

DRUG MONOGRAPH

Acetaminophen

Acephen | Aceta | Actamin | Adult Pain Relief | Anacin Aspirin Free ...

Drug Information Provided By Gold Standard

Description

Acetaminophen (APAP, paracetamol) is a para-aminophenol analgesic and the active metabolite of phenacetin. Due to the toxic effects of phenacetin at therapeutic doses and the availability of acetaminophen, phenacetin is no longer used. Acetaminophen possesses analgesic and antipyretic activity similar to aspirin; however, acetaminophen has no peripheral anti-inflammatory activity or effects on platelet function. Acetaminophen was first used in clinical medicine in the 1890s. It is effective in the relief of both acute and chronic pain and may be preferred over NSAIDs due to fewer hematologic, gastrointestinal, and renal effects. Acetaminophen is the preferred analgesic/antipyretic for patients in whom aspirin is contraindicated and in those with underlying renal disease for episodic, though not chronic, use.²³⁹⁷⁷ In addition, acetaminophen has been recommended by the American Lung Association as the first line treatment for aches and pains associated with the flu, by the American Geriatrics Society for both minor and persistent pain in elderly patients, and by the American College of Rheumatology as first-line therapy for osteoarthritis of the hip or knee.^{35614 35976} The drug has a history of safe and effective use; however, unintentional or intentional misuse of acetaminophen is the number one cause of acute hepatic failure in the U.S.³²²⁰² Acetaminophen was first approved by the FDA in 1950. Intravenous acetaminophen was approved by the FDA in November 2010 for the treatment of pain and fever in adults, adolescents, and children over the age of 2 years. In 2017, the indication for fever was expanded to include patients as young as premature neonates born at 32 weeks gestation.⁴²²⁸⁹

Mechanism of Action

The exact mechanism of action is unknown, but acetaminophen is thought to mediate its actions centrally through activation of the descending serotonergic pathways. Acetaminophen is believed to increase the pain threshold by inhibiting prostaglandin (PG) synthesis through the cyclooxygenase (COX) pathway, similar to nonsteroidal anti-inflammatory drugs (NSAIDs). Though acetaminophen's analgesic and antipyretic properties are similar to those of NSAIDs, acetaminophen does not have significant anti-inflammatory or antiplatelet effects. It has been suggested acetaminophen may inhibit a specific site on the prostaglandin H₂ synthetase (PGHS) molecule, the 2 isoforms of which, PGHS1 and PGHS2, are commonly referred to as COX-1 and COX-2. PGHS has 2 active sites, COX and peroxidase (POX). Acetaminophen acts as a reducing cosubstrate at the POX site and interferes with the conversion of arachidonic acid to PGH₂, thereby inhibiting PG synthesis. Other potential mechanisms may involve inhibition of the nitric oxide pathway mediated by a variety of neurotransmitter receptors (e.g., N-methyl-D-aspartate and substance p) and indirect activation of cannabinoid receptors. Acetaminophen produces its antipyretic effect by inhibiting PG synthesis in the CNS and blocking the actions of endogenous pyrogens at the hypothalamic thermoregulatory centers.^{54019 54020}

When supratherapeutic or repeated therapeutic doses of acetaminophen are consumed, hepatic stores of glucuronide and sulfate are depleted, resulting in an increased formation of N-acetyl-para-benzoquinoneimine (NAPQI), which is normally bound to and detoxified by glutathione. Insufficient glutathione results in NAPQI binding to cytosol proteins in the tissue, leading to cellular necrosis of the liver. Like the liver, the kidney is also susceptible to acetaminophen toxicity and may form a toxic metabolite when it is glutathione depleted. Administration of N-acetylcysteine may reduce toxicity by regenerating glutathione. Hepatic necrosis and failure

after acute overdose may be less common in young children than in older children and adults. This may be related to reduced rates of metabolism by the CYP450 system and/or an increased ability to synthesize glutathione.^{54022 54023 54024}

Pharmacokinetics

Acetaminophen is administered orally, rectally, or intravenously. At therapeutic concentrations, protein binding is about 10% to 25%. Acetaminophen is widely distributed throughout most body tissues except fat; low protein binding and molecular weight allow blood-brain barrier penetration. Vd is approximately 1 L/kg.

Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves 3 separate pathways: glucuronidation, sulfate conjugation, and cytochrome P450 (CYP450) oxidation. Glucuronidation and sulfate conjugation are the major routes of metabolism, while a small amount of drug undergoes oxidative metabolism via CYP2E1 producing the hepatotoxic metabolite, N-acetyl-p-benzoquinoneimine (NAPQI). At therapeutic doses, NAPQI is rapidly conjugated with glutathione to form inert cysteine and mercapturic acid metabolites. The P450 isoenzymes 1A2 and 3A4 appear to have a minor role in the metabolism of acetaminophen. Supratherapeutic or repeated therapeutic doses of acetaminophen, fasting, and alcoholism may deplete glutathione stores, leading to increased concentrations of NAPQI and hepatotoxicity. The elimination half-life of acetaminophen is 2 to 3 hours in healthy adult patients. Acetaminophen is renally excreted primarily as the glucuronide conjugate (40% to 65%) and sulfate metabolite (25% to 35%). Mercapturic acid and cysteine metabolites account for 5% to 12% of the urinary metabolites; less than 5% is excreted as unchanged drug.^{25460 28100 42289 54020}

Affected cytochrome P450 isoenzymes: CYP2E1

Although acetaminophen is primarily metabolized via glucuronidation and sulfate conjugation, it is also a substrate of CYP2E1. Drugs that induce CYP2E1 may increase the metabolism of acetaminophen to its toxic metabolite and therefore increase the risk of hepatotoxicity. Because CYP1A2 and CYP3A4 have negligible contribution to acetaminophen metabolism, the enzymes are unlikely to affect toxic metabolite formation.^{25460 42289 54020}

•Route-Specific Pharmacokinetics

Oral Route

Immediate-release acetaminophen is rapidly and almost completely absorbed from the gastrointestinal (GI) tract, primarily the small intestine. Bioavailability ranges from 85% to 98%. Peak plasma concentrations occur within 30 to 60 minutes and range from 7.7 to 17.6 mcg/mL after a single 1,000 mg dose and 7.9 to 27 mcg/mL at steady state after 1,000 mg every 6 hours in adult patients.⁵⁴⁰²⁰ In a study of febrile children 2 to 7 years of age, acetaminophen 12 mg/kg achieved maximum concentration (14.6 +/- 2.6 mcg/mL) within 0.55 +/- 0.08 hours.⁵⁴⁰²⁶ Maximum concentrations of acetaminophen are delayed with concurrent food administration, however the extent of absorption is not affected.⁵⁴⁰²⁰

Intravenous Route

The maximum concentration after administration of an IV dose of acetaminophen is up to 70% higher than that seen after the same dose is given orally; however, the overall exposure, described by area under the concentration time curve (AUC), is similar. The pharmacokinetic profile of IV acetaminophen in adults is dose proportional after administration of single doses of 500, 650, and 1,000 mg.⁴²²⁸⁹

Other Route(s)

Rectal Route

Rectal absorption of acetaminophen is prolonged and highly variable compared to other routes of administration; reported bioavailability ranges from 6.5% to 98%. Several factors may influence absorption, including lipophilicity of the vehicle, placement of the suppository, rectal contents, premature defecation of the suppository, suppository size, number of suppositories administered, and/or rectal pH. Compared to adult patients, pediatric patients appear to absorb acetaminophen from suppositories to a greater extent.^{54111 54112 54115 54116}

•Special Populations

Hepatic Impairment

The half-life of acetaminophen may be prolonged in patients with hepatic disease.^{54020 54066}

Renal Impairment

In severe renal impairment (CrCl 10 to 30 mL/minute), the elimination of acetaminophen is slightly delayed, with an elimination half-life of 2 to 5.3 hours. In addition, the elimination of sulfate and glucuronide conjugates is 3 times slower in patients with severe renal impairment than in healthy subjects, leading to potential accumulation.^{54126 54127 54131}

Pediatrics

Neonates and Infants

Slow and erratic gastric emptying in the neonate leads to a slower rate of oral acetaminophen absorption (0.21 hours); adult rates are reached by 6 to 8 months of age. Rectal absorption of an acetaminophen suppository decreases with increasing age; perhaps attributable to rectal insertion height and consequent rectal venous drainage patterns. Because of fetal body composition and water distribution, premature neonates and young infants have a slightly larger Vd compared to older pediatric patients and adults. At 28 weeks postconceptual age (PCA), Vd is 1.47 L/kg, whereas at 60 weeks PCA Vd is 1.04 L/kg.⁵⁴¹⁴⁴ Observed concentrations of IV acetaminophen are similar in neonates older than 32 weeks gestation at birth treated with 12.5 mg/kg/dose; infants, children, and adolescents treated with 15 mg/kg/dose; and adults treated with 1,000 mg/dose.⁴²²⁸⁹ Neonates and infants have a lower risk of acetaminophen-induced hepatotoxicity compared to older children and adults because of hepatic enzyme immaturity (specifically CYP2E1, which is responsible for producing the hepatotoxic metabolite NAPQI).⁵⁶⁵⁴⁷ However, immature hepatic pathways also result in a delayed drug clearance. In neonates, sulfate conjugation is pronounced, while glucuronide conjugation is deficient. The relative contribution of sulfate and glucuronide conjugation changes with age and normal adult ratios (2:1 glucuronide to sulfate conjugates) are reached by late childhood. Acetaminophen clearance also has great interpatient variability and appears to increase with patient weight and age. Clearance increases from 28 weeks PCA (0.01 L/kg/hour) with a maturation half-life of 11.3 weeks to reach 0.15 L/kg/hour by early infancy (60 weeks PCA); clearance approaches adult values by 1 year of age. Additionally, clearance may be reduced in the presence of high unconjugated bilirubin concentrations.^{54114 54117 54118} Approximate half-life of acetaminophen is as follows: neonate 28 to 32 weeks gestation = 11 hours, neonate 32 to 36 weeks gestation = 5 hours, term neonate = 3 to 3.5 hours, infant = 4 hours.^{54119 54120 54121}

Children and Adolescents

Acetaminophen is excreted primarily as the sulfate conjugate in children, due to a deficiency in glucuronide formation in younger pediatric patients. The relative contribution of sulfate and glucuronide conjugation changes with age and normal adult ratios (2:1 glucuronide to sulfate conjugates) are reached by 12 years of age.^{25459 54114} The AUC of acetaminophen in children and adolescents after a single IV dose of 15 mg/kg (38 and 41 mcg x hour/mL, respectively) is similar to that in adults after a single IV dose of 1,000 mg (43 mcg x hour/mL). In addition, the mean half-life of IV acetaminophen in pediatric patients is longer than the half-life in adults, with

younger patients having the slowest clearance (children = 3 hours, adolescents = 2.9 hours, adults = 2.4 hours). Observed concentrations of IV acetaminophen are similar in infants, children, and adolescents treated with 15 mg/kg/dose; adults treated with 1,000 mg/dose, and neonates at least 32 weeks gestation at birth treated with 12.5 mg/kg/dose.⁴²²⁸⁹

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Indications & Dosage

- arthralgia
- dental pain
- dysmenorrhea
- fever
- headache
- migraine
- mild pain
- moderate pain
- musculoskeletal pain
- myalgia
- osteoarthritis
- severe pain

NOTE: The FDA has advised healthcare professionals to discontinue prescribing and dispensing of combination prescription medications containing more than 325 mg acetaminophen per dosage unit. This action has been taken to reduce the risk of liver damage and severe hypersensitivity reactions associated with acetaminophen.^{43086 56615} Maximum daily doses of acetaminophen are based on all routes of administration (e.g., intravenous, oral, rectal) and all products containing acetaminophen, including combination products. Exceeding maximum daily doses may result in hepatic injury, hepatic failure, and death.⁴²²⁸⁹

For the treatment of fever

NOTE: Acetaminophen should not be used for self-medication of marked fever (greater than 39.5 degrees C or 103.1 degrees F), fever persisting longer than 3 days, or recurrent fever, unless directed by a physician.

Oral dosage (immediate-release formulations)

Adults:

325 to 650 mg PO every 4 to 6 hours, as needed. Alternatively, 1,000 mg PO 2 to 4 times per day can be given. Do not exceed 1 g/dose or 4 g/day.

Children and Adolescents weighing 60 kg or more:

325 mg to 650 mg PO every 4 to 6 hours as needed. Alternatively, 1,000 mg PO every 6 hours as needed. Max single dose: 1,000 mg/dose. Max daily dose: 4,000 mg/day.^{52221 54020 54150}

Children and Adolescents weighing less than 60 kg:

10 to 15 mg/kg/dose PO every 4 to 6 hours as needed. Max single dose: 15 mg/kg/dose or 1,000 mg/dose, whichever is less. Max daily dose: 75 mg/kg/day or 4,000 mg/day, whichever is less.^{54020 54154}

Infants:

10 to 15 mg/kg/dose PO every 4 to 6 hours as needed. Max single dose: 15 mg/kg/dose. Max daily dose: 75 mg/kg/day.^{54020 54154}

Neonates 10 to 29 days:

10 to 15 mg/kg/dose PO every 4 to 8 hours as needed. Some experts recommend an initial load of 20 mg/kg PO. Max: 90 mg/kg/day. Do not exceed 48 consecutive hours at the maximum dose.^{52218 54157}

Neonates 0 to 9 days:

10 to 15 mg/kg/dose PO every 6 to 8 hours as needed. Some experts recommend an initial load of 20 mg/kg PO. Max: 60 mg/kg/day. Do not exceed 48 consecutive hours at the maximum dose.^{52218 54157}

Premature Neonates 32 to 37 weeks gestation:

10 to 15 mg/kg/dose PO every 8 hours as needed. Some experts recommend an initial load of 20 mg/kg PO. Max: 60 mg/kg/day. Do not exceed 48 consecutive hours at the maximum dose.^{52218 54157}

Premature Neonates 28 to 31 weeks gestation:

10 to 15 mg/kg/dose PO every 12 hours as needed. Some experts recommend an initial load of 20 mg/kg PO. Max: 40 mg/kg/day. Do not exceed 48 consecutive hours at the maximum dose.^{52218 54157}

Oral dosage (extended-release formulations)*Adults:*

650 mg to 1,300 mg PO every 8 hours as needed. Max single dose: 1,300 mg/dose. Max daily dose: 3,900 mg/day.⁵⁴⁰²⁰

Children and Adolescents 12 to 17 years:

650 mg to 1,300 mg PO every 8 hours as needed. Max single dose: 1,300 mg/dose. Max daily dose: 3,900 mg/day.⁵⁴⁰²⁰

Rectal dosage*Adults:*

325 to 650 mg PR every 4 to 6 hours as needed. Alternatively, 1,000 mg PR 2 to 4 times per day can be given. Do not exceed 1 g/dose or 4 g/day.⁵²²²¹

Children and Adolescents weighing 60 kg or more:

325 to 650 mg PR every 4 to 6 hours as needed. Alternatively, 1,000 mg PR 2 to 4 times per day can be given. Max single dose: 1,000 mg/dose. Max daily dose: 4,000 mg/day.⁵²²²¹

Children and Adolescents weighing less than 60 kg:

10 to 20 mg/kg/dose PR every 4 to 6 hours as needed. Max single dose: 20 mg/kg/dose or 1,000 mg/dose, whichever is less. Max daily dose: 100 mg/kg/day or 4,000 mg/day, whichever is less.^{54116 54150 54153 54154}

Infants:

10 to 20 mg/kg/dose PR every 4 to 6 hours as needed. Max single dose: 20 mg/kg/dose. Max daily dose: 75 mg/kg/day.^{54111 54153 54154}

Neonates 10 to 29 days:

20 mg/kg/dose PR every 6 to 8 hours as needed. Some experts recommend an initial load of 30 mg/kg PR. Max: 90 mg/kg/day. Do not exceed 48 consecutive hours at the maximum dose.^{52218 54121 54157}

Neonates 0 to 9 days:

20 mg/kg/dose PR every 6 to 8 hours as needed. Some experts recommend an initial load of 30 mg/kg PR. Max: 60 mg/kg/day. Do not exceed 48 consecutive hours at the maximum dose.^{52218 54121 54157}

Premature Neonates 32 to 37 weeks gestation:

20 mg/kg/dose PR every 8 hours as needed. Some experts recommend an initial load of 30 mg/kg PR. Max: 60 mg/kg/day. Do not exceed 48 consecutive hours at the maximum dose.^{52218 54157}

Premature Neonates 28 to 31 weeks gestation:

15 mg/kg/dose PR every 12 hours as needed. Some experts recommend an initial load of 20 mg/kg PR. Max: 40 mg/kg/day. Do not exceed 48 consecutive hours at the maximum dose.^{52218 54157}

Intravenous dosage

Adults weighing 50 kg or more:

1,000 mg IV every 6 hours or 650 mg IV every 4 hours as needed. Max single dose: 1,000 mg/dose. Max daily dose: 4,000 mg/day.⁴²²⁸⁹

Adults weighing less than 50 kg:

15 mg/kg/dose IV every 6 hours or 12.5 mg/kg/dose IV every 4 hours as needed. Max single dose: 15 mg/kg/dose or 750 mg/dose, whichever is less. Max daily dose: 75 mg/kg/day or 3,750 mg/day, whichever is less.⁴²²⁸⁹

Adolescents weighing 50 kg or more:

1,000 mg IV every 6 hours or 650 mg IV every 4 hours as needed. Max single dose: 1,000 mg/dose. Max daily dose: 4,000 mg/day.⁴²²⁸⁹

Children 2 to 12 years and Adolescents weighing less than 50 kg:

15 mg/kg/dose IV every 6 hours or 12.5 mg/kg/dose IV every 4 hours as needed. Max single dose: 15 mg/kg/dose or 750 mg/dose, whichever is less. Max daily dose: 75 mg/kg/day or 3,750 mg/day, whichever is less.⁴²²⁸⁹

Infants and Children 1 to 23 months:

15 mg/kg/dose IV every 6 hours as needed. Max daily dose: 60 mg/kg/day.⁴²²⁸⁹

Neonates:

12.5 mg/kg/dose IV every 6 hours as needed. Max daily dose: 50 mg/kg/day.⁴²²⁸⁹

Premature Neonates 32 to 37 weeks gestation:

12.5 mg/kg/dose IV every 6 hours as needed. Max daily dose: 50 mg/kg/day.⁴²²⁸⁹

Premature Neonates 28 to 31 weeks postmenstrual age†:

Limited data available; dose not established. Some experts do not recommend use of IV acetaminophen in premature neonates less than 32 weeks PMA until sufficient pharmacokinetic and pharmacodynamic studies have been conducted.⁵⁴¹³⁹ A loading dose of 20 mg/kg IV, then 10 mg/kg/dose IV every 12 hours as needed has been recommended.^{54118 54141} Alternatively, 7.5 mg/kg/dose IV every 8 hours as needed has been suggested.⁵⁴¹⁴² Max single dose: 10 mg/kg/dose. Max daily dose: 22.5 mg/kg/day.^{54118 54141 54142}

For the treatment of mild pain or for the temporary relief of headache, myalgia, back pain, musculoskeletal pain, dental pain (e.g., toothache), dysmenorrhea, arthralgia, or minor aches and pains associated with the common cold or flu

NOTE: Acetaminophen should not be used for self-medication of pain for longer than 10 days in adults or 5 days in children.

Oral dosage (immediate-release formulations)

Adults:

325 to 650 mg PO every 4 to 6 hours, as needed. Alternatively, 1,000 mg PO, 2 to 4 times per day can be given. It is important to note that doses effective for acute pain relief (1 to 2 tablets/day) may not be effective in chronic pain states, which require higher daily doses. Do not exceed 1 g/dose or 4 g/day.

Children and Adolescents weighing 60 kg or more:

325 mg to 650 mg PO every 4 to 6 hours as needed. Alternatively, 1,000 mg PO every 6 hours as needed. Max single dose: 1,000 mg/dose. Max daily dose: 4,000 mg/day.^{52221 54020 54150}

Children and Adolescents weighing less than 60 kg:

10 to 15 mg/kg/dose PO every 4 to 6 hours as needed. Max single dose: 15 mg/kg/dose or 1,000 mg/dose, whichever is less. Max daily dose: 75 mg/kg/day or 4,000 mg/day, whichever is less.^{54020 54154}

Infants:

10 to 15 mg/kg/dose PO every 4 to 6 hours as needed. Max single dose: 15 mg/kg/dose. Max daily dose: 75 mg/kg/day.^{54020 54154}

Neonates 10 to 29 days:

10 to 15 mg/kg/dose PO every 4 to 8 hours as needed. Some experts recommend an initial load of 20 mg/kg PO. Max: 90 mg/kg/day. Do not exceed 48 consecutive hours at the maximum dose.^{52218 54157}

Neonates 0 to 9 days:

10 to 15 mg/kg/dose PO every 6 to 8 hours as needed. Some experts recommend an initial load of 20 mg/kg PO. Max: 60 mg/kg/day. Do not exceed 48 consecutive hours at the maximum dose.^{52218 54157}

Premature Neonates 32 to 37 weeks gestation:

10 to 15 mg/kg/dose PO every 8 hours as needed. Some experts recommend an initial load of 20 mg/kg PO. Max: 60 mg/kg/day. Do not exceed 48 consecutive hours at the maximum dose.^{52218 54157}

Premature Neonates 28 to 31 weeks gestation:

10 to 15 mg/kg/dose PO every 12 hours as needed. Some experts recommend an initial load of 20 mg/kg PO. Max: 40 mg/kg/day. Do not exceed 48 consecutive hours at the maximum dose.^{52218 54157}

Oral dosage (extended-release formulations)

Adults:

650 mg to 1,300 mg PO every 8 hours as needed. Max single dose: 1,300 mg/dose. Max daily dose: 3,900 mg/day.⁵⁴⁰²⁰

Children and Adolescents 12 to 17 years:

650 mg to 1,300 mg PO every 8 hours as needed. Max single dose: 1,300 mg/dose. Max daily dose: 3,900 mg/day.⁵⁴⁰²⁰

Rectal dosage

Adults:

325 to 650 mg PR every 4 to 6 hours as needed. Alternatively, 1,000 mg PR 2 to 4 times per day can be given. It is important to note that doses effective for acute pain relief may not be effective in chronic pain states, which require higher daily doses. Do not exceed 1 g/dose or 4 g/day.⁵²²²¹

Children and Adolescents weighing 60 kg or more:

325 to 650 mg PR every 4 to 6 hours as needed. Alternatively, 1,000 mg PR 2 to 4 times per day can be given. Max single dose: 1,000 mg/dose. Max daily dose: 4,000 mg/day.⁵²²²¹

Children and Adolescents weighing less than 60 kg:

10 to 20 mg/kg/dose PR every 4 to 6 hours as needed. Max single dose: 20 mg/kg/dose or 1,000 mg/dose, whichever is less. Max daily dose: 100 mg/kg/day or 4,000 mg/day, whichever is less. High-dose rectal acetaminophen (25 to 45 mg/kg/dose) has been studied and recommended as an initial loading dose for pain management, as well as for the scheduled management of peri- and postoperative pain, in pediatric patients. Its use is controversial, as optimal dosing has not been established.^{54111 54116 54150 54153 54154}

Infants:

10 to 20 mg/kg/dose PR every 4 to 6 hours as needed. Max single dose: 20 mg/kg/dose. Max daily dose: 75 mg/kg/day. High-dose rectal acetaminophen (25 to 45 mg/kg/dose) has been studied and recommended as an initial loading dose for pain management, as well as for the scheduled management of peri- and postoperative pain, in pediatric patients. Its use is controversial, as optimal dosing has not been established.^{32702 54111 54153 54154}

Neonates 10 to 29 days:

20 mg/kg/dose PR every 6 to 8 hours as needed. Some experts recommend an initial load of 30 mg/kg PR. Max: 90 mg/kg/day. Do not exceed 48 consecutive hours at the maximum dose.^{52218 54121 54157}

Neonates 0 to 9 days:

20 mg/kg/dose PR every 6 to 8 hours as needed. Some experts recommend an initial load of 30 mg/kg PR. Max: 60 mg/kg/day. Do not exceed 48 consecutive hours at the maximum dose.^{52218 54121 54157}

Premature Neonates 32 to 37 weeks gestation:

20 mg/kg/dose PR every 8 hours as needed. Some experts recommend an initial load of 30 mg/kg PR. Max: 60 mg/kg/day. Do not exceed 48 consecutive hours at the maximum dose.^{52218 54157}

Premature Neonates 28 to 31 weeks gestation:

15 mg/kg/dose PR every 12 hours as needed. Some experts recommend an initial load of 20 mg/kg PR. Max: 40 mg/kg/day. Do not exceed 48 consecutive hours at the maximum dose.^{52218 54157}

