HCV Drug Interactions and Side Effects





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DRUG SIDE EFFECTS OF HCV AGENTS – GENERAL CONSIDERATIONS

Summary
Direct acting agents are generally well tolerated. Common side effects which occur at a rate of 5-10% among all choices include:

- Headache
- Fatigue
- Weakness
- Nausea

The rate of these side effects increase to about 10-20% when sofosbuvir is included in the regimen. When ribavirin is added to the treatment regimen, patients may experience similar side effects as above plus insomnia & anemia.

BLACK BOX WARNING for all direct acting agents
Hepatitis B Virus reactivation in patients coinfected with HCV and HBV (during and post treatment) may result in fulminant hepatitis, hepatic failure, and death. Management: • Test all patients for evidence of current or prior HBV infection before initiating treatment with direct acting agents. • Monitor HCV/HBV coinfected patients for HBV reactivation and hepatitis flare during HCV treatment and post-treatment follow-up. • Initiate appropriate patient management for HBV infection as clinically indicated.

COMMON SIDE EFFECTS

Detail (from respective Prescribing Information)

elbasvir/grazoprevir (Zepatier)
Most common (≥5%): fatigue (11%), headache (10%), nausea (11%)
With ribavirin (≥5%): anemia (8%), headache (6%)
In HIV/HCV co-infected (≥5%): fatigue (7%), headache (7%), nausea (5%), insomnia (5%), diarrhea (5%)

glecaprevir/pibrentasvir (Mavyret)
Most common (≥5%): headache (13%), fatigue (11%), nausea (8%)

sofosbuvir/ledipasvir (Harvoni)
Most common (≥5%): fatigue (10%); headache (14%); asthenia (18%), nausea (7%), insomnia (5%)
With ribavirin (≥5%): asthenia (36%), headache (13%), cough (11%), dyspnea (9%), irritability (7%)
In HIV/HCV co-infected (≥10%): headache (20%), fatigue (17%)

paritaprevir/ritonavir/ombitasvir/dasabuvir (Viekira Pak)
Most common (≥5%): nausea (8%), pruritus (7%), insomnia (5%)

With ribavirin (≥10%): fatigue (34%), nausea (22%), pruritus (18%), other skin reactions (16%), insomnia (14%), asthenia (14%)
In HIV/HCV co-infected (≥10%): fatigue (48%), insomnia (19%), nausea (17%), headache (16%), pruritus (13%), cough (11%), irritability (10%), ocular icterus (10%)

paritaprevir/ritonavir/ombitasvir (Technivie)
Most common (≥5%): asthenia (25%), nausea (9%), fatigue (7%), insomnia (5%), pruritus (5%), skin reactions (5%)
With ribavirin (≥5%): asthenia (29%), nausea (14%), fatigue (15%), insomnia (13%), pruritus (7%), skin reactions (7%)

sofosbuvir (Sovaldi) – use with daclatasvir (Daklinza)
With ribavirin (≥10%): fatigue (38%), headache (24%), nausea (22%), insomnia (15%), pruritus (11%), anemia (10%), irritability (10%)
With ribavirin & peg-IFN (≥10%): fatigue (59%), headache (36%), nausea (34%), insomnia (25%), anemia (21%), rash (18%), decreased appetite (18%), pyrexia (18%), pruritus (17%), chills (17%), neutropenia (17%), flu-like symptoms (16%), myalgia (14%), irritability (13%), diarrhea (12%)

daclatasvir (Daklinza) – use with sofosbuvir (Sovladi)
Most common with Sovaldi (≥5%): headache (14%), fatigue (14%), nausea (8%), diarrhea (5%)
With ribavirin and Sovaldi (≥5%): anemia (20%), fatigue (15%), nausea (15%), headache (12%), rash (8%), somnolence (5%)
In HIV/HCV co-infected with Sovaldi (≥5%): fatigue (15%), nausea (9%), headache (8%), diarrhea (7%)

sofusbuvir/velpatasvir (Epclusa)
Most common (≥5%): headache (22%), fatigue (15%), nausea (9%), asthenia (5%), insomnia (5%)
With ribavirin (≥10%): fatigue (32%), anemia (26%), nausea (15%), headache (11%), insomnia (11%), diarrhea (10%)
In HIV/HCV co-infected (≥10%): fatigue (22%), headache (10%)

