Clinical Pharmacokinetics

A Systematic Review of Gastric Acid–Reducing Agent–Mediated Drug-Drug Interactions With Orally Administered Medications

Electronic Supplementary Material

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Supplementary Table 1 Medications with a Clinically Significant Gastric pH–Dependent Mechanism of Interaction With ARAs

Victim drug	ARA/ perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
Antineoplastic/chemotherapy agents					
Acalabrutinib [2]	Antacids	↓ acalabrutinib	pH-dependent solubility	▪ Coadministration with an antacid (1 g of calcium carbonate) decreased acalabrutinib AUC by 53% in healthy individuals ▪ Coadministration with a PPI (40 mg of omeprazole for 5 days) decreased acalabrutinib AUC by 43%	Separate dosing of acalabrutinib and antacids by at least 2 hours.
	H2RA				Take acalabrutinib 2 hours before taking the H2 receptor antagonist.
	PPIs				Avoid coadministration with PPI. Because of the long-lasting effect of PPIs, separation of doses may not eliminate the interaction with acalabrutinib.
Bosutinib [3, 4]	Antacids	↓ bosutinib	pH-dependent aqueous solubility in vitro	▪ In a drug interaction trial of 24 healthy volunteers, concomitant lansoprazole (60 mg) decreased C_{max} and AUC of bosutinib (400 mg) by 46% and 26%, respectively, relative to bosutinib alone	Administer antacids >2 hours before or after bosutinib.
	H2RA				Administer histamine H2RA >2 hours before or after bosutinib.
	PPIs				Consider alternatives to PPIs, such as antacids or H2RA.
Dasatinib [5–7]	Antacids	↓ dasatinib	pH-dependent; solubility based on nonclinical data	▪ The administration of 30 mL of aluminum hydroxide/magnesium hydroxide 2 hours prior to a single dose of dasatinib 50 mg in 24 healthy volunteers showed no relevant change in the mean AUC of dasatinib, but mean C_{max} increased by 26% ▪ The simultaneous administration of 30 mL of aluminum hydroxide/magnesium hydroxide with a single dose of dasatinib 50 mg in 24 healthy volunteers gave a 55% and 58% reduction in the mean AUC and mean C_{max}, of dasatinib, respectively	Consider the use of antacids in place of H2RA or PPIs. Administer the antacid at least 2 hours prior to or 2 hours after the dose of dasatinib. Avoid simultaneous administration of dasatinib with antacids.
	H2RA			▪ The administration of a single dose of dasatinib 50 mg 10 hours after famotidine 40 mg in 24 healthy volunteers reduced the mean AUC and C_{max} of dasatinib by 61% and 63%, respectively. Famotidine 40 mg taken 2 hours after dasatinib 50 mg was considered to have no effect on the AUC or C_{max} of	Do not administer H2RA with dasatinib.

Victim drug	ARA/ perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
				dasatinib ▪ In a study of 18 patients with chronic myeloid leukemia or Philadelphia chromosome–positive acute lymphoid leukemia who were administered dasatinib together with lansoprazole 30 mg, famotidine 20–40 mg/day, nizatidine 300 mg/day, or no acid suppressant, the median AUC was lower in those who took an H2 receptor antagonist or PPI vs those who did not (1.47 vs 3.51)	
	PPIs			▪ The administration of a single dose of dasatinib 100 mg 22 hours after omeprazole 40 mg at steady state in 14 healthy volunteers reduced the mean AUC of dasatinib by 43% and the mean C_{max} of dasatinib by 42% ▪ In a study of 18 patients with chronic myeloid leukemia or Philadelphia chromosome–positive acute lymphoid leukemia who were administered dasatinib together with lansoprazole 30 mg, famotidine 20–40 mg/day, nizatidine 300 mg/day, or no acid suppressant, the median AUC was lower in those who took an H2 receptor antagonist or PPI compared with those who did not (1.47 vs 3.51)	Do not administer PPIs with dasatinib.
Erlotinib [8–12]	Antacids	↓ erlotinib	pH-dependent solubility	▪ The effect of antacids on erlotinib PK has not been evaluated. However, from data on administration with H2RA and PPIs, the manufacturer suggests dose separation	If an antacid is necessary, dosing of antacid and erlotinib should be separated by several hours.
	H2RA			▪ When erlotinib was administered 2 hours following ranitidine 300 mg in 24 healthy volunteers, the AUC and C_{max} for erlotinib were reduced by 33% and 54%, respectively ▪ When erlotinib was administered with ranitidine 150 mg BID (at least 10 hours after the previous ranitidine evening dose and 2 hours before the ranitidine morning dose) in 24 healthy volunteers, the AUC and C_{max} for erlotinib were decreased by 15% and 17%, respectively ▪ A retrospective review of 544 patients taking erlotinib for non-small cell lung cancer found lower PFS and	Erlotinib must be taken 10 hours after the H2 receptor antagonist dosing and at least 2 hours before the next dose of the H2 receptor antagonist.

Victim drug	ARA/ perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
				OS in patients taking concomitant H2RA or PPIs compared with those not taking a gastric acid–reducing agent, indicating decreased efficacy of erlotinib	
	PPIs			▪ When omeprazole was coadministered with erlotinib in 24 healthy volunteers, the AUC and C_{max} for erlotinib decreased by 46% and 61%, respectively ▪ In a study of patients with non-small cell lung cancer, coadministration of 250 mL Coca-Cola Classic®, erlotinib (any dose), and omeprazole 40 mg led to 39% higher AUC and 42% higher C_{max} compared with the group who consumed omeprazole with water ▪ In a case report, a woman with non-small cell lung cancer taking erlotinib 150 mg QD exhibited subtherapeutic plasma concentrations of erlotinib during continuous infusion (8 mg/hr) of pantoprazole. Plasma concentrations of erlotinib returned to normal after switching to oral pantoprazole 40 mg BID ▪ A retrospective review of 544 patients taking erlotinib for non-small cell lung cancer found lower PFS and OS in patients taking concomitant H2RA or PPIs compared with those not taking a gastric acid–reducing agent, indicating decreased efficacy of erlotinib	Avoid concomitant use of PPIs and erlotinib if possible. Because PPIs affect the pH of the upper GI tract for an extended time, separation of doses may not eliminate the interaction.
Gefitinib [13–15]	Antacids	↓ gefitinib	pH-dependent solubility	▪ Concurrent use of ranitidine and sodium bicarbonate (to achieve and maintain gastric pH >5.0) in healthy volunteers was associated with an average 47% decrease in gefitinib AUC and 71% decrease in C_{max} ▪ A retrospective study of patients with non-small cell lung cancer found that gefitinib AUC tended to be lower in those concomitantly taking an H2 receptor antagonist and was significantly lower in those concomitantly taking a PPI ▪ The label for gefitinib cautions that concurrent use of drugs that cause sustained elevations in gastric pH (including antacids) may decrease gefitinib plasma concentrations, potentially reducing clinical efficacy	Take gefitinib 6 hours before or after taking an antacid.
	H2RA				Take gefitinib 6 hours before or after taking an H2 receptor antagonist.
	PPIs				Avoid concomitant use of gefitinib with PPIs, if possible. If treatment with a PPI is required, take gefitinib 12 hours after the last dose or 12 hours before the next dose of a PPI.

Victim drug	ARA/ perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
Lapatinib [16–18]	Antacids	↓ lapatinib	pH-dependent solubility and absorption	▪ According to the U.K. label for lapatinib, lapatinib exposure (1250 mg QD) was an average of 27% lower (range, 6%–49%) following pretreatment with esomeprazole 40 mg in women with metastatic HER2+ breast cancer ▪ The U.K. label recommends that combined use of lapatinib with drugs that increase gastric pH should be avoided; however, the US label for lapatinib states that the effect of esomeprazole (40 mg/day for 7 days) on lapatinib exposure was not clinically relevant, resulting in no such labeled warning	According to the US label, no change is needed. However, the U.K. label recommends avoiding the use of antacids with lapatinib.
	H2RA				According to the US label, no change is needed. However, the U.K. label recommends avoiding the use of H2RA with lapatinib.
	PPIs				According to the US label, no change is needed. However, the U.K. label recommends avoiding the use of PPIs with lapatinib.
Neratinib [19, 20]	Antacids	↓ neratinib	pH-dependent solubility	▪ The use of antacids and neratinib has not been evaluated in a clinical study	Separate dosing of neratinib by 3 hours after antacids.
	H2RA			▪ When neratinib (240 mg) was administered 2 hours before ranitidine 150 mg BID (administered in morning and evening, ~12 hours apart), neratinib C_{max} was reduced by 44% and AUC by 32%	Take neratinib at least 2 hours before an H2RA or 10 hours after an H2RA.
	PPIs			▪ In a PK study of 15 healthy volunteers, lansoprazole (30 mg once daily for 7 days) decreased the AUC and C_{max} for neratinib (240-mg single oral dose taken on day 5) by 65% and 71%, respectively	Avoid concomitant use of PPIs and neratinib.
Nilotinib [21–25]	Antacids	↓ nilotinib	pH-dependent solubility	▪ No significant change in nilotinib PK was observed when a single dose of nilotinib 400 mg was administered either 2 hours before or after an antacid (eg, aluminum hydroxide, magnesium hydroxide, simethicone) in healthy volunteers ▪ Healthy volunteers who received nilotinib 400 mg and calcium carbonate 4000 mg 15 minutes before nilotinib showed no change in nilotinib PK	As an alternative to PPIs, use antacids ~2 hours before or after nilotinib.
	H2RA			▪ The PK of nilotinib did not change significantly when a single dose of nilotinib 400 mg was administered 10 hours after and 2 hours before famotidine in healthy volunteers ▪ A retrospective analysis of patients with newly diagnosed Philadelphia chromosome–positive chronic myeloid leukemia found that concurrent use of	As an alternative to PPIs, use H2RA ~10 hours before or ~2 hours after the dose of nilotinib.

Victim drug	ARA/ perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
				nilotinib and H2RA or PPIs did not affect the efficacy of nilotinib	
	PPIs			▪ Coadministration of multiple doses of esomeprazole at 40 mg daily and nilotinib 400 mg decreased the nilotinib AUC by 34% and C_{max} by 27% ▪ A retrospective analysis of patients with newly diagnosed Philadelphia chromosome–positive chronic myeloid leukemia found that concurrent use of nilotinib and H2RA or PPIs did not affect the efficacy of nilotinib	Avoid concomitant use of PPIs with nilotinib.
Pazopanib [26–29]	Antacids	↓ pazopanib	pH-dependent solubility	▪ No formal study with antacids has been conducted. However, on the basis of data for esomeprazole, the package label advises separation with antacid use	Avoid the use of antacids in combination with pazopanib whenever possible. Separate doses by several hours if antacid treatment is considered necessary. The effect of dose separation has not been investigated.
	H2RA			▪ A retrospective analysis of phase 2 and 3 trials in patients with soft tissue sarcoma found an association between long-term concomitant use of pazopanib with H2RA or PPIs and significantly shorter PFS and OS ▪ However, another retrospective analysis of patients with metastatic renal cell carcinoma found no significant differences in PFS or OS with the use of H2RA or PPIs with pazopanib ▪ The package label indicates to avoid use of drugs that increase the gastric pH	Avoid the use of H2RA in combination with pazopanib.
	PPIs			▪ Concomitant administration of pazopanib with the PPI esomeprazole decreased the AUC and C_{max} of pazopanib by 40% and 42%, respectively, in a drug interaction trial in patients with solid tumors ▪ A retrospective analysis of phase 2 and 3 trials in patients with soft tissue sarcoma found an association between long-term concomitant use of pazopanib with H2RA or PPIs and significantly shorter PFS and OS ▪ However, another retrospective analysis of patients with metastatic renal cell carcinoma found no significant differences in PFS or OS with the use of H2RA or PPIs with pazopanib	Avoid the use of PPIs in combination with pazopanib.

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Anti-infective agents					
Atazanavir [30–33]	Antacids	↓ atazanavir	pH-dependent solubility	▪ According to the prescribing information, reduced plasma concentrations of atazanavir are expected with antacid coadministration	Atazanavir should be taken 2 hours before or 1 hour after antacids to minimize the risk of a clinically significant interaction.
	H2RA			▪ In a study of 40 HIV-positive individuals, the AUC and C_{max} of atazanavir each decreased by 23% when atazanavir/ritonavir (300 mg/100 mg QD) was simultaneously taken with famotidine 40 mg BID. Coadministration of famotidine 20 mg BID did not significantly change atazanavir exposure. In a separate phase of the same study, the AUC of atazanavir was an average of 21%–24% lower in those taking famotidine (20 mg to 40 mg BID, taken 2 hours before and 10 hours after antiviral administration) with both tenofovir 300 mg/day (a reverse transcriptase inhibitor) and atazanavir/ritonavir (300 mg/100 mg daily) ▪ According to the atazanavir prescribing information, administration of famotidine 40 mg BID simultaneously with atazanavir 400 mg daily in 15 healthy individuals decreased the AUC of atazanavir by 41%. Use of ritonavir-boosted therapy (atazanavir 300 mg with ritonavir 100 mg daily) under the same study conditions decreased the AUC of atazanavir by an average of 18% ▪ In a study of healthy volunteers, ranitidine 150 mg reduced the AUC and C_{max} of the boosted atazanavir (atazanavir/ritonavir 300/100 mg QD) by 48% and 52%, respectively	Monitor closely for reduced effects of atazanavir in all patients receiving H2RA. *For treatment-naive adult patients:* Patients receiving ritonavir-boosted therapy should take atazanavir 300 mg/ritonavir 100 mg QD with food simultaneously with and/or 10 hours after doses of H2RA (up to famotidine 40 mg BID or equivalent). Those unable to tolerate ritonavir should take atazanavir 400 mg QD with food at least 2 hours before and at least 10 hours after a dose of the H2RA (a single dose should not exceed a dose comparable to famotidine 20 mg, with a total daily dose not exceeding one comparable to famotidine 40 mg). The use of atazanavir without ritonavir is not recommended in pregnant women. *For HIV treatment–experienced adult patients:* Patients taking atazanavir and ritonavir should not exceed an H2 receptor antagonist dose comparable to famotidine 20 mg BID. Atazanavir and ritonavir should be taken simultaneously with and/or at least 10 hours after the H2RA. Recommended doses are: • Atazanavir 300 mg/ritonavir 100 mg QD (as a single dose with food) if taken with an H2RA • Atazanavir 400 mg/ritonavir 100 mg QD (as a single dose with food) if taken with both an H2RA and

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					tenofovir disoproxil fumarate Pregnant women in the 2nd or 3rd trimester should receive atazanavir 400 mg/ritonavir 100 mg QD (as a single dose with food) if taken with either an H2RA or tenofovir disoproxil fumarate. It is not recommended that pregnant women in the 2nd or 3rd trimester receive atazanavir with both an H2RA and tenofovir disoproxil fumarate.
	PPIs			▪ Coadministration of omeprazole 40 mg QD reduced the AUC of unboosted atazanavir (400 mg QD) by 94% and C_{max} by 96% (n = 16) ▪ Similarly, in a study of 10 healthy volunteers, coadministration of atazanavir 400 mg with lansoprazole 60 mg decreased the AUC_{0-24} of atazanavir by 94% and C_{max} by 91% ▪ With ritonavir-boosted therapy (atazanavir 300 mg with ritonavir 100 mg QD), the AUC of atazanavir was decreased by 76% and C_{max} by 72% with coadministration of omeprazole 40 mg ▪ In another study, omeprazole 20 mg QD reduced the AUC and C_{max} of the boosted atazanavir (atazanavir/ritonavir 300/100 mg QD) by 42% and 39%, respectively ▪ In a study of healthy volunteers, omeprazole 40 mg QD reduced the AUC and C_{max} of the boosted atazanavir (atazanavir/ritonavir 300/100 mg QD) by 62% and 59%, respectively	*For treatment-naive adult patients:* PPI dose should not exceed one comparable to omeprazole 20 mg and should be taken ~12 hours before atazanavir 300 mg/ritonavir 100 mg. *For HIV treatment–experienced adult patients:* The manufacturer of atazanavir recommends against concomitant use with PPIs in HIV treatment–experienced patients because of the potential for reduced efficacy of atazanavir and development of resistance.
Cefditoren pivoxil [34]	Antacids	↓ cefditoren	pH-dependent absorption	▪ The AUC of cefditoren 400 mg (single dose) decreased by 11% and the C_{max} decreased by 14% when coadministered with a single dose of an antacid containing magnesium hydroxide 800 mg and aluminum hydroxide 900 mg following a meal. The absorption of the cephalosporin appears to be impaired by the antacid. The clinical significance of this interaction is unknown	The prescribing information for cefditoren pivoxil recommends avoiding the concomitant use of antacids. Consider alternative methods to minimize/control acid reflux (e.g., diet modification) or alternative antimicrobial therapy.
	H2RA			▪ The AUC of cefditoren 400 mg (single dose) decreased by 22% and the C_{max} decreased by 27%	The prescribing information for cefditoren pivoxil recommends against concomitant use

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				when coadministered with a single dose of famotidine 20 mg following a meal. The clinical significance of this interaction is unknown	with H2RA. Alternative methods to minimize/control acid reflux (e.g., diet modification) should be considered. If the use of an H2RA cannot be avoided, alternative antimicrobial therapy can be considered.
	PPIs			▪ No information was available on the potential interaction of cefditoren pivoxil with PPIs	If possible, avoid the use of cefditoren pivoxil with PPIs. Consider the use of alternative methods to minimize/control acid reflux (e.g., diet modification) or the use of alternative antimicrobial therapy if the use of PPIs cannot be avoided.
Cefpodoxime proxetil [35–37]	Antacids (sodium bicarbonate and aluminum hydroxide)	↓ cefpodoxime	pH-dependent absorption	▪ The AUC of cefpodoxime proxetil (200 mg) decreased by 37% when administered 10 minutes after aluminum/magnesium hydroxide (7.68 g/mL) and by 41% with sodium bicarbonate (12.6 g in 240 mL) relative to maximal acid stimulation with pentagastrin in healthy volunteers; C_{max} decreased by 35% and 50%, respectively ▪ Concomitant administration of cefpodoxime proxetil and high doses of antacids (sodium bicarbonate and aluminum hydroxide) decreased cefpodoxime C_{max} and AUC by 24% and 27%, respectively ▪ When cefpodoxime proxetil 0.2 mg was administered 15 minutes after Maalox® 70 (600 mg magnesium hydroxide, 900 mg aluminum hydroxide) in healthy volunteers, the cefpodoxime C_{max} was decreased by 36%	If initiating the use of an antacid or increasing the dose of antacid, monitor for decreased therapeutic effects of oral cefpodoxime proxetil. Consider administering antacids and cefpodoxime proxetil at least 2 hours apart.
	H2RA			▪ The AUC of cefpodoxime decreased by 38% after two doses of ranitidine (administered 10 and 2 hours prior to cefpodoxime proxextil) relative to maximal acid stimulation with pentagastrin in healthy volunteers; C_{max} decreased by 43% ▪ Concomitant administration of H2RA with cefpodoxime proxetil decreased cefpodoxime C_{max} and AUC by 42% and 32%, respectively ▪ When cefpodoxime proxetil 0.2 mg was administered 1 hour after famotidine 40 mg in healthy volunteers, the cefpodoxime C_{max} was decreased by 48%	Separate oral doses of cefpodoxime proxetil and H2RA by at least 2 hours.

