Brand Names

Acid Reducer, Major Acid Reducer, Tagamet, Tagamet HB

Indication Specific Dosing

For the treatment of gastroesophageal reflux disease with esophagitis

Oral dosage

Adults

800 mg PO twice daily or 400 mg PO 4 times daily for 12 weeks.

Adolescents 16 to 17 years

800 mg PO twice daily or 400 mg PO 4 times daily for 12 weeks.

Infants†, Children†, and Adolescents† 1 to 15 years

10 mg/kg/dose PO 4 times daily for 8 to 12 weeks.

Premature and Term Neonates†

8 to 20 mg/kg/day PO in divided doses every 12 hours.

For the self-medication of pyrosis (heartburn), acid dyspepsia (acid indigestion), or sour stomach

Oral dosage (nonprescription OTC products)

Adults

200 mg PO twice daily as needed. Max: 400 mg/day.

Children and Adolescents 12 to 17 years

200 mg PO twice daily as needed. Max: 400 mg/day.

For the treatment of peptic ulcer disease (duodenal ulcer or gastric ulcer) or gastritis†

For acute treatment

Oral dosage

Adults and Adolescents 16 years and older

800 mg PO once daily at bedtime or 400 mg PO twice daily or 300 mg PO 4 times per day (with meals and at bedtime) for 8 to 12 weeks.

Children and Adolescents 1 to 15 years

20 to 40 mg/kg/day PO in divided doses every 6 hours.

Intravenous dosage

Adults and Adolescents 16 years and older

300 mg IV, appropriately diluted, every 6 hours. Alternatively, may give 37.5 mg/hour (i.e., 900 mg/day) by continuous IV infusion. Several studies have verified that cimetidine 37.5 mg/hour (i.e., 900 mg/day) adequately maintains intragastric pH above 4. For patients requiring a more rapid elevation of gastric pH, the continuous infusion may be preceded by a 150 mg loading dose.

Children and Adolescents 1 to 15 years

20 to 40 mg/kg/day IV in divided doses every 6 hours for active treatment.

Intramuscular dosage

Adults and Adolescents 16 years and older

300 mg IM every 6 hours for active treatment.

Children and Adolescents 1 to 15 years

20 to 40 mg/kg/day IM divided every 6 hours for active treatment.

For maintenance therapy of refractory duodenal ulcer or gastric ulcer due to peptic ulcer disease

Oral dosage

Adults and Adolescents 16 years and older

400 mg PO once daily at bedtime.

For the treatment of pathological hypersecretory conditions including Zollinger-Ellison syndrome, systemic mastocytosis, and multiple endocrine adenoma syndrome

Oral dosage

Adults

300 mg PO four times per day with meals and at bedtime. Do not exceed 2400 mg/day PO.

Intravenous dosage (intermittent IV injection)

Adults

300 mg IV, appropriately diluted, given over not less than 5 minutes every 6 hours. If increased dosage is necessary, give 300 mg doses more frequently, up to a maximum daily dose of 2400 mg.

Intravenous dosage (continuous IV infusion)

Adults

50 mg/hour (1200 mg/day) by continuous IV infusion. Alternatively, give 150 mg as a single IV bolus dose initially, followed with an infusion of cimetidine 37.5 mg/hour (i.e., 900 mg/day), and adjust dosage as indicated. In studies of patients with these conditions, the mean infused dose of cimetidine was 160 mg/hr with a range of 40 to 600 mg/hour to keep the intragastric acid secretion at 10 mEq/hr or less.

Adolescents 16 years and older

150 mg as a single IV bolus dose initially, followed with an infusion of cimetidine 37.5 mg/hour (i.e., 900 mg/day), and adjust dosage indicated. In studies of patients with these conditions, the mean infused dose of cimetidine was 160 mg/hour with a range of 40 to 600 mg/hour IV infusion to keep the intragastric acid secretion at 10 mEq/hour or less.

For stress gastritis prophylaxis or active treatment of stress gastritis† in critically ill patients

Oral dosage†

Adults

300 mg PO 4 times daily.

Continuous Intravenous Infusion dosage

Adults

50 mg/hour (1,200 mg/day) continuous IV infusion. Alternatively, 150 mg IV bolus, followed by 37.5 mg/hour (900 mg/day) continuous IV infusion.

Adolescents 16 to 17 years

50 mg/hour (1,200 mg/day) continuous IV infusion. Alternatively, 150 mg IV bolus, followed by 37.5 mg/hour (900 mg/day) continuous IV infusion.

Infants†, Children, and Adolescents 1 month to 15 years

20 to 40 mg/kg/day IV divided 4 to 6 times daily.

Premature and Term Neonates†

10 mg/kg/day IV divided every 6 to 12 hours; doses up to 20 mg/kg/day have been reported. Lower doses (e.g., 4 mg/kg/dose IV given every 12 hours or longer) have been used in very low weight premature infants.

For the treatment of upper GI bleeding†

Intravenous dosage (continuous IV infusion)

Adults and Adolescents 16 years and older

37.5 mg/hour (i.e., 900 mg/day) by continuous infusion. Several studies have verified that cimetidine 37.5 mg/hour (i.e., 900 mg/day) adequately maintains intragastric pH above 4.

For acid aspiration prophylaxis† prior to anesthesia

Oral dosage

Adults

300 mg PO single dose, 1.5 to 2 hours prior to surgery, before induction.

According to guidelines of the American Society of Anesthesiologists, routine preoperative use is NOT recommended in patients who have no apparent increased risk for pulmonary aspiration. However, some guidelines recommend an H2-receptor antagonist (PO or IV) for all women presenting for cesarean delivery.

Intravenous dosage (intermittent IV injection or infusion)

Adults

300 mg IV single dose, 1 hour prior to surgery, before induction. According to guidelines of the American Society of Anesthesiologists, routine preoperative use is NOT recommended in patients who have no apparent increased risk for pulmonary aspiration. However, some guidelines recommend an H2-receptor antagonist (PO or IV) for all women presenting for cesarean delivery.

For NSAID-induced ulcer prophylaxis†

Oral dosage

Adults

Several oral doses of cimetidine were assessed in a study of the ability of cimetidine to prevent gastric mucosal hemorrhage induced by a single 1296 mg oral dose of aspirin. The authors concluded that a single 200 mg or 400 mg oral dose of cimetidine administered at the time of the aspirin dose was successful in preventing endoscopically visible gastric mucosal damage.

For the treatment of acute, severe urticaria† or angioedema† associated with systemic symptoms in combination with an H1-blocker

For the prevention of urticaria and other histamine-mediated reactions to specific types of chemotherapy† (e.g., paclitaxel)

Intravenous dosage (intermittent IV infusion)

Adults

300 mg IV, appropriately diluted, in combination with an H1-blocker (e.g., diphenhydramine) and dexamethasone, administered 30 minutes prior to the initiation of the chemotherapy agent.

Intravenous dosage (intermittent IV injection or infusion)

Adults

300 mg IV (appropriately diluted), in combination with an H1-blocker.

For the treatment of viral warts†, including molluscum contagiosum† and verruca vulgaris†

For the treatment of molluscum contagiosum†

Oral dosage

Children and Adolescents

40 mg/kg/day PO in 2 to 3 divided doses for 2 months.

For the treatment of common warts (verruca vulgaris†)

Oral dosage

Children and Adolescents

30 to 40 mg/kg/day PO in 3 divided doses for 2 months.

For the treatment of short bowel syndrome†

Oral dosage

Adults

200 to 400 mg PO 4 times daily for at least 6 months.

Intravenous dosage

Adults

200 to 400 mg IV 4 times daily for at least 6 months.

For the treatment of interstitial cystitis†

Oral dosage

Adults

400 mg PO twice daily.

Adolescents

400 mg PO twice daily.

For the treatment of high output enterocutaneous fistula†

Oral dosage

Adults

400 mg PO 4 times daily.

Contraindications And Precaution

Drug Interactions

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

Hypersensitivity

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

General Information

Symptomatic response to therapy with cimetidine does not preclude the presence of gastric cancer. There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy. In the individual who is self-medicating with nonprescription (OTC) formulations, the continuation of heartburn, acid indigestion, or dyspepsia beyond 2 weeks signals the need to consult a health care professional for evaluation.

immunosuppression

In individuals with concomitant immunosuppression, decreased gastric acidity, including that produced by acid-suppressing agents such as cimetidine, may increase the possibility of a hyperinfection of strongyloidiasis.

neonates

Cimetidine injection multidose vials contain benzyl alcohol as a preservative and should be avoided in neonates. There have been reports of fatal 'gasping syndrome' in neonates (less than 1 month of age) after the administration of parenteral solutions

containing the preservative benzyl alcohol at dosages more than 99 mg/kg/day. The minimum amount of benzyl alcohol to cause toxicity is unknown. Therefore, use preservative-free cimetidine injection formulations in neonates.

hepatic failure, renal failure, renal impairment

Cimetidine non-selectively inhibits the hepatic cytochrome P450 oxidative enzymes system and many drug interactions have been described when cimetidine was added to, or discontinued from an established drug regimen. The clinician should review potential drug interactions prior to prescribing cimetidine. Cimetidine should be used cautiously in individuals with hepatic impairment or hepatic failure, such as cirrhosis, or in those with renal impairment or renal failure, because cimetidine clearance can be reduced. Reduced doses of cimetidine are recommended in individuals with renal impairment; further dose reduction may be necessary if hepatic impairment is also present. Various types of reversible confusional states have been attributed to cimetidine. While decreased clearance would seem to predispose individuals to adverse reactions, hepatic disease and/or renal disease have not been shown conclusively to increase the risk for central nervous system reactions.

pregnancy

There are no adequate and well-controlled studies on the use of cimetidine during human pregnancy. Unlike other H2-receptor antagonists (H2RAs), cimetidine exhibits weak anti-androgenic activity; however, animal studies have not demonstrated a risk to the fetus or fertility. Epidemiologic data show no evidence that use of cimetidine or other H2RAs during pregnancy increases fetal malformations compared with the general population, including first-trimester exposure. In human studies, H2RA exposure (including cimetidine) was not associated with a higher risk of congenital malformations (adjusted OR 1.03, 95% CI 0.8 to 1.32); results were similar when therapeutic pregnancy terminations were included (adjusted OR 1.17, 95% CI 0.93 to 1.46). No association was found with perinatal mortality, preterm delivery, low birth weight, or low Apgar scores. Guidelines recommend a trial of lifestyle modifications as first-line therapy for heartburn and gastroesophageal reflux disease (GERD) during pregnancy, followed by antacids if lifestyle adjustments are ineffective. For ongoing symptoms, an H2RA can be used. Other medications should be reserved for pregnant individuals who fail H2RA therapy. Self-medication with over-the-counter H2RAs during pregnancy is not recommended. Pregnant individuals should see their health care professional for a proper diagnosis and for treatment recommendations. Cimetidine has been used in limited circumstances at term in single doses to prevent acid aspiration during labor; some guidelines recommend an H2RA (oral or intravenous) for all individuals presenting for cesarean delivery.

geriatric

Reversible confusional states have been observed on occasion with cimetidine therapy, predominantly, but not exclusively, in severely ill individuals. Advancing age (50 years and older) and preexisting liver or renal impairment appear to be contributing factors. Because geriatric adults are more likely to have renal impairment or other organ dysfunction, care should be taken in dose selection. In some individuals, these confusional states have been mild and have not required discontinuation of cimetidine therapy. In cases where discontinuation was judged necessary, the condition usually cleared with 3 to 4 days of drug discontinuation. According to the Beers Criteria, H2-receptor antagonists are considered potentially inappropriate medications (PIMs) in geriatric individuals with delirium/high risk of delirium (potential for new-onset or worsening delirium) and should be avoided in this patient population. Dosage reduction of H2-antagonists is recommended in geriatric adults with a creatinine clearance less than 50 mL/minute due to the potential for mental status changes.

breast-feeding

Cimetidine is compatible with breast-feeding. Cimetidine is secreted in human milk in minimal amounts. There have been no reports of adverse effects in the breast-fed child. According to guidelines, if heartburn/gastroesophageal reflux (GERD) symptoms persist after delivery, antacids and sucralfate are safe to use during breast-feeding due to minimal passage into human milk. Other histamine 2-receptor antagonists are also excreted in human milk. Both cimetidine and famotidine are considered safe for use during breast-feeding and may be used if symptoms persist despite antacid use.

Pregnancy And Lactation

There are no adequate and well-controlled studies on the use of cimetidine during human pregnancy. Unlike other H2-receptor antagonists (H2RAs), cimetidine exhibits weak anti-androgenic activity; however, animal studies have not demonstrated a risk to the fetus or fertility. Epidemiologic data show no evidence that use of cimetidine or other H2RAs during pregnancy increases fetal malformations compared with the general population, including first-trimester exposure. In human studies, H2RA exposure (including cimetidine) was not associated with a higher risk of congenital malformations (adjusted OR 1.03, 95% CI 0.8 to 1.32); results were similar when therapeutic pregnancy terminations were included (adjusted OR 1.17, 95% CI 0.93 to 1.46). No association was found with perinatal mortality, preterm delivery, low birth weight, or low Apgar scores. Guidelines recommend a trial of lifestyle modifications as first-line therapy for heartburn

and gastroesophageal reflux disease (GERD) during pregnancy, followed by antacids if lifestyle adjustments are ineffective. For ongoing symptoms, an H2RA can be used. Other medications should be reserved for pregnant individuals who fail H2RA therapy. Self-medication with over-the-counter H2RAs during pregnancy is not recommended. Pregnant individuals should see their health care professional for a proper diagnosis and for treatment recommendations. Cimetidine has been used in limited circumstances at term in single doses to prevent acid aspiration during labor; some guidelines recommend an H2RA (oral or intravenous) for all individuals presenting for cesarean delivery.

Interactions

Acalabrutinib: (Moderate) The risk for a drug interaction varies by acalabrutinib dosage form. Administer acalabrutinib capsules 2 hours before an H2-blocker; simultaneous coadministration is expected to decrease capsule absorption and reduce acalabrutinib efficacy. Acalabrutinib tablets are unaffected by gastric acid reducing agents, such as H2-blockers, and may be administered without regard to the H2-blocker time of administration. Consider using acalabrutinib tablets in patients requiring a gastric acid reducing agent.
Acetaminophen; Aspirin, ASA; Caffeine: (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.
Acetaminophen; Aspirin, ASA; Caffeine: (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.
Acetaminophen; Caffeine: (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.
Acetaminophen; Caffeine; Dihydrocodeine: (Moderate) Concomitant use of dihydrocodeine with cimetidine may alter dihydrocodeine plasma concentrations, resulting in an unpredictable effect such as reduced efficacy or symptoms of opioid withdrawal or prolonged opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage adjustment of dihydrocodeine until stable drug effects are achieved. Discontinuation of cimetidine could alter dihydrocodeine plasma concentrations, resulting in an unpredictable effect such as prolonged opioid adverse reactions or decreased opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to dihydrocodeine. If cimetidine is discontinued, monitor the patient carefully and consider adjusting the opioid dosage if appropriate. Dihydrocodeine is primarily metabolized by CYP2D6 to dihydromorphine, and by CYP3A4. Cimetidine is a weak inhibitor of CYP3A4 and CYP2D6.

CYP3A4 inhibitors may increase dihydrocodeine-related adverse effects while CYP2D6 inhibitors may reduce efficacy. (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.
Acetaminophen; Caffeine; Pyrilamine: (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.
Acetaminophen; Codeine: (Minor) Cimetidine may inhibit the conversion of codeine to morphine, codeine's active metabolite, via the CYP2D6 hepatic isoenzyme and therefore may decrease the ability for codeine to produce analgesic effect.
Acetaminophen; HYDROcodone: (Moderate) Consider a reduced dose of hydrocodone with frequent monitoring for respiratory depression and sedation if concurrent use of cimetidine is necessary. It is recommended to avoid this combination when hydrocodone is being used for cough. Hydrocodone is a CYP2D6 and CYP3A4 substrate, and coadministration with CYP2D6 and CYP3A4 inhibitors like cimetidine can increase hydrocodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of hydrocodone. These effects could be more pronounced with a combined CYP2D6 and CYP3A4 inhibitor. If cimetidine is discontinued, hydrocodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to hydrocodone.
Acetaminophen; oxyCODONE: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of cimetidine is necessary. If cimetidine is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like cimetidine can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If cimetidine is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Acyclovir: (Minor) Cimetidine may cause a reduction in the clearance of acyclovir. The clinical significance of these pharmacokinetic interactions is unknown; however, no dosage adjustments are recommended for patients with normal renal function.
Adefovir: (Moderate) Adefovir is eliminated renally by a combination of glomerular filtration and active tubular secretion; coadministration of adefovir dipivoxil with drugs that reduce renal function or compete for active tubular secretion, such as cimetidine, may decrease adefovir elimination by competing for common renal tubular transport systems, thereby increasing serum concentrations of adefovir and/or cimetidine.

