Daclatasvir (Daklinza®) plus Sofosbuvir (Sovaldi™) for HCV Genotype 3

National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, VISN Pharmacist Executives and Office of Public Health

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information[1,2]

Description/ Mechanism of Action	Daclatasvir is a HCV direct acting antiviral; more specifically, it is an HCV NS5A inhibitor. Other NS5A inhibitors include ledipasvir and ombitasvir.
Indication(s) under Review in this document	Daclatasvir in combination with sofosbuvir is indicated for use in the treatment of chronic hepatitis C genotype 3 (GT3) infections. Limitation of use: Sustained virologic response (SVR) rates are reduced in HCV GT3 patients with cirrhosis, however, at present, this is the most effective regimen for this population.
Dosage Form(s) Under Review	Daclatasvir tablets (30mg and 60mg)
REMS	NO REMS
Pregnancy Rating	No data are available in pregnant women. Consider the benefits and risks when prescribing to a pregnant woman.

Executive Summary[1-3,5-6]

Efficacy	• Daclatasvir in combination with sofosbuvir for 12 weeks was evaluated in a Phase 3 open-label study (ALLY-3) conducted in HCV GT3 patients with compensated liver disease with or without cirrhosis. Primary efficacy endpoint was SVR at 12 weeks post-treatment. Overall, daclatasvir in combination with sofosbuvir achieved an SVR of 89% (135/152). However, SVR rates were reduced in HCV GT3 patients with cirrhosis (63%, 20/32) compared to those without cirrhosis (96%, 115/120). As a result, the PI states that the optimal duration of daclatasvir and sofosbuvir for HCV GT3 patients with cirrhosis has not been established. Although limited sample size, available data from ALLY-3 Plus indicate that DCV + SOF + RBV for 16 weeks provides SVR4 rate of >90%.
Safety	• In the ALLY-3 trial, the most common adverse reactions (≥10%) were fatigue and headache.
Potential Impact	• Daclatasvir in combination with sofosbuvir for 12 weeks is an FDA approved interferon-free regimen for patients with chronic HCV GT3 infection. However, SVR rates with this regimen are reduced in HCV GT3 patients with cirrhosis. As a result, the PI states that the optimal duration of daclatasvir in combination sofosbuvir for HCV GT3 patients with cirrhosis has not been established. • Based on the limited data available in GT3 cirrhotics, the Office of Public Health HCV Treatment Considerations and PBM MAP-VPE recommend daclatasvir in combination with sofosbuvir and ribavirin for 16 weeks in patients with cirrhosis. • In addition, baseline testing for NS5A resistance-associated variants (RAVs) is recommended to determine treatment options for any cirrhotic GT3 patients and any treatment-experienced patients.

Background

Purpose for review	The purpose of the review is to evaluate the efficacy and safety of daclatasvir in combination with sofosbuvir for HCV GT3 patients.

Other therapeutic options

Formulary Alternatives for HCV Genotype 3 Patients	Other Considerations
Sofosbuvir plus ribavirin	24 week regimen; lower efficacy rates
Sofosbuvir plus PEG/riba	Requires peginterferon; contraindicated in decompensated cirrhotics
Ledipasvir/sofosbuvir plus riba	Not FDA approved for GT3; limit use to non-cirrhotics due to lower efficacy rates in cirrhotics and risk of developing resistance in those that fail treatment

Efficacy (FDA Approved Indications)[1-10]

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to September 2015) using the search terms daclatasvir and Daklinza. The search was limited to studies performed in humans and published in the English language. The pivotal phase 3 clinical trial for HCV GT3 published in peer-reviewed journals was included along with pertinent abstracts from major HCV meetings.