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	PPIs			▪ While data for both antacids and H2RA suggest an increase in gastric pH may reduce cefpodoxime exposure, no direct studies of PPIs and cefpodoxime proxetil have confirmed this interaction	Monitor for decreased therapeutic effects of oral cefpodoxime if a PPI is initiated or PPI dose is increased. Consider administering antacids or an H2RA, separated from cefpodoxime proxetil administration by 2 hours, in place of a PPI when clinically appropriate.
Cefuroxime axetil [38–40]	Antacids	↓ cefuroxime	pH-dependent absorption	▪ In a clinical study of 6 healthy volunteers, the C_{max} of cefuroxime (taken as a single dose of cefuroxime axetil 1000 mg) decreased when coadministered with a combination of ranitidine and sodium bicarbonate, but the AUC was not significantly affected ▪ In contrast, in a pharmacokinetic study of 7 patients receiving dialysis, a single dose of aluminum hydroxide 1000 mg administered prior to a single dose of cefuroxime axetil 1000 mg had no effect on the AUC or C_{max} of cefuroxime ▪ The prescribing information for cefuroxime axetil states that drugs that reduce gastric acidity may reduce the bioavailability of cefuroxime	Administer cefuroxime axetil at least 1 hour before or 2 hours after short-acting antacids.
	H2RA			▪ The prescribing information of cefuroxime axetil states that the concomitant use of cefuroxime axetil and H2RA should be avoided because drugs that reduce gastric acidity may reduce the bioavailability of cefuroxime	Avoid concomitant use of oral cefuroxime axetil and H2RA.
	PPIs			▪ The pharmacokinetics of cefuroxime axetil during the concomitant use of cefuroxime and PPIs has not been evaluated in a clinical study, but the prescribing information of cefuroxime axetil states that concomitant use of PPIs should be avoided because of potential reduced bioavailability of cefuroxime axetil	Avoid concomitant use of oral cefuroxime axetil and PPIs.
COMPLERA® (emtricitabine, rilpivirine hydrochloride, tenofovir disoproxil fumarate) [41]	Antacids	↓ rilpivirine, loss of virologic response, and possible resistance to rilpivirine or to the class of NNRTIs	pH-dependent absorption	▪ Separation is warranted according to instructions in package insert	Antacids should be administered at least 2 hours before or at least 4 hours after COMPLERA®.
	H2RA			▪ In a DDI study of famotidine 40 mg taken 2 hours before COMPLERA®, AUC and C_{max} decreased by 76% and 85%, respectively ▪ When famotidine 20 mg was administered 12 hours	H2RA should be taken at least 12 hours before or at least 4 hours after COMPLERA®.

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				before COMPLERA®, the rilpivirine AUC decreased by 9% and C_{max} decreased by 1% ▪ When famotidine 40 mg was administered 4 hours after COMPLERA®, the rilpivirine AUC increased by 13% and C_{max} increased by 21%	
	PPIs			▪ In a DDI study of 16 individuals, the AUC of rilpivirine decreased by 40% when COMPLERA® was coadministered with omeprazole 20 mg QD. In addition, the C_{max} decreased by 40%	PPI use is a contraindication for COMPLERA®; consider an alternative agent.
Delavirdine [42]	Antacids	↓ delavirdine	pH-dependent absorption	▪ According to the prescribing information, the AUC of delavirdine 300 mg (single oral dose) decreased by 44% and the C_{max} by 52% when administered simultaneously with a magnesium-/aluminum-containing antacid (Maalox® TC)	Patients taking both delavirdine and antacids should take them at least 1 hour apart.
	H2RA			▪ Specific studies addressing the possible interaction between H2RA and delavirdine are lacking. However, because delavirdine exhibits pH-dependent solubility, the prescribing information for delavirdine recommends avoiding long-term acid suppression with delavirdine because of the possibility of decreased exposure	Long-term use of H2RA in combination with delavirdine is not recommended.
	PPIs			▪ Specific studies addressing the possible interaction between PPIs and delavirdine are lacking, but because delavirdine exhibits pH-dependent solubility, the delavirdine prescribing information recommends avoiding long-term acid suppression with delavirdine owing to the possibility of decreased exposure	Long-term use of PPIs in combination with delavirdine is not recommended.
EPCLUSA® (sofosbuvir/ velpatasvir) [43]	Antacids	↓ velpatasvir	pH-dependent solubility of velpatasvir	▪ Instructions as per the sofosbuvir/velpatasvir package insert mandates separate administration of antacids and sofosbuvir/velpatasvir; however, clinical data are not available for interaction	Separate the administration of velpatasvir and antacids by at least 4 hours.
	H2RA			▪ In 60 patients receiving a single dose of famotidine 40 mg administered simultaneously with sofosbuvir/velpatasvir 400/100 mg, the AUC and C_{max} decreased by 18% and 8%, respectively, for sofosbuvir and by 20% and 19%, respectively, for velpatasvir	H2RA may be taken simultaneously or 12 hours apart from sofosbuvir/velpatasvir at a dose that does not exceed doses comparable to famotidine 40 mg BID.

Victim drug	ARA/ perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
				▪ In 60 patients receiving a single dose of famotidine 40 mg administered 12 hours prior to sofosbuvir/velpatasvir 400/100 mg, the AUC and C_{max} decreased by 20% and 23%, respectively, for sofosbuvir and by 15% and 13%, respectively, for velpatasvir	
	PPIs			▪ In 60 patients receiving omeprazole 20 mg QD simultaneously with sofosbuvir/velpatasvir 400/100 mg under fasting conditions, the AUC and C_{max} decreased by 29% and 34%, respectively, for sofosbuvir and by 36% and 37%, respectively, for velpatasvir ▪ In 60 patients receiving omeprazole 20 mg QD 12 hours prior to sofosbuvir/velpatasvir 400/100 mg under fasting conditions, the AUC and C_{max} decreased by 44% and 45%, respectively, for sofosbuvir and by 55% and 57%, respectively, for velpatasvir ▪ When omeprazole 20 mg QD was administered 2 hours prior to sofosbuvir/velpatasvir 400/100 mg in 40 patients in the fed state, there was a 16% decrease in C_{max} of sofosbuvir, an 8% increase in AUC of sofosbuvir, a 48% decrease in C_{max} of velpatasvir, and a 38% decrease in AUC of velpatasvir ▪ When omeprazole 20 mg QD was administered 4 hours after sofosbuvir/velpatasvir 400/100 to 38 patients in the fed state, results show a 21% decrease in C_{max} of sofosbuvir, a 5% increase in AUC of sofosbuvir, a 33% decrease in C_{max} of velpatasvir, and a 26% decrease in AUC of velpatasvir ▪ When omeprazole 40 mg QD was administered 4 hours after sofosbuvir/velpatasvir 400/100 to 40 patients in the fed state, the AUC and C_{max} decreased by 9% and 30%, respectively, for sofosbuvir and by 53% and 56%, respectively, for velpatasvir	Coadministration of omeprazole or other PPIs is not recommended. If coadministration is medically necessary, sofosbuvir/velpatasvir should be taken with food and taken 4 hours before omeprazole 20 mg. Use with other PPIs has not been studied.
HARVONI® (ledipasvir and sofosbuvir) [44, 45]	Antacids	↓ ledipasvir	pH-dependent solubility of ledipasvir	▪ Although no clinical studies have been conducted, the prescribing information for the ledipasvir/sofosbuvir combination product states that the solubility of ledipasvir decreases with increasing gastric pH. As such, drugs that increase gastric pH (e.g., antacids) are	It is recommended to separate antacid and HARVONI® administration by 4 hours.

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				expected to decrease serum concentrations of ledipasvir	
	H2RA			▪ In 12 patients receiving famotidine 40 mg simultaneously with ledipasvir/sofosbuvir 90/400 mg, the AUC and C_{max} for ledipasvir decreased by 11% and 20%, respectively; in contrast, the AUC and the C_{max} for sofosbuvir increased by 11% and 15%, respectively ▪ When famotidine 40 mg was given 12 hours prior to ledipasvir/sofosbuvir 90/400 mg, the AUC and the C_{max} for ledipasvir decreased by 2% and 17%, respectively; the AUC for sofosbuvir decreased by 5%, and there was no change in C_{max}	H2RA may be administered simultaneously with or 12 hours apart from ledipasvir/sofosbuvir at a dose that does not exceed doses comparable to famotidine 40 mg BID.
	PPIs			▪ In 16 patients receiving omeprazole 20 mg QD simultaneously with ledipasvir/sofosbuvir 90/400 mg, the AUC and C_{max} of ledipasvir decreased by 4% and 11%, respectively; no change in the AUC of sofosbuvir was observed, with a 12% increase in C_{max} ▪ When omeprazole 20 mg once daily was given 2 hours prior to 30 mg of ledipasvir alone in 17 individuals, there was a 48% decrease in C_{max} and a 42% decrease in AUC ▪ A retrospective review determined that patients taking PPI BID had lower sustained virologic response at 12 weeks after treatment completion	PPI doses comparable to omeprazole 20 mg or lower can be administered simultaneously with ledipasvir/sofosbuvir under fasting conditions.
Indinavir[46–48]	H2RA	↓ indinavir	pH-dependent dissolution and absorption	▪ Coadministration of indinavir 400 mg and cimetidine 600 mg BID resulted in small changes to the indinavir AUC (2% decrease) and C_{max} (7% increase)	Monitor for decreased therapeutic effects of indinavir if an H2RA is initiated/dose increased or for increased effects if an H2RA is discontinued/dose decreased.
	PPIs			▪ Coadministration of omeprazole 20 or 40 mg with indinavir 800 mg significantly reduced the indinavir AUC from 30.0 to 19.7 or 16.0 mg × hour/L, respectively ▪ Indinavir 800 mg with ritonavir 200 mg and omeprazole 40 mg resulted in a significant increase in the mean indinavir AUC from 30.0 to 46.6 mg × hour/L; mean omeprazole concentrations were not	Monitor for decreased therapeutic effects of indinavir if a PPI is initiated/dose increased or for increased effects if a PPI is discontinued/dose decreased.

Victim drug	ARA/ perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
				affected ▪ In addition, a retrospective review of 9 patients receiving both indinavir 800 mg TID and omeprazole 20–40 mg QD found that 4 patients had a lower AUC value for indinavir than expected, based on population values	
Itraconazole [49–56]	Antacids	↓ itraconazole	pH-dependent absorption	▪ The C_{max} and AUC of itraconazole were reduced by an average of 70% and 66%, respectively, when itraconazole 200 mg (capsules) was administered with an antacid (aluminum hydroxide/magnesium hydroxide 220/120 mg in 240 mL) in a study of 12 healthy volunteers. In addition, absorption appeared to be delayed, with a 2 hour increase in the time to C_{max} (5.1 vs 3 hours)	The prescribing information for itraconazole states to use drugs that reduce gastric acidity with caution. Administer itraconazole at least 2 hours before or 2 hours after administration of any antacids. Itraconazole oral suspension may be less sensitive to the effects of decreased gastric acidity. In addition, itraconazole may be given with an acidic beverage (such as a cola that is not diet cola) to avoid possible interaction.
	H2RA			▪ Administration of itraconazole 200 mg in 12 healthy volunteers who had been pretreated with famotidine (40 mg × 2 doses) was associated with an average reduction of 53% and 51% in C_{max} and AUC of itraconazole, respectively ▪ Similarly, administration of itraconazole 200 mg with famotidine 40 mg was associated with an average reduction of 34% (peak)–39% (trough) in itraconazole concentrations in a study of patients undergoing chemotherapy for hematologic malignancies ▪ Concurrent use of ranitidine was associated with reductions of 47% and 52% in the AUC and C_{max} of itraconazole, respectively, in a study of 30 healthy volunteers who received itraconazole 200 mg following pretreatment with ranitidine 150 mg BID × 3 days. Equivalent bioavailability of itraconazole to itraconazole alone was seen when itraconazole was administered with 8 ounces of a cola beverage with concurrent use of ranitidine	The prescribing information for itraconazole states to use drugs that reduce gastric acidity with caution. Administer itraconazole at least 2 hours before or 2 hours after administration of H2RA. When using itraconazole with an H2RA, the itraconazole may be administered with a non-diet cola beverage (8 ounces) to ameliorate this interaction. Itraconazole oral suspension may be less sensitive to the effects of decreased gastric acidity. Monitor patients closely for signs of inadequate clinical response to itraconazole.

Victim drug	ARA/ perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
	PPIs			▪ The AUC and C_{max} of itraconazole were 64% and 66% lower, respectively, when itraconazole 200 mg QD (capsule) was administered after 14 days of omeprazole 40 mg daily in a study of 11 healthy volunteers ▪ Conversely, when itraconazole 400 mg (oral solution) was administered to healthy volunteers who had been pretreated with omeprazole 40 mg daily for 7 days, no significant differences were seen for the AUC and C_{max} of itraconazole	The prescribing information for itraconazole states to use drugs that reduce gastric acidity with caution. Administer itraconazole at least 2 hours before or 2 hours after administration of PPIs. When possible, consider avoiding concomitant administration of itraconazole capsules with a PPI to eliminate the risk of itraconazole therapeutic failure. Use of itraconazole oral solution (instead of the capsule) or administration of itraconazole with an acidic beverage (e.g., cola) may represent alternatives that could minimize the significance of this interaction. Monitor response to itraconazole closely when used together with a PPI.
Raltegravir [57–59]	Aluminum- and/or magnesium-containing antacids	↓ raltegravir	pH-dependent solubility	▪ When a single 20-mL dose of aluminum and magnesium hydroxide antacid was given with raltegravir 400 mg BID to 25 patients, there was a 49% reduction in AUC and a 44% reduction in C_{max} ▪ In further studies spacing the administration of aluminum and magnesium hydroxide antacid by 2, 4, or 6 hours before or after raltegravir 400 mg BID, the AUC and C_{max} continued to be consistently reduced (range, 11%–51% and range, 10%–51%, respectively), which was due to the antacid ▪ When a single 20-mL dose of aluminum and magnesium hydroxide antacid was given 12 hours after a single dose of raltegravir 1200 mg to 19 patients, there was a 14% reduction in both AUC and C_{max} ▪ When 30 mL of Maalox® Plus Extra Strength was given to 12 patients with a single dose of raltegravir 400 mg, there was no significant difference in AUC or C_{max}, but raltegravir concentration at 12 hours post dose was 67% lower, and an earlier time to C_{max} was seen (1 vs 3 hours)	Coadministration or staggered administration is not recommended for raltegravir 400 mg and raltegravir 1200 mg.

Victim drug	ARA/ perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
	Calcium carbonate antacid			▪ When a single dose of calcium carbonate antacid 3000 mg was given with raltegravir 400 mg BID to 24 patients, there was a 52% decrease in C_{max} and a 55% decrease in AUC ▪ When a single dose of calcium carbonate antacid 3000 mg was given with a single dose of raltegravir 1200 mg in 19 patients, there was a 74% decrease in C_{max} and a 72% decrease in AUC ▪ Small decreases in C_{max} (2%) and AUC (10%) were seen when a single dose of calcium carbonate antacid 3000 mg was given 12 hours after a single dose of raltegravir 1200 mg	For raltegravir, no dose adjustment is required. For high-dose raltegravir, coadministration is not recommended.
	PPI	↓ raltegravir	pH-dependent solubility	▪ When omeprazole 20 mg QD was given with raltegravir 400 mg BID in 18 HIV-infected patients, there was a 51% increase in C_{max} and a 37% increase in AUC ▪ When 14 healthy volunteers were given omeprazole 20 mg QD with a single dose of raltegravir 400 mg, the geometric mean ratio of raltegravir + omeprazole to raltegravir alone was 3.12 for AUC and 4.15 for C_{max}	No dose adjustment is necessary when raltegravir 400 mg BID or 1200 mg QD is coadministered with omeprazole.
Ketoconazole [60–65]	Antacids	↓ ketoconazole	pH-dependent dissolution	▪ The absorption of ketoconazole 200 mg was reduced by ~95% in 3 healthy volunteers when administered with oral sodium bicarbonate 500 mg 2 hours after a dose of cimetidine 400 mg ▪ In a study under fasting conditions, the AUC of ketoconazole 200 mg was ~40% lower in 4 patients receiving concurrent aluminum hydroxide/magnesium hydroxide (Maalox®) 30 mL compared to 10 patients who took ketoconazole alone	Administer oral ketoconazole at least 2 hours prior to or 1 hour after use of any antacid product. When cotreated with drugs that reduce gastric acidity, ketoconazole should be taken with an acidic beverage such as non-diet cola. Monitor patients closely for signs of inadequate clinical response to ketoconazole.
	H2RA			▪ In a study of 6 healthy volunteers, when ketoconazole was given with ranitidine 150 mg BID (started 2 days prior to ketoconazole 400 mg), the mean AUC and C_{max} of ketoconazole were reduced by approximately 95% and 93%, respectively ▪ Similarly, reductions of >50% in ketoconazole bioavailability have been reported from other studies with cimetidine	When cotreated with drugs that reduce gastric acidity, ketoconazole should be taken with an acidic beverage such as non-diet cola. Monitor patients closely for signs of inadequate clinical response to ketoconazole.

Victim drug	ARA/ perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
	PPIs		pH-dependent dissolution	▪ The AUC of ketoconazole 200 mg decreased by ~83% in 9 healthy volunteers when administered concomitantly with omeprazole 60 mg. The AUC decreased by 35% when these drugs were taken concomitantly with the acidic (pH 2.5) beverage Coca-Cola Classic®	When cotreated with drugs that reduce gastric acidity, ketoconazole should be taken with an acidic beverage such as non-diet cola. Monitor patients closely for signs of inadequate clinical response to ketoconazole.
Nelfinavir [66–68]	H2RA	↓ nelfinavir	pH-dependent solubility	▪ In a study of 20 healthy volunteers, concurrent use of nelfinavir with the PPI omeprazole was associated with an ~40% reduction in nelfinavir concentration ▪ Considering the pH-dependent solubility of nelfinavir (poor solubility at pH greater than 4.0) and the effect of PPIs on pH, it is likely that increased pH due to omeprazole contributed at least somewhat to this interaction. As a result, a similar interaction may be seen with concurrent use of H2RA, which are also capable of increasing gastric pH. With no specific data available regarding this possible interaction, the magnitude and clinical relevance of this interaction remain unclear	Monitor the concentration of and response to nelfinavir closely when using nelfinavir together with an H2RA.
	PPIs		pH-dependent solubility and CYP2C19 inhibition	▪ When nelfinavir 1250 mg BID was administered concurrently with omeprazole 40 mg daily for 4 days in a study of 19 patients, the AUC and C_{max} of nelfinavir decreased by 36% and 37%, respectively ▪ In a study of 20 healthy volunteers, the AUC, C_{max}, and C_{min} of nelfinavir decreased by an average of 36%, 37%, and 39%, respectively, when nelfinavir 1250 mg was administered every 12 hours concurrently with omeprazole 40 mg daily for 4 days. In addition, the AUC, C_{max}, and C_{min} of the active metabolite M8 of nelfinavir decreased by 92%, 89%, and 75%, respectively, with concurrent administration of omeprazole. On the basis of these changes, the authors of this study recommend avoiding use of omeprazole in patients receiving nelfinavir ▪ A cohort study found that the concomitant use of PPIs and nelfinavir did not have a great effect on achievement of an undetectable HIV viral load, but that there was a 51% increased risk of virologic rebound. Use of PPIs for <30 days was not associated	The nelfinavir package insert states that concomitant use of PPIs and nelfinavir may lead to a loss of virologic response and development of resistance.