Coadministration of these drugs has not been studied, but caution is warranted.
Albendazole: (Moderate) Cimetidine administration with albendazole has been reported to increase albendazole bioavailability. Concentrations of albendazole sulfoxide were increased in bile and cystic fluid about 2 fold in patients with hydatid cyst disease treated with cimetidine 10 mg per kg per day concomitantly with albendazole compared to administration of albendazole alone. More data are needed to elucidate the clinical consequence of this interaction.
Albuterol; Budesonide: (Moderate) Monitor for loss of oral, enteric-coated budesonide efficacy and budesonide-related adverse events during concomitant cimetidine use. Since the dissolution of oral, enteric-coated budesonide is pH dependent, the release properties and uptake of the drug may be altered when used after H2-blockers. In an open, non-randomized, cross-over study, coadministration of cimetidine resulted in a 52% and 31% increase in the budesonide peak plasma concentration and AUC, respectively, after administration of cimetidine 1 g/day (200 mg with meals and 400 mg at night) for 2 separate 3-day periods where oral, delayed-release budesonide 4 mg was administered either alone or on the last day of a cimetidine treatment period.
ALFentanil: (Minor) Cimetidine is an inhibitor of CYP3A4 and thus, reduces the clearance of alfentanil and may prolong the duration of action of alfentanil. Smaller alfentanil doses will be needed if prolonged alfentanil administration is used. Monitor patients for adverse effects of alfentanil, such as hypotension, nausea, itching, and respiratory depression.
Alfuzosin: (Moderate) Alfuzosin is extensively metabolized by hepatic enzymes. Administration of of cimetidine, an inhibitor of hepatic cytochrome P450, with alfuzosin may increase the serum concentration of alfuzosin.
Alogliptin; metFORMIN: (Moderate) Concomitant administration of metformin and cimetidine may increase metformin exposure and increase the risk for lactic acidosis. If these drugs are given together, monitor for signs of metformin toxicity; metformin dose adjustments may be needed. After administration of single doses of cimetidine 400 mg and metformin 850 mg, mean metformin exposure increased by 40%. Metformin is an OCT2 substrate; cimetidine is an OCT2 inhibitor that may decrease metformin elimination by blocking renal tubular secretion.
ALPRAZolam: (Major) Avoid coadministration of alprazolam and cimetidine due to the potential for elevated alprazolam concentrations, which may cause prolonged sedation and respiratory depression. If coadministration is necessary, consider reducing the dose of alprazolam as clinically appropriate and monitor for an increase in alprazolam-related adverse reactions. Lorazepam, oxazepam, or temazepam may be safer alternatives if a benzodiazepine must be administered in combination with cimetidine, as these benzodiazepines are not oxidatively metabolized. Alprazolam is a CYP3A4 substrate and cimetidine is a weak CYP3A4 inhibitor. Coadministration with cimetidine increased alprazolam maximum concentration by 82%, decreased clearance by 42%, and

increased half-life by 16%.
Amiodarone: (Major) Avoid concomitant use of amiodarone and cimetidine due to the risk for increased amiodarone exposure which may increase the risk for adverse effects.
Amitriptyline: (Moderate) Monitor for an increase in amitriptyline-related adverse reactions if coadministration with cimetidine is necessary; a dose reduction of amitriptyline may be necessary. Concurrent use may increase the plasma concentrations of amitriptyline. Amitriptyline is a CYP2D6 substrate and cimetidine is a CYP2D6 inhibitor.
amLODIPine; Atorvastatin: (Moderate) Use HMG-CoA reductase inhibitors with caution with concomitant drugs that may decrease the levels or activity of endogenous steroids, such as cimetidine. Evaluate patients with signs and symptoms of endocrine dysfunction appropriately. HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production.
amLODIPine; Celecoxib: (Minor) Since celecoxib is metabolized by cytochrome P450 2C9, concurrent administration with cimetidine, which can inhibit this enzyme, may result in increased levels of celecoxib. The clinical significance of this interaction has not been established.
Amoxapine: (Moderate) Cimetidine can inhibit the systemic clearance of drugs that undergo oxidative metabolism, such as amoxapine, resulting in increased plasma levels of the antidepressant. Patients should be monitored for amoxapine-related side effects and toxicity if cimetidine is added; when possible, choose an alternative H2-blocker for treatment.
Amphetamine: (Moderate) Use amphetamine; dextroamphetamine and H2-blockers concomitantly with caution. Gastrointestinal alkalinizing agents may increase exposure to amphetamine; dextroamphetamine and exacerbate its actions.
Amphetamine; Dextroamphetamine Salts: (Moderate) Use amphetamine; dextroamphetamine and H2-blockers concomitantly with caution. Gastrointestinal alkalinizing agents may increase exposure to amphetamine; dextroamphetamine and exacerbate its actions.
Amphetamine; Dextroamphetamine: (Moderate) Use amphetamine; dextroamphetamine and H2-blockers concomitantly with caution. Gastrointestinal alkalinizing agents may increase exposure to amphetamine; dextroamphetamine and exacerbate its actions.
Anagrelide: (Moderate) Anagrelide is partially metabolized by CYP1A2. Coadministration of anagrelide with drugs that inhibit CYP1A2, such as cimetidine, could theoretically decrease the elimination of anagrelide and increase the risk of side effects or toxicity. Patients should be monitored for increased adverse effects if these drugs are coadministered.
ARIPiprazole: (Major) Recommendations for managing aripiprazole and cimetidine vary by aripiprazole dosage form. For aripiprazole oral dosage forms, administer a quarter of

the usual dose. For monthly extended-release aripiprazole injections (Abilify Maintena), reduce the dosage from 400 mg to 200 mg/month or from 300 mg to 160 mg/month. Concomitant use may increase aripiprazole exposure and risk for side effects. Aripiprazole is CYP2D6 and CYP3A substrate; cimetidine is a weak CYP2D6 and weak CYP3A inhibitor.
Armodafinil: (Moderate) Armodafinil is partially metabolized by CYP3A4/5 isoenzymes. Interactions with potent inhibitors of CYP3A4 such as cimetidine are possible. However, because armodafinil is itself an inducer of the CYP3A4 isoenzyme, drug interactions due to CYP3A4 inhibition by other medications may be complex and difficult to predict. Observation of the patient for increased effects from armodafinil may be needed.
Artemether; Lumefantrine: (Moderate) Cimetidine is an inhibitor and artemether a substrate of the CYP3A4 isoenzyme; therefore, coadministration may lead to increased artemether concentrations. Concomitant use warrants caution due to the potential for increased side effects. (Moderate) Cimetidine is an inhibitor and lumefantrine a substrate of the CYP3A4 isoenzyme; therefore, coadministration may lead to increased lumefantrine concentrations. Concomitant use warrants caution due to the potential for increased side effects, including increased potentiation of QT prolongation.
Aspirin, ASA; Butalbital; Caffeine: (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.
Aspirin, ASA; Caffeine: (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.
Aspirin, ASA; Caffeine; Orphenadrine: (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.
Aspirin, ASA; Carisoprodol; Codeine: (Minor) Carisoprodol is extensively metabolized and is a significant substrate of CYP2C19 isoenzymes. Theoretically, CY2C19 inhibitors, such as cimetidine, could increase carisoprodol plasma levels, with potential for enhanced CNS depressant effects. (Minor) Cimetidine may inhibit the conversion of codeine to morphine, codeine's active metabolite, via the CYP2D6 hepatic isoenzyme and therefore may decrease the ability for codeine to produce analgesic effect.
Aspirin, ASA; oxyCODONE: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of cimetidine is necessary. If cimetidine is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like cimetidine can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If cimetidine is discontinued,

oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Atazanavir: (Major) Coadministration of H2-blockers with atazanavir reduces serum atazanavir concentrations; however, H2-blockers can be used under specific administration restrictions. Although data are insufficient to recommend atazanavir dosing in children < 40 kg receiving concomitant H2-blockers, the same recommendations regarding timing and maximum doses of concomitant H2-blockers should be followed. In treatment-naive patients >= 40 kg, do not exceed an H2- blocker dose equivalent to famotidine 40 mg twice daily, and give atazanavir 300 mg with ritonavir 100 mg once daily with food. Give atazanavir simultaneously with and/or at least 10 hours after the H2- blocker. If a treatment-naive adult or adolescent (>= 40 kg) cannot tolerate ritonavir, do not exceed an H2- blocker dose equivalent to famotidine 20 mg twice daily, and the atazanavir dose should be increased to 400 mg once daily with food given at least 2 hours before or 10 hours after the H2- blocker. Data are insufficent to recommend atazanavir dosing in children or adolescents < 40 kg not receiving ritonavir boosting. In treatment-naive patients on a cobicistat-boosted regimen, cobicistat and atazanavir may be administered without dosage adjustment if given at the same time or a minimum of 10 hours after dosing of the H2-blocker. The H2-blocker dose should not exceed a dose that is comparable to 40 mg/day of famotidine in treatment-naive patients. In treatment-experienced patients >= 40 kg, do not exceed an H2- blocker dose equivalent to famotidine 20 mg twice daily, and give atazanavir 300 mg with ritonavir 100 mg once daily with food. Give atazanavir simultaneously with and/or at least 10 hours after the H2- blocker. In treatment-experienced patients >= 40 kg receiving H2-antagonists and tenofovir, atazanavir should be dosed 400 mg with ritonavir 100 mg once daily with food. In antiretroviral-experienced patients on a cobicistat-boosted regimen, the dosage of cobicistat with atazanavir needs to be increased if administered with H2-blockers; the recommended dose is cobicistat 150 mg/day with atazanavir 400 mg/day and 20 mg/day or less of famotidine or other comparably dosed H2-blocker. Significant reductions in atazanavir serum concentrations may lead to therapeutic failure and the development of HIV resistance. Closely monitor patients for antiretroviral therapeutic failure and resistance development during treatment with an H2- blocker.
Atazanavir; Cobicistat: (Major) Coadministration of H2-blockers with atazanavir reduces serum atazanavir concentrations; however, H2-blockers can be used under specific administration restrictions. Although data are insufficient to recommend atazanavir dosing in children < 40 kg receiving concomitant H2-blockers, the same recommendations regarding timing and maximum doses of concomitant H2-blockers should be followed. In treatment-naive patients >= 40 kg, do not exceed an H2- blocker dose equivalent to famotidine 40 mg twice daily, and give atazanavir 300 mg with

ritonavir 100 mg once daily with food. Give atazanavir simultaneously with and/or at least 10 hours after the H2- blocker. If a treatment-naive adult or adolescent (>= 40 kg) cannot tolerate ritonavir, do not exceed an H2- blocker dose equivalent to famotidine 20 mg twice daily, and the atazanavir dose should be increased to 400 mg once daily with food given at least 2 hours before or 10 hours after the H2- blocker. Data are insufficent to recommend atazanavir dosing in children or adolescents < 40 kg not receiving ritonavir boosting. In treatment-naive patients on a cobicistat-boosted regimen, cobicistat and atazanavir may be administered without dosage adjustment if given at the same time or a minimum of 10 hours after dosing of the H2-blocker. The H2-blocker dose should not exceed a dose that is comparable to 40 mg/day of famotidine in treatment-naive patients. In treatment-experienced patients >= 40 kg, do not exceed an H2- blocker dose equivalent to famotidine 20 mg twice daily, and give atazanavir 300 mg with ritonavir 100 mg once daily with food. Give atazanavir simultaneously with and/or at least 10 hours after the H2- blocker. In treatment-experienced patients >= 40 kg receiving H2-antagonists and tenofovir, atazanavir should be dosed 400 mg with ritonavir 100 mg once daily with food. In antiretroviral-experienced patients on a cobicistat-boosted regimen, the dosage of cobicistat with atazanavir needs to be increased if administered with H2-blockers; the recommended dose is cobicistat 150 mg/day with atazanavir 400 mg/day and 20 mg/day or less of famotidine or other comparably dosed H2-blocker. Significant reductions in atazanavir serum concentrations may lead to therapeutic failure and the development of HIV resistance. Closely monitor patients for antiretroviral therapeutic failure and resistance development during treatment with an H2- blocker.

Atorvastatin: (Moderate) Use HMG-CoA reductase inhibitors with caution with concomitant drugs that may decrease the levels or activity of endogenous steroids, such as cimetidine. Evaluate patients with signs and symptoms of endocrine dysfunction appropriately. HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production.

Avutometinib; Defactinib: (Major) Avoid concomitant use of defactinib and H2-blockers. Concurrent use interferes with defactinib absorption which may decrease defactinib exposure and efficacy.

Azelastine: (Minor) The mean Cmax and AUC of azelastine may be increased when coadministered with cimetidine. Theoretically, systemic exposure of nasally administered azelastine may be increased by coadministration with cimetidine, although an interaction has not been documented.

Azelastine; Fluticasone: (Minor) The mean Cmax and AUC of azelastine may be increased when coadministered with cimetidine. Theoretically, systemic exposure of nasally administered azelastine may be increased by coadministration with cimetidine, although an interaction has not been documented.

Belzutifan: (Moderate) Monitor for anemia and hypoxia if concomitant use of cimetidine

with belzutifan is necessary due to increased plasma exposure of belzutifan which may increase the incidence and severity of adverse reactions. Reduce the dose of belzutifan as recommended if anemia or hypoxia occur. Belzutifan is a CYP2C19 substrate and cimetidine is a CYP2C19 inhibitor.
Bendamustine: (Major) Consider the use of an alternative therapy if cimetidine treatment is needed in patients receiving bendamustine. Cimetidine may increase bendamustine exposure, which may increase the risk of adverse reactions (e.g., myelosuppression, infection, hepatotoxicity). Bendamustine is a CYP1A2 substrate and cimetidine is a CYP1A2 inhibitor.
Benzhydrocodone; Acetaminophen: (Moderate) Concurrent use of benzhydrocodone with cimetidine may increase the risk of increased opioid-related adverse reactions, such as fatal respiratory depression. Consider a dose reduction of benzhydrocodone until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. Discontinuation of cimetidine in a patient taking benzhydrocodone may decrease hydrocodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to opioid agonists. If cimetidine is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Benzhydrocodone is a prodrug for hydrocodone. Hydrocodone is a substrate for CYP3A4 and CYP2D6. Cimetidine is an inhibitor of CYP3A4 and CYP2D6.
Bisacodyl: (Minor) The concomitant use of bisacodyl tablets with H2-blockers can cause the enteric coating of the bisacody tablet to dissolve prematurely, leading to possible gastric irritation or dyspepsia. Avoid H2-blockers within 1 hour before or after the bisacodyl dosage.
Bismuth Subcitrate Potassium; metroNIDAZOLE; Tetracycline: (Moderate) Monitor for metronidazole-related adverse effects during concomitant cimetidine use. Cimetidine decreases hepatic microsomal liver enzyme activity and may prolong the half-life and decrease plasma clearance of metronidazole.
Bismuth Subsalicylate: (Minor) H2-blockers may increase the systemic absorption of bismuth from bismuth-containing compounds like bismuth subsalicylate.
Bismuth Subsalicylate; metroNIDAZOLE; Tetracycline: (Moderate) Monitor for metronidazole-related adverse effects during concomitant cimetidine use. Cimetidine decreases hepatic microsomal liver enzyme activity and may prolong the half-life and decrease plasma clearance of metronidazole. (Minor) H2-blockers may increase the systemic absorption of bismuth from bismuth-containing compounds like bismuth subsalicylate.
Bortezomib: (Minor) Agents that inhibit cytochrome P450 3A4 may increase the exposure to bortezomib and increase the risk for toxicity; however, bortezomib is also metabolized by other CYP isoenzymes. Therefore, the clinical significance of concurrent administration of bortezomib with cimetidine is not known.

Bosutinib: (Moderate) Bosutinib displays pH-dependent aqueous solubility; therefore, concomitant use of bosutinib and H2-blockers may result in decreased plasma exposure of bosutinib. Separate the administration of bosutinib and H2-blockers by more than 2 hours.
Budesonide: (Moderate) Monitor for loss of oral, enteric-coated budesonide efficacy and budesonide-related adverse events during concomitant cimetidine use. Since the dissolution of oral, enteric-coated budesonide is pH dependent, the release properties and uptake of the drug may be altered when used after H2-blockers. In an open, non-randomized, cross-over study, coadministration of cimetidine resulted in a 52% and 31% increase in the budesonide peak plasma concentration and AUC, respectively, after administration of cimetidine 1 g/day (200 mg with meals and 400 mg at night) for 2 separate 3-day periods where oral, delayed-release budesonide 4 mg was administered either alone or on the last day of a cimetidine treatment period.
Budesonide; Formoterol: (Moderate) Monitor for loss of oral, enteric-coated budesonide efficacy and budesonide-related adverse events during concomitant cimetidine use. Since the dissolution of oral, enteric-coated budesonide is pH dependent, the release properties and uptake of the drug may be altered when used after H2-blockers. In an open, non-randomized, cross-over study, coadministration of cimetidine resulted in a 52% and 31% increase in the budesonide peak plasma concentration and AUC, respectively, after administration of cimetidine 1 g/day (200 mg with meals and 400 mg at night) for 2 separate 3-day periods where oral, delayed-release budesonide 4 mg was administered either alone or on the last day of a cimetidine treatment period.
Budesonide; Glycopyrrolate; Formoterol: (Moderate) Monitor for loss of oral, enteric-coated budesonide efficacy and budesonide-related adverse events during concomitant cimetidine use. Since the dissolution of oral, enteric-coated budesonide is pH dependent, the release properties and uptake of the drug may be altered when used after H2-blockers. In an open, non-randomized, cross-over study, coadministration of cimetidine resulted in a 52% and 31% increase in the budesonide peak plasma concentration and AUC, respectively, after administration of cimetidine 1 g/day (200 mg with meals and 400 mg at night) for 2 separate 3-day periods where oral, delayed-release budesonide 4 mg was administered either alone or on the last day of a cimetidine treatment period.
Buprenorphine: (Minor) Since the metabolism of buprenorphine is mediated by the CYP3A4 isozyme, co-administration of drugs that inhibit CYP3A4, such as cimetidine, may cause decreased clearance of buprenorphine. Thus, there is a potential for excessive buprenorphine-related side effects.
Buprenorphine; Naloxone: (Minor) Since the metabolism of buprenorphine is mediated by the CYP3A4 isozyme, co-administration of drugs that inhibit CYP3A4, such as cimetidine, may cause decreased clearance of buprenorphine. Thus, there is a potential for excessive buprenorphine-related side effects.

Butalbital; Acetaminophen; Caffeine: (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.
Butalbital; Acetaminophen; Caffeine; Codeine: (Minor) Cimetidine may inhibit the conversion of codeine to morphine, codeine's active metabolite, via the CYP2D6 hepatic isoenzyme and therefore may decrease the ability for codeine to produce analgesic effect. (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.
Butalbital; Aspirin; Caffeine; Codeine: (Minor) Cimetidine may inhibit the conversion of codeine to morphine, codeine's active metabolite, via the CYP2D6 hepatic isoenzyme and therefore may decrease the ability for codeine to produce analgesic effect. (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.
Cabotegravir; Rilpivirine: (Moderate) Coadministration with cimetidine may significantly decrease rilpivirine plasma concentrations, potentially resulting in treatment failure. To decrease the risk of virologic failure, avoid use of H2 receptor antagonist for at least 12 hours before and at least 4 hours after administering rilpivirine.
Caffeine: (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.
Caffeine; Sodium Benzoate: (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.
Canagliflozin; metFORMIN: (Moderate) Concomitant administration of metformin and cimetidine may increase metformin exposure and increase the risk for lactic acidosis. If these drugs are given together, monitor for signs of metformin toxicity; metformin dose adjustments may be needed. After administration of single doses of cimetidine 400 mg and metformin 850 mg, mean metformin exposure increased by 40%. Metformin is an OCT2 substrate; cimetidine is an OCT2 inhibitor that may decrease metformin elimination by blocking renal tubular secretion.
carBAMazepine: (Moderate) Monitor carbamazepine concentrations closely during coadministration of cimetidine; carbamazepine dose adjustments may be needed. Concomitant use may increase carbamazepine concentrations. Carbamazepine is a CYP3A4 substrate and cimetidine is a CYP3A4 inhibitor.
Carisoprodol: (Minor) Carisoprodol is extensively metabolized and is a significant substrate of CYP2C19 isoenzymes. Theoretically, CY2C19 inhibitors, such as cimetidine, could increase carisoprodol plasma levels, with potential for enhanced CNS depressant effects.

