



Daclatasvir (Daklinza™) Abbreviated New Drug Update

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OVERVIEW¹

- Daclatasvir (Daklinza) is a hepatitis C virus (HCV) NS5A inhibitor that is indicated for use with sofosbuvir (Sovaldi) with or without ribavirin for the treatment of chronic HCV genotype 1 or 3 infection.
- Daclatasvir was first approved in July 2015 to be used in combination with sofosbuvir for the treatment of chronic HCV genotype 3 infections. The additional indication for the treatment of genotype 1 patients was approved in February 2016.
- Sustained virologic response (SVR12) rates are reduced in genotype 3 patients with cirrhosis receiving daclatasvir in combination with sofosbuvir for 12 weeks.
- Dosage and Administration:
 - ❑ For genotype 1a patients with cirrhosis, consider testing for the presence of virus with NS5A polymorphisms at amino acid positions M28, Q30, L31, and Y93.
 - ❑ The recommended dose of daclatasvir is 60 mg taken orally once daily with or without food in combination with sofosbuvir for a treatment duration of 12 weeks.
 - ❑ The dosage should be reduced to 30 mg once daily if taken concomitantly with strong CYP3A inhibitors. The dosage should be increased to 90 mg once daily with moderate CYP3A inducers.

Genotype	Patient Population	Treatment and Duration
Genotype 1	Without cirrhosis	daclatasvir + sofosbuvir for 12 weeks
	Compensated (Child-Pugh A) cirrhosis	
	Decompensated (Child Pugh B or C) cirrhosis	daclatasvir + sofosbuvir + ribavirin for 12 weeks
	Post-transplant	
Genotype 3	Without cirrhosis	daclatasvir + sofosbuvir for 12 weeks
	Compensated (Child-Pugh A) or decompensated (Child-Pugh B or C) cirrhosis	daclatasvir + sofosbuvir + ribavirin for 12 weeks
	Post-transplant	

- Patients with HCV/HIV-1 coinfection should follow the same dose recommendations as monoinfected patients while accounting for drug-drug interactions.
- For HCV genotype 1 or 3 patients with Child-Pugh B or C cirrhosis or post-transplantation patients, the starting dose of ribavirin is 600 mg once daily, increasing up to 1,000 mg daily as tolerated. The starting dose and on-treatment dose of ribavirin can be decreased based on hemoglobin and creatinine clearance.
- For HCV genotype 3 patients with compensated cirrhosis (Child-Pugh A), the recommended dosing of ribavirin is based on weight (1,000 mg for patients weighing less than 75 kg and 1,200 mg for those weighing at least 75 kg administered orally in two divided doses with food).
- Contraindications:
 - ❑ Daclatasvir is contraindicated when used in combination with strong inducers of CYP3A, including phenytoin, carbamazepine, rifampin, and St. John's wort.
- Warnings:
 - ❑ Coadministration of sofosbuvir with amiodarone may cause serious symptomatic bradycardia, particularly in patients also receiving beta blockers or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with daclatasvir in combination with sofosbuvir is not recommended. In patients with no alternative treatment options, cardiac monitoring in an inpatient setting for the first 48 hours of coadministration is recommended, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment.
- Drug Interactions:
 - ❑ Daclatasvir is a substrate of CYP3A. Therefore, moderate or strong inducers of CYP3A may decrease the plasma levels and therapeutic effect of daclatasvir. Strong inhibitors of CYP3A (e.g., clarithromycin, itraconazole, ketoconazole, ritonavir) may increase the plasma levels of daclatasvir.
 - ❑ Daclatasvir is an inhibitor of P-glycoprotein transporter (P-gp), organic anion transporting polypeptide (OATP) 1B1 and 1B3, and breast cancer resistance protein (BCRP). Administration of daclatasvir may increase systemic exposure to medicinal products that are substrates of P-gp, OATP 1B1 or 1B3, or BCRP (e.g., digoxin, statins, dabigatran), which could increase or prolong their therapeutic effect or adverse reactions.

Concomitant Drug Class: Drug Name	Effect On Concentration	Clinical Comments
Anticonvulsants		
phenytoin, carbamazepine	loss of virologic response	Contraindicated
Antimycobacterial Agents		
Rifampin	loss of virologic response	Contraindicated
Herbal Products		
St. John's wort (<i>Hypericum perforatum</i>)	loss of virologic response	Contraindicated
HIV Antiviral Agents		
Protease inhibitors: Atazanavir with ritonavir Indinavir Nelfinavir Saquinavir	↑ daclatasvir	Decrease daclatasvir dose to 30 mg once daily.
Other antiretrovirals: Cobicistat-containing antiretroviral regimens Examples: atazanavir/cobicistat, elvitegravir/cobicistat/ emtricitabine/ tenofovir disoproxil fumarate	↑ daclatasvir	Decrease daclatasvir dose to 30 mg once daily except with darunavir combined with cobicistat.
Non-nucleoside reverse transcriptase inhibitors (NNRTI): Efavirenz Etravirine Nevirapine	↓ daclatasvir	Increase daclatasvir dose to 90 mg once daily.
Strong CYP3A Inhibitors		
Examples: clarithromycin, itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, voriconazole	↑ daclatasvir	Decrease daclatasvir dose to 30 mg once daily when coadministered with strong inhibitors of CYP3A.
Moderate CYP3A Inducers		
Examples: bosentan, dexamethasone, modafinil, nafcillin, rifapentine	↓ daclatasvir	Increase daclatasvir dose to 90 mg once daily when coadministered with moderate inducers of CYP3A.

