Clinical Policy: Daclatasvir (Daklinza)

Reference Number: CP.PHAR.274
Effective Date: 09/16
Last Review Date: 09/17 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. Prescribed by or in consultation with a gastroenterologist, hepatologist, or infectious disease specialist;
4. Age ≥ 18 years;
5. Life expectancy ≥ 12 months with HCV treatment;
6. Documented sobriety from alcohol and illicit IV drugs for ≥ 6 months prior to starting therapy, if applicable;
7. Advanced liver disease defined as a or b:
   a. Advanced fibrosis indicated by i or ii:
      i. Liver biopsy showing a METAVIR score of F3 or equivalent (Knodell, Scheuer, Batts-Ludwig – F3; Ishak – F4/5);
      ii. One serologic test and one radiologic test showing an equivalent score to METAVIR F3 per Appendix C;
   b. Cirrhosis indicated by i, ii or iii:
      i. Hepatocellular carcinoma (HCC) - and the HCC is 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. Both of the following:
a) One serologic test showing an equivalent score to METAVIR F4 per Appendix C;
b) One radiologic test showing an equivalent score to METAVIR F4 per Appendix C or other radiologic test showing evidence of cirrhosis (e.g., portal hypertension);

8. Prescribed regimen is consistent with an FDA or AASLD-IDSA recommended regimen (*see Section V Dosage and Administration for reference)*;
9. If member is without cirrhosis or with compensated cirrhosis (Child-Pugh A): contraindication or intolerance to Mavyret;
10. 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;
11. Member is hepatitis B virus (HBV) negative, or if positive, documentation that concurrent HBV infection is being treated (e.g., tenofovir alafenamide, adefovir, entecavir), unless contraindicated or clinically significant adverse effects are experienced (*see Appendix B*);
12. If prescribed with ribavirin, at the time of request, member has none of the following contraindications:
    a. Pregnancy;
    b. For Rebetol: creatinine clearance < 50 mL/min;
13. For genotype 1a with cirrhosis, laboratory testing confirming the absence of NS5A resistance associated polymorphisms at amino acid positions M28, Q30, L31 and Y93;
14. Prescribed for use in combination with Sovaldi;
15. 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 CP.PHAR.57 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 30 days;
2. Member is responding positively to therapy (e.g. decreased HCV RNA level, no unacceptable toxicity);

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 CP.PHAR.57 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 – CP.PHAR.57 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: General Information

- Hepatitis B Reactivation is a black box warning for all direct-acting antiviral drugs for the treatment of HCV. The provider must provide either:
  - Documentation of absence of concurrent HBV infection as evidenced by laboratory values showing absence of hepatitis B virus envelope antigen (HBeAg) and HBV DNA;
  - Documentation that HBV co-infected patient may not be candidates for therapy as evidenced by one of the following:
    - Absence of HBeAg, HBV DNA less than 2,000 international units/mL, and alanine aminotransferase (ALT) level within 1 to 2 times the upper limit of normal;
    - HBeAg-positive and HBV DNA greater than 1,000,000 international units/mL and ALT level within 1 to 2 times the upper limit of normal;
  - Documentation that concurrent HBV infection is being treated (e.g., tenofovir alafenamide, adefovir, entecavir), unless contraindicated or clinically significant adverse effects are experienced
- The 2016 AASLD/IDSA treatment guideline for HBV consider ALT levels <30 U/L for men and <19 U/L for women as upper limits of normal.

- The 2016 AASLD/IDSA treatment guideline for HBV recommend adults with compensated cirrhosis, even with low levels of viremia (<2,000 IU/mL) be treated with antiviral therapy to reduce the risk of decompensation, regardless of ALT level. The recommendation extends to adults with decompensated cirrhosis be treated with antiviral therapy indefinitely regardless of HBV DNA level, HBeAg status, or ALT level to decrease the risk of worsening liver-related complications.

Appendix C: 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 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			
Olysio				Simeprevir	
Sovaldi		Sofosbuvir			
Technivie*	Ombitasvir			Paritaprevir	Ritonavir
Viekira XR/PAK*	Ombitasvir		Dasabuvir	Paritaprevir	Ritonavir
Zepatier*	Elbasvir			Grazoprevir	