Carmustine, BCNU: (Moderate) Use cimetidine and carmustine together with caution; increased myelosuppression (e.g., leukopenia and neutropenia) may occur. Consider using an alternative agent in place of cimetidine.
Carvedilol: (Moderate) Monitor for an increased incidence of carvedilol-related adverse effects if cimetidine and carvedilol are used concomitantly. Inhibitors of the hepatic CYP450 isozyme CYP2D6 may inhibit the hepatic oxidative metabolism of carvedilol. Cimetidine inhibits several hepatic cytochrome isozymes, including CYP2D6 and has been shown to increase carvedilol steady-state area under the plasma-concentration time curve (AUC) by 30%. Maximum serum concentrations of carvedilol are not increased. The clinical significance of this pharmacokinetic interaction is unclear.
Cefpodoxime: (Moderate) H2-blockers should be avoided during treatment with cefpodoxime. Coadministration could result in antibiotic failure. H2-blockers increase gastric pH. Cefpodoxime proxetil requires low gastric pH for dissolution. While the rate of absorption is not affected, coadministration reduces cefpodoxime AUC, peak plasma concentration (by 42%), and extent of absorption (by 32%).
Cefuroxime: (Major) Avoid the concomitant use of H2-blockers and cefuroxime. Drugs that reduce gastric acidity, such as H2-blockers, can interfere with the oral absorption of cefuroxime axetil and may result in reduced antibiotic efficacy.
Celecoxib: (Minor) Since celecoxib is metabolized by cytochrome P450 2C9, concurrent administration with cimetidine, which can inhibit this enzyme, may result in increased levels of celecoxib. The clinical significance of this interaction has not been established.
Celecoxib; Tramadol: (Moderate) Concurrent use of tramadol with cimetidine may produce unpredictable effects, including prolonged opioid-related adverse reactions, such as fatal respiratory depression, a withdrawal syndrome in those with physical dependence to opioid agonists, seizures, or serotonin syndrome. Consider dose adjustments of tramadol until stable drug effects are achieved. Monitor patients closely for respiratory depression and sedation at frequent intervals. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs. Tramadol is primarily metabolized by CYP2D6 to the active metabolite M1, and by CYP3A; cimetidine is a dual weak CYP2D6 and weak CYP3A inhibitor. CYP3A inhibitors may increase tramadol-related adverse effects while CYP2D6 inhibitors may reduce efficacy. (Minor) Since celecoxib is metabolized by cytochrome P450 2C9, concurrent administration with cimetidine, which can inhibit this enzyme, may result in increased levels of celecoxib. The clinical significance of this interaction has not been established.
Cetrorelix: (Minor) Drugs that cause hyperprolactinemia, such as cimetidine, should not be administered concomitantly with gonadotropin releasing hormone analogs since hyperprolactinemia down-regulates the number of pituitary GnRH receptors.
chlordiazePOXIDE: (Moderate) Cimetidine can inhibit the hepatic clearance of some benzodiazepines that undergo oxidative metabolism, including chlordiazepoxide.
chlordiazePOXIDE; Amitriptyline: (Moderate) Cimetidine can inhibit the hepatic clearance

of some benzodiazepines that undergo oxidative metabolism, including chlordiazepoxide. (Moderate) Monitor for an increase in amitriptyline-related adverse reactions if coadministration with cimetidine is necessary; a dose reduction of amitriptyline may be necessary. Concurrent use may increase the plasma concentrations of amitriptyline. Amitriptyline is a CYP2D6 substrate and cimetidine is a CYP2D6 inhibitor.
chlordiazePOXIDE; Clidinium: (Moderate) Cimetidine can inhibit the hepatic clearance of some benzodiazepines that undergo oxidative metabolism, including chlordiazepoxide.
Chloroquine: (Major) Avoid concomitant use of chloroquine and cimetidine as cimetidine may inhibit the metabolism of chloroquine, increasing its plasma concentration.
Chlorpheniramine; Codeine: (Minor) Cimetidine may inhibit the conversion of codeine to morphine, codeine's active metabolite, via the CYP2D6 hepatic isoenzyme and therefore may decrease the ability for codeine to produce analgesic effect.
Chlorpheniramine; HYDROcodone: (Moderate) Consider a reduced dose of hydrocodone with frequent monitoring for respiratory depression and sedation if concurrent use of cimetidine is necessary. It is recommended to avoid this combination when hydrocodone is being used for cough. Hydrocodone is a CYP2D6 and CYP3A4 substrate, and coadministration with CYP2D6 and CYP3A4 inhibitors like cimetidine can increase hydrocodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of hydrocodone. These effects could be more pronounced with a combined CYP2D6 and CYP3A4 inhibitor. If cimetidine is discontinued, hydrocodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to hydrocodone.
chlorproMAZINE: (Minor) Cimetidine has been reported to alter the steady-state plasma concentrations of chlorpromazine. It is possible that cimetidine may also reduce the hepatic metabolism of chlorpromazine. Excessive sedation has been reported in a few case reports. There are limited data supporting the clinical significance of this interaction. Another H-2 blocker may be preferred. Monitor the patient for altered clinical response to therapy or excessive sedation if these drugs are co-administered.
Cilostazol: (Minor) Cilostazol is extensively metabolized by the CYP3A4 hepatic isoenzyme and appears to interact with medications that are potent inhibitors of this enzyme, including cimetidine. When significant CYP3A4 inhibitors are administered concomitantly, the cilostazol adult dosage should be reduced by 50%.
Cisapride: (Major) Consider alternatives to cimetidine in patients receiving cisapride. Coadministration of cimetidine and cisapride results in increased exposure to cisapride. Serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, torsade de pointes, and QT prolongation have been reported in patients taking cisapride with other drugs that inhibit CYP3A4. In a drug interaction study, cimetidine increased the AUC of cisapride by 45%. Cimetidine is a weak inhibitor of CYP3A4; cisapride is a

CYP3A4 substrate.
Citalopram: (Moderate) Limit the dose of citalopram to 20 mg/day if coadministered with cimetidine. Concurrent use may increase citalopram exposure increasing the risk of QT prolongation. In subjects who had received 21 days of citalopram 40 mg/day, combined administration of cimetidine 400 mg twice daily for 8 days resulted in an increase in citalopram AUC and Cmax of 43% and 39%, respectively. Citalopram is a sensitive CYP2C19 substrate; cimetidine is a moderate inhibitor of CYP2C19.
cloBAZam: (Moderate) A dosage reduction of clobazam may be necessary during co-administration of cimetidine. Metabolism of N-desmethylclobazam, the active metabolite of clobazam, occurs primarily through CYP2C19 and cimetidine is an inhibitor of CYP2C19. Extrapolation from pharmacogenomic data indicates that concurrent use of clobazam with moderate or potent inhibitors of CYP2C19 may result in up to a 5-fold increase in exposure to N-desmethylclobazam. Adverse effects, such as sedation, lethargy, ataxia, or insomnia may be potentiated.
Clofarabine: (Moderate) The concomitant use of clofarabine and cimetidine resulted in decreased clofarabine renal excretion in a preclinical study in rats. Cimetidine is a substrate for OAT3 and OCT2. Monitor for signs of clofarabine toxicity such as gastrointestinal toxicity (e.g., nausea, vomiting, diarrhea, mucosal inflammation), hematologic toxicity, and skin toxicity (e.g., hand and foot syndrome, rash, pruritus) in patients also receiving OAT3 or OCT2 substrates or inhibitors.
clomiPRAMINE: (Moderate) Cimetidine can inhibit the systemic clearance of tricyclic antidepressants that undergo oxidative metabolism, such as clomipramine, resulting in increased plasma levels of the antidepressant. Patients should be monitored for TCA-related side effects and toxicity if cimetidine is added; when possible, choose an alternative H2-blocker for treatment.
Clopidogrel: (Moderate) Monitor for reduced clopidogrel efficacy during concomitant use of cimetidine. Clopidogrel is primarily metabolized to its active metabolite by CYP2C19; cimetidine is a CYP2C19 inhibitor.
Clorazepate: (Moderate) Cimetidine can inhibit the hepatic clearance of some benzodiazepines that undergo oxidative metabolism, including clorazepate.
cloZAPine: (Moderate) Caution is advisable during concurrent use of cimetidine and clozapine. Cimetidine is an inhibitor of CYP3A4, CYP2D6, and CYP1A2, the isoenzymes responsible for the metabolism of clozapine. Treatment with clozapine has been associated with QT prolongation, torsade de pointes (TdP), cardiac arrest, and sudden death. Elevated plasma concentrations of clozapine occurring through inhibition of CYP1A2, 2D6, or 3A4 may potentially increase the risk of life-threatening arrhythmias, sedation, anticholinergic effects, seizures, orthostasis, or other adverse effects. According to the manufacturer, patients receiving clozapine in combination with an inhibitor of CYP3A4, CYP2D6, or CYP1A2 should be monitored for adverse reactions. Consideration should be given to reducing the clozapine dose if necessary. If the

inhibitor is discontinued after dose adjustments are made, monitor for lack of clozapine effectiveness and consider increasing the clozapine dose if necessary.
Cobimetinib: (Moderate) If concurrent use of cobimetinib and cimetidine is necessary, use caution and monitor for increased cobimetinib-related adverse effects. Cobimetinib is a CYP3A substrate in vitro, and cimetidine is a weak inhibitor of CYP3A. In healthy subjects (n = 15), coadministration of a single 10 mg dose of cobimetinib with itraconazole (200 mg once daily for 14 days), a strong CYP3A4 inhibitor, increased the mean cobimetinib AUC by 6.7-fold (90% CI, 5.6 to 8) and the mean Cmax by 3.2-fold (90% CI, 2.7 to 3.7). Simulations showed that predicted steady-state concentrations of cobimetinib at a reduced dose of 20 mg administered concurrently with short-term (less than 14 days) treatment of a moderate CYP3A inhibitor were similar to observed steady-state concentrations of cobimetinib 60 mg alone. The manufacturer of cobimetinib recommends avoiding coadministration with moderate to strong CYP3A inhibitors, and significantly reducing the dose of cobimetinib if coadministration with moderate CYP3A inhibitors cannot be avoided. Guidance is not available regarding concomitant use of cobimetinib with weak CYP3A inhibitors.
Codeine: (Minor) Cimetidine may inhibit the conversion of codeine to morphine, codeine's active metabolite, via the CYP2D6 hepatic isoenzyme and therefore may decrease the ability for codeine to produce analgesic effect.
Codeine; Dexbrompheniramine: (Minor) Cimetidine may inhibit the conversion of codeine to morphine, codeine's active metabolite, via the CYP2D6 hepatic isoenzyme and therefore may decrease the ability for codeine to produce analgesic effect.
Codeine; guaiFENesin: (Minor) Cimetidine may inhibit the conversion of codeine to morphine, codeine's active metabolite, via the CYP2D6 hepatic isoenzyme and therefore may decrease the ability for codeine to produce analgesic effect.
Codeine; guaiFENesin; Pseudoephedrine: (Minor) Cimetidine may inhibit the conversion of codeine to morphine, codeine's active metabolite, via the CYP2D6 hepatic isoenzyme and therefore may decrease the ability for codeine to produce analgesic effect.
Codeine; Phenylephrine; Promethazine: (Minor) Cimetidine may inhibit the conversion of codeine to morphine, codeine's active metabolite, via the CYP2D6 hepatic isoenzyme and therefore may decrease the ability for codeine to produce analgesic effect.
Codeine; Promethazine: (Minor) Cimetidine may inhibit the conversion of codeine to morphine, codeine's active metabolite, via the CYP2D6 hepatic isoenzyme and therefore may decrease the ability for codeine to produce analgesic effect.
cycloSPORINE: (Moderate) Additive nephrotoxicity can occur if cyclosporine is administered with other nephrotoxic drugs such as cimetidine.
Cysteamine: (Major) Monitor white blood cell (WBC) cystine concentration closely when administering delayed-release cysteamine (Procysbi) with H2-blockers. Drugs that increase the gastric pH may cause the premature release of cysteamine from delayed-release capsules, leading to an increase in WBC cystine concentration.

Dacomitinib: (Moderate) Administer dacomitinib at least 6 hours before or 10 hours after cimetidine. Taking these medications at the same time may reduce dacomitinib absorption and decrease its efficacy.
Dalfampridine: (Moderate) Concurrent treatment with OCT2 inhibitors, such as cimetidine, may cause increased exposure to dalfampridine. Elevated levels of dalfampridine increase the risk of seizures. The potential benefits of taking OCT2 inhibitors concurrently with dalfampridine should be considered against the risk of seizures in these patients. Consider alternatives to cimetidine.
Dapagliflozin; metFORMIN: (Moderate) Concomitant administration of metformin and cimetidine may increase metformin exposure and increase the risk for lactic acidosis. If these drugs are given together, monitor for signs of metformin toxicity; metformin dose adjustments may be needed. After administration of single doses of cimetidine 400 mg and metformin 850 mg, mean metformin exposure increased by 40%. Metformin is an OCT2 substrate; cimetidine is an OCT2 inhibitor that may decrease metformin elimination by blocking renal tubular secretion.
Darifenacin: (Moderate) The mean Cmax and AUC of darifenacin 30 mg once daily at steady state were 42 percent and 34 percent higher, respectively, in the presence of cimetidine. Monitor patients receiving these two drugs concomitantly for increased anticholinergic effects; dosage adjustments may be necessary.
Dasatinib: (Major) Avoid the concomitant use of H2-blockers with dasatinib film-coated oral tablets, such as Sprycel. Consider using an alternative dasatinib dosage form, such as Phyrago, or antacids. Separate the administration of all dasatinib oral tablet dosage forms and antacids by at least 2 hours. H2-blockers alter gastric pH and interfere with the absorption of some dasatinib dosage forms which may reduce dasatinib efficacy. The use of an H2-blocker with Sprycel reduced dasatinib overall exposure by 61%.
Degarelix: (Minor) In the absence of relevant data and as a precaution, drugs that cause hyperprolactinemia, such as cimetidine, should not be administered concomitantly with degarelix, as hyperprolactinemia downregulates the number of pituitary gonadotropin-releasing hormone receptors.
Desipramine: (Moderate) Cimetidine can inhibit the systemic clearance of tricyclic antidepressants that undergo oxidative metabolism, such as desipramine, resulting in increased plasma levels of the antidepressant.
Desogestrel: Ethinyl Estradiol; Ferrous Bisglycinate: (Minor) The bioavailability of oral iron salts is influenced by gastric pH, and the concomitant administration of H2-blockers can decrease iron absorption. The non-heme ferric form of iron needs an acidic intragastric pH to be reduced to ferrous and to be absorbed. Iron salts and polysaccharide-iron complex provide non-heme iron. H2-blockers have long-lasting effects on the secretion of gastric acid and thus, increase the pH of the stomach. The increase in intragastric pH can interfere with the absorption of iron salts.
Dextroamphetamine: (Moderate) Use amphetamine; dextroamphetamine and H2-

blockers concomitantly with caution. Gastrointestinal alkalinizing agents may increase exposure to amphetamine; dextroamphetamine and exacerbate its actions.
Dextromethorphan; quiNIDine: (Major) Quinidine concentrations should be monitored closely after cimetidine is added; choose an alternate acid-reducing therapy if possible. Quinidine is eliminated primarily by the CYP3A4 isoenzyme. Cimetidine can inhibit quinidine metabolism and produce quinidine toxicity.
diazePAM: (Moderate) Monitor for an increase in diazepam-related adverse reactions, including sedation and respiratory depression, if coadministration with cimetidine is necessary. Concurrent use may increase diazepam exposure. Diazepam is a CYP2C19 and CYP3A substrate and cimetidine is a CYP2C19 and CYP3A inhibitor.
diphenhydrAMINE; Naproxen: (Moderate) Avoid concomitant use of enteric-coated, delayed-release naproxen and H2-blockers due to the gastric pH elevating effects of H2-blockers. Enteric-coated, delayed-release naproxen tablets are designed to dissolve at a pH of 6 or more.
Dofetilide: (Contraindicated) Cimetidine is an inhibitor of renal cationic tubular secretion and is contraindicated with dofetilide due to the potential for increased plasma dofetilide concentrations and associated proarrhythmias. Cimetidine (400 mg PO twice daily) coadministered with dofetilide (500 mcg PO twice daily) for 7 days increased dofetilide plasma levels by 58%. Cimetidine, at over-the-counter doses of 100 mg PO twice daily, results in a 13% increase in dofetilide plasma concentrations following a single 500 mcg oral dose. Omeprazole, ranitidine, or antacids (aluminum and magnesium hydroxides) may be used as anti-ulcer therapy alternatives to cimetidine; these agents did not alter dofetilide pharmacokinetics.
Dolasetron: (Moderate) Coadministration of dolasetron and cimetidine, a nonselective inhibitor of cytochrome P450, increased the blood concentrations of dolasetron's active metabolite by 24%.
Dolutegravir; Rilpivirine: (Moderate) Coadministration with cimetidine may significantly decrease rilpivirine plasma concentrations, potentially resulting in treatment failure. To decrease the risk of virologic failure, avoid use of H2 receptor antagonist for at least 12 hours before and at least 4 hours after administering rilpivirine.
Donepezil; Memantine: (Moderate) Memantine is excreted in part by renal tubular secretion. Competition of memantine for excretion with other drugs that are also eliminated by tubular secretion, such as cimetidine, could result in elevated serum concentrations of one or both drugs.
Doxepin: (Moderate) Monitor for an increase in doxepin-related adverse reactions if concomitant use of cimetidine is necessary; a doxepin dose reduction may be necessary. Doxepin exposure is doubled with concomitant administration of cimetidine.
Doxercalciferol: (Moderate) CYP450 enzyme inhibitors, like cimetidine, may inhibit the 25-hydroxylation of doxercalciferol, thereby decreasing the formation of the active metabolite and thus, decreasing efficacy. Patients should be monitored for a decrease in

efficacy if CYP450 inhibitors are coadministered with doxercalciferol.
DOXOrubicin Liposomal: (Major) Cimetidine is a mild inhibitor of CYP2D6 and CYP3A4; doxorubicin is a major CYP2D6 and CYP3A4 substrate. Clinically significant interactions have been reported when doxorubicin was coadministered with inhibitors of CYP2D6 and/or CYP3A4, resulting in increased concentration and clinical effect of doxorubicin. Avoid coadministration of cimetidine and doxorubicin if possible. If not possible, closely monitor for increased side effects of doxorubicin including myelosuppression and cardiotoxicity.
DOXOrubicin: (Major) Cimetidine is a mild inhibitor of CYP2D6 and CYP3A4; doxorubicin is a major CYP2D6 and CYP3A4 substrate. Clinically significant interactions have been reported when doxorubicin was coadministered with inhibitors of CYP2D6 and/or CYP3A4, resulting in increased concentration and clinical effect of doxorubicin. Avoid coadministration of cimetidine and doxorubicin if possible. If not possible, closely monitor for increased side effects of doxorubicin including myelosuppression and cardiotoxicity.
droNABinol: (Moderate) Use caution if coadministration of dronabinol with cimetidine is necessary, and monitor for an increase in dronabinol-related adverse reactions (e.g., feeling high, dizziness, confusion, somnolence). Dronabinol is a CYP2C9 and 3A4 substrate; cimetidine is a weak inhibitor of CYP3A4. Concomitant use may result in elevated plasma concentrations of dronabinol.
Dronedarone: (Moderate) Dronedarone is metabolized by CYP3A. Cimetidine is an inhibitor CYP3A4. Concomitant use of dronedarone with cimetidine may also increase dronedarone concentrations. No data exist regarding the appropriate dose adjustment needed to allow safe administration of dronedarone with CYP3A4 inhibitors; therefore, use caution when coadministering dronedarone with CYP3A4 inhibitors such as cimetidine.
DULoxetine: (Moderate) Monitor for increased duloxetine-related adverse effects if coadministered with cimetidine. Concurrent use may result in increased duloxetine exposure. Duloxetine is a CYP1A2 and CYP2D6 substrate and cimetidine is a CYP1A2 and CYP2D6 inhibitor.
Dutasteride: (Moderate) Dutasteride is metabolized by CYP3A4 enzyme. The clearance of dutasteride may be reduced when co-administered with CYP3A4 inhibitors, such as cimetidine.
Dutasteride; Tamsulosin: (Moderate) Dutasteride is metabolized by CYP3A4 enzyme. The clearance of dutasteride may be reduced when co-administered with CYP3A4 inhibitors, such as cimetidine. (Moderate) Use caution if coadministration of cimetidine with tamsulosin is necessary, especially at a tamsulosin dose higher than 0.4 mg, as the systemic exposure of tamsulosin may be increased resulting in increased treatment-related adverse reactions including hypotension, dizziness, and vertigo. Treatment with cimetidine 400 mg every 6 hours for 6 days in healthy volunteers (n = 10) resulted in a