Intravenous dosage

Adults weighing 50 kg or more:

1,000 mg IV every 6 hours or 650 mg IV every 4 hours as needed. Max single dose: 1,000 mg/dose. Max daily dose: 4,000 mg/day.⁴²²⁸⁹

Adults weighing less than 50 kg:

15 mg/kg/dose IV every 6 hours or 12.5 mg/kg/dose IV every 4 hours as needed. Max single dose: 15 mg/kg/dose or 750 mg/dose, whichever is less. Max daily dose: 75 mg/kg/day or 3,750 mg/day, whichever is less.⁴²²⁸⁹

Adolescents weighing 50 kg or more:

1,000 mg IV every 6 hours or 650 mg IV every 4 hours as needed. Max single dose: 1,000 mg/dose. Max daily dose: 4,000 mg/day.⁴²²⁸⁹

Children 2 to 12 years and Adolescents weighing less than 50 kg:

15 mg/kg/dose IV every 6 hours or 12.5 mg/kg/dose IV every 4 hours as needed. Max single dose: 15 mg/kg/dose or 750 mg/dose, whichever is less. Max daily dose: 75 mg/kg/day or 3,750 mg/day, whichever is less.⁴²²⁸⁹

Infants and Children 1 to 23 months†:

The FDA-approved dose for fever in this age group is 15 mg/kg/dose IV every 6 hours as needed; Max daily dose: 60 mg/kg/day. Efficacy of IV acetaminophen for the treatment of acute pain has not been established in patients younger than 2 years. In clinical trials, there was no difference in analgesic effect, measured by the reduced need for additional opioid treatment for pain control, in those younger than 2 years receiving opioid plus acetaminophen vs. opioid plus placebo.⁴²²⁸⁹ 7.5 to 15 mg/kg/dose IV every 6 hours as needed is the most commonly used dose in infants according to a survey of anesthetists in the United Kingdom.⁵⁴¹³²

Neonates†:

The FDA-approved dose for fever in this age group is 12.5 mg/kg/dose IV every 6 hours as needed; Max daily dose: 50 mg/kg/day. Efficacy of IV acetaminophen for the treatment of acute pain has not been established in patients younger than 2 years. In clinical trials, there was no difference in analgesic effect, measured by the reduced need for additional opioid treatment for pain control, in those younger than 2 years receiving opioid plus acetaminophen vs. opioid plus placebo.⁴²²⁸⁹ In the literature, a loading dose of 20 mg/kg IV, then 7.5 to 15 mg/kg/dose IV every 6 hours as needed has been suggested.^{54118 54141 54142 56547} For scheduled postoperative analgesia in neonates, decreasing the dose by 50% after 4 days of continuously scheduled acetaminophen has been recommended; do not exceed 6 days of scheduled acetaminophen therapy.^{54118 54141 54142}

Premature Neonates 32 to 37 weeks gestation†:

The FDA-approved dose for fever in this age group is 12.5 mg/kg/dose IV every 6 hours as needed; Max daily dose: 50 mg/kg/day. Efficacy of IV acetaminophen for the treatment of acute pain has not been established in patients younger than 2 years. In clinical trials, there was no difference in analgesic effect, measured by the reduced need for additional opioid treatment for pain control, in those younger than 2 years receiving opioid plus acetaminophen vs. opioid plus placebo.⁴²²⁸⁹ In the literature, a loading dose of 20 mg/kg IV, then 10 mg/kg/dose IV every 8 hours as needed has been recommended.^{54141 54118} Alternatively, 7.5 to 10 mg/kg/dose IV every 6 hours as needed has been suggested.^{54118 54142} For scheduled postoperative analgesia in neonates, decreasing the dose by 50% after 4 days of continuously scheduled acetaminophen has been recommended; do not exceed 6 days of scheduled acetaminophen therapy.^{54118 54141 54142}

Premature Neonates 28 to 31 weeks postmenstrual age†:

Limited data available; dose not established. Some experts do not recommend use of IV acetaminophen in premature neonates less than 32 weeks PMA until sufficient pharmacokinetic and pharmacodynamic studies have been conducted.⁵⁴¹³⁹ A loading dose of 20 mg/kg IV, then 10 mg/kg/dose IV every 12 hours as needed has been recommended.^{54118 54141} Alternatively, 7.5 mg/kg/dose IV every 8 hours as needed has been suggested.⁵⁴¹⁴² Max single dose: 10 mg/kg/dose. Max daily dose: 22.5 mg/kg/day. For scheduled postoperative analgesia in neonates, decreasing the dose by 50% after 4 days of continuously scheduled acetaminophen has been recommended; do not exceed 6 days of scheduled acetaminophen therapy.^{54118 54141 54142}

For the treatment of moderate pain to severe pain with adjunctive opioid analgesicsIntravenous dosage*Adults weighing 50 kg or more:*

1,000 mg IV every 6 hours or 650 mg IV every 4 hours as needed. Max single dose: 1,000 mg/dose. Max daily dose: 4,000 mg/day.⁴²²⁸⁹

Adults weighing less than 50 kg:

15 mg/kg/dose IV every 6 hours or 12.5 mg/kg/dose IV every 4 hours as needed. Max single dose: 15 mg/kg/dose or 750 mg/dose, whichever is less. Max daily dose: 75 mg/kg/day or 3,750 mg/day, whichever is less.⁴²²⁸⁹

Adolescents weighing 50 kg or more:

1,000 mg IV every 6 hours or 650 mg IV every 4 hours as needed. Max single dose: 1,000 mg/dose. Max daily dose: 4,000 mg/day.⁴²²⁸⁹

Children 2 to 12 years and Adolescents weighing less than 50 kg:

15 mg/kg/dose IV every 6 hours or 12.5 mg/kg/dose IV every 4 hours as needed. Max single dose: 15 mg/kg/dose or 750 mg/dose, whichever is less. Max daily dose: 75 mg/kg/day or 3,750 mg/day, whichever is less.⁴²²⁸⁹

Infants and Children 1 to 23 months†:

The FDA-approved dose for fever in this age group is 15 mg/kg/dose IV every 6 hours as needed; Max daily dose: 60 mg/kg/day. Efficacy of IV acetaminophen for the treatment of acute pain has not been established in patients younger than 2 years. In clinical trials, there was no difference in analgesic effect, measured by the reduced need for

additional opioid treatment for pain control, in those younger than 2 years receiving opioid plus acetaminophen vs. opioid plus placebo.⁴²²⁸⁹ 7.5 to 15 mg/kg/dose IV every 6 hours as needed is the most commonly used dose in infants according to a survey of anesthetists in the United Kingdom.⁵⁴¹³²

Neonates†:

The FDA-approved dose for fever in this age group is 12.5 mg/kg/dose IV every 6 hours as needed; Max daily dose: 50 mg/kg/day. Efficacy of IV acetaminophen for the treatment of acute pain has not been established in patients younger than 2 years. In clinical trials, there was no difference in analgesic effect, measured by the reduced need for additional opioid treatment for pain control, in those younger than 2 years receiving opioid plus acetaminophen vs. opioid plus placebo.⁴²²⁸⁹ In the literature, a loading dose of 20 mg/kg IV, then 7.5 to 15 mg/kg/dose IV every 6 hours as needed has been suggested.^{54118 54141 54142 56547} For scheduled postoperative analgesia in neonates, decreasing the dose by 50% after 4 days of continuously scheduled acetaminophen has been recommended; do not exceed 6 days of scheduled acetaminophen therapy.^{54118 54141 54142}

Premature Neonates 32 to 37 weeks gestation†:

The FDA-approved dose for fever in this age group is 12.5 mg/kg/dose IV every 6 hours as needed; Max daily dose: 50 mg/kg/day. Efficacy of IV acetaminophen for the treatment of acute pain has not been established in patients younger than 2 years. In clinical trials, there was no difference in analgesic effect, measured by the reduced need for additional opioid treatment for pain control, in those younger than 2 years receiving opioid plus acetaminophen vs. opioid plus placebo.⁴²²⁸⁹ In the literature, a loading dose of 20 mg/kg IV, then 10 mg/kg/dose IV every 8 hours as needed has been recommended.^{54141 54118} Alternatively, 7.5 to 10 mg/kg/dose IV every 6 hours as needed has been suggested.^{54118 54142} For scheduled postoperative analgesia in neonates, decreasing the dose by 50% after 4 days of continuously scheduled acetaminophen has been recommended; do not exceed 6 days of scheduled acetaminophen therapy.^{54118 54141 54142}

Premature Neonates 28 to 31 weeks postmenstrual age†:

Limited data available; dose not established. Some experts do not recommend use of IV acetaminophen in premature neonates less than 32 weeks PMA until sufficient pharmacokinetic and pharmacodynamic studies have been conducted.⁵⁴¹³⁹ A loading dose of 20 mg/kg IV, then 10 mg/kg/dose IV every 12 hours as needed has been recommended.^{54118 54141} Alternatively, 7.5 mg/kg/dose IV every 8 hours as needed has been suggested.⁵⁴¹⁴² Max single dose: 10 mg/kg/dose. Max daily dose: 22.5 mg/kg/day. For scheduled postoperative analgesia in neonates, decreasing the dose by 50% after 4 days of continuously scheduled acetaminophen has been recommended; do not exceed 6 days of scheduled acetaminophen therapy.^{54118 54141 54142}

For minor osteoarthritis pain

Oral dosage

Adults:

The American College of Rheumatology has recommended acetaminophen as first-line therapy for osteoarthritis of the hip or knee. In a randomized, double-blind trial, acetaminophen 4 g/day PO was as effective as ibuprofen in doses of 2.4 or 1.2 g/day for the short-term relief of joint pain and improvement of function in patients with osteoarthritis of the knee.²⁵⁴⁵⁸ Due to a ceiling effect where side effects increase to negate any analgesic benefit, do not exceed single doses of 1 g/dose or 4 g/day.

For the treatment of headache pain due to acute migraine†

Oral dosage

Adults:

Single doses of 500 to 1,000 mg PO have been utilized. Due to a ceiling effect where side effects increase to negate any analgesic benefit, do not exceed single doses of 1 g/dose or 4 g/day.

Children and Adolescents 4 to 17 years:

15 mg/kg PO as a single dose at the onset of attack has been evaluated in a crossover study of pediatric patients (n = 88 intent to treat analysis; n = 66 efficacy analysis; age range: 4 to 16 years) in which 3 attacks were treated separately with acetaminophen (15 mg/kg), ibuprofen (10 mg/kg), or placebo. One hour after administration, acetaminophen was more than 3 times as effective as placebo with regard to pain relief (OR 3.9, 95% CI 1.4 to 11) and complete pain resolution (OR 3.3, 95% CI 1 to 11.1); there was no difference between the active drugs. Two hours after administration, acetaminophen was not superior to placebo and inferior to ibuprofen (OR 2.2, 95% CI 1.1 to 4 for acetaminophen vs. ibuprofen). In the intent to treat analysis, acetaminophen was twice as effective as placebo at both 1 and 2 hours with no clear difference in efficacy between the active drugs (OR 0.9, 95% CI 0.6 to 1.3 for acetaminophen vs. ibuprofen). At 2 hours, acetaminophen provided headache alleviation in 54% of patients (compared to 37% for placebo and 68% for ibuprofen). Complete resolution occurred in 39% of acetaminophen-treated, 60% of ibuprofen-treated, and 28% of placebo-treated patients.⁵⁶⁵⁴⁴ Based on this evidence, the American Academy of Neurology and Child Neurology Society states that acetaminophen is probably effective and should be considered in the acute treatment of migraine in children.³³³¹²

Maximum Dosage Limits:**•Adults**

1,000 mg/dose PO/PR/IV or 4,000 mg/day PO/PR/IV for most formulations; some OTC formulations have lower max doses, see individual products. For the extended-release oral product, 1,300 mg/dose PO, with the same overall daily dose limits as other formulations. The total daily maximum dose of 4,000 mg is the maximum dose of acetaminophen from all sources.

•Geriatric

1,000 mg/dose PO/PR/IV or 4,000 mg/day PO/PR/IV for most formulations; some OTC formulations have lower max doses, see individual products. For the extended-release oral product, 1,300 mg/dose PO, with the same overall daily dose limits as other formulations. The total daily maximum dose of 4,000 mg is the maximum dose of acetaminophen from all sources.

•Adolescents

Weighing 60 kg or more: 1,000 mg/dose PO/IV/PR (Max daily dose: 4,000 mg/day PO/IV/PR).

Weighing 50 to 59 kg: 15 mg/kg/dose PO (Max daily dose: 75 mg/kg/day [Max: 4,000 mg/day] PO); 20 mg/kg/dose PR (Max single dose: 1,000 mg/dose PR; Max daily dose: 100 mg/kg/day [Max: 4,000 mg/day] PR); 1,000 mg/dose IV (Max daily dose: 4,000 mg/day IV).

Weighing less than 50 kg: 15 mg/kg/dose PO/IV (Max daily dose: 75 mg/kg/day [Max: 3,750 mg/day] PO/IV); 20 mg/kg/dose PR (Max daily dose: 100 mg/kg/day [Max: 4,000 mg/day] PR).

•Children

2 to 12 years weighing 60 kg or more: 1,000 mg/dose PO/PR (Max daily dose: 4,000 mg/day PO/PR); 15 mg/kg/dose IV (Max single dose: 750 mg/dose IV; Max daily dose: 75 mg/kg/day [Max: 3,750 mg/day] IV).

2 to 12 years weighing 50 to 59 kg: 15 mg/kg/dose PO (Max daily dose: 75 mg/kg/day [Max: 4,000 mg/day] PO); 20 mg/kg/dose PR (Max single dose: 1,000 mg/dose PR; Max daily dose: 100 mg/kg/day [Max: 4,000 mg/day] PR); 15 mg/kg/dose IV (Max single dose: 750 mg/dose IV; Max daily dose: 75 mg/kg/day [Max: 3,750 mg/day] IV).

2 to 12 years weighing less than 50 kg: 15 mg/kg/dose PO/IV (Max daily dose: 75 mg/kg/day [Max: 3,750 mg/day] PO/IV); 20 mg/kg/dose PR (Max daily dose: 100 mg/kg/day [Max: 4,000 mg/day] PR).

1 to 2 years: 15 mg/kg/dose PO (Max daily dose: 75 mg/kg/day PO); 20 mg/kg/dose PR (Max daily dose: 100 mg/kg/day PR); 15 mg/kg/dose IV (Max daily dose: 60 mg/kg/day IV).

•Infants

15 mg/kg/dose PO (Max daily dose: 75 mg/kg/day PO); 20 mg/kg/dose PR (Max daily dose: 75 mg/kg/day PR); 15 mg/kg/dose IV (Max daily dose: 60 mg/kg/day IV).

•Neonates

10 to 29 days: 20 mg/kg PO load and 15 mg/kg/dose PO maintenance dose (Max daily dose: 90 mg/kg/day PO); 30 mg/kg PR load and 20 mg/kg/dose PR maintenance dose (Max daily dose: 90 mg/kg/day PR); 12.5 mg/kg/dose IV (Max daily dose: 50 mg/kg/day IV). A loading dose up to 20 mg/kg IV and maintenance doses up to 15 mg/kg IV (Max daily dose: 60 mg/kg/day IV) have been used off-label.

0 to 9 days: 20 mg/kg PO load and 15 mg/kg/dose PO maintenance dose (Max daily dose: 60 mg/kg/day PO); 30 mg/kg PR load and 20 mg/kg/dose PR maintenance dose (Max daily dose: 60 mg/kg/day PR); 12.5 mg/kg/dose IV (Max daily dose: 50 mg/kg/day IV). A loading dose up to 20 mg/kg IV and maintenance doses up to 15 mg/kg IV (Max daily dose: 60 mg/kg/day IV) have been used off-label.

32 to 37 weeks gestation: 20 mg/kg PO load and 15 mg/kg/dose PO maintenance dose (Max daily dose: 60 mg/kg/day PO); 30 mg/kg PR load and 20 mg/kg/dose PR maintenance dose (Max daily dose: 60 mg/kg/day PR); 12.5 mg/kg/dose IV (Max daily dose: 50 mg/kg/day IV). A loading dose up to 20 mg/kg IV and maintenance doses up to 10 mg/kg IV (Max daily dose: 40 mg/kg/day IV) have been used off-label.

28 to 31 weeks PMA: 20 mg/kg PO/PR load and 15 mg/kg/dose PO/PR maintenance dose (Max daily dose: 40 mg/kg/day PO/PR). Safety and efficacy of the IV formulation not established; however, loading doses up to 20 mg/kg IV and maintenance doses up to 10 mg/kg/dose IV (Max daily dose: 22.5 mg/kg/day IV) have been used off-label.

Patients with Hepatic Impairment Dosing

Use with caution in patients with hepatic dysfunction. In patients with chronic hepatic disease, acetaminophen can be used safely; use the smallest dose for the shortest duration necessary.^{23562 54020 54066}

Patients with Renal Impairment Dosing

CrCl ≤ 30 mL/minute: Reduced dosing and prolonged intervals are recommended for IV dosing; however no quantitative recommendations are available. For a CrCl < 10 mL/minute, administer acetaminophen (all dosage forms) at a minimum interval of every 8 hours. Chronic use should be discouraged in patients with underlying renal disease.^{32569 42289 54096}

Intermittent hemodialysis

Administer acetaminophen every 8 hours.³²⁵⁶⁹

Peritoneal dialysis

Administer acetaminophen every 8 hours.³²⁵⁶⁹

Continuous renal replacement therapy (CRRT)

No dosage adjustment necessary.³²⁵⁶⁹

Last revised: February 10, 2017

Administration

General Administration Information

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

NOTE: Acetaminophen-induced hepatotoxicity often involves the use of more than 1 acetaminophen-containing product. Ensure dosing intervals and maximum daily dosage limits are based on all routes of administration (e.g., intravenous, oral, rectal) and all products containing acetaminophen, including both single-entity and combination products.⁴²²⁸⁹

Route-Specific Administration

Oral Administration

- May be taken without regard to meals.

Oral Solid Formulations

- *Immediate-release tablets*: Administer with a sufficient amount of water.
- *Extended-release tablets*: Do not crush, chew, split, or dissolve in liquid.
- *Chewable tablets*: May be swallowed whole or chewed.
- *Effervescent tablets*: Dissolve tablet fully in 6 ounces of room temperature water. Do not chew or swallow whole tablets.
- *Oral granules*: Mix with a small amount of soft food (i.e., applesauce, ice cream, or jam) immediately prior to administration.
- *Oral powders*: Do not administer the capsules containing the powder whole. Open capsule and sprinkle over a small amount of water (less than 5 mL) or mix with a small amount of soft food (i.e., applesauce, ice cream, or jam) immediately prior to administration.⁵⁴⁰²⁰

Oral Liquid Formulations

- Liquid acetaminophen may be available in multiple concentrations. Always verify the concentration before administering each dose.
- For home administration, advise caregivers to administer the amount of medicine listed on the specific drug product label for the patient's weight and age or provide written instructions that specify the dose in milligrams (mg) and/or the concentration and the dose in milliliters (mL).

Oral solution:

- Administer using an oral calibrated measuring device to ensure accurate dosing.

Oral suspension:

- Shake well prior to each use.
- Administer using an oral calibrated measuring device to ensure accurate dosing.

Injectable Administration

- Visually inspect parenteral products for particulate matter and discoloration prior to administration whenever solution and container permit.
- To reduce the risk of dosing errors that can lead to accidental overdose, hepatotoxicity, and even death, use special care when preparing and administering acetaminophen intravenous injection. Specifically, ensure that:
 - the dose in milligrams (mg) and milliliters (mL) is not confused
 - weight-based dosing is used for patients weighing less than 50 kg
 - infusion pumps are properly programmed
 - the total daily acetaminophen dose from all sources does not exceed recommended daily maximum limits [42289](#)

Intravenous Administration

Intermittent IV Infusion Preparation

- No further dilution of acetaminophen injectable solution is required.
- Do not add other medications to the vial or infusion device.
- For doses less than 1,000 mg, the appropriate dose must be withdrawn from the container using aseptic technique and placed in a separate empty, sterile container (e.g., glass bottle, plastic intravenous container, or syringe) prior to administration.
- For patients (weighing 50 kg or more) requiring a 1,000 mg dose, administer the dose by inserting an intravenous set directly in the container; use a vented set for vials and a non-vented set for bags.
- **Storage:** Acetaminophen containers are preservative free. FDA-approved labeling recommends administering the dose within 6 hours once the seal on the container has been penetrated or the dose transferred to another container. Discard any unused portion. [\(WPS/RefShow.aspx?rid=42289\)42289](#) Of note, acetaminophen has retained physical and chemical stability in a range of volumes (10 to 90 mL) for up to 84 hours in opened vials and polypropylene syringes at room temperature (23 to 25 degrees C). According to USP 797 guidelines, a single transfer of acetaminophen from the original vial to a syringe would be classified as a low-risk condition. The maximum exposure time of low-risk-level compounded sterile products (CSPs) is 48 hours at room temperature when the CSP is compounded aseptically within ISO class 5 or higher air quality. [\(WPS/RefShow.aspx?rid=56385\)56385](#)

Intermittent IV Infusion Administration

- Infuse the dose over 15 minutes. [\(WPS/RefShow.aspx?rid=42289\)42289](#)

Rectal Administration

- Instruct patient or caregiver on proper use of suppository.
- Prior to insertion, carefully remove the wrapper. Avoid excessive handling as to avoid melting of the suppository.
- If suppository is too soft to insert, chill in the refrigerator for 30 minutes or run cold water over it before removing the wrapper.
- Moisten the suppository with cool water prior to insertion.
- Have patient lie down on their side, usually in the Sim's lateral position to provide support and comfort.
- Apply gentle pressure to insert the suppository completely into the rectum, pointed end first, using a gloved, lubricated index finger.
- After insertion, keep the patient lying down to aid retention. May gently hold the buttock cheeks close together to keep the patient from immediately expelling the suppository. The suppository must be retained in rectum to ensure complete absorption.

Monitoring Parameters

- LFTs
- serum creatinine/BUN: in chronic use or acute toxicity

Contraindications

- acetaminophen hypersensitivity
- alcoholism
- bone marrow suppression
- breast-feeding
- children
- ethanol intoxication
- G6PD deficiency
- geriatric
- hepatic disease
- hepatitis
- hepatotoxicity
- hypovolemia
- immunosuppression
- infants
- infection
- malnutrition
- neonates
- neutropenia
- phenylketonuria
- potential for overdose or poisoning
- pregnancy
- renal disease
- renal failure
- renal impairment
- tobacco smoking

Acetaminophen is contraindicated in patients with a known *acetaminophen hypersensitivity* or *hypersensitivity to any of the excipients* of the formulation to be used. Acetaminophen hypersensitivity reactions are rare, but severe sensitivity reactions are possible.

Intravenous (IV) acetaminophen is contraindicated in patients with *severe hepatic impairment* or *severe active hepatic disease*. Acetaminophen has the potential for overdose or poisoning causing hepatotoxicity and acute liver failure, at times resulting in liver transplantation and death. Most cases of liver injury are associated with the use of acetaminophen at doses exceeding 4 grams per day and often involve the use of more than one acetaminophen-

containing product. Caution must be used during the preparation and administration of IV acetaminophen, as well as the measurement of oral liquid dosage forms to minimize the risk of dosing errors that can result in accidental overdose. Advise patients receiving acetaminophen to carefully read OTC and prescription labels, to avoid excessive and/or duplicate medications, and to seek medical help immediately if more than 4 grams of acetaminophen is ingested in 1 day, even if they feel well. It is important to note that the risk of acetaminophen-induced hepatotoxicity is increased in patients with pre-existing hepatic disease (e.g., hepatitis), those who ingest alcohol (e.g., ethanol intoxication, alcoholism), those with chronic malnutrition, and those with severe hypovolemia. In patients with chronic hepatic disease, acetaminophen can be used safely in recommended doses and is often preferred to nonsteroidal anti-inflammatory drugs (NSAIDs) due to the absence of platelet impairment, gastrointestinal toxicity, and nephrotoxicity. Though the half-life of acetaminophen may be prolonged, repeated dosing does not result in drug or metabolite accumulation. In addition, cytochrome P450 activity is not increased and glutathione stores are not depleted in hepatically impaired patients taking therapeutic doses, therefore toxic metabolite formation and accumulation is not altered. Although it is always prudent to use the smallest dose of acetaminophen for the shortest duration necessary, courses less than 2 weeks in length have been administered safely to adult patients with stable chronic liver disease.^{23562 42289 54020 54066}

In patients with severe renal impairment or renal failure ($\text{CrCl} \leq 30 \text{ mL/minute}$), dosage adjustment of intravenous acetaminophen may be required.⁴²²⁸⁹ Some studies have suggested an association between chronic use of acetaminophen and renal effects. The National Kidney Foundation states that there is negligible evidence to suggest chronic use of acetaminophen causes analgesic nephropathy; however, there is a weak association between chronic acetaminophen use and the prevalence of chronic renal failure and end stage renal disease.⁵⁴⁰⁹⁶ In a case-controlled study of adult patients with early renal failure, the regular use of acetaminophen (without aspirin) was associated with a risk of chronic renal failure that was 2.5-times as high as that for non-acetaminophen users. The risk increased with an increasing cumulative acetaminophen lifetime dose. The average dose used during periods of regular acetaminophen use also correlated with risk, as those who took 1.4 grams/day or more during periods of regular use had an odds ratio for chronic renal failure of 5.3; duration of therapy was unrelated to risk.²⁷³⁶⁸ The National Kidney Foundation considers acetaminophen as the non-narcotic analgesic of choice for episodic pain in patients with chronic renal disease, but discourages habitual consumption.⁵⁴⁰⁹⁶

Patients with G6PD deficiency who overdose with acetaminophen may be at increased risk for drug-induced hemolysis. Practitioners should be aware of this potential complication and monitor at-risk patients for signs and symptoms of hemolysis. Conflicting data exists on whether therapeutic doses of acetaminophen can cause hemolysis in G6PD deficient patients. However, a direct cause and effect relationship has not been well established and therefore, therapeutic doses are generally considered safe in this population.^{54061 54063}

Symptoms of acute infection (e.g., fever, pain) can be masked during treatment with acetaminophen in patients with bone marrow suppression, especially neutropenia, or immunosuppression.

