

Clinical Policy: Daclatasvir (Daklinza)

Reference Number: HIM.PA.SP27

Effective Date: 01.01.17

Last Review Date: 08.19

Line of Business: HIM*

[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

Description

Daclatasvir (Daklinza[™]) is a hepatitis C virus (HCV) NS5A inhibitor.

**For Health Insurance Marketplace (HIM), Daklinza 90 mg tablet is non-formulary and cannot be approved using these criteria; refer to the formulary exception policy, HIM.PA.103.*

FDA Approved Indication(s)

Daklinza is indicated for use with sofosbuvir, with or without ribavirin, for the treatment of chronic HCV genotype 1 or 3 infection.

Limitation(s) of use: Sustained virologic response (SVR12) rates are reduced in genotype 3 patients with cirrhosis receiving Daklinza in combination with sofosbuvir for 12 weeks.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation[®] that Daklinza is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Chronic Hepatitis C Infection (must meet all):

1. Diagnosis of chronic HCV infection as evidenced by detectable serum HCV RNA levels by quantitative assay in the last 6 months;
2. Confirmed HCV genotype is 1, 2, 3, 4, 5, or 6;
**Chart note documentation and copies of lab results are required*
3. Documentation of treatment status of the member (treatment-naïve or treatment-experienced);
4. Documentation of cirrhosis status of the member (no cirrhosis, compensated cirrhosis, or decompensated cirrhosis);
5. Prescribed by or in consultation with a gastroenterologist, hepatologist, or infectious disease specialist;
6. Age \geq 18 years;
7. Prescribed for use in combination with Sovaldi[®];
8. For genotype 1a with cirrhosis, laboratory testing confirming the absence of NS5A resistance associated polymorphisms at amino acid positions M28, Q30, L31 and Y93;
9. Member has at least one of the following contraindications to Mavyret[™] (a or b):

- a. Decompensated cirrhosis (Child-Pugh B or C) confirmed by lab findings and clinical notes;
 - b. Receiving treatment with efavirenz or atazanavir;
**See Appendix E for additional details on acceptable contraindications*
10. Life expectancy \geq 12 months with HCV treatment;
11. Member agrees to participate in a medication adherence program meeting both of the following components (a and b):
- a. Medication adherence monitored by pharmacy claims data or member report;
 - b. Member's risk for non-adherence identified by adherence program or member/prescribing physician follow-up at least every 4 weeks;
12. Prescribed regimen is consistent with an FDA or AASLD-IDSAs recommended regimen (*see Section V for reference*);
13. Dose does not exceed 90 mg (1 tablet) per day.

Approval duration: up to a total of 24 weeks*

*(*Approved duration should be consistent with a regimen in Section V Dosage and Administration)*

B. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): HIM.PHAR.21 for health insurance marketplace.

II. Continued Therapy

A. Chronic Hepatitis C Infection (must meet all):

1. Member meets one of the following (a or b):
 - a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
 - b. Documentation supports that member is currently receiving Daklinza for chronic HCV infection and has recently completed at least 60 days of treatment with Daklinza;
2. Member is responding positively to therapy;
3. Dose does not exceed 90 mg (1 tablet) per day.

Approval duration: up to a total of 24 weeks*

*(*Approved duration should be consistent with a regimen in Section V Dosage and Administration)*

B. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): HIM.PHAR.21 for health insurance marketplace.

III. Diagnoses/Indications for which coverage is NOT authorized:

- A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policy – HIM.PHAR.21 for health insurance marketplace or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AASLD: American Association for the Study of Liver Diseases
 FDA: Food and Drug Administration
 HBV: hepatitis B virus
 HCV: hepatitis C virus
 HIV: human immunodeficiency virus

IDS: Infectious Diseases Society of America
 NS3/4A, NS5A/B: nonstructural protein
 PegIFN: pegylated interferon
 RBV: ribavirin
 RNA: ribonucleic acid

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Mavyret™ (glecaprevir /pibrentasvir)	Treatment-naïve: Genotypes 1, 2, or 3 Without cirrhosis: Three tablets PO QD for 8 weeks With compensated cirrhosis: Three tablets PO QD for 12 weeks	Mavyret: glecaprevir 300 mg/ pibrentasvir 120 mg (3 tablets) per day
Mavyret™ (glecaprevir /pibrentasvir)	Treatment-experienced with IFN/pegIFN + RBV +/- sofosbuvir CHC infection: Genotypes 1, 2, 4, 5, or 6 Without cirrhosis: Three tablets PO QD for 8 weeks With compensated cirrhosis: Three tablets PO QD for 12 weeks	Mavyret: glecaprevir 300 mg/ pibrentasvir 120 mg (3 tablets) per day
Mavyret™ (glecaprevir /pibrentasvir)	Treatment-experienced with IFN/pegIFN + RBV +/- sofosbuvir CHC infection: Genotype 3 Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 16 weeks	Mavyret: glecaprevir 300 mg/ pibrentasvir 120 mg (3 tablets) per day
Mavyret™ (glecaprevir /pibrentasvir)	Treatment-experienced with NS5A inhibitor without prior NS3/4A protease inhibitor CHC infection: Genotype 1 Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 16 weeks	Mavyret: glecaprevir 300 mg/ pibrentasvir 120 mg (3 tablets) per day
Mavyret™ (glecaprevir /pibrentasvir)	Treatment-experienced with NS3/4A protease inhibitor without prior NS5A inhibitor CHC infection:	Mavyret:

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Genotype 1 Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 12 weeks	glecaprevir 300 mg/ pibrentasvir 120 mg (3 tablets) per day

Therapeutic alternatives are listed as Brand name[®] (generic) when the drug is available by brand name only and generic (Brand name[®]) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):
 - When Daklinza is used in combination with other agents, the contraindications applicable to those agents are applicable to the combination regimen. Refer to the respective prescribing information for a list of contraindications.
 - Daklinza is contraindicated in combination with drugs that strongly induce CYP3A and, thus, may lead to lower exposure and loss of efficacy of Daklinza. Contraindicated drugs include, but are not limited to: phenytoin, carbamazepine, rifampin, and St. John’s wort.
- Boxed warning(s): risk of hepatitis B virus reactivation in patients coinfecting with HCV and HBV.

Appendix D: Direct-Acting Antivirals for Treatment of HCV Infection

Brand Name	Drug Class				
	NS5A Inhibitor	Nucleotide Analog NS5B Polymerase Inhibitor	Non-Nucleoside NS5B Palm Polymerase Inhibitor	NS3/4A Protease Inhibitor (PI)	CYP3A Inhibitor
Daklinza	Daclatasvir				
Epclusa*	Velpatasvir	Sofosbuvir			
Harvoni*	Ledipasvir	Sofosbuvir			
Mavyret*	Pibrentasvir			Glecaprevir	
Olysio				Simeprevir	
Sovaldi		Sofosbuvir			
Technivie*	Ombitasvir			Paritaprevir	Ritonavir
Viekira XR/PAK*	Ombitasvir		Dasabuvir	Paritaprevir	Ritonavir
Vosevi*	Velpatasvir	Sofosbuvir		Voxilaprevir	
Zepatier*	Elbasvir			Grazoprevir	

*Combination drugs

Appendix E: General Information

- Hepatitis B Virus Reactivation (HBV) is a Black Box Warning for all direct-acting antiviral drugs for the treatment of HCV. HBV reactivation has been reported when treating HCV for patients co-infected with HBV, leading to fulminant hepatitis, hepatic failure, and death, in some cases. Patients should be monitored for HBV reactivation and

hepatitis flare during HCV treatment and post-treatment follow-up, with treatment of HBV infection as clinically indicated.

- For patients infected with HCV Genotype 1a with cirrhosis: Testing for the presence of virus with NS5A resistance-associated polymorphisms is recommended.
- According to the September 2017 AASLD/IDSA HCV guidance updates, Daklinza plus Sovaldi is a treatment option for patients with genotypes 1 through 6 in decompensated cirrhosis and post-liver transplantation in the allograft.
- Child-Pugh Score:

	1 Point	2 Points	3 Points
Bilirubin	Less than 2 mg/dL Less than 34 umol/L	2-3 mg/dL 34-50 umol/L	Over 3 mg/dL Over 50 umol/L
Albumin	Over 3.5 g/dL Over 35 g/L	2.8-3.5 g/dL 28-35 g/L	Less than 2.8 g/dL Less than 28 g/L
INR	Less than 1.7	1.7 - 2.2	Over 2.2
Ascites	None	Mild / medically controlled	Moderate-severe / poorly controlled
Encephalopathy	None	Mild / medically controlled Grade I-II	Moderate-severe / poorly controlled. Grade III-IV

Child-Pugh class is determined by the total number of points: A = 5-6 points; B = 7-9 points; C = 10-15 points