26% decrease in the clearance of tamsulosin, which resulted in a 44% increase in tamsulosin AUC. Tamsulosin is a CYP2D6 and CYP3A substrate and cimetidine is a weak CYP2D6 and CYP3A inhibitor.
Eliglustat: (Major) In poor CYP2D6 metabolizers (PMs), coadministration of cimetidine and eliglustat is not recommended. In extensive CYP2D6 metabolizers (EM) with mild hepatic impairment, coadministration of these agents requires dosage reduction of eliglustat to 84 mg PO once daily. Cimetidine is a weak CYP3A (and CYP2D6) inhibitor; eliglustat is a CYP3A and CYP2D6 substrate. Coadministration with CYP2D6 and CYP3A inihibitors, such as cimetidine, may increase eliglustat exposure and the risk of serious adverse events (e.g., QT prolongation and cardiac arrhythmias).
Eltrombopag: (Moderate) Eltrombopag is metabolized by CYP1A2. The significance of administering inhibitors of CYP1A2, such as cimetidine, on the systemic exposure of eltrombopag has not been established. Monitor patients for signs of eltrombopag toxicity if these drugs are coadministered.
Elvitegravir; Cobicistat; Emtricitabine; Tenofovir Alafenamide: (Moderate) Caution is warranted when elvitegravir is administered with cimetidine as there is a potential for elevated elvitegravir concentrations. Cimetidine is a CYP3A4 and CYP2D6 inhibitor, while elvitegravir is a substrate of CYP3A4.
Elvitegravir; Cobicistat; Emtricitabine; Tenofovir Disoproxil Fumarate: (Moderate) Caution is warranted when elvitegravir is administered with cimetidine as there is a potential for elevated elvitegravir concentrations. Cimetidine is a CYP3A4 and CYP2D6 inhibitor, while elvitegravir is a substrate of CYP3A4.
Empagliflozin; Linagliptin; metFORMIN: (Moderate) Concomitant administration of metformin and cimetidine may increase metformin exposure and increase the risk for lactic acidosis. If these drugs are given together, monitor for signs of metformin toxicity; metformin dose adjustments may be needed. After administration of single doses of cimetidine 400 mg and metformin 850 mg, mean metformin exposure increased by 40%. Metformin is an OCT2 substrate; cimetidine is an OCT2 inhibitor that may decrease metformin elimination by blocking renal tubular secretion.
Empagliflozin; metFORMIN: (Moderate) Concomitant administration of metformin and cimetidine may increase metformin exposure and increase the risk for lactic acidosis. If these drugs are given together, monitor for signs of metformin toxicity; metformin dose adjustments may be needed. After administration of single doses of cimetidine 400 mg and metformin 850 mg, mean metformin exposure increased by 40%. Metformin is an OCT2 substrate; cimetidine is an OCT2 inhibitor that may decrease metformin elimination by blocking renal tubular secretion.
Emtricitabine; Rilpivirine; Tenofovir alafenamide: (Moderate) Coadministration with cimetidine may significantly decrease rilpivirine plasma concentrations, potentially resulting in treatment failure. To decrease the risk of virologic failure, avoid use of H2 receptor antagonist for at least 12 hours before and at least 4 hours after administering

rilpivirine.
Emtricitabine; Rilpivirine; Tenofovir Disoproxil Fumarate: (Moderate) Coadministration with cimetidine may significantly decrease rilpivirine plasma concentrations, potentially resulting in treatment failure. To decrease the risk of virologic failure, avoid use of H2 receptor antagonist for at least 12 hours before and at least 4 hours after administering rilpivirine.
Entecavir: (Moderate) Both entecavir and cimetidine are secreted by active tubular secretion. In theory, coadministration of entecavir with cimetidine may increase the serum concentrations of either drug due to competition for the drug elimination pathway. The manufacturer of entecavir recommends monitoring for adverse effects when these drugs are coadministered.
epiRUBicin: (Major) Discontinue cimetidine during treatment with epirubicin due to the risk of increased epirubicin exposure which may result in an increase of epirubicin-related adverse reactions. Coadministration of cimetidine increased the mean AUC of epirubicin by 50% and decreased its plasma clearance by 30%.
Ergotamine; Caffeine: (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.
Erlotinib: (Major) Avoid coadministration of erlotinib with cimetidine if possible due to altered plasma concentrations of erlotinib. If concomitant use is unavoidable, separate dosing is required, as the solubility of erlotinib is pH dependent, decreasing as the pH increases. Erlotinib must be taken 10 hours after the last dose of cimetidine and at least 2 hours before the next dose. Additionally, monitor for erlotinib-related adverse reactions; a dose reduction may be necessary for severe reactions. Coadministration of erlotinib with medications that increase the pH of the upper gastrointestinal tract may decrease the absorption of erlotinib. Erlotinib exposure was decreased by 33% and the Cmax by 54% when erlotinib was administered 2 hours after a single dose of an H2-antagonist. When administered at least 10 hours after an evening dose of an H2-antagonist and 2 hours before the morning dose, erlotinib exposure was decreased by 15% and Cmax by 17%. Increasing the dose of erlotinib is not likely to compensate for the loss of exposure. Erlotinib is also primarily metabolized by CYP3A4 and to a lesser extent by CYP1A2. Cimetidine is a weak CYP3A4 and CYP1A2 inhibitor.
Ertugliflozin; metFORMIN: (Moderate) Concomitant administration of metformin and cimetidine may increase metformin exposure and increase the risk for lactic acidosis. If these drugs are given together, monitor for signs of metformin toxicity; metformin dose adjustments may be needed. After administration of single doses of cimetidine 400 mg and metformin 850 mg, mean metformin exposure increased by 40%. Metformin is an OCT2 substrate; cimetidine is an OCT2 inhibitor that may decrease metformin elimination by blocking renal tubular secretion.
Estazolam: (Moderate) Cimetidine is a CYP3A4 inhibitor and may reduce the metabolism

of estazolam and increase the potential for benzodiazepine toxicity.
Estradiol; Progesterone: (Minor) The metabolism of progesterone may be inhibited by cimetidine, an inhibitor of cytochrome P450 3A4 hepatic enzymes.
Etonogestrel: (Minor) Coadministration of etonogestrel and moderate CYP3A4 inhibitors such as cimetidine may increase the serum concentration of etonogestrel.
Etonogestrel; Ethinyl Estradiol: (Minor) Coadministration of etonogestrel and moderate CYP3A4 inhibitors such as cimetidine may increase the serum concentration of etonogestrel.
Ezetimibe; Simvastatin: (Moderate) Use HMG-CoA reductase inhibitors with caution with concomitant drugs that may decrease the levels or activity of endogenous steroids, such as cimetidine. Evaluate patients with signs and symptoms of endocrine dysfunction appropriately. HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production.
Felodipine: (Moderate) Cimetidine is a potent inhibitor of many of the isoenzymes of the hepatic CYP450 oxidative enzyme system and the metabolism of calcium-channel blockers like felodipine is inhibited by cimetidine.
fentaNYL: (Moderate) Consider a reduced dose of fentanyl with frequent monitoring for respiratory depression and sedation if concurrent use of cimetidine is necessary. If cimetidine is discontinued, consider increasing the fentanyl dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Fentanyl is a CYP3A4 substrate, and coadministration with CYP3A4 inhibitors like cimetidine can increase fentanyl exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of fentanyl. If cimetidine is discontinued, fentanyl plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to fentanyl.
Ferric Maltol: (Minor) The bioavailability of oral iron salts is influenced by gastric pH, and the concomitant administration of H2-blockers can decrease iron absorption. The non-heme ferric form of iron needs an acidic intragastric pH to be reduced to ferrous and to be absorbed. Iron salts and polysaccharide-iron complex provide non-heme iron. H2-blockers have long-lasting effects on the secretion of gastric acid and thus, increase the pH of the stomach. The increase in intragastric pH can interfere with the absorption of iron salts.
Fezolinetant: (Contraindicated) Concomitant use of fezolinetant and cimetidine is contraindicated due to the risk of increased fezolinetant exposure which may increase the risk of fezolinetant-related adverse effects. Fezolinetant is a CYP1A2 substrate; cimetidine is a weak CYP1A2 inhibitor. Concomitant use increased fezolinetant overall exposure by 100%.
Finerenone: (Moderate) Monitor serum potassium during initiation or dose adjustment of either finerenone or cimetidine; a finerenone dosage reduction may be necessary.

Concomitant use may increase finerenone exposure and the risk of hyperkalemia. Finerenone is a CYP3A substrate and cimetidine is a weak CYP3A inhibitor. Coadministration with another weak CYP3A inhibitor increased overall exposure to finerenone by 21%.
Flecainide: (Moderate) Monitor for an increase in flecainide-related adverse reactions, including QT prolongation, if coadministration with cimetidine is necessary. Flecainide is a CYP2D6 substrate and cimetidine is a weak CYP2D6 inhibitor. Plasma concentrations of flecainide may increase, especially in extensive CYP2D6 metabolizers.
Flibanserin: (Moderate) The concomitant use of flibanserin and multiple weak CYP3A4 inhibitors, including cimetidine, may increase flibanserin concentrations, which may increase the risk of flibanserin-induced adverse reactions. Therefore, patients should be monitored for hypotension, syncope, somnolence, or other adverse reactions, and the potential outcomes of combination therapy with multiple weak CYP3A4 inhibitors and flibanserin should be discussed with the patient.
Floxuridine: (Minor) Data suggest chronic administration of cimetidine with fluorouracil, 5-FU, can increase 5-FU serum concentrations, but it is not clear if this interaction results in increased 5-FU efficacy or toxicity. Patients receiving either 5-FU or floxuridine should be monitored for a possible increased response to 5-FU if cimetidine is used concurrently.
Fluconazole: (Minor) Fluconazole 100 mg was administered as a single oral dose alone and 2 hours after a single dose of cimetidine 400 mg to healthy volunteers (n = 6); after administration of cimetidine, there was a mean decrease in fluconazole AUC of 13% and Cmax decreased by 19%. However, the administration of cimetidine 600 to 900 mg IV over 4 hours (from 1 hour before to 3 hours after a single oral dose of fluconazole 200 mg) did not affect the bioavailability or pharmacokinetics of fluconazole in healthy volunteers (n = 24).
Fluorouracil, 5-FU: (Minor) Chronic administration of cimetidine with fluorouracil, 5-FU, can increase 5-FU serum concentrations, but it is not clear if this interaction results in increased 5-FU efficacy or toxicity. Patients receiving either 5-FU should be monitored for a possible increased response to 5-FU if cimetidine is used concurrently.
FLUoxetine: (Moderate) Monitor for increased fluoxetine-related adverse effects if coadministered with cimetidine. Concomitant use may increase fluoxetine exposure. Fluoxetine is a CYP2D6 substrate and cimetidine is a weak CYP2D6 inhibitor.
Flurazepam: (Moderate) Cimetidine can inhibit the hepatic clearance of some benzodiazepines that undergo oxidative metabolism, including flurazepam.
Fluvastatin: (Moderate) Use HMG-CoA reductase inhibitors with caution with concomitant drugs that may decrease the levels or activity of endogenous steroids, such as cimetidine. Evaluate patients with signs and symptoms of endocrine dysfunction appropriately. HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production.

fluvoxaMINE: (Moderate) Cimetidine may inhibit the metabolism of fluvoxamine.
Fomepizole: (Minor) In healthy volunteers, moderate oral doses of fomepizole significantly reduced the rate of elimination of ethanol by approximately 40%. Similarly, ethanol decreased the rate of elimination of fomepizole by approximately 50%. Both interactions occur via alcohol dehydrogenase inhibition. Although not studied, reciprocal interactions may occur with concomitant use of fomepizole and drugs that increase or inhibit the cytochrome P450 enzyme system, like cimetidine.
Fosamprenavir: (Moderate) Monitor for decreased fosamprenavir efficacy if coadministered with H2-blockers. Concurrent use may decrease the plasma concentrations of fosamprenavir leading to a reduction of antiretroviral efficacy and the potential development of viral resistance.
Fosphenytoin: (Moderate) Monitor phenytoin concentrations during concomitant therapy with fosphenytoin and cimetidine due to risk for phenytoin toxicity. Concomitant use may increase phenytoin concentrations. Phenytoin is a CYP2C19 substrate and cimetidine is a CYP2C19 inhibitor.
Ganirelix: (Minor) In the absence of relevant data and as a precaution, drugs that cause hyperprolactinemia, such as cimetidine, should not be administered concomitantly with gonadotropin releasing hormone analogs since hyperprolactinemia down-regulates the number of pituitary GnRH receptors.
Gefitinib: (Major) Avoid coadministration of cimetidine with gefitinib if possible due to decreased exposure to gefitinib, which may lead to reduced efficacy. If concomitant use is unavoidable, take gefitinib 6 hours after the last dose or 6 hours before the next dose of cimetidine. Gefitinib exposure is affected by gastric pH. Coadministration with high doses of another H2-blocker to maintain gastric pH above 5 decreased gefitinib exposure by 47%.
Glimepiride: (Moderate) Monitor blood glucose during concomitant cimetidine and sulfonylurea use due to increased risk for hypoglycemia. Cimetidine has been shown to affect the pharmacokinetics of some sulfonylureas. The mechanism of this interaction may involve either increasing the absorption or decreasing the clearance of the sulfonylurea. Asymptomatic hypoglycemia has been observed during coadministration.
glipiZIDE: (Moderate) Monitor blood glucose during concomitant cimetidine and sulfonylurea use due to increased risk for hypoglycemia. Cimetidine has been shown to affect the pharmacokinetics of some sulfonylureas. The mechanism of this interaction may involve either increasing the absorption or decreasing the clearance of the sulfonylurea. Asymptomatic hypoglycemia has been observed during coadministration.
glipiZIDE; metFORMIN: (Moderate) Concomitant administration of metformin and cimetidine may increase metformin exposure and increase the risk for lactic acidosis. If these drugs are given together, monitor for signs of metformin toxicity; metformin dose adjustments may be needed. After administration of single doses of cimetidine 400 mg and metformin 850 mg, mean metformin exposure increased by 40%. Metformin is an

OCT2 substrate; cimetidine is an OCT2 inhibitor that may decrease metformin elimination by blocking renal tubular secretion. (Moderate) Monitor blood glucose during concomitant cimetidine and sulfonylurea use due to increased risk for hypoglycemia. Cimetidine has been shown to affect the pharmacokinetics of some sulfonylureas. The mechanism of this interaction may involve either increasing the absorption or decreasing the clearance of the sulfonylurea. Asymptomatic hypoglycemia has been observed during coadministration.
glyBURIDE: (Moderate) Monitor blood glucose during concomitant cimetidine and sulfonylurea use due to increased risk for hypoglycemia. Cimetidine has been shown to affect the pharmacokinetics of some sulfonylureas. The mechanism of this interaction may involve either increasing the absorption or decreasing the clearance of the sulfonylurea. Asymptomatic hypoglycemia has been observed during coadministration.
glyBURIDE; metFORMIN: (Moderate) Concomitant administration of metformin and cimetidine may increase metformin exposure and increase the risk for lactic acidosis. If these drugs are given together, monitor for signs of metformin toxicity; metformin dose adjustments may be needed. After administration of single doses of cimetidine 400 mg and metformin 850 mg, mean metformin exposure increased by 40%. Metformin is an OCT2 substrate; cimetidine is an OCT2 inhibitor that may decrease metformin elimination by blocking renal tubular secretion. (Moderate) Monitor blood glucose during concomitant cimetidine and sulfonylurea use due to increased risk for hypoglycemia. Cimetidine has been shown to affect the pharmacokinetics of some sulfonylureas. The mechanism of this interaction may involve either increasing the absorption or decreasing the clearance of the sulfonylurea. Asymptomatic hypoglycemia has been observed during coadministration.
HMG-CoA reductase inhibitors: (Moderate) Use HMG-CoA reductase inhibitors with caution with concomitant drugs that may decrease the levels or activity of endogenous steroids, such as cimetidine. Evaluate patients with signs and symptoms of endocrine dysfunction appropriately. HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production.
Homatropine; HYDROcodone: (Moderate) Consider a reduced dose of hydrocodone with frequent monitoring for respiratory depression and sedation if concurrent use of cimetidine is necessary. It is recommended to avoid this combination when hydrocodone is being used for cough. Hydrocodone is a CYP2D6 and CYP3A4 substrate, and coadministration with CYP2D6 and CYP3A4 inhibitors like cimetidine can increase hydrocodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of hydrocodone. These effects could be more pronounced with a combined CYP2D6 and CYP3A4 inhibitor. If cimetidine is discontinued, hydrocodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to hydrocodone.

