Brand Names

Cafcit, NoDoz, Stay Awake, Vivarin

Indication Specific Dosing

For the treatment of neonatal apnea (i.e., apnea of prematurity)

Intravenous dosage (caffeine citrate)

Premature neonates

20 to 25 mg/kg/dose caffeine citrate (equivalent to 10 to 12.5 mg/kg/dose anhydrous caffeine base) IV as a loading dose, then 5 to 10 mg/kg/day caffeine citrate (2.5 to 5 mg/kg/day anhydrous caffeine base) IV starting 24 hours later; adjust dose based on clinical response, and if necessary, caffeine blood concentrations. Under most circumstances, use is for a limited duration of treatment, usually not to exceed 10 to 12 days. Longer durations were reported in a study of premature neonates born between 23 and 28 weeks gestation; neonates received caffeine for a mean duration of 47 days. A loading dose of 50 mg/kg/dose caffeine citrate (25 mg/kg/dose anhydrous caffeine base) IV, then 12 mg/kg/day caffeine citrate (6 mg/kg/day anhydrous caffeine base) IV has also been reported. Due to the extended half-life, discontinue caffeine for at least 5 to 7 days prior to discharge unless neonate is discharged with apnea monitor.

Oral dosage (caffeine citrate oral solution)

Premature neonates

20 to 25 mg/kg/dose caffeine citrate (equivalent to 10 to 12.5 mg/kg/dose anhydrous caffeine base) as a loading dose, then 5 to 10 mg/kg/day caffeine citrate (2.5 to 5 mg/kg/day anhydrous caffeine base) PO starting 24 hours later; adjust based on clinical response, and if necessary, caffeine blood concentrations. Under most circumstances, use is for a limited duration of treatment, usually not to exceed 10 to 12 days. Longer durations were reported in a study of premature neonates born between 23 and 28 weeks gestation;

neonates received caffeine for a mean duration of 47 days. A loading dose of 50 mg/kg/dose caffeine citrate (25 mg/kg/dose anhydrous caffeine base) PO, then 12 mg/kg/day caffeine citrate (6 mg/kg/day anhydrous caffeine base) PO has also been reported. Due to the extended half-life, discontinue caffeine for at least 5 to 7 days prior to discharge unless the neonate is discharged with an apnea monitor.

To restore mental alertness when fatigue† or drowsiness† are present

Oral dosage (caffeine tablets)

Adults

100 to 200 mg (anhydrous caffeine) PO (dose dependent on product label); may repeat dose every 3 to 4 hours if needed. Do not exceed labeled dosage.

Children and Adolescents 12 years and older

100 to 200 mg (anhydrous caffeine) PO (dose dependent on product label); may repeat dose every 3 to 4 hours if needed. Do not exceed labeled dosage.

For the treatment of postdural lumbar puncture headache†

Oral dosage (anhydrous caffeine base)

Adults

300 mg of anhydrous caffeine PO as a single dose may be effective for the treatment of post-dural puncture headache (PDPH) in some patients, although the data are limited. In one small placebo-controlled trial, 40 postpartum patients with PDPH were randomized to receive a compounded PO capsule formulation containing 300 mg of anhydrous caffeine powder or placebo. Headache intensity, as measured by the visual analogue pain scale (VAS), was assessed prior to drug administration, and at 4 and 24 hours post-treatment. More patients in the caffeine group experienced improvement in VAS at 4 hours post-treatment compared to those in the placebo group (90% vs 60%). The magnitude of improvement in VAS was more than 300% greater in the caffeine group than the placebo group. VAS scores did not differ between the two groups at 24 hours. Among the patients whose PDPH was relieved at 4 hours, 30% had a recurrence of symptoms the following day. One patient from the caffeine group and one from the placebo group reported transient flushing and jitteriness; however, no significant adverse effects were associated with caffeine treatment. Larger, well-controlled trials in more generalized patient populations are needed

to systematically evaluate and establish the effectiveness of orally administered caffeine in the treatment of PDPH.

Intravenous dosage

Adults†

Based on available data for caffeine sodium benzoate, equipotent doses of other IV caffeine formulations may theoretically be beneficial; however, current published data are limited to the use of caffeine sodium benzoate; the use of caffeine citrate for example, has not been specifically studied. 500 mg IV of caffeine sodium benzoate (see separate monograph) may be effective for the treatment of post-dural puncture headache (PDPH) in some patients, although the data are limited. In one small placebo-controlled trial, a single 500 mg dose of caffeine sodium benzoate (250 mg of caffeine and 250 mg of sodium benzoate per 2 ml) resulted in a decrease in the proportion of patients with PDPH persistence and in the number of patients requiring supplementary interventions compared with placebo. One brief correspondence describes the use of 1 or 2 doses of caffeine sodium benzoate 500 mg each administered in 1 liter of IV fluid 4 hours apart, plus additional IV fluid hydration, which resulted in relief of PDP headache in about 14 of 18 patients (75%). Large, well-controlled trials are needed to systematically evaluate and establish the effectiveness of intravenously administered caffeine in the treatment of PDPH.

For extubation facilitation†

Intravenous or Enteral dosage

Premature Neonates

An initial loading dose of 20 to 25 mg/kg caffeine citrate (10 to 12.5 mg/kg anhydrous caffeine base) IV or PO for one dose is common; however, doses up to 80 mg/kg caffeine citrate (40 mg/kg anhydrous caffeine base) IV or PO have been reported. Begin maintenance dose 24 hours after load. Maintenance doses of 5 to 10 mg/kg/day caffeine citrate (2.5 to 5 mg/kg/day anhydrous caffeine base) IV or PO are common, but maintenance doses up to 20 mg/kg/day caffeine citrate (10 mg/kg/day anhydrous caffeine base) have been used. Duration of treatment may vary, but usually persists for at least 48 hours. Due to the extended half-life, caffeine should be discontinued for at least 5 to 7 days prior to discharge unless neonate is discharged with apnea monitor.

Contraindications And Precaution

Drug Interactions

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

Hypersensitivity

This medication is contraindicated in patients with a history of hypersensitivity to it or any of its components.

Treatment-Related Restrictions of Use

The safety and efficacy of the prescription use of caffeine in neonates and infants for longer than 12 days, prophylaxis of sudden infant death syndrome (SIDS), or for use prior to extubation in mechanically ventilated infants has not been established.

seizure disorder

In overdoses, caffeine has been associated with seizures and it should be use cautiously in individuals with a seizure disorder.

cardiovascular disease

Caffeine should be used cautiously in individuals with cardiovascular disease. Caffeine has been shown to increase heart rate, left ventricular output, and stroke volume.

hepatic failure, renal failure, renal impairment

Caffeine should be used cautiously in individuals with hepatic failure. Caffeine clearance may be delayed, leading to toxicity. Renal impairment or renal failure may also delay caffeine clearance. It should be noted that caffeine elimination is more dependent on renal clearance in premature neonates and term neonates than in older infants or adults, due to the underdeveloped hepatic metabolism and renal elimination of drugs in general. Thus monitoring of serum caffeine concentrations is recommended in neonates or premature neonates, especially those with renal or hepatic impairment.

pregnancy

When used during pregnancy, caffeine easily crosses the placenta; fetal blood and tissue concentrations approximate concentrations in the pregnant individual. There are no large, well-controlled studies of caffeine administration during human pregnancy. It is generally recommended that the intake of caffeine-containing beverages, like coffee, teas, and sodas, be limited in pregnancy (usually no more than 1 to 2 caffeine-containing beverages/day) or avoided if possible. Caffeine-containing medications should likewise

be limited to use only when necessary. Low to moderate caffeine intake does not appear to increase the risk of congenital malformation, spontaneous abortion, pre-term birth, or low birth weight. The association between high daily intake (more than 500 mg/day) of caffeine and increased rates of low birth weight, spontaneous abortion, difficulty in getting pregnant, or infertility is still controversial, as some studies have not controlled for concomitant cigarette smoking. Neonatal arrhythmias (e.g., tachycardia, premature atrial contractions) and tachypnea have been reported when caffeine was consumed during pregnancy in amounts more than 500 mg/day; caffeine withdrawal after birth may account for these symptoms. In animal studies, giving pregnant mice 50 mg/kg of caffeine base as sustained release oral pellets during organogenesis caused a small increase in cleft palate and exencephaly in the fetuses.

breast-feeding

Use caffeine with caution during breast-feeding. Although mild to moderate use of caffeinated beverages is generally considered to be compatible with lactation, individuals who are breast-feeding should limit their intake of caffeinated beverages if possible. Caffeine-containing drug products should be used cautiously during lactation due to their high caffeine content. Caffeine appears in human milk rapidly after ingestion. Peak caffeine milk levels usually occur within 1 hour after the ingestion of a caffeinated beverage, with milk: plasma ratios of 0.5 to 0.7 reported. Some sources suggest limiting caffeine intake (e.g., 300 to 500 mg per day or less) if breast-feeding. Lower intake is suggested for those who are breast-feeding preterm and newborn infants, as these infants have slower caffeine metabolism and may have caffeine concentrations after breast-feeding that approximate maternal levels. High caffeine intake (more than 500 mg/day or 10 cups of coffee or more) by a breast-feeding individual may cause irritability or poor sleeping patterns in the breast-fed child.

Pregnancy And Lactation

When used during pregnancy, caffeine easily crosses the placenta; fetal blood and tissue concentrations approximate concentrations in the pregnant individual. There are no large, well-controlled studies of caffeine administration during human pregnancy. It is generally recommended that the intake of caffeine-containing beverages, like coffee, teas, and sodas, be limited in pregnancy (usually no more than 1 to 2 caffeine-containing beverages/day) or avoided if possible. Caffeine-containing medications should likewise be limited to use only when necessary. Low to moderate caffeine intake does not appear to increase the risk of congenital malformation, spontaneous abortion, pre-term birth, or low birth weight. The association between high daily intake (more than 500 mg/day) of caffeine and increased rates of low birth weight, spontaneous abortion, difficulty in

getting pregnant, or infertility is still controversial, as some studies have not controlled for concomitant cigarette smoking. Neonatal arrhythmias (e.g., tachycardia, premature atrial contractions) and tachypnea have been reported when caffeine was consumed during pregnancy in amounts more than 500 mg/day; caffeine withdrawal after birth may account for these symptoms. In animal studies, giving pregnant mice 50 mg/kg of caffeine base as sustained release oral pellets during organogenesis caused a small increase in cleft palate and exencephaly in the fetuses.