- Acceptable medical justification for inability to use Mavyret (preferred product):
 - Severe hepatic disease (Child-Pugh C): use of Mavyret is not recommended due to higher exposures of glecaprevir and pibrentasvir.
 - Alternatives on the formulary: Harvoni, Epclusa, Sovaldi, Daklinza
 - Moderate hepatic disease (Child-Pugh B): although not an absolute contraindication, use of Mavyret is not recommended in patients with moderate hepatic disease (Child-Pugh B) due to lack of safety and efficacy data.
 - Alternatives on the formulary: Harvoni, Epclusa, Sovaldi, Daklinza
 - Following administration of Mavyret in HCV infected subjects with *compensated* cirrhosis (Child-Pugh A), exposure of glecaprevir was approximately 2-fold and pibrentasvir exposure was similar to non-cirrhotic *HCV infected* subjects.
 - At the clinical dose, compared to *non-HCV infected* subjects with *normal hepatic function*, glecaprevir AUC was 100% higher in Child-Pugh B subjects, and increased to 11-fold in Child-Pugh C subjects. Pibrentasvir AUC was 26% higher in Child-Pugh B subjects, and 114% higher in Child-Pugh C subjects.
 - Drug-drug interactions with one or more the following agents:
 - Atazanavir
 - Alternatives on the formulary: Harvoni, Epclusa, Sovaldi, Daklinza
 - Efavirenz:
 - Alternatives on the formulary: Harvoni, Sovaldi, Daklinza
- Unacceptable medical justification for inability to use Mavyret (preferred product):
 - Black Box Warning (BBW): currently or previously infected with hepatitis B virus. This BBW is not unique to Mavyret, and it applies across the entire therapeutic class of direct-acting antivirals for treatment of HCV infection. Therefore it is not a valid clinical reason not to use Mavyret.

- Concurrent anticoagulant therapy: Fluctuations in International Normalized Ratio (INR) have been observed in warfarin recipients who were also receiving treatment for HCV infections. This BBW is not unique to Mavyret, and it applies across the entire therapeutic class of direct-acting antivirals for treatment of HCV infection. Although caution is advised when using Mavyret while receiving concurrent anticoagulant therapy, specifically warfarin, this is not an absolute contraindication as long as patient is adequately monitored and educated during therapy.
- Drug-drug interactions with one or more of the following agents:
 - Rifampin, carbamazepine, or St. John’s wort:
 - These drug-drug interactions are not unique to Mavyret, and they apply across the entire therapeutic class of direct-acting antivirals for treatment of HCV infection.
- The World Health Organization (WHO) estimates that at the global level, there are approximately 2,278,400 HIV-HCV co-infections (IQR 1,271,300 to 4,417,000) of which 1,362,700 (IQR 847,770 to 1,381,800) in people who inject drugs (PWID), equaling an overall co-infection prevalence in HIV-infected individuals of **6.2%** (IQR 3.4 to 1.9). In North America specifically, the meta-analysis showed that the best estimate for the percentage of total HIV-infected individuals with HCV co-infection was about **14%**. On the other hand, the Centers of Disease Control and Prevention (CDC) estimates that about **25%** of people with HIV in the US are co-infected with HCV.
- As of March 2018, there are a total of 1.38 million members enrolled in Centene Health Insurance Marketplace. Out of those members, about 6,300 members are estimated to be diagnosed with HIV based on claims data, with about 173 members with recent claims for atazanavir and/or efavirenz. And based on the CDC as well as WHO prevalence estimation for North America, we can predict that about 14% to 25%, or 882 to 1,575 members, with HIV infection may be co-infected with HCV, with about 25 to 44 members who may not be eligible for treatment with Mavyret due to drug interactions involving atazanavir and/or efavirenz.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose	Reference
Genotype 1: Treatment-naïve or treatment-experienced without cirrhosis	Daklinza 60 mg PO QD plus Sovaldi 400 mg PO QD for 12 weeks	Daklinza: 90 mg per day	1) FDA-approved labeling 2) AASLD-IDSA (updated May 2018)
Genotype 1, 2 [†] , 3 or 4 [‡] : Decompensated cirrhosis (including those with hepatocellular carcinoma)	Daklinza 60 mg PO QD plus Sovaldi 400 mg PO QD with low initial dose of RBV (600 mg) and increased as tolerated for 12 weeks	Daklinza: 90 mg per day	1) FDA-approved labeling 2) AASLD-IDSA (updated May 2018)