sofosbuvir/velpatasvir/voxilaprevir (Vosevi)
Most common (≥5%): headache (21%), fatigue (17%), diarrhea (13%), nausea (13%), asthenia (6%), insomnia (6%)

ribavirin (Copegus, Rebetol)
With direct acting agents: See individual agents above
With peg-IFN (Pegasys) (≥10%): fatigue/asthenia (65%), pyrexia (41%), rigors (25%), pain (10%), nausea/vomiting (25%), diarrhea (11%), lymphopenia (14%), anemia (11%), neutropenia (27%), anorexia (24%), wt loss (10%), myalgia (40%), arthralgia (22%), headache (43%), dizziness (14%), irritability (33%), insomnia (30%), depression (20%), poor concentration (10%), dyspnea (13%), cough (10%), alopecia (28%), pruritus (19%), dermatitis (16%), dry skin (10%)
In HIV/HCV co-infected with peg-IFN that were more frequent than mono-infected: neutropenia (40%), anemia (14%), thrombocytopenia (8%), wt loss (16%), mood alteration (9%)

DRUG INTERACTIONS – GENERAL CONSIDERATIONS

Direct acting agents have major drug interactions with commonly used drugs such as anticlotting agents, statins, and antihypertensives not to mention HIV medications. These interactions may lead to subtherapeutic doses of direct acting agents leading to HCV treatment failure or supratherapeutic levels of the interacting agent. **Because of the risks involved, a full medication history and review as well as drug interaction checking with all prescription medications, over the counter medications, vitamins, as well as supplements is imperative.** Below are drug interaction checking resources grouped by most preferred to least preferred. If you use a phone app, ensure that the app is always kept up to date.

Tier 1: Professional drug references (preferred, if available)
Lexicomp (also available through UpToDate) Micromedex
Tier 2: Recommended free resources; comprehensive, but may not include all prescription drugs or supplements
https://www.hep-druginteractions.org/checker https://online.epocrates.com/interaction-check
Tier 3: Freely available; comprehensive, but may be incomplete or not up to date; use at your own risk; recommend using at least 2-3 resources to cross verify information
https://reference.medscape.com/drug-interactionchecker https://www.webmd.com/interaction-checker/default.htm https://www.drugs.com/drug_interactions.php https://www.umms.org/ummc/patients-visitors/health-library/drug-interaction-tool

HCV DRUG-DRUG INTERACTIONS AND CONTRAINDICATED COMBINATIONS

elbasvir/grazoprevir (Zepatier)

Important drug interactions with Zepatier by class:

Class	**Drug**	**Effect on Concentration**	**Recommendation**
Antibiotic	nafcillin	↓ Zepatier	Avoid co-administration
Anticoagulant	warfarin	↑↓ warfarin	Monitor INR frequently
Antifungal	ketoconazole	↑ Zepatier	Avoid co-administration
Endothelin Antagonist	bosentan	↓ Zepatier	Avoid co-administration
HIV Medication	**etravirine**	**↓ Zepatier**	**Avoid co-administration**
HIV Medication	**cobicistat**	**↑ Zepatier**	**Avoid cobicistat-containing regimens**

Immunosuppressant	tacrolimus	↑ tacrolimus	Monitor tacrolimus levels
Statin	atorvastatin	↑ atorvastatin	Max 20 mg atorvastatin
Statin	rosuvastatin	↑ rosuvastatin	Max 10 mg rosuvastatin
Statin	fluvastatin lovastatin simvastatin	↑ statin	Monitor for statin side effects; use lowest necessary statin dose
Wakefulness Agent	modafinil	↓ Zepatier	Avoid co-administration

Drugs contraindicated with Zepatier by class:

Class	**Contraindicated Drugs**
Anticonvulsants	phenytoin carbamazepine
Antimycobacterials	rifampin
Herbal Products	St. John's Wort
HIV Medications	**atazanavir** **efavirenz** **darunavir** **lopinavir** **saquinavir** **tipraniavir**
Immunosuppressants	cyclosporine

glecaprevir/pibrentasvir (Mavyret)

Important drug interactions with Mavyret by class:

Class	**Drug**	**Effect on Concentration**	**Recommendation**
Antiarrhythmic	digoxin	↑ digoxin	Reduce digoxin by 50%; monitor digoxin levels
Anticoagulant	warfarin	↑↓ warfarin	Monitor INR frequently
Anticoagulant	dabigatran	↑ dabigatran	Adjust dabigatran dose
Anticonvulsant	carbamazepine	↓ Mavyret	Avoid co-administration
Herbal Product	St. John's Wort	↓ Mavyret	Avoid co-administration
HIV Medication	**efavirenz**	**↓ Mavyret**	**Avoid co-administration**
HIV Medication	**darunavir** **lopinavir** **ritonavir**	**↑ Mavyret**	**Avoid co-administration**
Hormonal Agent	ethinyl estradiol & containing including oral contraceptives	No effect on drug concentration; may ↑ ALT with co-administration	Avoid co-administration
Immunosuppressant	cyclosporine	↑ Mavret	Avoid co-administration in pt requiring >100 mg cyclosporine daily
Statin	atorvastatin lovastatin	↑ statin	Avoid co-administration

	simvastatin		
Statin	pravastatin	↑ pravastatin	Reduce pravastatin by 50%
Statin	rosuvastatin	↑ rosuvastatin	Max 10 mg rosuvastatin
Statin	fluvastatin pitavastatin	↑ statin	Monitor for statin side effects; use lowest necessary statin dose

Drugs contraindicated with Mavyret by class:

Class	**Contraindicated Drugs**
Antimycobacterials	rifampin
HIV Medications	**atazanavir**

sofosbuvir/ledipasvir (Harvoni)

Important drug interactions with Harvoni by class:

Class	**Drug**	**Effect on Concentration**	**Recommendation**
Acid Reducing Agent	antacids (Al, Mg)	↓ Harvoni	Separate by 4 hours
Acid Reducing Agent	H2-blocker (e.g. famotidine)	↓ Harvoni	Give at same time or separate by 12 hours; Max 40 mg famotidine 2x/d or equivalent
Acid Reducing Agent	PPI (e.g. omeprazole)	↓ Harvoni	Give at same time fasting; Max omeprazole 20 mg or equivalent
Antiarrhythmic	amiodarone	Unknown	Avoid co-administration & recent discontinuation due to serious symptomatic bradycardia; if unavoidable, initiate in hospital with cardiac monitoring
Antiarrhythmic	digoxin	↑ digoxin	Monitor digoxin levels
Anticoagulant	warfarin	↑↓ warfarin	Monitor INR frequently
Anticonvulsant	carbamazepine phenytoin phenobarbital oxcarbazepine	↓ Harvoni	Avoid co-administration
Antimycobacterial	rifabutin rifampin rifapentine	↓ Harvoni	Avoid co-administration
Herbal Product	St. John's Wort	↓ Harvoni	Avoid co-administration
HIV Medication	**tenofovir DF containing *without* HIV protease inhibitor/ritonavir or cobicistat**	**↑ tenofovir**	**Monitor for tenofovir-associated adverse reactions**

HIV Medication	**tenofovir DF containing *<u>with</u>* HIV protease inhibitor/ritonavir or cobicistat**	**↑ tenofovir**	**Safety of ↑ tenofovir concentrations not established; Consider alternative HCV or antiretroviral therapy. If unavoidable, monitor for tenofovir-associated adverse reactions**
HIV Medication	**elvitegravir, cobicistat, emtricitabine, tenofovir DF**	**↑ tenofovir**	**Avoid co-administration**
HIV Medication	**tipranavir/ ritonavir**	**↓ Harvoni**	**Avoid co-administration**
Statin	atorvastatin	↑ atorvastatin	Monitor for statin side effects
Statin	rosuvastatin	↑ rosuvastatin	Avoid co-administration

Drugs contraindicated with Harvoni by class:

Class	**Contraindicated Drugs**
Antiarrhythmic	amiodarone (see above)

<u>paritaprevir/ritonavir/ombitasvir/dasabuvir (Viekira Pak)</u>

Important drug interactions with Viekira by class:

Class	**Drug**	**Effect on Concentration**	**Recommendation**
Acid Reducing Agent (PPI)	omeprazole	↓ omeprazole	Monitor for ↓ omeprazole efficacy; increase dose if not well controlled; Max 40 mg omeprazole daily
Angiotensin receptor blocker (ARB)	valsartan losartan candesartan	↑ ARB	Decrease ARB; monitor for hypotension
Antiarrhythmic	amiodarone bepridil disopyramide flecainide lidocaine (systemic) mexiletine propafenone quinidine	↑ antiarrhythmic	Therapeutic concentration monitoring (if available)
Antidiabetic	metformin	↑↓ metformin	Monitor for signs of lactic acidosis; Avoid co-administration in patients with renal insufficiency or hepatic impairment.
Anticoagulant	warfarin	↑↓ warfarin	Monitor INR frequently
Antifungal	ketoconazole	↑ ketoconazole	Max 200 mg ketoconazole daily

Antifungal	voriconazole	↓ voriconazole	Avoid co-administration unless benefit > risk
Antipsychotic	quetiapine	↑ quetiapine	Consider alternative HCV treatment; if unavoidable, reduce quetiapine to 1/6th current dose & monitor for quetiapine adverse reactions
Calcium channel blocker (CCB)	amlodipine nifedipine diltiazem verapamil	↑ CCB	Decrease CCB; Decrease amlodipine by at least 50%; monitor for edema and/or hypotension
Corticosteroids	fluticasone	↑ fluticasone	Consider alternative corticosteroid
Diuretic	furosemide	↑ furosemide	Monitor for dehydration, creatinine level, and electolytes
HIV Medication	**atazanavir/ritonavir once daily**	**↑ Viekira**	**Give atazanavir 300 mg daily (without ritonavir) in the morning.**
HIV Medication	**darunavir/ritonavir**	**↓ darunavir**	**Darunavir 800 mg daily (no ritonavir) OK with Viekira. Avoid co-administration with darunavir/ritonavir 600/100 mg 2x/d.**
HIV Medication	**lopinavir/ritonavir**	**↑ Viekira**	**Avoid co-administration**
HIV Medication	**rilpivirine**	**↑ rilpivirine**	**Avoid co-administration**
Immunosuppressant	cyclosporine	↑ cyclosporine	Reduce cyclosporine to 1/5th current dose; monitor cyclosporine levels & renal function.
Long Acting Beta Agonist (LABA)	salmeterol	↑ salmeterol	Avoid co-administration; increased risk of CV events
Muscle relaxants	carisoprodol cyclobenzaprine	↓ muscle relaxant & metabolites	Increase dose if clinically indicated
Narcotic analgesic	hydrocodone/ acetaminophen	↑ hydrocodone	Decrease hydrocodone by 50%; monitor for respiratory depression & sedation frequently
Narcotic analgesic	buprenorphine/ naloxone	↑ buprenorphine & metabolites	Monitor closely for sedation & cognitive effects
Sedative/Hypnotic	alprazolam	↑ alprazolam	Monitor; decrease alprazolam based on clinical response
Sedative/Hypnotic	diazepam	↓ diazepam & metabolites	Monitor; increase diazepam if clinically indicated
Statin	pravastatin	↑ pravastatin	Max 40 mg pravastatin
Statin	rosuvastatin	↑ rosuvastatin	Max 10 mg rosuvastatin

Drugs contraindicated with Viekira by class:

Class	**Contraindicated Drugs**
Alpha 1 receptor antagonist	alfuzosin
Anti-anginal	ranolazine

Antiarrhythmic	dronedarone
Anticonvulsants	carbamazepine phenytoin phenobarbital
Anti-gout	colchicine
Antihyperlipidemic agent	gemfibrozil
Antimycobacterials	rifampin
Antipsychotic	lurasidone pimozide
Ergot derivatives	ergotamine dihydroergotamine methylergonovine
GI Motility Agent	cisapride
Herbal Products	St. John's Wort
HIV Medications	**efavirenz**
Hormonal agents	ethinyl estradiol-containing including oral contraceptives
Immunosuppressants	everolimus sirolimus tacrolimus
PDE-5 inhibitors	sildenafil when dosed as Revatio for PAH
Sedatives/hypnotics	triazolam midazolam
Statins	atorvastatin lovastatin simvastatin

paritaprevir/ritonavir/ombitasvir (Technivie)

Important drug interactions with Technivie by class:

