Clinical Policy: Daclatasvir (Daklinza)

Reference Number: LA.PHAR.274
Effective Date: 09/16
Last Review Date: 07/18 Revision Log
Line of Business: Medicaid

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.

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

Limitation 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 (including office chart notes and lab results) 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 HCV RNA (ribonucleic acid) levels in the last 6 months;
2. Confirmed HCV genotype is 1, 2, 3, 4, 5, or 6;
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. Age ≥ 18 years;
6. Prescribed for use in combination with Sovaldi;
7. For genotype 1a with cirrhosis, laboratory testing confirming the absence of NS5A resistance associated polymorphisms at amino acid positions M28, Q30, L31 and Y93;
8. 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 F for additional details on acceptable contraindications*

9. Life expectancy ≥ 12 months with HCV treatment;
10. Documentation required that member is not actively participating in alcohol and/or illicit IV drugs use, if applicable;
11. Advanced liver disease defined as (a,b or c):
    a. Advanced fibrosis indicated by i, ii, or iii:
        i. Liver biopsy showing a METAVIR score of F3 or equivalent (Knodell, Scheuer, Batts-Ludwig – F3; Ishak – F4/5);
        ii. One serologic test showing an equivalent score to METAVIR F3
        iii. One radiologic test showing an equivalent score to METAVIR F3 per Appendix C;
    b. Cirrhosis indicated by i, ii, iii, iv or v:
        i. Hepatocellular carcinoma (HCC) amenable to resection, ablation or transplant;
        ii. Liver biopsy showing a METAVIR score of F4 or equivalent (Knodell, Scheuer, Batts-Ludwig – F4; Ishak - F5/6);
        iii. One serologic test showing an equivalent score to METAVIR F4 per Appendix C;
        iv. One radiologic test showing an equivalent score to METAVIR F4 per Appendix C;
        v. Other radiologic test showing evidence of cirrhosis (e.g., portal hypertension);
    c. If member is HIV/HCV co-infected, there shall be no METAVIR score requirements.
12. Member agrees to participate in a medication adherence program meeting both of the following components;
    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;
13. Prescribed for use in combination with Sovaldi;
14. Dose does not exceed 90 mg (1 tablet) per day.

Approval duration: up to 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): CP.PMN.53 for Medicaid

II. Continued Therapy

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

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Daklinza for chronic hepatitis C virus infection and has received this medication for at least 60 days;
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): CP.PMN.53 for Medicaid.

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 policies – CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALT: alanine aminotransferase
APRI: AST to platelet ratio
AASLD: American Association for the Study of Liver Diseases
FIB-4: Fibrosis-4 index
HBeAg: hepatitis B virus envelope antigen
HBV: hepatitis B virus
HCC: hepatocellular carcinoma
HCV: hepatitis C virus
FDA: Food and Drug Administration
IDSA: Infectious Diseases Society of America
MRE: magnetic resonance elastography
NS3/4A, NS5A/B: nonstructural protein
Peg-IFN: pegylated interferon
PI: protease inhibitor
PO: by mouth
RBV: ribavirin
QD: once per day

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	Mavyret: glecaprevir 300 mg/ pibrentasvir 120 mg (3 tablets) per day
Mavyret™ (glecaprevir/ pibrentasvir	Treatment-experienced with IFN/pegIFN + RBV: **Genotypes 1, 2, or 3** Without cirrhosis: Three tablets PO QD for 8 weeks	Mavyret: glecaprevir 300 mg/ pibrentasvir 120 mg (3

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Genotype 3 With compensated cirrhosis: Three tablets PO QD for 12 weeks	tablets) per day
Mavyret™ (glecaprevir/ pibrentasvir	Treatment-naïve or treatment-experienced, post-liver transplantation in the allograft with or without compensated cirrhosis: **Genotypes 1, 4, 5, or 6** Three tablets PO QD for 12 weeks	Mavyret: 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.

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Appendix C: Contraindications

- 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.

Appendix D: Approximate Scoring Equivalencies using METAVIR F3/F4 as Reference

Fibrosis/ Cirrhosis	Serologic Tests*				Radiologic Tests†		Liver Biopsy‡	
	Fibro Test	FIBRO Spect II	APRI	FIB-4	FibroScan (kPa)	MRE (kPa)	METAVIR	Ishak
Advanced fibrosis	≥0.59	≥42	>1.5	>3.25	≥9.5	≥4.11	F3	F4-5
Cirrhosis	≥0.75	≥42	>1.5	>3.25	≥12.0	≥4.71	F4	F5-6

*Serologic tests:
FibroTest (available through Quest as FibroTest or LabCorp as FibroSure)
FIBROSpect II (available through Prometheus Laboratory)
APRI (AST to platelet ratio index)
FIB-4 (Fibrosis-4 index: includes age, AST level, platelet count)

†Radiologic tests:
FibroScan (transient elastography)
MRE (magnetic resonance elastography)

‡Liver biopsy (histologic scoring systems):
METAVIR F3/F4 is equivalent to Knodell, Scheuer, and Batts-Ludwig F3/F4 and Ishak F4-5/F5-6
METAVIR fibrosis stages: F0 = no fibrosis; F1 = portal fibrosis without septa; F2 = few septa; F3 = numerous septa without cirrhosis; F4 = cirrhosis

Appendix E: 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			
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 F: 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.
  - 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.
    - 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
    - Efavirenz
- 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.