Victim drug	ARA/ perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
				with an increased risk of virologic rebound	
Posaconazole oral suspension [69–75]	H2RA	↓ of posaconazole	pH-dependent dissolution	▪ The mean C_{max} and AUC of posaconazole (tablets, 200 mg/day × 10 days) were each reduced by 39% following coadministration with cimetidine (400 mg BID × 10 days) in a study of healthy volunteers ▪ According to the prescribing information for posaconazole, the presumed mechanism of this interaction is cimetidine-mediated alteration of gastric pH. Despite these data with cimetidine and the presumed pH-based mechanism, the posaconazole prescribing information recommends avoiding concurrent use of cimetidine but notes that clinically relevant bioavailability changes have not been observed with other H2RA, suggesting that no dose adjustments are necessary. However, in response to questions regarding this apparently conflicting recommendation (i.e., prolonged/sustained pH changes may be associated with altered posaconazole bioavailability, but cimetidine somehow is unique among the H2RA for its interaction potential), some authors have argued that the recommendation to avoid concurrent use when possible should be extended to all H2RA ▪ In contrast, concomitant administration of ranitidine 150 mg BID led to minimal effects on the C_{max} (4% increase) and AUC (3% decrease) of posaconazole delayed-release tablets 400 mg in healthy volunteers ▪ Adding to this uncertainty are a series of studies examining factors associated with posaconazole concentrations and/or clearance in cohorts of patients with multiple serum posaconazole concentration determinations. Estimates of PK of posaconazole found that concomitant ranitidine had no effect. In contrast, another analysis identified concurrent ranitidine as being significantly associated with lower posaconazole concentrations in a multiple linear regression analysis	Avoiding the concomitant use of cimetidine and esomeprazole with posaconazole oral suspension is recommended unless the benefit outweighs the risks. However, if concomitant administration is required, close monitoring for breakthrough fungal infections is recommended. No clinically relevant effects were observed when posaconazole oral suspension was concomitantly used with antacids and H2RA other than cimetidine. No dosage adjustment of posaconazole oral suspension is required when posaconazole oral suspension is concomitantly used with antacids and H2RA other than cimetidine. The prescribing information states that use of posaconazole delayed-release tablets with an H2RA requires no dosage adjustment. Famotidine, when prepared in 5% dextrose in water or 0.9% sodium chloride, is listed in the prescribing information as being compatible with intravenous line administration of posaconazole.

Victim drug	ARA/ perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
	PPIs			▪ In healthy volunteers who received a single dose of posaconazole 400 mg (40 mg/mL suspension) with esomeprazole 40 mg daily for 3 days (starting 2 days prior to posaconazole), the mean C_{max} and AUC of posaconazole decreased by 46% and 32%, respectively. Coadministration of posaconazole, esomeprazole, and an acidic carbonated beverage led to smaller decreases in the C_{max} and AUC of posaconazole (33% and 21%, respectively) ▪ Another study in healthy volunteers found similar results: when posaconazole (10 mL of 40 mg/mL suspension) and esomeprazole 40 mg QD were coadministered, the C_{max} and AUC of posaconazole decreased by 79% and 84%, respectively. Coadministration of posaconazole, espomeprazole, and 330 mL of Coca-Cola led to decreases in the C_{max} and AUC of posaconazole of 53% and 73%, respectively ▪ The prescribing information for posaconazole also states that there was no significant effect on the pharmacokinetics of posaconazole delayed-release tablets with concurrent esomeprazole 40 mg. However, a 46% reduction in C_{max} and a 32% reduction in AUC was seen with concomitant posaconazole oral suspension 400 mg and esomeprazole 40 mg ▪ In addition, a pharmacokinetic model developed using data from 84 patients with acute myeloid leukemia or myelodysplastic syndrome receiving prophylactic posaconazole identified that the concurrent use of pantoprazole was associated with a significant (1.6-fold) increase in the apparent oral clearance of posaconazole ▪ An earlier study by the same group that was based on data from 32 patients found that concurrent use of pantoprazole was significantly associated with the apparent clearance of posaconazole ▪ A multiple linear regression analysis identified concurrent PPIs as being significantly associated with	Avoid the concurrent use of a PPI in patients taking the posaconazole oral suspension when possible because of the risk for decreased posaconazole absorption and impaired clinical antifungal response. The prescribing information states that use of posaconazole delayed-release tablets with a PPI requires no dosage adjustment.

Victim drug	ARA/ perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
				lower posaconazole concentrations in a multiple linear regression analysis	
Central nervous system agents					
Phenytoin [76–88]	Antacids (calcium carbonate, aluminum hydroxide, magnesium hydroxide)	↓ phenytoin	pH-dependent absorption	▪ Pharmacokinetic studies report that when phenytoin was administered with various antacids (aluminum hydroxide, magnesium hydroxide, or calcium carbonate), the AUC of phenytoin decreased 16% to 24% ▪ In contrast, other studies have shown that administration of phenytoin with antacid therapies (magnesium trisilicate, aluminum hydroxide, magnesium hydroxide, or calcium carbonate) resulted in no change in phenytoin AUC, C_{max}, or time to C_{max} ▪ The prescribing information for phenytoin suggests separating the administration of phenytoin and antacids to avoid this interaction, although this strategy has not been evaluated in a clinical study	Phenytoin and antacids should not be taken at the same time of day.
	H2RA	↑ phenytoin		▪ In 4 patients with epilepsy, coadministration of cimetidine 200 mg TID + 400 mg QD with phenytoin resulted in significant increases in plasma phenytoin levels ▪ In another study of 4 patients with chronic epilepsy, concomitant administration of phenytoin and ranitidine 150 mg BID gave no significant increase in plasma phenytoin levels. In contrast, coadministration of cimetidine 200 mg TID + 400 mg QD led to significantly higher plasma phenytoin levels ▪ Coadministration of cimetidine 300 mg QID with phenytoin 100 mg oral capsule in 10 healthy volunteers showed a 16% decrease in the plasma clearance of phenytoin. In a separate phase of this study, no effect on phenytoin kinetics was observed with coadministration of famotidine 40 mg and phenytoin 100 mg oral capsule ▪ A dose-dependent effect of cimetidine on phenytoin	

Victim drug	ARA/ perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
				pharmacokinetics has been observed in 8 healthy volunteers, with reductions in phenytoin clearance from 10%–21% and increases in 48-hour phenytoin plasma concentrations from 47%–141% and in AUC from 10%–26% when phenytoin 250 mg infusion was coadministered with cimetidine 300 mg QID, 600 mg QID, or 400 mg QD	
	PPIs	↑ phenytoin		▪ A study of 8 healthy volunteers showed a decrease of 15% in phenytoin plasma clearance and increase in the elimination half-life of 27% when phenytoin (250 mg/50 mL infusion) and omeprazole 40 mg were coadministered ▪ Another study of 10 healthy volunteers found that omeprazole 40 mg was associated with a significant 19% increase in the AUC of single-dose phenytoin 300 mg, which may be clinically important owing to the low therapeutic window of phenytoin ▪ In contrast, a study of 24 healthy volunteers administered a single dose of oral phenytoin 300 mg and pantoprazole 40 mg (for 7 days) found no effect on the AUC or C_{max} of phenytoin	
GI agents					
APRISO® (mesalamine) [89]	Antacids	↓ mesalamine	pH-dependent dissolution	▪ N/A, formulation necessity	Because the pH-dependent dissolution of the coating of the granules in APRISO® extended-release capsules, they should not be coadministered with antacids.
Bisacodyl DR [90]	Antacids	Premature release from DR dosage form leading to gastric irritation and/or cramping	pH-dependent dissolution from DR dosage form	▪ The manufacturer of bisacodyl-containing products recommends that antacids or dairy products not be taken within 1 hour prior to taking bisacodyl.	Do not take antacids within 1 hour of bisacodyl DR tablets.
PYLERA® (bismuth subcitrate potassium, metronidazole, tetracycline	Antacids	↓ tetracycline	pH-dependent absorption	▪ The prescribing information for PYLERA® (bismuth subcitrate potassium/metronidazole/tetracycline hydrochloride) warns that its absorption may be reduced if taken concomitantly with aluminum-, calcium-, or magnesium-containing antacids; in preparations containing iron, zinc, or sodium	Avoid the concomitant administration of antacids with administration PYLERA®.

Victim drug	ARA/ perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
hydrochloride) [91-–93]				bicarbonate; or with dairy products because they may interact with tetracycline	
	Cimetidine	↑ metronidazole	Inhibition of CYP450 enzymes	▪ Concomitant administration of cimetidine and PYLERA® may result in a longer half-life and decreased plasma clearance of metronidazole	Avoid the concomitant administration of PYLERA® and cimetidine or other drugs that inhibit CYP450.
	Omeprazole	↑ bismuth		▪ In a study of 34 healthy volunteers, bismuth absorption from PYLERA® (given as three capsules, each with bismuth biskalcitrate 140 mg, metronidazole 125 mg, and tetracycline 125 mg QID) was significantly increased in the presence of omeprazole 20 mg BID. However, this effect was deemed unlikely to be clinically significant because bismuth blood levels remained well below the threshold for toxicity ▪ A small placebo-controlled crossover study also found that omeprazole increased the absorption of bismuth	The prescribing information for PYLERA® indicates that it may be used in combination with omeprazole.
Cardiovascular agents					
Captopril [94]	Antacids	↓ captopril	Unknown	▪ In a pharmacokinetic study of 10 healthy volunteers, the C_{max} and AUC of captopril (50-mg single dose) was reduced by 50% and 42%, respectively, when coadministered with an antacid (aluminum hydroxide, magnesium hydroxide, and magnesium carbonate). No changes in the hypotensive effect of captopril were observed. The mechanism of this interaction is unknown, and the utility of separating the administration of captopril and antacids has not been evaluated	Monitor for decreased captopril effects if administered with antacids.

Victim drug	ARA/ perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
Digoxin [95–103]	Antacids	↓ digoxin	pH-dependent absorption	▪ In one pharmacokinetic study of 10 healthy volunteers, the AUC of digoxin 0.75 mg (single dose) was reduced by 38% after the coadministration of magnesium trisilicate 60 mL (single dose) ▪ In this same study, the AUC of digoxin was reduced by 26% and 25%, respectively, by single doses of aluminum hydroxide (60 mL of a 4% gel) and magnesium hydroxide (60 mL of an 8% gel), but neither change reached statistical significance ▪ In another study of 12 healthy volunteers, administration of a single dose of aluminum hydroxide/magnesium hydroxide (Maalox®; 60 mL of 45 mg and 40 mg per mL) decreased the C_{max} of digoxin 0.4-mg capsules by 34% but had no significant effect on the C_{max} of digoxin 0.4 mg tablets. No change in digoxin AUC was noted with either formulation ▪ In a letter to the editor, it was reported that the administration of aluminum hydroxide (10 mL TID for 7 days) or magnesium trisilicate (10 mL TID for 7 days) had no effect on the bioavailability of digoxin (0.25 to 0.5 mg) in 4 patients	Before initiating concomitant drugs, serum digoxin concentrations should be measured when taking digoxin tablets. As necessary, continue monitoring and increasing the digoxin dose by approximately 20%–40%.
	PPIs			▪ The AUC of digoxin (1-mg oral single dose) increased ~10% when administered following an 11-day course of omeprazole 20 mg/day. The increase was still within the accepted range for bioequivalence. Of note, the individual increase was ~30% in 2 study participants. Another study found no effect of coadministration of omeprazole on digoxin exposure in patients with heart failure. Although early findings suggested that rabeprazole coadministration increased digoxin exposure, another study found no effects	

Victim drug	ARA/ perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
Riociguat [104, 105]	Antacids	↓ riociguat	pH dependent	▪ In a study in which 12 healthy volunteers received cotreatment with 10 mL of aluminum hydroxide/magnesium hydroxide plus riociguat 2.5 mg or riociguat 2.5 mg alone (n = 12), cotreatment with aluminum hydroxide/magnesium hydroxide resulted in a decrease in the bioavailability of riociguat (mean decrease of 34% in AUC and 56% in C_{max}) ▪ In another study, 12 healthy volunteers were pretreated for 4 days with omeprazole 40 mg and then received cotreatment with riociguat 2.5 mg or riociguat 2.5 mg with no pretreatment on day 5. Riociguat bioavailability was decreased by pre- and cotreatment with omeprazole; mean decreases in AUC and C_{max} were 26% and 35%, respectively	Antacids should not be taken within an hour of receiving riociguat, but no dose adjustment is required for coadministration of PPIs.
Bisphosphonates					
Risedronate sodium, risedronate sodium DR [106, 107]	Antacids	↓ risedronate	pH-dependent release	▪ Drugs that increase the pH in the stomach have the potential to accelerate pH-sensitive dissolution of risedronate DR, an enteric-coated bisphosphonate. According to the prescribing information for risedronate DR, antacids, H2RA, and PPIs should be avoided with the DR product of risedronate ▪ In a study of 60 healthy volunteers, risedronate DR 35 mg was administered after 6 days of esomeprazole magnesium DR 40 mg; the C_{max} and AUC of risedronate DR increased by 60% and 22%, respectively	Coadministration of antacids with risedronate or risedronate DR is not recommended.
	H2RA				Coadministration of H2RA with risedronate DR tablets is not recommended.
	PPIs				Coadministration of PPIs with risedronate DR tablets is not recommended.
Analgesics					
Mefenamic Acid [108, 109]	Antacids	↑ mefenamic acid	pH-dependent solubility	▪ In a single-dose study of 6 healthy volunteers, concomitant administration of an antacid containing magnesium hydroxide 1.7 g with mefenamic acid 500 mg increased the C_{max} of mefenamic acid by 125% and AUC by 36%	Because of the possibility of increased adverse events, concomitant use of mefenamic acid and antacids is not generally recommended.

Victim drug	ARA/ perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
Blood-modifying agents					
Dabigatran etexilate [110–114]	Antacids	↓ dabigatran etexilate	pH-dependent solubility	▪ According to the Canadian product monograph for dabigatran etexilate, when taken with antacids, a 35% reduction in dabigatran exposure was observed in postoperative patients up to 24 hours after surgery. Dabigatran exposure was reduced by 11% >24 hours post-surgery. Because of this larger risk for a decreased clinical (anticoagulant) effect, concomitant use of antacids with dabigatran should be avoided for 24 hours following orthopedic surgery. It is also recommended that dabigatran etexilate be taken 2 hours prior to antacids ▪ The US product label for dabigatran etexilate does not include similar recommendations ▪ A randomized crossover study of 37 patients with nonvalvular atrial fibrillation found that coadministration of PPIs with dabigatran significantly decreased the peak and trough dabigatran concentration, raising the possibility of decreased bioavailability of dabigatran ▪ A prospective pilot study of 31 patients with nonvalvular atrial fibrillation treated with dabigatran and omeprazole 20 mg BID or pantoprazole 40 mg QD found significantly lower peak and trough levels of dabigatran in patients treated with a PPI compared with those who were not ▪ A retrospective, population-wide cohort study found lower risk of GI bleeding in patients newly prescribed dabigatran with concomitant use of H2RA (incidence rate ratio, 0.61) or PPIs (incidence rate ratio, 0.53) ▪ Ranitidine 150 mg QD administered with dabigatran showed little change in dabigatran AUC and C_{max} ▪ Pantoprazole 40 mg BID when administered with dabigatran 150 mg BID decreased the dabigatran AUC by 24% and C_{max} by 28% in elderly individuals. The concomitant use of PPIs and H2RA did not appreciably change the trough concentration of dabigatran. The interaction with H2RA and PPIs are	The Canadian product monograph for dabigatran etexilate recommends avoiding concomitant use with antacids in the 24-hour period after orthopedic surgery. In other situations where antacids and dabigatran are to be used together, administer dabigatran 2 hours prior to the antacid. Monitor for decreased clinical response to dabigatran therapy. The dabigatran etexilate US product labeling does not include similar recommendations. The interaction with H2RA and PPIs are deemed not clinically significant and do not require action when coadministered.

Victim drug	ARA/ perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
				deemed not clinically significant and do not require action when coadministered	
Iron supplements					
Ferrous sulfate [115, 116]	Antacids	↓ iron salts	pH-dependent absorption (exception: calcium carbonate, which forms an insoluble complex with ferrous sulfate)	▪ Iron absorption significantly decreased when taken as ferrous sulfate 5 mg coadministered with magnesium trisilicate 35 g Plasma iron at 2 hours was not significantly decreased by coadministration of iron 10 mg (as ferrous sulfate) with aluminum hydroxide/magnesium hydroxide/simethicone 400/400/30 mg (Mylanta® II). In contrast, coadministration of iron 10 mg (as ferrous sulfate) with sodium bicarbonate 1 g or calcium carbonate 500 mg led to a 50% and 67% lower plasma iron increase compared with iron 10 mg alone	Separate dosing of oral iron preparations and antacids by as much time as possible to minimize effect on therapeutic efficacy of the iron preparation. Monitor for decreased therapeutic effects of oral iron preparations if an antacid is coadministered.
Anticholinergic agents					
Hyoscyamine [117]	Antacids	↓ hyoscyamine	pH-dependent immediate-release dosage form	▪ Patients receiving these products in combination with antacids should take hyoscyamine before meals and antacids after meals because antacids may interfere with hyoscyamine absorption	Administer hyoscyamine before meals and antacids after meals.

ARA, acid-reducing agent; AUC, area under the curve; BID, twice daily; C_{max}, maximum serum concentration; C_{min}, minimum serum concentration; CYP, cytochrome P450; DDI, drug-drug interaction; DR, delayed release; GI, gastrointestinal; H2, histamine H_2; H2RA, H2 receptor antagonists; HER2+, human epidermal growth factor receptor 2 positive; HIV, human immunodeficiency virus; LA, long acting; N/A, not applicable; NNRTI, nonnucleoside reverse transcriptase inhibitor; OS, overall survival; PK, pharmacokinetics; PFS, progression-free survival; PPI, proton pump inhibitor; QD, once daily; QID, 4 times daily; TID, 3 times daily; XR, extended release.

Supplementary Table 2 Medications That Interact With ARAs Via a Non–Gastric pH–Based Mechanism

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
Anti-infective agents					
Azithromycin [118, 119]	Magnesium-/aluminum -containing antacids	↓ azithromycin	Not specified; more likely to be chelation related than pH related	▪ In a clinical study of 10 healthy volunteers, administration just after a single oral dose of aluminum hydroxide/magnesium hydroxide 350/1200 mg decreased the C_{max} of azithromycin (administered as a 500-mg single oral dose) by 24% without affecting time to C_{max} or AUC. The clinical significance of these data is questionable given the magnitude of effect and the expected correlation between azithromycin efficacy and its AUC rather than C_{max}. Information on this potential interaction was included in US prescribing information for azithromycin as recently as 2013 but has since been removed. The patient counseling information for azithromycin recommends that patients should be cautioned not to take azithromycin and aluminum- or magnesium-containing antacids simultaneously	Patients should be cautioned not to take aluminum- and magnesium-containing antacids and azithromycin simultaneously.
Bictegravir [120]	Antacids	↓ bictegravir	Not specified; more likely to be chelation related than pH related	▪ The AUC of bictegravir decreased by an average of 52% when administered 2 hours after a nonspecified maximum-strength antacid (20 mL) under fasting conditions ▪ Similarly, the AUC of bictegravir decreased by an average of 47% and 79% when administered with a nonspecified maximum strength antacid (20 mL) under fed or fasting conditions, respectively ▪ When bictegravir was administered while fasting and 2 hours before the maximum-strength antacid, the AUC decreased by only 13%	Regular coadministration of bictegravir with or 2 hours after an aluminum-, magnesium-, or calcium-containing antacid is not recommended. Bictegravir can be administered under fasting conditions at least 2 hours before antacids.