Class	**Drug**	**Effect on Concentration**	**Recommendation**
Acid Reducing Agent (PPI)	omeprazole	↓ omeprazole	Monitor for ↓ omeprazole efficacy; increase dose if not well controlled; Max 40 mg omeprazole daily
Angiotensin receptor blocker (ARB)	valsartan losartan candesartan	↑ ARB	Decrease ARB; monitor for hypotension
Antiarrhythmic	amiodarone bepridil disopyramide digoxin flecainide lidocaine (systemic) mexiletine	↑ antiarrhythmic	Therapeutic concentration monitoring (if available). Reduce digoxin by 30-50% and monitor levels

	propafenone quinidine		
Antidiabetic	metformin	↑↓ metformin	Monitor for signs of lactic acidosis; Avoid co-administration in patients with renal insufficiency or hepatic impairment.
Anticoagulant	warfarin	↑↓ warfarin	Monitor INR frequently
Antifungal	ketoconazole	↑ ketoconazole	Max 200 mg ketoconazole daily
Antifungal	voriconazole	↓ voriconazole	Avoid co-administration unless benefit > risk
Antipsychotic	quetiapine	↑ quetiapine	Consider alternative HCV treatment; if unavoidable, reduce quetiapine to 1/6th current dose & monitor for quetiapine adverse reactions
Calcium channel blocker (CCB)	amlodipine nifedipine diltiazem verapamil	↑ CCB	Decrease CCB; Decrease amlodipine by at least 50%; monitor for edema and/or hypotension
Corticosteroids	fluticasone	↑ fluticasone	Consider alternative corticosteroid
Diuretic	furosemide	↑ furosemide	Monitor
HIV Medication	**atazanavir** **atazanavir/ritonavir**	**↑ Viekira**	**Avoid co-administration**
HIV Medication	**darunavir/ritonavir**	**↓ darunavir**	**Darunavir 800 mg daily (no ritonavir) OK with Viekira.** **Avoid co-administration with darunavir/ritonavir 600/100 mg 2x/d.**
HIV Medication	**lopinavir/ritonavir**	**↑ Viekira**	**Avoid co-administration**
HIV Medication	**rilpivirine**	**↑ rilpivirine**	**Avoid co-administration**
Immunosuppressant	cyclosporine	↑ cyclosporine	Reduce cyclosporine to 1/5th current dose; monitor cyclosporine levels & renal function.
Long Acting Beta Agonist (LABA)	salmeterol	↑ salmeterol	Avoid co-administration; increased risk of CV events
Muscle relaxants	carisoprodol cyclobenzaprine	↓ muscle relaxant & metabolites	Increase dose if clinically indicated
Narcotic analgesic	hydrocodone/ acetaminophen	↑ hydrocodone	Decrease hydrocodone by 50%; monitor for respiratory depression & sedation frequently
Narcotic analgesic	buprenorphine/ naloxone	↑ buprenorphine & metabolites	Monitor closely for sedation & cognitive effects
Sedative/Hypnotic	alprazolam	↑ alprazolam	Monitor; decrease alprazolam based on clinical response
Sedative/Hypnotic	diazepam	↓ diazepam & metabolites	Monitor; increase diazepam if clinically indicated

Statin	pravastatin	↑ pravastatin	Max 40 mg pravastatin

Drugs contraindicated with Technivie by class:

Class	**Contraindicated Drugs**
Alpha 1 receptor antagonist	alfuzosin
Anti-anginal	ranolazine
Antiarrhythmic	dronedarone
Anticonvulsants	carbamazepine phenytoin phenobarbital
Antimycobacterials	rifampin
Antipsychotic	lurasidone pimozide
Ergot derivatives	ergotamine dihydroergotamine methylergonovine
GI Motility Agent	cisapride
Herbal Products	St. John's Wort
HIV Medications	**efavirenz**
Hormonal agents	ethinyl estradiol-containing including oral contraceptives
Immunosuppressants	everolimus sirolimus tacrolimus
PDE-5 inhibitors	sildenafil when dosed as Revatio for PAH
Sedatives/hypnotics	triazolam midazolam
Statins	atorvastatin lovastatin simvastatin

<u>sofosbuvir (Sovaldi) – use with daclatasvir (Daklinza)</u>

Important drug interactions with Sovaldi by class:

Class	**Drug**	**Effect on Concentration**	**Recommendation**
Anticoagulant	warfarin	↑↓ warfarin	Monitor INR frequently
Anticonvulsant	carbamazepine phenytoin phenobarbital oxcarbazepine	↓ Solvadi	Avoid co-administration
Antimycobacterial	rifabutin rifapentine	↓ Solvadi	Avoid co-administration
HIV Medication	**tipranavir/ritonavir**	**↓ Sovaldi**	**Avoid co-administration**