Tobacco smoking induces the cytochrome P450 isoenzyme CYP1A2 and may potentially increase the risk for acetaminophen-induced hepatotoxicity during overdose via enhanced generation of acetaminophen's hepatotoxic metabolite, N-acetyl-p-benzoquinoneimine (NAPQI). In a retrospective chart review of 602 patients (13 to 86 years of age) admitted for acetaminophen toxicity, current daily tobacco use was registered in 70% of patients. Multivariate analyses found tobacco smoking to be an independent risk factor for hepatotoxicity, hepatic encephalopathy, and death.^{28001 28215}

Caution must be taken when administering acetaminophen to pediatric patients to ensure appropriate dosing. Liquid acetaminophen is available in multiple concentrations; verify the concentration before administering each dose. Other factors that can lead to inadvertent overdoses include substituting adult acetaminophen formulations for pediatric formulations for convenience, misreading or interpreting instructions, or administering more acetaminophen due to persistent fever.²⁵⁴⁶¹ Repeated overdoses of acetaminophen in infants or children in

combination with decreased nutrition may lead to changes in the metabolism of acetaminophen leading to hepatotoxicity. This combination leads to decreases in sulfation, glucuronidation, and glutathione production. Efficacy of IV acetaminophen for the treatment of acute pain has not been established in neonates, infants, and children younger than 2 years. In clinical trials, there was no difference in analgesic effect, measured by the reduced need for additional opioid treatment for pain control, in patients younger than 2 years receiving opioid plus acetaminophen vs. opioid plus placebo. Intravenous acetaminophen is indicated for the treatment of fever in patients as young as 32 weeks gestation.⁴²²⁸⁹

Published epidemiological studies have not reported a clear association with acetaminophen use during pregnancy and birth defects, miscarriage, or adverse maternal or fetal outcomes. Large observational studies of newborns exposed to oral acetaminophen during the first trimester have not shown an increased risk for congenital malformations or major birth defects; however, these studies cannot definitely establish the absence of risk because of methodological limitations.⁴²²⁸⁹ Acetaminophen does cross the placenta and should be used during pregnancy only if the benefits to the mother outweigh the potential risks to the fetus or infant. No overall increase in fetal mortality, determined by pregnancy outcomes of mothers that overdosed on various amounts of oral acetaminophen, was apparent amongst 300 women.²⁷⁷³¹ Treatment with acetylcysteine or methionine did not appear to affect fetal or neonatal toxicity. Of 235 infants exposed to an overdose of only acetaminophen, 168 were normal, 8 had malformations, 16 were spontaneously aborted, and 43 were electively terminated. None of the infants with malformations were exposed during the first trimester, but all of the spontaneous abortions were subsequent to first trimester exposure.

There is no information regarding the presence of intravenous acetaminophen in human milk, the effects on the breastfed infant, or the effects on milk production. However, limited published studies report acetaminophen passes rapidly into human milk with similar concentrations in the milk and plasma. Average and maximum neonatal doses of 1% and 2%, respectively, of the weight-adjusted maternal dose are reported after a single oral dose of 1,000 mg. There is a well-documented report of rash occurring in a breastfed infant that resolved with drug discontinuation and recurred with resumption.⁴²²⁸⁹ According to previous recommendations from the American Academy of Pediatrics (AAP), acetaminophen has not been associated with any observable changes in nursing infants of mothers that took acetaminophen while breast-feeding. The AAP and other experts regard acetaminophen as a maternal medicine that is usually compatible with breast-feeding.²⁷⁵⁰⁰ Consider the benefits of breast-feeding, the risk of potential infant drug exposure, and the risk of an untreated or inadequately treated condition. If a breast-feeding infant experiences an adverse effect related to a maternally ingested drug, healthcare providers are encouraged to report the adverse effect to the FDA.

Some, but not all, acetaminophen products (particularly certain chewable tablets) contain aspartame and should be used with caution in patients with phenylketonuria, since aspartame is a source of phenylalanine. Consult specific product labeling for inactive ingredient content.

The federal Omnibus Budget Reconciliation Act (OBRA) regulates medication use in residents (e.g., geriatric adults) of long-term care facilities (LTCFs). According to OBRA, daily doses of acetaminophen greater than 4 grams/day from all sources (alone or as part of combination products) may increase the risk of hepatotoxicity. For acetaminophen doses greater than the maximum recommended daily dose, OBRA guidelines recommend a documented assessment reflecting periodic monitoring of liver function and an indication that the benefits of therapy outweigh the risks.⁶⁰⁷⁴²

Last revised: February 3, 2017

Interactions

- Abacavir; Lamivudine, 3TC; Zidovudine, ZDV
- Acarbose

- Acetaminophen; Aspirin, ASA; Caffeine
- Acetaminophen; Butalbital
- Acetaminophen; Butalbital; Caffeine
- Acetaminophen; Butalbital; Caffeine; Codeine
- Acetaminophen; Caffeine; Magnesium Salicylate; Phenyltoloxamine
- Acetaminophen; Chlorpheniramine; Dextromethorphan; Phenylephrine
- Acetaminophen; Chlorpheniramine; Dextromethorphan; Pseudoephedrine
- Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine
- Acetaminophen; Dextromethorphan; Guaifenesin; Phenylephrine
- Acetaminophen; Dextromethorphan; Phenylephrine
- Acetaminophen; Dextromethorphan; Pseudoephedrine
- Acetaminophen; Dichloralphenazone; Isometheptene
- Acetaminophen; Guaifenesin; Phenylephrine
- Acetaminophen; Pseudoephedrine
- Acrivastine; Pseudoephedrine
- Adenosine
- Albuterol
- Albuterol; Ipratropium
- Amantadine
- Amiodarone
- Amobarbital
- Amphetamine
- Amphetamine; Dextroamphetamine
- Amphetamine; Dextroamphetamine Salts
- Anagrelide
- Antacids
- Aprepitant, Fosaprepitant
- Arformoterol
- Armodafinil
- Articaine; Epinephrine

- Aspirin, ASA
- Aspirin, ASA; Butalbital; Caffeine
- Aspirin, ASA; Butalbital; Caffeine; Codeine
- Aspirin, ASA; Caffeine; Dihydrocodeine
- Aspirin, ASA; Carisoprodol
- Aspirin, ASA; Carisoprodol; Codeine
- Aspirin, ASA; Dipyridamole
- Aspirin, ASA; Omeprazole
- Aspirin, ASA; Oxycodone
- Aspirin, ASA; Pravastatin
- Atropine; Hyoscyamine; Phenobarbital; Scopolamine
- Barbiturates
- Belladonna Alkaloids; Ergotamine; Phenobarbital
- Benzodiazepines
- Benzphetamine
- Beta-agonists
- Bismuth Subsalicylate
- Bismuth Subsalicylate; Metronidazole; Tetracycline
- Boceprevir
- Brompheniramine; Carbetapentane; Phenylephrine
- Brompheniramine; Hydrocodone; Pseudoephedrine
- Brompheniramine; Pseudoephedrine
- Budesonide; Formoterol
- Bupivacaine
- Bupivacaine Liposomal
- Bupivacaine; Lidocaine
- Bupropion
- Bupropion; Naltrexone
- Busulfan
- Butabarbital

- Caffeine
- Cannabidiol
- Carbamazepine
- Carbetapentane; Chlorpheniramine; Phenylephrine
- Carbetapentane; Diphenhydramine; Phenylephrine
- Carbetapentane; Guaifenesin; Phenylephrine
- Carbetapentane; Phenylephrine
- Carbetapentane; Phenylephrine; Pyrilamine
- Carbetapentane; Pseudoephedrine
- Carbinoxamine; Dextromethorphan; Pseudoephedrine
- Carbinoxamine; Hydrocodone; Phenylephrine
- Carbinoxamine; Hydrocodone; Pseudoephedrine
- Carbinoxamine; Phenylephrine
- Carbinoxamine; Pseudoephedrine
- Cetirizine; Pseudoephedrine
- Charcoal
- Chlophedianol; Dexchlorpheniramine; Pseudoephedrine
- Chlophedianol; Guaifenesin; Phenylephrine
- Chlorprocaine
- Chlorpheniramine; Dextromethorphan; Phenylephrine
- Chlorpheniramine; Dihydrocodeine; Phenylephrine
- Chlorpheniramine; Dihydrocodeine; Pseudoephedrine
- Chlorpheniramine; Guaifenesin; Hydrocodone; Pseudoephedrine
- Chlorpheniramine; Hydrocodone; Phenylephrine
- Chlorpheniramine; Hydrocodone; Pseudoephedrine
- Chlorpheniramine; Phenylephrine
- Chlorpheniramine; Pseudoephedrine
- Cholestyramine
- Choline Salicylate; Magnesium Salicylate
- Cimetidine

- Ciprofloxacin
- Clozapine
- Codeine; Phenylephrine; Promethazine
- Darifenacin
- Dasabuvir; Ombitasvir; Paritaprevir; Ritonavir
- Desloratadine; Pseudoephedrine
- Dexchlorpheniramine; Dextromethorphan; Pseudoephedrine
- Dexmethylphenidate
- Dextroamphetamine
- Dextromethorphan; Diphenhydramine; Phenylephrine
- Dextromethorphan; Guaifenesin; Phenylephrine
- Dextromethorphan; Guaifenesin; Pseudoephedrine
- Diethylpropion
- Diflunisal
- Dihydrocodeine; Guaifenesin; Pseudoephedrine
- Diphenhydramine; Hydrocodone; Phenylephrine
- Diphenhydramine; Phenylephrine
- Dipyridamole
- Disulfiram
- Dobutamine
- Dopamine
- Drospirenone; Ethinyl Estradiol
- Drospirenone; Ethinyl Estradiol; Levomefolate
- Dyphylline
- Dyphylline; Guaifenesin
- Echinacea
- Efavirenz
- Efavirenz; Emtricitabine; Tenofovir
- Efavirenz; Lamivudine; Tenofovir Disoproxil Fumarate
- Eltrombopag

- Ephedrine
- Epinephrine
- Erythromycin
- Erythromycin; Sulfisoxazole
- Eszopiclone
- Ethanol
- Ethinyl Estradiol
- Ethinyl Estradiol; Desogestrel
- Ethinyl Estradiol; Ethynodiol Diacetate
- Ethinyl Estradiol; Etonogestrel
- Ethinyl Estradiol; Levonorgestrel
- Ethinyl Estradiol; Levonorgestrel; Ferrous bisglycinate
- Ethinyl Estradiol; Levonorgestrel; Folic Acid; Levomefolate
- Ethinyl Estradiol; Norelgestromin
- Ethinyl Estradiol; Norethindrone
- Ethinyl Estradiol; Norethindrone Acetate
- Ethinyl Estradiol; Norethindrone Acetate; Ferrous fumarate
- Ethinyl Estradiol; Norethindrone; Ferrous fumarate
- Ethinyl Estradiol; Norgestimate
- Ethinyl Estradiol; Norgestrel
- Exenatide
- Fesoterodine
- Fexofenadine; Pseudoephedrine
- Fluconazole
- Fluticasone; Salmeterol
- Fluticasone; Umeclidinium; Vilanterol
- Fluticasone; Vilanterol
- Fluvoxamine
- Formoterol
- Formoterol; Mometasone

- Glycopyrrolate; Formoterol
- grapefruit juice
- Green Tea
- Guaifenesin; Hydrocodone; Pseudoephedrine
- Guaifenesin; Phenylephrine
- Guaifenesin; Pseudoephedrine
- Guarana
- Hydantoins
- Hydrocodone; Phenylephrine
- Hydrocodone; Potassium Guaiacolsulfonate; Pseudoephedrine
- Hydrocodone; Pseudoephedrine
- Hydroxyprogesterone
- Ibuprofen; Pseudoephedrine
- Imatinib
- Indacaterol
- Indacaterol; Glycopyrrolate
- Insulin Glargine; Lixisenatide
- Isavuconazonium
- Isocarboxazid
- Isoniazid, INH
- Isoniazid, INH; Pyrazinamide, PZA; Rifampin
- Isoniazid, INH; Rifampin
- Isoproterenol
- Ketoconazole
- Ketoprofen
- Lamivudine, 3TC; Zidovudine, ZDV
- Lamotrigine
- Lanthanum Carbonate
- Levalbuterol
- Lidocaine

- Linezolid
- Lisdexamfetamine
- Lithium
- Lixisenatide
- Lomitapide
- Lopinavir; Ritonavir
- Loratadine; Pseudoephedrine
- Magnesium Salicylate
- Melatonin
- Mephobarbital
- Mepivacaine
- Mepivacaine; Levonordefrin
- Mestranol; Norethindrone
- Metaproterenol
- Methamphetamine
- Methohexital
- Methylphenidate
- Metyrapone
- Mexiletine
- Midodrine
- Mipomersen
- Mitotane
- Modafinil
- Monoamine oxidase inhibitors
- Naproxen; Pseudoephedrine
- Non-Ionic Contrast Media
- Norepinephrine
- Obeticholic Acid
- Olodaterol
- Ombitasvir; Paritaprevir; Ritonavir

- Omeprazole; Sodium Bicarbonate
- Oxybutynin
- Peginterferon Alfa-2b
- Pemoline
- Penicillin G Benzathine; Penicillin G Procaine
- Penicillin G Procaine
- Pentobarbital
- Phendimetrazine
- Phenelzine
- Phenobarbital
- Phentermine
- Phentermine; Topiramate
- Phenylephrine
- Phenylephrine; Promethazine
- Pirbuterol
- Pneumococcal Vaccine, Polyvalent
- Posaconazole
- Pramlintide
- Prilocaine
- Prilocaine; Epinephrine
- Primidone
- Procarbazine
- Pseudoephedrine
- Racepinephrine
- Ramelteon
- Rasagiline
- Regadenoson
- Rifabutin
- Rifampin
- Ritodrine

- Ritonavir
- Ropivacaine
- Rucaparib
- Salmeterol
- Salsalate
- Secobarbital
- Selegiline
- Sodium Bicarbonate
- Sodium Oxybate
- Solifenacin
- St. John's Wort, *Hypericum perforatum*
- Sulfinpyrazone
- Suvorexant
- Tasimelteon
- Telaprevir
- Telotristat Ethyl
- Terbinafine
- Terbutaline
- Teriflunomide
- Tetracaine
- Theophylline, Aminophylline
- Thiabendazole
- Thiopental
- Tiotropium; Olodaterol
- Tizanidine
- tobacco
- Tolterodine
- Trandolapril; Verapamil
- Tranlycypromine
- Trimetrexate

- Umeclidinium; Vilanterol
- Vemurafenib
- Verapamil
- Warfarin
- Yohimbine
- Zaleplon
- Zidovudine, ZDV
- Zileuton
- Zolmitriptan
- Zolpidem

Abacavir; Lamivudine, 3TC; Zidovudine, ZDV: (Minor) Both acetaminophen and zidovudine, ZDV undergo glucuronidation. Competition for the metabolic pathway is thought to have caused a case of acetaminophen-related hepatotoxicity. This interaction may be more clinically significant in patients with depleted glutathione stores, such as patients with acquired immunodeficiency syndrome, poor nutrition, or alcoholism. [4928](#)

Acarbose: (Minor) It has been suggested by in vitro and in vivo animal studies that acarbose augments the activity of the hepatic isoenzyme CYP2E1, which is responsible for metabolism of acetaminophen to its toxic reactive metabolite. Patients should avoid the combination of acarbose with acetaminophen and ethanol until more is known about the potential for clinically significant interactions. [2500](#)

Acetaminophen; Aspirin, ASA; Caffeine: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. High-dose, chronic administration of the combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy. [4064](#)

Acetaminophen; Butalbital: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites. [4939](#) [6522](#) (Minor) The metabolism of caffeine can be increased by concurrent use with barbiturates. The hypnotic effects of barbiturates can be reduced by caffeine administration. [4718](#)

Acetaminophen; Butalbital; Caffeine: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites. [4939](#) [6522](#) (Minor) The metabolism of caffeine can be increased by concurrent use with barbiturates. The hypnotic effects of barbiturates can be reduced by caffeine administration. [4718](#)

Acetaminophen; Butalbital; Caffeine; Codeine: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites. [4939](#) [6522](#) (Minor) The metabolism of caffeine can be increased by concurrent use with barbiturates. The hypnotic effects of barbiturates can be reduced by caffeine administration. [4718](#)

Acetaminophen; Caffeine; Magnesium Salicylate; Phenyltoloxamine: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. Although salicylates are rarely associated with nephrotoxicity, high-dose, chronic administration of salicylates combined other analgesics, including acetaminophen, significantly

increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Additive hepatic toxicity may occur, especially in combined overdose situations. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy. ⁴⁰⁶⁴

Acetaminophen; Chlorpheniramine; Dextromethorphan; Phenylephrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. ²⁷⁹⁵⁰

Acetaminophen; Chlorpheniramine; Dextromethorphan; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. ²⁷⁹⁵⁰

Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. ²⁷⁹⁵⁰

Acetaminophen; Dextromethorphan; Guaifenesin; Phenylephrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. ²⁷⁹⁵⁰

Acetaminophen; Dextromethorphan; Phenylephrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. ²⁷⁹⁵⁰

Acetaminophen; Dextromethorphan; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. ²⁷⁹⁵⁰

Acetaminophen; Dichloralphenazone; Isometheptene: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants. ⁴⁶⁶⁶

Acetaminophen; Guaifenesin; Phenylephrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. ²⁷⁹⁵⁰

Acetaminophen; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. ²⁷⁹⁵⁰

Acrivastine; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. [27950](#)

Adenosine: (Major) Methylxanthines, such as theophylline, aminophylline, or caffeine, competitively block the effects of adenosine. If possible, stop use of methylxanthines at least 5 half-lives prior to administering adenosine. Patients receiving theophylline, aminophylline and adenosine should be monitored for adenosine efficacy; larger doses of adenosine may be required to achieve antiarrhythmic goals in some patients. In addition, larger doses of adenosine may be required for therapeutic effect if administered to patients with high daily caffeine intake (including caffeine from foods and beverages such as coffee, green tea, other teas, colas, and chocolate). Theophylline, aminophylline may increase the risk of seizures associated with adenosine; avoid methylxanthine use in patients who have experienced an adenosine-associated seizure. Methylxanthines, such as caffeine, theophylline, and theobromine, are also found in guarana. [43606](#) [4654](#)

Albuterol: (Moderate) Sensitive patients may wish to limit or avoid excessive caffeine intake from foods, beverages, dietary supplements and medications during therapy with beta-agonists. Additive side effects may occur between caffeine and beta-agonists. Caffeine is a CNS-stimulant and beta-agonists are sympathomimetic agents. Sensitive patients might experience tremor, sleep difficulties, or mild increases in heart rate. [27950](#)

Albuterol; Ipratropium: (Moderate) Sensitive patients may wish to limit or avoid excessive caffeine intake from foods, beverages, dietary supplements and medications during therapy with beta-agonists. Additive side effects may occur between caffeine and beta-agonists. Caffeine is a CNS-stimulant and beta-agonists are sympathomimetic agents. Sensitive patients might experience tremor, sleep difficulties, or mild increases in heart rate. [27950](#)

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. [4771](#)

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. [4718](#) [4950](#)

Amobarbital: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites. [4939](#) [6522](#) (Minor) The metabolism of caffeine can be increased by concurrent use with barbiturates. The hypnotic effects of barbiturates can be reduced by caffeine administration. [4718](#)

Amphetamine: (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. [27950](#) [29332](#) [29786](#) [53320](#) [59396](#) [60070](#)

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. [27950](#) [29332](#) [29786](#) [53320](#) [59396](#) [60070](#)

Amphetamine; Dextroamphetamine: (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. [27950](#) [29332](#) [29786](#) [53320](#) [59396](#) [60070](#)

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. [30163](#) [30802](#)

Antacids: (Minor) Antacids can delay the oral absorption of acetaminophen, but the interactions are not likely to be clinically significant as the extent of acetaminophen absorption is not appreciably affected. [6086](#)

Aprepitant, Fosaprepitant: (Minor) Use caution if acetaminophen and aprepitant are used concurrently and monitor for an increase in acetaminophen-related adverse effects for several days after administration of a multi-day aprepitant regimen. Acetaminophen is a minor (10 to 15%) substrate of CYP3A4. Aprepitant, when administered as a 3-day oral regimen (125 mg/80 mg/80 mg), is a moderate CYP3A4 inhibitor and inducer and may increase plasma concentrations of acetaminophen. For example, a 5-day oral aprepitant regimen increased the AUC of another CYP3A4 substrate, midazolam (single dose), by 2.3-fold on day 1 and by 3.3-fold on day 5. After a 3-day oral aprepitant regimen, the AUC of midazolam (given on days 1, 4, 8, and 15) increased by 25% on day 4, and then decreased by 19% and 4% on days 8 and 15, respectively. As a single 125 mg or 40 mg oral dose, the inhibitory effect of aprepitant on CYP3A4 is weak, with the AUC of midazolam increased by 1.5-fold and 1.2-fold, respectively. After administration, fosaprepitant is rapidly converted to aprepitant and shares many of the same drug interactions. However, as a single 150 mg intravenous dose, fosaprepitant only weakly inhibits CYP3A4 for a duration of 2 days; there is no evidence of CYP3A4 induction. Fosaprepitant 150 mg IV as a single dose increased the AUC of midazolam (given on days 1 and 4) by approximately 1.8-fold on day 1; there was no effect on day 4. Less than a 2-fold increase in the midazolam AUC is not considered clinically important. [25460](#) [28100](#) [30676](#) [40027](#)

Arformoterol: (Moderate) Sensitive patients may wish to limit or avoid excessive caffeine intake from foods, beverages, dietary supplements and medications during therapy with beta-agonists. Additive side effects may occur between caffeine and beta-agonists. Caffeine is a CNS-stimulant and beta-agonists are sympathomimetic agents. Sensitive patients might experience tremor, sleep difficulties, or mild increases in heart rate. [27950](#)

Armodafinil: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with armodafinil. Caffeine should be used cautiously with armodafinil. Intake of caffeine should be limited. Excessive intake may cause nervousness, irritability, insomnia, or other side effects. [33467](#) [4666](#)

Articaine; Epinephrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants. [4666](#) (Moderate) Coadministration of articaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue articaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. [28996](#)

Aspirin, ASA: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. High-dose, chronic administration of the combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy. [4064](#)

Aspirin, ASA; Butalbital; Caffeine: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. High-dose, chronic administration of the combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Do not exceed the recommended

individual maximum doses when these agents are given concurrently for short-term therapy. ⁴⁰⁶⁴ (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites. ^{4939 6522} (Minor) The metabolism of caffeine can be increased by concurrent use with barbiturates. The hypnotic effects of barbiturates can be reduced by caffeine administration. ⁴⁷¹⁸

Aspirin, ASA; Butalbital; Caffeine; Codeine: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. High-dose, chronic administration of the combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy. ⁴⁰⁶⁴ (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites. ^{4939 6522} (Minor) The metabolism of caffeine can be increased by concurrent use with barbiturates. The hypnotic effects of barbiturates can be reduced by caffeine administration. ⁴⁷¹⁸

Aspirin, ASA; Caffeine; Dihydrocodeine: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. High-dose, chronic administration of the combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy. ⁴⁰⁶⁴

Aspirin, ASA; Carisoprodol: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. High-dose, chronic administration of the combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy. ⁴⁰⁶⁴

