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Medication Policy Manual | **Policy No:** dru422

Topic: Daklinza™, daclatasvir | **Date of Origin:** July 24, 2015

Committee Approval Date: November 10, 2017 | **Next Review Date:** June 2018

Effective Date: November 10, 2017

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Daclatasvir (Daklinza) is an oral direct-acting antiviral medication that is given in combination sofosbuvir (Sovaldi) with or without ribavirin for the treatment of chronic genotype 3 hepatitis C virus (HCV) infection.

Policy/Criteria

I. Most contracts require prior authorization approval of daclatasvir (Daklinza) prior to coverage. Daclatasvir (Daklinza) may be considered medically necessary when criterion A and B below are met.

A. There is a diagnosis of chronic genotype 3 hepatitis C virus (HCV) infection and criteria 1 through 4 below are met:

1. There is clinical documentation indicating a medical reason why sofosbuvir-velpatasvir (Epclusa) and glecaprevir-pibrentasvir (Mavyret) are not treatment options.

AND

2. Daclatasvir (Daklinza) will be used in combination with sofosbuvir (Sovaldi).

AND

3. The member has not been previously treated with a sofosbuvir-based regimen.

AND

4. Daclatasvir (Daklinza) will be used in combination with ribavirin if used in the following treatment groups:

a. Compensated cirrhosis (Child-Pugh A)

b. Decompensated cirrhosis (Child-Pugh B and C)

c. Post-transplant

AND

B. Cycle Management Program requirements are met [refer to Medication Policy Manual, *Cycle Management Program*, dru404].

II. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers daclatasvir (Daklinza) to be a self-administered medication.

B. When prior authorization is approved, daclatasvir (Daklinza) may be authorized as follows:

1. **Genotype 3 in combination with sofosbuvir (Sovaldi):** up to #28 daclatasvir (Daklinza) tablets per 28 days for a total duration of 12 weeks (one treatment course).

III. Daclatasvir (Daklinza) is considered not medically necessary in the following situation:

A. When used for the treatment of HCV genotypes other than genotype 3, including genotype 1.

B. When used for the treatment of HCV/HIV coinfection in patients with genotypes other than genotype 3, including HCV genotype 1.

C. When used in combination with any other direct-acting antiviral for HCV, except sofosbuvir (Sovaldi) (see *Appendix 1*).

IV. Daclatasvir (Daklinza) is considered investigational when used:

A. As monotherapy.

B. As retreatment when there has been relapse after, or no response to, a prior treatment course with a direct-acting antiviral for HCV (see *Appendix 1*).

Position Statement

- Daclatasvir (Daklinza) is an oral hepatitis C virus (HCV) NS5A inhibitor that is used in combination with sofosbuvir (Sovaldi) for the treatment of chronic genotype 3 HCV infection.
- Daclatasvir (Daklinza) in combination with sofosbuvir (Sovaldi) has been shown to be safe and effective for treating chronic HCV genotype 3 infection in treatment-naïve patients, as well as patients who relapsed after or did not respond to prior treatment with peginterferon and ribavirin. There is currently insufficient evidence to support the efficacy of daclatasvir (Daklinza) in patients who have failed prior therapy with a direct-acting oral antiviral for HCV infection (see *Appendix 1*).
- Daclatasvir (Daklinza) has been studied in patients with decompensated cirrhosis and patients with HCV/human immunodeficiency virus (HIV) coinfection.
- Although sustained virological response (SVR) is measured by a series of HCV RNA levels and is considered a surrogate endpoint, it is accepted as a measure of efficacy for the treatment of HCV.
- The combination of daclatasvir (Daklinza) and sofosbuvir (Sovaldi) has not been shown to be superior to other regimens for HCV genotype 1, including other sofosbuvir-containing regimens.
- The duration of treatment with daclatasvir (Daklinza) in combination with sofosbuvir (Sovaldi) for HCV genotype 3 is 12 weeks. The dose of daclatasvir (Daklinza) is 60 mg once daily and the dose of sofosbuvir (Sovaldi) is 400 mg once daily.
- The safety and efficacy of daclatasvir (Daklinza) monotherapy have not been established.
- Although daclatasvir (Daklinza) plus sofosbuvir (Sovaldi) and sofosbuvir (Sovaldi) in combination with peginterferon and ribavirin have not been directly compared, they appear to offer similar overall rates of SVR. However, for daclatasvir (Daklinza), rates of SVR are reduced in patients with cirrhosis.
- Among all regimens for chronic genotype 3 HCV infection, sofosbuvir-velpatasvir (Epclusa) and glecaprevir-pibrentasvir (Mavyret) provide the best value.
- While guidelines list daclatasvir (Daklinza) plus sofosbuvir (Sovaldi) as a treatment option for HCV genotype 1, other FDA-approved regimens, such as ledipasvir-sofosbuvir (Harvoni), provide better value to members while offering high rates of viral cure.
- Daclatasvir (Daklinza) has not been adequately studied in patients who have failed a prior sofosbuvir-based regimen. While guidelines recommend the combination of daclatasvir (Daklinza), sofosbuvir (Sovaldi), and ribavirin for patients with HCV genotype 3 who have failed a sofosbuvir-based regimen, the recommendations are based on expert opinion only.

