



Daclatasvir (Daklinza™) New Drug Update

July 2015

Drug Name:	Daclatasvir
Trade Name (Manufacturer):	Daklinza (Bristol-Myers Squibb)
Form:	Tablets
Strength:	30 mg; 60 mg
FDA Approval:	July 24, 2015
Market Availability:	Currently Available
FDA Approval Classification:	Priority Review
Classification:	Specific Therapeutic Class (HIC3): Hepatitis C Virus – NS5A Replication Complex Inhibitors (WOA)

INDICATION¹

Daklinza (daclatasvir) is a hepatitis C virus (HCV) NS5A inhibitor indicated for use with sofosbuvir for the treatment of chronic HCV genotype 3 infections. Sustained virologic response (SVR) rates are reduced in patients with cirrhosis.

CONTRAINDICATIONS/WARNINGS

Daclatasvir is contraindicated when used in combination with strong inducers of CYP3A, including phenytoin, carbamazepine, rifampin, and St. John's wort.

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 two 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
Strong CYP3A Inhibitors		
Examples: atazanavir/ritonavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, saquinavir, telithromycin, voriconazole	↑ daclatasvir	Decrease daclatasvir dose to 30 mg once daily when coadministered with strong inhibitors of CYP3A.
Moderate CYP3A Inhibitors		
Examples: atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil	↑ daclatasvir	Monitor for daclatasvir adverse events.
Moderate CYP3A Inducers		
Examples: bosentan, dexamethasone, efavirenz, etravirine, modafinil, nafcillin, rifapentine	↓ daclatasvir	Increase daclatasvir dose to 90 mg once daily when coadministered with moderate inducers of CYP3A.
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	<p>Patients already receiving daclatasvir initiating digoxin:</p> <ul style="list-style-type: none"> ▪ Initiate digoxin using the lowest appropriate dosage. Monitor digoxin concentrations; adjust digoxin doses if necessary and continue monitoring. <p>Patients already receiving digoxin prior to initiating daclatasvir:</p> <ul style="list-style-type: none"> ▪ 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.

COMMON ADVERSE EFFECTS

Most common adverse reactions ($\geq 10\%$) observed with daclatasvir in combination with sofosbuvir were headache (14%) and fatigue (14%).

SPECIAL POPULATIONS

Pregnancy

No data with daclatasvir in pregnant women are available to inform a drug-associated risk. Benefits and risks should be considered when prescribing daclatasvir to a pregnant woman.

Pediatrics

Safety and effectiveness of daclatasvir in pediatric patients younger than 18 years of age have not been established.

Geriatrics

Safety was similar across older and younger subjects and there were no safety findings unique to subjects 65 years and older. Sustained virologic response (SVR) rates were comparable among older and younger subjects.

Hepatic/Renal Impairment

No dosage adjustment of daclatasvir is required for patients with mild (Child-Pugh A), moderate (Child-Pugh B), or severe (Child-Pugh C) hepatic impairment. Safety and efficacy of daclatasvir have not been established in patients with decompensated cirrhosis. No dosage adjustment of daclatasvir is required for patients with any degree of renal impairment.

Liver Transplant Patients

The safety and efficacy of daclatasvir combination therapy have not been established in liver transplant patients.

DOSAGES

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 optimal duration of daclatasvir and sofosbuvir for patients with cirrhosis has not been established. 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.

CLINICAL TRIALS²

A literature search was conducted using “daclatasvir” and “hepatitis C.”

ALLY-3: A phase III trial conducted in patients with HCV genotype 3 infection evaluated the 12-week regimen of daclatasvir 60 mg plus sofosbuvir 400 mg in treatment naïve (n=101) or treatment experienced (n=51) patients. Overall, 21% of patients had cirrhosis (treatment naïve: 19%; treatment experienced: 25%). Co-primary endpoints were the proportions of treatment-naïve and treatment-

experienced patients achieving a sustained virologic response (SVR) at post-treatment week 12 (SVR12). 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%). SVR12 was achieved by 25 of 31 patients with previous relapse and by all seven null responders, two partial responders, and two patients who experienced virologic breakthrough. Of whom, five of seven patients previously failed treatment with a sofosbuvir containing regimen, two patients previously failed telaprevir containing regimens, and two 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.