Aspirin, ASA; Carisoprodol; Codeine: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. High-dose, chronic administration of the combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy. ⁴⁰⁶⁴

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 methylxanthines (caffeine, caffeinated beverages and foods, theophylline, etc.) be discontinued for at least 24 hours prior to stress testing. An interaction is not expected when methylxanthines are used concomitantly with chronic dipyridamole therapy. ²⁹⁹¹¹ (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. High-dose, chronic administration of the combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy. ⁴⁰⁶⁴

Aspirin, ASA; Omeprazole: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. High-dose, chronic administration of the combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy. ⁴⁰⁶⁴

Aspirin, ASA; Oxycodone: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. High-dose, chronic administration of the combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy. ⁴⁰⁶⁴

Aspirin, ASA; Pravastatin: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. High-dose, chronic administration of the combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy. [4064](#)

Atropine; Hyoscyamine; Phenobarbital; Scopolamine: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites. [4939](#) [6522](#) (Minor) The metabolism of caffeine can be increased by concurrent use with barbiturates. The hypnotic effects of barbiturates can be reduced by caffeine administration. [4718](#)

Barbiturates: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites. [4939](#) [6522](#) (Minor) The metabolism of caffeine can be increased by concurrent use with barbiturates. The hypnotic effects of barbiturates can be reduced by caffeine administration. [4718](#)

Belladonna Alkaloids; Ergotamine; Phenobarbital: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites. [4939](#) [6522](#) (Minor) The metabolism of caffeine can be increased by concurrent use with barbiturates. The hypnotic effects of barbiturates can be reduced by caffeine administration. [4718](#)

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. [4678](#) [4764](#)

Benzphetamine: (Moderate) Avoid excessive caffeine intake during use of benzphetamine. 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. [27950](#) [28456](#) [53320](#)

Beta-agonists: (Moderate) Sensitive patients may wish to limit or avoid excessive caffeine intake from foods, beverages, dietary supplements and medications during therapy with beta-agonists. Additive side effects may occur between caffeine and beta-agonists. Caffeine is a CNS-stimulant and beta-agonists are sympathomimetic agents. Sensitive patients might experience tremor, sleep difficulties, or mild increases in heart rate. [27950](#)

Bismuth Subsalicylate: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. Although salicylates are rarely associated with nephrotoxicity, high-dose, chronic administration of salicylates combined other analgesics, including acetaminophen, significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Additive hepatic toxicity may occur, especially in combined overdose situations. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy. [4064](#)

Bismuth Subsalicylate; Metronidazole; Tetracycline: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. Although salicylates are rarely associated with nephrotoxicity, high-dose, chronic administration of salicylates combined other analgesics, including acetaminophen, significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Additive hepatic toxicity may occur, especially in combined overdose situations. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy. [4064](#)

Boceprevir: (Moderate) Close clinical monitoring is advised when administering acetaminophen with boceprevir due to an increased potential for acetaminophen-related adverse events. If acetaminophen dose adjustments are made, re-adjust the dose upon completion of boceprevir treatment. Although this interaction has not been studied, predictions about the interaction can be made based on the metabolic pathway of acetaminophen. Acetaminophen is partially metabolized by the hepatic isoenzyme CYP3A4; boceprevir inhibits this isoenzyme. Coadministration may result in elevated acetaminophen plasma concentrations. [25460](#) [28100](#) [44314](#)

Brompheniramine; Carbetapentane; Phenylephrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. [27950](#)

Brompheniramine; Hydrocodone; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. [27950](#)

Brompheniramine; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. [27950](#)

Budesonide; Formoterol: (Moderate) Sensitive patients may wish to limit or avoid excessive caffeine intake from foods, beverages, dietary supplements and medications during therapy with beta-agonists. Additive side effects may occur between caffeine and beta-agonists. Caffeine is a CNS-stimulant and beta-agonists are sympathomimetic agents. Sensitive patients might experience tremor, sleep difficulties, or mild increases in heart rate. [27950](#)

Bupivacaine Liposomal: (Moderate) Coadministration of bupivacaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue bupivacaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. [52331](#)

Bupivacaine: (Moderate) Coadministration of bupivacaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue bupivacaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. [52331](#)

Bupivacaine; Lidocaine: (Moderate) Coadministration of bupivacaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue bupivacaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. [52331](#) (Moderate) Coadministration of lidocaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue

lidocaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. [43383](#)

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. [28058](#)

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. [28058](#)

Busulfan: (Moderate) Use busulfan and acetaminophen together with caution; concomitant use may result in increased busulfan levels and increased busulfan toxicity. Separating the administration of these drugs may mitigate this interaction; avoid giving acetaminophen within 72 hours prior to or concurrently with busulfan. Busulfan is metabolized in the liver through conjugation with glutathione; acetaminophen decreases glutathione levels in the blood and tissues and may reduce the clearance of busulfan. [60818](#)

Butabarbital: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites. [4939](#) [6522](#) (Minor) The metabolism of caffeine can be increased by concurrent use with barbiturates. The hypnotic effects of barbiturates can be reduced by caffeine administration. [4718](#)

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. [27950](#) [59396](#) [60064](#)

Cannabidiol: (Moderate) Consider a dose adjustment of caffeine when coadministered with cannabidiol. Coadministration may alter plasma concentrations of caffeine resulting in an increased risk of adverse reactions and/or decreased efficacy. Caffeine is a sensitive CYP1A2 substrate. In vitro data predicts inhibition or induction of CYP1A2 by cannabidiol potentially resulting in clinically significant interactions. [63309](#)

Carbamazepine: (Minor) Carbamazepine may induce caffeine metabolism via induction of the hepatic CYP1A2 isoenzyme. [4666](#) [4718](#) (Minor) Carbamazepine may potentially accelerate the hepatic metabolism of acetaminophen. In addition, due to enzyme induction, carbamazepine may increase the risk for acetaminophen-induced hepatotoxicity via generation of a greater percentage of acetaminophen's hepatotoxic metabolite, NAPQI. Clinicians should be alert to decreased effect of acetaminophen. Dosage adjustments may be necessary, and closer monitoring of clinical and/or adverse effects is warranted. [4718](#) [4754](#) [4939](#)

Carbetapentane; Chlorpheniramine; Phenylephrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. [27950](#)

Carbetapentane; Diphenhydramine; Phenylephrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. [27950](#)

Carbetapentane; Guaifenesin; Phenylephrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. [27950](#)

Carbetapentane; Phenylephrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. [27950](#)

Carbetapentane; Phenylephrine; Pyrilamine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. [27950](#)

Carbetapentane; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. [27950](#)

Carbinoxamine; Dextromethorphan; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. [27950](#)

Carbinoxamine; Hydrocodone; Phenylephrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. [27950](#)

Carbinoxamine; Hydrocodone; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. [27950](#)

Carbinoxamine; Phenylephrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. [27950](#)

Carbinoxamine; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. [27950](#)

Cetirizine; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. [27950](#)

Charcoal: (Minor) Activated charcoal binds many drugs within the gut. Administering charcoal dietary supplements at the same time as a routine acetaminophen dosage would be expected to interfere with the analgesic and antipyretic efficacy of acetaminophen. Charcoal is mostly used in the setting of acetaminophen overdose; however, patients should never try to treat an acetaminophen overdose with charcoal dietary supplements. Advise patients to get immediate medical attention for an acetaminophen overdose. [219](#) [2744](#) [4944](#)

Chlophedianol; Dexchlorpheniramine; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. [27950](#)

Chlophedianol; Guaifenesin; Phenylephrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. [27950](#)

Chloroprocaine: (Moderate) Coadministration of chloroprocaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue chloroprocaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. [29062](#)

Chlorpheniramine; Dextromethorphan; Phenylephrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. [27950](#)

Chlorpheniramine; Dihydrocodeine; Phenylephrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. [27950](#)

Chlorpheniramine; Dihydrocodeine; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. [27950](#)

Chlorpheniramine; Guaifenesin; Hydrocodone; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. [27950](#)

Chlorpheniramine; Hydrocodone; Phenylephrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. [27950](#)

Chlorpheniramine; Hydrocodone; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. [27950](#)

Chlorpheniramine; Phenylephrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. [27950](#)

Chlorpheniramine; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. [27950](#)

Cholestyramine: (Moderate) Cholestyramine has been shown to decrease the absorption of acetaminophen by roughly 60%. Experts have recommended that cholestyramine not be given within 1 hour of acetaminophen if analgesic or antipyretic effect is to be achieved. [4944](#) [4973](#)

Choline Salicylate; Magnesium Salicylate: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. Although salicylates are rarely associated with nephrotoxicity, high-dose, chronic administration of salicylates combined other analgesics, including acetaminophen, significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Additive hepatic toxicity may occur, especially in combined overdose situations. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy. [4064](#)

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. [4660](#) [4666](#)

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. [27950](#) [28764](#) [43411](#) [43570](#)

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. [27947](#)

Codeine; Phenylephrine; Promethazine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. [27950](#)

Darifenacin: (Minor) Consuming > 400 mg/day caffeine has been associated with the development of urinary incontinence. Caffeine may aggravate bladder symptoms, increase urination, 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). [5985](#)

Dasabuvir; Ombitasvir; Paritaprevir; Ritonavir: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [25460](#) [28100](#) [58664](#)

Desloratadine; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. [27950](#)

Dexchlorpheniramine; Dextromethorphan; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. [27950](#)

Dexmethylphenidate: (Moderate) Caffeine is a CNS stimulant and such actions are expected to be additive when coadministered with psychostimulants such as dexmethylphenidate. Avoid excessive caffeine intake during use of dexmethylphenidate. 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, tachycardia, or tremor. Patients should avoid medications and dietary supplements which contain high amounts of caffeine. [28519](#) [53320](#)

Dextroamphetamine: (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. [27950](#) [29332](#) [29786](#) [53320](#) [59396](#) [60070](#)

Dextromethorphan; Diphenhydramine; Phenylephrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. [27950](#)

Dextromethorphan; Guafenesin; Phenylephrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. [27950](#)

Dextromethorphan; Guafenesin; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. [27950](#)

Diethylpropion: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants. [4666](#) [5851](#)

Diflunisal: (Moderate) Acetaminophen plasma concentrations can increase by approximately 50% following administration of diflunisal. Acetaminophen has no effect on diflunisal concentrations. Acetaminophen in high doses has been associated with severe hepatotoxic reactions; therefore, caution should be exercised when using these agents concomitantly. [28370](#)

Dihydrocodeine; Guaifenesin; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. [27950](#)

Diphenhydramine; Hydrocodone; Phenylephrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. [27950](#)

Diphenhydramine; Phenylephrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. [27950](#)

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 methylxanthines (caffeine, caffeinated beverages and foods, theophylline, etc.) be discontinued for at least 24 hours prior to stress testing. An interaction is not expected when methylxanthines are used concomitantly with chronic dipyridamole therapy. [29911](#)

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 in caffeine clearance could be significant in some patients, including some patients with cardiovascular disease. [29908](#)

Dobutamine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants. [4666](#)

Dopamine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants. [4666](#)

Drospirenone; Ethinyl Estradiol: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects. [41929](#) (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 to minimize caffeine-related side effects such as nausea or tremors. [31082](#)

Drospirenone; Ethinyl Estradiol; Levomefolate: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects. [41929](#) (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 to minimize caffeine-related side effects such as nausea or tremors. [31082](#)

Dyphylline: (Major) Due to the risk for additive adverse effects, avoid the concurrent administration of caffeine and dyphylline-containing products when possible. Concurrent administration can produce excessive xanthine-related adverse events such as nausea, irritability, nervousness, and insomnia. More severe adverse effects such as tremors, seizures, or cardiac arrhythmias are also possible with excessive dosages and in sensitive patients. In addition, counsel patients to limit dietary caffeine intake while taking dyphylline. [27950](#) [47047](#)

Dyphylline; Guaifenesin: (Major) Due to the risk for additive adverse effects, avoid the concurrent administration of caffeine and dyphylline-containing products when possible. Concurrent administration can produce excessive xanthine-related adverse events such as nausea, irritability, nervousness, and insomnia. More severe adverse effects such as tremors, seizures, or cardiac arrhythmias are also possible with excessive dosages and in sensitive patients. In addition, counsel patients to limit dietary caffeine intake while taking dyphylline. [27950](#) [47047](#)

Echinacea: (Moderate) Echinacea may inhibit the metabolism of caffeine. Echinacea reduces the oral clearance of caffeine by 27 percent and increases the mean AUC by 129 percent. Monitor patients for signs of increased caffeine serum concentrations if these drugs are coadministered until more data are available. [30802](#) [32082](#)

Efavirenz: (Minor) Drugs that induce the hepatic isoenzymes CYP2E1 and CYP1A2, such as efavirenz, may potentially increase the risk for acetaminophen-induced hepatotoxicity via generation of a greater percentage of acetaminophen's hepatotoxic metabolite, NAPQI. Also, the analgesic activity of acetaminophen may be reduced. [4718](#) [4939](#)

Efavirenz; Emtricitabine; Tenofovir: (Minor) Drugs that induce the hepatic isoenzymes CYP2E1 and CYP1A2, such as efavirenz, may potentially increase the risk for acetaminophen-induced hepatotoxicity via generation of a greater percentage of acetaminophen's hepatotoxic metabolite, NAPQI. Also, the analgesic activity of acetaminophen may be reduced. [4718](#) [4939](#)

Efavirenz; Lamivudine; Tenofovir Disoproxil Fumarate: (Minor) Drugs that induce the hepatic isoenzymes CYP2E1 and CYP1A2, such as efavirenz, may potentially increase the risk for acetaminophen-induced hepatotoxicity via generation of a greater percentage of acetaminophen's hepatotoxic metabolite, NAPQI. Also, the analgesic activity of acetaminophen may be reduced. [4718](#) [4939](#)

Eltrombopag: (Moderate) Eltrombopag is a UDP-glucuronyltransferase inhibitor. Acetaminophen is a substrate of UDP-glucuronyltransferases. The significance or effect of this interaction is not known; however, elevated concentrations of acetaminophen are possible. Monitor patients for adverse reactions if these drugs are coadministered. [11579](#)

Ephedrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants like ephedrine. Adverse effects such as nervousness, irritability, insomnia, and/or cardiac arrhythmias are also possible when excessive dosages of caffeine are taken concurrently with ephedrine. Patients may also need to limit their intake of caffeine-containing beverages or foods (e.g., coffee, green tea, other teas, guarana, colas, or chocolate) to avoid caffeine-like side effects. [26815](#) [27950](#)

Epinephrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants. [4666](#)

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. [27950](#)

Erythromycin; Sulfoxazole: (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. [27950](#)

Eszopiclone: (Minor) Patients taking eszopiclone for sleep should avoid caffeine-containing medications, dietary supplements, foods, and beverages close to bedtime, as well as excessive total daily caffeine intake, as part of proper sleep hygiene, since caffeine intake can interfere with proper sleep. Limit use of caffeine-containing products including medications, dietary supplements (e.g., guarana), and beverages (e.g., coffee, green tea, other teas, or colas). [60064](#)

Ethanol: (Major) The risk of developing hepatotoxicity from acetaminophen appears to be increased in patients who regularly consume ethanol. Patients who drink more than 3 alcoholic drinks a day and take acetaminophen are at increased risk of developing hepatotoxicity. Acute or chronic ethanol use increases acetaminophen-induced hepatotoxicity by inducing cytochrome P450 CYP 2E1 leading to increased formation of the hepatotoxic metabolite of acetaminophen. Also, chronic alcohol use can deplete liver glutathione stores. Administration of acetaminophen should be limited or avoided altogether in patients with alcoholism or patients who consume ethanol regularly. [24018](#)
[25035](#) [28210](#)

Ethinyl Estradiol: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects. [41929](#) (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 to minimize caffeine-related side effects such as nausea or tremors. [31082](#)

Ethinyl Estradiol; Desogestrel: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects. [41929](#) (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 to minimize caffeine-related side effects such as nausea or tremors. [31082](#)

Ethinyl Estradiol; Ethynodiol Diacetate: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects. [41929](#) (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 to minimize caffeine-related side effects such as nausea or tremors. [31082](#)

Ethinyl Estradiol; Etonogestrel: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects. [41929](#) (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 to minimize caffeine-related side effects such as nausea or tremors. [31082](#)

Ethinyl Estradiol; Levonorgestrel: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects. [41929](#) (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 to minimize caffeine-related side effects such as nausea or tremors. [31082](#)

Ethinyl Estradiol; Levonorgestrel; Ferrous bisglycinate: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects. ⁴¹⁹²⁹ (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 to minimize caffeine-related side effects such as nausea or tremors. ³¹⁰⁸²

Ethinyl Estradiol; Levonorgestrel; Folic Acid; Levomefolate: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects. ⁴¹⁹²⁹ (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 to minimize caffeine-related side effects such as nausea or tremors. ³¹⁰⁸²

Ethinyl Estradiol; Norelgestromin: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects. ⁴¹⁹²⁹ (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 to minimize caffeine-related side effects such as nausea or tremors. ³¹⁰⁸²

Ethinyl Estradiol; Norethindrone Acetate: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects. ⁴¹⁹²⁹ (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 to minimize caffeine-related side effects such as nausea or tremors. ³¹⁰⁸²

Ethinyl Estradiol; Norethindrone Acetate; Ferrous fumarate: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects. ⁴¹⁹²⁹ (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 to minimize caffeine-related side effects such as nausea or tremors. ³¹⁰⁸²

Ethinyl Estradiol; Norethindrone: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects. ⁴¹⁹²⁹ (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 to minimize caffeine-related side effects such as nausea or tremors. ³¹⁰⁸²

Ethinyl Estradiol; Norethindrone; Ferrous fumarate: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects. ⁴¹⁹²⁹ (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 to minimize caffeine-related side effects such as nausea or tremors. ³¹⁰⁸²

Ethinyl Estradiol; Norgestimate: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects. ⁴¹⁹²⁹ (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 to minimize caffeine-related side effects such as nausea or tremors. ³¹⁰⁸²

Ethinyl Estradiol; Norgestrel: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects. [41929](#) (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 to minimize caffeine-related side effects such as nausea or tremors. [31082](#)

Exenatide: (Minor) Although an interaction is possible, these drugs may be used together. To avoid potential pharmacokinetic interactions that might alter effectiveness of acetaminophen, it may be advisable for patients to take acetaminophen at least 1 hour prior to an exenatide injection. When 1,000 mg acetaminophen elixir was given with 10 mcg exenatide (at 0 hours) and at 1, 2 and 4 hours after exenatide injection, acetaminophen AUCs were decreased by 21%, 23%, 24%, and 14%, respectively; C_{max} was decreased by 37%, 56%, 54%, and 41%, respectively. Additionally, acetaminophen T_{max} was delayed from 0.6 hours in the control period to 0.9, 4.2, 3.3, and 1.6 hours, respectively. Acetaminophen AUC, C_{max}, and T_{max} were not significantly changed when acetaminophen was given 1 h before exenatide injection. The mechanism of this interaction is not available (although it may be due to delayed gastric emptying from exenatide use) and the clinical impact has not been assessed. [44456](#) [48491](#)

Fesoterodine: (Minor) Beverages containing caffeine or ethanol may aggravate bladder symptoms and counteract the effectiveness of fesoterodine 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) and alcoholic beverages. [5985](#)

Fexofenadine; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. [27950](#)

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. [6582](#)

Fluticasone; Salmeterol: (Moderate) Sensitive patients may wish to limit or avoid excessive caffeine intake from foods, beverages, dietary supplements and medications during therapy with beta-agonists. Additive side effects may occur between caffeine and beta-agonists. Caffeine is a CNS-stimulant and beta-agonists are sympathomimetic agents. Sensitive patients might experience tremor, sleep difficulties, or mild increases in heart rate. [27950](#)

Fluticasone; Umeclidinium; Vilanterol: (Moderate) Sensitive patients may wish to limit or avoid excessive caffeine intake from foods, beverages, dietary supplements and medications during therapy with beta-agonists. Additive side effects may occur between caffeine and beta-agonists. Caffeine is a CNS-stimulant and beta-agonists are sympathomimetic agents. Sensitive patients might experience tremor, sleep difficulties, or mild increases in heart rate. [27950](#)

Fluticasone; Vilanterol: (Moderate) Sensitive patients may wish to limit or avoid excessive caffeine intake from foods, beverages, dietary supplements and medications during therapy with beta-agonists. Additive side effects may occur between caffeine and beta-agonists. Caffeine is a CNS-stimulant and beta-agonists are sympathomimetic agents. Sensitive patients might experience tremor, sleep difficulties, or mild increases in heart rate. [27950](#)

Fluvoxamine: (Moderate) Strong inhibitors of CYP1A2, such as fluvoxamine, may inhibit the metabolism of caffeine. No specific management is recommended except in patients with caffeine-related side effects after initiating fluvoxamine. In such patients, the dosage of caffeine containing medications or the ingestion of caffeine containing products may need to be reduced. [47184](#)

Formoterol: (Moderate) Sensitive patients may wish to limit or avoid excessive caffeine intake from foods, beverages, dietary supplements and medications during therapy with beta-agonists. Additive side effects may occur between caffeine and beta-agonists. Caffeine is a CNS-stimulant and beta-agonists are sympathomimetic agents. Sensitive patients might experience tremor, sleep difficulties, or mild increases in heart rate. [27950](#)

Formoterol; Mometasone: (Moderate) Sensitive patients may wish to limit or avoid excessive caffeine intake from foods, beverages, dietary supplements and medications during therapy with beta-agonists. Additive side effects may occur between caffeine and beta-agonists. Caffeine is a CNS-stimulant and beta-agonists are sympathomimetic agents. Sensitive patients might experience tremor, sleep difficulties, or mild increases in heart rate. [27950](#)

Glycopyrrolate; Formoterol: (Moderate) Sensitive patients may wish to limit or avoid excessive caffeine intake from foods, beverages, dietary supplements and medications during therapy with beta-agonists. Additive side effects may occur between caffeine and beta-agonists. Caffeine is a CNS-stimulant and beta-agonists are sympathomimetic agents. Sensitive patients might experience tremor, sleep difficulties, or mild increases in heart rate. [27950](#)

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. [27960](#) [27961](#)

Green Tea: (Moderate) Many green tea products contain caffeine. Due to the risk for adverse effects, avoid the concurrent administration of caffeine and green tea products that contain caffeine when possible. Concurrent administration can produce excessive caffeine-related adverse events such as nausea, irritability, nervousness, and insomnia. [27950](#) [29828](#)

Guaifenesin; Hydrocodone; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. [27950](#)

Guaifenesin; Phenylephrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. [27950](#)

Guaifenesin; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. [27950](#)

Guarana: (Major) Caffeine and, to a small extent, theophylline are active constituents of guarana. The concurrent administration of guarana to patients taking methylxanthines 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 guarana are taken concurrently with caffeine, aminophylline or theophylline, or with dyphylline. Patients prescribed these methylxanthine-containing medications should avoid ingesting dietary supplements containing guarana. Patients may also need to limit their intake of guarana-containing beverages to avoid caffeine-like side effects. [27950](#) [4679](#)

Hydantoin: (Minor) Hydantoin anticonvulsants induce hepatic microsomal enzymes and may increase the metabolism of other drugs, leading to reduced efficacy of medications like acetaminophen. In addition, the risk of hepatotoxicity from acetaminophen may be increased with the chronic dosing of acetaminophen along with phenytoin. Adhere to recommended acetaminophen dosage limits. Acetaminophen-related hepatotoxicity has occurred clinically with the concurrent use of acetaminophen 1300 mg to 6200 mg daily and phenytoin.

