Concise Review of Drug Interactions between Hepatitis C Direct Acting Antiviral Agents and Acid Reducing Agents

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Clinical importance of drug-drug interactions between hepatitis C virus direct acting antivirals and acid reducing agents

Maximal efficacy of direct acting antivirals (DAAs) for the treatment of hepatitis C virus (HCV) requires adequate drug absorption and bioavailability. However, the use of acid-reducing agents in patients treated with DAAs is common and may induce clinically significant drug-drug interactions that alter plasma DAA concentrations, which may lead to inadequate virologic response or adverse events. As plasma DAA concentrations are not routinely monitored in patients, it is important to understand the risk of these interactions and counsel patients appropriately, thereby maximizing antiviral potential and achieving sustained virologic response.

We therefore reviewed DAA product package inserts and utilized both the Liverpool HIV drug interaction website and Lexicomp database to collect information on the effect of various acid-reducing agents (i.e., proton pump inhibitors, histamine H2 receptor antagonists, and antacids containing aluminum, magnesium, calcium, or sodium) on the pharmacokinetics of DAAs in order to provide clinicians with a single easy-to-use reference for co-administering medications from these drug classes (Tables 1-3). We also gathered dose equivalency tables to allow prescribers to switch between acid reducing agents within and between therapeutic classes and to calculate dose equivalencies (Tables 4-5). Certain acid-reducing agents may negatively affect the bioavailability of ledipasvir and velpatasvir to varying degrees. Additionally, reductions in proton pump inhibitor plasma concentrations may occur when combined with paritaprevir, ritonavir, and ombitasvir with and without dasabuvir.

Reviewed resources suggest that some of the interactions between DAAs and acid-reducing agents may be mitigated by temporal separation of dose administration. Educating patients about the importance of reporting the use of any acid-reducing agents, whether prescription or over-the-counter, is essential to optimizing the treatment of HCV infection, as is the need for care providers and patients to agree upon strategies for managing gastric symptoms and HCV simultaneously. Clinicians should be aware of the potential drug-drug interactions between some HCV DAAs and acid-reducing agents.

Table 1: Proton pump inhibitor (PPI) interactions with hepatitis C direct acting antivirals (HCV DAAs)

	Dexlansoprazole	**Esomeprazole**	**Lansoprazole**	**Omeprazole**	**Pantoprazole**	**Rabeprazole**
Daclatasvir (Daklinza)	Insufficient data.[1]	No clinically significant interaction expected. No dose adjustment of daclatasvir is required.[2]	No clinically significant interaction expected. No dose adjustment of daclatasvir is required.[2]	No clinically significant interaction.[3] No dose adjustment of daclatasvir is required.[2]	No clinically significant interaction expected. No dose adjustment of daclatasvir is required.[2]	No clinically significant interaction expected. No dose adjustment of daclatasvir is required.[2]
Elbasvir/Grazoprevir (Zepatier)	No dose adjustment is required.[4]	No dose adjustment is required.[2, 4]	No dose adjustment is required.[2, 4]	No dose adjustment is required.[2, 4]	No dose adjustment is required.[2, 4]	No dose adjustment is required.[2, 4]

Glecaprevir/Pibrentasvir (Mavyret)	Insufficient data.[1]	No dose adjustment is required.[2]	No dose adjustment is required.[2]	No clinically significant interaction. No dose adjustment is required.[2, 5]	No dose adjustment is required.[2]	No dose adjustment is required.[2]
Ledipasvir/Sofosbuvir (Harvoni)	PPI doses comparable to omeprazole 20 mg or lower can be administered simultaneously under fasted conditions.[6] PPI doses should not be taken before Harvoni.[2]	PPI doses comparable to omeprazole 20 mg or lower can be administered simultaneously under fasted conditions.[6] PPI doses should not be taken before Harvoni.[2]	PPI doses comparable to omeprazole 20 mg or lower can be administered simultaneously under fasted conditions.[6] PPI doses should not be taken before Harvoni.[2]	Omeprazole 20 mg or lower can be administered simultaneously under fasted conditions.[6] PPI doses should not be taken before Harvoni.[2]	PPI doses comparable to omeprazole 20 mg or lower can be administered simultaneously under fasted conditions.[6] PPI doses should not be taken before Harvoni.[2]	PPI doses comparable to omeprazole 20 mg or lower can be administered simultaneously under fasted conditions.[6] PPI doses should not be taken before Harvoni.[2]
Paritaprevir/Ritonavir/Ombitasvir (Technivie)	Insufficient data.[1]	Monitor for potential decreased efficacy of esomeprazole. Use higher doses of esomeprazole if clinically indicated.[2]	Monitor for potential decreased efficacy of lansoprazole. Use higher doses of lansoprazole if clinically indicated.[2]	Monitor for decreased efficacy of omeprazole.[7] Use higher doses of omeprazole if clinically indicated.[2] Avoid use of more than 40 mg per day of omeprazole.[7]	Monitor for potential decreased efficacy of pantoprazole. Use higher doses of pantoprazole if clinically indicated.[2]	Monitor for potential decreased efficacy of rabeprazole. Use higher doses of rabeprazole if clinically indicated.[2]