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
Chloroquine [121, 122]	Cimetidine	↑ chloroquine	Cimetidine inhibiting hepatic mixed-function oxidases, exact mechanism not elucidated	▪ In 10 healthy, male volunteers, chloroquine (300 mg, base) elimination was impaired with low dose cimetidine coadministration (400 mg daily for 4 days). Oral clearance of chloroquine decreased by 53% (from 0.49 L/day/kg to 0.23 L/day/kg) and the elimination half-life increased by 48.6%. These pharmacokinetic changes were well tolerated in this study group ▪ Prescribing information indicates cimetidine and chloroquine coadministration should be avoided because of increased exposure to chloroquine	Monitor for increased chloroquine effects/toxicities when combined with cimetidine.
Ciprofloxacin [123–127]	Magnesium-/aluminum -containing antacids	↓ ciprofloxacin	Chelation	▪ Concurrent administration of antacids containing magnesium hydroxide or aluminum hydroxide may reduce the bioavailability of ciprofloxacin by as much as 90%	Ciprofloxacin should be taken at least 2 hours before or 6 hours after multivalent cation-containing products administration.
	Omeprazole		Increased gastric pH	▪ The prescribing information indicates that slight (20%) decreases in absorption of ciprofloxacin extended release were seen with concomitant administration of omeprazole. However, a study in 27 healthy individuals found no differences in ciprofloxacin PK following coadministration of omeprazole and an extended release formulation of ciprofloxacin with a different mechanism of drug delivery	
	H2 receptor antagonists			▪ The prescribing information states that H2RAs appear to have no significant effect on the bioavailability of ciprofloxacin	No interaction studies have been conducted with PPIs and H2RAs; monitor closely with co-administration and report any adverse effects.

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
Dolutegravir [128, 129]	Calcium-based antacids	↓ dolutegravir	Chelation	▪ In a clinical study summarized in the US prescribing information of dolutegravir, simultaneous administration of dolutegravir (50-mg single dose) and calcium carbonate (1200 mg) in a fasted state decreased the C_{max}, C_{min}, and AUC of dolutegravir by 37%, 39%, and 39%, respectively. When calcium carbonate was given either 2 hours after dolutegravir or simultaneously with dolutegravir but combined with food, there was no change in dolutegravir C_{max}, C_{min}, or AUC	The prescribing information for the dolutegravir/rilpivirine combination product recommends administering dolutegravir/rilpivirine at least 4 hours before or 6 hours after oral calcium salts.
Doxycycline [130–134]	Antacids containing aluminum, calcium, or magnesium; PPIs	↓ doxycycline	May be > 1 mechanism responsible, most likely chelation between oral tetracyclines and aluminum, calcium, and magnesium	▪ The ability of antacids to significantly reduce the absorption of tetracyclines, possibly resulting in subtherapeutic serum antibiotic concentrations, is well established. In a study summarized in the package insert for demeclocycline, coadministration with antacids containing aluminum, calcium, or magnesium decreased the extent of demeclocycline absorption by >50% ▪ Further studies confirm these findings, reporting >80% reduction in oral bioavailability of tetracycline, doxycycline, and demeclocycline when magnesium-aluminum hydroxide was coadministered in healthy volunteers; no effect was observed after coadministration of ranitidine ▪ One study also observed a decrease in the AUC of intravenously administered doxycycline when coadministered with aluminum hydroxide ▪ Absorption of doxycycline is decreased by PPIs	Separate administration of antacids and oral tetracycline derivatives by several hours, when possible, to minimize the extent of this potential interaction. Consider using an alternative ARA in place of the antacid when possible. Monitor for decreased therapeutic effects of tetracyclines if this combination is used.

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
Gemifloxacin [135]	Magnesium-/aluminum -containing antacids	↓ gemifloxacin	Chelation	▪ Concomitant administration of an aluminum and magnesium–containing antacid significantly reduced the systemic availability of gemifloxacin (AUC decreased by 85%; C_{max} decreased by 87%) ▪ Administration of an aluminum and magnesium–containing antacid or ferrous sulfate 325 mg at 3 hours before or at 2 hours after gemifloxacin did not significantly alter the systemic availability of gemifloxacin ▪ Therefore, aluminum- and/or magnesium-containing antacids, ferrous sulfate (iron), multivitamin preparations containing zinc or other metal cations, or didanosine (Videx®) chewable/buffered tablets or the pediatric powder for oral solution should not be taken within 3 hours before or 2 hours after taking gemifloxacin tablets ▪ Calcium carbonate 1000 mg given either 2 hours before or 2 hours after gemifloxacin administration showed no notable reduction in the systemic availability of gemifloxacin. Calcium carbonate administered simultaneously with gemifloxacin resulted in a small, but not clinically significant, decrease in gemifloxacin exposure ($AUC_{0-\infty}$ decreased 21%)	Magnesium- and/or aluminum-containing antacids should not be taken within 3 hours before or 2 hours after taking gemifloxacin tablets. Calcium carbonate can be used as an alternative (showed no clinically relevant PK changes).
Levofloxacin [136, 137]	Magnesium-/aluminum -containing antacids	↓ levofloxacin	Chelation	▪ Simultaneous administration of aluminum hydroxide significantly reduced levofloxacin AUC and C_{max} by 44% and 65%, respectively ▪ Simultaneous administration of magnesium oxide significantly reduced levofloxacin availability to a lesser degree (AUC by 22% and C_{max} by 38%) ▪ In a study of healthy volunteers, coadministration of levofloxacin and cimetidine resulted in no significant changes	Levofloxacin tablets and oral solution should be administered at least 2 hours before or 2 hours after antacids containing magnesium or aluminum.

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
				to levofloxacin C_{max} but an increase in AUC. The package insert states that dose adjustments are not needed when levofloxacin and cimetidine are coadministered	
Methenamine [138, 139]	Antacids	↓ methenamine	Methenamine requires a urinary pH < 6 to be hydrolyzed into formaldehyde and provide antiseptic activity	▪ Methenamine requires a urinary pH <6 to be hydrolyzed into formaldehyde and thus provide antiseptic activity. Agents that alkalinize the urine (e.g., carbonic anhydrase inhibitors, sodium bicarbonate, and some other antacids if taken in sufficient quantities) can render methenamine ineffective. The product label states that restriction of such agents is desirable	Consider using an agent other than methenamine or discontinue the use of an antacid. Sodium bicarbonate is of most concern. Other antacids are likely of concern only if taken in large doses. Spacing the doses may help minimize the effects; however, the success of this action is unknown. Monitor for decreased therapeutic effects of methenamine if used concomitantly with antacids.
Minocycline [131, 132, 140–142]	Antacids containing aluminum, calcium, or magnesium	↓ minocycline	May be > 1 mechanism responsible, most likely chelation between oral tetracyclines and aluminum, calcium, and magnesium	▪ The ability of antacids to significantly reduce the absorption of tetracyclines, possibly resulting in subtherapeutic serum antibiotic concentrations, is well established. The minocycline package insert states that coadministration with antacids containing aluminum, calcium, or magnesium decreases the extent of minocycline absorption. Additional studies with other drugs in this class confirm these findings, reporting > 80% reduction in oral bioavailability of tetracycline, doxycycline, and demeclocycline when magnesium-aluminum hydroxide was coadministered in healthy volunteers	Separate administration of antacids and oral tetracycline derivatives by several hours when possible to minimize the extent of this potential interaction. Consider using an alternative ARA in place of the antacid when possible. Monitor for decreased therapeutic effects of tetracyclines if this combination is used.
Moxifloxacin [143, 144]	Magnesium-/aluminum -containing antacids	↓ moxifloxacin	Chelation	▪ When a single dose of moxifloxacin 400 mg (tablet) was administered 2 hours before, concomitantly, or 4 hours after a single oral dose of an antacid containing aluminum hydroxide 900 mg and magnesium hydroxide 600 mg to 12 healthy volunteers,	Moxifloxacin should be taken at least 4 hours before or 8 hours after cation-containing antacids.

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
				there was a 26%, 60%, and 23% reduction in the mean AUC of moxifloxacin, respectively	
Norfloxacin [145, 146]	Cation-containing antacids	↓ norfloxacin	Chelation	▪ When norfloxacin was given 5 minutes after Maalox® or Titralac™ (calcium carbonate), the bioavailabilities were 9.0% and 37.5%, respectively, relative to that for norfloxacin 400 mg alone ▪ When Maalox® was given 2 hours after norfloxacin, C_{max} of norfloxacin in plasma occurred between 1 and 1.5 hours post dose and absorption was reduced to a lesser extent, with a relative bioavailability of 81.31%	Norfloxacin should be administered at least 2 hours before or 2 hours after administration of an antacid.
Quinine sulfate [147]	Antacids	↓ quinine	Chelation	▪ No clinical studies have been conducted in humans that describe the effects of antacids on the PK of quinine. However, the prescribing information for quinine recommends against the concomitant administration of antacids containing aluminum and/or magnesium because of a potential to delay or decrease the absorption of quinine	Concomitant administration of antacids with quinine should be avoided.
	H2 receptor antagonists	↑ quinine	The apparent existence of this interaction with cimetidine but not with ranitidine suggests that the primary mechanism of any interaction is via inhibition of CYP3A4 (and possibly other CYPs), given that cimetidine, unlike ranitidine and the other H2 receptor antagonists, is known to be an inhibitor of	▪ In healthy individuals, the apparent oral clearance of quinine decreased and the mean half-life increased significantly when given with cimetidine but not with ranitidine, and the mean AUC of quinine increased by 20% with ranitidine and by 42% with cimetidine ($P < 0.05$) without a significant change in the mean C_{max} of quinine	Consider using ranitidine in place of cimetidine. Although cimetidine and ranitidine may be used concomitantly with quinine, patients should be monitored closely for adverse events associated with quinine.

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
			several CYP enzymes		
Tetracycline [132, 141, 148]	Antacids containing aluminum, calcium, or magnesium	↓ tetracycline	May be > 1 mechanism responsible, most likely chelation between oral tetracyclines and aluminum, calcium, and magnesium	▪ The ability of antacids to significantly reduce the absorption of tetracyclines, possibly resulting in subtherapeutic serum antibiotic concentrations, is well established. The tetracycline package insert states that coadministration with antacids containing aluminum, calcium, or magnesium will impair absorption of tetracycline. Additional studies confirm these findings. In healthy volunteers, coadministration of magnesium-aluminum hydroxide reduced the oral bioavailability of tetracycline, doxycycline, and demeclocycline by > 80% in healthy volunteers	Separate the administration of antacids and oral tetracycline derivatives by several hours when possible to minimize the extent of this potential interaction. Consider using an alternative ARA in place of the antacid when possible. Monitor for decreased therapeutic effects of tetracyclines if this combination is used.
Central nervous system agents					
Alprazolam [149]	Cimetidine	↑ alprazolam	CYP3A4 inhibition by cimetidine	▪ Coadministration of cimetidine increased the C_{max} of alprazolam by 86%, decreased clearance by 42%, and increased half-life by 16%	Exercise caution and consideration of appropriate alprazolam dose reduction during coadministration with cimetidine.
Carbamazepine [150–154]	Cimetidine	↑ carbamazepine	The mechanism of this interaction is likely due to cimetidine-mediated inhibition of CYP3A4, an enzyme involved in carbamazepine metabolism. Carbamazepine autoinduction of CYP3A4 may account for the diminished magnitude of the interaction seen when these drugs are	▪ In a pharmacokinetic study conducted in 8 healthy volunteers receiving carbamazepine 300 mg BID administered for 42 days, the steady-state serum concentration of carbamazepine transiently increased by 17% after 2 days of concomitant use with cimetidine (400 mg TID on days 29 to 35) and returned to pre-cimetidine levels by the seventh day of cimetidine treatment. In 2 pharmacokinetic studies of healthy volunteers, cimetidine (1000 mg to 1200 mg per day) increased the AUC of carbamazepine (400-mg to 600-mg single dose) up to 26%. In another analysis,	Monitor for increased carbamazepine concentration and toxicity if initiating or increasing the dose of cimetidine considering that this may transiently increase serum concentration of carbamazepine during the first few days of treatment.

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
			combined for extended periods of time	concomitant use of cimetidine 400 mg BID with carbamazepine 200 mg QD increased the serum concentration of carbamazepine (administered as a daily dose of 200 mg) by 33% after 2 weeks of concomitant use. In 1 case report, an elderly woman receiving carbamazepine 600 mg QD experienced neurologic symptoms and toxic serum concentration of carbamazepine after the initiation of cimetidine (800 mg to 1000 mg daily)	
Citalopram [155–157]	Cimetidine	↑ SSRI's	The mechanism of these interactions is likely related to the ability of cimetidine to inhibit CYP isoenzymes involved in metabolizing SSRIs	▪ The AUC of citalopram 40 mg QD increased by 43% in healthy individuals when coadministered with cimetidine 400 mg BID for 7 days	Consider using an alternative H2RA to avoid the risk of SSRI toxicity. Monitor for increased therapeutic or toxic effects of SSRI if cimetidine is initiated/dose increased or for decreased effects if cimetidine is discontinued/dose decreased.
	Omeprazole	↑ citalopram	Inhibition of citalopram (S-citalopram) metabolism via CYP2C19 inhibition leading to increased citalopram concentration	▪ The prescribing information for citalopram recommends limiting the dose of citalopram to a maximum of 20 mg/day in patients who are receiving a CYP2C19 inhibitor because of the likelihood for increased citalopram concentrations and the possible increased risk for toxicities such as QT prolongation, and the labeling specifically lists omeprazole as an example of a potent CYP2C19 inhibitor ▪ In a study of healthy volunteers, the average concentration of (+)-(S)-citalopram was ~2.2-fold higher with concurrent use of omeprazole 20 mg/day for 18 days ▪ A case-control study of serum samples obtained from a routine therapeutic drug monitoring database found that the concentration-to-dose ratio for citalopram was ~35% higher in patients who were also treated with omeprazole compared with	Limit the dose of citalopram to a maximum of 20 mg/day if used with omeprazole. Patients using this combination should be monitored closely for evidence of citalopram toxicity (e.g., serotonin syndrome, QT prolongation, etc.).

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
				those who were not	
Clobazam [158, 159]	Omeprazole	↑ clobazam	CYP2C19 inhibition by omeprazole	▪ The AUC of the active clobazam metabolite, N-desmethylclobazam, was an average of 36% higher with concurrent use of omeprazole in a study of 36 healthy volunteers who received a single clobazam 10-mg dose on day 6 of omeprazole 40 mg/day. Parent clobazam concentrations were not significantly changed	Monitor closely for evidence of dose-related clobazam adverse reactions when used with omeprazole. Dose adjustments of clobazam may be necessary.
Clozapine [160–162]	Cimetidine	↑ clozapine levels and lead to adverse reactions	CYP3A4 inhibition by cimetidine	▪ The average serum concentration of clozapine (900 mg/day) for a patient increased by ~60% following the addition of oral cimetidine 800 mg/day. No clinical problems accompanied this concentration change. Approximately 3 months later, when the cimetidine dose was increased to 1200 mg, the patient had symptoms of clozapine toxicity (e.g., diaphoresis, dizziness, vomiting, and weakness) within 3 days. The symptoms resolved following discontinuation of the cimetidine and a reduction in the dose of clozapine. The clozapine dose was subsequently returned to 900 mg daily, and the patient received ranitidine (300 mg/day) without incident	Monitor for adverse reactions. Consider reducing the clozapine dose if necessary or consider another H2RA agent.
Dalfampridine [163, 164]	Cimetidine	↑ dalfampridine	OCT2 (renal uptake transporter) inhibition by cimetidine	▪ The AUC of dalfampridine was an average of 25% higher with concurrent cimetidine in a study of 23 volunteers who received cimetidine 400 mg every 6 hours and a single dose of dalfampridine 10 mg. In the US and Canada, 4-aminopyridine is referred to as dalfampridine and fampridine, respectively. The Canadian product monograph for fampridine contraindicates concomitant use with cimetidine and other drugs that inhibit OCT2. In contrast, the US label for dalfampridine recommends caution	The potential benefits of taking OCT2 inhibitors concurrently with dalfampridine should be considered against the risk of seizures in these patients.

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
				and an assessment of the potential risks against the potential benefits	
Desipramine [165, 166]	Cimetidine	↑ desipramine	The mechanism of these interactions is likely related to the ability of cimetidine to inhibit the CYP isoenzymes that may metabolize tricyclic antidepressants	▪ Concurrent administration of cimetidine and tricyclic antidepressants can increase plasma concentrations of the tricyclic antidepressants. Decreased plasma concentrations of tricyclic antidepressants upon discontinuation of cimetidine have also been reported ▪ A study of 8 patients taking maintenance doses of desipramine who received 4 days of concurrent cimetidine showed a mean 46% increase in plasma desipramine levels	Monitor therapy.
Doxepin [167]	Cimetidine	↑ doxepin	The mechanism of these interactions is likely related to the ability of cimetidine to inhibit CYP isoenzymes that may metabolize doxepin	▪ The effect of cimetidine, a nonspecific inhibitor of CYP1A2, 2C19, 2D6, and 3A4, on doxepin plasma concentrations was evaluated in healthy individuals. When cimetidine 300 mg BID was coadministered with a single dose of doxepin 6 mg (Silenor®), there was an ~2-fold increase in the C_{max} and AUC of doxepin (Silenor®) compared with doxepin given alone	A maximum dose of 3 mg is recommended in adults and elderly when cimetidine is coadministered with doxepin.
Escitalopram [156, 158, 168, 169]	Cimetidine	↑ escitalopram	The mechanism of this interaction is likely related to the ability of cimetidine to inhibit CYP isoenzymes involved in metabolizing escitalopram	▪ A study of 16 healthy individuals administered cimetidine 400 mg BID for 4 days and a single dose of escitalopram 20 mg on day 4 found an increase of 72% in AUC of escitalopram and a small, statistically insignificant increase in C_{max}	Consider using an alternative H2RA to avoid risk of escitalopram toxicity. Monitor for increased escitalopram toxicity if cimetidine is initiated/dose increased. Canadian labeling for escitalopram recommends a maximum escitalopram dose of 10 mg/day when given concomitantly with cimetidine.
	PPI		CYP2C19 inhibition by PPIs, which is the pathway of metabolism for SSRIs	▪ A case-control study of serum samples obtained from a routine therapeutic drug monitoring database found that the concentration-to-dose ratio for escitalopram was higher in patients who were also treated with omeprazole (+93.9%; $P < 0.001$),	The effect of comedication with PPIs on the serum concentration of SSRIs is more pronounced for omeprazole and esomeprazole than for lansoprazole and pantoprazole. When omeprazole

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
				esomeprazole (+81.8%; $P < 0.001$), lansoprazole (+20.1%; $P = 0.008$), and pantoprazole (+21.6%; $P = 0.002$) compared with those who were not	or esomeprazole are used in combination with escitalopram, a 50% dose reduction of the latter should be considered.
Gabapentin [170, 171]	Antacid containing aluminum and magnesium, such as Maalox®, Mylanta®, Gelusil®, Gaviscon®, or Di-Gel®	↓ gabapentin	The mechanism for this interaction is uncertain, although it does not appear to be related to an increase in gastric pH. Formation of a chelate complex is a possible mechanism for this interaction, but this has not been clearly established	▪ Antacid (Maalox®) containing magnesium and aluminum hydroxides reduced the mean bioavailability of gabapentin by ~20%–43%. This decrease in bioavailability was ~10% when gabapentin was administered 2 hours after Maalox®. There was no significant effect of coadministration of omeprazole	It is recommended that gabapentin be taken at least 2 hours following the administration of aluminum and magnesium–containing antacid.
Lisdexamfetamine [172–174]	Sodium bicarbonate	↑ lisdexamfetamine	Increase in urinary pH causes prolonged circulation of lisdexamfetamine	▪ The pH-dependent renal excretion of amphetamines has been repeatedly demonstrated. In 1 study, alkalinization of the urine (with sodium bicarbonate) was shown to decrease renal excretion of (+)-amphetamine to 45% in the first 24 hours compared with 70% under acidic conditions. In another study, alkalinization of the urine (to pH ~8.0) resulted in a decrease in mean 16-hour excretion of amphetamine to 0.6%–2.0% (compared with 55%–70% under acidic conditions). Alkalinization of the urine has also been shown to prolong elimination half-life, possibly by several-fold compared with that of acidic urine	Adjust the dosage of lisdexamfetamine dosage accordingly. Patients should be monitored closely for excessive amphetamine effects.
Memantine [175]	Antacids (sodium bicarbonate)	↑ memantine	Urinary pH–mediated clearance	▪ The manufacturer reports that memantine clearance was reduced by ~80% when the urinary pH was raised to 8	Memantine should be used with caution under these conditions.