Acetaminophen cessation led to serum transaminase normalization within 2 weeks. ^{4718 4927} (Minor) The metabolism of caffeine, can be increased by concurrent use with medications that cause induction of hepatic CYP450 enzymes like the hydantoin anticonvulsants. ^{4666 5265 5503}

Hydrocodone; Phenylephrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. ²⁷⁹⁵⁰

Hydrocodone; Potassium Guaiacolsulfonate; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. ²⁷⁹⁵⁰

Hydrocodone; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. ²⁷⁹⁵⁰

Hydroxyprogesterone: (Moderate) In vitro studies indicate that hydroxyprogesterone increases the metabolic rate of CYP2A6 isoenzymes. The metabolism of drugs metabolized by CYP2A6, such as acetaminophen may be increased during treatment with hydroxyprogesterone. ⁴³³¹⁶

Ibuprofen; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. ²⁷⁹⁵⁰

Imatinib: (Major) Imatinib, STI-571 may affect the metabolism of acetaminophen. In vitro, imatinib was found to inhibit acetaminophen O-glucuronidation at therapeutic levels. Therefore, systemic exposure to acetaminophen is expected to be increased with coadministration of imatinib. Chronic acetaminophen therapy should be avoided in patients receiving imatinib. ⁴⁹⁶⁶

Indacaterol: (Moderate) Sensitive patients may wish to limit or avoid excessive caffeine intake from foods, beverages, dietary supplements and medications during therapy with beta-agonists. Additive side effects may occur between caffeine and beta-agonists. Caffeine is a CNS-stimulant and beta-agonists are sympathomimetic agents. Sensitive patients might experience tremor, sleep difficulties, or mild increases in heart rate. ²⁷⁹⁵⁰

Indacaterol; Glycopyrrolate: (Moderate) Sensitive patients may wish to limit or avoid excessive caffeine intake from foods, beverages, dietary supplements and medications during therapy with beta-agonists. Additive side effects may occur between caffeine and beta-agonists. Caffeine is a CNS-stimulant and beta-agonists are sympathomimetic agents. Sensitive patients might experience tremor, sleep difficulties, or mild increases in heart rate. ²⁷⁹⁵⁰

Insulin Glargine; Lixisenatide: (Minor) When 1,000 mg acetaminophen was given 1 or 4 hours after 10 mcg lixisenatide, the AUC was not significantly changed, but the acetaminophen C_{max} was decreased by 29% and 31%, respectively and median T_{max} was delayed by 2 and 1.75 hours, respectively. Acetaminophen AUC, C_{max}, and T_{max}

were not significantly changed when acetaminophen was given 1 h before lixisenatide injection. The mechanism of this interaction is not available (although it may be due to delayed gastric emptying) and the clinical impact has not been assessed. To avoid potential pharmacokinetic interactions that might alter effectiveness of acetaminophen, it may be advisable for patients to take acetaminophen at least one hour prior to lixisenatide subcutaneous injection. [61024](#)

Isavuconazonium: (Moderate) Concomitant use of isavuconazonium with acetaminophen may result in increased serum concentrations of acetaminophen. Acetaminophen is a substrate of the hepatic isoenzyme CYP3A4; isavuconazole, the active moiety of isavuconazonium, is a moderate inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are used together. [25460](#) [28100](#) [59042](#)

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. Ordinarily, selegiline may be an exception, it can only be used safely without dietary restrictions at doses where it presumably selectively inhibits MAO-B (e.g., 10 mg/day). At doses of 20 mg/day, selegiline can interact with foods and beverages. The precise dose at which selegiline becomes a non-selective inhibitor of all MAO is unknown, but may be in the range of 30 to 40 mg per day. Attention to the dose dependent nature of selegiline's selectivity is critical if it is to be used without elaborate restrictions being placed on diet. [27957](#) [29656](#) [53440](#) [61157](#)

Isoniazid, INH: (Major) Agents which induce the hepatic isoenzyme CYP2E1, such as isoniazid, may potentially increase the risk for acetaminophen-induced hepatotoxicity via generation of a greater percentage of acetaminophen's hepatotoxic metabolites. The combination of isoniazid and acetaminophen has caused severe hepatotoxicity in at least one patient; studies in rats have demonstrated that pre-treatment with isoniazid potentiates acetaminophen hepatotoxicity. [27050](#) [42734](#) (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. [4673](#)

Isoniazid, INH; Pyrazinamide, PZA; Rifampin: (Major) Agents which induce the hepatic isoenzyme CYP2E1, such as isoniazid, may potentially increase the risk for acetaminophen-induced hepatotoxicity via generation of a greater percentage of acetaminophen's hepatotoxic metabolites. The combination of isoniazid and acetaminophen has caused severe hepatotoxicity in at least one patient; studies in rats have demonstrated that pre-treatment with isoniazid potentiates acetaminophen hepatotoxicity. [27050](#) [42734](#) (Moderate) Agents which induce the hepatic isoenzymes CYP2E1 and CYP1A2, such as rifampin, may potentially increase the risk for acetaminophen-induced hepatotoxicity via generation of a greater percentage of acetaminophen's hepatotoxic metabolites. [4718](#) [4929](#) (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. [4673](#) (Minor) Rifampin is a potent inducer of the cytochrome P450 hepatic enzyme system and can reduce the plasma concentrations and possibly the efficacy of caffeine, including caffeine found in green tea products. [5550](#)

Isoniazid, INH; Rifampin: (Major) Agents which induce the hepatic isoenzyme CYP2E1, such as isoniazid, may potentially increase the risk for acetaminophen-induced hepatotoxicity via generation of a greater percentage of acetaminophen's hepatotoxic metabolites. The combination of isoniazid and acetaminophen has caused severe hepatotoxicity in at least one patient; studies in rats have demonstrated that pre-treatment with isoniazid

potentiates acetaminophen hepatotoxicity. [27050](#) [42734](#) (Moderate) Agents which induce the hepatic isoenzymes CYP2E1 and CYP1A2, such as rifampin, may potentially increase the risk for acetaminophen-induced hepatotoxicity via generation of a greater percentage of acetaminophen's hepatotoxic metabolites. [4718](#) [4929](#) (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. [4673](#) (Minor) Rifampin is a potent inducer of the cytochrome P450 hepatic enzyme system and can reduce the plasma concentrations and possibly the efficacy of caffeine, including caffeine found in green tea products. [5550](#)

Isoproterenol: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants. [4666](#)

Ketoconazole: (Moderate) Ketoconazole has been shown to inhibit the clearance of caffeine by 11 percent. The clinical significance of these interactions has not been determined. [6582](#)

Ketoprofen: (Minor) Caffeine administered concurrently with ketoprofen reduced the urine volume in 4 healthy volunteers. The clinical significance of the interaction in preterm neonates is not known. [4666](#)

Lamivudine, 3TC; Zidovudine, ZDV: (Minor) Both acetaminophen and zidovudine, ZDV undergo glucuronidation. Competition for the metabolic pathway is thought to have caused a case of acetaminophen-related hepatotoxicity. This interaction may be more clinically significant in patients with depleted glutathione stores, such as patients with acquired immunodeficiency syndrome, poor nutrition, or alcoholism. [4928](#)

Lamotrigine: (Major) Acetaminophen can be hepatotoxic, and lamotrigine appears to be a potential cause of progressive and fatal hepatotoxicity despite drug discontinuation. A 35 year-old developed fulminant liver failure possibly caused by lamotrigine. She was taking several other drugs including acetaminophen. In a randomized, single-dose study, the serum half-life of lamotrigine after a 300 mg dose decreased by 15% and the area under the plasma concentration-time curve decreased by 20% when given with acetaminophen 900 mg 3 times a day as compared with administration of lamotrigine with placebo. As the lamotrigine maximum serum concentration (C_{max}) and time to C_{max} was similar between the groups, and the lamotrigine renal clearance increased by 7%, acetaminophen appears to enhance removal of lamotrigine from the circulation. [5101](#) [5102](#)

Lanthanum Carbonate: (Minor) The manufacturer recommends that oral compounds known to interact with antacids, such as acetaminophen, should not be taken within 2 hours of dosing with lanthanum carbonate. [9126](#)

Levalbuterol: (Moderate) Sensitive patients may wish to limit or avoid excessive caffeine intake from foods, beverages, dietary supplements and medications during therapy with beta-agonists. Additive side effects may occur between caffeine and beta-agonists. Caffeine is a CNS-stimulant and beta-agonists are sympathomimetic agents. Sensitive patients might experience tremor, sleep difficulties, or mild increases in heart rate. [27950](#)

Lidocaine: (Moderate) Coadministration of lidocaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue lidocaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. [43383](#)

Linezolid: (Moderate) Caffeine use should be minimized or avoided during and for 1 to 2 weeks after discontinuation of linezolid. Linezolid is an antibiotic that is also a weak, reversible nonselective inhibitor of monoamine oxidase (MAO). Dangerous cardiac arrhythmias or severe hypertension can occur because of the potentiation of caffeine's sympathomimetic effects by MAOIs. [32308](#) [61157](#) [61880](#)

Lisdexamfetamine: (Moderate) Avoid excessive caffeine intake during use of lisdexamfetamine. 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. [27950](#) [29786](#) [53320](#) [59396](#)

Lithium: (Major) Caffeine appears to reduce serum lithium concentrations. Adverse reactions to lithium have also been noted to increase simultaneously with a reduction in caffeine intake. Patients taking lithium should be counseled regarding their intake of caffeine. [4672](#)

Lixisenatide: (Minor) When 1,000 mg acetaminophen was given 1 or 4 hours after 10 mcg lixisenatide, the AUC was not significantly changed, but the acetaminophen C_{max} was decreased by 29% and 31%, respectively and median T_{max} was delayed by 2 and 1.75 hours, respectively. Acetaminophen AUC, C_{max}, and T_{max} were not significantly changed when acetaminophen was given 1 h before lixisenatide injection. The mechanism of this interaction is not available (although it may be due to delayed gastric emptying) and the clinical impact has not been assessed. To avoid potential pharmacokinetic interactions that might alter effectiveness of acetaminophen, it may be advisable for patients to take acetaminophen at least one hour prior to lixisenatide subcutaneous injection. [61024](#)

Lomitapide: (Moderate) Caution should be exercised when lomitapide is used with other medications known to have potential for hepatotoxicity, such as acetaminophen (> 4 g/day PO for ≥ 3 days/week). The effect of concomitant administration of lomitapide with other hepatotoxic medications is unknown. More frequent monitoring of liver-related tests may be warranted. [52698](#)

Lopinavir; Ritonavir: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [25460](#) [28100](#) [58664](#)

Loratadine; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. [27950](#)

Magnesium Salicylate: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. Although salicylates are rarely associated with nephrotoxicity, high-dose, chronic administration of salicylates combined other analgesics, including acetaminophen, significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Additive hepatic toxicity may occur, especially in combined overdose situations. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy. [4064](#)

Melatonin: (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking melatonin for sleep should avoid caffeine-containing medications, dietary supplements, foods, and beverages close to bedtime, as well as excessive total daily caffeine intake, as part of proper sleep hygiene, since caffeine intake can interfere with proper sleep. [60064](#)

Mephobarbital: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites. [4939](#) [6522](#) (Minor) The metabolism of caffeine can be increased by concurrent use with barbiturates. The hypnotic effects of barbiturates can be reduced by caffeine administration. [4718](#)

Mepivacaine: (Moderate) Coadministration of mepivacaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue mepivacaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. [29100](#)

Mepivacaine; Levonordefrin: (Moderate) Coadministration of mepivacaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue mepivacaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. [29100](#)

Mestranol; Norethindrone: (Minor) Serum concentrations of caffeine may be increased during concurrent administration with ethinyl estradiol or combined hormonal oral contraceptives. This interaction occurs from the inhibition of methylxanthine oxidation in the liver. Patients may need to be informed about increased caffeine side effects, like nausea or tremors. [4664](#)

Metaproterenol: (Moderate) Sensitive patients may wish to limit or avoid excessive caffeine intake from foods, beverages, dietary supplements and medications during therapy with beta-agonists. Additive side effects may occur between caffeine and beta-agonists. Caffeine is a CNS-stimulant and beta-agonists are sympathomimetic agents. Sensitive patients might experience tremor, sleep difficulties, or mild increases in heart rate. [27950](#)

Methamphetamine: (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 methamphetamine. 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. [10214](#) [27950](#) [29786](#) [53320](#) [59396](#)

Methohexital: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites. [4939](#) [6522](#) (Minor) The metabolism of caffeine can be increased by concurrent use with barbiturates. The hypnotic effects of barbiturates can be reduced by caffeine administration. [4718](#)

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. 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. [27950](#) [31289](#) [53320](#)

Metyrapone: (Major) Coadministration of metyrapone and acetaminophen may result in acetaminophen toxicity. Acetaminophen glucuronidation is inhibited by metyrapone. It may be advisable for patients to avoid acetaminophen while taking metyrapone. [10379](#)

Mexiletine: (Moderate) Mexiletine is an inhibitor of CYP1A2 isoenzymes, and may reduce CYP1A2-mediated caffeine metabolism. Mexiletine has been shown to increase caffeine concentrations by as much as 23 percent after a single 200 mg dose of mexiletine (nonsignificant increase, $p < 0.1$). Another study has reported that the elimination of

caffeine is decreased by 50 percent. While the clinical significance of this interaction is not known, elevated plasma caffeine levels may be of concern in patients with arrhythmias. Patients with cardiac arrhythmias on mexiletine should be cautioned to limit their intake of caffeine. [28001](#) [28280](#) [29836](#)

Midodrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants. [4666](#)

Mipomersen: (Moderate) Caution should be exercised when mipomersen is used with other medications known to have potential for hepatotoxicity, such as acetaminophen (> 4 g/day for >= 3 days/week). The effect of concomitant administration of mipomersen with other hepatotoxic medications is unknown. More frequent monitoring of liver-related tests may be warranted. [53015](#)

Mitotane: (Minor) Use caution if mitotane and acetaminophen are used concomitantly, and monitor for decreased efficacy of acetaminophen. Mitotane is a strong CYP3A4 inducer and acetaminophen is a minor (10% to 15%) CYP3A4 substrate; coadministration may result in decreased plasma concentrations of acetaminophen. [25460](#) [28100](#) [41934](#)

Modafinil: (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 used cautiously with modafinil. Excessive intake should be limited. Excessive intake may cause nervousness, irritability, insomnia or other side effects. [41243](#) [4666](#)

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. Ordinarily, selegiline may be an exception, it can only be used safely without dietary restrictions at doses where it presumably selectively inhibits MAO-B (e.g., 10 mg/day). At doses of 20 mg/day, selegiline can interact with foods and beverages. The precise dose at which selegiline becomes a non-selective inhibitor of all MAO is unknown, but may be in the range of 30 to 40 mg per day. Attention to the dose dependent nature of selegiline's selectivity is critical if it is to be used without elaborate restrictions being placed on diet. [27957](#) [29656](#) [53440](#) [61157](#)

Naproxen; Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. [27950](#)

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. [28963](#) [57419](#)

Norepinephrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants. [4666](#)

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. [27950](#)
[60840](#)

Olodaterol: (Moderate) Sensitive patients may wish to limit or avoid excessive caffeine intake from foods, beverages, dietary supplements and medications during therapy with beta-agonists. Additive side effects may occur between caffeine and beta-agonists. Caffeine is a CNS-stimulant and beta-agonists are sympathomimetic agents. Sensitive patients might experience tremor, sleep difficulties, or mild increases in heart rate. [27950](#)

Ombitasvir; Paritaprevir; Ritonavir: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [25460](#) [28100](#) [58664](#)

Omeprazole; Sodium Bicarbonate: (Minor) Antacids can delay the oral absorption of acetaminophen, but the interactions are not likely to be clinically significant as the extent of acetaminophen absorption is not appreciably affected. [6086](#)

Oxybutynin: (Minor) Consuming greater than 400 mg/day caffeine has been associated with the development of urinary incontinence. Caffeine may aggravate bladder symptoms, increase urine output, and counteract the effectiveness of drugs used to treat overactive bladder such as oxybutynin. 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). [5985](#)

Peginterferon Alfa-2b: (Moderate) The effects of peginterferon alfa-2b on CYP1A2 were evaluated in drug interaction studies. Administration of peginterferon alfa-2b with caffeine, a CYP1A2 substrate, resulted in an 18% to 39% increase in the geographic mean exposure for caffeine, suggesting inhibition of CYP1A2. Monitor for adverse effects associated with increased exposure to caffeine if peginterferon alfa-2b is coadministered with caffeine. [29627](#)
[43887](#)

Pemoline: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants. [4666](#)

Penicillin G Benzathine; Penicillin G Procaine: (Moderate) Coadministration of penicillin G procaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue penicillin G procaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. [31217](#)

Penicillin G Procaine: (Moderate) Coadministration of penicillin G procaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue penicillin G procaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. [31217](#)

Pentobarbital: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites. [4939](#) [6522](#) (Minor) The metabolism of caffeine can be increased by concurrent use with barbiturates. The hypnotic effects of barbiturates can be reduced by caffeine administration. [4718](#)

Phendimetrazine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants. [4666](#)

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. Ordinarily, selegiline may be an exception, it can only be used safely without dietary restrictions at doses where it presumably selectively inhibits MAO-B (e.g., 10 mg/day). At doses of 20 mg/day, selegiline can interact with foods and beverages. The precise dose at which selegiline becomes a non-selective inhibitor of all MAO is unknown, but may be in the range of 30 to 40 mg per day. Attention to the dose dependent nature of selegiline's selectivity is critical if it is to be used without elaborate restrictions being placed on diet. [27957](#) [29656](#) [53440](#) [61157](#)

Phenobarbital: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites. [4939](#) [6522](#) (Minor) The metabolism of caffeine can be increased by concurrent use with barbiturates. The hypnotic effects of barbiturates can be reduced by caffeine administration. [4718](#)

Phentermine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants. [27950](#)

Phentermine; Topiramate: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants. [27950](#)

Phenylephrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. [27950](#)

Phenylephrine; Promethazine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants like phenylephrine; caffeine should be avoided or used cautiously. 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. [27950](#)

Pirbuterol: (Moderate) Sensitive patients may wish to limit or avoid excessive caffeine intake from foods, beverages, dietary supplements and medications during therapy with beta-agonists. Additive side effects may occur between caffeine and beta-agonists. Caffeine is a CNS-stimulant and beta-agonists are sympathomimetic agents. Sensitive patients might experience tremor, sleep difficulties, or mild increases in heart rate. [27950](#)

Pneumococcal Vaccine, Polyvalent: (Moderate) Concomitant administration of antipyretics, such as acetaminophen, may decrease an individual's immunological response to the pneumococcal vaccine. A post-marketing study conducted in Poland using a non-US vaccination schedule (2, 3, 4, and 12 months of age) evaluated the impact of prophylactic oral acetaminophen on antibody responses to Prevnar 13. Data show that acetaminophen, given at the time of vaccination and then dosed at 6 to 8 hour intervals for 3 doses on a scheduled basis, reduced the antibody response to some serotypes after the third dose of Prevnar 13 when compared to the antibody responses of infants who only received antipyretics 'as needed' for treatment. However, reduced antibody responses were not observed after the fourth dose of Prevnar 13 with prophylactic acetaminophen. [39165](#)

Posaconazole: (Moderate) Posaconazole and acetaminophen should be coadministered with caution due to an increased potential for acetaminophen-related adverse events. Posaconazole is a potent inhibitor of CYP3A4, an isoenzyme partially responsible for the metabolism of acetaminophen. These drugs used in combination may result in elevated acetaminophen plasma concentrations, causing an increased risk for acetaminophen-related adverse events. [32723](#) [4718](#)

Pramlintide: (Minor) Because pramlintide has the potential to delay the absorption of concomitantly administered medications, medications should be administered at least 1 hour before or 2 hours after pramlintide injection when the rapid onset of a concomitantly administered oral medication is a critical determinant of effectiveness (i.e., analgesics). [8010](#)

Prilocaine: (Moderate) Coadministration of prilocaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue prilocaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. [29064](#)

Prilocaine; Epinephrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants. [4666](#) (Moderate) Coadministration of prilocaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue prilocaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. [29064](#)

Primidone: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites. [4939](#) [6522](#) (Minor) The metabolism of caffeine can be increased by concurrent use with barbiturates. The hypnotic effects of barbiturates can be reduced by caffeine administration. [4718](#)

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. [45905](#) [4673](#) [4679](#) [5595](#)

Pseudoephedrine: (Moderate) CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants; caffeine should be avoided or used cautiously. 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. [27950](#)

Racipinephrine: (Moderate) Patients who are using racipinephrine 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 racipinephrine. 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 racipinephrine for the treatment of asthma. [54280](#) [54298](#)

Ramelteon: (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking melatonin or the melatonin analogs (ramelteon, tasimelteon) for sleep should avoid caffeine-containing medications, dietary supplements, foods, and beverages close to bedtime. Patients should be encouraged to avoid excessive total daily caffeine intake, as part of proper sleep hygiene, since caffeine intake can interfere with proper sleep. [60064](#)

Rasagiline: (Moderate) Although sympathomimetics and psychostimulants are contraindicated for use with other monoamine oxidase inhibitors (MAOIs), hypertensive reactions generally are not expected to occur during concurrent use with rasagiline because of the selective monoamine oxidase-B (MAO-B) inhibition of rasagiline at manufacturer recommended doses. [32223](#)

Regadenoson: (Major) Caffeine is a non-specific adenosine receptor antagonist and can interfere with the efficacy of regadenoson. 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. [10762](#) [10764](#) [10765](#) [10766](#) [33906](#)

Rifabutin: (Moderate) As a cytochrome P450 isoenzyme inducers, rifabutin could induce the metabolism of acetaminophen. An increase in acetaminophen-induced hepatotoxicity may be seen by increasing the metabolism of acetaminophen to its toxic metabolite, NAPQI. Also, the analgesic activity of acetaminophen may be reduced. [4718](#)

Rifampin: (Moderate) Agents which induce the hepatic isoenzymes CYP2E1 and CYP1A2, such as rifampin, may potentially increase the risk for acetaminophen-induced hepatotoxicity via generation of a greater percentage of acetaminophen's hepatotoxic metabolites. [4718](#) [4929](#) (Minor) Rifampin is a potent inducer of the cytochrome P450 hepatic enzyme system and can reduce the plasma concentrations and possibly the efficacy of caffeine, including caffeine found in green tea products. [5550](#)

Ritodrine: (Moderate) Caffeine is a CNS-stimulant and such actions are expected to be additive when coadministered with other CNS stimulants or psychostimulants. [4666](#)

Ritonavir: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [25460](#) [28100](#) [58664](#)

Ropivacaine: (Moderate) Coadministration of ropivacaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue ropivacaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. [52330](#)

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. [27950](#) [61608](#)

Salmeterol: (Moderate) Sensitive patients may wish to limit or avoid excessive caffeine intake from foods, beverages, dietary supplements and medications during therapy with beta-agonists. Additive side effects may occur between caffeine and beta-agonists. Caffeine is a CNS-stimulant and beta-agonists are sympathomimetic agents. Sensitive patients might experience tremor, sleep difficulties, or mild increases in heart rate. [27950](#)

Salsalate: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. Although salicylates are rarely associated with nephrotoxicity, high-dose, chronic administration of salicylates combined other analgesics, including acetaminophen, significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Additive hepatic toxicity may occur, especially in combined overdose situations. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy. [4064](#)

Secobarbital: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites. [4939](#) [6522](#) (Minor) The metabolism of caffeine can be increased by concurrent use with barbiturates. The hypnotic effects of barbiturates can be reduced by caffeine administration. [4718](#)

Selegiline: (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. Ordinarily, selegiline may be an exception, it can only be used safely without dietary restrictions at doses where it presumably selectively inhibits MAO-B (e.g., 10 mg/day). At doses of 20 mg/day, selegiline can interact with foods and beverages. The precise dose at which selegiline becomes a non-selective inhibitor of all MAO is unknown, but may be in the range of 30 to 40 mg per day. Attention to the dose dependent nature of selegiline's selectivity is critical if it is to be used without elaborate restrictions being placed on diet. [27957](#) [29656](#) [53440](#) [61157](#)

Sodium Bicarbonate: (Minor) Antacids can delay the oral absorption of acetaminophen, but the interactions are not likely to be clinically significant as the extent of acetaminophen absorption is not appreciably affected. [6086](#)

Sodium Oxybate: (Moderate) Caffeine should be avoided or used cautiously with sodium oxybate. This combination may be associated with adverse effects such as nervousness, irritability, insomnia, and/or cardiac arrhythmias. [27950](#) [28528](#)

Solifenacin: (Minor) Consuming > 400 mg/day caffeine has been associated with the development of urinary incontinence. Beverages containing caffeine may aggravate bladder symptoms, increase urine output, and counteract the effectiveness of solifenacin to some degree. Patients may wish to limit their intake of caffeinated drugs, dietary supplements, or beverages. [5985](#) [7273](#)

St. John's Wort, *Hypericum perforatum*: (Moderate) Inducers of CYP1A2, such as St. John's wort, *Hypericum perforatum*, may induce the hepatic oxidative metabolism of caffeine. [4666](#) [4935](#) (Minor) St. John's wort, *Hypericum perforatum* induces cytochrome P450 1A2. About 10 to 15% of the acetaminophen dose undergoes oxidative metabolism via cytochrome P450 isoenzymes CYP2E1, 3A4 and 1A2, which produces the hepatotoxic metabolite, N-acetyl-p-benzoquinonimine. Thus, theoretically St. John's wort might increase the risk of acetaminophen-induced hepatotoxicity by increasing the metabolism of acetaminophen to NAPQI. [2678](#) [4935](#)

Sulfinpyrazone: (Minor) Sulfinpyrazone can induce hepatic oxidative microsomal enzymes and the drug has been shown to increase acetaminophen clearance by roughly 23%. Theoretically, it is thought that the induction of acetaminophen metabolism by sulfinpyrazone may increase the risk of acetaminophen hepatotoxicity due to the formation of increased amounts of toxic acetaminophen metabolites, but there is no confirmatory evidence. [4939](#)