Paritaprevir/Ritonavir/Ombitasvir with Dasabuvir (Viekira)	Insufficient data.[1]	Monitor for potential decreased efficacy of esomeprazole. Use higher doses of esomeprazole if clinically indicated.[2]	Monitor for potential decreased efficacy of lansoprazole. Use higher doses of lansoprazole if clinically indicated.[2]	Monitor for decreased efficacy of omeprazole. Use higher doses of omeprazole if clinically indicated.[2] Avoid use of more than 40 mg per day of omeprazole.[8]	Monitor for potential decreased efficacy of pantoprazole. Use higher doses of pantoprazole if clinically indicated.[2]	Monitor for potential decreased efficacy of rabeprazole. Use higher doses of rabeprazole if clinically indicated.[2]
Sofosbuvir (Sovaldi)	Insufficient data.[1]	No clinically significant interaction expected.[2]	No clinically significant interaction expected.[2]	No clinically significant interaction expected.[2]	No clinically significant interaction expected.[2]	No clinically significant interaction expected.[2]
Sofosbuvir/Velpatasvir (Epclusa)	As per US prescribing information, coadministration with PPIs is not recommended.[9] As per European SPC, Epclusa could be taken with food and 4 hours before a PPI at a dose not to exceed that comparable to omeprazole 20 mg.[2]	As per US prescribing information, coadministration with PPIs is not recommended.[2, 9] As per European SPC, Epclusa could be taken with food and 4 hours before a PPI at a dose not to exceed that comparable to omeprazole 20 mg.[2]	As per US prescribing information, coadministration with PPIs is not recommended.[2, 9] As per European SPC, Epclusa could be taken with food and 4 hours before a PPI at a dose not to exceed that comparable to omeprazole 20 mg.[2]	As per US prescribing information, coadministration with PPIs is not recommended. If considered medically necessary; take Epclusa with food and 4 hours before omeprazole 20 mg.[2, 9]	As per US prescribing information, coadministration with PPIs is not recommended.[2, 9] As per European SPC, Epclusa could be taken with food and 4 hours before a PPI at a dose not to exceed that comparable to omeprazole 20 mg.[2]	As per US prescribing information, coadministration with PPIs is not recommended.[2, 9] As per European SPC, Epclusa could be taken with food and 4 hours before a PPI at a dose not to exceed that comparable to omeprazole 20 mg.[2]

Sofosbuvir/Velpatasvir/Voxilaprevir (Vosevi)	As per US prescribing information, coadministration of PPIs is not recommended.[2] If considered medically necessary, as per European SPC, Vosevi could be taken with a PPI at a dose not to exceed that comparable to omeprazole 20 mg.[2]	As per US prescribing information, coadministration of PPIs is not recommended.[2] If considered medically necessary, as per European SPC, Vosevi could be taken with a PPI at a dose not to exceed that comparable to omeprazole 20 mg.[2]	As per US prescribing information, coadministration of PPIs is not recommended.[2] If considered medically necessary, as per European SPC, Vosevi could be taken with a PPI at a dose not to exceed that comparable to omeprazole 20 mg.[2]	Omeprazole 20 mg can be administered with Vosevi.[10]	As per US prescribing information, coadministration of PPIs is not recommended.[2] If considered medically necessary, as per European SPC, Vosevi could be taken with a PPI at a dose not to exceed that comparable to omeprazole 20 mg.[2]	As per US prescribing information, coadministration of PPIs is not recommended.[2] If considered medically necessary, as per European SPC, Vosevi could be taken with a PPI at a dose not to exceed that comparable to omeprazole 20 mg.[2]

Key: SPC= summary of product characteristics

Table 2: Histamine H2 antagonist (H2RA) interactions with hepatitis C direct acting antivirals (HCV DAAs)