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 September 2017)
Genotype 1, 2‡, 3 or 4‡: Decompensated cirrhosis (including those with	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 September 2017)

Indication	Dosing Regimen	Maximum Dose	Reference
hepatocellular carcinoma)			
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 September 2017)
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 September 2017)
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 September 2017)
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 September 2017)
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 September 2017)
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 September 2017
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 September 2017
Daklinza dose modification	Reduce dosage to 30 mg PO QD with strong CYP3A4 inhibitors and increase to 90	Daklinza: 90 mg per day	FDA-approved labeling

Indication	Dosing Regimen	Maximum Dose	Reference
	mg PO QD with moderate CYP3A inducers.		

**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.*

ǂ *Off-label, AASLD-IDSA guideline-supported dosing regimen*

VI. Product Availability

Tablet: 30 mg, 60 mg, 90mg

VII. References

A. Daklinza Prescribing Information. Princeton, NJ: Bristol-Myers Squibb Company; November 2017. Available at http://packageinserts.bms.com/pi/pi_daklinza.pdf. Accessed May 1, 2018.

B. 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 September 21, 2017. Available at: https://www.hcvguidelines.org/. Accessed May 1, 2018.

C. Centers for Disease Control and Prevention. HIV and viral hepatitis: fact sheet. June 2016. Available at: https://www.cdc.gov/hiv/pdf/library/factsheets/hiv-viral-hepatitis.pdf. Accessed March 13, 2018.

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E. Bonder A, Afdhal N. Utilization of FibroScan in clinical practice. Curr Gastroenterol Rep. 2014; 16(372): 1-7. DOI 10.1007/s11894-014-0372-6.

F. Halfon P, Bourliere M, Deydier R, et al. Independent prospective multicenter validation of biochemical markers (Fibrotest–Actitest) for the prediction of liver fibrosis and activity in patients with chronic hepatitis C: The Fibropaca study. Am J Gastroenterol. 2006; 101: 547-555. DOI: 10.1111/j.1572-0241.2006.0411.x

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I. Hepatitis C Virus (HCV) FIBROSpect II. Prometheus Therapeutics and Diagnostics. Available at http://www.prometheuslabs.com/Resources/Fibrospect/Fibrospect_II_Product_Detail_Sheet_FIB16005_04-16.pdf. April 2016. Accessed May 1, 2018.

J. Hsieh YY, Tung SY, Lee K, et al. Routine blood tests to predict liver fibrosis in chronic hepatitis C. World J Gastroenterol. February 28, 2012; 18(8): 746-53. doi: 10.3748/wjg.v18.i8.746.

Reviews, Revisions, and Approvals	Date	Approval Date
New policy created, split from CP.PHAR.17 Hepatitis C Therapies. HCV RNA levels over six-month period added to confirm infection is chronic. Life expectancy "≥12 months if HCC and awaiting transplant" is modified to indicate "≥12 months with HCV therapy." Testing criteria reorganized by "no cirrhosis"/"cirrhosis" consistent with the regimen tables; HCC population is included under "cirrhosis" and broadened to incorporate HCC amenable to curative measures (resection, ablation, transplant). Methods to diagnose fibrosis/cirrhosis are modified to require presence of HCC, liver biopsy or a combination of one serologic and one radiologic test. Serologic and radiologic tests are updated and correlated with METAVIR per Appendix B. Removed creatinine clearance restriction. Criteria added excluding post-liver transplantation unless regimens specifically designate. Dosing regimens are presented in Appendix D and E per AASLD guidelines and FDA-approved indications. The initial approval is shortened to 8 weeks.	08/16	09/16
Policy converted to new template. Added requirement for prevention of HBV reactivation; expanded genotypes to reflect AASLD/IDSA CHC treatment guidelines. Consolidated appendix D and E into dosing and administration in section V; added maximum dose requirement; initial approval duration expanded to full 12 weeks, limited continued therapy approval duration to 12 weeks, deleted viral load and adherence requirement in continued therapy, added documentation of positive response to therapy and continuity of care, and removed CIs in section II, added reference column in section V. Added preferencing information requiring Mavyret for FDA-approved indications. Safety criteria was applied according to the safety guidance discussed at CPAC and endorsed by Centene Medical Affairs. Exception made to require Hep B screening for all patients prior to treatment to ensure that proper risk reduction measures are taking, though this is not specifically addressed in boxed warning.	08/17	09/17
Removed the following language: "If a lower cost alternative regimen carries an equal or higher AASLD-IDSA rating, a clinical contraindication or intolerance must be present for the alternative regimen prior to approval."	09/17	
Due to State requirements, removed prescriber restrictions regarding who can prescribe Hepatitis C DAA agents; Removed the abstinence period of 6 months and added documentation required that member is not actively participating in alcohol and/or illicit IV drugs use,; Added statement for NO Fibrosis score required for HIV/HCV co-infected members	5/18	5/18

Reviews, Revisions, and Approvals	Date	Approval Date
Changed language to one serologic test OR one radiologic test from one serologic test and one radiologic test		
3Q 2018 annual review: removed requirement for HBV verification; added requirement for documentation of previous treatment and cirrhosis status; expanded duration of tx required for COC from 30 days to 60 days; removed conditional requirement for RBV CI; references reviewed and updated.	07.18	07.18

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.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.