Suvorexant: (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking medications for sleep, such as suvorexant, eszopiclone, zaleplon, or zolpidem should avoid caffeine-containing medications, dietary supplements, foods, and beverages close to bedtime. Patients should be encouraged to avoid excessive total daily

caffeine intake, as part of proper sleep hygiene, since caffeine intake can interfere with proper sleep. [60064](#)

Tasimelteon: (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking melatonin or the melatonin analogs (ramelteon, tasimelteon) for sleep should avoid caffeine-containing medications, dietary supplements, foods, and beverages close to bedtime. Patients should be encouraged to avoid excessive total daily caffeine intake, as part of proper sleep hygiene, since caffeine intake can interfere with proper sleep. [60064](#)

Telaprevir: (Moderate) Close clinical monitoring is advised when administering acetaminophen with telaprevir due to an increased potential for acetaminophen-related adverse events. If acetaminophen dose adjustments are made, re-adjust the dose upon completion of telaprevir treatment. Although this interaction has not been studied, predictions about the interaction can be made based on the metabolic pathway of acetaminophen. Acetaminophen is partially metabolized by the hepatic isoenzyme CYP3A4; telaprevir inhibits this isoenzyme. Coadministration may result in elevated acetaminophen plasma concentrations. [25460](#) [28100](#) [44393](#)

Telotristat Ethyl: (Moderate) Use telotristat ethyl and CYP3A4 substrates, such as acetaminophen, together with caution; the systemic exposure of acetaminophen may be decreased resulting in reduced efficacy. If these drugs are used together, monitor patients for suboptimal efficacy of acetaminophen; consider increasing the dose of acetaminophen if necessary. The systemic exposure of a sensitive CYP3A4 substrate was significantly decreased (by 48%) when it was coadministered with telotristat ethyl. The mechanism of this drug interaction appears to be that telotristat ethyl increases the glucuronidation of the CYP3A4 substrate. [28100](#) [61795](#)

Terbinafine: (Minor) Terbinafine has been shown to inhibit the clearance of caffeine. The clinical significance of this interaction has not been determined. [6582](#)

Terbutaline: (Moderate) Sensitive patients may wish to limit or avoid excessive caffeine intake from foods, beverages, dietary supplements and medications during therapy with beta-agonists. Additive side effects may occur between caffeine and beta-agonists. Caffeine is a CNS-stimulant and beta-agonists are sympathomimetic agents. Sensitive patients might experience tremor, sleep difficulties, or mild increases in heart rate. [27950](#)

Teriflunomide: (Minor) Teriflunomide may be a weak inducer of CYP1A2. When teriflunomide was given concurrently with caffeine in vivo, a CYP1A2 substrate, the C_{max} and AUC of caffeine decreased by 18% and 55%, respectively. Closely monitor patients taking CYP1A2 substrates with teriflunomide as efficacy of CYP1A2 substrates may be reduced. [51794](#)

Tetracaine: (Moderate) Coadministration of tetracaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue tetracaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. [31353](#)

Theophylline, Aminophylline: (Major) Caffeine is a CNS stimulant. The concurrent administration of caffeine to patients taking aminophylline 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. 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. [4666](#) [6856](#) (Major) 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. In neonates, theophylline is metabolized to caffeine; initiating caffeine after theophylline therapy is halted may result in caffeine toxicity in neonates if serum caffeine levels are not monitored prior to the initiation of caffeine therapy. Concurrent use of theophylline with caffeine in neonates is not recommended due to the potential for additive toxicity. [4666](#) [6856](#)

Thiabendazole: (Moderate) Thiabendazole is a potent inhibitor of CYP1A2 hepatic enzymes. Thiabendazole can interfere with the CYP1A2 metabolism of xanthine derivatives such as caffeine, reducing clearance by up to 50%. Excessive caffeine-related side effects, such as nausea, tremor, or nervousness, may result. Reduction or limitation of the caffeine dosage in medications and limitation of caffeine in beverages and food may be necessary during concomitant treatment. [10104](#) [29797](#) [4718](#)

Thiopental: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites. [4939](#) [6522](#) (Minor) The metabolism of caffeine can be increased by concurrent use with barbiturates. The hypnotic effects of barbiturates can be reduced by caffeine administration. [4718](#)

Tiotropium; Olodaterol: (Moderate) Sensitive patients may wish to limit or avoid excessive caffeine intake from foods, beverages, dietary supplements and medications during therapy with beta-agonists. Additive side effects may occur between caffeine and beta-agonists. Caffeine is a CNS-stimulant and beta-agonists are sympathomimetic agents. Sensitive patients might experience tremor, sleep difficulties, or mild increases in heart rate. [27950](#)

Tizanidine: (Minor) Tizanidine delays the time to attain peak concentrations of acetaminophen by about 16 minutes. The clinical significance of this interaction is unknown. [6899](#)

Tobacco: (Moderate) Inducers of the hepatic CYP450 isoenzyme CYP1A2 may induce the hepatic oxidative metabolism of caffeine. Tobacco smoke contains hydrocarbons that induce hepatic CYP450 microsomal enzymes (e.g., CYP1A1, CYP1A2, CYP2E1). The increased clearance of caffeine by smokers may contribute to the higher consumption of caffeinated beverages reported to occur in this group. Because the effect on hepatic microsomal enzymes is not related to the nicotine component of tobacco, the sudden cessation of tobacco smoking may result in a reduced clearance of caffeine, despite the initiation of a nicotine replacement product. Following several days of abstinence from chronic tobacco smoking, caffeine clearance may decrease by roughly 40%, leading to the possible occurrence of caffeine-related side effects like nausea, nervousness, irritability, tremors, or insomnia, if caffeine use remains the same. [4666](#) [5056](#) (Moderate) Tobacco smoking induces the cytochrome P450 isoenzyme CYP1A2 and may potentially increase the risk for acetaminophen-induced hepatotoxicity during overdose via enhanced generation of acetaminophen's hepatotoxic metabolite, NAPQI. In one study, current tobacco smoking was found to be very frequent in patients admitted with acetaminophen poisoning. Tobacco smoking appears to be an independent risk factor of severe hepatotoxicity, acute liver failure and death following acetaminophen overdose. [4718](#) [4940](#)

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. [5985](#)

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. [6582](#)

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. Ordinarily, selegiline may be an exception, it can only be used safely without dietary restrictions at doses where it presumably selectively inhibits MAO-B (e.g., 10 mg/day). At doses of 20 mg/day, selegiline can interact with foods and beverages. The precise dose at which selegiline becomes a non-selective inhibitor of all MAO is unknown, but may be in the range of 30 to 40 mg per day. Attention to the dose dependent nature of selegiline's selectivity is critical if it is to be used without elaborate restrictions being placed on diet. [27957](#) [29656](#) [53440](#) [61157](#)

Trimetrexate: (Moderate) Acetaminophen can inhibit oxidative hepatic enzymes responsible for metabolizing trimetrexate. Concurrent use can decrease the clearance of trimetrexate and thus increase its plasma levels. [5221](#)
[5224](#)

Umeclidinium; Vilanterol: (Moderate) Sensitive patients may wish to limit or avoid excessive caffeine intake from foods, beverages, dietary supplements and medications during therapy with beta-agonists. Additive side effects may occur between caffeine and beta-agonists. Caffeine is a CNS-stimulant and beta-agonists are sympathomimetic agents. Sensitive patients might experience tremor, sleep difficulties, or mild increases in heart rate. [27950](#)

Vemurafenib: (Moderate) Concomitant use of vemurafenib and acetaminophen may result in altered concentrations of acetaminophen. Vemurafenib is an inhibitor of CYP1A2 and CYP2A6, and an inducer of CYP3A4. Acetaminophen is a substrate of CYP1A2, CYP2A6, and CYP3A4. Use caution and monitor patients for toxicity and efficacy. [25460](#)
[28100](#) [45335](#)

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. [6582](#)

Warfarin: (Minor) Although acetaminophen is routinely considered safer than aspirin and agent of choice when a mild analgesic/antipyretic is necessary for a patient receiving therapy with warfarin, acetaminophen has also been shown to augment the hypoprothrombinemic response to warfarin. Concomitant acetaminophen ingestion may result in increases in the INR in a dose-related fashion. Clinical bleeding has been reported. Single doses or short (i.e., several days) courses of treatment with acetaminophen are probably safe in most patients taking warfarin. Clinicians should be alert for an increased INR if acetaminophen is administered in large daily doses for longer than 10 to 14 days. [1628](#)

Yohimbine: (Moderate) Dangerous cardiac arrhythmias or severe hypertension can occur because of the potentiation of caffeine's sympathomimetic effects by drugs with MAOI activity such as high doses of yohimbine. [4673](#) [6282](#)

Zaleplon: (Minor) Caffeine is a central nervous system (CNS) stimulant. Patients taking medications for sleep, such as zaleplon should avoid caffeine-containing medications, dietary supplements, foods, and beverages close to bedtime. Patients should be encouraged to avoid excessive total daily caffeine intake, as part of proper sleep hygiene, since caffeine intake can interfere with proper sleep. [60064](#)

Zidovudine, ZDV: (Minor) Both acetaminophen and zidovudine, ZDV undergo glucuronidation. Competition for the metabolic pathway is thought to have caused a case of acetaminophen-related hepatotoxicity. This interaction may be more clinically significant in patients with depleted glutathione stores, such as patients with acquired immunodeficiency syndrome, poor nutrition, or alcoholism. [4928](#)

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. [27950](#) [28001](#)

Zolmitriptan: (Minor) Zolmitriptan can delay the Tmax of acetaminophen by one hour. A single 1 g dose of acetaminophen does not alter the pharmacokinetics of zolmitriptan and its active metabolite. The interaction between zolmitriptan and acetaminophen is not likely to be clinically significant. [5175](#)

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. [27962](#) [29730](#) [57789](#) [60064](#)

Last revised: February 1, 2019

Adverse Reactions

- acute generalized exanthematous pustulosis (AGEP)
- agitation
- agranulocytosis
- anaphylactic shock
- anaphylactoid reactions
- anemia
- angioedema
- anorexia
- anxiety
- constipation
- contact dermatitis
- diarrhea
- dyspnea
- elevated hepatic enzymes
- erythema
- exfoliative dermatitis
- fatigue
- fever
- headache

- hearing loss
- heart failure
- hemolysis
- hemolytic anemia
- hepatic encephalopathy
- hepatic failure
- hepatic necrosis
- hepatotoxicity
- hypertension
- hypoalbuminemia
- hypokalemia
- hypomagnesemia
- hypophosphatemia
- hypoprothrombinemia
- hypotension
- injection site reaction
- insomnia
- interstitial nephritis
- jaundice
- maculopapular rash
- malaise
- muscle cramps
- myocarditis
- nausea
- neutropenia
- oliguria
- pancytopenia
- peripheral edema
- pleural effusion
- pruritus

- pulmonary edema
- purpura
- renal failure (unspecified)
- renal papillary necrosis
- renal tubular necrosis
- rhabdomyolysis
- Stevens-Johnson syndrome
- thrombocytopenia
- thrombocytosis
- toxic epidermal necrolysis
- trismus
- urticaria
- vomiting
- wheezing

Headache can occur after acetaminophen administration. In clinical trials of adult patients receiving IV acetaminophen, headache occurred in 10% of patients compared to 9% of those receiving placebo. Headache ($\geq 1\%$) was also reported in clinical trials of IV acetaminophen in pediatric patients.⁴²²⁸⁹ Overuse of acetaminophen by headache-prone patients frequently produces drug-induced rebound headache or medication overuse headache that is accompanied by dependence on symptomatic medication, tolerance (refractoriness to prophylactic medication), and withdrawal symptoms. When increasing doses of analgesia are required, the cause may be multi-factorial, including tolerance, progression of disease or psychologic distress. Overuse of acetaminophen (i.e., simple analgesic) has been defined as taking 3 or more doses per day more often than 5 days per week.²⁷³⁴⁷ The frequency of use may be more important than the dose. Features of a rebound headache include morning headache, end-of-dosing interval headache, or headache improvement with discontinuation of overused medication. Stopping the symptomatic medication may result in a period of increased headache and then headache improvement. Analgesic overuse may be responsible for the transformation of episodic migraine or episodic tension headache into daily headache and may perpetuate the syndrome.²⁷³⁴⁷

Gastrointestinal adverse events, such as nausea, vomiting, constipation, and diarrhea may occur after parenteral acetaminophen administration. The most common gastrointestinal side effects reported in clinical trials of IV acetaminophen in adults were nausea, occurring in 34% of patients who received acetaminophen versus 31% of those who received placebo, and vomiting, occurring in 15% of the acetaminophen group versus 11% of those who received placebo. Gastrointestinal side effects in pediatric patients receiving IV acetaminophen in clinical trials also included nausea and vomiting, as well as constipation (5% or more of patients). Diarrhea (1% or more) was also reported in pediatric patients.⁴²²⁸⁹ Oral therapy is not usually associated with significant adverse effects in usual and prudent use as recommended. If a patient who has taken oral acetaminophen presents with significant gastrointestinal symptoms (e.g., nausea, vomiting, and abdominal pain), acetaminophen-induced liver toxicity should be considered.

The hepatic effects of acetaminophen are well-known. In a study of combined data collected over a 5-year period (1998 to 2003) from 22 specialty medical centers in the United States, acetaminophen-induced liver injury was the leading cause of acute hepatic failure. Unintentional overdose accounted for almost half of the reported cases; acetaminophen toxicity may occur as the result of acute overdose or chronic excessive dosing.^{32202 44683} Young children appear to be at less risk of developing hepatotoxicity, possibly because of an age-related difference in the metabolism of the drug.³²²⁰² Acetaminophen-induced hepatotoxicity is manifested as hepatic necrosis, jaundice, and hepatic encephalopathy. Early nonspecific symptoms include nausea/vomiting, anorexia, abdominal pain, and malaise.^{42289 54184} After acute overdose, elevated hepatic enzymes occur within 12 to 36 hours and maximal liver damage and hepatic impairment peak 3 to 5 days after ingestion.⁵⁴¹⁸⁴ GI bleeding can occur secondary to hypoprothrombinemia. Administration of intravenous vitamin K is recommended for hypoprothrombinemia due to acetaminophen overdosage. If more than 150 to 200 mg/kg, 10 g, or an unknown amount of acetaminophen is ingested, a serum acetaminophen concentration should be obtained 4 hours after ingestion or as soon as possible thereafter.^{42289 54020 54184} Prompt administration of N-acetylcysteine (NAC), which serves as a substitute sulfhydryl donor for glutathione, should occur if the acetaminophen concentration plots above the treatment line on the Rumack-Matthew nomogram. NAC treatment should begin immediately if the estimated time after ingestion approaches 8 hours.^{54020 54184} Acetaminophen misuse should be avoided; recommended doses should not be exceeded and intake should be accounted for from all sources (e.g., single-entity products and combination products). Excessive acetaminophen exposure, malnutrition, concurrent ethanol consumption (acute and chronic), and/or concurrent use of enzyme-inducing drugs (e.g., isoniazid) may lead to greater exposure of the toxic metabolite, N-acetyl-para-benzoquinoneimine (NAPQI), and increase the risk for toxicity.^{54020 54184 54187}

Acetaminophen can rarely cause acute renal tubular necrosis and chronic analgesic nephropathy, which is characterized by interstitial nephritis and renal papillary necrosis, in patients receiving high doses (e.g., 2.5 to 10 g/day for adults) chronically or after acute overdose. Acute renal failure (unspecified) may occur in 25% to 30% of patients who have acetaminophen-induced hepatotoxicity. Rarely, acute renal failure may occur without severe hepatic toxicity. The risk of renal complications appears to be higher in patients with alcoholism. Chronic acetaminophen use has been implicated as a contributing factor in the decline of renal function in patients with underlying renal disease, including diabetic nephropathy.²³⁹⁷⁷ Oliguria ($\geq 1\%$) has also been reported in clinical trials of pediatric patients receiving IV acetaminophen.⁴²²⁸⁹

Hypokalemia and peripheral edema occurred in at least 1% of patients in clinical trials. Other metabolic disturbances reported in at least 1% of pediatric patients after administration of IV acetaminophen included hypoalbuminemia, hypomagnesemia, and hypophosphatemia.⁴²²⁸⁹

Cardiovascular adverse events reported in clinical trials of IV acetaminophen in at least 1% of adult and pediatric patients include both hypertension and hypotension.⁴²²⁸⁹

Anemia ($\geq 1\%$) and fever ($\geq 1\%$) have been reported during pediatric clinical trials of IV acetaminophen. In addition, sporadic case reports of agranulocytosis, thrombocytopenia, thrombocytosis, neutropenia, and pancytopenia have been described in patients taking acetaminophen. Symptoms such as unusual tiredness or weakness, unusual bleeding or bruising, and unexplained sore throat or fever should be investigated promptly.^{31419 31420 42289 54020} Acetaminophen sulfate, a metabolite of acetaminophen, may rarely cause immune-mediated thrombocytopenia.³¹⁴¹⁹ Symptoms such as unusual tiredness or weakness, unusual bleeding or bruising, and unexplained sore throat or fever should be investigated promptly.

Drug-induced hemolysis and hemolytic anemia have been associated with acetaminophen overdose in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Though several case reports of hemolytic anemia in G6PD-deficient patients receiving therapeutic doses of acetaminophen exist, a direct cause and effect relationship has not

been well established. G6PD-deficient patients presenting with acetaminophen toxicity should be monitored closely for signs and symptoms of hemolysis.^{54061 54063}

Dermatological adverse reactions of varying severity have been reported after acetaminophen administration, including the rare but serious skin reactions Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis (AGEP). These reactions may occur at any time during treatment and in patients who have taken acetaminophen previously with no reaction. Stevens-Johnson syndrome and toxic epidermal necrolysis may begin with flu-like symptoms, followed by skin rash and blistering producing extensive damage. Blindness and internal organ damage may also occur which can be fatal.^{55541 55544} Acute generalized exanthematous pustulosis (AGEP) is characterized by acute onset, fever, and nonfollicular pustules on an erythematous rash, and typically resolves within 2 weeks following drug discontinuation.^{27736 55544} From 1969 to 2012, 107 cases of serious skin reactions associated with acetaminophen use were reported to the FDA, resulting in 67 hospitalizations and 12 deaths.⁵⁵⁵⁴⁴ Toxic epidermal necrolysis (TEN) occurred in a 7 year old girl after she took 3 doses of oral acetaminophen to treat a fever and sore throat. Twelve hours after the last dose, an erythematous rash appeared, which became generalized and vesicular over the next few hours. The patient developed a fever, low blood pressure, and an elevated erythrocyte sedimentation rate and liver function tests. Skin biopsy was positive for subepidermal blister formation with full-thickness necrolysis of the epidermis. Acetaminophen re-challenge, performed 6 months later in an allergy clinic, produced similar symptoms within 30 minutes of administration and confirmed the initial diagnosis.²⁷⁷³² Pruritus was reported in pediatric patients during clinical trials of IV acetaminophen. Other hypersensitivity reactions may be manifested by urticaria, erythema, maculopapular rash, and fever. Though rare, anaphylactic shock, angioedema, and anaphylactoid reactions have been reported.^{42289 54020} Multiple cases of allergic contact dermatitis (delayed hypersensitivity type) have been reported in the literature. Various reactions, including generalized pruriginous micropapular eruption, facial edema, generalized pruriginous exanthem, exfoliative dermatitis, and generalized exanthema occurred within several hours after ingestion.^{27734 27735} Patients who develop allergic or hypersensitivity reactions should discontinue acetaminophen immediately and seek medical attention for symptomatic treatment.

A case of acquired purpura fulminans developed in a 32 year old woman who was instructed to take acetaminophen 1,000 mg every 4 to 6 hours as needed for pain. The patient noted rapidly spreading purpuric lesions and associated edema. Her lesions were nonblanchable and enlarging, and she had multiple purplish-black hemorrhagic and necrotic areas. Purpura fulminans is usually associated with disseminated intravascular coagulation and can occur in patients with inherited or acquired deficiencies of the protein C anticoagulant pathway. Based on the patient's history of alcohol use and poor nutritional status, the authors concluded that reduced hepatic glutathione stores were further reduced by the introduction of acetaminophen, leading to impaired protein C and S synthesis and propagation of the disseminated intravascular coagulation cascade. Discontinuation of alcohol and acetaminophen and administration of vitamin K, heparin, and a systemic antibiotic led to almost complete purpuric lesion and hepatotoxicity resolution in 6 days.²⁷⁷³³

Insomnia occurred in 7% of adult patients who received IV acetaminophen in clinical trials versus 5% of those who received placebo. Anxiety and fatigue also occurred in adult patients treated with IV acetaminophen. In clinical trials of pediatric patients receiving IV acetaminophen, agitation occurred in $\geq 1\%$ of patients.⁴²²⁸⁹

Respiratory adverse effects seen after administration of IV acetaminophen in at least 1% of adults in clinical trials included dyspnea and abnormal breath sounds. Atelectasis, pleural effusion, pulmonary edema, stridor, and wheezing were reported in $\geq 1\%$ of pediatric patients.⁴²²⁸⁹ There is epidemiological evidence in children and adults associating acetaminophen use with asthma symptoms. In addition, evidence suggests in utero and early infancy exposure may be associated with an increased risk of childhood asthma. Researchers hypothesize that acetaminophen may contribute to asthma through depletion of airway mucosal glutathione, increasing oxidative stress, epithelial damage, and airway inflammation.^{54102 54104 54107}

Muscle cramps or spasms occurred in $\geq 1\%$ of adult and pediatric patients treated with IV acetaminophen in clinical trials. Other musculoskeletal events included trismus in adult patients.⁴²²⁸⁹ Acetaminophen-induced rhabdomyolysis has been described in a single case report. A 17 year old male with a past medical history of drug-induced reactions (hepatitis, agranulocytosis, desquamative dermatitis, and pyrexia) after receiving acetaminophen with or without concurrent antibiotics, was re-challenged with oral acetaminophen 400 mg. Within 5 hours of administration, the adolescent presented with febrile exanthema, neutropenia, and increased C-reactive protein, creatine phosphokinase, tumor necrosis factor-alpha, interleukin-6, and interleukin-10; the skin eruption and fever lasted 36 hours. Symptoms such as unusual tiredness, weakness or unusual pain and swelling of the extremities, nausea and vomiting, and dark-colored urine should be investigated promptly.³¹⁴²⁰

Myocyte injury was reported in a 15-year-old female. She developed fatal heart failure due to toxic myocarditis after an unspecified intentional overdose of acetaminophen.³¹⁴²¹

Prospective studies have shown there to be a slight but consistent association between regular analgesic use and hearing loss. Acetaminophen related ototoxicity may result from depletion of glutathione, which protects the cochlea from noise damage.⁵³⁷²⁰ As a true long-term association may exist, counsel patients to minimize long-term treatment with acetaminophen as much as possible. A prospective analysis examining the association between analgesic use and the risk of hearing loss was conducted in 62,261 women 31 to 48 years of age at study enrollment who were originally enrolled in the Nurses' Health Study II. The association between self-reported hearing loss and analgesic use (including acetaminophen, aspirin, and NSAIDs) was examined over 14 years. During 764,247 person-years of follow-up, 10,012 cases of hearing loss were reported. After adjustment for confounders, acetaminophen use 2 or more days per week was independently associated with an increased risk of hearing loss, with the relative risk of hearing loss increasing with increasing frequency of use. Acetaminophen use 2 to 3, 4 to 5, or 6 or more days per week was associated with relative risks of 1.11 (95% CI 1.02 to 1.19), 1.21 (95% CI 1.07 to 1.37), and 1.08 (95% CI 0.95 to 1.22), respectively ($p = 0.0007$). Of note, those with more frequent use of acetaminophen had higher body mass indices; were more likely to smoke, have hypertension, or have diabetes; and were less physically active.⁵³⁷²⁰ In a similar study in male patients, the association between professionally diagnosed hearing loss and analgesic use (including acetaminophen, aspirin, and NSAIDs) was prospectively analyzed in 26,917 patients 40 to 74 years of age at study enrollment over 18 years. During 369,079 person-years of follow-up, 3,488 cases of hearing loss were reported. After adjustment for confounders, the hazard ratio (HR) for acetaminophen associated hearing loss was 1.22 (95% CI 1.07 to 1.39, $p = 0.09$) in patients who were regular users of the drug (at least 2 times weekly) compared to those with less use. Men who regularly used acetaminophen for 4 years or more were 33% (14% to 56%) more likely to develop hearing loss than those with shorter use. In men younger than 50 years, the HR of hearing loss was 1.99 (95% CI 1.34 to 2.95); the degree of association generally decreased with aging.⁵³⁷¹⁹ These studies do suggest association; however, data are based on patient reporting of the outcomes. Information regarding noise exposure and analgesic doses was not provided.⁵³⁷¹⁹ ⁵³⁷²⁰