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
Mirtazapine [176, 177]	Cimetidine	↑ mirtazapine	The mechanism of this interaction has not been fully investigated, but cimetidine inhibition of various enzymes involved in mirtazapine metabolism (e.g., CYP1A2, CYP2D6, CYP3A4) likely contributes	▪ In a pharmacokinetic study of 12 healthy volunteers, cimetidine (800 mg BID × 14 days) increased the AUC and C_{max} of mirtazapine (30 mg daily × 7 days) by 54% and 22%, respectively. Mirtazapine had no effect on the PK of cimetidine	Monitor for increased mirtazapine effects/toxicities if combined with cimetidine. Decreased mirtazapine doses may be required.
Paroxetine [178, 179]	Cimetidine	↑ paroxetine	The mechanism of these interactions is likely related to the ability of cimetidine to inhibit CYP isoenzymes involved in metabolizing SSRIs	▪ 7-day studies using paroxetine coadministered with cimetidine showed a 51% increase in paroxetine AUC	Consider using an alternative H2RA to avoid the risk of SSRI toxicity. Monitor for increased therapeutic or toxic effects of SSRI if cimetidine is initiated/dose increased or for decreased effects if cimetidine is discontinued/dose decreased. The prescribing information for Paxil® states that dosage adjustment for Paxil® after the 20-mg starting dose should be guided by clinical effect if cimetidine is concurrently administered.
Pramipexole [180]	Cimetidine	↑ pramipexole	Inhibition of pramipexole renal tubular section by cimetidine, which is a known inhibitor of certain organic cation transporters	▪ The AUC of pramipexole increased by an average of 50% when administered with cimetidine (n = 12), and the half-life of pramipexole was an average of 40% greater with cimetidine according to the prescribing information for pramipexole	Monitor patients closely for signs/symptoms of pramipexole toxicity when used together with cimetidine. Advise patients of risk of increased sedative effects of pramiexole when taken concomitantly with cimetidine.
Sulpiride [181]	Antacids	↓ sulpiride	Unknown—not likely to be pH related	▪ According to the sulpiride summary of product characteristics, antacids reduce the absorption of sulpiride. As a result, it is recommended that antacids and sulpiride be administered at least 2 hours apart from one another to minimize the potential for any significant interaction	Separate the administration of antacids and sulpiride by at least 2 hours to minimize the effect of antacids on sulpiride absorption.

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
Tizanidine [182]	Cimetidine	↑ tizanidine	Weak CYP1A2 inhibition by cimetidine	▪ The prescribing information for tizanidine states that potential drug interactions may occur with concomitant administration of weak inhibitors of CYP1A2 such as cimetidine and famotidine	Avoid the use of tizanidine with weak CYP1A2 inhibitors when possible. If combined use cannot be avoided, initiate tizanidine at an adult dose of 2 mg and increase in 2- to 4-mg increments based on patient response. Monitor for increased effects of tizanidine, including adverse reactions (e.g., hypotension, bradycardia, drowsiness).
Zolmitriptan [183–185]	Cimetidine	↑ zolmitriptan	The mechanism of this interaction has not been fully investigated but is likely related to cimetidine inhibition of CYP isoenzymes	▪ The manufacturer reports that the AUC of a single dose of zolmitriptan 5 mg approximately doubled when administered following a dose of cimetidine ▪ In a study in 16 healthy individuals, coadministration of cimetidine with a 5-mg dose of zolmitriptan resulted in a 48% increase in the AUC of zolmitriptan and a 105% increase in the AUC of its active metabolite	Monitor for increased effects/toxicity of zolmitriptan when coadministred with cimetidine. The prescribing information advises limiting the maximum single dose to 2.5 mg (not to exceed 5 mg in a 24-hour period) when coadministered with cimetidine.
Cardiovascular agents					
Carvedilol [186]	Cimetidine	↑ carvedilol	The mechanism of this interaction is uncertain but is likely related to the ability of cimetidine to inhibit enzymes responsible for carvedilol metabolism (i.e., CYP2C9, CYP3A4, CYP2D6, others)	▪ When coadministered with cimetidine 1000 mg/day, the steady state AUC of carvedilol in 10 healthy volunteers increased by an average of 30%. No change in C_{max} was observed	Monitor therapy.
Diltiazem [187, 188]	Cimetidine	↑ diltiazem	The likely primary mechanism of interaction between cimetidine and most calcium-channel blockers is cimetidine	▪ The AUCs of calcium-channel blockers frequently increase in patients who also receive cimetidine. A study in 6 healthy individuals showed that concurrent administration of cimetidine increased diltiazem AUC by ~50%	Consider alternatives to cimetidine in patients receiving diltiazem. If no suitable alternative to cimetidine exists, monitor for increased effects of these calcium-channel blockers

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
			inhibition of CYP3A4-mediated calcium-channel blocker metabolism		following cimetidine initiation/dose increase, or for decreased effects following. cimetidine discontinuation/dose decrease.
Dofetilide [189, 190]	Cimetidine	↑ dofetilide	The likely mechanism is related to cation transport system inhibition by cimetidine, resulting in reduced clearance of dofetilide	▪ Cimetidine at 400 mg BID (the usual prescription dose) coadministered with dofetilide 500 µg BID for 7 days increased the plasma levels of dofetilide by 58%. Cimetidine 100 mg BID (over-the-counter dose) resulted in a 13% increase in dofetilide plasma levels (500 µg single dose)	The prescribing information for dofetilide lists the combination of cimetidine and dofetilide as contraindicated. Consider using an alternative H2RA to avoid the potential toxic effects of dofetilide. Monitor for increased toxic effects (e.g., corrected QT prolongation) of dofetilide if cimetidine is initiated/dose increased or for decreased effects if cimetidine is discontinued/dose decreased.
Felodipine [191, 192]	Cimetidine	↑ felodipine	Cimetidine inhibition of CYP3A4-mediated metabolism of felodipine	▪ The AUCs of calcium-channel blockers frequently increase in patients who also receive cimetidine. In 12 healthy individuals, concurrent administration of cimetidine resulted in an ~30% increase in felodipine AUC	The Plendil® package insert states that caution should be used when coadministering cimetidine with felodipine, with a conservative approach to felodipine dosing. Consider alternatives to cimetidine in patients receiving felodipine. If no suitable alternative to cimetidine exists, monitor for increased effects of these calcium-channel blockers following cimetidine initiation/dose increase or for decreased effects following cimetidine discontinuation/dose decrease.

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
Fosinopril [193, 194]	Antacids	↓ fosinopril	The mechanism of this potential interaction is unknown, but on the basis of the manufacturer recommendation to separate administration (instead of avoiding all gastric acid suppression therapy), it may relate to direct inhibition of fosinopril absorption instead of reduced absorption due to elevated gastric pH	▪ In a clinical study described by both the US and Canadian product labels for fosinopril, the coadministration of an antacid (aluminum hydroxide, magnesium hydroxide, and simethicone) with fosinopril reduced the serum levels and the urinary excretion of fosinoprilat (the active moiety of the prodrug fosinopril) compared with fosinopril administration alone. No details of the study or magnitude of the PK changes were provided	The US and Canadian manufacturer labels for fosinopril recommend separating the doses of antacids and fosinopril by 2 hours.
Nifedipine [195–197]	Cimetidine	↑ nifedipine	Cimetidine inhibition of CYP-mediated metabolism of nifedipine	▪ The AUCs of calcium-channel blockers frequently increase in patients who also receive cimetidine. In a study of 6 healthy volunteers who received nifedipine 10 mg 4 times daily, coadministration of cimetidine once daily for 7 days increased mean peak plasma levels of nifedipine by ~80%	Consider alternatives to cimetidine in patients receiving nifedipine. If no suitable alternative to cimetidine exists, monitor for increased effects of these calcium-channel blockers following cimetidine initiation/dose increase or decreased effects following cimetidine discontinuation/dose decrease. Prescribing information suggests cautious titration if nifedipine therapy must be initiated in a patient currently receiving cimetidine.

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
Nimodipine [198–200]	Cimetidine	↑ nimodipine	Cimetidine inhibition of CYP3A4-mediated metabolism of nimodipine	▪ The AUCs of calcium-channel blockers frequently increase in patients who also receive cimetidine. Studies in healthy volunteers who received nimodipine have shown that coadministration of cimetidine increased the mean AUC by ~74%–90%	Consider alternatives to cimetidine in patients receiving nimodipine. If no suitable alternative to cimetidine exists, monitor for increased effects of these calcium-channel blockers following cimetidine initiation/dose increase or for decreased effects following cimetidine discontinuation/dose decrease.
Nisoldipine [201, 202]	Cimetidine	↑ nisoldipine	The likely primary mechanism of interaction between cimetidine and most calcium-channel blockers is cimetidine inhibition of CYP3A4-mediated calcium-channel blocker metabolism	▪ The bioavailability of calcium-channel blockers frequently increases in patients who also receive cimetidine. In 8 healthy volunteers who received nisoldipine, coadministration of cimetidine increased systemic availability by ~46% ▪ The prescribing information for nisoldipine states that concomitant administration of cimetidine and nisoldipine increased nisoldipine AUC and C_{max} by 30%–45%	Consider alternatives to cimetidine in patients receiving nisoldipine. If no suitable alternative to cimetidine exists, monitor for increased effects of these calcium-channel blockers following cimetidine initiation/dose increase or for decreased effects following cimetidine discontinuation/dose decrease.
Nitrendipine [203]	Cimetidine	↑ nitrendipine	The likely primary mechanism of action is cimetidine inhibition of CYP3A4-mediated nitrendipine metabolism	▪ The AUCs of calcium-channel blockers are frequently increased in patients who also receive cimetidine. In a placebo-controlled crossover study of 9 healthy men, coadministration of cimetidine and nitrendipine increased the concentration of nitrendipine by up to 154%	Consider alternatives to cimetidine in patients receiving nitrendipine. If no suitable alternative to cimetidine exists, monitor for increased effects of these calcium-channel blockers following cimetidine initiation/dose increase or for decreased effects following cimetidine discontinuation/dose decrease.

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
Pindolol [204–206]	Cimetidine	↑ pindolol	Cimetidine is a relatively weak inhibitor of several individual CYP enzymes, suggesting that cimetidine may be inhibiting pindolol metabolism. Cimetidine has also been shown to inhibit the renal clearance of pindolol, and such an effect could also explain the observed increase in pindolol concentrations	▪ The AUC of pindolol has been shown to increase by an average of 30% with concurrent administration of cimetidine. The clinical significance of this is uncertain	Exercise caution when given concomitantly with cimetidine, and monitor for symptoms of pindolol toxicity (e.g., hypotension).
Procainamide [207–209]	Cimetidine	↑ procainamide	The mechanism of this interaction is likely inhibition of the renal tubular secretion of procainamide by cimetidine	▪ Several studies have evaluated the effect of cimetidine on procainamide PK. In 4 studies (N = 6–9), cimetidine 400 mg (administered as single dose or multiple daily doses) increased the AUC of procainamide from 35% to 43% and increased the AUC of N-acetylprocainamide from 25% to 45%. Renal clearance of procainamide decreased from 31% to 44%, and renal clearance of N-acetylprocainamide decreased from 16% to 27% in 3 studies, but remained unchanged in 1 study ▪ Ranitidine coadministration did not alter procainamide AUC	Consider an alternative H2 receptor antagonist in patients taking procainamide. If combined, monitor for increased therapeutic effects/toxicity of procainamide. Consider reducing or carefully titrating dosage of procainamide when coadministered with cimetidine.
Propafenone [210, 211]	Cimetidine	↑ propafenone	The mechanism of this interaction is uncertain, but it is likely related to cimetidine inhibition of propafenone metabolism	▪ Prescribing information for this drug states that concomitant administration of propafenone and cimetidine in 12 healthy individuals resulted in a 20% increase in steady-state plasma concentrations of propafenone ▪ In a study of 12 healthy volunteers receiving propafenone 225 mg every 8 hours, the C_{max} of propafenone increased by an average of 24% following 5 days of concomitant	Monitor for toxic effects of propafenone if cimetidine is initiated/dose increased or decreased effects if cimetidine is discontinued/dose decreased.

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
				therapy with cimetidine 400 mg given every 8 hours, but the effect was not statistically significant. Approximately 40% of individuals experienced decreased serum concentration (an average of 4%), and the other 60% experienced an average increase of 32%	
Quinidine [212–214]	Cimetidine	↑ quinidine	The likely primary mechanism of interaction between these drugs is cimetidine inhibition of CYP3A4-mediated quinidine metabolism. Additionally, on the basis of a trend toward decreased renal clearance of quinidine seen in 1 study, cimetidine inhibition of quinidine renal clearance may also contribute	▪ The half-life of quinidine increased by 54% in 4 healthy volunteers when concomitantly administered with cimetidine 1200 mg/day for 5 days. Several case reports and small studies have confirmed this effect, showing increased quinidine concentrations, decreased clearance, or both with cimetidine coadministration. When reported, the increase in the AUC of quinidine has generally been small (<20%)	Consider alternatives to cimetidine in patients receiving quinidine. If the combination cannot be avoided, monitor for increased quinidine concentration/toxicity with cimetidine initiation/dose increase or for decreased concentration/effects with cimetidine discontinuation/dose decrease.
Rosuvastatin [215, 216]	Antacids	↓ rosuvastatin	Unknown, but may be due to antacid binding or chelating rosuvastatin in the gastrointestinal tract, preventing absorption	▪ In a pharmacokinetic study of 14 healthy volunteers, coadministration of an antacid (magnesium hydroxide/aluminum hydroxide) and rosuvastatin (40 mg single dose) decreased the rosuvastatin AUC by 54%. When the antacid was administered 2 hours after rosuvastatin, the rosuvastatin AUC decreased by only 22%	Monitor for decreased effects of rosuvastatin (e.g., cholesterol changes) in patients who consistently take antacids concomitantly. The rosuvastatin prescribing information states that antacids should be taken at least 2 hours after rosuvastatin administration.
Sotalol [217]	Magnesium- and/or aluminum-containing antacids	↓ sotalol	The mechanism of this potential interaction is likely adsorption of sotalol onto the antacid, forming a poorly absorbable complex leading to decreased	▪ Administration of sotalol within 2 hours of antacids containing aluminum oxide and magnesium hydroxide should be avoided because it may result in a reduction in C_{max} and AUC of 26% and 20%, respectively, and consequently in a 25% reduction in the bradycardic effect at rest. Administration of	Administer antacid 2 hours before or after sotalol.

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
			sotalol exposure	the antacid 2 hours after sotalol has no effect on the PK or pharmacodynamics of sotalol	
Verapamil [218, 219]	Cimetidine	↑ verapamil	The likely primary mechanism of interaction between cimetidine and most calcium-channel blockers is cimetidine inhibition of CYP3A4-mediated calcium-channel blocker metabolism	▪ Because of interaction with other calcium-channel blockers, concurrent administration of verapamil and cimetidine warrants monitoring. The kinetics and dynamics of single doses of verapamil (10 mg intravenously and 120 mg oral) were followed in 8 individuals receiving oral cimetidine 300 mg every 6 hours and placebo. Although there was a significant increase in the bioavailability of the orally administered verapamil, after cimetidine, there was no change in PR interval prolongation with oral verapamil. The prescribing information states that variable results on clearance have been obtained in acute studies of healthy volunteers. Further studies must be completed for clinical significance; however, on the basis of available information, caution is recommended	Consider alternatives to cimetidine in patients receiving verapamil. If no suitable alternative to cimetidine exists, monitor for increased effects of these calcium-channel blockers following cimetidine initiation/dose increase or decreased effects following cimetidine discontinuation/dose decrease.
Immunosuppressant agents					
Cyclosporine [220–223]	H2 receptor antagonists	↑ cyclosporine	Unknown	▪ Data are inconsistent. Some reports implicate cimetidine as increasing or decreasing cyclosporine clearance, while other reports suggest that neither cimetidine nor ranitidine affect cyclosporine concentration	Monitor serum cyclosporine concentrations and renal function (in particular serum creatinine) if an H2RA is initiated or discontinued or if the dose is changed.
Mycophenolate mofetil [224–227]	Antacids with magnesium and/or aluminum hydroxide	↓ mycophenolate	Mycophenolate apparently binds to aluminum and/or	▪ When administered simultaneously with aluminum hydroxide/magnesium hydroxide, The C_{max} and AUC of mycophenolate 2 g	Separate doses of mycophenolate and antacids by at least 2 hours. Monitor for reduced effects of

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
Mycophenolic acid [228, 229]			magnesium ions in the gastrointestinal tract, forming a less soluble/absorbable complex	(single dose) decreased by 33% and 17%, respectively, in 10 patients ▪ The C_{max} and AUC of mycophenolic acid in 12 stable kidney transplant recipients were 25% and 37% lower, respectively, when taken with magnesium-/aluminum-containing antacids compared with taken alone under fasting conditions	mycophenolate if taken concomitantly with antacids. The prescribing information for mycophenolic acid states that concomitant use of antacids is not recommended.
Tacrolimus [230–232]	PPIs	↑ tacrolimus	Lansoprazole and omeprazole, as CYP2C19 and CYP3A4 substrates, may potentially inhibit the CYP3A4 metabolism of tacrolimus	▪ In several case reports and clinical studies, concurrent PPI therapy increased tacrolimus concentration by 50%–300%. Among the PPIs, omeprazole, lansoprazole, and rabeprazole have been associated with significantly increased tacrolimus concentration. However, several reports have presented evidence that rabeprazole may be less likely to significantly interact with tacrolimus than omeprazole or lansoprazole	Monitoring of whole blood concentrations of tacrolimus and appropriate dosage adjustments of tacrolimus are recommended when these drugs and tacrolimus are used concomitantly.
Blood-modifying agents					
Acenocoumarol [233, 234]	Cimetidine	↑ acenocoumarol (vitamin K antagonists)	Inhibition of CYP metabolism of acenocoumarol by cimetidine	▪ The class of vitamin K antagonists is known to interact with cimetidine, and because of the interaction with warfarin, caution should be used with acenocoumarol ▪ Cimetidine has been demonstrated in a number of reports to increase the hypoprothrombinemic effect of warfarin in warfarin-stable patients, at times resulting in bleeding. The effect appears to be dose related (with higher doses of cimetidine producing greater effects) and mediated by a cimetidine-induced inhibition of warfarin metabolism in the liver (hydroxylation)	If possible, use an alternative H2RA to avoid an interaction with concurrent coumarin derivative administration. If cimetidine must be used, monitor the patient for either increased therapeutic effects of coumarin derivative when the cimetidine is initiated/dose increased or for decreased therapeutic effects if cimetidine is discontinued/dose decreased.