Interactions

Acetaminophen; Aspirin, ASA; Caffeine: (Moderate) Certain foods that contain high amounts of caffeine or theobromine should be limited during the therapeutic use of caffeine in order to limit additive methylxanthine effects. While taking Caffeine-containing medicines, limit the use of foods, beverages (examples: coffee, tea, colas), herbs (examples: guarana, green tea) and other products that contain additional caffeine, such as chocolate and some non-prescription medications or dietary supplements for headache, insomnia, or weight loss. Too much Caffeine can cause effects like nausea, nervousness, or sleeplessness. Some drug products for adults that contain caffeine have about as much caffeine as a cup of coffee.
Acetaminophen; Caffeine: (Moderate) Certain foods that contain high amounts of caffeine or theobromine should be limited during the therapeutic use of caffeine in order to limit additive methylxanthine effects. While taking Caffeine-containing medicines, limit the use of foods, beverages (examples: coffee, tea, colas), herbs (examples: guarana, green tea) and other products that contain additional caffeine, such as chocolate and some non-prescription medications or dietary supplements for headache, insomnia, or weight loss. Too much Caffeine can cause effects like nausea, nervousness, or sleeplessness. Some drug products for adults that contain caffeine have about as much caffeine as a cup of coffee.
Acetaminophen; Caffeine; Dihydrocodeine: (Moderate) Certain foods that contain high amounts of caffeine or theobromine should be limited during the therapeutic use of caffeine in order to limit additive methylxanthine effects. While taking Caffeine-containing medicines, limit the use of foods, beverages (examples: coffee, tea, colas), herbs (examples: guarana, green tea) and other products that contain additional caffeine, such as chocolate and some non-prescription medications or dietary supplements for headache, insomnia, or weight loss. Too much Caffeine can cause effects like nausea, nervousness, or sleeplessness. Some drug products for adults that contain caffeine have about as much caffeine as a cup of coffee.
Acetaminophen; Caffeine; Pyrilamine: (Moderate) Certain foods that contain high amounts of caffeine or theobromine should be limited during the therapeutic use of caffeine in order to limit additive methylxanthine effects. While taking Caffeine-containing medicines, limit the use of foods, beverages (examples: coffee, tea, colas),

herbs (examples: guarana, green tea) and other products that contain additional caffeine, such as chocolate and some non-prescription medications or dietary supplements for headache, insomnia, or weight loss. Too much Caffeine can cause effects like nausea, nervousness, or sleeplessness. Some drug products for adults that contain caffeine have about as much caffeine as a cup of coffee.
Acetaminophen; Chlorpheniramine; Dextromethorphan; Phenylephrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Acetaminophen; Chlorpheniramine; Dextromethorphan; Pseudoephedrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Acetaminophen; Chlorpheniramine; Phenylephrine : (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Acetaminophen; Dextromethorphan; guaiFENesin; Phenylephrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Acetaminophen; Dextromethorphan; guaiFENesin; Pseudoephedrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Acetaminophen; Dextromethorphan; Phenylephrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Acetaminophen; Dextromethorphan; Pseudoephedrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Acetaminophen; guaiFENesin; Phenylephrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Acetaminophen; Phenylephrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Acetaminophen; Pseudoephedrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Aclidinium; Formoterol: (Moderate) Caffeine may enhance the cardiac inotropic effects of beta-agonists.
Adenosine: (Major) Larger doses of adenosine may be required or adenosine may not be effective in the presence of methylxanthines. The effects of adenosine are antagonized by methylxanthines. When used for diagnostic purposes, instruct patients to avoid

caffeine-containing foods/beverages for at least 5 half-lives prior to the imaging study.
Albuterol: (Moderate) Caffeine may enhance the cardiac inotropic effects of beta-agonists.
Albuterol; Budesonide: (Moderate) Caffeine may enhance the cardiac inotropic effects of beta-agonists.
ALPRAZolam: (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Amantadine: (Major) Amantadine used concomitantly with psychostimulants, such as caffeine, can result in increased stimulant effects, such as nervousness, irritability, or insomnia, and can lead to seizures or cardiac arrhythmias. Close monitoring of the patient is recommended.
Amiodarone: (Minor) Amiodarone is an inhibitor of CYP1A2 isoenzymes, and could theoretically reduce CYP1A2-mediated caffeine metabolism. The clinical significance of this potential interaction is not known.
Amobarbital: (Moderate) Caffeine has been reported to increase the metabolism of barbiturates, and barbiturates increase caffeine elimination. Higher caffeine doses may be needed after barbiturate administration.
Amphetamine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants. Patients may need to reduce, limit, or avoid caffeine intake. Excessive caffeine ingestion (via medicines, supplements or beverages including coffee, green tea, other teas, guarana, colas) may contribute to side effects like nervousness, irritability, insomnia, or tremor.
Amphetamine; Dextroamphetamine Salts: (Moderate) Avoid excessive caffeine intake during use of the amphetamine salts. Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants. Excessive caffeine ingestion (via medicines, foods like chocolate, dietary supplements, or beverages including coffee, green tea, other teas, colas) may contribute to side effects like nervousness, irritability, nausea, insomnia, or tremor. Patients should avoid medications and dietary supplements which contain high amounts of caffeine.
Amphetamine; Dextroamphetamine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants. Patients may need to reduce, limit, or avoid caffeine intake. Excessive caffeine ingestion (via medicines, supplements or beverages including coffee, green tea, other teas, guarana, colas) may contribute to side effects like nervousness, irritability, insomnia, or tremor.
Anagrelide: (Moderate) Anagrelide has been shown to inhibit CYP1A2. In theory, coadministration of anagrelide with substrates of CYP1A2, including caffeine, could lead to increases in the serum concentrations of caffeine and, thus, adverse effects.
Arformoterol: (Moderate) Caffeine may enhance the cardiac inotropic effects of beta-

agonists.
Armodafinil: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with psychostimulants such as armodafinil. Patients taking armodafinil may need to be cautioned to avoid excessive intake of caffeine.
Articaine; EPINEPHrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Aspirin, ASA; Butalbital; Caffeine: (Moderate) Caffeine has been reported to increase the metabolism of barbiturates, and barbiturates increase caffeine elimination. Higher caffeine doses may be needed after barbiturate administration. (Moderate) Certain foods that contain high amounts of caffeine or theobromine should be limited during the therapeutic use of caffeine in order to limit additive methylxanthine effects. While taking Caffeine-containing medicines, limit the use of foods, beverages (examples: coffee, tea, colas), herbs (examples: guarana, green tea) and other products that contain additional caffeine, such as chocolate and some non-prescription medications or dietary supplements for headache, insomnia, or weight loss. Too much Caffeine can cause effects like nausea, nervousness, or sleeplessness. Some drug products for adults that contain caffeine have about as much caffeine as a cup of coffee.
Aspirin, ASA; Caffeine: (Moderate) Certain foods that contain high amounts of caffeine or theobromine should be limited during the therapeutic use of caffeine in order to limit additive methylxanthine effects. While taking Caffeine-containing medicines, limit the use of foods, beverages (examples: coffee, tea, colas), herbs (examples: guarana, green tea) and other products that contain additional caffeine, such as chocolate and some non-prescription medications or dietary supplements for headache, insomnia, or weight loss. Too much Caffeine can cause effects like nausea, nervousness, or sleeplessness. Some drug products for adults that contain caffeine have about as much caffeine as a cup of coffee.
Aspirin, ASA; Caffeine; Orphenadrine: (Moderate) Certain foods that contain high amounts of caffeine or theobromine should be limited during the therapeutic use of caffeine in order to limit additive methylxanthine effects. While taking Caffeine-containing medicines, limit the use of foods, beverages (examples: coffee, tea, colas), herbs (examples: guarana, green tea) and other products that contain additional caffeine, such as chocolate and some non-prescription medications or dietary supplements for headache, insomnia, or weight loss. Too much Caffeine can cause effects like nausea, nervousness, or sleeplessness. Some drug products for adults that contain caffeine have about as much caffeine as a cup of coffee.
Aspirin, ASA; Dipyridamole: (Major) Methylxanthines, through antagonism of adenosine and thus pharmacologic-induced coronary vasodilation, have been associated with false-negative results during dipyridamole-thallium 201 stress testing. It is recommended that caffeine be discontinued for at least 24 hours prior to stress testing. An interaction is not

expected when methylxanthines are used concomitantly with the chronic dipyridamole therapy.
Barbiturates: (Moderate) Caffeine has been reported to increase the metabolism of barbiturates, and barbiturates increase caffeine elimination. Higher caffeine doses may be needed after barbiturate administration.
Barium Sulfate: (Major) Avoid caffeine containing products for at least 48 hours before myelography and for at least 24 hours postprocedure.
Benzodiazepines: (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Benzphetamine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants. Patients may need to reduce, limit, or avoid caffeine intake. Excessive caffeine ingestion (via medicines, supplements or beverages including coffee, green tea, other teas, guarana, colas) may contribute to side effects like nervousness, irritability, insomnia, or tremor.
Beta-agonists: (Moderate) Caffeine may enhance the cardiac inotropic effects of beta-agonists.
Brompheniramine; Dextromethorphan; Phenylephrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Brompheniramine; Phenylephrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Brompheniramine; Pseudoephedrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Brompheniramine; Pseudoephedrine; Dextromethorphan: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Budesonide; Formoterol: (Moderate) Caffeine may enhance the cardiac inotropic effects of beta-agonists.
Budesonide; Glycopyrrolate; Formoterol: (Moderate) Caffeine may enhance the cardiac inotropic effects of beta-agonists.
BUPivacaine; EPINEPHrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
buPROPion: (Moderate) Bupropion is associated with a dose-related risk of seizures. Excessive use of psychostimulants, including caffeine, is associated with an increased seizure risk and may increase this risk during the concurrent use of bupropion. Carefully consider a patient's caffeine intake from all sources, including medicines. Monitor for