Drugs contraindicated with Sovaldi by class:

Class	Contraindicated Drugs
Antiarrhythmic	amiodarone
Antimycobacterials	rifampin
Herbal Products	St. John's Wort

daclatasvir (Daklinza) – use with sofosbuvir (Sovaldi)

Important drug interactions with Daklinza by class:

Class	Drug	Effect on Concentration	Recommendation
Antiarrhythmic	amiodarone	Unknown	Avoid co-administration & recent discontinuation due to serious symptomatic bradycardia; if unavoidable, cardiac monitoring inpatient x48 hrs recommended, then heart rate monitoring daily for next 2 weeks for bradycardia
Antiarrhythmic	digoxin	↑ antiarrhythmic	Therapeutic concentration monitoring (if available). Start digoxin at lowest appropriate dose, monitor levels, & adjust as indicated. Decrease current digoxin by 15-30%, monitor levels, & adjust as indicated.
Antibiotic	nafcillin	↓ Daklinza	Increase Daklinza to 90 mg daily
Antibiotic	clarithromycin telithromycin	↑ Daklinza	Decrease Daklinza to 30 mg daily
Anticoagulant	dabigatran	↑ dabigatran	Co-administration not recommended in renal impairment. Refer to dabigatran dosing.
Anticoagulant	warfarin	↑↓ warfarin	Monitor INR frequently
Antidepressant	nefazodone	↑ Daklinza	Decrease Daklinza to 30 mg daily
Antifungal	ketoconazole itraconazole posaconazole voriconazole	↑ Daklinza	Decrease Daklinza to 30 mg daily
Antimycobacterial	rifapentine	↓ Daklinza	Increase Daklinza to 90 mg daily
Corticosteroids	dexamethasone	↓ Daklinza	Increase Daklinza to 90 mg daily
Endothelin Antagonist	bosentan	↓ Daklinza	Increase Daklinza to 90 mg daily

HIV Medication (Protease inhibitors)	**atazanavir/ritonavir indinavir nelfinavir saquinavir**	**↑ Daklinza**	**Decrease Daklinza to 30 mg daily**
HIV Medication	**cobicistat-containing regimens EXCEPT darunavir+cobicistat**	**↑ Daklinza**	**Decrease Daklinza to 30 mg daily**
HIV Medication (NNRTI)	**efavirenz etravirine nevirapine**	**↓ Daklinza**	**Increase Daklinza to 90 mg daily**
Narcotic analgesic	buprenorphine +/- naloxone	↑ buprenorphine & metabolites	Monitor closely for sedation & cognitive effects
Statin	atorvastatin fluvastatin pitavastatin pravastatin rosuvastatin simvastatin	↑ statin	Monitor for statin side effects such a myopathy
Wakefulness Agent	modafinil	↓ Daklinza	Increase Daklinza to 90 mg daily

Drugs contraindicated with Daklinza by class:

Class	**Contraindicated Drugs**
Anticonvulsants	phenytoin, carbamazepine
Antimycobacterials	rifampin
Herbal Products	St. John's Wort

<u>sofusbuvir/velpatasvir (Epclusa)</u>

Important drug interactions with Epclusa by class:

Class	**Drug**	**Effect on Concentration**	**Recommendation**
Acid Reducing Agent	antacids (Al, Mg)	↓ Epclusa	Separate by 4 hours
Acid Reducing Agent	H2-blocker (e.g. famotidine)	↓ Epclusa	Give at same time or separate by 12 hours; Max 40 mg famotidine 2x/d or equivalent
Acid Reducing Agent	PPI (e.g. omeprazole)	↓ Epclusa	Avoid co-administration; if unavoidable, take Epclusa with food 4 hours <u>prior</u> to omeprazole 20 mg daily max. Other PPIs have not been studied.
Antiarrhythmic	amiodarone	Unknown	Avoid co-administration & recent discontinuation due to serious symptomatic bradycardia; if