Review of Efficacy

The FDA approval of daclatasvir in combination with sofosbuvir for patients with HCV GT3 was primarily based upon one pivotal Phase 3 single-arm, open-label trial (ALLY-3) conducted in the United States and Puerto Rico.[1] The ALLY-3 trial evaluated HCV GT3 patients with compensated liver disease with and without cirrhosis for treatment duration of 12 weeks. Primary efficacy endpoint was SVR at 12 weeks post-treatment. Demographics included 59% male, median age of 55 years old, 90% white, 21% cirrhotics, and 71% had baseline HCV RNA ≥ 800,000 IU/mL. Refer to Table 1 for SVRs of daclatasvir in combination with sofosbuvir according to data provided in the prescribing information.[1] SVR rates were reduced in HCV GT3 patients with cirrhosis compared to those without cirrhosis. No differences in SVRs were noted based upon age, gender, IL28B status, or baseline HCV RNA level. SVR rates were lower in patients harboring Y93H polymorphism at baseline [54% (7/13), 95% CI (25%, 81%)] compared to those without [92% (128/139), 95% CI (86%, 96%)].[2] Daclatasvir in combination sofosbuvir for 12 weeks achieved non-inferiority compared to historical control, sofosbuvir in combination with ribavirin for 24 weeks [3%, 95% CI (-4%, 9%)].

Based upon these results, the FDA approved the use of daclatasvir in combination with sofosbuvir for 12 weeks in HCV GT3 patients with compensated liver disease with or without cirrhosis. However, the FDA stated a limitation of use of this regimen was that SVR rates were lower in HCV GT3 patients with cirrhosis and that the optimal duration of daclatasvir and sofosbuvir for HCV GT3 patients with cirrhosis has not been established. The FDA has required a postmarket requirement to "conduct a trial to determine if a longer duration of treatment or addition of ribavirin improves the efficacy (i.e., SVR rate) of daclatasvir plus sofosbuvir for hepatitis C virus genotype 3 infected subjects with cirrhosis." Prior to the postmarket requirement trial, BMS has conducted an open-label, randomized trial (called ALLY-3 Plus) entitled "Safety and Efficacy Study of Daclatasvir 60mg, Sofosbuvir 400mg, and Ribavirin (Dosed Based Upon Weight) in Subjects With Chronic Genotype 3 Hepatitis C Infection With or Without Prior Treatment Experience and Compensated Advanced Cirrhosis for 12 or 16 Weeks". In the ALLY-3 Plus study (abstract data only), 21/24 (6/6 with advanced fibrosis and 15/18 with cirrhosis) patients receiving 12 weeks of DCV+SOF+RBV achieved an SVR4, whereas 25/26 (8/8 with advanced fibrosis and 17/18 with cirrhosis) patients receiving 16 weeks of DCV+SOF+RBV achieved an SVR4.[6]

Table 1. Summary of Phase 3 Clinical Trial (ALLY-3) supporting FDA indication of Daclatasvir plus Sofosbuvir for 12 weeks in HCV GT3 Patients[a]

SVR12	Treatment-Naïve N=101	Treatment-Experienced N=51	Total N=152
HCV GT3 patients	90% (91/101) 95% CI (83%, 95%)	86% (44/51) 95% CI (74%, 94%)	89% (135/152) 95% CI (83%, 93%)
Without Cirrhosis	98% (80/82) 95% CI (91%, 100%)	92% (35/38) 95% CI (79%, 98%)	96% (115/120) 95% CI of (91%, 99%)

With Cirrhosis	58% (11/19) 95% CI (34%, 80%)	69% (9/13) 95% CI (39%, 91%)	63% (20/32) 95% CI (44%, 79%)

[a]Data reported according to prescribing information[1-2]
Overall Quality of Evidence: Moderate (Refer to Appendix A; pivotal clinical trial sponsored by BMS)

Of note, the Y93H polymorphism was detected in 9% (13/148) of patients at baseline and was associated with reduced SVR rates; SVR 67% (6/9) in non-cirrhotics and SVR 25% (1/4) in cirrhotics.[2]

Additional Data in Cirrhotics
Additional data on the use of daclatasvir and sofosbuvir with or without RBV in patients with cirrhosis are available in a Phase 3 trial in liver transplant receipts (ALLY-1) and several early access programs (EAPs) described below in the Office of Public Health HCV Treatment Considerations.[3]