irritability, tremor, increased blood pressure, insomnia and seizures. Many non-prescription medicines and weight loss aids may contain caffeine and patients should read labels carefully. Examples of foods and beverages containing caffeine include coffee, teas, colas, energy drinks, chocolate, and some herbal or dietary supplements. Patients should be advised to limit excessive caffeine intake during bupropion therapy.
buPROPion; Naltrexone: (Moderate) Bupropion is associated with a dose-related risk of seizures. Excessive use of psychostimulants, including caffeine, is associated with an increased seizure risk and may increase this risk during the concurrent use of bupropion. Carefully consider a patient's caffeine intake from all sources, including medicines. Monitor for irritability, tremor, increased blood pressure, insomnia and seizures. Many non-prescription medicines and weight loss aids may contain caffeine and patients should read labels carefully. Examples of foods and beverages containing caffeine include coffee, teas, colas, energy drinks, chocolate, and some herbal or dietary supplements. Patients should be advised to limit excessive caffeine intake during bupropion therapy.
Butalbital; Acetaminophen: (Moderate) Caffeine has been reported to increase the metabolism of barbiturates, and barbiturates increase caffeine elimination. Higher caffeine doses may be needed after barbiturate administration.
Butalbital; Acetaminophen; Caffeine: (Moderate) Caffeine has been reported to increase the metabolism of barbiturates, and barbiturates increase caffeine elimination. Higher caffeine doses may be needed after barbiturate administration. (Moderate) Certain foods that contain high amounts of caffeine or theobromine should be limited during the therapeutic use of caffeine in order to limit additive methylxanthine effects. While taking Caffeine-containing medicines, limit the use of foods, beverages (examples: coffee, tea, colas), herbs (examples: guarana, green tea) and other products that contain additional caffeine, such as chocolate and some non-prescription medications or dietary supplements for headache, insomnia, or weight loss. Too much Caffeine can cause effects like nausea, nervousness, or sleeplessness. Some drug products for adults that contain caffeine have about as much caffeine as a cup of coffee.
Butalbital; Acetaminophen; Caffeine; Codeine: (Moderate) Caffeine has been reported to increase the metabolism of barbiturates, and barbiturates increase caffeine elimination. Higher caffeine doses may be needed after barbiturate administration. (Moderate) Certain foods that contain high amounts of caffeine or theobromine should be limited during the therapeutic use of caffeine in order to limit additive methylxanthine effects. While taking Caffeine-containing medicines, limit the use of foods, beverages (examples: coffee, tea, colas), herbs (examples: guarana, green tea) and other products that contain additional caffeine, such as chocolate and some non-prescription medications or dietary supplements for headache, insomnia, or weight loss. Too much Caffeine can cause effects like nausea, nervousness, or sleeplessness. Some drug products for adults that contain caffeine have about as much caffeine as a cup of coffee.

Butalbital; Aspirin; Caffeine; Codeine: (Moderate) Caffeine has been reported to increase the metabolism of barbiturates, and barbiturates increase caffeine elimination. Higher caffeine doses may be needed after barbiturate administration. (Moderate) Certain foods that contain high amounts of caffeine or theobromine should be limited during the therapeutic use of caffeine in order to limit additive methylxanthine effects. While taking Caffeine-containing medicines, limit the use of foods, beverages (examples: coffee, tea, colas), herbs (examples: guarana, green tea) and other products that contain additional caffeine, such as chocolate and some non-prescription medications or dietary supplements for headache, insomnia, or weight loss. Too much Caffeine can cause effects like nausea, nervousness, or sleeplessness. Some drug products for adults that contain caffeine have about as much caffeine as a cup of coffee.
Caffeine; Sodium Benzoate: (Moderate) Certain foods that contain high amounts of caffeine or theobromine should be limited during the therapeutic use of caffeine in order to limit additive methylxanthine effects. While taking Caffeine-containing medicines, limit the use of foods, beverages (examples: coffee, tea, colas), herbs (examples: guarana, green tea) and other products that contain additional caffeine, such as chocolate and some non-prescription medications or dietary supplements for headache, insomnia, or weight loss. Too much Caffeine can cause effects like nausea, nervousness, or sleeplessness. Some drug products for adults that contain caffeine have about as much caffeine as a cup of coffee.
Calcium, Magnesium, Potassium, Sodium Oxybates: (Moderate) Caffeine should be avoided or used cautiously with oxybates. Monitor for potential side effects such as nervousness, irritability, insomnia, and/or cardiac arrhythmias.
Cannabidiol: (Moderate) Coadministration of cannabidiol and caffeine-containing foods/beverages may alter plasma concentrations of caffeine resulting in an increased risk of adverse reactions and/or decreased efficacy. Caffeine is a substrate of CYP1A2; cannabidiol may inhibit and/or induce CYP1A2 at clinically relevant concentrations.
Capmatinib: (Moderate) Reduction or limitation of the caffeine dosage in medications or caffeine in beverages and food may be necessary during concurrent capmatinib therapy. Monitor for an increase in caffeine-related adverse reactions if coadministration with capmatinib is necessary. Caffeine is a sensitive CYP1A2 substrate and capmatinib is a weak CYP1A2 inhibitor. Coadministration with capmatinib increased caffeine exposure by 134%.
Cetirizine; Pseudoephedrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Chlophedianol; Dexchlorpheniramine; Pseudoephedrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
chlordiazePOXIDE: (Minor) Patients taking benzodiazepines for insomnia should not use

caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
chlordiazePOXIDE; Amitriptyline: (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
chlordiazePOXIDE; Clidinium: (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Chlorpheniramine; Dextromethorphan; Phenylephrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Chlorpheniramine; Dextromethorphan; Pseudoephedrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Chlorpheniramine; Ibuprofen; Pseudoephedrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Chlorpheniramine; Phenylephrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Chlorpheniramine; Pseudoephedrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Chromium: (Major) Some green tea products contain caffeine. Additive CNS stimulant effects are likely to occur when caffeine is coadministered with green tea. Avoid this combination. (Moderate) Certain foods that contain high amounts of caffeine or theobromine should be limited during the therapeutic use of caffeine in order to limit additive methylxanthine effects. While taking Caffeine-containing medicines, limit the use of foods, beverages (examples: coffee, tea, colas), herbs (examples: guarana, green tea) and other products that contain additional caffeine, such as chocolate and some non-prescription medications or dietary supplements for headache, insomnia, or weight loss. Too much Caffeine can cause effects like nausea, nervousness, or sleeplessness. Some drug products for adults that contain caffeine have about as much caffeine as a cup of coffee.
Cimetidine: (Minor) Inhibitors of CYP1A2, such as cimetidine, may inhibit the hepatic oxidative metabolism of caffeine. In patients who complain of caffeine-related side effects caffeine dosage or intake may need to be reduced.
Ciprofloxacin: (Moderate) Reduction or limitation of the caffeine dosage in medications and limitation of caffeine in beverages and food may be necessary during concurrent ciprofloxacin therapy. Ciprofloxacin can decrease the clearance of caffeine. Caffeine

toxicity may occur and can manifest as nausea, vomiting, anxiety, tachycardia, or seizures. Ciprofloxacin is a CYP1A2 inhibitor and caffeine is a CYP1A2 substrate.
clonazePAM: (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Clorazepate: (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
cloZAPine: (Major) Caffeine may inhibit clozapine metabolism via CYP1A2. Clozapine clearance has been decreased by roughly 14 percent during coadministration of caffeine, and a documented increase in clozapine serum concentrations has occurred in selected patients. In addition, a single case report associates the appearance of psychiatric symptoms with caffeine ingestion in one patient taking clozapine. Until more data are available, caffeine consumption should be minimized during clozapine treatment.
Codeine; guaiFENesin; Pseudoephedrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Codeine; Phenylephrine; Promethazine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Darifenacin: (Minor) Consuming > 400 mg/day caffeine has been associated with the development of urinary incontinence. Caffeine may aggravate bladder symptoms and counteract the effectiveness of darifenacin to some degree. Patients may wish to limit their intake of caffeinated drugs, dietary supplements (e.g., guarana), or beverages (e.g., green tea, other teas, coffee, colas).
Desloratadine; Pseudoephedrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Desogestrel: Ethinyl Estradiol; Ferrous Bisglycinate: (Minor) Serum concentrations of caffeine may be increased during concurrent administration with ethinyl estradiol. Patients may desire to limit products that contain high amounts of caffeine in an effort to minimize caffeine-related side effects such as nausea or tremors.
Desogestrel; Ethinyl Estradiol: (Minor) Serum concentrations of caffeine may be increased during concurrent administration with ethinyl estradiol. Patients may desire to limit products that contain high amounts of caffeine in an effort to minimize caffeine-related side effects such as nausea or tremors.
Dexbrompheniramine; Dextromethorphan; Phenylephrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.

Dexbrompheniramine; Pseudoephedrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Dexchlorpheniramine; Dextromethorphan; Pseudoephedrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Dexmethylphenidate: (Moderate) Caffeine is a CNS stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants. Avoid excessive caffeine intake during use of methylphenidate derivatives. Excessive caffeine ingestion (via medicines, foods like chocolate, dietary supplements, or beverages including coffee, green tea, other teas, colas) may contribute to side effects like nervousness, irritability, nausea, insomnia, or tremor. Patients should avoid medications and dietary supplements which contain high amounts of caffeine.
Dextroamphetamine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants. Patients may need to reduce, limit, or avoid caffeine intake. Excessive caffeine ingestion (via medicines, supplements or beverages including coffee, green tea, other teas, guarana, colas) may contribute to side effects like nervousness, irritability, insomnia, or tremor.
Dextromethorphan; buPROPion: (Moderate) Bupropion is associated with a dose-related risk of seizures. Excessive use of psychostimulants, including caffeine, is associated with an increased seizure risk and may increase this risk during the concurrent use of bupropion. Carefully consider a patient's caffeine intake from all sources, including medicines. Monitor for irritability, tremor, increased blood pressure, insomnia and seizures. Many non-prescription medicines and weight loss aids may contain caffeine and patients should read labels carefully. Examples of foods and beverages containing caffeine include coffee, teas, colas, energy drinks, chocolate, and some herbal or dietary supplements. Patients should be advised to limit excessive caffeine intake during bupropion therapy.
Dextromethorphan; diphenhydrAMINE; Phenylephrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Dextromethorphan; guaiFENesin; Phenylephrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Dextromethorphan; guaiFENesin; Pseudoephedrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
diazePAM: (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.