- There is no clinical evidence to support the combination of daclatasvir (Daklinza) and sofosbuvir (Sovaldi) with or without ribavirin in patients with genotype 1 or 2 who have failed a sofosbuvir-based regimen. The evidence for patients with genotype 3 is limited to the ALLY-3 study, in which five of seven patients who failed a sofosbuvir-based regimen achieved an SVR. While promising, larger studies are needed to confirm the benefit and determine the ideal regimen and treatment duration.
- Daclatasvir (Daklinza) is currently being studied in a variety of HCV clinical settings; however, there is currently no published data to support the efficacy and safety of daclatasvir (Daklinza) in these settings.

Clinical Efficacy

Genotype 3

The addition of daclatasvir (Daklinza) to sofosbuvir (Sovaldi) has been shown to produce high viral cure rates in patients with chronic genotype 3 HCV infection. [1]

- ALLY-3 was an open-label, phase III study of daclatasvir (Daklinza) 60 mg plus sofosbuvir (Sovaldi) 400 mg for 12 weeks. It included 101 treatment-naive patients and demonstrated an SVR at 12 weeks (SVR12) rate of 90%. In treatment-naive patients without cirrhosis (Metavir F0-F3), 97% achieved SVR12. In treatment-naive patients with cirrhosis (Metavir F4), 58% achieved SVR12.
- ALLY-3 included seven patients who had failed a prior sofosbuvir-based regimen. SVR was achieved in five of the seven patients. While promising, the findings in patients who have failed a prior sofosbuvir-based regimen must be confirmed in larger studies.
- ALLY-3+ was an open-label, phase III study of daclatasvir (Daklinza) 60 mg plus sofosbuvir (Sovaldi) 400 mg with ribavirin for 12 or 16 weeks in treatment-naïve (n=13) and treatment-experienced (n=36) patients with advanced fibrosis or compensated cirrhosis. It included 50 patients and demonstrated an overall SVR12 rate of 90% (100% in advanced fibrosis arm vs 86% in compensated cirrhosis arm). SVR12 rates were similar between the 12 and 16 week groups. [2]
- Although there is no direct comparative evidence between daclatasvir (Daklinza) plus sofosbuvir and sofosbuvir plus peginterferon and ribavirin, both regimens offer similar rates of SVR. [3]

Hepatocellular Carcinoma in Patients Awaiting Liver Transplantation

There are no published randomized controlled trials evaluating daclatasvir (Daklinza) in patients with chronic HCV infection and hepatocellular carcinoma who are awaiting liver transplantation.

Post-Transplant Patients

One trial has evaluated daclatasvir (Daklinza) in patients with decompensated liver cirrhosis or post-transplant HCV recurrence.

- ALLY-1 was an open-label, phase III study of daclatasvir (Daklinza) 60 mg plus sofosbuvir (Sovaldi) 400 mg with ribavirin for 12 weeks in patients with either advanced cirrhosis (n = 60) or post-liver transplant recurrence of HCV (n = 53). The primary endpoint was SVR at 12 weeks. Among all genotypes, SVR was achieved in 94% of patients with post-transplant HCV recurrence and 83% of patients with advanced cirrhosis achieved cure. For patients with genotype 1 only, SVR was achieved in 95% of post-transplant and 82% of patients with advanced cirrhosis. [4]