			unavoidable, cardiac monitoring inpatient x48 hrs recommended, then heart rate monitoring daily for next 2 weeks for bradycardia
Antiarrhythmic	digoxin	↑ digoxin	Monitor digoxin levels and adjust as indicated
Anticancer	topotecan	↑ topotecan	Avoid co-administration
Anticoagulant	warfarin	↑↓ warfarin	Monitor INR frequently
Anticonvulsant	carbamazepine phenytoin phenobarbital oxcarbazepine	↓ Epclusa	Avoid co-administration
Antimycobacterial	rifabutin rifampin rifapentine	↓ Epclusa	Avoid co-administration
Herbal Product	St. John's Wort	↓ Epclusa	Avoid co-administration
HIV Medication	**efavirenz**	**↓ Epclusa**	**Avoid co-administration**
HIV Medication	**tenofovir DF containing regimens**	**↑ tenofovir**	**Monitor for tenofovir-associated adverse reactions**
HIV Medication	**tipranavir/ ritonavir**	**↓ Epclusa**	**Avoid co-administration**
Statin	atorvastatin	↑ atorvastatin	Monitor for statin side effects
Statin	rosuvastatin	↑ rosuvastatin	Max 10 mg rosuvastatin

Drugs contraindicated with Epclusa by class:

Class	**Contraindicated Drugs**
Antiarrhythmic	Amiodarone (see above)

<u>sofosbuvir/velpatasvir/voxilaprevir (Vosevi)</u>

Important drug interactions with Vosevi by class:

Class	**Drug**	**Effect on Concentration**	**Recommendation**
Acid Reducing Agent	antacids (Al, Mg)	↓ Vosevi	Separate by 4 hours
Acid Reducing Agent	H2-blocker (e.g. famotidine)	↓ Vosevi	Give at same time or separate by 12 hours; Max 40 mg famotidine 2x/d or equivalent
Acid Reducing Agent	PPI (e.g. omeprazole)	↓ Vosevi	Omeprazole 20 mg daily max may be administered with Vosevi. Other PPIs have not been studied.
Antiarrhythmic	amiodarone	Unknown	Avoid co-administration & recent discontinuation due to serious symptomatic bradycardia; if unavoidable, cardiac monitoring

			inpatient x48 hrs recommended, then heart rate monitoring daily for next 2 weeks for bradycardia
Antiarrhythmic	digoxin	↑ digoxin	Monitor digoxin levels and adjust as indicated
Anticancer	methotrexate mitoxantrone imatinib irinotecan lapatinib topotecan	↑↓ Vosevi and/or anticancer agent	Avoid co-administration
Anticoagulant	dabigatran	↑ dabigatran	Monitor clinically; reduce dabigatran for moderate renal impairment
Anticoagulant	warfarin	↑↓ warfarin	Monitor INR frequently
Anticonvulsant	carbamazepine phenytoin phenobarbital oxcarbazepine	↓ Vosevi	Avoid co-administration
Anti-inflammatory	sulfasalazine	↑ sulfasalazine	Avoid co-administration
Antimycobacterial	rifabutin rifapentine	↓ Vosevi	Avoid co-administration
Herbal Product	St. John's Wort	↓ Vosevi	Avoid co-administration
HIV Medication	**efavirenz**	**↓ Vosevi**	**Avoid co-administration**
HIV Medication	**tenofovir DF containing regimens**	**↑ tenofovir**	**Monitor for tenofovir-associated adverse reactions and renal function**
HIV Medication	**atazanavir lopinavir**	**↑ Vosevi**	**Avoid co-administration**
HIV Medication	**tipranavir/ ritonavir**	**↓ Vosevi**	**Avoid co-administration**
Immunosuppressant	cyclosporine	↑ cyclosporine	Avoid co-administration
Statin	atorvastatin fluvastatin lovastatin simvastatin	↑ statin	Use lowest approved statin dose (atorvastatin 10 mg, fluvastatin 20 mg, lovastatin 10 mg, simvastatin 5 mg). If higher doses required, use lowest necessary dose based on risk/benefit assessment.
Statin	pravastatin	↑ pravastatin	Max 40 mg pravastatin
Statin	rosuvastatin	↑ rosuvastatin	Avoid co-administration
Statin	pitavastatin	↑ pitavastatin	Avoid co-administration

Drugs contraindicated with Vosevi by class:

Class	**Contraindicated Drugs**
Antiarrhythmic	amiodarone (see above)
Antimycobacterial	rifampin

ribavirin (Copegus, Rebetol)

Important drug interactions with ribavirin by class:

Class	Drug	Effect on Concentration	Recommendation
HIV Medication	**NRTI (generally)**	**↑ NRTI**	**Monitor for NRTI adverse reactions including hepatic decompensation and anemia. Discontinue of NRTI should be considered as medically appropriate.**
HIV Medication	**didanosine**	**↑ didanosine**	**Avoid co-administration (contraindicated)**
HIV Medication	**zidovudine**		**Avoid co-administration due to increased risk of severe neutropenia and severe anemia**
Immunosuppressant	azathioprine	↑ azathioprine	Monitor CBC & platelets weekly for 1st month, then q2wks for months 2 & 3, then monthly

Drugs contraindicated with ribavirin by class:

Class	Contraindicated Drugs
HIV Medication	didanosine (see above)
Specific populations	Pregnancy & men whose female partners are pregnant; hemoglobinopathies (thalassemia major & sickle-cell anemia); autoimmune hepatitis

RENAL DOSE ADJUSTMENT & MONITORING

elbasvir/grazoprevir (Zepatier)
CrCl >50 ml/min: No dosage adjustment necessary.
CrCl ≤50 ml/min: No dosage adjustment necessary. With ribavirin, refer to ribavirin dosing.
ESRD/hemodialysis: No dosage adjustment necessary. Not removed by hemodialysis.

glecaprevir/pibrentasvir (Mavyret)
No dosage adjustment necessary.

sofosbuvir/ledipasvir (Harvoni)
eGFR ≥30 ml/min: No dosage adjustment necessary
eGFR <30 ml/min: No dosage adjustment provided in label. Sofosbuvir & metabolite accumulate in pt with severely impaired renal function.

ESRD/hemodialysis: No dosage adjustment provided in label. Sofosbuvir & metabolite accumulate in pt with severely impaired renal function. In a 4hr dialysis session, 18% sofosbuvir dose was removed.

paritaprevir/ritonavir/ombitasvir/dasabuvir (Viekira Pak)
CrCl ≥15 ml/min: No dosage adjustment necessary.
ESRD on dialysis: No dosage adjustment necessary.

paritaprevir/ritonavir/ombitasvir (Technivie)
CrCl ≥15 ml/min: No dosage adjustment necessary.
ESRD on dialysis: No dosage adjustment provided in label (has not been studied).

sofosbuvir (Sovaldi) – use with daclatasvir (Daklinza)
eGFR ≥30 ml/min: No dosage adjustment necessary
eGFR <30 ml/min: No dosage adjustment provided in label (has not been studied). Sofosbuvir metabolite accumulates in impaired renal function.
ESRD/hemodialysis: No dosage adjustment provided in label (has not been studied). Sofosbuvir metabolite accumulates in impaired renal function.

daclatasvir (Daklinza) – use with sofosbuvir (Sovaldi)
No dosage adjustment necessary.

sofusbuvir/velpatasvir (Epclusa)
eGFR ≥30 ml/min: No dosage adjustment necessary
eGFR <30 ml/min: No dosage adjustment provided in label. Sofosbuvir & metabolite accumulate in pt with severe renal impairment.
ESRD/hemodialysis: No dosage adjustment provided in label. Sofosbuvir & metabolite accumulate in pt with severe renal impairment.

sofosbuvir/velpatasvir/voxilaprevir (Vosevi)
eGFR ≥30 ml/min: No dosage adjustment necessary
eGFR <30 ml/min: No dosage adjustment provided in label (has not been studied). Sofosbuvir metabolite accumulates in impaired renal function.
ESRD/hemodialysis: No dosage adjustment provided in label (has not been studied). Sofosbuvir metabolite accumulates in impaired renal function.

ribavirin (Copegus, Rebetol)
Rebetol capsules/solution
CrCl ≥50 ml/min: No dosage adjustment necessary
CrCl <50 ml/min: Use is contraindicated

Ribasphere ***capsules***
CrCl ≥50 ml/min: No dosage adjustment necessary
CrCl <50 ml/min: Use is contraindicated

Ribasphere ***tablets***
CrCl ≥50 ml/min: No dosage adjustment necessary
CrCl <50 ml/min: Use is not recommended

Copegus and Moderiba tablets
CrCl >50 ml/min: No dosage adjustment necessary
CrCl 30-50 ml/min: Alternate 200 mg and 400 mg every other day
CrCl <30 ml/min including ESRD with hemodialysis: Reduce to 200 mg once daily