Diethylpropion: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
diphenhydrAMINE; Phenylephrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Dipyridamole: (Major) Methylxanthines, through antagonism of adenosine and thus pharmacologic-induced coronary vasodilation, have been associated with false-negative results during dipyridamole-thallium 201 stress testing. It is recommended that caffeine be discontinued for at least 24 hours prior to stress testing. An interaction is not expected when methylxanthines are used concomitantly with the chronic dipyridamole therapy.
Disulfiram: (Moderate) Disulfiram has been shown to inhibit caffeine elimination. Caffeine elimination decreased by 30 percent in those patients that were not recovering alcoholics and by 24 percent in those patients that were recovering alcoholics. During disulfiram therapy, patients may need to limit their caffeine intake if nausea, nervousness, tremor, restlessness, palpitations, or insomnia complaints occur. Adverse events were not noted during this pharmacokinetic study; however, the decrease could be significant in some patients, including some patients with cardiovascular disease.
DOBUTamine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
DOPamine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Drospirenone; Ethinyl Estradiol: (Minor) Serum concentrations of caffeine may be increased during concurrent administration with ethinyl estradiol. Patients may desire to limit products that contain high amounts of caffeine in an effort to minimize caffeine-related side effects such as nausea or tremors.
Drospirenone; Ethinyl Estradiol; Levomefolate: (Minor) Serum concentrations of caffeine may be increased during concurrent administration with ethinyl estradiol. Patients may desire to limit products that contain high amounts of caffeine in an effort to minimize caffeine-related side effects such as nausea or tremors.
Echinacea: (Moderate) Echinacea may inhibit the metabolism of caffeine. Monitor patients for signs of increased caffeine serum concentrations if these drugs are coadministered until more data are available.
Enasidenib: (Major) Advise patients to avoid or minimize caffeine consumption during enasidenib treatment due to the risk for increased caffeine exposure which may increase the risk for caffeine-related adverse reactions, such as nervousness, irritability, insomnia, tachycardia, and tremor. Caffeine is a CYP1A2 substrate and enasidenib is a CYP1A2 inhibitor.
ePHEDrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.

ePHEDrine; guaiFENesin: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
EPINEPHrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Ergotamine; Caffeine: (Moderate) Certain foods that contain high amounts of caffeine or theobromine should be limited during the therapeutic use of caffeine in order to limit additive methylxanthine effects. While taking Caffeine-containing medicines, limit the use of foods, beverages (examples: coffee, tea, colas), herbs (examples: guarana, green tea) and other products that contain additional caffeine, such as chocolate and some non-prescription medications or dietary supplements for headache, insomnia, or weight loss. Too much Caffeine can cause effects like nausea, nervousness, or sleeplessness. Some drug products for adults that contain caffeine have about as much caffeine as a cup of coffee.
Erythromycin: (Moderate) Inhibitors of the hepatic CYP4501A2, such as erythromycin, may inhibit the hepatic oxidative metabolism of caffeine. No specific management is recommended except in patients who complain of caffeine related side effects. In such patients, the dosage of caffeine containing medications or the ingestion of caffeine containing products may need to be reduced.
Esketamine: (Moderate) Patients who regularly consume caffeine-containing foods or beverages may need to limit caffeine intake during esketamine treatment. Blood pressure should be closely monitored in patients treated with esketamine who regularly consume caffeine. Esketamine can increase blood pressure at all recommended doses and caffeine is a stimulant that may cause additive effects on blood pressure when combined with esketamine.
Estazolam: (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Estrogens (selected): (Moderate) Monitor for an increase in caffeine-related adverse reactions, including nervousness, irritability, insomnia, tachycardia, or tremor, if concomitant use of estrogens is necessary; lower caffeine doses may be required. Concomitant use may increase caffeine exposure; caffeine is a CYP1A2 substrate and estrogens are CYP1A2 inhibitors.
Eszopiclone: (Moderate) In general, patients taking medications for insomnia should not use caffeine-containing products including medications, dietary supplements (e.g., guarana), and beverages (e.g., coffee, green tea, other teas, or colas) prior to going to bed as these products, theoretically, may pharmacodynamically antagonize the sedative effects of eszopiclone.
Ethinyl Estradiol; Norelgestromin: (Minor) Serum concentrations of caffeine may be increased during concurrent administration with ethinyl estradiol. Patients may desire to

limit products that contain high amounts of caffeine in an effort to minimize caffeine-related side effects such as nausea or tremors.
Ethinyl Estradiol; Norethindrone Acetate: (Minor) Serum concentrations of caffeine may be increased during concurrent administration with ethinyl estradiol. Patients may desire to limit products that contain high amounts of caffeine in an effort to minimize caffeine-related side effects such as nausea or tremors.
Ethinyl Estradiol; Norgestrel: (Minor) Serum concentrations of caffeine may be increased during concurrent administration with ethinyl estradiol. Patients may desire to limit products that contain high amounts of caffeine in an effort to minimize caffeine-related side effects such as nausea or tremors.
Ethiodized Oil: (Major) Use of medications that lower the seizure threshold should be carefully evaluated when considering intrathecal radiopaque contrast agents. Caffeine and caffeine containing products should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours postprocedure.
Ethynodiol Diacetate; Ethinyl Estradiol: (Minor) Serum concentrations of caffeine may be increased during concurrent administration with ethinyl estradiol. Patients may desire to limit products that contain high amounts of caffeine in an effort to minimize caffeine-related side effects such as nausea or tremors.
Etonogestrel; Ethinyl Estradiol: (Minor) Serum concentrations of caffeine may be increased during concurrent administration with ethinyl estradiol. Patients may desire to limit products that contain high amounts of caffeine in an effort to minimize caffeine-related side effects such as nausea or tremors.
Fexofenadine; Pseudoephedrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Fluconazole: (Moderate) Fluconazole has been shown to inhibit the clearance of caffeine by 25 percent. The clinical significance of these interactions has not been determined.
Flurazepam: (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Fluticasone; Salmeterol: (Moderate) Caffeine may enhance the cardiac inotropic effects of beta-agonists.
Fluticasone; Umeclidinium; Vilanterol: (Moderate) Caffeine may enhance the cardiac inotropic effects of beta-agonists.
Fluticasone; Vilanterol: (Moderate) Caffeine may enhance the cardiac inotropic effects of beta-agonists.
fluvoxaMINE: (Moderate) Inhibitors of CYP1A2, such as fluvoxamine, may inhibit the hepatic oxidative metabolism of caffeine. No specific management is recommended except in patients who complain of caffeine-related side effects. In such patients, the dosage of caffeine-containing medications or the ingestion of caffeine-containing

products may need to be reduced.
Formoterol: (Moderate) Caffeine may enhance the cardiac inotropic effects of beta-agonists.
Formoterol; Mometasone: (Moderate) Caffeine may enhance the cardiac inotropic effects of beta-agonists.
Fosphenytoin: (Moderate) Higher caffeine doses may be needed after hydantoin administration; hydantoins increase caffeine elimination.
Givosiran: (Major) Avoid concomitant use of givosiran and caffeine due to the risk of increased caffeine-related adverse reactions. If use is necessary, consider decreasing the caffeine dose. Caffeine is a sensitive CYP1A2 substrate. Givosiran may moderately reduce hepatic CYP1A2 enzyme activity because of its pharmacological effects on the hepatic heme biosynthesis pathway.
Glycopyrrolate; Formoterol: (Moderate) Caffeine may enhance the cardiac inotropic effects of beta-agonists.
Grapefruit juice: (Minor) Data are limited and conflicting as to whether grapefruit juice significantly alters the serum concentrations and/or AUC of caffeine. Caffeine is primarily a CYP1A2 substrate, and grapefruit juice appears to have but a small effect on this enzyme in vivo. One report suggests that grapefruit juice decreases caffeine elimination by inhibition of flavin-containing monooxygenase, a P450 independent system. This interaction might increase caffeine levels and mildly potentiate the clinical effects and common side effects of caffeine. If side effects appear, patients may need to limit either caffeine or grapefruit juice intake.
Green Tea: (Major) Some green tea products contain caffeine. Additive CNS stimulant effects are likely to occur when caffeine is coadministered with green tea. Avoid this combination. (Moderate) Certain foods that contain high amounts of caffeine or theobromine should be limited during the therapeutic use of caffeine in order to limit additive methylxanthine effects. While taking Caffeine-containing medicines, limit the use of foods, beverages (examples: coffee, tea, colas), herbs (examples: guarana, green tea) and other products that contain additional caffeine, such as chocolate and some non-prescription medications or dietary supplements for headache, insomnia, or weight loss. Too much Caffeine can cause effects like nausea, nervousness, or sleeplessness. Some drug products for adults that contain caffeine have about as much caffeine as a cup of coffee.
guaiFENesin; Phenylephrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
guaiFENesin; Pseudoephedrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Hydantoins: (Moderate) Higher caffeine doses may be needed after hydantoin