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
Cilostazol [235]	Omeprazole	↑ cilostazol active metabolites	Via CYP2C19 inhibition by omeprazole	▪ Coadministration with CYP2C19 inhibitors (eg, omeprazole) increases systemic exposure of cilostazol active metabolites ▪ Coadministration of omeprazole did not significantly affect the metabolism of cilostazol, but the systemic exposure to 3,4-dehydro-cilostazol increased by 69%, probably the result of the potent inhibition of CYP2C19 of omeprazole	Reduce cilostazol dose to 50 mg BID when coadministered with strong or moderate inhibitors of CYP2C19.
Clopidogrel [236]	PPIs (esomeprazole, omeprazole)	↓ clopidogrel	Clopidogrel undergoes metabolism to its active metabolism via CYP2C19. Inhibition of CYP2C19 by certain PPIs results in a decrease in active metabolite formation and decreased exposure	▪ Coadministration of omeprazole 80 mg with a single dose of clopidogrel (PLAVIX®) reduced AUC of by the clopidogrel active metabolite by ~40%. Dexlansoprazole, lansoprazole, and pantoprazole had less effect on the antiplatelet activity of clopidogrel than omeprazole or esomeprazole	Avoid the concomitant use of clopidogrel with omeprazole or esomeprazole.
Eltrombopag [237]	Cation-containing antacids	↓ eltrombopag	Chelation	▪ In a clinical trial, administration of eltrombopag with a polyvalent cation-containing antacid decreased plasma eltrombopag systemic exposure by approximately 70%	To avoid a significant reduction in absorption of eltrombopag (due to chelation), take eltrombopag at least 2 hours before or 4 hours after any medications or products containing polyvalent cations such as antacids, dairy products, and mineral supplements.
Warfarin [238–243]	Cimetidine	↑ warfarin (vitamin K antagonists)	Cimetidine-induced inhibition of warfarin hydroxylation in the liver, which is a major pathway of metabolism for warfarin	▪ In a number of reports, cimetidine increased the hypoprothrombinemic effect of warfarin in warfarin-stable patients, at times resulting in bleeding. The effect appeared to be dose related (with higher doses of cimetidine producing greater effects) and mediated by a cimetidine-induced inhibition of warfarin metabolism in the liver (hydroxylation)	If possible, use an alternative H2RA with concurrent coumarin derivative administration. If cimetidine must be used, monitor for either increased therapeutic effects of the coumarin derivative when cimetidine is initiated/dose increased or for decreased therapeutic effects if cimetidine is discontinued/dose decreased.

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
Metal chelators					
Deferasirox [244]	Aluminum-containing antacids	↓ deferasirox	Because of the mechanism of action of deferasirox, the prescribing information warns that the affinity of deferasirox for aluminum, although lower than that for iron, may disrupt the efficacy of the drug	▪ The concomitant administration of deferasirox (EXJADE®) and aluminum-containing antacid preparations has not been formally studied, but the package label states to avoid use because of the way deferasirox works	Avoid the use of aluminum-containing antacids.
Deferiprone [245]	Antacids	↓ deferiprone	Chelation	▪ The prescribing information for deferiprone recommends separating the administration of deferiprone and medications or supplements containing polyvalent cations by at least 4 hours. Deferiprone chelates iron and has a lower binding affinity for copper, aluminum, and zinc. Coadministration of any of these cations, or other polyvalent cations such as magnesium and calcium, with deferiprone could theoretically bind deferiprone in the gastrointestinal tract and limit its systemic exposure	Separate the administration of deferiprone and oral medications or supplements that contain polyvalent cations by at least 4 hours.
Trientine [246]	Antacids	↓ trientine	Metal binding/chelation	▪ The manufacturer of trientine (SYPRINE®) states that it should be taken at least 1 hour apart from any other drug, food, or milk. This permits maximum absorption and reduces the likelihood of inactivation of the drug by metal binding in the gastrointestinal tract	Separate the dosing of trientine from those of other oral drugs (e.g., antacids) by at least 1 hour. Monitor for decreased therapeutic effects of trientine if an antacid is initiated/dose increased or increased effects if an antacid is discontinued/dose decreased.
Antidiabetic agents					
Glimepiride [247, 248]	H2 receptor antagonists (cimetidine, famotidine, nizatidine, ranitidine)	↑ glimepiride and risk of hypoglycemia	Possibly due to decreased hepatic metabolism and/or impaired renal transport of sulfonylureas caused by cimetidine	▪ In a randomized, open-label, 3-way crossover study, healthy individuals received either a single 4-mg dose of glimepiride alone, glimepiride with ranitidine (150 mg BID for 4 days; glimepiride was administered on day 3), or	Monitor the patient closely for hypoglycemia. When H2RAs are withdrawn from a patient receiving glimepiride, monitor the patient closely for worsening glycemic control.

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
				glimepiride with cimetidine (800 mg daily for 4 days; glimepiride was administered on day 3). Coadministration of cimetidine or ranitidine with a single 4-mg oral dose of glimepiride did not significantly alter the absorption and disposition of glimepiride	
Glipizide [248–250]	H2 receptor antagonists (cimetidine, famotidine, nizatidine, ranitidine)	↑ glipizide and risk of hypoglycemia	Possibly due to decreased hepatic metabolism and/or impaired renal transport of sulfonylureas caused by cimetidine	▪ In a randomized placebo-controlled study of 2 groups of 6 patients with maturity-onset diabetes, cimetidine (400 mg) and ranitidine (150 mg) given 3 hours before a standardized meal significantly reduced the postprandial rise in blood glucose by a mean of 40% and 25%, respectively, and increased plasma AUC of glipizide by ~20%	Caution should be exercised when initiating treatment with H2RAs in diabetic patients receiving sulfonylurea hypoglycemic agents.
Metformin [251–254]	Cimetidine	↑ metformin	The presumed primary mechanism of this interaction is cimetidine inhibition of OCTs, particularly OCT2, resulting in reduced renal tubular secretion of metformin. On the basis of in vitro data, gastric pH elevations induced by cimetidine or cimetidine inhibition of human multidrug and toxin extrusion 1 (hMATE1/*SLC47A1*) and human multidrug and toxin extrusion 2-K (*SLC47A2*)–mediated metformin transport may also contribute	▪ The AUC of metformin 250 mg/day was increased by 50% in 7 healthy volunteers following concomitant administration with cimetidine 400 mg BID for 5 days ▪ In a second study of 15 healthy volunteers, cimetidine administration decreased metformin renal tubular clearance by 26%–42% depending on the individual's OCT2 genotype. Participants carrying the OCT2 808G>T polymorphism had lower baseline tubular clearance of metformin and a correspondingly lower magnitude of interaction with cimetidine	Consider the benefits and risks of concomitant use.
Tolbutamide [255, 256]	Cimetidine	↑ tolbutamide	Due to decreased hepatic metabolism and/or impaired renal transport of sulfonylureas caused by	▪ Twelve healthy men were given a 1-g oral dose of tolbutamide on 3 occasions. The men were randomly assigned to 3 treatments in a crossover fashion: cimetidine 1200 mg QD, ranitidine 300 mg QD, and placebo.	Monitor for increased therapeutic effects of sulfonylureas if cimetidine is initiated/dose increased or for decreased effects if cimetidine is discontinued/dose

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
			cimetidine	Cimetidine significantly increased the AUC of tolbutamide by 20% (range, −5% to 42%), increased the half-life by 19%, and decreased the carboxytolbutamide: tolbutamide AUC ratio from 0.042 to 0.036. Ranitidine did not significantly alter tolbutamide PK	decreased.
Bisphosphonates					
Alendronate [257]	Antacids	↓ alendronate	The likely primary mechanism of this interaction is binding of the bisphosphonate derivative to polyvalent cations to form a nonabsorbable (or very poorly absorbable) chelate	▪ The manufacturers of all oral bisphosphonate derivatives caution that absorption may be impaired by concomitant oral intake of antacids	Instruct patients to take other oral medications at least a half hour after taking alendronate.
Antirheumatic agents					
Penicillamine [253, 258]	Antacids	↓ penicillamine	Likely formation of a relatively unabsorbable chelate between antacid and penicillamine	▪ In a PK study of 6 healthy volunteers, coadministration of a single dose of an antacid (magnesium hydroxide 1200 mg/aluminum hydroxide 1350 mg/simethicone 150 mg) with a single dose of penicillamine 500 mg decreased the AUC and C_{max} of penicillamine by 52% and 44%, respectively	The prescribing information for penicillamine states that penicillamine should be administered at least 1 hour apart from any other drug, food, milk, antacid, zinc, or iron-containing preparation. This permits maximum absorption and reduces the likelihood of inactivation by metal binding in the gastrointestinal tract.
Chemotherapy					
5-Fluorouracil [259, 260]	Cimetidine	↑ 5-fluorouracil	The basis of interaction between 5-fluorouracil and cimetidine is uncertain but probably a combination of inhibited drug metabolism and reduced liver blood	▪ The peak plasma concentration of oral 5-fluorouracil after 4-week pretreatment with cimetidine increased by 74% (from mean ± standard error 18.7 ± 4.5 µg/mL to 32.6 ± 4.4 µg/mL; $P < 0.05$) and AUC increased by 72% (from 528 ± 133 µg/mL-1 min to 911 ± 152 µg mL-1 min; $P < 0.05$) ▪ The prescribing information for injectable 5-	Therapeutic implications are considerable, and additional care should be taken in patients receiving the 2 drugs concomitantly.

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
			flow	fluorouracil does not mention an interaction with cimetidine	
Exchange resin					
Sodium polystyrene sulfonate [261–263]	Antacids	↑ sodium polystyrene sulfonate	The exact mechanism of this interaction is unknown. Sodium polystyrene sulfonate binds magnesium and calcium ions and may thereby prevent binding and neutralizing of bicarbonate ions in the small intestine. Additionally, the binding of sodium polystyrene sulfonate to cations from antacid preparations may attenuate the therapeutic effects of sodium polystyrene sulfonate	▪ Serum bicarbonate concentration increased in 11 patients who received concomitant antacids (containing magnesium or calcium) and sodium polystyrene sulfonate Additional reports support these findings	To minimize this interaction, consider: (1) separating the doses of sodium polystyrene sulfonate and antacids by ≥ 2 hours; (2) administering sodium polystyrene sulfonate rectally, or (3) choosing an alternative ARA (e.g., H2RA). Monitor for metabolic alkalosis and attenuation of sodium polystyrene sulfonate effects if concomitant therapy cannot be avoided. Avoid magnesium hydroxide.
Gastrointestinal agents					
Alosetron [264]	Cimetidine	↑ alosetron	CYP1A2 inhibition by cimetidine	▪ Data are only available for 1 strong inhibitor of CYP1A2, fluvoxamine, which increased the AUC and half-life of alosetron by 6- and 3-fold, respectively. Similar results for a moderate CYP1A2 inhibitor (such as cimetidine) are expected, but no evaluation has been conducted thus far	Concomitant administration of alosetron and moderate CYP1A2 inhibitors, such as cimetidine, has not been evaluated but should be avoided unless clinically necessary because of the potential for similar drug interactions (increased AUC and half-life).
Respiratory agents					
Roflumilast [265]	Cimetidine	↑ roflumilast	Via CYP3A4 inhibition by cimetidine	▪ Cimetidine coadministration resulted in an 85% increase in roflumilast AUC and a 27% increase in AUC for roflumilast N-oxide	Exercise caution when given concomitantly with cimetidine. The prescribing information cautions that risk of concurrent use should be weighed carefully

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
					against benefit.
Urinary agents					
Tamsulosin [266, 267]	Cimetidine	↑ tamsulosin	The mechanism of this potential interaction is that CYP3A4 is responsible for a significant portion of tamsulosin metabolism, and that the inhibition of CYP3A4 by cimetidine may lead to increased exposure and effects	▪ In a PK study of 10 healthy volunteers (described in the product label of tamsulosin), administering cimetidine 400 mg every 6 hours for 6 days increased the AUC of tamsulosin (single dose of 0.4 mg) by 44% ▪ The prescribing information for tamsulosin recommends caution when using with cimetidine, particularly at higher doses (i.e., 0.8 mg daily), because increased exposure could lead to increased effects	Tamsulosin capsules should be used with caution in combination with cimetidine, particularly at a dose higher than 0.4 mg.
Lanthanum carbonate [268, 269]	Antacids	↓ lanthanum	It is possible that antacid components may bind with lanthanum	▪ In the patient counseling section of the prescribing information for lanthanum, the administration of antacid products is recommended at least 2 hours before or 2 hours after lanthanum administration. However, this interaction warning is not present in other sections of the labeling (although there is a warning about potential interactions with drugs that interact with antacids)	Take antacid 2 hours before or 2 hours after lanthanum.
Cholinergic agonists					
Varenicline [270–272]	H2 receptor antagonists (cimetidine, famotidine, nizatidine, ranitidine)	↑ varenicline	The mechanism for the observed interaction is believed to be a reduction in varenicline renal clearance. H2RAs are known to inhibit OCT2, which is used for varenicline secretion into renal tubules	▪ Coadministration of cimetidine 300 mg QID with a single dose of varenicline (2 mg) in 12 smokers increased systemic exposure of varenicline by 29%	Monitor for increased varenicline adverse effects with concomitant use of cimetidine or other H2RAs, particularly in patients with severe renal impairment. The varenicline US prescribing information recommends a dose reduction in patients with severe renal impairment regardless of cimetidine use but does not prohibit use in patients receiving concomitant cimetidine or other H2RA s. The Canadian product

Victim drug	ARA/perpetrator	Clinical effect on victim drug	Mechanism of interaction	Evidence of interaction	Intervention strategy [1]
					monograph states that no dose adjustment is required in patients with normal renal function but recommends avoiding concomitant use with cimetidine or ranitidine in patients with severe renal impairment (estimated creatinine clearance < 30 mL/minute).

ARA, acid-reducing agent; AUC, area under the curve; BID, twice daily; C_{max}, maximum serum concentration; C_{min}, minimum serum concentration; CYP, cytochrome P450; H2, histamine H_2; H2RA, H2 receptor antagonist; OCT2, organic cation transporter 2; PK, pharmacokinetics; PPI, proton pump inhibitor; QD, once daily; QID, 4 times daily; SSRI, selective serotonin reuptake inhibitor; TID, 3 times daily.

Supplementary Table 3 Medications That Can be Concomitantly Used With ARAs Without Therapy Change

Medication name	Directions of use with ARA [1]	Clinical data
Antineoplastic agents/chemotherapy agents		
Alectinib [273, 274]	Can be taken with ARAs.	The prescribing information states that no clinically meaningful effects were seen with coadministration of alectinib and esomeprazole. Coadministration of alectinib and esomeprazole had no clinically relevant effect on the combined exposure of alectinib and M4 (its metabolite). Alectinib should be taken under fed conditions to maximize its bioavailability, whereas no restrictions are required with antisecretory agents (antacids).
Axitinib [275]	Can be taken with ARAs without a dose adjustment.	When an antacid, rabeprazole 20 mg QD for 5 days, was taken with axitinib, the C_{max} and AUC slightly decreased. Dose adjustment of axitinib was not required when taken with ARAs.
Azacitidine [269, 276]	Can be taken with ARAs.	The mean AUC_{∞} and C_{max} of azacitidine increased with coadministration of omeprazole (18% and 13%, respectively) relative to oral azacitidine alone but not to a clinically meaningful extent. Dose adjustment is not required when taken with a PPI.
Bortezomib [277, 278]	Can be taken with ARAs.	No clinically meaningful effect was observed with coadministration of bortezomib and omeprazole. Coadministration of bortezomib and omeprazole, a strong inhibitor of CYP2C19, had no effect on the exposure of bortezomib in 17 patients.
Cabozantinib [279-281]	Can be taken with ARAs.	No clinically relevant effect on exposure of cabozantinib was seen after coadministration with esomeprazole. A phase 1 study in 21 healthy individuals found that mean peak cabozanitinib plasma concentration and overall exposure after coadministration with esomeprazole were similar to those observed following cabozanitinib alone. The 90% CI for the ratio of least squares means of cabozantinib with esomeprazole vs cabozantinib alone for $AUC_{0-\infty}$ was within the 80%–125% limits, and the upper 90% CI for C_{max} was 125.1%. Therefore, concomitant use of PPIs or weak gastric pH–altering agents with cabozantinib is not contraindicated.
Ceritinib [282, 283]	Can be taken with ARAs.	In healthy individuals, coadministration of ceritinib 750 mg with esomeprazole 40 mg for 6 days decreased ceritinib $AUC_{0-\infty}$ by 76% and C_{max} by 79%. However, data from a similar study in patients with anaplastic lymphoma kinase–positive non-small cell lung cancer suggested less effect on ceritinib exposure than that observed in healthy individuals (AUC_{0-24} decreased by 30% and C_{max} decreased by 25%). There was no clinically meaningful effect on steady-state exposure. Therefore, administration of ceritinib with PPIs is not expected to affect the PK and efficacy of ceritinib in patients with anaplastic lymphoma kinase–positive cancer.
Cobimetinib [284, 285]	Can be taken with ARAs.	Coadministration of a PPI, rabeprazole 20 mg QD for 5 days, with a single dose of 20-mg cobimetinib under fed and fasted conditions did not result in a clinically important change in cobimetinib exposure.
Crizotinib [286, 287]	Can be taken with ARAs.	In healthy individuals, coadministration of a single, oral dose of crizotinib 250 mg following administration of esomeprazole 40 mg daily for 5 days did not result in a clinically relevant change in crizotinib exposure (AUC_{∞} decreased by 10% and C_{max} remained unchanged).