Indication	Dosing Regimen	Maximum Dose	Reference
Genotype 1, 2 [†] , 3, or 4 [†] : Decompensated cirrhosis (including those with hepatocellular carcinoma) and intolerant to RBV	Daklinza 60 mg PO QD plus Sovaldi 400 mg PO QD for 24 weeks	Daklinza: 90 mg per day	1) FDA-approved labeling 2) AASLD-IDSA (updated May 2018)
Genotype 1, 4 [†] , 5 [†] , or 6 [†] : Treatment-naïve or treatment-experienced, post-liver transplantation in the allograft with or without compensated cirrhosis	Daklinza 60 mg PO QD plus Sovaldi 400 mg PO QD with low initial dose of RBV (600 mg) and increased as tolerated for 12 weeks	Daklinza: 90 mg per day	1) FDA-approved labeling 2) AASLD-IDSA (updated May 2018)
Genotype 2 [†] : Treatment-naïve or treatment-experienced without cirrhosis	Daklinza 60 mg PO plus Sovaldi 400 mg PO QD for 12 weeks	Daklinza: 90 mg per day	AASLD-IDSA (updated May 2018)
Genotype 2 [†] : Treatment-naïve or treatment-experienced with compensated cirrhosis	Daklinza 60 mg PO plus Sovaldi 400 mg PO QD for 16 to 24 weeks	Daklinza: 90 mg per day	AASLD-IDSA (updated May 2018)
Genotype 2 [†] or 3: Treatment-naïve or treatment-experienced, post-liver transplantation in the allograft with or without compensated or decompensated cirrhosis	Daklinza 60 mg PO QD plus Sovaldi 400 mg PO QD with low initial dose of RBV (600 mg) and increased as tolerated for 12 weeks	Daklinza: 90 mg per day	1) FDA-approved labeling 2) AASLD-IDSA (updated May 2018)
Genotype 3: Treatment-naïve or treatment-experienced without cirrhosis	Daklinza 60 mg PO plus Sovaldi 400 mg PO QD for 12 weeks	Daklinza: 90 mg per day	1) FDA-approved labeling 2) AASLD-IDSA (updated May 2018)
Genotype 3: Treatment-naïve with compensated cirrhosis	Daklinza 60 mg PO plus Sovaldi 400 mg PO QD with or without weight-based RBV for 24 weeks	Daklinza: 90 mg per day	AASLD-IDSA (updated May 2018)

Indication	Dosing Regimen	Maximum Dose	Reference
Daklinza dose modification	Reduce dosage to 30 mg PO QD with strong CYP3A4 inhibitors and increase to 90 mg PO QD with moderate CYP3A inducers.	Daklinza: 90 mg per day	FDA-approved labeling

AASLD/IDSA treatment guidelines for chronic hepatitis C infection are updated at irregular intervals; refer to the most updated AASLD/IDSA guideline for most accurate treatment regimen.

Treatment-experienced refers to previous treatment with peginterferon/RBV unless otherwise stated

‡ Off-label, AASLD-IDSA guideline-supported dosing regimen

VI. Product Availability

Tablets: 30 mg, 60 mg, 90 mg

VII. References

1. Daklinza Prescribing Information. Princeton, NJ: Bristol-Myers Squibb Company; November 2017. Available at http://packageinserts.bms.com/pi/pi_daklinza.pdf. Accessed May 1, 2019.
2. American Association for the Study of Liver Diseases/ Infectious Disease Society of America (AASLD-IDSA). HCV guidance: recommendations for testing, managing, and treating hepatitis C. Last updated May 24, 2018. Available at: <https://www.hcvguidelines.org/>. Accessed May 1, 2019.
3. Platt L, Easterbrook P, Gower E, et al. Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. *Lancet Infect Dis* 2016;16:797-808. <http://dx.doi.org/10.1016/>
4. Centers for Disease Control and Prevention. HIV and viral hepatitis: fact sheet. June 2017. Available at: <https://www.cdc.gov/hiv/pdf/library/factsheets/hiv-viral-hepatitis.pdf>. Accessed May 1, 2019.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created.	01.17	
Added preferencing for Mavyret; removed preferencing for Epclusa and Harvoni	09.14.17	
Expanded genotypes to reflect AASLD/IDSA CHC treatment guidelines updated April 2017. Initial approval duration expanded to up to full 24 weeks, deleted viral load and adherence requirement in continued therapy section since appropriate full regimen is provided through initial approval duration per specialist feedback to prevent barriers to adherence, added documentation of positive response to therapy and continuity of care. Added section V: dosage and administration	09.14.17	11.17
3Q18 annual review: added specific scenarios of clinically acceptable and unacceptable rationale for inability to use Mavyret; removed requirement for contraindications such as pregnancy and	05.22.18	06.18

Reviews, Revisions, and Approvals	Date	P&T Approval Date
CrCl with RBV; added requirement for documentation of previous treatment and cirrhosis status; expanded duration of tx required for COC from 30 days to 60 days; required verification of genotype for COC; removed requirement for advanced liver disease; references reviewed and updated.		
2Q 2019 annual review: no significant changes; references reviewed and updated.	02.05.19	05.19
3Q 2019 annual review: removed documented sobriety from alcohol and illicit IV drugs for ≥ 6 months prior to starting therapy; references reviewed and updated.	07.02.19	08.19

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible

for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note:

For Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the formulary exception policy.

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