HYDROcodone: (Moderate) Consider a reduced dose of hydrocodone with frequent monitoring for respiratory depression and sedation if concurrent use of cimetidine is necessary. It is recommended to avoid this combination when hydrocodone is being used for cough. Hydrocodone is a CYP2D6 and CYP3A4 substrate, and coadministration with CYP2D6 and CYP3A4 inhibitors like cimetidine can increase hydrocodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of hydrocodone. These effects could be more pronounced with a combined CYP2D6 and CYP3A4 inhibitor. If cimetidine is discontinued, hydrocodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to hydrocodone.
HYDROcodone; Ibuprofen: (Moderate) Consider a reduced dose of hydrocodone with frequent monitoring for respiratory depression and sedation if concurrent use of cimetidine is necessary. It is recommended to avoid this combination when hydrocodone is being used for cough. Hydrocodone is a CYP2D6 and CYP3A4 substrate, and coadministration with CYP2D6 and CYP3A4 inhibitors like cimetidine can increase hydrocodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of hydrocodone. These effects could be more pronounced with a combined CYP2D6 and CYP3A4 inhibitor. If cimetidine is discontinued, hydrocodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to hydrocodone.
Hydroxychloroquine: (Major) Avoid concomitant use of hydroxychloroquine and cimetidine as cimetidine may inhibit the metabolism of hydroxychloroquine, increasing its plasma concentration. This interaction has been observed on treatment with the structurally similar chloroquine and cannot be ruled out for hydroxychloroquine.
Imatinib: (Minor) Imatinib, STI-571 is metabolized by cytochrome P450 3A4, which can be inhibited by cimetidine. During concurrent use, clinicians should be aware of the potential increase risk of imatinib toxicity.
Imipramine: (Moderate) Cimetidine can inhibit the hepatic clearance of some tricyclic antidepressants that undergo oxidative metabolism, such as imipramine. Choose an alternate H2-blocker when possible; alternatively, observe patients closely for TCA-induced side effects or toxicity if the concurrent use of cimetidine is unavoidable.
Infigratinib: (Moderate) Separate the administration of infigratinib and H2-receptor antagonists if concomitant use is necessary. Coadministration may decrease infigratinib exposure resulting in decreased efficacy. Administer infigratinib two hours before or ten hours after an H2-receptor antagonist.
Iron Salts: (Minor) The bioavailability of oral iron salts is influenced by gastric pH, and the concomitant administration of H2-blockers can decrease iron absorption. The non-heme ferric form of iron needs an acidic intragastric pH to be reduced to ferrous and to be

absorbed. Iron salts and polysaccharide-iron complex provide non-heme iron. H2-blockers have long-lasting effects on the secretion of gastric acid and thus, increase the pH of the stomach. The increase in intragastric pH can interfere with the absorption of iron salts.
Iron Salts: (Minor) The bioavailability of oral iron salts is influenced by gastric pH, and the concomitant administration of H2-blockers can decrease iron absorption. The non-heme ferric form of iron needs an acidic intragastric pH to be reduced to ferrous and to be absorbed. Iron salts and polysaccharide-iron complex provide non-heme iron. H2-blockers have long-lasting effects on the secretion of gastric acid and thus, increase the pH of the stomach. The increase in intragastric pH can interfere with the absorption of iron salts.
Iron: (Minor) The bioavailability of oral iron salts is influenced by gastric pH, and the concomitant administration of H2-blockers can decrease iron absorption. The non-heme ferric form of iron needs an acidic intragastric pH to be reduced to ferrous and to be absorbed. Iron salts and polysaccharide-iron complex provide non-heme iron. H2-blockers have long-lasting effects on the secretion of gastric acid and thus, increase the pH of the stomach. The increase in intragastric pH can interfere with the absorption of iron salts.
Isavuconazonium: (Moderate) Concomitant use of isavuconazonium with cimetidine may result in increased serum concentrations of isavuconazonium. Isavuconazole, the active moiety of isavuconazonium, is a sensitive substrate of the hepatic isoenzyme CYP3A4; cimetidine is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are used together.
Isradipine: (Moderate) Cimetidine is a potent inhibitor of many of the isoenzymes of the hepatic CYP450 oxidative enzyme system and may decrease the metabolism of isradipine.
Itraconazole: (Moderate) When administering H2-blockers with the 100 mg itraconazole capsule and 200 mg itraconazole tablet formulations, systemic exposure to itraconazole is decreased. Conversely, exposure to itraconazole is increased when H2-blockers are administered with the 65 mg itraconazole capsule. Administer H2-blockers at least 2 hours before or 2 hours after the 100 mg capsule or 200 mg tablet. Monitor for increased itraconazole-related adverse effects if H2-blockers are administered with itraconazole 65 mg capsules.
Ixabepilone: (Moderate) Monitor for ixabepilone toxicity and reduce the ixabepilone dose as needed if concurrent use of cimetidine is necessary. Concomitant use may increase ixabepilone exposure and the risk of adverse reactions. Ixabepilone is a CYP3A substrate and cimetidine is a weak CYP3A inhibitor.
Ketoconazole: (Major) Avoid use of H2-blockers with ketoconazole. Medications that increase gastric pH may impair ketoconazole absorption.
Labetalol: (Moderate) Monitor blood pressure and heart rate during coadministration of

labetalol with cimetidine. Coadministration increases the bioavailability of labetalol, either by enhanced absorption or altered hepatic metabolism.
lamoTRIgine: (Minor) Coadministration of cimetidine and lamotrigine may decrease cimetidine clearance, resulting in increased plasma concentrations and the potential for cimetidine-related adverse events. Lamotrigine is an inhibitor of renal tubular secretion via organic cationic transporter 2 (OCT2) proteins, and cimetidine is excreted via this route.
Ledipasvir; Sofosbuvir: (Major) Solubility of ledipasvir decreases as gastric pH increases; thus, coadministration of ledipasvir; sofosbuvir with H2-blockers may result in lower ledipasvir plasma concentrations. Ledipasvir; sofosbuvir can be administered with H2-blockers if given simultaneously or separated by 12 hours. The H2-blocker dose should not exceed a dose that is comparable to famotidine 40 mg twice daily.
Leflunomide: (Moderate) Closely monitor for cimetidine-induced side effects when these drugs are used together. In some patients, a dosage reduction of cimetidine may be required. Following oral administration, leflunomide is metabolized to an active metabolite, teriflunomide, which is responsible for essentially all of leflunomide's in vivo activity. Teriflunomide is an inhibitor of the renal uptake organic anion transporter OAT3. Use of teriflunomide with cimetidine, a substrate of OAT3, may increase cimetidine plasma concentrations.
Lemborexant: (Major) Limit the dose of lemborexant to a maximum of 5 mg PO once daily if coadministered with cimetidine as concurrent use may increase lemborexant exposure and the risk of adverse effects. Lemborexant is a CYP3A4 substrate; cimetidine is a weak CYP3A4 inhibitor. Consider if an alternative to cimetidine would be appropriate for the patient. Coadministration of lemborexant with a weak CYP3A4 inhibitor is predicted to increase lemborexant exposure by less than 2-fold.
Levoketoconazole: (Major) Avoid use of H2-blockers with ketoconazole. Medications that increase gastric pH may impair ketoconazole absorption.
Levonorgestrel; Ethinyl Estradiol; Ferrous Bisglycinate: (Minor) The bioavailability of oral iron salts is influenced by gastric pH, and the concomitant administration of H2-blockers can decrease iron absorption. The non-heme ferric form of iron needs an acidic intragastric pH to be reduced to ferrous and to be absorbed. Iron salts and polysaccharide-iron complex provide non-heme iron. H2-blockers have long-lasting effects on the secretion of gastric acid and thus, increase the pH of the stomach. The increase in intragastric pH can interfere with the absorption of iron salts.
Levonorgestrel; Ethinyl Estradiol; Ferrous Fumarate: (Minor) The bioavailability of oral iron salts is influenced by gastric pH, and the concomitant administration of H2-blockers can decrease iron absorption. The non-heme ferric form of iron needs an acidic intragastric pH to be reduced to ferrous and to be absorbed. Iron salts and polysaccharide-iron complex provide non-heme iron. H2-blockers have long-lasting effects on the secretion of gastric acid and thus, increase the pH of the stomach. The

increase in intragastric pH can interfere with the absorption of iron salts.
Lidocaine: (Moderate) Concomitant use of systemic lidocaine and cimetidine may increase lidocaine plasma concentrations. Monitor for lidocaine toxicity if used together. Lidocaine is a CYP1A2 and CYP3A4 substrate; cimetidine inhibits both of these isoenzymes. Concomitant use of lidocaine with a weak CYP1A2 and CYP3A4 inhibitor has reportedly increased lidocaine plasma concentrations by 24% to 75%.
Lidocaine; EPINEPHrine: (Moderate) Concomitant use of systemic lidocaine and cimetidine may increase lidocaine plasma concentrations. Monitor for lidocaine toxicity if used together. Lidocaine is a CYP1A2 and CYP3A4 substrate; cimetidine inhibits both of these isoenzymes. Concomitant use of lidocaine with a weak CYP1A2 and CYP3A4 inhibitor has reportedly increased lidocaine plasma concentrations by 24% to 75%.
Lidocaine; Prilocaine: (Moderate) Concomitant use of systemic lidocaine and cimetidine may increase lidocaine plasma concentrations. Monitor for lidocaine toxicity if used together. Lidocaine is a CYP1A2 and CYP3A4 substrate; cimetidine inhibits both of these isoenzymes. Concomitant use of lidocaine with a weak CYP1A2 and CYP3A4 inhibitor has reportedly increased lidocaine plasma concentrations by 24% to 75%.
Linagliptin; metFORMIN: (Moderate) Concomitant administration of metformin and cimetidine may increase metformin exposure and increase the risk for lactic acidosis. If these drugs are given together, monitor for signs of metformin toxicity; metformin dose adjustments may be needed. After administration of single doses of cimetidine 400 mg and metformin 850 mg, mean metformin exposure increased by 40%. Metformin is an OCT2 substrate; cimetidine is an OCT2 inhibitor that may decrease metformin elimination by blocking renal tubular secretion.
Lithium: (Moderate) Moderate to significant dietary sodium changes, or changes in sodium and fluid intake, may affect lithium excretion. Systemic sodium chloride administration may result in increased lithium excretion and therefore, decreased serum lithium concentrations. In addition, high fluid intake may increase lithium excretion. For patients receiving sodium-containing intravenous fluids, symptom control and lithium concentrations should be carefully monitored. It is recommended that patients taking lithium maintain consistent dietary sodium consumption and adequate fluid intake during the initial stabilization period and throughout lithium treatment. Supplemental oral sodium and fluid should be only be administered under careful medical supervision.
Lomitapide: (Major) Concomitant use of lomitapide and cimetidine may significantly increase the serum concentration of lomitapide. Therefore, the lomitapide dose should not exceed 30 mg/day PO during concurrent use. Cimetidine is a weak CYP3A4 inhibitor; the exposure to lomitapide is increased by approximately 2-fold in the presence of weak CYP3A4 inhibitors.
Lomustine, CCNU: (Major) Avoid coadministration of cimetidine and lomustine. Concomitant use of cimetidine and lomustine causes an increase in bone marrow

toxicity. The mechanism of this effect is not clear, and may not be related to cimetidine's inhibition of the hepatic CYP450 enzyme system.
Lonafarnib: (Major) Avoid coadministration of lonafarnib and cimetidine; concurrent use may increase the exposure of lonafarnib and the risk of adverse effects. If coadministration is unavoidable, reduce to or continue lonafarnib at a dosage of 115 mg/m2 and closely monitor patients for lonafarnib-related adverse reactions. Resume previous lonafarnib dosage 14 days after discontinuing cimetidine. Lonafarnib is a sensitive CYP3A4 substrate and cimetidine is a weak CYP3A4 inhibitor.
Lopinavir; Ritonavir: (Moderate) Concurrent administration of cimetidine with ritonavir may result in elevated plasma concentrations of ritonavir. Cimetidine is an inhibitor of the hepatic isoenzymes CYP3A4 and CYP2D6; ritonavir is partially metabolized by both of these enzymes. Monitor for adverse events if these drugs are administered together.
Lovastatin: (Moderate) Use HMG-CoA reductase inhibitors with caution with concomitant drugs that may decrease the levels or activity of endogenous steroids, such as cimetidine. Evaluate patients with signs and symptoms of endocrine dysfunction appropriately. HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production.
Lurasidone: (Moderate) Because lurasidone is primarily metabolized by CYP3A4, concurrent use of CYP3A4 inhibitors, such as cimetidine, can theoretically lead to an increased risk of lurasidone-related adverse reactions.
Maprotiline: (Moderate) Cimetidine can inhibit the systemic clearance of drugs that undergo oxidative metabolism, such as maprotiline, resulting in increased plasma levels of the antidepressant. Patients should be monitored for maprotiline-related side effects and toxicity if cimetidine is added; when possible, choose an alternative H2-blocker for treatment.
Maraviroc: (Minor) Use caution if coadministration of maraviroc with cimetidine is necessary, due to a possible increase in maraviroc exposure. Maraviroc is a CYP3A substrate and cimetidine is a weak CYP3A4 inhibitor. Monitor for an increase in adverse effects with concomitant use.
Mavacamten: (Major) Reduce the mavacamten dose by 1 level (i.e., 15 to 10 mg, 10 to 5 mg, or 5 to 2.5 mg) in patients receiving mavacamten and starting cimetidine therapy. Avoid initiation of cimetidine in patients who are on stable treatment with mavacamten 2.5 mg per day because a lower dose of mavacamten is not available. Initiate mavacamten at a reduced starting dose of 2.5 mg PO once daily in patients who are on stable cimetidine therapy. Concomitant use increases mavacamten exposure, which may increase the risk of adverse drug reactions. Mavacamten is a CYP2C19 substrate and cimetidine is a moderate CYP2C19 inhibitor.
Mebendazole: (Minor) Cimetidine may reduce the metabolism of mebendazole and increase mebendazole serum concentrations. Adverse hematological effects have been observed during concurrent use of cimetidine with high doses or prolonged

mebendazole therapy. In a study of 7 patients, cimetidine significantly increased mebendazole concentrations; however, it was not considered to be of therapeutic relevance. In another study of 8 patients, concomitant use of cimetidine and a 30-day mebendazole treatment regimen resulted in a significant increase in mebendazole serum concentrations.
Mefloquine: (Moderate) H2-blockers may increase plasma concentrations of mefloquine. Patients on chronic mefloquine therapy might be at increased risk of adverse reactions, especially patients with a neurological or psychiatric history. In a small study involving 6 healthy subjects and 6 peptic ulcer patients, cimetidine increased the Cmax and AUC of mefloquine. In the study, the pharmacokinetics of mefloquine were determined after receiving a single oral mefloquine 500 mg dose alone and after 3-days of cimetidine 400 mg PO twice daily. In both healthy subjects and peptic ulcer patients, Cmax was increased 42.4% and 20.5%, respectively. The AUC was increased by 37.5% in both groups. Elimination half-life, total clearance, and volume of distribution were not significantly affected. An increase in adverse reactions was not noted.
Melatonin: (Moderate) Monitor for an increase in melatonin-related adverse reactions if concomitant use of cimetidine is necessary. Concomitant use may increase melatonin exposure; melatonin is a CYP1A2 and CYP2C19 substrate and cimetidine is a CYP1A2 and CYP2C19 inhibitor.
Memantine: (Moderate) Memantine is excreted in part by renal tubular secretion. Competition of memantine for excretion with other drugs that are also eliminated by tubular secretion, such as cimetidine, could result in elevated serum concentrations of one or both drugs.
Meperidine: (Minor) Excessive sedation and respiratory depression may occur if meperidine is used with cimetidine. When used in high doses (i.e., more than 600 mg/day), cimetidine has decreased the metabolism of certain opiate agonists leading to increased serum opiate concentrations and toxicity in some patients. In healthy subjects, cimetidine reduced the clearance and volume of distribution of meperidine.
metFORMIN: (Moderate) Concomitant administration of metformin and cimetidine may increase metformin exposure and increase the risk for lactic acidosis. If these drugs are given together, monitor for signs of metformin toxicity; metformin dose adjustments may be needed. After administration of single doses of cimetidine 400 mg and metformin 850 mg, mean metformin exposure increased by 40%. Metformin is an OCT2 substrate; cimetidine is an OCT2 inhibitor that may decrease metformin elimination by blocking renal tubular secretion.
metFORMIN; sAXagliptin: (Moderate) Concomitant administration of metformin and cimetidine may increase metformin exposure and increase the risk for lactic acidosis. If these drugs are given together, monitor for signs of metformin toxicity; metformin dose adjustments may be needed. After administration of single doses of cimetidine 400 mg and metformin 850 mg, mean metformin exposure increased by 40%. Metformin is an

OCT2 substrate; cimetidine is an OCT2 inhibitor that may decrease metformin elimination by blocking renal tubular secretion.
metFORMIN; SITagliptin: (Moderate) Concomitant administration of metformin and cimetidine may increase metformin exposure and increase the risk for lactic acidosis. If these drugs are given together, monitor for signs of metformin toxicity; metformin dose adjustments may be needed. After administration of single doses of cimetidine 400 mg and metformin 850 mg, mean metformin exposure increased by 40%. Metformin is an OCT2 substrate; cimetidine is an OCT2 inhibitor that may decrease metformin elimination by blocking renal tubular secretion.
Methylergonovine: (Moderate) Monitor for an increase in the incidence and severity of vasospastic adverse reactions, including cerebral and peripheral ischemia, during concomitant use of methylergonovine and cimetidine. Concomitant use may increase methylergonovine exposure. Methylergonovine is a CYP3A substrate and cimetidine is a weak CYP3A inhibitor.
Metoprolol: (Moderate) Monitor for metoprolol-related adverse reactions, including bradycardia and hypotension, during coadministration with cimetidine. Concomitant use may increase metoprolol serum concentrations which would decrease the cardioselectivity of metoprolol.
Metoprolol; hydroCHLOROthiazide, HCTZ: (Moderate) Monitor for metoprolol-related adverse reactions, including bradycardia and hypotension, during coadministration with cimetidine. Concomitant use may increase metoprolol serum concentrations which would decrease the cardioselectivity of metoprolol.
metroNIDAZOLE: (Moderate) Monitor for metronidazole-related adverse effects during concomitant cimetidine use. Cimetidine decreases hepatic microsomal liver enzyme activity and may prolong the half-life and decrease plasma clearance of metronidazole.
Mexiletine: (Moderate) Cimetidine exerts variable effects on the serum levels of mexiletine, so patients should be monitored closely during concomitant therapy with these two agents.
Midazolam: (Moderate) Midazolam is metabolized by hepatic isozyme CYP3A4. Inhibitors of this pathway, such as cimetidine, can potentiate the clinical effects of midazolam.
Midodrine: (Minor) Midodrine may potentially interact with drugs that are actively secreted by the base-secreting system of the kidney, including cimetidine.
Mirtazapine: (Moderate) Monitor for an increase in mirtazapine-related adverse reactions if coadministration with cimetidine is necessary; reduce the mirtazapine dose if needed. Coadministration may increase mirtazapine exposure and risk for side effects. In healthy subjects (n = 12), when cimetidine 800 mg twice daily at steady-state was coadministered with mirtazapine 30 mg/day at steady-state, mirtazapine AUC increased by more than 50%. Mirtazapine is a CYP1A2, CYP2D6, and CYP3A substrate and cimetidine is a CYP1A2, CYP2D6, and CYP3A inhibitor.
Modafinil: (Moderate) Modafinil is extensively metabolized by the CYP3A4 hepatic