In the UK Early Access Program, GT3 patients with decompensated cirrhosis received 12 weeks of treatment with DCV + SOF ± RBV (n=114) or LDV/SOF ± RBV (n=61) as determined by the provider. In this cohort, 74% were Caucasian, 47% were treatment-experienced, 10% had received a liver transplant, and 94% had current or previous decompensated cirrhosis (CPT B 66%, CPT C 10%, mean MELD score 11.6). The SVR rates for each regimen were as follows: DCV + SOF + RBV, 70% (80/114); DCV + SOF, 71% (5/7); LDV/SOF + RBV, 59% (36/61). In the overall cohort, 9% of patients discontinued treatment and serious adverse events related to liver disease or HCV therapy occurred in 21% of patients.[5]

The phase lll ALLY-1 study evaluated a 12-week regimen of DCV + SOF + RBV in GT3-infected patients with advanced cirrhosis or recurrent infection after liver transplant. SVR rates were 83% (5/6) in the group with advanced cirrhosis and 91% (10/11) in the post-transplant group.[6]

The suboptimal SVR rates observed in cirrhotic patients receiving DCV+ SOF for 12 weeks has prompted investigation of longer treatment duration in several compassionate use programs. In the French Multicenter Compassionate Use Program, 601 patients received DCV + SOF for 12 or 24 weeks with RBV added at the provider's discretion. These patients were primarily treatment-experienced (73%) and cirrhotic (77%); 70%, 9% and 3% were Child-Pugh class A (F3/F4), B or C, respectively. HIV co-infection was present in 16%. RBV was included in the regimen for approximately 20% of patients and 93% of patients received treatment for 24 weeks. In non-cirrhotic patients receiving DCV + SOF for 12 (n=12) or 24 weeks (n=3), interim SVR rates were 100% for both groups. In cirrhotic patients receiving DCV + SOF for 12 or 24 weeks interim SVR rates were 82% (23/28) and 93% (39/42), respectively. For cirrhotic patients who received DCV + SOF + RBV for 12 or 24 weeks, interim SVR rates were 100% (3/3) and 93% (13/14), respectively.[7]

The European Multicenter Compassionate Use study (A1444-237), included a small number of GT3 patients treated with DCV + SOF with or without RBV as determined by the provider. Interim results indicate an interim SVR rate of 100% in cirrhotic patients treated for 12 weeks (n=3) or 24 weeks (n=7) with DCV+SOF. Interim SVR rates in cirrhotic patients treated for 12 or 24 weeks with DCV + SOF + RBV were 75% (3/4) and 88% (7/8), respectively.[8]

These data indicate that patients with GT3 infection and cirrhosis may benefit from: 1) an extended treatment duration and 2) addition of RBV. However, if a patient cannot tolerate RBV, then DCV + SOF alone can be considered for the remainder of therapy. These recommendations should be interpreted with caution because much of the data are available only from abstracts, non-randomized preliminary studies (e.g., SVR 4 or interim SVR12 data), and sub-analyses with small sample sizes.

Summary of efficacy
- In the pivotal phase 3 ALLY- 3 trial, daclatasvir in combination with sofosbuvir achieved an SVR of 89% (135/152). However, SVR rates were reduced in HCV GT3 patients with cirrhosis (63%, 20/32) compared to those without cirrhosis (96%, 115/120). As a result, the PI states that the optimal duration of daclatasvir and sofosbuvir for HCV GT3 patients with cirrhosis has not been established.

Potential Off-Label Use

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM intranet site only).

- Patients with HCV Genotype 1, 2, 4, 5 or 6
- Patients with decompensated cirrhosis

Safety (for more detailed information refer to the product package insert)[1,2]

	Comments
Boxed Warning	• None
Contraindications	• Strong inducers of CYP3A, including phenytoin, carbamazepine, rifampin, and St. John's wort.
Warnings/Precautions	• Bradycardia: Serious symptomatic bradycardia may occur in patients taking amiodarone with sofosbuvir in combination with another HCV direct-acting agent, including, daclatasvir, and particularly in patients also receiving beta blockers or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration is not recommended. In patients with no alternative treatment options, cardiac monitoring is recommended.