HCV/HIV Coinfection

One trial has evaluated daclatasvir (Daklinza) in patients with HCV/HIV coinfection. ALLY-2 was an open-label, phase III study of daclatasvir (Daklinza) 60 mg plus sofosbuvir 400 mg for 12 weeks. It included 151 treatment-naive patients and 52 treatment-experienced patients. Patients had HCV genotypes 1 through 4 (83% with genotype 1), and 14% had compensated cirrhosis; 98% were receiving antiretroviral therapy. The following overall SVR rates for all genotypes were: [5]

Population	Duration	SVR
Treatment-naïve (n = 101)	12 weeks	96.4%
Treatment-naïve (n = 50)	8 weeks	75.6%
Treatment-experienced (n = 52)	12 weeks	97.7%

Not Medically Necessary and Investigational Uses

- Daclatasvir (Daklinza) is currently being studied in a variety of HCV clinical settings, including patients with other HCV genotypes; however, there is currently no high-quality evidence to support the efficacy and safety of daclatasvir (Daklinza) in these settings.
- Although AASLD/IDSA guidelines list daclatasvir (Daklinza) in combination with sofosbuvir (Sovaldi) as an alternative treatment for HCV genotype 2, the recommendation was based on low-level evidence. There are no high-quality studies supporting the use of daclatasvir (Daklinza) in combination with sofosbuvir (Sovaldi) in HCV genotype 2.

Clinical Guidelines [6]

- As of September 2017, the Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) clinical guidelines recommend the following regimens for treatment-naïve patients with HCV.

Genotype	Recommended Regimens		Alternative Regimens
Treatment-naïve patients			
1a	Without Cirrhosis	• Elbasvir-grazoprevir (Zepatier) x 12 weeks (if no baseline NS5A RAVs) • Glecaprevir-pibrentasvir (Mavyret) x 8 weeks • Ledipasvir-sofosbuvir (Harvoni) x 12 weeks • Sofosbuvir-velpatasvir (Epclusa) x 12 weeks	• Elbasvir-grazoprevir (Zepatier) + RBV x 16 weeks (if baseline NS5A RAVs are present) • Viekira Pak x 12 weeks • Daclatasvir (Daklinza) + sofosbuvir (Sovaldi) x 12 weeks • Sofosbuvir (Sovaldi) + simeprevir (Olysio) x 12 weeks
	Compensated Cirrhosis	• Elbasvir-grazoprevir (Zepatier) x 12 weeks (if no baseline NS5A RAVs) • Glecaprevir-pibrentasvir (Mavyret) x 8 weeks • Ledipasvir-sofosbuvir (Harvoni) x 12 weeks • Sofosbuvir-velpatasvir (Epclusa) x 12 weeks	• Elbasvir-grazoprevir + RBV x 16 weeks (if baseline NS5A RAVs are present)
1b	Without Cirrhosis	• Elbasvir-grazoprevir (Zepatier) x 12 weeks • Glecaprevir-pibrentasvir (Mavyret) x 8 weeks • Ledipasvir-sofosbuvir (Harvoni) x 12 weeks • Sofosbuvir-velpatasvir (Epclusa) x 12 weeks	• Viekira Pak x 12 weeks • Daclatasvir (Daklinza) + sofosbuvir (Sovaldi) x 12 weeks • Sofosbuvir (Sovaldi) + simeprevir (Olysio) x 12 weeks
	Compensated Cirrhosis	• Elbasvir-grazoprevir (Zepatier) x 12 weeks • Glecaprevir-pibrentasvir (Mavyret) x 12 weeks • Ledipasvir-sofosbuvir (Harvoni) x 12 weeks • Sofosbuvir-velpatasvir (Epclusa) x 12 weeks	• Viekira Pak x 12 weeks
2	Without Cirrhosis	• Glecaprevir-pibrentasvir (Mavyret) x 8 weeks Sofosbuvir-velpatasvir (Epclusa) x 12 weeks	Daclatasvir (Daklinza) + sofosbuvir (Sovaldi) x 12 weeks
	Compensated Cirrhosis	• Glecaprevir-pibrentasvir (Mavyret) x 8 weeks Sofosbuvir-velpatasvir (Epclusa) x 12 weeks	Daclatasvir (Daklinza) + sofosbuvir (Sovaldi) x 16-24 weeks
3	Without Cirrhosis	• Glecaprevir-pibrentasvir (Mavyret) x 8 weeks • Sofosbuvir-velpatasvir (Epclusa) x 12 weeks	Daclatasvir (Daklinza) + sofosbuvir (Sovaldi) x 12 weeks
	Compensated Cirrhosis	• Elbasvir-grazoprevir (Zepatier) x 12 weeks (if no baseline NS5A RAVs) • Glecaprevir-pibrentasvir (Mavyret) x 8 weeks • Ledipasvir-sofosbuvir (Harvoni) x 12 weeks • Sofosbuvir-velpatasvir (Epclusa) x 12 weeks	• Elbasvir-grazoprevir (Zepatier) + RBV x 16 weeks (if baseline NS5A RAVs are present) • Viekira Pak x 12 weeks • Daclatasvir (Daklinza) + sofosbuvir (Sovaldi) x 12 weeks • Sofosbuvir (Sovaldi) + simeprevir (Olysio) x 12 weeks
4	Without Cirrhosis	• Elbasvir-grazoprevir (Zepatier) x 12 weeks (if no baseline NS5A RAVs) • Glecaprevir-pibrentasvir (Mavyret) x 8 weeks • Ledipasvir-sofosbuvir (Harvoni) x 12 weeks • Sofosbuvir-velpatasvir (Epclusa) x 12 weeks	Elbasvir-grazoprevir + RBV x 16 weeks (if baseline NS5A RAVs are present)
	Compensated Cirrhosis	• Elbasvir-grazoprevir (Zepatier) x 12 weeks	• Viekira Pak x 12 weeks