isoenzyme. When significant CYP3A4 inhibitors like cimetidine are administered concomitantly with modafinil, the health care professional may need to observe the patient for increased effects from modafinil.
Morphine: (Moderate) Concurrent use of morphine and cimetidine may increase the adverse effects of morphine, especially if a large cimetidine dose is used or if the patient is not young and healthy. One patient undergoing hemodialysis experienced confusion and severe respiratory depression when given morphine and cimetidine concurrently. As determined by data obtained from healthy patients, the mean systemic exposure, half-life, volume of distribution, and plasma clearance of morphine were similar after 4 days of pretreatment with either placebo or cimetidine 300 mg every 6 hours by mouth. In another crossover study, the concurrent receipt of cimetidine 600 mg orally and 10 mg morphine intramuscularly by 8 healthy adults led to a more profound depression of the CO2 response and delay in its recovery as compared with only morphine receipt; cimetidine alone had negligible respiratory effects. Also, concomitant administration of morphine and cimetidine has been reported to precipitate apnea, confusion, and muscle twitching in an isolated report. Monitor patients for increased respiratory and CNS depression when receiving both cimetidine and morphine.
Nafarelin: (Minor) Cimetidine causes hyperprolactinemia and should not be administered concomitantly with nafarelin since hyperprolactinemia down-regulates the number of pituitary GnRH receptors.
Naloxegol: (Minor) Although naloxegol is metabolized primarily by the CYP3A enzyme system, concomitant use with weak CYP3A4 inhibitors, such as cimetidine, is not expected to effect naloxegol concentrations in a clinically significant manner. No dosage adjustments are necessary.
Nanoparticle Albumin-Bound Sirolimus: (Major) Reduce the nab-sirolimus dose to 56 mg/m2 during concomitant use of cimetidine. Coadministration may increase sirolimus concentrations and increase the risk for sirolimus-related adverse effects. Sirolimus is a CYP3A substrate and cimetidine is a weak CYP3A inhibitor.
Naproxen: (Moderate) Avoid concomitant use of enteric-coated, delayed-release naproxen and H2-blockers due to the gastric pH elevating effects of H2-blockers. Enteric-coated, delayed-release naproxen tablets are designed to dissolve at a pH of 6 or more.
Naproxen; Esomeprazole: (Moderate) Avoid concomitant use of enteric-coated, delayed-release naproxen and H2-blockers due to the gastric pH elevating effects of H2-blockers. Enteric-coated, delayed-release naproxen tablets are designed to dissolve at a pH of 6 or more.
Naproxen; Pseudoephedrine: (Moderate) Avoid concomitant use of enteric-coated, delayed-release naproxen and H2-blockers due to the gastric pH elevating effects of H2-blockers. Enteric-coated, delayed-release naproxen tablets are designed to dissolve at a pH of 6 or more.
Neratinib: (Major) Take neratinib at least 2 hours before the next dose of an H2-blocker

or 10 hours after the last dose of an H2-blocker due to decreased absorption and systemic exposure of neratinib; the solubility of neratinib decreases with increasing pH of the GI tract. The Cmax and AUC of neratinib were reduced by 57% and 48%, respectively, when administered 2 hours after a daily dose of ranitidine 300 mg. The Cmax and AUC of neratinib were reduced by 44% and 32%, respectively, when administered 2 hours before ranitidine 150 mg twice daily (given approximately 12 hours apart).
NiCARdipine: (Moderate) Cimetidine is a potent inhibitor of many of the isoenzymes of the hepatic CYP450 oxidative enzyme system and has been shown to increase the oral bioavailability of nicardipine. Patients should be monitored closely and lower doses of nicardipine may be considered during concomitant therapy with cimetidine.
NIFEdipine: (Moderate) Cimetidine has been shown to increase the oral bioavailability of dihydropyridines. Cimetidine can potentially affect the disposition of nifedipine due to inhibitory effects on cytochrome P-450 and, therefore, first-pass metabolism of nifedipine, increasing nifedipine bioavailability and serum concentrations. Lower doses of nifedipine may be considered during concomitant therapy with cimetidine.
Nilotinib: (Moderate) If concomitant use of these agents is necessary, administer the H2-blocker approximately 10 hours before and approximately 2 hours after the nilotinib dose. Nilotinib displays pH-dependent solubility with decreased solubility at a higher pH. The concomitant use of nilotinib and H2-blockers that elevate the gastric pH may reduce the bioavailability of nilotinib. In a study in healthy subjects, there was no significant change in nilotinib pharmacokinetics when a single 400-mg nilotinib dose was given 10 hours after and 2 hours prior to famotidine.
niMODipine: (Moderate) Cimetidine has been shown to increase the oral bioavailability of nimodipine due to cimetidine's effects on the cytochrome P-450 hepatic enzymes. Lower doses of nimodipine may be necessary in patients receiving cimetidine.
Nirmatrelvir; Ritonavir: (Moderate) Concurrent administration of cimetidine with ritonavir may result in elevated plasma concentrations of ritonavir. Cimetidine is an inhibitor of the hepatic isoenzymes CYP3A4 and CYP2D6; ritonavir is partially metabolized by both of these enzymes. Monitor for adverse events if these drugs are administered together.
Nirogacestat: (Major) Avoid concomitant use of nirogacestat and H2 receptor blockers. Concurrent use may impair nirogacestat absorption which may decrease nirogacestat exposure and reduce its efficacy. Antacids may be used with nirogacestat but administration should be separated by at least 2 hours.
Nisoldipine: (Moderate) Avoid coadministration of nisoldipine with cimetidine due to increased plasma concentrations of nisoldipine. Coadministration of cimetidine and nisoldipine increased nisoldipine exposure by 30% to 45%. If coadministration is unavoidable, monitor blood pressure closely during concurrent use of these medications. Nisoldipine is a CYP3A4 substrate and cimetidine is a weak CYP3A4

inhibitor.
Norethindrone Acetate; Ethinyl Estradiol; Ferrous fumarate: (Minor) The bioavailability of oral iron salts is influenced by gastric pH, and the concomitant administration of H2-blockers can decrease iron absorption. The non-heme ferric form of iron needs an acidic intragastric pH to be reduced to ferrous and to be absorbed. Iron salts and polysaccharide-iron complex provide non-heme iron. H2-blockers have long-lasting effects on the secretion of gastric acid and thus, increase the pH of the stomach. The increase in intragastric pH can interfere with the absorption of iron salts.
Norethindrone; Ethinyl Estradiol; Ferrous fumarate: (Minor) The bioavailability of oral iron salts is influenced by gastric pH, and the concomitant administration of H2-blockers can decrease iron absorption. The non-heme ferric form of iron needs an acidic intragastric pH to be reduced to ferrous and to be absorbed. Iron salts and polysaccharide-iron complex provide non-heme iron. H2-blockers have long-lasting effects on the secretion of gastric acid and thus, increase the pH of the stomach. The increase in intragastric pH can interfere with the absorption of iron salts.
Nortriptyline: (Moderate) Cimetidine can inhibit the systemic clearance of tricyclic antidepressants that undergo oxidative metabolism, such as nortriptyline, resulting in increased plasma levels of the antidepressant.
Octreotide: (Moderate) Coadministration of oral octreotide with H2-blockers may require increased doses of octreotide. Coadministration of oral octreotide with drugs that alter the pH of the upper GI tract, including H2-blockers, may alter the absorption of octreotide and lead to a reduction in bioavailability.
OLANZapine: (Minor) Inhibitors of CYP1A2, such as cimetidine, could potentially decrease the elimination of olanzapine.
OLANZapine; FLUoxetine: (Moderate) Monitor for increased fluoxetine-related adverse effects if coadministered with cimetidine. Concomitant use may increase fluoxetine exposure. Fluoxetine is a CYP2D6 substrate and cimetidine is a weak CYP2D6 inhibitor. (Minor) Inhibitors of CYP1A2, such as cimetidine, could potentially decrease the elimination of olanzapine.
OLANZapine; Samidorphan: (Minor) Inhibitors of CYP1A2, such as cimetidine, could potentially decrease the elimination of olanzapine.
oxyCODONE: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of cimetidine is necessary. If cimetidine is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like cimetidine can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If cimetidine is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential

withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
oxyMORphone: (Minor) When used in high doses (i.e., > 600 mg/day), cimetidine has decreased the metabolism of certain opiate agonists leading to increased opiate levels and opiate toxicity in some patients. Monitor patients for increased respiratory and CNS depression during coadministration.
PARoxetine: (Moderate) Monitor for an increase in paroxetine-related adverse reactions, including serotonin syndrome, if concomitant use with cimetidine is necessary. Concomitant use may increase paroxetine exposure. Paroxetine is a CYP2D6 substrate and cimetidine is a weak CYP2D6 inhibitor.
PAZOPanib: (Major) Avoid coadministration of pazopanib with H2-blockers due to decreased absorption of pazopanib, which may decrease efficacy. If concomitant administration with a gastric acid-reducing agent is unavoidable, consider the use of a short-acting antacid in place of an H2-blocker; separate administration of the short-acting antacid and pazopanib by several hours to avoid a reduction in pazopanib exposure. Concomitant use of pazopanib with a proton pump inhibitor decreased pazopanib exposure (AUC and Cmax) by approximately 40%.
Pentoxifylline: (Moderate) Cimetidine, a known hepatic enzyme inhibitor, can increase pentoxifylline serum concentrations. Patients should be monitored for increased pentoxifylline adverse reactions if cimetidine is added.
Perphenazine; Amitriptyline: (Moderate) Monitor for an increase in amitriptyline-related adverse reactions if coadministration with cimetidine is necessary; a dose reduction of amitriptyline may be necessary. Concurrent use may increase the plasma concentrations of amitriptyline. Amitriptyline is a CYP2D6 substrate and cimetidine is a CYP2D6 inhibitor.
Pexidartinib: (Moderate) Administer pexidartinib 2 hours before or 10 hours after H2-blockers as concurrent administration may reduce pexidartinib exposure. Although the effects of H2-blockers on pexidartinib pharmacokinetics have not been studied, other acid-reducing agents have been shown to decrease pexidartinib exposure by 50%.
Phenytoin: (Moderate) Monitor phenytoin concentrations during concomitant therapy with cimetidine due to risk for phenytoin toxicity. Concomitant use may increase phenytoin concentrations. Phenytoin is a CYP2C19 substrate and cimetidine is a CYP2C19 inhibitor.
Pimozide: (Contraindicated) Because post-marketing surveillance reports have documented QT prolongation and ventricular arrhythmias, including torsade de pointes and death when known and potent inhibitors of CYP3A4 are coadministered with pimozide, the use of cimetidine should be considered contraindicated in patients taking pimozide. Pimozide is metabolized primarily through CYP3A4, and to a lesser extent CYP1A2 and CYP2D6. Cimetidine is an inhibitor of CYP3A4, CYP2D6, and CYP1A2. Elevated pimozide concentrations can lead to QT prolongation, ventricular arrhythmias,

and sudden death.
Pioglitazone; Glimepiride: (Moderate) Monitor blood glucose during concomitant cimetidine and sulfonylurea use due to increased risk for hypoglycemia. Cimetidine has been shown to affect the pharmacokinetics of some sulfonylureas. The mechanism of this interaction may involve either increasing the absorption or decreasing the clearance of the sulfonylurea. Asymptomatic hypoglycemia has been observed during coadministration.
Pioglitazone; metFORMIN: (Moderate) Concomitant administration of metformin and cimetidine may increase metformin exposure and increase the risk for lactic acidosis. If these drugs are given together, monitor for signs of metformin toxicity; metformin dose adjustments may be needed. After administration of single doses of cimetidine 400 mg and metformin 850 mg, mean metformin exposure increased by 40%. Metformin is an OCT2 substrate; cimetidine is an OCT2 inhibitor that may decrease metformin elimination by blocking renal tubular secretion.
Pirfenidone: (Major) Discontinue cimetidine prior to beginning pirfenidone because it may increase exposure to pirfenidone. Cimetidine is a moderate inhibitor of CYP1A2, CYP2C19, and to a lesser extent CYP2D6. Pirfenidone is primarily metabolized by CYP1A2 with minor contributions from CYP2C9, CYP2C19, CYP2D6, and CYP2E1.
Pitavastatin: (Moderate) Use HMG-CoA reductase inhibitors with caution with concomitant drugs that may decrease the levels or activity of endogenous steroids, such as cimetidine. Evaluate patients with signs and symptoms of endocrine dysfunction appropriately. HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production.
Polyethylene Glycol; Electrolytes; Bisacodyl: (Minor) The concomitant use of bisacodyl tablets with H2-blockers can cause the enteric coating of the bisacody tablet to dissolve prematurely, leading to possible gastric irritation or dyspepsia. Avoid H2-blockers within 1 hour before or after the bisacodyl dosage.
Posaconazole: (Major) The concurrent use of posaconazole immediate-release oral suspension and cimetidine should be avoided, if possible, due to the potential for decreased posaconazole efficacy. If this combination is required, closely monitor for breakthrough fungal infections. When posaconazole oral suspension (200 mg PO daily) was administered with cimetidine (400 mg PO twice daily), the mean reductions in both posaconazole Cmax and AUC were 39%. The administration of posaconazole oral suspension with antacids and H2-blockers other than cimetidine has not resulted in clinically significant adverse events; no dosage adjustments of posaconazole are required when administered concomitantly with antacids or H2-blockers other than cimetidine. The pharmacokinetics of posaconazole delayed-release tablets and oral suspension are not significantly affected by antacids or H2-blockers.
Pravastatin: (Moderate) Use HMG-CoA reductase inhibitors with caution with concomitant drugs that may decrease the levels or activity of endogenous steroids, such

as cimetidine. Evaluate patients with signs and symptoms of endocrine dysfunction appropriately. HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production.
Praziquantel: (Moderate) Drugs that inhibit hepatic metabolism via the microsomal CYP450 enzyme system, such as cimetidine, may increase the bioavailability of praziquantel.
Procainamide: (Moderate) H2-blockers, such as cimetidine, inhibit the renal tubular secretion of procainamide. Clearance of procainamide is reduced and serum concentrations are increased by cimetidine.
Progesterone: (Minor) The metabolism of progesterone may be inhibited by cimetidine, an inhibitor of cytochrome P450 3A4 hepatic enzymes.
Propafenone: (Major) Avoid concurrent use of propafenone and cimetidine; concurrent use may increase plasma concentrations of propafenone, which may lead to cardiac arrhythmias and exaggerated beta-blocking activity. Concomitant administration of propafenone immediate-release tablets and cimetidine in healthy subjects (n = 12) resulted in a 20% increase in steady-state plasma concentrations of propafenone. Propafenone is a CYP1A2, CYP2D6, and CYP3A substrate; propafenone is a weak CYP1A2 inhibitor, weak CYP2D6 inhibitor, and weak CYP3A inhibitor.
Propranolol: (Moderate) Monitor for increased propranolol adverse reactions, including bradycardia and hypotension, during coadministration of cimetidine as concurrent use may increase propranolol exposure. Propranolol is a CYP2D6 substrate and cimetidine is weak CYP2D6 inhibitor.
Protriptyline: (Moderate) Cimetidine can inhibit the systemic clearance of tricyclic antidepressants that undergo oxidative metabolism, resulting in increased plasma levels of the antidepressant. Patients should be monitored for TCA-related side effects and toxicity if cimetidine is added.
Quazepam: (Moderate) Cimetidine can inhibit the hepatic clearance of some benzodiazepines that undergo oxidative metabolism, including quazepam.
QUEtiapine: (Minor) Cimetidine may cause a decrease in quetiapine clearance. Although it is not usually necessary to adjust the dose of quetiapine when cimetidine is coadministered, patients should be monitored for a potential increase in the pharmacologic effects of quetiapine.
quiNIDine: (Major) Quinidine concentrations should be monitored closely after cimetidine is added; choose an alternate acid-reducing therapy if possible. Quinidine is eliminated primarily by the CYP3A4 isoenzyme. Cimetidine can inhibit quinidine metabolism and produce quinidine toxicity.
quiNINE: (Minor) Cimetidine reduced the hepatic clearance of quinine and prolonged its half-life. Peak quinine serum concentrations were not affected. The clinical significance of this pharmacokinetic interaction is unclear.
Ramelteon: (Major) Caution is recommended during concurrent use of ramelteon and

cimetidine. Because ramelteon is metabolized via CYP3A4 and CYP1A2, use with CYP3A4 and CYP1A2 inhibitors, such as cimetidine, may increase exposure to ramelteon and the potential for adverse reactions. Other CYP1A2 inhibitors have been shown to have significant interactions with ramelteon, leading to elevated AUC of ramelteon > 190-fold and Cmax > 70 fold. If cimetidine must be administered with ramelteon, monitor the patient closely for toxicity due to elevated ramelteon serum concentrations. Alternatives to cimetidine may be considered, such as famotidine or nizatidine.
Ranolazine: (Moderate) Coadminister ranolazine and cimetidine with caution. Cimetidine is a substrate of the OCT2 transporter. Dosage reduction for metformin, another OCT2 transporter substrate, is recommended by the manufacturer of ranolazine. Coadministration of metformin and ranolazine 1000 mg twice daily results in increased plasma concentrations of metformin. Doses of metformin do not require reduction if coadministered with ranolazine 500 mg twice daily. Cimetidine also is a CYP2D6 and CYP3A4 inhibitor, and ranolazine is a substrate for these enzymes; however, coadministration of cimetidine does not increase the plasma concentrations of ranolazine in healthy volunteers.
Rasagiline: (Moderate) Monitor for dopaminergic adverse effects during concurrent use of rasagiline and cimetidine. Coadministration may result in increased rasagiline concentrations. A dose reduction of rasagiline may be necessary. Rasagiline is primarily metabolized by CYP1A2; cimetidine is a weak CYP1A2 inhibitor. When administered with a strong CYP1A2 inhibitor, the AUC of rasagiline was increased by 83%.
Repaglinide: (Minor) In healthy volunteers, the coadministration of cimetidine with repaglinide did not significantly alter the absorption or disposition of repaglinide. Repaglinide is partly metabolized by CYP3A4. Drugs that inhibit CYP3A4 may increase plasma concentrations of repaglinide. Cimetidine has been shown to be a mild inhibitor of CYP3A4. If these drugs are co-administered, dose adjustment of repaglinide may rarely be necessary. Consider other H2-blockers as alternatives.
Rilpivirine: (Moderate) Coadministration with cimetidine may significantly decrease rilpivirine plasma concentrations, potentially resulting in treatment failure. To decrease the risk of virologic failure, avoid use of H2 receptor antagonist for at least 12 hours before and at least 4 hours after administering rilpivirine.
Rilzabrutinib: (Moderate) Separate the administration of rilzabrutinib and H2-blockers if concomitant use is necessary: administer rilzabrutinib at least 2 hours before the H2-blocker. Simultaneous coadministration may decrease rilzabrutinib exposure and reduce rilzabrutinib efficacy. Rilzabrutinib is pH soluble and H2-blockers alter gastric pH. Administering rilzabrutinib 2 hours before an H2-blocker mitigates this interaction and has been observed to reduce rilzabrutinib overall exposure by 28%.
Risedronate: (Major) Use of H2-blockers with delayed-release risedronate tablets (Atelvia) is not recommended. Co-administration of drugs that raise stomach pH increases risedronate bioavailability due to faster release of the drug from the enteric

coated tablet. This interaction does not apply to risedronate immediate-release tablets.
Ritonavir: (Moderate) Concurrent administration of cimetidine with ritonavir may result in elevated plasma concentrations of ritonavir. Cimetidine is an inhibitor of the hepatic isoenzymes CYP3A4 and CYP2D6; ritonavir is partially metabolized by both of these enzymes. Monitor for adverse events if these drugs are administered together.
Roflumilast: (Moderate) Coadminister cimetidine and roflumilast cautiously as increased systemic exposure to roflumilast has been demonstrated in pharmacokinetic study. Increased roflumilast-induced adverse reactions may result. Cimetidine is an inhibitor of CYP3A4 and CYP1A2; roflumilast is a CYP3A4 and CYP1A2 substrate. In an open-label crossover study in 16 healthy volunteers, the coadministration of cimetidine (400 mg twice daily for 7 days) with a single oral dose of roflumilast 500 mcg resulted in a 46% and 85% increase in roflumilast Cmax and AUC; and a 4% decrease in Cmax and 27% increase in AUC for the active metabolite roflumilast N-oxide.
romiDEPsin: (Moderate) Romidepsin is a substrate for CYP3A4. Cimetidine is a mild inhibitor of CYP3A4. Concurrent administration of romidepsin with a mild CYP3A4 inhibitor may cause an increase in systemic romidepsin concentrations. Use caution when concomitant administration of these agents is necessary.
rOPINIRole: (Moderate) Coadministration of cimetidine and ropinirole may result in increased ropinirole concentrations. Cimetidine is a weak CYP1A2 inhibitor; ropinirole is a CYP1A2 substrate.
ROPivacaine: (Major) Known inhibitors of cytochrome P450 1A2, such as cimetidine, may increase the systemic levels of ropivacaine and increase the risk of toxicity when given concurrently.
Rosuvastatin: (Moderate) Use HMG-CoA reductase inhibitors with caution with concomitant drugs that may decrease the levels or activity of endogenous steroids, such as cimetidine. Evaluate patients with signs and symptoms of endocrine dysfunction appropriately. HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production.
Rosuvastatin; Ezetimibe: (Moderate) Use HMG-CoA reductase inhibitors with caution with concomitant drugs that may decrease the levels or activity of endogenous steroids, such as cimetidine. Evaluate patients with signs and symptoms of endocrine dysfunction appropriately. HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production.
Ruxolitinib: (Moderate) Ruxolitinib is a CYP3A4 substrate. When used with drugs that are mild or moderate inhibitors of CYP3A4 such as cimetidine, a dose adjustment is not necessary, but monitoring patients for toxicity may be prudent. There was an 8% and 27% increase in the Cmax and AUC of a single dose of ruxolitinib 10 mg, respectively, when the dose was given after a short course of erythromycin 500 mg PO twice daily for 4 days. The change in the pharmacodynamic marker pSTAT3 inhibition was consistent with the increase in exposure.