administration; hydantoins increase caffeine elimination.
Hyoscyamine; Methenamine; Methylene Blue; Phenyl Salicylate; Sodium Biphosphate: (Major) Sodium phosphates should be used with caution in patients using concomitant medications that lower the seizure threshold like psychostimulants.
Ibritumomab Tiuxetan: (Major) Sodium phosphates should be used with caution in patients using concomitant medications that lower the seizure threshold like psychostimulants.
Ibuprofen; Pseudoephedrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Indacaterol; Glycopyrrolate: (Moderate) Caffeine may enhance the cardiac inotropic effects of beta-agonists.
Iodixanol: (Major) Use of medications that lower the seizure threshold should be carefully evaluated when considering intrathecal radiopaque contrast agents. Caffeine and caffeine containing products should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours postprocedure.
Iohexol: (Major) Use of medications that lower the seizure threshold should be carefully evaluated when considering intrathecal radiopaque contrast agents. Caffeine and caffeine containing products should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours postprocedure.
Iomeprol: (Major) Use of medications that lower the seizure threshold should be carefully evaluated when considering intrathecal radiopaque contrast agents. Caffeine and caffeine containing products should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours postprocedure.
Iopamidol: (Major) Use of medications that lower the seizure threshold should be carefully evaluated when considering intrathecal radiopaque contrast agents. Caffeine and caffeine containing products should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours postprocedure.
Iopromide: (Major) Use of medications that lower the seizure threshold should be carefully evaluated when considering intrathecal radiopaque contrast agents. Caffeine and caffeine containing products should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours postprocedure.
Ioversol: (Major) Use of medications that lower the seizure threshold should be carefully evaluated when considering intrathecal radiopaque contrast agents. Caffeine and caffeine containing products should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours postprocedure.
Ipratropium; Albuterol: (Moderate) Caffeine may enhance the cardiac inotropic effects of beta-agonists.
Isocarboxazid: (Major) Excessive use of caffeine in any form should be avoided in patients receiving Monoamine oxidase inhibitors (MAOIs). Limit caffeine intake during

MAOI use and for 1 to 2 weeks after discontinuation of any MAOI. The use of non-prescription medicines or dietary supplements containing caffeine should be avoided. Patients should try to avoid or limit the intake of all items containing caffeine such as tea, coffee, chocolate, and cola. Cardiac arrhythmias or severe hypertension may occur because of the potentiation of caffeine's sympathomimetic effects by MAOIs if caffeine intake is excessive.
Isoniazid, INH: (Moderate) Although isoniazid does not inhibit mitochondrial MAO, it does appear to inhibit plasma MAO. Dangerous cardiac arrhythmias or severe hypertension can occur because of the potentiation of caffeine's sympathomimetic effects by MAOIs. Caffeine use should be minimized or avoided during and for 1 to 2 weeks after discontinuation of any MAOI.
Isosulfan Blue: (Major) Use of medications that lower the seizure threshold should be carefully evaluated when considering intrathecal radiopaque contrast agents. Caffeine and caffeine containing products should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours postprocedure.
Ketoconazole: (Minor) Ketoconazole has been shown to inhibit the clearance of caffeine by 11 percent. The clinical significance of this interaction has not been determined.
Levalbuterol: (Moderate) Caffeine may enhance the cardiac inotropic effects of beta-agonists.
Levoketoconazole: (Minor) Ketoconazole has been shown to inhibit the clearance of caffeine by 11 percent. The clinical significance of this interaction has not been determined.
Levonorgestrel; Ethinyl Estradiol: (Minor) Serum concentrations of caffeine may be increased during concurrent administration with ethinyl estradiol. Patients may desire to limit products that contain high amounts of caffeine in an effort to minimize caffeine-related side effects such as nausea or tremors.
Levonorgestrel; Ethinyl Estradiol; Ferrous Bisglycinate: (Minor) Serum concentrations of caffeine may be increased during concurrent administration with ethinyl estradiol. Patients may desire to limit products that contain high amounts of caffeine in an effort to minimize caffeine-related side effects such as nausea or tremors.
Levonorgestrel; Ethinyl Estradiol; Ferrous Fumarate: (Minor) Serum concentrations of caffeine may be increased during concurrent administration with ethinyl estradiol. Patients may desire to limit products that contain high amounts of caffeine in an effort to minimize caffeine-related side effects such as nausea or tremors.
Lidocaine; EPINEPHrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Linezolid: (Moderate) Linezolid is an antibiotic that is also a reversible, non-selective inhibitor of MAO. Dangerous cardiac arrhythmias or severe hypertension can occur because of the potentiation of caffeine's sympathomimetic effects by MAOIs. Caffeine

use should be minimized or avoided during and for 1 to 2 weeks after discontinuation of any MAOI.
Lisdexamfetamine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants. Patients may need to reduce, limit, or avoid caffeine intake. Excessive caffeine ingestion (via medicines, supplements or beverages including coffee, green tea, other teas, guarana, colas) may contribute to side effects like nervousness, irritability, insomnia, or tremor.
Lithium: (Major) Caffeine appears to reduce serum lithium concentrations. In 11 coffee-drinking patients stabilized on lithium, serum lithium concentrations increased during 2 weeks when coffee was withheld and fell when coffee was resumed. Lithium ADRs have also been noted to increase simultaneously with a reduction in caffeine intake. Patients taking lithium should be counseled regarding their intake of caffeine. Clinicians should note, however, that coffee, not pure caffeine, was the variable in this study. Other beverages that contain significant amounts of caffeine include green tea, other teas, and cola. Because guarana contains a substantial caffeine content, this herb should be avoided in patients taking lithium.
Loratadine; Pseudoephedrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
LORazepam: (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Metaproterenol: (Moderate) Caffeine may enhance the cardiac inotropic effects of beta-agonists.
Methamphetamine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants. Patients may need to reduce, limit, or avoid caffeine intake. Excessive caffeine ingestion (via medicines, supplements or beverages including coffee, green tea, other teas, guarana, colas) may contribute to side effects like nervousness, irritability, insomnia, or tremor.
Methenamine; Sodium Acid Phosphate; Methylene Blue; Hyoscyamine: (Major) Sodium phosphates should be used with caution in patients using concomitant medications that lower the seizure threshold like psychostimulants.
Methohexital: (Moderate) Caffeine has been reported to increase the metabolism of barbiturates, and barbiturates increase caffeine elimination. Higher caffeine doses may be needed after barbiturate administration.
Methylphenidate Derivatives: (Moderate) Caffeine is a CNS stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants. Avoid excessive caffeine intake during use of methylphenidate or its derivatives. Excessive caffeine ingestion (via medicines, foods like chocolate, dietary supplements, or beverages including coffee, green tea, other teas, colas) may contribute

to side effects like nervousness, irritability, nausea, insomnia, or tremor. Patients should avoid medications and dietary supplements which contain high amounts of caffeine.
Methylphenidate: (Moderate) Caffeine is a CNS stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants. Avoid excessive caffeine intake during use of methylphenidate derivatives. Excessive caffeine ingestion (via medicines, foods like chocolate, dietary supplements, or beverages including coffee, green tea, other teas, colas) may contribute to side effects like nervousness, irritability, nausea, insomnia, or tremor. Patients should avoid medications and dietary supplements which contain high amounts of caffeine.
Midazolam: (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Midodrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
migALAstat: (Moderate) Advise patients to avoid consuming caffeine at least 2 hours before or after taking migalastat to give a minimum 4 hour fast. Simultaneous use may decrease migalastat exposure and efficacy. Coadministration of 190 mg caffeine reduced the mean migalastat AUC by 55%.
Modafinil: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Monoamine oxidase inhibitors: (Major) Excessive use of caffeine in any form should be avoided in patients receiving Monoamine oxidase inhibitors (MAOIs). Limit caffeine intake during MAOI use and for 1 to 2 weeks after discontinuation of any MAOI. The use of non-prescription medicines or dietary supplements containing caffeine should be avoided. Patients should try to avoid or limit the intake of all items containing caffeine such as tea, coffee, chocolate, and cola. Cardiac arrhythmias or severe hypertension may occur because of the potentiation of caffeine's sympathomimetic effects by MAOIs if caffeine intake is excessive.
Naproxen; Pseudoephedrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Non-Ionic Contrast Media: (Major) Use of medications that lower the seizure threshold should be carefully evaluated when considering intrathecal radiopaque contrast agents. Caffeine and caffeine containing products should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours post-procedure.
Norepinephrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Norethindrone Acetate; Ethinyl Estradiol; Ferrous fumarate: (Minor) Serum concentrations of caffeine may be increased during concurrent administration with ethinyl estradiol. Patients may desire to limit products that contain high amounts of

caffeine in an effort to minimize caffeine-related side effects such as nausea or tremors.
Norethindrone; Ethinyl Estradiol: (Minor) Serum concentrations of caffeine may be increased during concurrent administration with ethinyl estradiol. Patients may desire to limit products that contain high amounts of caffeine in an effort to minimize caffeine-related side effects such as nausea or tremors.
Norethindrone; Ethinyl Estradiol; Ferrous fumarate: (Minor) Serum concentrations of caffeine may be increased during concurrent administration with ethinyl estradiol. Patients may desire to limit products that contain high amounts of caffeine in an effort to minimize caffeine-related side effects such as nausea or tremors.
Norgestimate; Ethinyl Estradiol: (Minor) Serum concentrations of caffeine may be increased during concurrent administration with ethinyl estradiol. Patients may desire to limit products that contain high amounts of caffeine in an effort to minimize caffeine-related side effects such as nausea or tremors.
Obeticholic Acid: (Moderate) Obeticholic acid may increase the exposure to concomitant drugs that are CYP1A2 substrates, such as caffeine. Concomitant administration of 200 mg caffeine as a single dose with obeticholic acid 10 mg once daily resulted in a 42% increase in caffeine AUC and a 6% increase in caffeine Cmax. Therapeutic monitoring is recommended with coadministration. No specific management is recommended except in patients who complain of caffeine-related side effects like nausea, tremor, or palpitations. In such patients, the dosage of caffeine-containing medications or the ingestion of caffeine-containing products may need to be reduced.
Olodaterol: (Moderate) Caffeine may enhance the cardiac inotropic effects of beta-agonists.
Oxazepam: (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
oxyBUTYnin: (Minor) Consuming greater than 400 mg/day caffeine has been associated with the development of urinary incontinence. Caffeine may aggravate bladder symptoms and counteract the effectiveness of drugs used to treat overactive bladder such as oxybutynin.
Oxymetazoline: (Moderate) Caffeine is a CNS stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants. Caffeine should be avoided or used cautiously with oxymetazoline.
PENTobarbital: (Moderate) Caffeine has been reported to increase the metabolism of barbiturates, and barbiturates increase caffeine elimination. Higher caffeine doses may be needed after barbiturate administration.
Phendimetrazine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Phenelzine: (Major) Excessive use of caffeine in any form should be avoided in patients receiving Monoamine oxidase inhibitors (MAOIs). Limit caffeine intake during MAOI use