		• Glecaprevir-pibrentasvir (Mavyret) x 8 weeks • Ledipasvir-sofosbuvir (Harvoni) x 12 weeks • Sofosbuvir-velpatasvir (Epclusa) x 12 weeks	• Daclatasvir (Daklinza) + sofosbuvir (Sovaldi) x 12 weeks Sofosbuvir (Sovaldi) + simeprevir (Olysio) x 12 weeks
5 or 6	With or without Cirrhosis	• Elbasvir-grazoprevir (Zepatier) x 12 weeks • Glecaprevir-pibrentasvir (Mavyret) x 12 weeks • Ledipasvir-sofosbuvir (Harvoni) x 12 weeks • Sofosbuvir-velpatasvir (Epclusa) x 12 weeks	Viekira Pak x 12 weeks

RBV = ribavirin; Technivie = ombitasvir, paritaprevir, and ritonavir; Viekira Pak = ombitasvir, paritaprevir, and ritonavir plus dasabuvir

- AASLD/IDSA guidelines state that patients with HCV/HIV coinfection should be treated similarly to non-coinfected patients; however, the potential for drug-drug interactions should be taken into consideration.
- Specific recommendations for treatment-experienced patients are based on HCV genotype, prior treatments received, and cirrhosis status.
- For patients with HCV genotype 2 or 3 who have failed a sofosbuvir-based regimen, guidelines recommend the combination of daclatasvir (Daklinza), sofosbuvir (Sovaldi), and ribavirin for 24 weeks. However, these recommendations are based on expert opinion and there is little clinical evidence to support these regiments. Additional studies are needed to determine the ideal duration and regimen.
- For patients with HCV genotype 3 and compensated cirrhosis, AASLD/IDSA guidelines recommend a 24-week regimen of daclatasvir (Daklinza) and sofosbuvir (Sovaldi) with or without ribavirin. However, this recommendation was based on expert opinion and low quality studies. Daclatasvir (Daklinza) plus sofosbuvir (Sovaldi) with ribavirin for 12 weeks is supported by both the ALLY-3+ study (SVR12 rate of 86% in patients with compensated cirrhosis) and the FDA-approved labeling. [2,7]

Safety [7]

- The combination of daclatasvir (Daklinza) and sofosbuvir (Sovaldi) is genally well tolerated. The most common adverse events observed with the combination of daclatasvir (Daklinza) and sofosbuvir (Sovaldi) in the ALLY-3 study were headache, fatigue, and nausea.

Dosing [7]

- The recommended dosing for daclatasvir (Daklinza) is 60 mg (one tablet) by mouth once daily with or without food with sofosbuvir (Sovaldi) with or without ribavirin.
- The recommended dosing for sofosbuvir (Sovaldi) is 400 mg (one tablet) by mouth once daily with or without food.
- The duration of therapy with the combination of daclatasvir (Daklinza) and sofosbuvir (Sovaldi) is 12-weeks.
- The dose of daclatasvir (Daklinza) should be reduced if given with strong CYP3A inhibitors and increased if given with moderate CYP3A inhibitors.