Saquinavir: (Moderate) The concurrent use of saquinavir boosted with ritonavir and cimetidine should be avoided if possible due to the potential for life-threatening cardiac arrhythmias such as torsades de pointes (TdP). Cimetidine is an inhibitor of several CYP isoenzymes including CYP3A4; an isoenzyme responsible for the metabolism of saquinavir. Increased plasma concentrations of saquinavir may occur during coadministration; saquinavir boosted with ritonavir has been found to cause dose-dependent QT and PR prolongation. The interaction between saquinavir not boosted with ritonavir and cimetidine has not been found to produce clinically relevant effects, although some patients could experience and increase in adverse effects if saquinavir and cimetidine are coadministered.
Secretin: (Major) Discontinue H2-blockers at least 2 days before performing a secretin stimulation test for gastrinoma. H2-blockers may cause a hyperresponse in gastrin secretion and interfere with the test's diagnostic accuracy.
Segesterone Acetate; Ethinyl Estradiol: (Minor) Coadministration of segesterone and moderate CYP3A4 inhibitors such as cimetidine may increase the serum concentration of segesterone.
Selpercatinib: (Major) Avoid coadministration of selpercatinib with cimetidine due to the risk of decreased selpercatinib exposure which may reduce its efficacy. If concomitant use is unavoidable, take selpercatinib 2 hours before or 10 hours after administration of cimetidine. Coadministration with acid-reducing agents decreases selpercatinib plasma concentrations; however, no clinically significant differences in the pharmacokinetics of selpercatinib were observed when given under fasting conditions with multiple daily doses of another H2-receptor antagonist given 10 hours prior to and 2 hours after the selpercatinib dose.
Sildenafil: (Moderate) Monitor for an increase in sildenafil-related adverse reactions if coadministration with cimetidine is necessary. Concomitant use may increase sildenafil plasma concentrations. Cimetidine 800 mg caused a 56% increase in plasma sildenafil concentrations when coadministered with sildenafil 50 mg to healthy volunteers. Sildenafil is a CYP2C9 and CYP3A substrate and cimetidine is a nonspecific CYP inhibitor.
Simvastatin: (Moderate) Use HMG-CoA reductase inhibitors with caution with concomitant drugs that may decrease the levels or activity of endogenous steroids, such as cimetidine. Evaluate patients with signs and symptoms of endocrine dysfunction appropriately. HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production.
Sirolimus: (Moderate) Monitor sirolimus concentrations and adjust sirolimus dosage as appropriate during concomitant use of cimetidine. Coadministration may increase sirolimus concentrations and increase the risk for sirolimus-related adverse effects. Sirolimus is a CYP3A substrate and cimetidine is a weak CYP3A inhibitor.
Sodium Ferric Gluconate Complex; Ferric Pyrophosphate Citrate: (Minor) The bioavailability of oral iron salts is influenced by gastric pH, and the concomitant

administration of H2-blockers can decrease iron absorption. The non-heme ferric form of iron needs an acidic intragastric pH to be reduced to ferrous and to be absorbed. Iron salts and polysaccharide-iron complex provide non-heme iron. H2-blockers have long-lasting effects on the secretion of gastric acid and thus, increase the pH of the stomach. The increase in intragastric pH can interfere with the absorption of iron salts.
Sofosbuvir; Velpatasvir: (Major) H2-blockers may be administered simultaneously with or 12 hours apart from velpatasvir. H2-blocker doses should not exceed doses comparable to famotidine 40 mg twice daily. Velpatasvir solubility decreases as pH increases; therefore, drugs that increase gastric pH are expected to decrease the concentrations of velpatasvir, potentially resulting in loss of antiviral efficacy.
Sofosbuvir; Velpatasvir; Voxilaprevir: (Major) H2-blockers may be administered simultaneously with or 12 hours apart from velpatasvir. H2-blocker doses should not exceed doses comparable to famotidine 40 mg twice daily. Velpatasvir solubility decreases as pH increases; therefore, drugs that increase gastric pH are expected to decrease the concentrations of velpatasvir, potentially resulting in loss of antiviral efficacy.
Sonidegib: (Moderate) Use sonidegib and cimetidine together with caution; sonidegib levels and/or exposure may be altered. Cimetidine is a weak CYP3A4 inhibitor and may increase the level of the CYP3A4 substrate, sonidegib, resulting in an increased risk of adverse events, particularly musculoskeletal toxicity. Based on population PK analysis, the concomitant administration of a histamine-2-receptor antagonist such as cimetidine decreases the geometric mean sonidegib steady-state AUC (0-24 hours) value by 34%.
Sotorasib: (Major) Avoid coadministration of sotorasib and gastric acid-reducing agents, such as H2-receptor antagonists. Coadministration may decrease sotorasib exposure resulting in decreased efficacy. If necessary, sotorasib may be administered 4 hours before or 10 hours after a locally acting antacid. Coadministration with an H2-receptor antagonist decreased sotorasib exposure by 38% under fed conditions.
Sparsentan: (Major) Avoid concurrent use of sparsentan and H2 receptor antagonists due to the risk for decreased sparsentan exposure which may reduce its efficacy. Medications that affect gastric pH may reduce sparsentan absorption.
SUFentanil: (Moderate) Because the dose of the sufentanil sublingual tablets cannot be titrated, consider an alternate opiate if cimetidine must be administered. Consider a reduced dose of sufentanil injection with frequent monitoring for respiratory depression and sedation if concurrent use of cimetidine is necessary. If cimetidine is discontinued, consider increasing the sufentanil injection dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Sufentanil is a CYP3A4 substrate, and coadministration with a weak CYP3A4 inhibitor like cimetidine can increase sufentanil exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of sufentanil. If cimetidine is discontinued, sufentanil plasma concentrations will decrease resulting in

reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to sufentanil.
Sulfonylureas: (Moderate) Monitor blood glucose during concomitant cimetidine and sulfonylurea use due to increased risk for hypoglycemia. Cimetidine has been shown to affect the pharmacokinetics of some sulfonylureas. The mechanism of this interaction may involve either increasing the absorption or decreasing the clearance of the sulfonylurea. Asymptomatic hypoglycemia has been observed during coadministration.
SUMAtriptan; Naproxen: (Moderate) Avoid concomitant use of enteric-coated, delayed-release naproxen and H2-blockers due to the gastric pH elevating effects of H2-blockers. Enteric-coated, delayed-release naproxen tablets are designed to dissolve at a pH of 6 or more.
Tacrolimus: (Major) Tacrolimus is metabolized via the hepatic cytochrome P-450 system. Drugs that inhibit this enzyme system, including cimetidine, may decrease the metabolism of tacrolimus. Subsequent increased plasma concentrations of tacrolimus may lead to nephrotoxicity.
Taletrectinib: (Major) Avoid concomitant use of taletrectinib and H2-receptor antagonists (H2RAs). Concurrent use may decrease taletrectinib exposure, which may reduce its efficacy. Taletrectinib oral absorption is pH dependent and H2RAs alter gastric pH.
Tamsulosin: (Moderate) Use caution if coadministration of cimetidine with tamsulosin is necessary, especially at a tamsulosin dose higher than 0.4 mg, as the systemic exposure of tamsulosin may be increased resulting in increased treatment-related adverse reactions including hypotension, dizziness, and vertigo. Treatment with cimetidine 400 mg every 6 hours for 6 days in healthy volunteers (n = 10) resulted in a 26% decrease in the clearance of tamsulosin, which resulted in a 44% increase in tamsulosin AUC. Tamsulosin is a CYP2D6 and CYP3A substrate and cimetidine is a weak CYP2D6 and CYP3A inhibitor.
Tasimelteon: (Moderate) Caution is recommended during concurrent use of tasimelteon and cimetidine. Because tasimelteon is metabolized via CYP3A4 and CYP1A2, use with CYP3A4 and CYP1A2 inhibitors, such as cimetidine, may increase exposure to tasimelteon and the potential for adverse reactions.
Teriflunomide: (Moderate) Teriflunomide is an inhibitor of the renal uptake organic anion transporter OAT3. Use of teriflunomide with cimetidine, a substrate of OAT3, may increase cimetidine plasma concentrations. Monitor for increased adverse effects from cimetidine, such as dose-related elevations in hepatic enzymes. Adjust the dose of cimetidine as necessary and clinically appropriate.
Thalidomide: (Moderate) Thalidomide and other agents that slow cardiac conduction such as H2-blockers should be used cautiously due to the potential for additive bradycardia.
Theophylline, Aminophylline: (Major) Aminophylline is primarily metabolized in the liver by the CYP1A2 isoenzyme. Cimetidine inhibits the CYP1A2 isoenzyme and not only

reduces the hepatic metabolism of aminophylline, but a reduction in the renal clearance of theophylline may occur via competition for renal tubular secretion. However, the hepatic-based interaction is more significant. In patients receiving aminophylline, an alternative to cimetidine should be considered when possible. Alternatively, if concomitant therapy is necessary, patients should be monitored closely for increased effects of theophylline and the need for aminophylline dosage adjustments. The Beers criteria recommends that this drug combination be avoided in older adults. (Major)
Theophylline is primarily metabolized in the liver by the CYP1A2 isoenzyme. Cimetidine inhibits the CYP1A2 isoenzyme and not only reduces the hepatic metabolism of theophylline, but a reduction in the renal clearance of theophylline may occur via competition for renal tubular secretion. However, the hepatic-based interaction is more significant. In patients receiving theophylline, an alternative to cimetidine should be considered when possible. Alternatively, if concomitant therapy is necessary, patients should be monitored closely for increased effects of theophylline and the need for theophylline dosage adjustments.
Thioridazine: (Contraindicated) Cimetidine is a moderate inhibitor of CYP2D6 and the use of thioridazine concomitantly with CYP2D6 inhibitors is contraindicated due to the possible risk of QT prolongation and subsequent arrhythmias, or other serious side effects, due to elevated serum concentrations of thioridazine. Consider an alternative to cimetidine for patients taking thioridazine.
Tinidazole: (Major) Coadministration may result in increased tinidazole concentrations. Cimetidine is an enzyme inhibitor that can decrease the hepatic metabolism of tinidazole.
tiZANidine: (Major) Avoid concomitant use of tizanidine and cimetidine as increased tizanidine exposure may occur. If use together is necessary, initiate tizanidine at 2 mg and increase by 2 to 4 mg/day based on clinical response. Discontinue tizanidine if hypotension, bradycardia, or excessive drowsiness occurs. Tizanidine is a CYP1A2 substrate and cimetidine is a weak CYP1A2 inhibitor.
Tolvaptan: (Moderate) Coadministration of tolvaptan and hypertonic saline (e.g., 3% NaCl injection solution) is not recommended. The use of hypertonic sodium chloride in combination with tolvaptan may result in a too rapid correction of hyponatremia and increase the risk of osmotic demyelination (i.e., central pontine myelinolysis).
traMADol: (Moderate) Concurrent use of tramadol with cimetidine may produce unpredictable effects, including prolonged opioid-related adverse reactions, such as fatal respiratory depression, a withdrawal syndrome in those with physical dependence to opioid agonists, seizures, or serotonin syndrome. Consider dose adjustments of tramadol until stable drug effects are achieved. Monitor patients closely for respiratory depression and sedation at frequent intervals. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs. Tramadol is primarily metabolized by CYP2D6 to the active metabolite M1, and by CYP3A; cimetidine is a dual

weak CYP2D6 and weak CYP3A inhibitor. CYP3A inhibitors may increase tramadol-related adverse effects while CYP2D6 inhibitors may reduce efficacy.
Tramadol; Acetaminophen: (Moderate) Concurrent use of tramadol with cimetidine may produce unpredictable effects, including prolonged opioid-related adverse reactions, such as fatal respiratory depression, a withdrawal syndrome in those with physical dependence to opioid agonists, seizures, or serotonin syndrome. Consider dose adjustments of tramadol until stable drug effects are achieved. Monitor patients closely for respiratory depression and sedation at frequent intervals. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs. Tramadol is primarily metabolized by CYP2D6 to the active metabolite M1, and by CYP3A; cimetidine is a dual weak CYP2D6 and weak CYP3A inhibitor. CYP3A inhibitors may increase tramadol-related adverse effects while CYP2D6 inhibitors may reduce efficacy.
Trandolapril; Verapamil: (Moderate) Monitor blood pressure and heart rate during coadministration of verapamil with cimetidine. Coadministration may increase the exposure of verapamil.
Triazolam: (Moderate) Monitor for signs of triazolam toxicity during coadministration with cimetidine and consider appropriate dose reduction of triazolam if clinically indicated. Coadministration may increase triazolam exposure. Triazolam is a sensitive CYP3A substrate and cimetidine is a weak CYP3A inhibitor.
Trimipramine: (Moderate) Cimetidine can inhibit the systemic clearance of tricyclic antidepressants that undergo oxidative metabolism, such as trimipramine, resulting in increased plasma levels of the antidepressant. Patients should be monitored for TCA-related side effects and toxicity if cimetidine is added; when possible, choose an alternative H2-blocker for treatment.
Trospium: (Moderate) Monitor for an increase in adverse effects from both medications if concomitant use of cimetidine and trospium is necessary. Concomitant use may increase cimetidine and trospium exposure. Both medications are eliminated via active tubular secretion and may compete with one another to impair elimination.
Ubrogepant: (Major) Limit the initial and second dose of ubrogepant to 50 mg if coadministered with cimetidine. Concurrent use may increase ubrogepant exposure and the risk of adverse effects. Ubrogepant is a CYP3A4 substrate; cimetidine is a weak CYP3A4 inhibitor.
valACYclovir: (Minor) Cimetidine may cause a reduction in the clearance of acyclovir. The clinical significance of these pharmacokinetic interactions is unknown; however, no dosage adjustments are recommended for patients with normal renal function.
Varenicline: (Minor) Inhibitors of OCT2 (e.g., cimeditine) may increase the exposure of varenicline but these changes may not necessitate a dose adjustment of varenicline as the increase in systemic exposure is not expected to be clinically meaningful. Administration cimetidine (300 mg four times daily), with varenicline (2 mg single dose)

to 12 smokers increased the systemic exposure of varenicline by 29% due to a reduction in varenicline renal clearance. In vitro studies demonstrated the active renal secretion of varenicline is mediated by the human organic cation transporter OCT2. Another H2 antagonist may be preferable to cimetidine in patients taking varenicline.
Vemurafenib: (Moderate) Concomitant use of vemurafenib and cimetidine may result in increased vemurafenib concentrations. Vemurafenib is CYP3A4 substrate and cimetidine is a CYP3A4 inhibitor. Use caution and monitor patients for increased side effects.
Verapamil: (Moderate) Monitor blood pressure and heart rate during coadministration of verapamil with cimetidine. Coadministration may increase the exposure of verapamil.
vinCRIStine Liposomal: (Moderate) Cimetidine is a mild CYP3A4 inhibitor, and vincristine is a CYP3A substrate. Coadministration could increase exposure to vincristine; monitor patients for increased side effects if these drugs are given together.
vinCRIStine: (Moderate) Cimetidine is a mild CYP3A4 inhibitor, and vincristine is a CYP3A substrate. Coadministration could increase exposure to vincristine; monitor patients for increased side effects if these drugs are given together.
Vinorelbine: (Moderate) Monitor for an earlier onset and/or increased severity of vinorelbine-related adverse reactions, including constipation and peripheral neuropathy, if coadministration with cimetidine is necessary. Vinorelbine is a CYP3A4 substrate and cimetidine is a weak CYP3A4 inhibitor.
Vorapaxar: (Moderate) Use caution during concurrent use of vorapaxar and cimetidine. Increased serum concentrations of vorapaxar are possible when vorapaxar, a CYP3A4 substrate, is coadministered with cimetidine, a mild CYP3A inhibitor. Increased exposure to vorapaxar may increase the risk of bleeding complications.
Warfarin: (Moderate) Closely monitor the INR if coadministration of warfarin with cimetidine is necessary as concurrent use may increase the exposure of warfarin leading to increased bleeding risk. Cimetidine is a CYP1A2 and weak CYP3A4 inhibitor and the R-enantiomer of warfarin is a CYP1A2/CYP3A4 substrate. The S-enantiomer of warfarin exhibits 2 to 5 times more anticoagulant activity than the R-enantiomer, but the R-enantiomer generally has a slower clearance.
Xanomeline; Trospium: (Moderate) Monitor for an increase in adverse effects from both medications if concomitant use of cimetidine and trospium is necessary. Concomitant use may increase cimetidine and trospium exposure. Both medications are eliminated via active tubular secretion and may compete with one another to impair elimination.
Zaleplon: (Major) Reduce the initial dose of zaleplon to 5 mg in patients receiving concomitant cimetidine therapy. Concomitant administration of cimetidine 800 mg with zaleplon 10 mg resulted in an 85% increase in the Cmax and AUC of zaleplon. Cimetidine inhibits both aldehyde oxidase and CYP3A4, the primary and secondary enzymes, respectively, responsible for zaleplon metabolism.
Ziftomenib: (Moderate) Separate the administration of ziftomenib and an H2-blocker if concomitant use is necessary: administer ziftomenib at least 2 hours before or 10 hours

after the H2-blocker. Simultaneous coadministration may decrease ziftomenib absorption and reduce ziftomenib exposure and efficacy. Ziftomenib is pH soluble and H2-blockers alter gastric pH. Administering ziftomenib 2 hours before or 10 hours after an H2-blocker is expected to mitigate this interaction.
ZOLMitriptan: (Moderate) If cimetidine and zolmitriptan are used concomitantly, limit the maximum single dose of zolmitriptan to 2.5 mg and do not exceed 5 mg in any 24-hour period. After the coadministration of cimetidine, the half-life and AUC of zolmitriptan (5 mg PO) and its active metabolite are roughly doubled.