Concomitant Drug Class: Drug Name	Effect On Concentration	Clinical Comments
Anticoagulants		
dabigatran etexilate mesylate	↑ dabigatran	Use of daclatasvir with dabigatran etexilate is not recommended in specific renal impairment groups, depending on the indication. Please see the dabigatran prescribing information for specific recommendations.
Cardiovascular Agents		
Amiodarone	effects unknown	Coadministration of amiodarone with daclatasvir in combination with sofosbuvir is not recommended because it may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. If coadministration is required, cardiac monitoring is recommended.
Digoxin	↑ digoxin	Patients already receiving daclatasvir initiating digoxin: Initiate digoxin using the lowest appropriate dosage. Monitor digoxin concentrations; adjust digoxin doses if necessary and continue monitoring. Patients already receiving digoxin prior to initiating daclatasvir: Measure serum digoxin concentrations before initiating daclatasvir. Reduce digoxin concentrations by decreasing digoxin dosage by approximately 30 % to 50% or by modifying the dosing frequency and continue monitoring.
Lipid-Lowering Agents		
HMG-CoA reductase inhibitors: Atorvastatin Fluvastatin Pitavastatin Pravastatin Rosuvastatin Simvastatin	↑ Atorvastatin ↑ Fluvastatin ↑ Pitavastatin ↑ Pravastatin ↑ Rosuvastatin ↑ Simvastatin	Monitor for HMG-CoA reductase inhibitor associated adverse events such as myopathy.
Narcotic Analgesic/Treatment of Opioid Dependence		
buprenorphine buprenorphine/naloxone	↑ buprenorphine ↑ norbuprenorphine	For buprenorphine or buprenorphine/naloxone, no adjustment is needed, but clinical monitoring for buprenorphine associated adverse events is recommended.

- Adverse Reactions:
 - ❑ Most common adverse reactions ($\geq 10\%$) observed with daclatasvir in combination with sofosbuvir was headache (14%) and fatigue (14%).

CLINICAL CONSIDERATIONS^{2,3,4,5,6}

- ALLY-1: A prospective, phase III, open-label study evaluated a 12-week regimen of daclatasvir, sofosbuvir, and ribavirin in HCV patients with either cirrhosis (Child-Pugh class A, B, or C) and potential need for future liver transplantation, or with recurrence of HCV after a liver transplant. Of the 113 patients enrolled, 58% of subjects had HCV genotype 1a, 19% had HCV genotype 1b, 4% had genotype 2, 15% had genotype 3, 4% had genotype 4, and 1% had genotype 6. Fifty-eight percent and 60% of patients were treatment experienced in the post-transplant and the cirrhosis group, respectively. The primary efficacy endpoint was SVR12. In the advanced cirrhosis group, 82% of genotype 1 patients reached SVR12 as well as 95% of genotype 1 patients in the post-transplant group. Overall, among genotype 1 cirrhotic patients, SVR12 were 91%, 92%, and 50%, respectively for Child-Pugh class A, B, and C. The most common adverse effects ($>10\%$ of patients) reported were headache, fatigue, anemia, diarrhea, nausea and arthralgia, with no deaths reported to be related to treatment. Two patients in both the cirrhosis group and transplant group experienced a grade 3-4 adverse effect (anemia and non-cardiac chest pain; arthralgia and headache).
- ALLY-2: An open-label trial evaluated daclatasvir plus sofosbuvir for 12 weeks in HCV treatment-naïve ($n=101$) or HCV treatment-experienced ($n=52$) HCV/HIV coinfection patients. Sixty-eight percent of subjects had HCV genotype 1a, 15% had HCV genotype 1b, 8% had genotype 2, 7% had genotype 3, and 2% had genotype 4. Twenty-nine patients (14%) had cirrhosis. In the genotype 1 subgroup, SVR12 was 96% in treatment naïve patients and 98% in treatment-experienced patients. SVR12 rates were high in patients with cirrhosis (91%) and patients without cirrhosis (98%). Patients with HCV genotype 3 infection showed an overall SVR12 rate of 100%. There were no study-drug discontinuations because of adverse events. The most common adverse events were fatigue, nausea, and headache.
- ALLY-3: A phase III trial conducted in patients with HCV genotype 3 infection evaluated the 12-week regimen of daclatasvir plus sofosbuvir in treatment-naïve ($n = 101$) or treatment-experienced ($n = 51$) patients. Overall, 21% of patients had cirrhosis (treatment naïve: 19%; treatment experienced: 25%). SVR12 rates were 90% in treatment-naïve patients (98% non-cirrhosis and 58% with cirrhosis) and 86% in treatment-experienced patients (92% non-cirrhosis and 69% with cirrhosis), respectively. Overall, SVR12 rates were higher in patients without cirrhosis (96%) than in those with cirrhosis (63%). An SVR12 was achieved by 25 of 31 patients with previous relapse and by all 7 null responders, 2 partial responders, and 2 patients who experienced virologic breakthrough. Of whom, 5 of 7 patients previously failed treatment with a sofosbuvir containing regimen, 2 patients previously failed telaprevir containing regimens, and 2 patients previously failed alisporivir-containing regimens. Daclatasvir and sofosbuvir were well tolerated; there were no deaths or adverse events (AEs) leading to discontinuation. The most common AEs (in $>10\%$ of patients) were headache, fatigue, and nausea, and the incidence of grade 3 AEs was low (2%), with no grade 4 AEs reported.
- Currently, the AASLD/IDSA Recommendations for Testing, Managing, and Treating Hepatitis C recommends the use of daily daclatasvir in combination with sofosbuvir in treatment-naïve and treatment-experienced patients with HCV genotype 1, 2 or 3 infections.

REFERENCES

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