OTHER DRUGS USED FOR CONDITION³

Other AASLD/IDSA recommended treatment options for patients with chronic HCV genotype 3 infections include daily sofosbuvir plus weight based ribavirin with weekly interferon for 12 weeks or daily sofosbuvir plus weight based ribavirin without weekly interferon for 24 weeks (FDA-approved) for both treatment-naïve and treatment experienced patients.

PLACE IN THERAPY

Daclatasvir is approved for use in combination with sofosbuvir for treatment in patients with chronic HCV genotype 3 infections. Currently, the AASLD/IDSA Recommendations for Testing, Managing, and Treating Hepatitis C recommends the use of daclatasvir plus sofosbuvir in treatment-naïve and treatment experienced-patients genotypes 3 with or without cirrhosis. In addition, for genotype 3 patients, AASLD/IDSA also recommends daily sofosbuvir plus weight based ribavirin plus weekly interferon for 12 weeks in treatment-naïve and treatment-experienced (previously failed interferon plus ribavirin) patients who qualify for interferon based therapy. For patients who are not interferon eligible, daily sofosbuvir plus weight based ribavirin for 24 weeks may be considered. In clinical trials, sofosbuvir plus ribavirin for 24 weeks resulted in SVR12 of 93% in patients with genotype 3 infections who are treatment naïve (93% non-cirrhosis versus 92% cirrhosis) and 77% in patients with genotype 3 infections who are treatment experienced (85% non-cirrhosis versus 60% cirrhosis). Compared to sofosbuvir plus ribavirin with or without interferon, daclatasvir plus sofosbuvir provided a higher rate of SVR12 and offer another option to patients with genotype 3 infections who have previously failed sofosbuvir based therapy. Even though the AASLD/IDSA Recommendations also included daclatasvir plus sofosbuvir for patients with genotype 1 and 2, daclatasvir is not FDA approved in these two genotypes.

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	Hepatitis C Agents
Clinical Edit	<ul style="list-style-type: none"> ▪ Age \geq 18 years ▪ Diagnosis of chronic HCV genotype 3 infection ▪ Must be used in combination with sofosbuvir 400 mg tablet daily for the entire 12 week duration ▪ For patients without cirrhosis (F2-F3), daclatasvir will be approved regardless of previous treatments ▪ For patients who are treatment-naïve with cirrhosis (F4), daclatasvir will be approved after the patient has tried and failed sofosbuvir+ribavirin+peginterferon for 12 weeks OR sofosbuvir+ribavirin for 24 weeks ▪ For patients who are treatment-experienced with cirrhosis (F4), daclatasvir will be approved if the patient has tried and failed sofosbuvir+ribavirin+peginterferon or if interferon ineligible ▪ Deny is patient is also taking any of the following contraindicated medications: phenytoin, carbamazepine, rifampin, and St. John's wort ▪ Approve 30 mg daily if patient is taking a strong CYP3A inhibitor (e.g., atazanavir/ritonavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, saquinavir, telithromycin, voriconazole) ▪ Approve 90 mg daily if patient is taking moderate CYP3A inducers (e.g., bosentan, dexamethasone, efavirenz, etravirine, modafinil, nafcillin, rifapentine) ▪ Treatment must be prescribed by or in consultation with a gastroenterologist, hepatologist, or infectious disease specialist ▪ Patient must be evaluated for current alcohol and substance abuse
Quantity Limit	28 tablets/28 days
Duration of Approval	12 weeks

REFERENCES

1 Daklinza [package insert]. Princeton, NJ; Bristol-Myers Squibb; July 2015.

2 Nelson DR, Cooper JN, Lalezari JP, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. *Hepatology*. 2015 Apr;61(4):1127-35.

3 HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. American Association for the Study of Liver Diseases. Available at: <http://www.hcvguidelines.org/full-report>. Accessed August 21, 2015.