and for 1 to 2 weeks after discontinuation of any MAOI. The use of non-prescription medicines or dietary supplements containing caffeine should be avoided. Patients should try to avoid or limit the intake of all items containing caffeine such as tea, coffee, chocolate, and cola. Cardiac arrhythmias or severe hypertension may occur because of the potentiation of caffeine's sympathomimetic effects by MAOIs if caffeine intake is excessive.
PHENobarbital: (Moderate) Caffeine has been reported to increase the metabolism of barbiturates, and barbiturates increase caffeine elimination. Higher caffeine doses may be needed after barbiturate administration.
PHENobarbital; Hyoscyamine; Atropine; Scopolamine: (Moderate) Caffeine has been reported to increase the metabolism of barbiturates, and barbiturates increase caffeine elimination. Higher caffeine doses may be needed after barbiturate administration.
Phentermine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Phentermine; Topiramate: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Phenylephrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Phenytoin: (Moderate) Higher caffeine doses may be needed after hydantoin administration; hydantoins increase caffeine elimination.
Potassium Phosphate; Sodium Phosphate: (Major) Sodium phosphates should be used with caution in patients using concomitant medications that lower the seizure threshold like psychostimulants.
Prilocaine; EPINEPHrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Primidone: (Moderate) Caffeine has been reported to increase the metabolism of barbiturates, and barbiturates increase caffeine elimination. Higher caffeine doses may be needed after barbiturate administration.
Procarbazine: (Major) Ingestion of certain products should be minimized while receiving procarbazine therapy, as the drug has some MAO inhibiting actions. Caffeine may produce hypertension or hypertensive crisis or induce cardiac arrhythmias if administered to patients taking drugs with strong MAOI properties. All preparations containing caffeine should be used sparingly such as teas, coffee, chocolate, cola, guarana, or 'stay awake' products. Some non-prescription medicines also contain caffeine and should not be taken without health care professional advice. Following discontinuation of procarbazine, dietary restrictions should continue for at least 2 weeks due to the slow recovery from the enzyme-inhibiting effects.
Promethazine; Phenylephrine: (Moderate) Caffeine is a CNS-stimulant and such actions

are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Pseudoephedrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Pseudoephedrine; Triprolidine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants.
Quazepam: (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Racepinephrine: (Moderate) Patients who are using racepinephrine inhalation are advised to avoid foods and beverages that contain caffeine. They should also avoid dietary supplements containing ingredients, such as caffeine, that are reported or claimed to have a stimulant effect. If a patient is taking prescribed medications containing caffeine, then they should seek health care professional advice prior to the use of racepinephrine. Additive adverse effects on the cardiovascular and nervous system are possible, some which may be undesirable. Side effects such as nausea, tremor, nervousness, difficulty with sleep, and increased heart rate may be additive. Consider alternatives to racepinephrine for the treatment of asthma.
Regadenoson: (Major) Regadenoson may cause an increased coronary blood flow without regard to prior caffeine ingestion. Patients should avoid consumption of any products containing caffeine (including caffeine from foods and beverages such as coffee, green tea, other teas, colas, and chocolate) for at least 12 hours before regadenoson administration.
Remimazolam: (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Rucaparib: (Moderate) Monitor for an increase in caffeine-related adverse reactions if coadministration with rucaparib is necessary. Some patients may need to reduce or limit their caffeine intake. Caffeine is a sensitive CYP1A2 substrate and rucaparib is a weak CYP1A2 inhibitor. Concomitant use increased the AUC of caffeine by 2.55-fold.
Salmeterol: (Moderate) Caffeine may enhance the cardiac inotropic effects of beta-agonists.
Secobarbital: (Moderate) Caffeine has been reported to increase the metabolism of barbiturates, and barbiturates increase caffeine elimination. Higher caffeine doses may be needed after barbiturate administration.
Segesterone Acetate; Ethinyl Estradiol: (Minor) Serum concentrations of caffeine may be increased during concurrent administration with ethinyl estradiol. Patients may desire to limit products that contain high amounts of caffeine in an effort to minimize caffeine-related side effects such as nausea or tremors.

Serdexmethylphenidate; Dexmethylphenidate: (Moderate) Caffeine is a CNS stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants. Avoid excessive caffeine intake during use of methylphenidate derivatives. Excessive caffeine ingestion (via medicines, foods like chocolate, dietary supplements, or beverages including coffee, green tea, other teas, colas) may contribute to side effects like nervousness, irritability, nausea, insomnia, or tremor. Patients should avoid medications and dietary supplements which contain high amounts of caffeine.
Sodium Oxybate: (Moderate) Caffeine should be avoided or used cautiously with oxybates. Monitor for potential side effects such as nervousness, irritability, insomnia, and/or cardiac arrhythmias.
Sodium Phosphate Monobasic Monohydrate; Sodium Phosphate Dibasic Anhydrous: (Major) Sodium phosphates should be used with caution in patients using concomitant medications that lower the seizure threshold like psychostimulants.
Solifenacin: (Minor) Beverages containing caffeine may aggravate bladder symptoms and counteract the effectiveness of solifenacin to some degree. Patients may wish to limit their intake of caffeinated drugs, dietary supplements, or beverages.
Solriamfetol: (Moderate) Patients who regularly consume caffeine-containing foods or beverages may need to limit caffeine intake during solriamfetol treatment. Blood pressure and heart rate should be closely monitored in patients treated with solriamfetol who regularly consume caffeine. Solriamfetol can increase blood pressure and heart rate; caffeine is a stimulant that may cause additive effects on blood pressure or heart rate when combined with solriamfetol.
Temazepam: (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Terbinafine: (Minor) Terbinafine has been shown to inhibit the clearance of caffeine. The clinical significance of this interaction has not been determined.
Terbutaline: (Moderate) Caffeine may enhance the cardiac inotropic effects of beta-agonists.
Theophylline, Aminophylline: (Major) Caffeine is a CNS stimulant. The concurrent administration of caffeine to patients taking aminophyllinemay produce excessive caffeine-like side effects, such as nausea, irritability or nervousness. Adverse effects such as tremors, insomnia, seizures, or cardiac arrhythmias are also possible when excessive dosages of caffeine are taken concurrently. Patients should avoid medications containing caffeine when possible. Patients may also need to limit their intake of caffeine-containing beverages or foods (e.g., coffee, green tea, other teas, colas, or chocolate) to avoid caffeine-like side effects. (Moderate) Caffeine is a CNS stimulant. The concurrent administration of caffeine to patients taking theophylline may produce excessive caffeine-like side effects, such as nausea, irritability or nervousness. Adverse

effects such as tremors, insomnia, seizures, or cardiac arrhythmias are also possible when excessive dosages of caffeine are taken concurrently with theophylline. Patients taking theophylline should avoid medications containing caffeine when possible. Patients may also need to limit their intake of caffeine-containing beverages or foods (e.g., coffee, green tea, other teas, colas, or chocolate) to avoid caffeine-like side effects.
Tiotropium; Olodaterol: (Moderate) Caffeine may enhance the cardiac inotropic effects of beta-agonists.
Tobacco: (Major) Advise patients who are taking caffeine to avoid smoking tobacco. Smoking tobacco has been observed to increase caffeine clearance by 50% to 70%. Caffeine is a CYP1A2 substrate and smoking tobacco induces CYP1A2.
Tolterodine: (Minor) Beverages containing caffeine may aggravate bladder symptoms and counteract the effectiveness of tolterodine to some degree. Patients may wish to limit their intake of caffeinated drugs, dietary supplements, or beverages.
Trandolapril; Verapamil: (Minor) Verapamil reduces the clearance of caffeine and increases serum caffeine concentrations, presumably via inhibition of hepatic metabolism. During concomitant therapy with verapamil, it may be prudent to advise patients to limit or minimize the intake of caffeinated products to minimize caffeine-related side effects.
Tranylcypromine: (Major) Excessive use of caffeine in any form should be avoided in patients receiving Monoamine oxidase inhibitors (MAOIs). Limit caffeine intake during MAOI use and for 1 to 2 weeks after discontinuation of any MAOI. The use of non-prescription medicines or dietary supplements containing caffeine should be avoided. Patients should try to avoid or limit the intake of all items containing caffeine such as tea, coffee, chocolate, and cola. Cardiac arrhythmias or severe hypertension may occur because of the potentiation of caffeine's sympathomimetic effects by MAOIs if caffeine intake is excessive.
Triazolam: (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Trospium: (Minor) Consuming > 400 mg/day caffeine has been associated with the development of urinary incontinence. Caffeine may aggravate bladder symptoms and counteract the effectiveness of drugs used to treat overactive bladder, like trospium, to some degree. Patients with overactive bladder may wish to limit their intake of caffeine including caffeine from drugs, dietary supplements (i.e., guarana), beverages (i.e., teas, coffee, colas), or foods (i.e., chocolate).
Umeclidinium; Vilanterol: (Moderate) Caffeine may enhance the cardiac inotropic effects of beta-agonists.
Vemurafenib: (Minor) Coadministration of vemurafenib and caffeine increased the caffeine AUC by 2.6-fold. Vemurafenib is a CYP1A2 inhibitor and caffeine is a CYP1A2 substrate. The manufacturer of vemurafenib suggests that concomitant use with agents