An injection site reaction, described as infusion site pain, occurred in $\geq 1\%$ of patients receiving IV acetaminophen during clinical trials.⁴²²⁸⁹

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Classifications

- Analgesics
- Analgesics with and without Antipyretic Activity
- Analgesics with and without Antipyretic Activity Combinations
- Central Nervous System

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Global Drug Names

Argentina

Acetolit - (Mertens)
 Alikal Dolor - (GSK)
 Apracur Antifebril - (Higate)
 Apracur Te Antifebril - (HMA)
 Bio Grip-T - (Sanofi-Aventis)
 Causalon - (Phoenix)
 Custodial - (Schwabe)
 Dirox - (Gramon)
 Doxidol - (Savant)
 Dristancito - (Wyeth-Whitehall)
 Fiebrolex - (Vitarum)
 Fiebrolo - (Fabop)
 Flash - (Vent-3)
 Guemusin - (Fada)
 Inmunogrip T - (Gezzi)
 Invernosan - (Excelentia)
 Isagrip - (ISA)
 Itedal - (Dicofar)
 Mejoral - (Elisium)
 Multifebrin - (Bajer)
 Nodipir - (Klonal)
 Nodolex - (Bago)
 Novo Asat - (Gezzi)
 Para-Z-Mol - (Cabuchi)
 Parageniol - (GSK)
 Paratral - (Austral)
 Parclen - (Lepetit)
 PH 4 Plus - (Sintesina)
 Plovacal - (Medipharma)
 Predualito - (BMS)
 T-Apracur - (Lepetit)
 Tafirol - (Genomma)

Tafirol T - (Sidus)
Termofren - (Roemmers)
Tetradox - (Richmond)
Tylenol - (Johnson & Johnson)
Vick Vitapyrena - (Procter & Gamble)
Viclor - (Richet)

Australia

Asprol - (Nicholas)
Ceetamol - (CP Protea)
Chemists Own Pain & Fever - (Chemists Own)
Childrens Panadol - (GSK Consumer)
Dymadon - (Aspen)
Febridol - (Amneal)
Junior Disprol - (Reckitt & Colman)
Kiddy Calm - (Marpa)
Lemsip - (Reckitt Benckiser)
Lemsip Headcold - (Reckitt Benckiser)
Ordov Febrigesic - (Or-Dov)
Panacete - (Prosana)
Panadol - (GSK Consumer)
Panamax - (Sanofi-Aventis)
Parahexal - (Hexal)
Paralgin - (Arrow)
Parasin - (Nelson)
Paraspen - (Parke, Davis)
Parmol - (Rorer)
Perfalgan - (BMS)
Setamol - (Reckitt Benckiser)
Tempra - (Mead Johnson)
Tylenol - (Johnson & Johnson)

Austria

Apacet - (Merck)
Becetamol - (Gebro)
Ben-u-ron - (Sigmapharm)
Dolonerv - (Gerot)
Duaneo - (Klosterfrau)
Enelfa - (Sanova)
Gewadal-Pamol - (Takeda)
Gewamol - (Nycomed)
Grippostad - (Stada)
Kratofin simplex - (Kwizda)
Mexalen - (Ratiopharm)
Momentum - (CSC)
OSA - (Schmidgall)
Paradolor - (Stada)
Parakapton - (Rosch & Handel)
Paraspeed - (Nycomed)
Peinfort - (Ebewe)
Perfalgan - (BMS)
Trimedil - (Novartis Consumer)

Tylenol - (Johnson & Johnson)

Belgium

Algostase Mono - (SMB)
Antigrippine Midy - (SmithKline Beecham)
Croix Blanche Mono - (SMB)
Curpol - (McNeil)
Dafalgan - (BMS)
Docpara - (Docpharma)
Dolol-Instant - (Takeda)
Dolprone - (Melisana)
Efferalgan - (Upsamedica)
Latepyrine - (Solvay)
Lemgrip - (Reckitt & Colman)
Lemsip - (Reckitt Benckiser)
Lonarid Mono - (Boehringer Ingelheim)
Mobistix - (Neocare)
Neuridon - (Synthelabo)
Panadol - (GSK)
Pe-Tam - (Qualiphar)
Perdolan - (Johnson & Johnson)
Perfusalgan - (BMS)
Sanicopyrine - (Sanico)
Supadol Mono - (Bios)
Tempra - (BMS)

Brazil

Acetamil - (Ducto)
Acetamol - (Bergamo)
Acetofen - (Medley)
Anador PRT - (Boehringer Ingelheim)
Analgisen - (TKS)
Anatyl - (Sanval)
Baicurina - (Regius)
Calpol - (Glaxo Wellcome)
Cefabrina - (Neo Quimica)
Cetafrin - (Neo Quimica)
Cetynol - (Brasmedica)
Chalena - (Sibras)
Cimegripe Bebe - (Cimed)
Cimegripe-77c - (Cimed)
Contradol - (Gemballa)
Coristina Termus - (Mantecorp)
Cyfenol - (Cifarma)
Din - (Cosmed)
Dordendril - (Heralds)
Dorfen - (Cazi)
Dorfenol - (Vitamedic)
Dorib - (Ibfarma)
Dorsanol - (Multilab)
Dorvan - (Simoès)
Dôrico - (Sanofi-Aventis)

Emsgrip - (EMS)
Febralgin - (Boehringer Ingelheim)
Fervex - (Hertz)
Gripeonil - (Faria)
Gripotermon - (Prodotti)
Otonal - (Biochimico)
Pacemol - (Gemballa)
Paracemil - (Sinterapico)
Paracen - (Greenpharma)
Paracetrex - (Royton)
Parador - (Boehringer Ingelheim)
Paraflan - (Pharlab)
Paralgen - (EMS)
Paramol - (Belfar)
Paratermol - (INQ)
Piramin - (Elofar)
Pratium - (Mantecorp)
Pyrimel - (Catarinense)
Regulador Gesteira - (CIF)
Resfenol Thermus - (Hertz)
Sonridor - (GSK)
Termo-Ped - (Stiefel)
Termol - (Uniao Quimica)
Thylom - (Osorio de Moraes)
Tilekin - (Kinder)
Trifen - (Hertz)
Trimedal D&F - (Novartis)
Tyflen - (Brasterapica)
Tylalgin - (Geolab)
Tylecetamol - (Sandoz)
Tyleflan - (Eversil)
Tylenol - (Janssen-Cilag)
Tylephen - (IQB)
Tylidol - (Teuto)
Tyneo - (Neo Quimica)
Unigrip - (Uniao Quimica)
Zuplyn - (Arrow)

Canada

222 AF - (Johnson & Johnson)
Abenol - (Pendopharm)
Acet - (Pharmascience)
Acetab - (Romilo)
AF Anacin - (Whitehall-Robins)
Alsiphene - (Alsi)
Anacin-3 - (Whitehall)
Apap - (Medique)
Arthritis Pain - (Vita Health)
Artritol - (Bio-Sante)
Atasol - (Church & Dwight)
Cephanol - (Riva)

Childrens Feverhalt - (Pendopharm)
Fortolin - (Fortune)
Headarest - (Medinex)
Infants Tylenol - (McNeil Consumer)
Multi-gesic - (Multi-Pro)
Novo-Gesic - (Novopharm)
Painaid Free - (Zee)
Panadol - (GSK Consumer)
Pediaphen - (Euro-Pharm)
Pediatrix - (Teva)
Rapid Action - (Actavis)
Relief - (Pendopharm)
Robigesic - (Whitehall-Robins)
Rounox - (Rougier)
Taminol - (Viva)
Tantaphen - (Tanta)
Tempra - (Paladin)
Tylenol - (McNeil Consumer)
Tylenol Arthritis Pain - (McNeil Consumer)
Tylenol Muscle Aches & Body Pain - (McNeil Consumer)
Vicks Custom Care Body Aches - (Procter & Gamble)

Chile

Acamol - (Eurofarma)
Algiafin - (Interpharma)
Cotibin Analgesico Antipiretico - (Andromaco)
Cotibin Compuesto - (Andromaco)
Cotibin Infantil - (Andromaco)
Cryogenine Plus - (Andromaco)
Daimeton - (Drag)
Dolo-Esan - (Esan)
Fibrimol - (Andromaco)
Focus - (Bayer)
Geniol - (Mintlab)
Gesidol - (Medipharm)
Kitadol - (Laboratorios Chile)
Panadol - (GSK)
Panagesic - (Chemopharma)
Parox Meltab - (Saval)
Rapidol - (Pfizer)
Sinflu - (Valma)
Supracalm - (Tecnofarma)
Tapsin Infantil - (Maver)
Tapsin Puro - (Maver)
Tapsin Puro sin Cafeina - (Maver)
Tapsin SC - (Maver)
Winasorb - (Recalcine)
Xumadol - (ITF)
Zolben - (Novartis)

China

Ai Er Xing - (Shi Dai)

Ai Sen - (Dinghengsheng)
 AnYi - (Baiyunshan)
 Bei Le Xin - (Hengrui)
 Ben-u-ron - (Bene)
 Bufferin - (BMS)
 Childrens Bufferin - (BMS)
 Childrens Tylenol - (Johnson & Johnson)
 Er He Yi - (Zhenguo)
 Er Re An - (Twinluck)
 Fan Nuo - (Kang Dini)
 Fortolin - (Fortune)
 Infant's Tylenol - (Johnson & Johnson)
 Pa La Xin - (Sine)
 Panadol - (GSK)
 Pu Le Er - (Lu Yin)
 Shi Ning - (Baiyunshan)
 Snaplets-FR - (Baker Norton)
 Su Ting - (Chung-Hwa)
 Tylenol - (Johnson & Johnson)
 Xing Le Ning - (Xing'an)
 Yi Di Qing - (Hanyin)
 Yi Li Miao - (Gerui)
 Yi Shang - (Xinhua)

Czech Republic

Ben-u-ron - (Bene)
 Calpol - (McNeil)
 Daleron - (KRKA)
 Effect Comfort - (Ivax)
 Effergal - (BMS)
 Gelocatil - (Gelos)
 Medipyrin - (Glenmark)
 Mexalen - (Ratiopharm)
 Panadol - (GSK Consumer)
 Parafizz - (Cipla)
 Paralen - (Zentiva)
 Paralgil - (Teva)
 Paramax Rapid - (Vitabalans)
 Paramegal - (Glenmark)
 Perfalgan - (BMS)

Denmark

Arax - (Vitabalans)
 Pamol - (Takeda)
 Panam - (Sandoz)
 Panodil - (GSK Consumer)
 Paratabs - (Actavis)
 Perfalgan - (BMS)
 Pinex - (Actavis)

Finland

Pamol - (Takeda)

Pamol F - (Takeda)
Panadol - (GSK Consumer)
Para-Hot - (Orion)
Para-Suppo - (Orion)
Para-Tabs - (Orion)
Paraceon - (Verman)
Paramax - (Vitabalans)
Perfalgan - (BMS)
Pinex - (Actavis)
Rolod - (Sandoz)

France

Aféradol - (Oberlin)
Akindol - (Fournier)
Algodol - (Pharmastra)
Brilivo - (Sanofi-Aventis)
Claradol - (Bayer Consumer)
Compralsol - (Gifrer Barbezat)
Dafalgan - (BMS)
Dafalganhop - (BMS)
Dolflash - (Sanofi Winthrop)
Doliprane - (Sanofi-Aventis)
Dolipranelib - (Sanofi-Aventis)
Dolipraneoro - (Sanofi-Aventis)
Dolko - (Therabel)
Dolotec - (Innotech)
Efferalgan - (BMS)
Efferalganodis - (BMS)
Efferalgantab - (UPSA)
Expandox - (Expanpharm)
Febrectol - (Sanofi-Aventis)
Febrectol - (Winthrop)
Gynospasmine - (Synthelabo)
Géluprane - (Sanofi-Aventis)
Malgis - (SmithKline Beecham)
Oralgan - (Pierre Fabre)
Panadol - (GSK Sante)
Paralyoc - (Cephalon)
Perfalgan - (BMS)
Sédarène - (Jolly-Jatel)
Tylenol - (Polive)

Germany

Anaflon - (Sanofi Winthrop)
Anti-Algos - (Truw)
Antipanin N - (Michallik)
Antipanin P - (Michallik)
Ben-u-ron - (Bene)
Captin - (Krewel)
Cetebe duoEffekt - (GSK Consumer)
Contac Erkältungs-Trunk - (GSK Consumer)
Dignocetamol - (Luitpold)

Dolarist - (Steiner)
Dolofugin - (Sanol)
Doloreduct - (Azupharma)
Dolorfug - (Wolff)
Dorocoff-Paracetamol - (Hevert)
duracetamol - (Merck dura)
Enelfa - (Dolorgiet)
Eu-Med P mono - (Med Fabrik)
Eu-Med Schmerzapschen - (Zyma)
Fensum - (Merckle)
Finiweh - (Dentinox)
Freka-cetamol - (Fresenius)
Gardan P - (Hoechst)
Gepodan - (Pohl)
Grippex - (Hexal)
Grippostad Heissgetränk - (Stada)
Kinder-Finiweh - (Dentinox)
Larylin Heissgetränk gegen Schmerzen und Fieber - (Bayer)
Logomed Schmerz- /Fieber - (Logomed)
Lonarid Mono - (Boehringer Ingelheim)
Mandrogripp - (Dolorgiet)
Mogil - (OTW)
Momentum Analgetikum - (Much)
Mono Praecimed - (Molimin)
Mono-Trimedil - (Zyma)
NeoCitran - (Sandoz)
NilnOcen - (Zeppenfeldt)
Octadon N - (Thiemann)
Ophinal - (Kettelhack Riker)
Ozothin - (SmithKline Beecham)
Paedialgon - (Rosen)
Pantalgin - (UCB)
Parapaed - (Ritsert)
PCM - (Hemopharm)
Perdiphen-N - (Spitzner)
Perfalgan - (BMS)
Pyromed - (Sanofi Synthelabo)
RubieMol - (Rubiepharm)
Schmerzex - (Roland)
Sinpro junior - (Bayer)
Sinpro N - (Worwag)
Togal - (Togal)
Treupel mono - (Asta Medica)
Tylenol - (Janssen-Cilag)
Verlapyrin N - (Verla)
Vips - (Lichtwer)
Vivimed - (Mann)
Vivimed N - (Mann)

Greece

Algocit - (Demo)

Anadin - (Wyeth)
Apotel - (Unipharma)
Apyresyn - (Farmasyn)
Biocetamol - (Biospray)
Calmodor - (Gerolymatos)
Cetinject - (Lamda (Λαμδα))
Dalminette - (Norma (Νορμα))
Depoforte - (Terix)
Depon - (BMS)
Depon Maximum - (BMS)
Depon Odis - (BMS)
Dolal - (Alapis)
Effergal - (BMS)
Genspir - (Vocate)
Lonarid Aplo - (Boehringer Ingelheim)
Neo-Kalmol - (Specifar (Σπεσιφαρ))
Panadol - (GSK)
Par - (Angelini)
Paramin - (Elvipe)
Perfalgan - (IFET (ΙΦΕΤ))
Prest - (Olvos)
protAlgon - (Lavipharm)
Temptra - (BMS)
Tunelzin - (Lavipharm)
Tylenol - (Johnson & Johnson)
Zenol - (Vianex (Βιανεξ))

Hong Kong

Acephen - (Nice)
Acet - (T-Boma)
Acetamol - (Vickmans)
Afebrin - (Westmont)
Analgiser - (CNW)
Anapar - (Meyer)
Anaphen - (Meyer)
Angenol - (APT)
Angtab - (APT)
Apap - (Sheraton)
Arfen - (Star)
Ben-u-ron - (Bene-Chemie)
BF-Paracetal - (Bright Future)
BF-Paradac - (Bright Future)
Biogesic - (Biomedis)
Calpenol - (APT)
Calpol - (GSK)
Campo - (Quality)
Carmol - (Nice)
Cetal - (Julius Chen)
Children's Tylenol - (Johnson & Johnson)
Childrens Fortolin - (Fortune)
Christamol - (Christo)

Chun Tung - (Hong Kong Medical)
Cortal for Children - (GSK)
Dhamol - (DHA)
Dolo-Neurobion N - (Merck)
Dolorol - (Julius Chen)
Endopain - (Medipharma)
Energex - (APT)
Ensid - (LSB)
Europain - (Europharm)
Extramol - (Vickmans)
Fara - (HealthCare PharmaScience)
Felpenol - (APT)
Fevandol - (APT)
Fortolin - (Fortune)
Hoemal - (Hoe)
Infant's Tylenol - (Johnson & Johnson)
Junior Strength Tylenol - (McNeil)
Kenamose - (APT)
Konaton - (Hitpharm)
Lemsip Cold + Flu Max - (Reckitt Benckiser)
Macropol - (Natural Health)
Napa - (Wilcome)
New-Eurogesic - (Europharm)
Pamidol - (APT)
Panadol - (GSK)
Panamol - (Vast Resources)
Panon - (Wings)
Paracet - (Vickmans)
Paragram - (Vickmans)
Paramol - (Advance)
Paramolan - (CNW)
Paratab - (Primal)
Paraway - (Synco)
Parcemol - (Synco)
Parmol - (Hovid)
Paromon - (Pharmasky)
Partamol - (Meyer)
Pharmacin - (Unicorn)
Pharmadol - (Bright Future)
Pinocine - (Unicorn)
Po On Ling - (National Pharmaceutical)
Poro - (Yung Shin)
Pritamol - (Leamyk)
Progesic - (Xepa-Soul Pattinson)
Promol - (Medreich)
Punortor - (Vast Resources)
Pymadon - (Hitpharm)
Pyramol - (Meyer)
Pyrogesic - (National Pharmaceutical)
Pyrudon - (Vast Resources)

Qualamol - (Quality)
Qualimol - (Quality)
Rectol - (Hind Wing)
Reset - (Noble)
Rolonvens - (Frankin)
Roter - (Vemedia)
S-Paramol - (Advance)
Saplingtan-S - (Ling Chi Med)
Serimol - (Pharmaniaga)
Setamol - (Hovid)
Shiling - (Ling Chi Med)
Tarphen - (Nice)
Thamol - (Vickmans)
Tiffany - (Star)
Tygenol - (APT)
Tylenol - (Johnson & Johnson)
U-B - (Charmaine)
U-C - (Charmaine)
U-Cetol - (Neochem)
U-G - (Charmaine)
U-H - (Charmaine)
U-I - (Charmaine)
U-J - (Charmaine)
Uni-Febrin - (Universal)
Uni-Pamol - (Jean-Marie)
Uphamol - (Vast Resources)
Vidamol - (Vickmans)
Xykaa - (Evercare)

Hungary

Ben-u-ron - (Bene)
Doloramol - (Actavis)
Efferalgan - (BMS)
Febrilin - (Beres)
Grippostad - (Stada)
Mexalen - (Teva)
Panadol - (GSK Consumer)
Paramax - (Vitabalans)
Perfalgan - (BMS)
Rubophen - (Sanofi-Aventis)

India

A-125 - (Adventure Life Science)
Alcocin - (Alicon)
Algina - (Geno)
Alice - (Ind-Swift)
Anamol - (Elder)
Anthol - (Anthiea)
Asimol - (Willow)
Babygesic - (Meyer)
Bactpar - (Bactolac)
Bambiti - (Dey's)

Bepamol - (Biological E)
Calpol - (GSK)
Cemol - (Inga)
Cetanil - (Dabur)
Cetofeb - (Worth)
Cofamol - (Adcock Ingram)
Copanat - (Natco)
Crocic - (GSK)
Cropara - (Shalaks)
Disprin Paracetamol - (Reckitt Benckiser)
Doliprane - (Piramal)
Dolko - (Medicon)
Dolo - (Micro)
Dolodart - (Juggat)
Dolopar - (Micro)
Essmol - (Sresan)
Eupyrlic - (Euphoric)
Ezeepara - (Abbott)
F-Nil - (Laksun)
Fastpara - (Santiago)
Febrex - (Indoco)
Febridol - (Cipla)
Febrinil - (Svizera)
Fenace - (Invision)
Fenil - (Tan)
Fep - (Madhav)
Fepamol - (Vensat)
Fepanil - (Citadel)
Fevastin - (Tablets)
Flupara - (BMW)
Genmole - (Cadila)
Hidol - (Haledew)
Histacold - (Minova)
Hitem-MD - (Sigman)
Hitz - (Dexter)
Ibumax - (Mission Happiness)
Ifimol - (JB Chemicals)
Infadil - (Shince)
Jagcin - (Jagsonpal)
Junimol - (Elder)
Kelvin - (Leben)
Lanol - (Hetero)
Lit-King - (Bestochem)
Lotemp - (Raptakos)
Low-Deg - (Invision)
Lupipara - (Lupin)
Malidens - (Abbott)
Medomol - (Medopharm)
Metacin - (Themis)
Metalgin - (Mount Mettur)

Mino - (Rhine)
Mol - (Gufic)
Mortrin - (Daffohils)
Narmo - (Kevin)
Neomol - (Neon)
Nofiva - (Agio)
Orimol - (Orion)
Oyup - (Unikid)
P-125 - (Apex)
P-37 - (Moraceae)
Pacimol - (Ipca)
Pamol - (Finecure)
Panact - (DWD)
Parabig - (Winsome)
Paracetanal - (Zydus)
Paracin - (Stadmed)
Paracip - (Cipla)
Parafizz - (Cipla)
Parafort - (Auspi)
Parage - (Allenge)
Paraglow - (Aglowmed)
Paral - (Hauz)
Paralife - (Lifeon)
Parameter - (Invision)
Parasym - (Symbiosis)
Paratel - (Intel)
Parazine - (David)
PF Drops - (Candor)
Pyrexon - (Wockhardt)
Pyrigesic - (East India Pharma)
Ultragin - (Wyeth)

Indonesia

Afebrin - (Konimex)
Alphagesic - (Apex)
Alphamol - (Molex Ayus)
Biogesic - (Biomedis)
Bodrex Forte - (Tempo Scan Pacific)
Bodrexin Demam - (Bode)
Calapol - (GSK)
Cetapain - (Darya-Varia)
Contratemp - (Mugi)
Cupanol - (Guardian)
Dapyrin - (Hexpharm)
Dumin - (Actavis)
Erphamol - (Erlimpex)
Eterfix - (Novell)
Farmadol - (Fahrenheit)
Fasgo - (Hexpharm)
Fevrin - (Armoxindo)
Grafadon - (Graha)

Gunaceta - (Sunthi Sepuri)
Ikacetamol - (Ikapharmindo)
Itamol - (Berlico Mulia)
Kamolas - (Solas)
Lanamol - (Landson)
Maganol - (Guardian)
Moretic - (Gracia)
Naprex - (Darya-Varia)
Nasamol - (Nicholas)
Nofebril - (Yarindo)
Nufadol - (Exeltis)
Ottopan - (Otto)
Pamol - (Interbat)
Panadol - (Sterling)
Paracetol - (Prafa)
Pehamol - (Bernofarm)
Piosfen - (Kalbe)
Pireta - (Mahakam Beta)
Poro - (Ethica)
Praxion - (Pharos)
Progesic - (Metiska)
Propyretic - (Combiphar)
Pyrex - (Novell)
Pyrexin - (Meprofarm)
Pyridol - (Pyridam)
Sanmol - (Sanbe)
Sumagesic - (Darya-Varia)
Tamoliv - (Kalbe)
Tempra - (Taisho)
Termagon - (Mecosin)
Termorex - (Konimex)
Turpan - (Corsa)
Xepamol - (Metiska)

Ireland

Anadin Paracetamol - (Wyeth)
Calpol - (McNeil Healthcare)
Cetamol - (Antigen)
Disprol - (Reckitt Benckiser)
Dolflash - (Ethypharm)
Hedex - (Chefaro)
Lemsip Children's Cold Relief - (Reckitt Benckiser)
Medinol - (Cupal)
Padolieve - (Stasisport)
Panadol - (GSK Consumer)
Panagram Max - (GSK Consumer)
Paralief - (Clonmel)
Paralink - (Rice Steele)
Parapaed - (Pinewood)
Parasol - (Rice Steele)
Paratabs - (Pinewood)

Perfalgan - (BMS)
Rimadol - (Ranbaxy)
Rowalief - (Rowa)
Suotex - (Pinewood)
Tipol - (Carysfort)
Tylenol - (Johnson & Johnson)