*Combination drugs

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: 90mg once daily	1) FDA-approved labeling 2) AASLD-04/17)
Genotype 1: Treatment-naïve or treatment-experienced with compensated cirrhosis	Daklinza 60 mg PO QD plus Sovaldi 400 mg PO QD with or without weight-based RBV for 24 weeks	Daklinza: 90mg once daily	AASLD-IDSA (updated 04/17)
Genotype 1, 4ǂ, 5ǂ, or 6ǂ: 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: 90mg once daily	1) FDA-approved labeling 2) ǂ AASLD-IDSA (updated 04/17)
Genotype 1, 4ǂ, 5ǂ, or 6ǂ: 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: 90mg once daily	ǂ AASLD-IDSA (updated 04/17)
Genotype 1 or 4ǂ: Treatment-naïve or treatment-experienced, post-liver transplantation including those with 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: 90mg once daily	1) FDA-approved labeling 2) ǂ AASLD-IDSA (updated 04/17)
Genotype 1 or 4ǂ: Treatment -naïve, post-liver transplantation with compensated liver disease, who are ribavirin ineligible	Daklinza 60 mg PO QD plus Sovaldi 400 mg PO QD for 24 weeks	Daklinza: 90mg once daily	ǂ AASLD-IDSA (updated 04/17)
Genotype 2: Treatment-naïve or treatment-experienced without cirrhosis	Daklinza 60 mg PO plus Sovaldi 400 mg PO QD for 12 weeks	Daklinza: 90mg once daily	AASLD-IDSA (updated 04/17)
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: 90mg once daily	AASLD-IDSA (updated 04/17)

Indication	Dosing Regimen	Maximum Dose	Reference
Genotype 2: In whom previous treatment with Sovaldi/RBV has failed	Daklinza 60 mg PO plus Sovaldi 400 mg PO QD with or without weight-based RBV for 24 weeks	Daklinza: 90mg once daily	AASLD-IDSA (updated 04/17)
Genotype 2ǂ or 3: Decompensated cirrhosis (including those with hepatocellular carcinoma)	Daklinza 60 mg PO plus Sovaldi 400 mg PO QD with low initial dose of RBV (600 mg) and increased as tolerated for 12 weeks	Daklinza: 90mg once daily	1) FDA-approved labeling 2) ǂ AASLD-IDSA (updated 04/17)
Genotype 2: Treatment-naïve or treatment-experienced, post-liver transplantation, including those with 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: 90mg once daily	AASLD-IDSA (updated 04/17)
Genotype 2: Treatment - naïve or treatment-experienced, post-liver transplantation, including those with compensated cirrhosis, who are ribavirin ineligible	Daklinza 60 mg PO QD plus Sovaldi 400 mg PO QD for 24 weeks	Daklinza: 90mg once daily	AASLD-IDSA (updated 04/17)
Genotype 3: Treatment-naïve or treatment-experienced with Peg IFN/RBV without cirrhosis	Daklinza 60 mg PO plus Sovaldi 400 mg PO QD for 12 weeks	Daklinza: 90mg once daily	1) FDA-approved labeling 2) AASLD-IDSA (updated 04/17)
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: 90mg once daily	AASLD-IDSA (updated 04/17)
Genotype 3: Treatment-experienced with Peg IFN/RBV or with sofosbuvir-based treatment without prior experience with NS5A inhibitor with compensated cirrhosis	Daklinza 60 mg PO plus Sovaldi 400 mg PO QD with weight-based RBV for 24 weeks	Daklinza: 90mg once daily	AASLD-IDSA (updated 04/17)
Genotype 3: In whom previous treatment with Sovaldi/RBV has failed	Daklinza 60 mg PO plus Sovaldi 400 mg PO QD with weight-based RBV for 24 weeks	Daklinza: 90mg once daily	AASLD-IDSA (updated 04/17)
Genotype 3: Treatment-naïve or treatment-experienced, post-liver	Daklinza 60 mg PO plus Sovaldi 400 mg PO QD with low initial dose RBV	Daklinza: 90mg once daily	AASLD-IDSA (updated 04/17)

Indication	Dosing Regimen	Maximum Dose	Reference
transplantation, in the allograft, including those with compensated cirrhosis	(600mg, increased as tolerated) for 12 weeks		
Genotype 3: Treatment-naïve or treatment-experienced, post-liver transplantation, in the allograft, including those with compensated cirrhosis, who are ribavirin ineligible	Daklinza 60 mg PO plus Sovaldi 400 mg PO QD for 24 weeks	Daklinza: 90mg once daily	AASLD-IDSA (updated 04/17
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: 90mg once daily	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.*

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

VI. Product Availability

Tablet: 30 mg, 60 mg, 90mg

VII. References

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http://www.prometheuslabs.com/Resources/Fibrospect/Fibrospect_II_Product_Detail_Sheet_FIB16005_04-16.pdf. April 2016. Accessed July 15, 2016.
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9. Bruix J and Sherman M. Management of hepatocellular carcinoma: An update. American Association for the Study of Liver Diseases (AASLD) Practice Guideline. Hepatology. 2011; 53(3): 1020-22.
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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

Reviews, Revisions, and Approvals	Date	Approval Date
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	

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 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.