with narrow therapeutic windows that are metabolized by CYP1A2 is not recommended. Theophylline (or aminophylline), another methylxanthine, is also primarily a CYP1A2 substrate with a narrow therapeutic index. If coadministration cannot be avoided, the manufacturer recommends considering a dose reduction of the concomitant drug; it may also be prudent to monitor for signs and symptoms of theophylline toxicity during coadministration. Some patients may need to reduce intake of caffeine from non-drug sources (e.g., beverages) during treatment to avoid caffeine-related side effects.
Verapamil: (Minor) Verapamil reduces the clearance of caffeine and increases serum caffeine concentrations, presumably via inhibition of hepatic metabolism. During concomitant therapy with verapamil, it may be prudent to advise patients to limit or minimize the intake of caffeinated products to minimize caffeine-related side effects.
vinCRIStine Liposomal: (Major) Sodium phosphates should be used with caution in patients using concomitant medications that lower the seizure threshold like psychostimulants.
Xanomeline; Trospium: (Minor) Consuming > 400 mg/day caffeine has been associated with the development of urinary incontinence. Caffeine may aggravate bladder symptoms and counteract the effectiveness of drugs used to treat overactive bladder, like trospium, to some degree. Patients with overactive bladder may wish to limit their intake of caffeine including caffeine from drugs, dietary supplements (i.e., guarana), beverages (i.e., teas, coffee, colas), or foods (i.e., chocolate).
Zileuton: (Moderate) Inhibitors of CYP1A2, such as zileuton, may inhibit the hepatic oxidative metabolism of caffeine. No specific management is recommended except in patients who complain of caffeine-related side effects like nausea, tremor, or palpitations. In such patients, the dosage of caffeine-containing medications or the ingestion of caffeine-containing products may need to be reduced.
Zolpidem: (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking medications for sleep, such as zolpidem should avoid caffeine-containing medications, dietary supplements, foods, and beverages within the hours close to bedtime. Patients should be encouraged to avoid excessive total daily caffeine intake, as part of proper sleep hygiene, since caffeine intake can interfere with proper sleep. However, in healthy subjects (without insomnia) in a pharmacokinetic study, coadministration of caffeine at a dosage of 150 to 300 mg with zolpidem did not counteract the sedative effects of a single 10 mg dose of zolpidem.

Adverse Reaction

diarrhea, dyspepsia, enterocolitis, gastritis, gastroesophageal reflux, GI bleeding, nausea, vomiting

Caffeine has been noted to produce a variety of gastrointestinal (GI) effects. At

therapeutic or nontoxic doses, caffeine can stimulate gastric secretions and may cause GI upset (dyspepsia), nausea, loose stools, and may aggravate gastroesophageal reflux disease (GERD). Occasionally diarrhea is reported. The mild dehydration that caffeine produces may aggravate constipation. A temporary reduction in weight gain has also been reported. In a study comparing caffeine to placebo, the mean difference in weight gain was the greatest after 2 weeks of therapy. Feeding intolerance (8.7%), gastritis (2.2%), and GI bleeding (2.2%) also occurred in the caffeine treatment groups. During a controlled clinical trial of caffeine citrate in premature infants (n = 85 neonates), necrotizing enterocolitis was reported in 6 patients, 5 of whom were administered caffeine. Three of the infants died. The incidence was 4.3% in caffeine-treatment groups vs. 2.6% of placebo-treated infants. In a much larger clinical trial (n = 2,000 neonates) evaluating the use of caffeine citrate in apnea of prematurity, necrotizing enterocolitis was not more common in caffeine treated patients compared to placebo. In a study evaluating the effect of caffeine on the splanchnic perfusion after a caffeine loading dose, the blood flow velocity was depressed for 2 to 3 hours after the infusion and slowly returned to baseline after approximately 6 hours. Clinicians should be alert for signs and symptoms of gastric distress, abdominal bloating, nausea, vomiting, bloody stools, and lethargy in treated infants. Excessive caffeine intake or intoxication in children, adolescents, and adults may cause vomiting along with other signs of caffeine intoxication. In humans, a caffeine concentration of greater than 50 mg/L may produce toxic symptoms.

anxiety, headache, insomnia, intracranial bleeding, irritability, seizures, tremor

Caffeine is a CNS stimulant. Many adverse reactions to caffeine are an extension of caffeine's pharmacologic actions. At therapeutic or nontoxic doses, caffeine can commonly cause nervousness, mild tremor, and heightened attentiveness. Less frequent adverse reactions with usual consumption also include excitement, irritability, insomnia, headache, and muscle twitches. Increased caffeine use among children and adolescents has been associated with insomnia, chronic headache, motor tics, irritability, learning difficulties, and other adverse health effects. After excessive doses, caffeine can cause considerable anxiety. Seizures and delirium are also possible. In humans, a caffeine level of > 50 mg/L may produce toxic symptoms. Other neurologic events have been reported in preterm neonates. In clinical trials of caffeine citrate in preterm neonates, cerebral hemorrhage (intracranial bleeding) was reported in 2.2% of treated patients versus 0% of neonates receiving placebo.

hypercalciuria, increased urinary frequency, polyuria

Caffeine is a mild diuretic and patients may have increased urinary frequency. Polyuria

can occur. Increased creatinine clearance and increased urinary calcium (hypercalciuria) and sodium excretion are reported in the literature.

hyperglycemia, hypoglycemia

Adverse events to caffeine that have been described in the published literature include alterations in serum glucose such as hypoglycemia and hyperglycemia.

dyspnea, pulmonary edema, rash (unspecified), renal failure (unspecified), tachypnea, xerosis

In controlled clinical trials of caffeine citrate injection in premature neonates, the following adverse events occurred more commonly in caffeine-treatment groups than with placebo: accidental injury (2.2%), bleeding (2.2%), disseminated intravascular coagulation (2.2%), dyspnea (2.2%), pulmonary edema (2.2%), metabolic acidosis (2.2%), xerosis (2.2%), rash (unspecified) (8.7%), renal failure (unspecified) (2.2%), retinopathy of prematurity (2.2%), and skin breakdown (2.2%). In neonates, intolerance or overdose of caffeine may manifest as tachypnea. No deaths have been reported in relation to overdose of caffeine in neonates.

palpitations, sinus tachycardia

Too much caffeine may occasionally cause rapid heartbeat. Cardiovascular effects of caffeine have been reported in the literature (i.e., palpitations, sinus tachycardia, increased left ventricular output, and increased stroke volume).

spermatogenesis inhibition

High caffeine intake has been reported to negatively affect sperm quality, including spermatogenesis inhibition). The propensity for caffeine to negatively affect fertility is controversial. Although controversial, infertility, as manifested by increased difficulty in getting pregnant, has been reported in females. Couples who are pursuing pregnancy should probably limit excessive intake of caffeine.

withdrawal

A distinct caffeine withdrawal syndrome has been described. Patients who consume or receive caffeine daily for several weeks experience notable physical and psychiatric responses including lethargy, anxiety, dizziness, or rebound headache upon caffeine withdrawal.

Description

Caffeine is a naturally occurring xanthine derivative used as a CNS and respiratory stimulant, or as a mild diuretic. Other xanthine derivatives include the bronchodilator theophylline and theobromine, a compound found in cocoa and chocolate. Caffeine is found in many beverages and soft drinks. Caffeine is often combined with analgesics or with ergot alkaloids for the treatment of migraine and other types of headache. Caffeine is also sold without a prescription in products marketed to treat drowsiness, or in products for mild water-weight gain. Clinically, it is used both orally and parenterally as a respiratory stimulant in neonates with apnea of prematurity. Caffeine reduces the frequency of apneic episodes by 30% to 50% within 24 hours of administration. Additionally, studies have found that caffeine reduces the risk of bronchopulmonary dysplasia, PDA, and decreases the need for reintubation. Caffeine is preferred over theophylline in neonates due to the ease of once per day administration, reliable oral absorption, more predictable plasma concentrations, and a wide therapeutic window.

Mechanism Of Action

Caffeine is a mild, direct stimulant at all levels of the CNS and also stimulates the heart and cardiovascular system. The related xanthine, theophylline, shares these properties and is widely used in the treatment of pulmonary disease. Both caffeine and theophylline are CNS stimulants, with theophylline exerting more dramatic effects than caffeine at higher concentrations. Caffeine also stimulates the medullary respiratory center and relaxes bronchial smooth muscle. Caffeine stimulates voluntary muscle and gastric acid secretion, increases renal blood flow, and is a mild diuretic.

While the clinical responses to caffeine are well known, the cellular mechanism of action is uncertain. Several theories have been proposed. At high concentrations, caffeine interferes with the uptake and storage of calcium by sarcoplasmic reticulum of striated muscle. While this action would explain the effects of caffeine on cardiac and skeletal muscle, it does not appear to occur at clinically achievable concentrations. Inhibition of phosphodiesterases (and subsequent accumulation of cyclic nucleotides) also does not appear to occur at clinically achievable concentrations.

It is believed that xanthines act as adenosine-receptor antagonists. Adenosine acts as an autocoid, and virtually every cell contains adenosine receptors within the plasma membrane. Adenosine exerts complex actions. It inhibits the release of neurotransmitters from presynaptic sites but works in concert with norepinephrine or

angiotensin to augment their actions. Antagonism of adenosine receptors by caffeine would appear to promote neurotransmitter release, thus explaining the stimulatory effects of caffeine. A distinct syndrome has been associated with caffeine withdrawal. It is possible that the manifestations of caffeine withdrawal may be secondary to catecholamine or neurotransmitter depletion.

The following mechanisms of action are hypothesized for caffeine's action in apnea of prematurity: 1) stimulation of the respiratory center, 2) increased minute ventilation, 3) decreased threshold to hypercapnia, 4) increased response to hypercapnia, 5) increased skeletal muscle tone, 6) decreased diaphragmatic fatigue, 7) increased metabolic rate, and 8) increased oxygen consumption. All of these actions are thought to be related to adenosine receptor antagonism.