Safety Considerations

Overall, approximately 1900 patients with HCV infection have been treated with daclatasvir in combination with other HCV agents in clinical trials. The safety assessment described in the PI was primarily based on the Phase 3 clinical trial (ALLY-3) in patients with HCV GT3 chronic hepatitis C with compensated liver disease with and without cirrhosis.[1]

Adverse Reactions

Common adverse reactions	Incidence ≥10%: fatigue and headache
Death/Serious adverse reactions	No deaths occurred in ALLY-3. One patient experienced a serious adverse event but it was considered unrelated to daclatasvir.
Discontinuations due to adverse reactions	No patients were discontinued due to adverse reactions in ALLY-3.
Laboratory Abnormalities	Lipase Elevations: Transient, asymptomatic lipase elevations of greater than 3xULN were observed in 2% patients in ALLY-3.

Drug-Drug Interactions[1-2]

- Consult the prescribing information prior to use of daclatasvir for potential drug interactions.
- Daclatasvir is a substrate of CYP3A; thus, moderate/strong inducers and strong inhibitors of CYP3A may decrease and increase plasma levels of daclatasvir, respectively. Note that strong inducers of CYP3A are contraindicated with co-administration of daclatasvir while dosage modifications are required with moderate inducers or strong inhibitors.
- Daclatasvir is also inhibitor of drug transporter P-gp, organic anion transporting polypeptide (OATP) 1B1 and 1B3, and breast cancer resistance protein (BCRP); thus, daclatasvir may increase plasma levels of drugs that are substrates of these transporters.
- Strong Inducers CYP3A: Daclatasvir should NOT be co-administered with strong inducers of CYP3A including rifampin, St. John's wort, carbamazepine, and phenytoin.
- Moderate CYP3A inducers: Increase daclatasvir dose to 90mg once daily when co-administered with moderate CYP3A inducers including bosentan, dexamethasone, efavirenz, etravirine, modafinil, nafcillin, and rifapentine.
- Strong CYP3A inhibitors: Decrease daclatasvir dose to 30mg once daily when co-administered with strong CYP3A inhibitors including atazanavir/ritonavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, saquinavir, telithromycin and voriconazole.
- Moderate CYP3A inhibitors: Monitor for adverse events of daclatasvir when co-administered with moderate CYP3A inhibitors including atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, and verapamil.
- Amiodarone (refer to Warnings/Precautions Section)
- Other potentially significant drug interactions may include:
    - Dabigatran: Potential for increase in dabigatran. Refer to PI for specific recommendations.
    - Digoxin: Potential for increase in digoxin. Refer to PI for specific recommendations.
    - HMG-CoA reductase inhibitor (e.g., atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin,

simvastatin): Monitor for HMG-CoA reductase inhibitor associated adverse events such as myopathy

Risk Evaluation

As of October 2014	Comments
Sentinel event advisories	• Serious symptomatic bradycardia has been reported in patients taking amiodarone with sofosbuvir in combination with another HCV direct-acting agent.
Look-alike/sound-alike error potentials	• Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List):

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Daclatasvir 30, 60mg tab	None	None	None	Denavir Darunavir Ledipasvir
Daklinza	None	None	None	Simbrinza Zolinza Avinza

Other Considerations[1-3]

Resistance and Resistance Testing: In the ALLY-3 trial, the NS5A resistance-associated variant (RAV) Y93H was detected in 9% (13/148) of patients at baseline and was associated with reduced SVR rates; SVR 67% (6/9) in non-cirrhotics and SVR 25% (1/4) in cirrhotics. Due to lower SVRs in patients harboring Y93H RAV, baseline testing for NS5A RAVs is recommended to determine treatment options for all cirrhotic GT3 patients regardless of prior treatment as well as in treatment-experienced patients who have received any regimen (this includes patients who previously received only PEG/riba). If the Y93H RAV is present, the patient should be informed of the potential for a lower chance of SVR. Consult a practitioner with expertise to weigh the risks versus benefits of treatment.