Medication name	Directions of use with ARA [1]	Clinical data
Imatinib [288, 289]	Can be taken with ARAs.	A 2-period, open-label, single-institution, randomized, crossover, fixed-schedule study of 12 individuals evaluated the effect of administering imatinib 400 mg alone and after 5 days of treatment with omeprazole 40 mg. Omeprazole did not significantly affect the AUC of imatinib (34.1 µg·hour/mL alone vs 33.1 µg·hour/mL with omeprazole; P = 0.64), C_{max} of imatinib (2.04 µg/mL alone vs 2.02 µg/mL with omeprazole; P = 0.97), or half-life of imatinib (13.4 hours alone vs 14.1 hours with omeprazole; P = 0.13). These data indicate that the use of omeprazole does not significantly affect the pharmacokinetics of imatinib.
Letrozole [290]	Can be taken with ARAs.	An interaction study with cimetidine showed no clinically significant effect on letrozole pharmacokinetics.
Nintedanib [291]	Can be taken with ARAs.	Nintedanib has a pH-dependent solubility profile with increased solubility at acidic pH <3. However, in clinical trials, coadministration with PPIs or H2RAs did not influence the exposure (trough concentrations) of nintedanib.
Osimertinib [292, 293]	Can be taken with ARAs.	An open-label, 2-period, fixed-sequence study assessed the effect of omeprazole on osimertinib exposure in healthy male volunteers. In period 1, volunteers received omeprazole 40 mg (days 1-4), then omeprazole 40 mg plus osimertinib 80 mg (day 5). In period 2, volunteers received osimertinib 80 mg alone (single dose). Coadministration with omeprazole did not affect osimertinib exposure. Dose restriction is not required in patients whose gastric pH may be altered by concomitant agents or medical conditions.
Palbociclib [294, 295]	Can be taken with ARAs.	A study, conducted under fed conditions, demonstrated that coadministration of rabeprazole decreased palbociclib C_{max} by 41% but had limited effect on $AUC_{0-\infty}$ (13% decrease). This study also showed that famotidine and local antacid with staggered dosing had no effect on palbociclib exposure under fed conditions. Another study in healthy volunteers under fasted conditions found decreases of 62% and 80% in the palbociclib AUC and C_{max}, respectively. Under fed conditions, there was no effect of ARAs on palbociclib exposure. Palbociclib free base capsule should be taken with food, and ARA use does not need to be avoided.
Ponatinib [296]	Can be taken with gastric pH–elevating medications.	Coadministration of a single dose of ponatinib 45 mg with lansoprazole 60 mg daily to 18 healthy volunteers decreased the AUC_{0-inf} and C_{max} of ponatinib by 6% and 25%, respectively. The prescribing information indicates that ICLUSIG® may be co-administered with gastric pH-elevating medications.
Raloxifene [297]	Can be taken with ARAs.	The systemic exposure of raloxifene was not affected by concomitant administration of calcium carbonate or aluminum and magnesium hydroxide–containing antacids.
Sorafenib [298]	Can be taken with ARAs with no change to sorafenib dose.	Coadministration of sorafenib following omeprazole 40 mg administered QD for 5 days did not result in a clinically meaningful change in sorafenib exposure. No dose adjustment for sorafenib is necessary.
Temozolomide [299, 300]	Can be taken with ARAs.	In a multiple-dose study, administration of temozolomide capsules with ranitidine did not change the C_{max} or AUC values for temozolomide or its active metabolite MTIC. A population analysis found that H2 receptor antagonists did not influence the clearance of temozolomide.
Topotecan [301, 302]	Can be taken with pH-elevating agents.	The PK of oral topotecan was unchanged when coadministered with ranitidine.

Medication name	Directions of use with ARA [1]	Clinical data
Vandetanib [303, 304]	Can be taken with pH–elevating agents.	In a crossover study of 14 healthy volunteers receiving a single oral dose of vandetanib 300 mg taken alone or in combination with omeprazole 40 mg QD for 5 days, coadministration of vandetanib and omeprazole had no clinically meaningful change on the geometric mean $AUC_{0–504h}$ and C_{max} of vandetanib. In a crossover study of 16 healthy volunteers where a single oral dose of vandetanib 300 mg was taken alone and after 2 oral doses of ranitidine 150 mg ~12 hours apart, coadministration had no effect on the geometric mean $AUC_{0–504h}$ and C_{max} of vandetanib.
Vismodegib [305, 306]	Can be taken with ARAs.	Concomitant administration of vismodegib and rabeprazole resulted in no clinically significant differences in vismodegib pharmacokinetics. Cohorts included a control arm (n = 22), in which vismodegib 150 mg was administered QD for 7 days, and an arm in which vismodegib was coadministered QD for 7 days with rabeprazole 20 mg (including a 4-day lead in; n = 24). The AUC_{0-24} of vismodegib at steady state was lower with concomitant rabeprazole administration relative to vismodegib alone (42% reduction in geometric mean AUC and 35% reduction in C_{max}). These results were not considered to be clinically meaningful because plasma concentrations for vismodegib remained above the therapeutic threshold. Results from this study suggest that vismodegib can be administered with ARAs.
Anti-infective agents		
Boceprevir [307, 308]	Can be taken with ARAs.	Omeprazole 40 mg QD for 5 days was administered with boceprevir 800 mg TID for 5 days. Results show a small decrease in AUC and C_{max} (geometric mean ratios of 0.92 and 0.94, respectively). These results were not deemed clinically significant, and no dose adjustment of boceprevir is required.
Cephalexin [297, 309]	Can be taken with ARAs.	Coadministration of cephalexin with ranitidine or omeprazole produced minor changes in C_{max}, AUC_{∞}, half-life, or oral clearance, but significantly prolonged the time to reach C_{max} of cephalexin. This was considered clinically important only in cases of pathogens with high minimum inhibitory concentrations because this may reduce the time that drug concentrations are above this threshold.
Danoprevir [310]	Can be taken without regard to acid suppressing agents.	In healthy individuals who received a single dose of DNVr (ritonavir boosted danoprevir) alone or with ranitidine 150 mg (single dose) or omeprazole 40 mg (multiple doses), neither ranitidine nor omeprazole had a clinically significant effect on danoprevir PK. The danoprevir Geometric Mean Ratios % (90% CI) for $AUC_{0-\infty}$, C_{max} and C_{12h} with ranitidine administration was 81.9 (68.3–98.1), 104 (86.9–123) and 87.5 (69.3–111), respectively, and that with omeprazole was 83.0 (67.4–102), 92.7 (70.6–122) and 93.3 (65.6–133), respectively.
Dapsone [311]	Can be taken with gastric pH–modifying agents.	Neither the $AUC_{0-\infty}$ nor the half-life of dapsone were significantly altered by nizatidine. Coadministration of nizatidine had no clinically significant effect on the PK of monoacetyldapsone. Elevation of gastric pH by H2RAs, such as nizatidine, does not result in clinically important changes in the rate or extent of oral dapsone absorption.
Darunavir [312, 313]	Can be takenwithout regard to acid suppressing agents.	When omeprazole 20 mg QD was administered with darunavir/ritonavir 400/100 mg BID in 16 patients, there was no change in the PK (a 2% increase in C_{max} and 4% increase in AUC) of darunavir. Coadministration of ranitidine 150 mg BID with darunavir/ritonavir 400/100 mg BID in 16 patients did not change the PK of darunavir (a 4% decrease in C_{max} and a 5% decrease in AUC). No dosage adjustments are recommended with these medications because there is no clinically significant interaction.

Medication name	Directions of use with ARA [1]	Clinical data
Efavirenz [314]	Can be taken with antacids. and H2RAs.	Single doses of famotidine or an aluminum and magnesium antacid with simethicone had no effect on efavirenz exposure.
Etravirine [315, 316]	Can be taken with drugs that elevate gastric pH.	In healthy individuals, the absorption of etravirine is not affected by coadministration with oral ranitidine or omeprazole, and no dose adjustment is needed. A study of 18 healthy individuals found that the AUC of etravirine was decreased by 14% when coadministered with ranitidine and increased by 41% when coadministered with omeprazole. These changes were considered to be not clinically relevant because of the lack of a relationship between etravirine PK and adverse effects observed in other studies.
Famciclovir [317]	Can be taken with ARAs.	No clinically significant alterations in penciclovir PK were observed following single-dose administration of famciclovir (prodrug of penciclovir) 500 mg after pretreatment with multiple doses of cimetidine or when taken shortly after an antacid (magnesium and aluminum hydroxide).
Fluconazole [55, 318, 319]	Can be taken with ARAs.	A study in 12 healthy individuals showed that median bioavailability ratio of fluconazole before and after omeprazole treatment was 1.00. A separate study found no effect of coadministration of famotidine on peak serum concentration or median 48-hour concentrations of fluconazole. There was no effect on the absorption or elimination of fluconazole when Maalox® 20 mL was taken immediately prior to fluconazole 100 mg. Administration of a single dose of cimetidine 400 mg 2 hours prior to a single oral dose of fluconazole 100 mg led to mean decreases in fluconazole AUC of 13% and C_{max} of 19%. In contrast, the bioavailability and pharmacokinetics of fluconazole were not affected when cimetidine 600 mg to 900 mg was given intravenously over 4 hours. These findings suggest that changes in gastric pH, as in patients with acquired immune deficiency syndrome or those being treated with antiulcer drugs, should not influence the pharmacokinetics of fluconazole.
Fosamprenavir [320–323]	Can be taken with ARAs.	The prescribing information for LEXIVA® indicates that coadministration of fosamprenavir with a single dose of magnesium-containing antacid (Maalox® TC) reduced C_{max} by 35% and AUC by 18% in 30 healthy volunteers, and therefore caution should be used. Studies in healthy volunteers and 1 case report in a patient with HIV have shown no effect of coadministration of fosamprenavir with omeprazole or esomeprazole on amprenavir PK.
Garenoxacin [324]	Can be taken with ARAs.	Coadministration of omeprazole did not alter the bioavailability of oral garenoxacin in 14 healthy individuals. Geometric means for C_{max} and $AUC_{0-\infty}$ were 9.6 µg/mL (18.2%) and 132.0 µg·hour/mL (18.9%), respectively, for garenoxacin alone and 9.3 µg/mL (21.6%) and 140.4 µg·hour/mL (22.1%), respectively, for garenoxacin and omeprazole coadministration.
Indinavir [46]	Can be taken with cimetidine.	In a drug interaction study of 12 participants coadminstered cimetidine 600 mg BID × 6 days and a single dose of indinavir 400 mg, there was a 7% increase in the C_{max} and a 2% decrease in the AUC of indinavir. These results were not significant, and cimetidine can be taken with indinavir.
Isavuconazonium sulfate [325, 326]	Can be taken with medications that increase gastric pH.	The geometric least squares mean ratios were similar for isavuconazole coadministered with esomeprazole vs administered alone (AUC_{τ} and C_{max} were 108% [90% CI, 89%–130%] and 105% [90% CI, 89%–124%], respectively). Dose adjustments are not required when switching between oral and intravenous formulations, regardless of drugs that increase gastric pH.
Isoniazid [327]	Can be taken with ARAs.	A phase 1 study in 14 healthy male and female volunteers found that coadministration of aluminum-magnesium antacid did not significantly alter isoniazid C_{max} or AUC.
Itraconazole oral suspension [52, 316]	Interaction likely with capsule dosage form, but suspension can be taken without regard to ARAs.	Omeprazole did not significantly affect the C_{max}, time to C_{max}, or AUC_{0-8} of itraconazole or hydroxyitraconazole when itraconazole was administered as an oral suspension. The prescribing information for the oral suspension states that the effect of H2RA coadministration is expected to be substantially less than that observed with itraconazole

Medication name	Directions of use with ARA [1]	Clinical data
		capsules, but nonetheless recommends that caution be used when coadministering H2 receptor antagonists with the oral suspension.
Lopinavir and ritonavir [32, 328, 329]	Can be taken with ARAs.	In a study involving omeprazole 40 mg QD administered for 5 days along with Kaletra® 400/100 mg tablet BID for 10 days, there was a 1.08-fold increase in C_{max} and a 1.07-fold increase in AUC; neither difference was significant. Another study found that coadministration of omeprazole increased C_{max} and AUC_{12} for lopinavir by 26% and 23%, respectively, but these results were not clinically significant.
MAVYRET™ (glecaprevir/pibrentasvir) [330]	Can be taken with ARAs.	When omeprazole 20 mg QD was administered with a single dose of MAVYRET™ 300/120 mg, C_{max} decreased by 22% and AUC decreased by 29%. No dose adjustment of MAVYRET™ is required in the presence of omeprazole. Omeprazole was deemed not to be a clinically important drug interaction.
Metronidazole [331–333]	Can be taken with cimetidine.	The prescribing information for metronidazole states that drugs that inhibit CYP3A4 (such as cimetidine) may decrease plasma clearance of metronidazole. However, 3 pharmacokinetics studies of 6 to 7 patients demonstrated that cimetidine 600 mg BID and 1000 mg QD, or single 1000 mg dose, had no effect on the exposure or clearance of metronidazole. One study did find that the renal clearance of metronidazole was reduced in the presence of cimetidine, but because the renal clearance only accounts for <15% of total metronidazole clearance, metronidazole exposure was unchanged.
Nevirapine [334]	Can be taken with ARAs.	In a trial of 6 individuals infected with HIV-1, the steady-state systemic exposure (AUCτ) of nevirapine was not significantly altered by coadministration of nevirapine with antacid (Maalox) or didanosine, which is formulated with an alkaline buffering agent. Nevirapine may be administered with or without food, antacid, or didanosine.
Posaconazole [69–71, 73–75]	Interaction with cimetidine likely with oral suspension form, but delayed-release capsules can be takenwith drugs that elevate gastric pH.	Coadministration of PPIs significantly decreased exposure to posaconazole in oral suspension; however, concomitant use of antacids, H2RAs, or PPIs with posaconazole delayed-release tablets did not have clinically relevant effects on the PK of posaconazole. No dosage adjustment of posaconazole delayed-release tablets is required when concomitantly used with antacids, H2RAs, and PPIs. When posaconazole oral suspension was concomitantly administered with antacids or H2RAs other than cimetidine, no clinically relevant effects were seen and thus no dose adjustment of posaconazole oral suspension is needed.
Telithromycin [335]	Can be taken with ARAs.	There was no clinically relevant pharmacokinetic interaction of ranitidine or antacids containing aluminum and magnesium hydroxide on telithromycin.
Valacyclovir [336, 337]	Can be taken with gastric pH–elevating agents.	The pharmacokinetics of acyclovir after a single dose of valacyclovir were unchanged by coadministration of antacids (Al^{+3} or Mg^{+2}). The C_{max} and AUC of acyclovir following a single dose of valacyclovir increased by 8% and 32%, respectively, after a single dose of cimetidine. Another study found no effect of cimetidine coadministration on acyclovir C_{max} and a small increase (~23%) in AUC. These results were not clinically significant.
Voriconazole [338, 339]	Can be taken with gastric pH–elevating agents.	The absorption of voriconazole was not affected by concomitant administration of cimetidine, ranitidine, or omeprazole in healthy volunteers. Cimetidine increased steady state C_{max} and AUCτ of voriconazole by an average of 18% (90% CI, 6%–32%) and 23% (90% CI, 13%–33%), respectively, following oral doses of voriconazole in healthy individuals. Ranitidine had no significant effect on the C_{max} and AUCτ of voriconazole following oral doses of voriconazole in healthy individuals. None of the differences were considered clinically relevant. In healthy volunteers, coadministration of voriconazole and omeprazole resulted in increases in the voriconazole C_{max} and AUC of 15% and 40%, respectively; no dose adjustment is needed. Significant increases in omeprazole plasma exposure were seen when coadministered with voriconazole. If patients initiating voriconazole are already receiving

Medication name	Directions of use with ARA [1]	Clinical data
		omeprazole 40 mg or greater, reduce the omeprazole dose by half. Voriconazole may also inhibit the metabolism of other PPIs that are CYP2C19 substrates, which may lead to increased plasma concentrations of those PPIs.
Elbasvir and grazoprevir [340]	Can be taken with gastric pH–elevating agents.	When famotidine 20 mg was coadministered with elbasvir/grazoprevir in 16 patients, there was an 11% increase in the C_{max} of elbasvir, a 5% increase in the AUC of elbasvir, an 11% decrease in the C_{max} of grazoprevir, and a 10% decrease in the AUC of grazoprevir. Coadministration of pantoprazole 40 mg QD and elbasvir/grazoprevir 50/100 mg in 16 patients increased the C_{max} and AUC of elbasvir by 2% and 5%, respectively, and that of grazoprevir by 10% and 12%, respectively.
Cardiovascular agents		
Ambrisentan [341]	Can be taken with gastric pH–elevating agents.	In a study based on population pharmacokinetics analysis in patients with pulmonary arterial hypertension, omeprazole showed a slight decrease in AUC that was not deemed clinically significant. This did not require any dose adjustments.
Amlodipine [342]	Can be taken with gastric pH–elevating agents.	Coadministration of amlodipine with cimetidine did not alter the PK of amlodipine. Coadministration of magnesium or aluminum hydroxide antacids also has no effect on amlodipine exposure.
Carvedilol [186]	Can be taken with gastric pH–elevating agents.	In a trial of 10 healthy male individuals, cimetidine 1000 mg/day increased the steady-state AUC of carvedilol by 30% with no change in C_{max}.
Dronedarone [343]	Can be taken with gastric pH–elevating agents.	Coadministration of pantoprazole did not have a significant effect on dronedarone pharmacokinetics.
Eprosartan [337, 344]	Can be taken with H2RAs.	The pharmacokinetics of eprosartan was not affected by concomitant administration of ranitidine.
Ezetimibe [345]	Can be taken with gastric pH–elevating agents.	Coadministration of cimetidine with ezetimibe resulted in a 6% increase in ezetimibe AUC and a 22% increase in $C_{max.}$
Fenofibric acid [346, 347]	No significant change in exposure with gastrointestinal-modifying agent.	Omeprazole 40 mg QD for 5 days with a single fasting dose of Trilipix® 135 mg increased AUC by 6% and C_{max} by 17%. In a second study conducted with the same dose taken with food, AUC increased by 4% and C_{max} decreased by 2%.
Fluvastatin [348]	Can be taken with gastric pH–elevating agents.	Coadministration of omeprazole 40 mg QD for 6 days and fluvastatin 20 mg QD increased AUC by 20% and C_{max} by 37%. These results were concluded to be not clinically significant.
Losartan [349]	Can be taken with gastric pH–elevating agents.	No clinically significant drug interactions have been found in studies of losartan potassium with cimetidine.
Moexipril [350]	Can be taken with gastric pH–elevating agents.	No clinically important pharmacokinetic interactions occurred when moexipril was taken concomitantly with cimetidine.
Nebivolol [351]	Can be taken with gastric pH–elevating agents.	Using population pharmacokinetics analyses derived from patients with hypertension, esomeprazole was observed to not have an effect on the pharmacokinetics of nebivolol.