Appendix 1: Direct-acting Antivirals for HCV
boceprevir (Victrelis)
daclatasvir (Daklinza)
grazoprevir-elbasvir (Zepatier)
ledipasvir-sofosbuvir (Harvoni)
paritaprevir/ritonavir-ombitasvir (Technivie)
paritaprevir/ritonavir-ombitasvir plus dasabuvir (Viekira Pak, Viekira XR)
simeprevir (Olysio)
sofosbuvir (Sovaldi)
sofosbuvir-velpatasvir (Epclusa)
telaprevir (Incivek)

Appendix 2: Definitions of Member Treatment History [6]	
Treatment-naïve	Patients who have never received therapy for the treatment of hepatitis C.
Relapser	Patients who had an undetectable HCV RNA level at the end of prior therapy with peginterferon and ribavirin, but had a subsequent detectable HCV RNA level during the follow-up period.
Partial responder	Patients who had a HCV RNA reduction of ≥ 2 $\log_{10}$ after 12 weeks of prior therapy with peginterferon and ribavirin, but still had a detectable HCV RNA level during the treatment period.
Null responder	Patients who had a < 2 $\log_{10}$ reduction in HCV RNA after 12 weeks of prior therapy with peginterferon and ribavirin.

Cross References
Epclusa®, sofosbuvir-velpatasvir, dru457
Harvoni®, ledipasvir-sofosbuvir, dru366
Mavyret™, glecaprevir-pibrentasvir, dru525
Olysio®, simeprevir, dru331
Sovaldi®, sofosbuvir, dru332
Technivie™, paritaprevir/ritonavir-ombitasvir, dru412
Viekira Pak®, paritaprevir/ritonavir-ombitasvir plus dasabuvir, dru387
Vosevi™, sofosbuvir/velpatasvir/voxilaprevir, dru509
Zepatier™, grazoprevir/elbasvir, dru435

Cross References
Medical Policy Lab 47, Multianalyte Assays with Algorithmic Analysis for the Evaluation and Monitoring of Patients with Chronic Liver Disease (http://blue.regence.com/trgmedpol/lab/lab47.pdf)

Codes	Number	Description
N/A		

References

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2. Leroy, V, Angus, P, Bronowicki, JP, et al. Daclatasvir, sofosbuvir, and ribavirin for hepatitis C virus genotype 3 and advanced liver disease: A randomized phase III study (ALLY-3+). *Hepatology*. 2016 May;63(5):1430-41. PMID: 26822022
3. Gilead Announces Results From Studies Evaluating Sofosbuvir-Based Regimens in Chronic Hepatitis C Patients With Genotypes 2-5 - [cited 7/24/15]; Available from: http://www.gilead.com/news/press-releases/2015/4/gilead-announces-results-from-studies-evaluating-sofosbuvirbased-regimens-in-chronic-hepatitis-c-patients-with-genotypes-25
4. Poordad, F, Schiff, ER, Vierling, JM, et al. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. *Hepatology*. 2016 May;63(5):1493-505. PMID: 26754432
5. Wyles, DL, Ruane, PJ, Sulkowski, MS, et al. Daclatasvir plus Sofosbuvir for HCV in Patients Coinfected with HIV-1. *N Engl J Med*. 2015 Jul 21. PMID: 26196502
6. American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA). Recommendations for testing, managing, and treating hepatitis C. October 2016a. [cited 01/22/2017]; Available from: http://hcvguidelines.org.
7. Daklinza™ [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; April 2016.

Revision History

Revision Date	Revision Summary
11/10/2017	Clarified preferred products and associated step-therapy (Mavyret, in addition to Epclusa).
2/17/2017	• Clarified that there cannot be prior treatment with sofosbuvir-based regimens. • Removed recurrent HCV infection follow liver transplantation from list of investigational uses.
11/11/2016	• Clarified inclusion in the Cycle Management Program, *dru404*.
8/12/2016	• Removed requirement for medical documentation why sofosbuvir (Sovaldi), peginterferon, and ribavirin is not a treatment option. • Added a requirement that there is a medical reason in clinical documentation why sofosbuvir-velpatasvir (Epclusa) is not a treatment option. • Clarified settings when ribavirin is required. • Update investigational and not medically necessary uses.
2/12/2016	• Removed requirement for advanced fibrosis, other end-organ disease manifestations, or other comorbid conditions. • Updated list of investigational uses.