Adverse Reaction

agitation, anxiety, confusion, depression, dizziness, drowsiness, hallucinations, headache, psychosis

Mild to severe headache occurred in 2.1% of patients who received cimetidine 800 mg/day (n = 2225) and 3.5% of patients who received 1600 mg/day (n = 924) compared with 2.3% of patients who received placebo (n = 1897) in clinical trials. Dizziness and drowsiness, most cases mild, were reported in approximately 1% of patients who received 800 mg/day or 1600 mg/day in clinical trials. Mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation, have been reported mostly in severely ill patients. These central nervous system adverse effects usually developed within 2—3 days after starting and resolved within 3—4 days of stopping cimetidine therapy.

agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia

Rare cases of thrombocytopenia (3 cases per million patients) and decreased white blood counts such as neutropenia and leukopenia (1 case per 100,000 patients) or agranulocytosis (3 cases per million patients) have been reported with cimetidine therapy. Some cases have recurred on rechallenge. Pancytopenia, aplastic anemia, and immune hemolytic anemia have also been reported rarely.

galactorrhea, gynecomastia, hyperprolactinemia, impotence (erectile dysfunction)

Gynecomastia has been reported in patients who received cimetidine therapy for longer than 1 month. Gynecomastia occurred in approximately 4% of adult patients with pathological hypersecretory conditions and in 0.3% to 1% of patients with other conditions in clinical trials. Galactorrhea and hyperprolactinemia have been reported in patients taking cimetidine; in some cases, a switch to an alternative H2-blocker resolved

symptoms. Although reversible impotence (erectile dysfunction) was reported in patients with pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome) and mostly in patients who received high doses of cimetidine for greater than 12 months (mean, 38 months; range, 12 to 79 months), large surveillance studies have not shown an increased risk of erectile dysfunction in patients who received a regular cimetidine dosage.

cholestasis, elevated hepatic enzymes, pancreatitis

Dose-related elevated hepatic enzymes (e.g., increased transaminase levels) have been reported with cimetidine therapy; however, most transaminase level elevations did not worsen with continued therapy and returned to normal by the end of therapy. Cholestatic (cholestasis) or mixed cholestatic hepatocellular effects and pancreatitis have also occurred rarely, most cases reversible. There has been 1 report of biopsy proven periportal hepatic fibrosis. Rarely, fatal hepatic injury has been reported with H2-receptor antagonist use.

alopecia, erythema multiforme, exfoliative dermatitis, rash (unspecified), Stevens-Johnson syndrome, toxic epidermal necrolysis

Rash (unspecified) and rarely reversible alopecia occurred with cimetidine therapy. Very rarely, generalized skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, and generalized exfoliative erythroderma have been reported with H2-receptor antagonist use.

infection

There have been extremely rare reports of strongyloidiasis infection in some immunocompromised patients during cimetidine use. Additionly, increasing evidence suggests a link between acid-suppression therapy and pneumonia (community- and hospital-acquired). Several mechanisms have been proposed to account for this association. One such mechanism states that gastric pH serves as a barrier against pathogenic colonization of the gastrointestinal tract. An increase in gastric pH allows for bacterial and viral invasion which, in theory, can precipitate respiratory infections. Another proposed mechanism accounts for the role that gastric acid may have on stimulating the cough reflex that allows for the clearing of infectious agents from the respiratory tract. Finally, the fact that acid-suppressive therapy may impair white blood cell function, which in turn may lead to a depressed immune response to an infection, is listed among possible mechanisms. Regardless of the mechanism, the use of H2-blockers and/or PPIs has been associated with the development of pneumonia. Data from a large epidemiological trial, including 364,683 individuals who developed 5551

first occurrences of community-acquired pneumonia (CAP), suggest an increased risk of developing CAP among users of acid-suppressive therapy compared to those who stopped therapy. After adjusting for confounders, the adjusted relative risk (RR) for CAP among PPI users compared to those who stopped therapy was 1.89 (95% CI, 1.36—2.62). Likewise, users of H2-blockers had an adjusted RR of 1.63 (95% CI, 1.07—2.48) compared to those who stopped therapy. In a second large cohort trial, including 63,878 hospital admissions, acid-suppressive therapy was ordered in 52% (83% PPI and 23% H2- blocker, with some patients exposed to both) of new admissions. Hospital-acquired pneumonia occurred in 2,219 admissions (3.5%) with a higher incidence recorded among acid-suppressive therapy exposed patients compared to non-exposed patients. A subset analysis found a statistically significant association between PPI use (OR, 1.3; 95% CI, 1.1—1.4) and pneumonia. A non-significant association was found with H2-blockers (OR, 1.2; 95% CI, 0.98—1.4); however, the lack of significance was attributed to the studies lack of power to detect significance for an OR of less than 1.3. Until more is known about the relationship between acid-suppression and pneumonia, clinicians are encouraged to carefully select patients before empirically initiating acid-suppressive therapy with H2-blockers or PPIs. A causal relationship between the use of cimetidine and pneumonia has not been established.

AV block, bradycardia, hypotension, sinus tachycardia

Atrioventricular heart block (AV block), bradycardia, and sinus tachycardia have been reported rarely with H2-receptor antagonist use. Additionally, hypotension and cardiac arrhythmias have occurred rarely following rapid IV bolus administration of cimetidine.

arthralgia, myalgia

Reversible arthralgia and myalgia have occurred rarely with cimetidine use. Some patients with pre-existing arthritis have reported increased joint symptoms that were alleviated with a cimetidine dosage reduction. Rare cases of polymyositis have also been reported rarely.

atrophic gastritis

Atrophic gastritis, a precursor for gastric cancer, has been associated with prolonged acid suppression with high dose H2-blockers in patients who are H. pylori positive. A 'test and treat' approach for baseline H. pylori infections is recommended for patients with reflux esophagitis on long term acid suppression therapy. Treatment of baseline infection decreases inflammation and may reverse corpus gastritis.

anaphylactoid reactions, fever, vasculitis

Fever and allergic reactions (e.g., anaphylactoid reactions, hypersensitivity vasculitis)

have been reported with cimetidine therapy rarely. Resolution of these adverse events occurred when therapy was stopped.

interstitial nephritis, urinary retention

Increased plasma creatinine, slight and possibly related to the dose, has been reported with cimetidine use and does not appear to signify a deterioration in renal function. Interstitial nephritis and urinary retention have occurred with cimetidine therapy rarely. Resolution of these adverse events occurred when therapy was stopped.

diarrhea

Diarrhea, most cases mild, has been reported in approximately 1% of patients who received cimetidine in clinical trials.

pernicious anemia, vitamin B12 deficiency

Long-term (e.g., generally > 3 years) treatment with acid-suppressing agents can lead to malabsorption of vitamin B12 (cyanocobalamin). One large case-controlled study compared patients with and without an incident diagnosis of vitamin B12 deficiency (n = 25,956 and 184,199, respectively). A correlation was demonstrated between vitamin B12 deficiency and gastric acid-suppression therapy. Patients receiving >= 2 years of a proton pump inhibitor (PPI)(OR, 1.65 [95% CI, 1.58—1.73]) or >= 2 years of a H2-receptor antagonist (OR, 1.25 [95% CI, 1.17—1.34]) were associated with having an increased risk for vitamin B12 deficiency. A dose-dependant relationship was evident, as daily doses > 1.5 PPI pills/day were more strongly associated with vitamin B12 deficiency (OR, 1.95 [95% CI, 1.77—2.15]) compared to daily doses < 0.75 pills/day (OR, 1.63 [95% CI, 1.48—1.78]; p = 0.007 for interaction). The possibility of cyanocobalamin deficiency and pernicious anemia should be considered if clinical symptoms are observed. Neurological manifestations of pernicious anemia can occur in the absence of hematologic changes.

Description

Cimetidine is an oral and parenteral histamine type 2-receptor antagonist (H2RA). It is primarily used in the treatment of various gastrointestinal (GI) disorders such as peptic ulcer and gastroesophageal reflux disease (GERD). Nonprescription(OTC) products are available to treat heartburn and dyspepsia (acid indigestion). The actions and indications for cimetidine differ little from other H2RAs; however, cimetidine is a known inhibitor of many of the isoenzymes of the hepatic CYP450 enzyme system. Thus, it exhibits many clinically significant drug interactions with other medications. Cimetidine has been shown to be useful off-label to treat several other conditions. Both proton pump inhibitors (PPIs) and H2RAs provide symptom control in non-erosive GERD. However,

PPIs are preferred over H2RAs for the healing and maintenance treatment of erosive GERD (i.e., erosive esophagitis) due to superior healing rates. H2RAs may be selected when PPIs are not tolerated due to serious adverse effects or hypersensitivity, are contraindicated, or are not available. Cimetidine and other H2-blockers are also first-line treatment options, along with PPIs, for stress-ulcer prophylaxis in critically ill patients with selected risk factors for upper GI bleeding. Cimetidine was initially FDA approved in 1977.

Mechanism Of Action

Cimetidine blocks the effects of histamine at the receptor located on the basolateral membrane of the parietal cell (designated as the H2-receptor). The result is a reduction of both gastric acid volume and gastric acidity. Cimetidine also decreases the amount of gastric acid released in response to other stimuli including food, caffeine, insulin, betazole, or pentagastrin. Because gastric secretions respond to multiple stimuli, cimetidine does not reduce acid-output as dramatically as the proton-pump inhibiting medications (e.g., omeprazole). Cimetidine does not appear to alter gastric motility, gastric emptying, esophageal pressure, or the secretion rate of the gallbladder or pancreas. Cimetidine also exhibits weak anti-androgenic effects.

In combination with an H1-receptor antagonist, cimetidine can suppress the formation of edema, flare, and pruritus that results from histaminic activity. Human skin mast cells express both H1- and H2-receptors. Stimulation of H2-receptors leads to changes in membrane permeability (activating the cyclic AMP-PKA pathway) causing vasodilation. The resultant dilation develops more slowly and is more sustained, as compared to H1-stimulation. Combination therapy blocks both the initial and delayed histaminic response.

Pharmacokinetics

Cimetidine is administered orally and parenterally. The drug distributes throughout body tissues. Both oral and parenteral administration provide comparable periods of therapeutically effective blood levels; blood concentrations remain above that required to provide 80% inhibition of basal gastric acid secretion for 4 to 5 hours in adults. The principal route of excretion of cimetidine is the urine. Following parenteral administration, most of the drug is excreted as the parent compound; following oral administration, the drug is more extensively metabolized, the sulfoxide being the major metabolite. Approximately 48% of an oral dose and approximately 75% of an IV or IM dose of cimetidine is recovered from the urine after 24 hours as the parent compound. The remainder is excreted in the feces. The half-life is roughly 2 hours in adults with

normal renal function.

Affected cytochrome P450 isoenzymes and drug transporters: CYP1A2, CYP2C19, CYP2D6, and CYP3A4
Cimetidine is the classic example of a drug that inhibits cytochrome oxidative hepatic metabolism, and it inhibits this system non-selectively. Cimetidine has been shown to inhibit a number of CYP isoenzymes, including CYP1A2, CYP2C19, and to a lesser extent CYP2D6 and CYP3A4.

Route-Specific Pharmacokinetics

- **Oral Route**

Cimetidine is rapidly and completely absorbed in the GI tract, but first-pass metabolism reduces oral bioavailability to 60% to 70%. The rate but not the extent of absorption can be affected by food. Peak plasma concentrations occur in 45 to 90 minutes.

- **Intravenous Route**

Peak concentration (Cmax) generally occurs within 15 minutes of intermittent intravenous dosing. Cimetidine blood concentrations with other infusion rates vary in direct proportion to the infusion rate.

- **Intramuscular Route**

Intramuscular administration provides comparatively effective cimetidine blood concentrations to oral and intravenous routes.

- **Hepatic Impairment**

Uncompensated cirrhosis is associated with decreased clearance of cimetidine. Dosage reductions are recommended for severe hepatic impairment (e.g., Child-Pugh grade C cirrhosis).

- **Renal Impairment**

Renal dysfunction is associated with an increased cimetidine half-life; the half-life is increased to 5 hours in anephric adults. Those with renal dysfunction require lower doses and/or increased intervals between doses.

- **Pediatrics**

Neonates
Cimetidine is effectively eliminated via hepatic metabolism as well as renal routes. Following administration of 15 to 20 mg/kg/day, the half-life ranges from 2.1 to 3.4 hours. The half-life decreases as total body clearance increases. Variabilities in clearance are primarily due to differences in renal development. Premature neonates generally require lower dosing rates and/or increased intervals between doses. Approximately 90% of a dose is recovered in the urine as cimetidine and its metabolites. Accumulation of cimetidine metabolites may occur with prolonged dosing.

Children
In children, the overall clearance of cimetidine is generally higher than that observed in adults; faster clearance is especially observed in the critically ill or children with burns. Increased clearance has also been reported in children with cystic fibrosis. Elimination half-lives for cimetidine, cimetidine sulfoxide, and hydroxymethyl cimetidine of 1.39, 2.6, and 4.7 hours, respectively are observed after a mean dose of cimetidine of 26 +/- 6.6 mg/kg/day administered intravenously over 15 minutes in four divided doses. With doses of 20 mg/kg/day or more, children exhibit plasma concentrations maintained at or above 0.5 mcg/mL for a significantly longer period of time when compared with lower daily doses.

Administration

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

Oral Administration

May be administered without regard to meals. Administer with food, water, or milk to minimize gastric irritation.
Do not administer concomitantly with antacids.

Injectable Administration

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

Intravenous Administration

IV Push
NOTE: Must be diluted before use. Do not use prefilled syringes for IV injection.
Do not administer any dosage > 300 mg via IV injection—see intermittent infusion.
Dilute to a maximum of 15 mg/mL using 0.9% Sodium Chloride for injection or other compatible IV solution.
Inject over a period of not less than 5 minutes. Do not inject rapidly; cardiac arrhythmias or hypotension may develop.

Intermittent IV infusion
Dilute dosage, not to exceed 300 mg, to a maximum of 6 mg/mL using 5% Dextrose for injection or other compatible IV solution.
If using ADD-Vantage vials, dilute in ADD-Vantage containers containing 50 or 100 mL of

0.9% Sodium Chloride for injection or 5% Dextrose for injection.
Infuse dosage over 15—20 minutes.
The diluted infusion is stable for 48 hours at room temperature.

Continuous IV infusion
Dilute up to 900 mg of cimetidine in 100—1000 mL of a compatible solution.
For IV infusion volumes less than 250 mL, a controlled infusion pump is recommended.
Adjust rate/hour according to individual patient dosage requirements.
The diluted infusion is stable for 48 hours at room temperature.

Intramuscular Administration

No dilution necessary.
Prefilled syringes are available. DO NOT USE PREFILLED SYRINGES FOR IV INJECTION.
Inject into a large muscle. Aspirate prior to injection to avoid injection into a blood vessel.

Maximum Dosage Limits

- **Adults**
  1200 mg/day PO for most indications, 1600 mg/day PO for GERD. Up to 2400 mg/day PO for pathologic hypersecretory conditions.
- **Geriatric**
  1200 mg/day PO for most indications, 1600 mg/day PO for GERD. Up to 2400 mg/day PO for pathologic hypersecretory conditions.
- **Adolescents**
  < 16 years: 40 mg/kg/day PO for most indications; data are limited.
  >= 16 years: 1200 mg/day PO or IV for most indications. 1600 mg/day PO for GERD. Up to 2400 mg/day PO for pathologic hypersecretory conditions.
- **Children**
  40 mg/kg/day PO or IV for most indications; data are limited.
- **Infants**
  40 mg/kg/day PO or IV; data are limited.
- **Neonates**
  20 mg/kg/day PO or IV; data are limited.

Dosage Forms

- Cimetidine 10% Topical cream, Lidocaine 5% Topical cream, Salicylic Acid 40% Topical cream with Compounding Base
- Cimetidine 200mg Oral tablet
- Cimetidine 300mg Oral tablet
- Cimetidine 400mg Oral tablet
- Cimetidine 800mg Oral tablet
- Cimetidine Bulk powder
- Cimetidine Hydrochloride 300mg/5mL Oral solution
- CVS Heartburn Relief 200mg Tablet
- GNP Heartburn Relief 200mg Tablet
- GoodSense Heartburn Relief 200mg Tablet
- Publix Acid Reducer 200mg Tablet
- Select Brand Cimetidine 200mg Tablet
- Tagamet HB 200mg Tablet
- Top Care Heartburn Relief 200mg Tablet
- Walgreens Cimetidine 200mg Tablet

Dosage Adjustment Guidelines

Hepatic Impairment

Recommendations vary with the degree of hepatic impairment exhibited by the patient, but no quantitative recommendations are available. In general, consider a decreased dosage for those patients with severe hepatic disease (e.g., Child-Pugh grade C cirrhosis).

Renal Impairment

CrCl 30 mL/min and higher: No specific recommendations are available.
CrCl less than 30 mL/min: The manufacturer recommends an adult dosage of 300 mg every 12 hours, PO or IV (intermittently), which reflects an approximate 50% reduction in daily usual dose. The hourly adult continuous infusion rate should be reduced by 50% (i.e.,: not to exceed 25 mg/hour or 600 mg/day in adults). Patients being treated for stress gastritis prophylaxis should receive half the recommended dose. Specific pediatric dose adjustment recommendations are not available. Dosing frequency for intermittent doses may be increased to every 8 hours if necessary, although the lowest frequency of dosing should be used, while assuring adequate patient response, as cimetidine accumulates in renal failure.

Intermittent Hemodialysis
Cimetidine is removed to some degree by hemodialysis. The patient's normal dosage

schedule based on CrCl should be adjusted, when possible, so that the timing of a regularly scheduled intermittent dose coincides with the end of a hemodialysis session.