Dosing and Administration[1]

The FDA approved Dosage Regimen is the following:

Daclatasvir 60mg once daily with or without food in combination with sofosbuvir for 12 weeks; note that the optimal duration of daclatasvir and sofosbuvir regimen in patients with cirrhosis is unknown.

Note:
If co-administered with **strong** CYP3A inhibitors, reduce daclatasvir to 30mg once daily
If co-administered with **moderate** CFY3A inducers, increase daclatasvir to 90mg once daily

VHA PBM MAP/VPE and Office of Public Health Dosage Recommendations (off-label) for HCV GT3 are the following:

Daclatasvir 60mg orally once daily and sofosbuvir 400mg orally once daily with or without food in combination with ribavirin (in 2 divided doses) with food (<75 kg: 1000 mg/day or ≥75 kg: 1200 mg/day)

Drug	Dosage Regimen	Length of Therapy
HCV Genotype 3		
Treatment-naïve without cirrhosis	Ledipasvir/sofosbuvir plus ribavirin	12 weeks
Treatment-naïve with compensated cirrhosis	Daclatasvir plus sofosbuvir and ribavirin OR Sofosbuvir plus peginterferon and ribavirin	16 weeks 12 week

Treatment-experienced (PEG/riba only) without cirrhosis	Ledipasvir/sofosbuvir plus ribavirin	12 weeks
Treatment-experienced (PEG/riba only) with compensated cirrhosis	Daclatasvir plus sofosbuvir and ribavirin OR Sofosbuvir plus peginterferon and ribavirin	16 weeks 12 week
Decompensated cirrhosis	Daclatasvir plus sofosbuvir and ribavirin	24 weeks

Special Populations (Adults)[1]

	Comments
Elderly	• No overall differences in safety or effectiveness were observed.
Pregnancy	• Based upon studies performed in animals, no evidence of fetal harm was observed with daclatasvir during organogenesis at doses that produced exposures up to 6 and 22 times human dose. Embryofetal toxicity was observed in rats and rabbits at maternally toxic doses that produced exposures of 33 and 98 times human dose. • Consider the benefits and risks when prescribing to a pregnant woman.
Lactation	• It is not known if daclatasvir is present in human breast milk. According to PI, the developmental and health benefits of breastfeeding should be considered along with mother's clinical need and potential adverse effects on child from drugs or underlying maternal condition.
Renal Impairment	• No dosage adjustment of daclatasvir is necessary in patients with any degree of renal impairment.
Hepatic Impairment	• No dosage adjustment is necessary for patients with mild, moderate or severe hepatic impairment.
Pharmacogenetics/genomics	• No data identified in prescribing information.

Projected Place in Therapy

- The VHA Office of Public Health HCV Registry Reports indicates that there were 7, 290 HCV GT3 infected Veterans with HCV viremia in VHA care in 2014.[11]
- Daclatasvir plus sofosbuvir is an interferon-free regimen that is FDA approved for the treatment of HCV Genotype 3 patients. In ALLY-3, daclatasvir in combination with sofosbuvir achieved an overall SVR of 89% (135/152). However, SVR rates were reduced in HCV GT3 patients with cirrhosis (63%, 20/32) compared to those without cirrhosis (96%, 115/120). As a result, the PI states that the optimal duration of daclatasvir and sofosbuvir for HCV GT3 patients with cirrhosis has not been established. Most common adverse reactions (≥10%) were fatigue and headache.
- Based on the limited data available in GT3 cirrhotics, the Office of Public Health HCV Treatment Considerations and PBM MAP-VPE recommend daclatasvir in combination with sofosbuvir and ribavirin for 16 weeks in patients with compensated cirrhosis.[3] In addition, baseline testing for NS5A RAVs is recommended to determine treatment options for all cirrhotic GT3 patients and all treatment-experienced GT3 patients.

References

1. DAKLINZA [package insert]. Bristol-Myers Squibb Company, Princeton, NJ 08543, USA; July 2015.
2. Daclatasvir. Drugs@FDA. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206843Orig1s000TOC.cfm
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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.