	Cimetidine	**Famotidine**	**Nizatidine**	**Ranitidine**
Daclatasvir (Daklinza)	No clinically significant interaction expected.[2]	No clinically significant interaction expected.[2,3]	No clinically significant interaction expected.[2,3]	No clinically significant interaction expected.[2,3]
Elbasvir/Grazoprevir (Zepatier)	No clinically significant interaction expected.[2,4]	No clinically significant interaction expected.[2,4]	No clinically significant interaction expected.[2,4]	No clinically significant interaction expected.[2,4]
Glecaprevir/Pibrentasvir (Mavyret)	No clinically significant interaction expected.[2,5]	No clinically significant interaction expected.[2,5]	No clinically significant interaction expected.[2,5]	No clinically significant interaction expected. [2,5]
Ledipasvir/Sofosbuvir (Harvoni)	Acid reducing agents decreases Ledipasvir: May be administered simultaneously with or 12 hours apart or a dose that does not exceed doses comparable to famotidine 40 mg twice daily. [6]			
Paritaprevir/Ritonavir/Ombitasvir (Technivie)	No clinically significant interaction expected.[2,7]	No clinically significant interaction expected.[2,7]	No clinically significant interaction expected. [2,7]	No clinically significant interaction expected. [2,7]
Paritaprevir/Ritonavir/Ombitasvir	No clinically significant	No clinically significant	No clinically significant	No clinically significant

with Dasabuvir (Viekira)	interaction expected.[2,8]	interaction expected.[2,8]	interaction expected. [2,8]	interaction expected. [2,8]
Sofosbuvir (Sovaldi)	No clinically significant interaction expected.[2]	No clinically significant interaction expected. [2]	No clinically significant interaction expected. [2]	No clinically significant interaction expected. [2]
Sofosbuvir/Velpatasvir (Epclusa)	Acid reducing agents decreases Velpatasvir: May be administered simultaneously with or 12 hours apart from Epclusa at a dose that does not exceed doses comparable to famotidine 40 mg twice daily. [9]			
Sofosbuvir/Velpatasvir/Voxilaprevir (Vosevi)	Acid reducing agents decreases Velpatasvir: May be administered simultaneously with or staggered from Vosevi at a dose that does not exceed doses comparable to famotidine 40 mg twice daily. [10]			

Table 3: Antacid interactions with hepatitis C direct acting antivirals (HCV DAAs)

	Antacids containing aluminum hydroxide, calcium carbonate, magnesium hydroxide or sodium bicarbonate
Daclatasvir (Daklinza)	No clinically significant interaction is expected.[2, 3]
Elbasvir/Grazoprevir (Zepatier)	No dose adjustment is required.[2, 4]
Glecaprevir/Pibrentasvir (Mavyret)	No dose adjustment is required.[2]
Ledipasvir/Sofosbuvir (Harvoni)	Separate administration by 4 hours.[2, 6]
Paritaprevir/Ritonavir/Ombitasvir (Technivie)	No dose adjustment is required.[2]
Paritaprevir/Ritonavir/Ombitasvir with Dasabuvir (Viekira)	No dose adjustment is required. [2]
Sofosbuvir (Sovaldi)	Separate doses by 2 hours. [2]
Sofosbuvir/Velpatasvir (Epclusa)	Separate administration by 4 hours. [2, 9]
Sofosbuvir/Velpatasvir/Voxilaprevir (Vosevi)	Separate administration by 4 hours [2, 10]

Table 4: Proton pump inhibitor (PPI) dose comparison[11]

	Daily Dose Providing Similar Efficacy for GERD and/or Effects on Gastric pH	
PPI	**Low Dose**	**High Dose**
Dexlansoprazole	30 mg	60 mg
Esomeprazole	10 mg	20 mg to 40 mg
Lansoprazole	15 mg	30 mg
Omeprazole	10 mg	20 mg
Pantoprazole	20 mg	40 mg
Rabeprazole	N/A	20 mg

Key: GERD= Gastroesophageal reflux disease; N/A= not applicable

Table 5: Histamine H2 antagonist (H2RA) dose comparison[12]

	Maintenance Dose	**Active Ulcer**	**GERD/Erosive Esophagitis**
Cimetidine	400 mg HS	800 mg HS	1600 mg BID or QID
Famotidine	20 mg HS	40 mg HS	20 mg BID (GERD), 20 or 40 mg BID (erosive esophagitis)
Nizatidine	150 mg HS	300 mg HS	150 mg BID
Ranitidine	150 mg HS	300 mg HS	150 mg BID (GERD), 150 mg QID (erosive esophagitis)

Key: GERD= Gastroesophageal reflux disease; HS= at bedtime

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