Pharmacokinetics

Caffeine is administered orally and intravenously. Therapeutic concentrations have been reported to be 5 to 25 mg/L in adults. Caffeine is rapidly distributed to all body tissues and readily crosses the blood-brain barrier. It also distributes into breast milk. Caffeine is roughly 36% bound to plasma proteins, the volume of distribution is 630 mL/kg, and the clearance is 90 mL/hour/kg. Caffeine is partially metabolized in the liver via demethylation reactions dependent on the CYP-450 1A2 isoenzyme; major metabolites include paraxanthine (80%), theobromine (10%), and theophylline (4%). The plasma half-life is 3 to 7 hours in adults.

Affected cytochrome P450 isoenzymes: CYP1A2
Caffeine is a substrate of the hepatic cytochrome isoenzyme CYP1A2.

Route-Specific Pharmacokinetics

- **Oral Route**

Caffeine and citrated caffeine are well absorbed from the GI tract. Following oral administration, peak plasma concentrations in adults are reached within 50—75 minutes. In neonates, the oral administration of caffeine results in peak concentrations in 0.5—2 hours; formula feedings do not affect the time to maximum concentrations after oral dosing.

- **Hepatic Impairment**

The pharmacokinetics of caffeine have not been studied in neonates with impaired hepatic function. Caffeine elimination is more dependent on renal clearance in premature neonates and neonates than in older infants or adults due to underdeveloped hepatic metabolism. However, if hepatic impairment is present,

caffeine elimination may be reduced, and the manufacturer recommends monitoring serum concentrations and adjusting dosages accordingly to avoid toxicity.

- **Renal Impairment**

The pharmacokinetics of caffeine have not been studied in neonates with impaired renal function; however, caffeine elimination is more dependent on renal clearance in premature neonates and neonates than in older infants or adults due to underdeveloped hepatic metabolism. If renal impairment is present, caffeine elimination may be reduced, and the manufacturer recommends monitoring serum concentrations and adjusting dosages accordingly to avoid toxicity.

- **Pediatrics**

Infants and Children

The mean volume of distribution of caffeine in infants (0.8 to 0.9 L/kg) is slightly higher than that in adults (0.6 L/kg). Young infants have a plasma half-life of caffeine of 3 to 4 days. By 9 months of age post-term, the plasma half-life (5 hours) approximates that of adults. During the first 3 months, unchanged caffeine is predominantly excreted in the urine, but the percentage gradually decreases to the adult value of less than 2% in infants 7 to 9 months of age. Additionally, the partially demethylated xanthines and urates found in adults are attained by 7 to 9 months of age. Cytochrome P450 (CYP) metabolism of caffeine is inhibited in neonates and infants who are breast-fed; formula feeding does not appear to affect the pharmacokinetics of caffeine in neonates and infants.

Neonates

Plasma half-life for neonates may vary widely, from 52 to 100 hours, decreasing with increasing gestational age and postnatal age. Caffeine metabolism in neonates is limited due to their immature hepatic enzyme systems, therefore the large majority of the drug is cleared by the kidneys. Unchanged caffeine and its metabolites are excreted in the urine. The fraction of caffeine excreted unchanged in the urine, from term neonates up to 1 month old, is roughly 86%. Studies have found that gestational age, postnatal age, and patient weight are all determinants in the maturation of caffeine metabolism.

Premature Neonates

In premature neonates, a half-life of 52 to 144 hours has been reported. In two studies including 199 extremely premature neonates, the average half-life was 101 hours (mean gestational age 27.5 weeks, average postnatal age 12 days) and 144 hours (mean gestational age 28.2 weeks, average postnatal age 4 days). In a study with 17 premature neonates (mean gestational age 29.7 weeks, average postnatal age 20.7 days), the average half-life was 52.03 hours. In these studies, the volume of distribution (Vd) ranged from 780 to 970 mL/kg and the clearance was 4.9 to 6.96 mL/hour/kg. As expected, the Vd decreased and the clearance increased with rising postnatal age.

Caffeine metabolism in premature neonates is limited due to their immature hepatic enzyme systems. In this population, it is interesting to note that interconversion from theophylline to caffeine has been noted. After theophylline administration, caffeine concentrations are approximately 25% of theophylline concentrations and 3% to 8% of caffeine would be expected to convert to theophylline. Caffeine concentrations in the cerebrospinal fluid of premature neonates are approximately the same as plasma concentrations.

Administration

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

Oral Administration

Do not take at bedtime.

Oral Solid Formulations

Tablets: Caffeine tablets may be crushed.

Oral Liquid Formulations

Oral solution (Cafcit): In infants, the solution may be administered concomitantly with formula feedings. Use a calibrated oral syringe to measure dose. Alternatively, the available intravenous injection may be administered by the oral route (Cafcit).
Storage of Cafcit oral solution: Once oral solution vial is opened, use immediately and discard the unused portion, it is preservative-free.

Other Oral Formulations

Powder: Stir into water or other liquid or place on the tongue and follow with liquid.

Extemporaneous Compounding-Oral

Extemporaneous compounding instructions for citrated caffeine oral solution (20 mg/mL caffeine citrate; 10 mg/mL anhydrous caffeine base):
NOTE: The extemporaneous preparation of caffeine is not approved by the FDA.
Dissolve 10 grams of citrated caffeine powder (purified) in 250 mL of Sterile Water for Irrigation, USP. Stir the mixture until completely clear. Add a flavoring agent (simple syrup and cherry syrup in a 2:1 ratio) to the solution to increase the volume to 500 mL. The resulting enteral solution contains the equivalent of 20 mg/mL of caffeine citrate (10

mg/mL of anhydrous caffeine base) and is stable for 3 months when protected from light and stored at room temperature or under refrigeration.

Injectable Administration

Visually inspect parenteral products for particulate matter and discoloration prior to administration whenever solution and container permit.

Intravenous Administration

Intravenous injection:
Using a syringe infusion pump, administer caffeine citrate dose slowly over 10 minutes into a vein or into the tubing of a freely-flowing compatible IV solution. Compatible IV solutions for Cafcit include: Dextrose 5%, Dextrose 50%, Aminosyn 8.5% solution, and Intralipid 20% emulsion.
Administer daily IV dose at the same time each day (every 24 hours).
Storage of Cafcit injection: Once vial is opened, use immediately and discard the unused portion, it is preservative-free.

Extemporaneous Compounding-Injectable

Compounding Instructions for preservative-free citrated caffeine injection:
NOTE: The extemporaneous preparation of caffeine is not approved by the FDA.
Perform all intravenous compounding operations using aseptic techniques.
Dissolve 10 grams of citrated caffeine powder (purified) in 250 mL of Sterile Water for Injection, USP. Transfer to a 500-mL sterile empty evacuated container (EEC) and fill to the 500-mL mark with Sterile Water for Injection, USP. Filter through a 0.22-micron filter into another 500-mL sterile EEC. Transfer injectable solution to 2-mL or 10-mL sterile glass vials and autoclave at 121 degrees C for 15 minutes and allow to cool. The resulting parenteral solution contains the equivalent of 20 mg/mL of caffeine citrate (10 mg/mL of anhydrous caffeine base) and is stable for 3 months at room temperature or under refrigeration. Each vial prepared is for single-use only. Once vial is opened, use immediately and discard the unused portion, it is preservative-free. Protect from light. Quality assurance testing for sterility and caffeine concentration is recommended when preparing compounded products for parenteral administration; each batch should be quarantined until testing is complete.

Maximum Dosage Limits

- **Adults**
  1200 mg/day PO has been suggested.
- **Geriatric**
  1200 mg/day PO has been suggested.

- **Adolescents**
  1200 mg/day PO has been suggested.
- **Children**
  < 12 years: Maximum dosage information is not available.
  12 years: 1200 mg/day PO has been suggested.
- **Infants**
  Caffeine base 2.5—5 mg/kg/day PO or IV for maintenance dosage.
- **Neonates**
  Caffeine base 2.5—5 mg/kg/day PO or IV for maintenance dosage.

Dosage Forms

- Cafcit 60mg/3ml Solution for Injection
- Caffeine 125mg/1mL, Sodium Benzoate 125mg/1mL Solution for injection
- Caffeine Bulk powder
- Caffeine Citrate 20mg/1mL Oral solution
- Caffeine Citrate 20mg/1mL Solution for injection
- Caffeine Citrate Bulk powder
- CVS Caffeine 200mg Tablet
- CVS Caffeine Maximum Strength 200mg Caplet
- CVS Super Green Tea Extract 250mg Softgel
- Equaline Stay Awake Maximum Strength 200mg Tablet
- Equate Stay Awake 200mg Tablet
- Foster & Thrive Stay Awake 200mg Tablet
- GNP Alert Aid 200mg Tablet
- GNP Stay Awake 200mg Tablet
- GoodSense Stay Awake 200mg Tablet
- GoodSense Stay Awake 200mg Tablet
- GoodSense Stay Awake Maximum Strength 200mg Tablet
- Leader Alertness Aid Maximum Strength 200mg Tablet
- Leader Caffeine 200mg Tablet
- NoDoz Maximum Strength 200mg Caplet
- Premier Value Alertness Aid 200mg Tablet
- Quality Choice Stay Awake 200mg Tablet
- RITE AID Stay Alert 200mg Tablet
- RITE AID Stay Awake Maximum Strength 200mg Caplet
- Today's Health Stay Awake Maximum Strength 200mg Tablet
- Top Care Stay Awake Maximum Strength 200mg Tablet
- Vivarin 200mg Tablet

- Walgreens Awake Maximum Strength 200mg Caplet
- Walgreens Awake Maxium Strength 200mg Caplet
- Walgreens Stay Awake 200mg Tablet

Dosage Adjustment Guidelines

Hepatic Impairment

Specific guidelines for dosage adjustments in hepatic impairment in adults are not available. In premature infants and neonates, caffeine metabolism is limited due to immature hepatic enzyme systems; dosage adjustments may be needed in neonates with impaired hepatic function and should be guided by clinical response and serum caffeine levels.

Renal Impairment

Specific guidelines for dosage adjustments in renal impairment are not available. Premature infants and neonates are more dependent on renal function for proper caffeine elimination; dosage adjustments may be needed in neonates with impaired renal function and should be guided by clinical response and serum caffeine levels.