Israel

Abrol - (Rekah)
Abrolet - (Rekah)
Acamol - (Teva)
Acamoli - (Teva)
Aldolor - (CTI)
Apotel - (Easy Care)
Avcamol - (SLE)
Avcamoli - (SLE)
Dexamol - (Dexcel)
Dexamol Kid - (Dexcel)
Efferalgan - (BMS)
Liqiprin - (SmithKline Beecham)
Maccabimol - (Perrigo)
Novimol - (CTS)
Panadol - (GSK)
Paracet - (Vitamed)
Paramol - (Dexcel)
Paramolan - (Trima)
Perfalgan - (BMS)
Rokamol - (Taro)
Sensamol - (Perrigo)
Supramol - (Sam-On)
Vimoli - (Vitamed)

Italy

Acetamol - (Abiogen)
Adolef - (Biomed)
Babyrinolo Feb Dol - (Bruno)
Calpol - (Wellcome)
Efferalgan - (BMS)
Levadol - (Italfar)
Liatamolo - (Sigillata)
Minofen - (Crinos)
Neo-Fepramol - (Istoria)
Normaflu - (Ratiopharm)
Panadol - (GSK Consumer)
Perfalgan - (BMS)
Piros - (Menarini)
Puernol - (Formenti)
Sanipirina - (Bayer)
Tachipirina - (Angelini)
Termol - (Ratiopharm)

Japan

Acelio - (Terumo)
Anyrume - (Choseido)
Atmiphen - (Takata)
Calonal - (Ayumi)
Calsil - (Teva)
Cocarl - (Sanwa)
Sarutu - (Towa)

Malaysia

Acet - (Pharmascience)
Arfen - (Medochemie)
Avadol - (Advance)
AxPain - (Kotra)
Biogesic - (Biomedis)
Cortal - (Aspen)
Dhamol - (DHA)
Dumin - (Alpharma)
Fepril - (Idaman)
Hoemal - (Intact)
Naprex - (Pediatrix)
Panadol - (GSK Consumer)
Paracap - (Umeda)
Parafizz - (Cipla)
Partamol - (Atlantic)
Porol - (YSP)
Progesic - (Xepa-Soul Pattinson)
Rapidol - (Ranbaxy)
Remedol - (Remedica)
Serimol - (Raza)
Setromol - (Strand)
Tempol - (CCM)
Uphamol - (CCM)

Mexico

Abatem - (Wermar)
Ac-Fast - (Hormona)
Acetafen - (Rayere)
Acetif - (Novag)
Alpirex - (Berman)
Amolgen - (Solfran)
Analmex - (Ofimex)
Analphen - (Randall)
Andopan - (Atlantis)
Andox - (Atlantis)
Antidol - (Quimica y Farmacia)
Biofer - (Bioresearch)
Bremotel - (Alpharma)
Brontonyl - (Rhone-Poulenc Rorer)
Calinofen - (Medimport)
Calpol - (Glaxo Wellcome)
Colderina - (Wayne)
Coriver - (Maver)

Datril - (BMS)
Dismifen - (Best)
Dolgan Flash - (Sanofi-Aventis)
Dolotemp - (GSK)
Doluvital - (Valdecasas)
Dolviran - (Bayer)
Facetol - (Nafar)
Farpik - (Farcoral)
Febran - (Columbia)
Febraxito - (Rhein)
Febrim - (Interlab)
Febronyl - (Rhone-Poulenc Rorer)
Ferridal - (Parggon)
Filanc - (Continetales)
Frilen - (Offenbach)
Ginol - (Tocogino)
Icetazol - (IQFA)
Ifutemp - (Ifusa)
Infalgina - (Pisa)
Magnidol-Plus - (Streger)
Mejoral - (GSK)
Mejoral Acti-Rapido - (GSK)
Mejoralito - (GSK)
Minofen - (Liomont)
Minomex - (Liferpal)
Neodol - (Diba)
Neodolito - (Diba)
Nordinet Infantil - (Nordin)
Notem - (Teva)
Panadol - (SmithKline Beecham)
Panofen - (Liferpal)
Parengesico - (Hoechst Marion Roussel)
Pharmacen - (Alpharma)
Piraldin - (Vitae)
Piralgina - (Diba)
Piralgina 650 - (Diba)
Piralyn - (Kener)
Piremol - (Loeffler)
Precifen - (Precimex)
Prosedal - (Loeffler)
Quitadol - (Biomep)
Resfin - (Jofrain)
Sedalito - (Merck)
Sedalmerck Infantil - (Merck)
Sedalmerck Pediatrico - (Merck)
Sinedol - (Italmex)
Soltadol - (Aspen)
Sons Piral - (Sons)
Tafirol - (Asofarma)
Temperal - (Allen)

Tempire - (Collins)
Tempofin - (Collins)
Tempra - (Reckitt Benckiser)
Tempre - (Collins)
Temprin - (Continental)
Temzzard - (Pizzard)
Termotrin - (Loren)
Terol - (Mavi)
Tylenol - (Johnson & Johnson Consumer)
Tylex - (Janssen-Cilag)
Ulpafie - (Ultra)
Verbalem - (Lemery)
Wifibrin - (Willmar)
Winasorb - (Rudefsa)

Netherlands

Apotel - (Unipharma)
Daro - (Remark)
Darocet - (Heca)
Demneg - (Genmed)
Democyl - (Vifor)
Finimal Junior - (Roche)
Hedex - (GSK Consumer)
Kinder Finimal - (Roche)
Lagalgin - (Lagap)
Momentum - (Pfizer)
Panadol - (GSK Consumer)
Perfalgan - (BMS)
Pinex - (Aurobindo)
Prest - (Olvos)
Sinaspriol-Paracetamol - (Bayer)
Tylenol - (Johnson & Johnson)
Vicks Paracetamol - (Procter & Gamble)

New Zealand

Coldrex Hot Remedy Cold & Flu - (GSK Consumer)
Disprol - (Reckitt Benckiser)
Lemsip Cold & Flu Hot Drink, Max Cold & Flu Hot Drink - (Reckitt Benckiser)
Pacimol - (Multichem)
Pamol - (Healthcare Logistics)
Panadol - (GSK Consumer)
Panadol Cold & Flu Max - (GSK)
Paracare - (PSM)
Parafast - (Actavis)
Paragesic - (Rex)
Paralgin - (Healthcare Logistics)
Parapaed - (AFT)
Paratabs - (PSM)
Perfalgan - (BMS)

Norway

Alvedon - (Astra)

Pamol - (Takeda)
Panodil - (GSK)
Paracet - (Weifa)
Perfalgan - (BMS)
Pinex - (Actavis)
Therimin - (Novartis)

Philippines

Acet - (Euro-Med)
Acetadol - (Medi-Rx)
Aeknil - (Therapeutic)
Aeknol - (IE Medica)
Alvedon - (Multicare)
Anaseran - (Medhaus)
Baropyrine - (Am-Europharma)
Biocet - (Endure)
Biogesic - (Unilab)
Biopain - (Endure)
Bioretic - (Jinling)
Calpol - (GSK)
Cemol - (SRS)
Clocephen - (Boie)
Cloxina - (Lewison)
Corgic - (Jumont)
Crocin - (Solvay)
Detramol - (Filadams)
Dolexpel - (Morishita)
Dolo-Jaga - (Lloyd)
Dolonil - (Lloyd)
Dynacet - (Pasteur)
Eurogesic - (Saga)
Fastamol - (Tianjin)
Febrile Free - (NCPC)
Febrinil - (Oboi)
Gendol - (Dynamic)
Geran - (GPC)
Gifaril P - (Wander)
Ifimol - (Unique)
Kiddilets - (United Laboratories)
Lexalgin - (Danlex)
Medgenol - (MedGen)
Myremol - (Myrex Ethica)
Nahalgesic - (Hubei Huazhong)
Napalgin - (Doctors)
Napran - (Orchid)
Naprex - (Pediatrix)
Nektol - (Vamsler)
Neo-Kiddielets - (United Laboratories)
Nordex - (Ashford)
Opigesic - (Bayer)
Oxydol - (Vhermann)

Pacetamol - (Bal)
Panadene - (Basic)
Para-4-Kids - (Blue Sky)
Para-IV - (Jiangsu Sihuan)
Paracef - (SPM)
Paragesic - (Bliss)
Paramed - (Tolmann)
Parvid - (Genesis)
Poro - (Yung Shin)
PRC - (Croesus)
Pyreset - (Amanta)
Rapidol - (Hexagon)
Raxem - (Square)
Rexidol - (United American)
Riber - (Solvang)
Rongesic - (Virgo)
Sanmol - (Sanbe)
Saridon - (Bayer)
Selegesic - (Sel-J)
Sinomol - (Sinochem)
Sintos - (Square)
Tempain - (Blooming Fields)
Tempcaire - (PediaCare)
Tempra - (Taisho)
Teramol - (Terramedic)
Tylenol - (Johnson & Johnson)
Ultragesic - (Medic+Aid)
Zestagesic - (Ad-Drugstel)
Zydinol - (More)

Poland

Acenol - (Galena)
Apap - (US Pharmacia)
Bolopax - (NP)
Calpol - (McNeil)
Codipar - (Angelini)
Efferalgan - (BMS)
Gemipar - (Gemi)
Grippostad - (Steigerwald)
Novo-Gesic - (Novopharm)
Panadol - (GSK Consumer)
Paramax - (Vitabalans)
Pedicetamol - (Sequoia)
Perfalgan - (BMS)
Tazamol - (Polfa Tarchomin)
Theraflu Grip - (Novartis Consumer)

Portugal

Anadin Paracetamol - (Home)
Anti-Gripe Asclepius - (Plough)
Apotel - (Unipharma)
Atralidon - (Atral)

Beluron - (Neo-Farmaceutica)
Ben-u-ron - (Bene)
Bisolgrip - (Unilfarma)
Calpol - (Janssen-Cilag)
Cetol - (Helm)
Codoforme - (Quimedical)
Cofedron - (Azevedos)
Dafalgan - (BMS)
Efferalgan - (BMS)
Febridol - (Sidefarma)
Fludeten - (Alodial)
Gelocatil - (Ferrer)
Huber - (Helm)
Katagrip - (Lepori)
Kelin - (Helm)
Lisopan - (Azevedos)
Molpireos - (Generis)
Neogrip - (Bene)
Olpira - (Helm)
Panadol - (GSK Consumer)
Panasorbe - (Sanofi-Aventis)
Pantadolor - (Labialfarma)
Paracetol - (Almus)
Paramolan - (Medinfar)
Parsel - (GSK Consumer)
Perdolan Mono - (Janssen-Cilag)
Perfalgan - (BMS)
Piraldol - (Infosaude)
Pirantamol - (Infosaude)
Singrips - (Confar)
Supofen - (Basi)
Takipirina - (Angelini)
Tylenol - (Johnson & Johnson)
Xumadol - (Italfarmaco)
Zaramol - (APS)

Russian Federation

Apap - (US Pharmacia)
Apotel - (Unipharm)
Calpol - (GSK)
Cefecon D - (Nizpharm)
Daleron - (KRKA)
Dolomol - (Hikma)
Efferalgan - (BMS)
Flutabs - (Farmstandart)
Ifimol - (Unique)
Panadol - (GSK Consumer)
Perfalgan - (BMS)
Strimol - (Natur Produkt)
Xumapar - (Italfarmaco)

Singapore

Acet - (Pharmascience)
Alcetamol - (Sunward)
Biogesic - (Biomedis)
Calpol - (GSK)
Cetamol - (Xepa-Soul Pattinson)
Childrens Panadol - (GSK)
Decolgen Pain & Fever - (Medifarma)
Dhamol - (DHA)
Dolo - (Micro)
Double Parrot Brand - (Beacons)
Familin - (DHA)
Fepril - (Idaman)
Fibrexin - (Menarini)
Hoemal - (Hoe)
Kame - (Kotra)
Lemsip Cold & Flu Head Cold - (Reckitt Benckiser)
Mei-Mei Children's Fever - (Sunward)
Milidon - (Malayan)
Napa - (Beximco)
Naprex - (Pediatrix)
Pacemol - (Malaysia Chemist)
Panadol - (GSK)
Panamol - (Beacons)
Paramol-F - (Beacons)
Paratab - (Sunward)
Parcemol - (Synco)
Parmol - (Hovid)
Paximol - (ICM)
Poro - (Yung Shin)
Pritamol - (Prime)
Progesic - (Xepa-Soul Pattinson)
Rapidol - (Ranbaxy)
Remedol - (Remedica)
Senkon Junior Fever - (Beacons)
Setamol - (Hovid)
SP-Febril - (Sunward)
Sunny Fever - (Beacons)
Tempra - (Mead Johnson)
Tylenol - (Johnson & Johnson)
Uphamol - (Upha)

South Africa

Actamol - (Ascendis)
Adco-Napamol - (Adcock Ingram)
Adco-Prolief - (Adcock Ingram)
Anadin-3 - (SA Druggists Self Med)
Antalgic - (Caps)
Arcanagesic - (Arcana)
Brunamol - (Brunel)
Brunomol - (Brunel)
Calpol - (GSK)

Cetapon - (Pharmagen)
Compu-Pain - (Compu)
Dolorol - (Aspen)
Dynadol - (Ascendis)
Empaped - (Takeda)
Ennagesic - (Propan)
Entalgic - (Ascendis)
Farmacetamol - (Docmed)
Fevamol - (Aspen)
Feverpain - (Ascendis)
Gencetamol - (Ascendis)
Go-Pain P - (Glenmark)
Junior Disprin - (Reckitt Benckiser)
Lyteca - (Zurich)
Maxadol-P - (Restan)
Medpramol - (Schwulst)
Merck-Gesic - (Xixia)
Micro-Gesic - (Pharma-Q)
Pacimol - (Nat Druggists)
Painamol - (Sun)
Painblok - (Gulf Drug)
Painogesic - (Austell)
Pamol - (Docmed)
Panado - (Adcock Ingram)
Paracet - (Be-Tabs)
Paradco - (Adco)
Paramed - (Litha)
Parapane - (Pharma-Q)
Perfalgan - (BMS)
Pyradol - (Xixia)
Pyragesic - (Noristan)
Pyralen - (Ascendis)
Setamol - (Reckitt & Colman)
Temol - (Rolab)
Tylenol - (Johnson & Johnson)
Varipan - (LeBasi)
Winpain - (Brunel)

Spain

Acecat - (Tiedra)
Acertol - (Lacer)
Actron - (Bayer)
Akindol - (Fournier)
Alador - (Alboran)
Alginina - (Upsamedica)
Analter - (Alter)
Antidol - (Cinfa)
Apiredol - (Ionfarma)
Apiretal - (Ern)
Aspac - (Inexfa)
Asplin - (Diafarm)

Auxidor - (Fher)
Bandol - (Pharmacia)
Bolidol - (Kern)
Calmanticold - (Perez Gimenez)
Cupanol - (Ern)
Dafalgan - (Esteve)
Desfebre - (Lasa)
Dolefin Paracetamol - (Pharmacia)
Dolgesic - (Novag)
Dolocatil - (Ferrer)
Dolostop - (Kern)
Drazin - (Wellcome)
Duorol - (Chefaro)
Efetamol - (Italfarmaco)
Efferalgan - (BMS)
Eftazid - (Mundogen)
Febranine - (Roche Nicholas)
Febrectal - (Romofarm)
Frenagial - (McNeil)
Gelocatil - (Ferrer)
Hedex - (SmithKline Beecham)
Melabon Infantil - (Lacer)
Nofedol - (Aventis)
Nupeldol - (Nupel)
Octomol - (Diasa)
Panadol - (GSK Consumer)
Panrectal - (Quimifar)
Parafludeten - (Alter)
Pediapirin - (Docta)
Perfalgan - (BMS)
Pirinasol - (Bayer)
Prontina - (Abello)
Resakal - (Puerto Galiano)
Resolvebohm - (Bohm)
Sinmol - (Maxfarma)
Stopain - (Britisfarma)
Sudafed Co - (Wellcome)
Takipirina - (Angelini)
Talgo - (Ern)
Temperal - (Diviser Aquilea)
Tempra - (Upsamedica)
Termalgin - (GSK Consumer)
Termocatil - (Gelos)
Tylenol - (Johnson & Johnson)
Unebril - (Onedose)
Xumadol - (Italfarmaco)
Zatinol - (Efarmes)
Zolben - (Novartis)

Sweden

Alvedon - (GSK Consumer)

Curadon - (AstraZeneca)
Lemsip - (Meda)
Pamol - (Takeda)
Panodil - (GSK Consumer)
Paracut - (Vitabalans)
Perfalgan - (BMS)
Pinex - (Actavis)
Quramol - (Orion)
Reliv - (GSK Consumer)
Therimin - (Novartis)

Switzerland

Acetalgin - (Streuli)
Antigrippine Comp. - (Sanofi Winthrop)
Arthrolur - (Drossapharm)
Bebesan N - (Sanopharm)
Becetamol - (Gebro)
Ben-u-ron - (Nutrimerdis)
Comprimés analgésiques no 534 - (Renapharm)
Contre-Douleurs P - (Wild)
Dafalgan - (BMS)
Democyl - (Democal)
Demogripal - (Democal)
Dololur - (Drossapharm)
Doloran - (Labatec)
DoloStop nouvelle formule - (Zeller)
Dolprone - (Sanofi-Aventis)
Fortalidon P - (Novartis Consumer)
Influbene N - (Mepha)
Kafa - (Vifor)
Malex - (Ecosol)
Neo-Treupine - (Asta Medica)
Nina - (Medichemie)
Ortensan - (Cimex)
Osa Suppositoires contre douleurs et fièvre - (Iromedica)
Panadol - (GSK Consumer)
Panadol Extend - (GSK Consumer)
Para-schmerz - (Abdi-Med)
Paraconica - (Acino)
Perfalgan - (BMS)
Pharmacard Family Douleurs & Fièvre - (Pharmacard)
Rivodol - (Rivopharm)
Seranex N - (Vifor)
Siniphen Nouvelle formule - (Singer)
Spalt N - (Whitehall-Robins)
Stellacyl nouvelle formule - (Roche)
Termalgin - (Novartis Consumer)
Treupel Dolo Paracetamol - (Meda)
Treupel N - (Asta Medica)
Treuphadol - (Treupha)
Tylenol - (Janssen-Cilag)

Zolben - (Welti)

Thailand

A-Mol - (Siam Bheasach)
Aceta - (Suphong)
Aceta-P - (PP Lab)
Acetasil - (Silom)
Algogen - (Nakornpatana)
Ampol - (Asian Pharm)
Angela - (T Man)
Aoricet - (Medicine Products)
Aspamol - (Pharmahof)
Asumol - (Asian Union)
Bakamol - (Medicpharma)
Biogesic - (Biomedis)
Calpol - (GSK)
Cemol - (Central)
Cetamol - (BJ Benjaosoth)
Cetapol - (Utopian)
Cetta - (Suphong)
Codamol - (ANH)
Cotemp - (Community Pharmacy)
Daga - (Sanofi-Aventis)
Denamol - (TO-Chemicals)
Depyret - (TO-Chemicals)
Detamol - (PD)
Diamol - (Chinta)
Faron - (Newcharoen)
Fenn - (Sriprasit)
Foramol - (The Forty-Two)
KB Gin - (KB)
Kit - (Continental Pharma)
Lotemp - (Biolab)
M-Aceta - (2M)
Mymol - (Burapha)
Mypara - (Greater Pharma)
Nasa - (Millimed)
New-um - (New York Chemical)
Newtol - (New York Chemical)
Nutamol - (Osotspa)
Pamol - (Patar)
Panadol - (GSK)
Para - (ANH)
Para-G - (Millimed)
Paracap - (Masa)
Paracet - (Osotspa)
Paragin - (Central)
Paraman - (T Man)
Paramed - (Medicpharma)
Paramol - (General Drugs)
Paramol TP - (TP)

Paranal - (Siam Bheasach)
Paranal-L - (Siam Bheasach)
Parano - (Milano)
Paranol - (Utopian)
Parapro - (Medicine Products)
Parat - (Asian Pharm)
Paratol - (Chew)
Parcet - (Pharmahof)
Pardon - (Acdhon)
Parnox - (Charoen)
Partamol - (Atlantic)
Pat - (TNP)
Patum - (Picco)
Pemol - (Chinta)
Poro - (YSP)
Pyracon - (Hua)
Pyretal - (Shiwa)
Pyrimed - (Utopian)
Ramol - (Nakornpatana)
Saebegin - (Chinta)
Salenol - (Pharmahof)
Sara - (TNP)
Saridon - (Roche)
St Luke's Fever - (British Dispensary)
Temnol - (Pharmahof)
Temolan - (Olan-Kemed)
Tempra - (Taisho)
Thoho - (T Man)
TM Gin - (T Man)
Totamol - (TO-Chemicals)
Tumdi - (Sriprasit)
Tylenol - (Janssen-Cilag)
Tylenol Arthritis Pain - (Janssen-Cilag)
Tymol - (Pharmaland)
Typanol - (Pharmahof)
Umeda Para-J - (Umeda)
Unicap - (Unison)
Unimol - (Unison)
Uracet - (Umeda)
Vemol - (PP Lab)
Vetamol - (Vesco)
Vikool - (United Drug)
Xebramol - (Medicine Products)

Turkey

A-Per - (Aroma)
Asomal - (Casel)
Babinoks - (Sistas)
Berko-Setamol - (Berko)
Calpol - (GSK)
Derman - (Dermanci)

Durapan - (Munir)
Effergal - (Wyeth)
Efpal - (Adeka)
Ekosetol - (Sifar)
Gergaline-P - (Munir)
Gripin - (Gripin)
Kalmet - (Lafar)
Kataprin - (Sanli)
Medaset - (Kocak)
Mihamol - (Pharmactive)
Minafen - (Drogsan)
Minoset - (Bayer)
Noral - (Ulagay)
Panadol - (GSK)
Para-Cold - (Keymen)
Paracerol - (Polifarma)
Paracet - (Gripin)
Paradine - (Hakay)
Paranox - (Sanofi-Aventis)
Parasedol - (Kocak)
Parcetol - (Rasyonel)
Parol - (Atabay)
Paroma - (Sanovel)
Partemol - (Vem)
Pedipar - (Adeka)
Perfalgan - (BMS)
Pharmadol - (Sodhan)
Pirofen - (Deva)
Polmofen - (Yeni)
Sedalon - (Gunsan)
Seskamol - (SSK)
Setamol - (Yeni)
Sifenol - (Hiperonline)
Tamol - (Sandoz)
Tempo - (Akdeniz)
Termacet - (Toprak)
Termalgine - (Novartis)
Tylol - (Nobel)
Vermidon - (Sandoz)
Volpan - (Husnu Arsan)
Zaldaks - (Ilacsan)

Ukraine

Cefecon D - (Nizhfarm)
Effergal - (BMS)
Infulgan - (Yuri)
Milistan For Children - (Mili)
Panadol - (GSK Consumer)
Piaron - (Kusum)
Rapidol - (Actavis)

United Arab Emirates

Adol - (Julphar)

United Kingdom

Abdine Cold Relief - (Bell)
Alvedon - (Intrapharm)
Anadin Paracetamol - (Pfizer Consumer)
Aspro Paraclear - (Roche Consumer)
Boots Pain Relief Suspension 6 Years Plus - (Boots)
Calpol - (McNeil)
Disprol - (Reckitt Benckiser)
Elkamol - (Kendon)
Fanalgic - (Mitchell)
Fennings Childrens Cooling Powders - (Anglian)
Galpamol - (Galpharm)
Hedex - (GSK Consumer)
Infadrops - (Goldshield)
Mandanol - (Pharmachem)
Medinol - (SSL)
Miradol - (Durbin)
Obimol - (Ayrton)
Pain Relief Syrup for Children - (Unichem)
Paldesic - (Rosemont)
Panadol - (GSK Consumer)
Panaleve - (Pinewood)
Paracets - (Sussex)
Paraclear - (Roche Consumer)
Paramin - (Wallis)
Parapaed - (Pinewood)
Perfalgan - (BMS)
Placidex - (De Witt)
Salzone - (Wallace Mfg Chem.)
Tixymol - (Novartis Consumer)
Tramil - (Whitehall)

Venezuela

Acetafen - (Infinity)
Acetalis - (Proula)
Aceval - (Valmor)
Agurin - (Nolver)
Alivax - (Vivax)
Amifen - (Meyer)
Ananty - (Plusandex)
Apyret - (Oftalmi)
Apyrene - (Vincenti)
Atamel - (Pfizer)
Brexin - (Cofasa)
Cadafen - (Drovepat)
Colprin - (Ronava)
Menpirin - (Intra)
Paracor - (Corsalud)
Parafen - (SM)

Parstelin - (Novartis)
Tachiforte - (Elmor)
Tachipirin - (Elmor)
Temptra - (BMS)
Tylenol - (Johnson & Johnson)
Tylex - (Janssen-Cilag)
Ultrafen - (Infinity)
Vestax - (Vargas)
Vick Pyrena - (Procter & Gamble)
Winadol - (Konsuma)

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