-0.1% Topical Spray
- Quality Choice Nighttime Sleep Aid 25mg Tablet
- Quality Choice Nighttime Sleep-Aid 25mg Softgel
- Quality Choice Nighttime Sleep-Aid Maximum Strength 50mg Softgel
- Quality Choice Rest Simply Nighttime Sleep-Aid 25mg Caplet
- Quality Choice Rest Simply Nighttime Sleep-Aid 25mg Caplet
- RITE AID Allergy Relief 25mg Capsule
- RITE AID Allergy Relief 25mg Minitab
- RITE AID Anti-Itch & Skin Protectant Extra Strength 2%-0.1% Topical Cream
- RITE AID Anti-Itch Extra Strength 2% Topical Gel
- RITE AID Anti-Itch Extra Strength Spray
- RITE AID Children's Allergy 12.5mg/5mL Solution (Bubble Gum)
- RITE AID Children's Allergy Relief 12.5mg Orally Chewable Tablet
- RITE AID Children's Allergy Relief 12.5mg/5mL Liquid (Cherry)
- RITE AID Children's Allergy Relief 12.5mg/5mL Solution (Cherry)
- RITE AID Diphenhydramine Hydrochloride 12.5mg/5mL Elixir
- RITE AID Diphenhydramine Hydrochloride 12.5mg/5mL Liquid
- RITE AID Night Time Sleep-Aid 25mg Caplet
- RITE AID Nighttime Sleep-Aid 25mg Caplet
- RITE AID Nighttime Sleep-Aid 50mg Softgel
- RITE AID Sleep Aid 25mg Caplet
- RITE AID Sleep Aid 25mg Tablet
- Select Brand Allergy Medicine 25mg Capsule
- Select Brand Allergy Medicine Liquid (Cherry)
- Simply Sleep 25mg Caplet
- Sleep Tabs 25mg Tablet
- Sleepinal 50mg Capsule
- Sominex 25mg Tablet
- Sominex 25mg Tablet
- Sominex 50mg Maximum Strength Caplet
- Sudafed PE Day/Night Sinus Congestion Tablet
- Tecnu Ivy Complete Kit
- Tecnu Rash Relief Maximum Strength Pain Relieving 2% Topical Spray
- Today's Health Allergy Relief 25mg Capsule
- Today's Health Allergy Relief 25mg Tablet
- Today's Health Children's Allergy Liquid
- Today's Health Rest Simply 25mg Tablet

- Today's Health Sleep Aid 25mg Tablet
- Today's Health Sleep Aid Liquid Gels Maximum Strength Softgel
- Top Care Allergy 25mg Capsule
- Top Care Allergy 25mg Tablet
- Top Care Allergy Relief 25mg Tablet
- Top Care Children's Allergy Relief Liquid
- Top Care Children's NightTime Triacting Cold & Cough Solution (Grape)
- Top Care Nighttime Sleep Aid 25mg Caplet
- Top Care Nighttime Sleep Aid 25mg Mini-Caplet
- TopCare Anti-Itch Extra Strength 2%-0.1% Topical Cream
- TopCare Children's Allergy Relief 12.5mg Rapid Melt Tablet (Grape)
- Unisom SleepGels 50mg Softgel
- Unisom SleepMinis 25mg Capsule
- up & up Children's Allergy 12.5mg/5mL Solution (Cherry)
- Valu-Dryl 25mg Capsule
- Vanamine PD 6.25mg/mL Solution
- Vicks ZzzQuil Nighttime Sleep-Aid Liquicap
- Vicks ZzzQuil Nighttime Sleep-Aid Liquid (Calming Vanilla Cherry)
- Vicks ZzzQuil Nighttime Sleep-Aid Liquid (Soothing Mango Berry)
- Vicks ZzzQuil Nighttime Sleep-Aid Liquid (Warming Berry)
- Wal-dryl 25mg Allergy Mini Tablet
- Wal-dryl Allergy 25mg Capsule
- Wal-Dryl Allergy 25mg Dye-Free Liquid Capsule
- Wal-Dryl Allergy 25mg/10mL Liquid (Cherry)
- Wal-dryl Allergy Liquid Gels Capsule
- Wal-dryl Allergy Minitab
- Wal-dryl Anti-Itch 2%-0.1% Topical Cream
- Wal-dryl Anti-Itch Spray
- Wal-Dryl Children's Allergy 12.5mg Chewable Tablet (Cherry)
- Wal-Dryl Children's Allergy 12.5mg Chewable Tablet (Grape)
- Wal-Dryl Children's Allergy 12.5mg/5mL Liquid (Cherry)
- Wal-dryl Children's Allergy Liquid
- Wal-Dryl Children's Allergy Solution (Cherry)
- Wal-Dryl Children's Dye-Free Allergy 12.5mg/5mL Liquid (Bubble Gum)
- Wal-Dryl Maximum Strength 2%-0.1% Topical Cream
- Wal-Dryl PE Children's Allergy & Congestion 12.5mg-5mg/5mL Sugar Free Solution (Grape)
- Wal-dryl-D 25mg-10mg Tablet
- Wal-Sleep Z 25mg Caplet
- Wal-Sleep Z 25mg Softgel

- Wal-Sleep Z Nighttime 50mg/30mL Solution (Berry)
- Wal-Som Diphenhydramine Hydrochloride 25mg Tablet (Cherry)
- Wal-Som Maximum Strength 50mg Softgel
- Wal-Som Nighttime Sleep Aid Maximum Strength 50mg Gelcap
- Wal-Som Nighttime Sleep Aid Maximum Strength 50mg Gelcap
- Wal-Som Nighttime Sleep Aid Maximum Strength 50mg Softgel
- Walgreens All Night Pain Relief PM 220mg Caplet
- Walgreens Allergy Relief 25mg Capsule
- Walgreens Allergy Relief 25mg Dye-Free Liquid Capsule
- Walgreens Allergy Relief 25mg Mini Tablet
- Walgreens Allergy Relief 25mg Minitab
- Walgreens Allergy Relief 25mg Tablet
- Walgreens Allergy Relief 25mg/10mL Dye & Sugar Free Solution (Cherry)
- Walgreens Allergy Relief Plus Congestion 25mg-10mg Tablet
- Walgreens Anti-Itch 1% Topical Spray
- Walgreens Anti-Itch Original Strength 1%-0.1% Topical Cream
- Walgreens Children's Allergy Relief 12.5mg Chewable Tablet (Cherry)
- Walgreens Children's Allergy Relief 12.5mg Chewable Tablet (Grape)
- Walgreens Children's Allergy Relief 12.5mg/5mL Solution (Cherry)
- Walgreens Children's Allergy Relief Dye Free 12.5mg/5mL Solution (Cherry)
- Walgreens Nighttime Allergy Relief 25mg Caplet
- Walgreens Sleep Aid 25mg Nighttime Caplet
- Walgreens Sleep II Tablet

Dosage Adjustment Guidelines

Hepatic Impairment

Specific recommendations for dosage adjustment in hepatic impairment are not available; individualize dosage.

Renal Impairment

No dosage adjustments are needed.