Medication name	Directions of use with ARA [1]	Clinical data
Nifedipine [195-197, 352]	Can be taken with omeprazole.	A study in 10 nonsmoking healthy male individuals found no significant effect of single-dose omeprazole coadministration on PK parameters of nifedipine. Short-term omeprazole treatment increased the AUC of nifedipine by 26% (95% CI, 9%–46%), but all other PK parameters of nifedipine were not significantly changed. This effect was considered not likely to be of major clinical relevance. The exposure to nifedipine was not changed in the presence of pantoprazole in healthy volunteers. Coadministration of nifedipine and ranitidine did not affect exposure to nifedipine or blood pressure or heart rate in hypertensive or normotensive individuals. However, several studies on the coadministration of cimetidine and nifedipine found increases in AUC and C_{max} of ~50%–200% and relevant increase in blood pressure in both normotensive and hypertensive individuals. Thus, blood pressure should be monitored and a reduction of the nifedipine dose considered when coadministered with cimetidine.
Propranolol [353]	Can be taken with gastric pH–elevating agents.	No interaction was observed with omeprazole. No interactions were observed with either ranitidine or lansoprazole.
Sildenafil [354]	Can be taken with gastric pH–elevating agents.	Cimetidine coadministered with sildenafil increased AUC and C_{max} by 1.5-fold. Single doses of magnesium and aluminum hydroxide antacids did not affect sildenafil bioavailability.
Trandolapril [355]	Can be taken with gastric pH–elevating agents.	Coadministration of trandolapril and cimetidine increased C_{max} of trandolapril by ~44%, but had no effect on the pharmacokinetics of trandolapril or in angiotensin-converting enzyme inhibition.
Valsartan [356]	Can be taken with gastric pH–elevating agents.	No clinically significant pharmacokinetic interactions were observed when valsartan was coadministered with cimetidine.
Central nervous system agents		
Aripiprazole [357]	No dose adjustment is required when taken with H2RAs.	Famotidine, an H2RA, when taken with aripiprazole somewhat decreased AUC and C_{max}. Only slight changes in aripiprazole AUC and C_{max} were observed with coadministration with omeprazole. These results indicate no adjustment in dose of aripiprazole is required with coadministration.
Asenapine [358]	Can be taken with H2RAs without a dose adjustment.	No dose adjustment of asenapine is required.
Brexpiprazole [359]	Can be taken with pH-modifying agents without a dose adjustment to brexpiprazole.	Dose adjustment of brexpiprazole is not required when taken concomitantly with gastric pH modifiers (e.g., omeprazole) based on pharmacokinetic studies.
Diazepam [360]	Can be taken with antacids.	When antacids were concurrently taken, diazepam peak concentrations were 30% lower, but there was no effect on the extent of absorption. The lower peak concentrations appeared to be due to a slower rate of absorption, with an additional 20 to 25 minutes required to achieve peak concentrations in the presence of antacids. However, this difference was not statistically significant.
Divalproex [361, 362]	Can be taken with antacids and H2RAs.	Cimetidine and ranitidine do not affect the clearance of valproate (active moiety). A single study demonstrated a 3% to 28% increase in the AUC of valproate when valproic acid was coadministered with aluminum/magnesium hydroxide. The same study showed no effect from coadministration with magnesium trisilicate or calcium carbonate. The mechanism of this interaction is unknown. No adverse clinical effects were noted. In addition, there is no clinically meaningful increase in AUC and C_{max} with concomitant administration of carvedilol extended-release capsules with pantoprazole.

Medication name	Directions of use with ARA [1]	Clinical data
Donepezil [363]	Can be taken with H2RAs.	No effects of cimetidine on the PK of donepezil were observed in formal studies.
Duloxetine [364]	Can be taken with antacids. and H2RAs.	Coadministration of duloxetine delayed-release 40 mg with aluminum- and magnesium-containing antacids (51 mEq) or with famotidine had no significant effect on the rate or extent of duloxetine absorption. It is not known if duloxetine absorption is affected by concomitant administration of PPI.
Gabapentin [170, 171]	Can be taken with H2RA receptor antagonists and PPIs, but gabapentin should be taken at least 2 hours after administration of antacid (Maalox® [magnesium hydroxide and aluminum hydroxide]).	Coadministration of cimetidine 300 mg decreased the apparent oral clearance of gabapentin by 14% and clearance of creatinine, a marker of renal function, by 10%. This decrease is not expected to be clinically significant. The effect of gabapentin immediate release on cimetidine was not evaluated. In addition, in an open-label, randomized, crossover study evaluating the influence of concomitant administration of orally administered gabapentin 200 mg and omeprazole 20 mg in 13 healthy human individuals, plasma disposition parameters of gabapentin did not significantly differ between the treatments with and without omeprazole. Maalox® (magnesium hydroxide and aluminum hydroxide) reduced the mean bioavailability of gabapentin by ~20%, but this decrease was ~10% when gabapentin was administered 2 hours after Maalox®.
Gabapentin enacarbil [365]	Can be taken with H2RAs.	PK studies examining the potential interaction of coadministering gabapentin enacarbil with cimetidine revealed no significant interactions. Gabapentin released from gabapentin enacarbil is eliminated by renal clearance via OCT2, and cimetidine is a known substrate of this elimination pathway. Coadministration of gabapentin enacarbil 1200 mg QD with cimetidine 400 mg QID showed no effect on cimetidine exposure. The 24% increase in AUC of gabapentin and 20% decrease in renal clearance of gabapentin are not expected to be clinically relevant. No clinically relevant pharmacokinetic interactions are expected between gabapentin enacarbil and other substrates of OCT2 and monocarboxylate transporter type 1.
Lamotrigine XR [366]	Can be taken with gastric pH–elevating agents.	No significant change in lamotrigine levels and a small decrease in time to C_{max} were seen in a study of 30 individuals in whom lamotrigine was coadministered with esomeprazole. Gastric pH did not change compared with pre-lamotrigine dosing.
Lisdexamfetamine dimesylate [172, 367]	Can be taken with PPIs.	In a drug interaction study in healthy adults, coadministration of omeprazole did not change the AUC or C_{max} of lisdexamfetamine dimesylate. No dose adjustment is needed when lisdexamfetamine dimesylate is coadministered with omeprazole or lansoprazole.
Oxcarbazepine [368]	Can be taken with H2RAs.	Administration of cimetidine had no effect on the PK of the active metabolite of oxycarbazepine, 10-monohydroxy derivative.
Ramelteon [369]	Can be taken with PPIs.	Interaction studies of concomitant administration of ramelteon with omeprazole (CYP2C19 substrate) did not produce clinically meaningful changes in either peak or total exposures to ramelteon.
Risperidone [370]	Can be taken with H2RAs.	Ranitidine 150 mg BID when administered with a single dose of risperidone 1 mg resulted in a 20% increase in AUC and a 40% increase in C_{max}. Cimetidine 400 mg BID administered with a single dose of risperidone 1 mg resulted in a 10% increase in AUC and a 30% decrease in C_{max}. These results did not warrant any change to the dose of risperidone.
Sertindole [371]	Can be taken with antacids.	In a 4-way crossover study in 16 healthy volunteers, the mean relative bioavailability of sertindole 4 mg administered with Maalox® 45 mL was 98% compared with sertindole alone. Thus, sertindole can be administered with antacids.
Sodium oxybate [372]	Can be taken with PPIs.	Alteration of gastric pH with omeprazole produced no significant change in the PK of gamma-hydroxybutyrate, of

Medication name	Directions of use with ARA [1]	Clinical data
		which sodium oxybate is the sodium salt.
Valproic acid [373]	Can be taken with antacids. and H2RAs.	The absorption of valproate 500 mg was not affected when coadministered with antacids (Maalox, Trisogel, or Titralac, all 160 mEq doses). Cimetidine and ranitidine do not affect the clearance of valproate.
Venlafaxine [374, 375]	Can be taken with H2RAs.	Concomitant administration of venlafaxine and cimetidine in 18 healthy volunteers in steady state study showed inhibition of first-pass metabolism of venlafaxine. The AUC and C_{max} of venlafaxine were increased by ~60%. However, there was no apparent effect on the pharmacokinetics of O-desmethylvenlafaxine, the active metabolite of venlafaxine, which is present in the circulation in much greater quantities than venlafaxine. Thus, the overall pharmacologic activity of venlafaxine and O-desmethylvenlafaxine is expected to only slightly increase, so no dosage adjustment should be necessary in most normal adults. However, caution is advised for patients with pre-existing hypertension, elderly patients, and patients with hepatic dysfunction, given that the interaction associated with the concomitant use of venlafaxine and cimetidine is not known and could potentially be more pronounced. A retrospective cohort study of venlafaxine-treated patients found that patients who received venlafaxine coadministered with omeprazole or pantoprazole (each n = 40) had median plasma venlafaxine concentrations that were each 27% higher than those who received venlafaxine alone (n = 906). Additionally, median plasma concentrations of O-desmethylvenlafaxine were 36% higher in patients receiving venlafaxine with pantoprazole and 55% higher in patients receiving venlafaxine with omeprazole compared with patients who received venlafaxine alone. Variation in sample timing, lack of control for potential confounders, and lack of correlation to clinical outcomes all limit general applicability of these study results. The mechanism of this interaction has not been fully investigated, but omeprazole-/pantoprazole-mediated inhibition of CYP2C19-mediated venlafaxine metabolism may contribute.
Vilazodone hydrochloride [376]	Can be taken with PPIs.	The rate or extent of vilazodone absorption, time to C_{max}, and terminal elimination rate were not affected by coadministration with pantoprazole.
Zolpidem [377]	Can be taken with H2RAs.	A study of coadministration of zolpidem tartrate and cimetidine or ranitidine revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of zolpidem.
Analgesics		
Aspirin [378]	Can be taken with PPIs.	There was no pharmacokinetics interaction between esomeprazole 40 mg and aspirin 325 mg during repeated coadministration in healthy volunteers.
Diclofenac [362, 379, 380]	Can be taken without regard to acid suppressing agents.	In a crossover study of 18 healthy volunteers coadministered diclofenac 100 mg and ranitidine 300 mg, no significant effects on the pharmacokinetics of diclofenac were observed. Omeprazole pretreatment did not change the absorption parameters. Both of these treatments altered the diclofenac clearance, as assessed by the $AUC_{0-\infty}$/half-life, half-life, and elimination rate constant values; however, these changes were not considered to be clinically significant because of the wide therapeutic range for diclofenac.
Fenoprofen [381]	Can be taken with antacids.	The absorption of fenoprofen was not affected by the concomitant administration of antacid (containing both aluminum and magnesium hydroxide).
Meloxicam [382]	Can be taken with antacids. and H2RAs.	Concomitant administration of cimetidine 200 mg QID did not alter the pharmacokinetics of single-dose meloxicam 30 mg. No PK interaction was seen with concomitant administration of meloxicam and antacids.
Naproxen DR [383]	Can be taken with antacids.	The pharmacokinetics of naproxen were not significantly affected by concomitant administration of antacid.

Medication name	Directions of use with ARA [1]	Clinical data
Piroxicam [384]	Can be taken with antacids.	The concomitant administration of antacids had no effect on the plasma levels of piroxicam.
Sulindac [385]	Can be taken with antacids.	The extent of sulindac absorption was not significantly decreased with antacids containing magnesium hydroxide 200 mg and aluminum hydroxide 225 mg per 5 mL.
Tapentadol [386]	Can be used with gastric pH–elevating agents.	The pharmacokinetics of tapentadol were not affected when gastric pH was increased by omeprazole.
Tramadol [387]	Can be used with cimetidine.	Concomitant administration of tramadol immediate-release tablets and cimetidine did not result in clinically significant changes in tramadol pharmacokinetics. Thus, no alteration of the tramadol dosage regimen with cimetidine is recommended.
Blood-modifying agents		
Aspirin and extended-release dipyridamole [388]	Can be taken with PPIs.	A dedicated drug interaction study of omeprazole 80 mg QD and aspirin/dipyridamole BID in 60 healthy volunteers found similar dipyridamole C_{max} and AUC at steady state with and without omeprazole coadministration. The pharmacokinetics of acetylsalicylic acid were not characterized, but the antiplatelet activity (as measured by arachidonic acid–induced platelet aggregation) was similar between the treatment arms at steady state.
Betrixaban [389]	Can be taken with antacids. Can be taken with antacids. and PPIs.	Esomeprazole or antacids when coadministered with betrixaban had little effect on the betrixaban C_{max} and AUC.
Dabigatran etexilate [110–114, 390]	Can be taken with H2RA receptor antagonists and PPIs.	According to the Canadian product monograph for dabigatran etexilate, when taken with antacids, a 35% reduction in dabigatran exposure was observed in postoperative patients up to 24 hours after surgery. Dabigatran exposure was reduced by 11% >24 hours post surgery. Because of this larger risk for a decreased clinical (anticoagulant) effect, concomitant use of antacids with dabigatran should be avoided for 24 hours following orthopedic surgery. It is also recommended that dabigatran etexilate be taken 2 hours prior to antacids. The US product label for dabigatran etexilate does not include similar recommendations. A randomized crossover study of 37 patients with nonvalvular atrial fibrillation found that coadministration of PPIs with dabigatran significantly decreased the peak and trough dabigatran concentration, raising the possibility of decreased bioavailability of dabigatran. A prospective pilot study of patients with nonvalvular atrial fibrillation treated with dabigatran and omeprazole 20 mg BID or pantoprazole 40 mg QD found significantly lower peak and trough levels of dabigatran in patients treated with a PPI compared with those who were not. A retrospective, population-wide cohort study found lower risk of gastrointestinal bleeding in patients newly prescribed dabigatran with concomitant use of H2RAs (incidence rate ratio, 0.61) or PPIs (incidence rate ratio, 0.53). Ranitidine 150 mg QD taken with dabigatran showed little change in dabigatran AUC and C_{max}. Pantoprazole 40 mg BID when taken with dabigatran 150 mg BID decreased the dabigatran AUC by 24% and C_{max} by 28%. The concomitant use of PPIs and H2RAs did not appreciably change the trough concentration of dabigatran. The interaction with H2RAs and PPIs are deemed not clinically significant and do not require action when coadministered.
Prasugrel [391–393]	Can be taken with drugs that elevate gastric pH.	Daily coadministration of ranitidine or lansoprazole decreased the C_{max} of the prasugrel active metabolite by 14% and 29%, respectively, but the AUC and time to C_{max} of the active metabolite were unchanged. Prasugrel was administered in a large randomized trial without regard to coadministration of a PPI or H2 blocker.
Rivaroxaban [394]	Can be taken with drugs that elevate gastric pH.	Coadministration of single-dose rivaroxaban 30 mg with ranitidine 150 mg BID and aluminum hydroxide/magnesium hydroxide (10 mL) or single dose rivaroxaban 20 mg with omeprazole 40 mg QD did not affect the bioavailability or exposure of rivaroxaban.

Medication name	Directions of use with ARA [1]	Clinical data
Vorapaxar [395, 396]	Can be taken with antacids. Can be taken with antacids. and PPIs.	Coadministration of aluminum hydroxide/magnesium carbonate (Gaviscon® extra strength) 20 mL modestly decreased vorapaxar AUC by 15% and C_{max} by 38% and increased median time to C_{max} by 1 hour. The AUC and C_{max} of vorapaxar were 41% and 29% higher, respectively, in elderly vs young individuals. A dose adjustment of vorapaxar 40 mg is not needed for coadministration of an antacid containing aluminum hydroxide/magnesium carbonate (Gaviscon extra strength) 20 mL. The coadministration of pantoprazole 40 mg with vorapaxar did not affect the AUC or C_{max} of vorapaxar, and a dose adjustment of vorapaxar is not needed.
Diabetes agents		
Glimepiride [247]	Can be taken with H2RAs.	H2RAs may increase the glucose-lowering effect of sulfonylureas, including glimepiride, thus increasing the susceptibility to and/or intensity of hypoglycemia. Coadministration of cimetidine 800 mg QD or ranitidine 150 mg BID with a single oral dose of glimepiride 4 mg did not significantly alter the absorption and disposition of glimepiride in a randomized, open-label, 3-way crossover study in healthy volunteers.
Pioglitazone [397]	Can be taken with H2RAs.	Co-administration of pioglitazone 45 mg for 7 days with ranitidine 150 mg BID for either 4 or 7 days resulted in no significant effect on the AUC or C_{max} of pioglitazone.
Repaglinide [398]	Can be taken with H2RAs.	The absorption and disposition of repaglinide were not significantly altered by coadministration with cimetidine.
Saxagliptin [399]	Can be taken with gastric pH–elevating agents without a dose adjustment.	In a study conducted with saxagliptin 10 mg and omeprazole 40 mg QD for 5 days, there was a 13% increase in AUC and a 2% decrease in C_{max}. With aluminum hydroxide 2400 mg/magnesium hydroxide 2400 mg/simethicone 240 mg, AUC decreased by 3% and C_{max} by 26%. With famotidine 40 mg, AUC and C_{max} increased by 3% and 14%, respectively. No dosing adjustments of saxagliptin are needed with omeprazole, aluminum hydroxide/magnesium hydroxide/simethicone, or famotidine.
Gastrointestinal agents		
Obeticholic acid [400]	Can be taken with PPIs.	Concomitant administration of omeprazole 20 mg QD with obeticholic acid 10 mg QD increased obeticholic acid AUC by <1.2-fold, but this is not expected to be clinically relevant. Concomitant administration of omeprazole 20 mg QD with obeticholic acid 10 mg QD led to increases in omeprazole AUC and C_{max} of 32% and 33%, respectively, but the clinical significance of these increases is not known.
Sulfasalazine [401]	Can be taken with H2RA receptor antagonists and PPIs.	In a 3-period crossover study of 36 healthy volunteers, the pharmacokinetics of enteric-coated sulfasalazine 500 mg were not affected by pantoprazole 40 mg or famotidine 40 mg in any genotypic cohort for breast cancer resistance protein.
Endocrine agents		
Eliglustat [402]	Can be taken with antacids. Can be taken with antacids and PPIs.	Gastric pH–modifying agents (aluminum hydroxide, magnesium hydroxide, calcium carbonate, or pantoprazole) did not have a clinically significant effect on eliglustat pharmacokinetics.
Paricalcitol [403, 404]	Can be taken with gastric pH–elevating agents.	A single-dose crossover study in 26 healthy volunteers found that administration of omeprazole 40 mg ~2 hours before paricalcitol 16 µg did not affect the pharmacokinetics of paricalcitol, with point estimates of bioavailability of 1.032 for C_{max} and 1.041 for AUC.
Musculoskeletal agents		
Febuxostat [405]	Can be taken with antacids. Can be taken with antacids.	Concomitant ingestion of magnesium hydroxide/aluminum hydroxide with a single dose of febuxostat 80 mg delayed absorption of febuxostat by ~1 hour and decreased C_{max} by 31% and AUC_{∞} by 15%. Because AUC rather than C_{max} was related to drug effect, the change observed in AUC is not considered to be clinically significant. Thus, febuxostat

Medication name	Directions of use with ARA [1]	Clinical data
		80 mg may be taken without regard to antacid use.
Dermatological Agents		
Acitretin [406]	Can be taken with cimetidine.	In studies of in vivo pharmacokinetic drug interactions, no interaction was seen between acitretin and cimetidine.
Contraceptives		
Ulipristal acetate [407]	Can be taken with drugs increasing gastric pH.	In a study of 18 healthy volunteers who were coadministered ulipristal acetate 10 mg and esomeprazole 20 mg, the ulipristal acetate C_{max} decreased by 65%, but $AUC_{0-\infty}$ increased by 11%. No clinically significant effects are expected from coadministration with drugs increasing gastric pH with chronic administration of ulipristal acetate.

ARA, acid-reducing agent; AUC, area under the curve; BID, twice daily; CI, confidence interval; C_{max}, maximum serum concentration; CYP, cytochrome P450; H2, histamine H_2; H2RA, h2 resistor antagonist, HIV, human immunodeficiency virus; OCT2, organic cation transporter 2; PK, pharmacokinetics; PPI, proton pump inhibitor; QD, once daily; QID, 4 times daily; TID, 3 times daily.

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