Clinical Policy: Hepatitis C Direct-Acting Antivirals

Reference Number: OR.CP.PHAR.1003
Effective Date: 04.01.22
Last Review Date: 09.24
Line of Business: Medicaid – Trillium Oregon Health Plan

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
The following direct-acting antivirals (DAA) agents indicated for the treatment of hepatitis C virus (HCV) and require prior authorization: daclatasvir (Daklinza), dasabuvir-ombitasvir-paritaprevir-ritonavir (Vikira XR, Viekira Pak), elbasvir-grazoprevir (Zepatier), glecaprevir-pibrentasvir (Mavyret), ledipasvir-sofosbuvir (Harvoni), ombitasvir-paritaprevir-ritonavir (Technivie), simeprevir (Olysio), sofosbuvir (Sovaldi), sofosbuvir-velpatasvir (Epclusa), sofosbuvir-velpatasvir-voxilaprevir (Vosevi).

Goals
- Approve use of cost-effective treatments supported by the medical evidence.
- Provide consistent patient evaluations across all hepatitis C treatments.
- Ensure appropriate patient regimen based on prior treatment experience and genotype.

Length of Authorization:
- 8-24 weeks

Requires PA:
- Non-preferred direct acting antivirals (DAAs)
- Preferred regimens for patients with treatment experience with a DAA

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.

Approval Criteria		
1. What is diagnosis is being treated?	Record ICD-10 code.	
2. Is the request for treatment of Hepatitis C infection?	**Yes:** Go to #3 Document baseline quantitative HCV RNA level _____	**No:** Pass to RPh. Deny; medical appropriateness
3. Has all the following pre-treatment testing been documented: a. Genotype testing in past 3 years is required if the patient has decompensated cirrhosis, prior treatment experience with a DAA regimen, and if prescribed a regimen which is not pan-genotypic;	**Yes:** Record results of each test and go to #4	**No:** Pass to RPh. Request updated testing.

b. History of previous HCV treatment**,** viral load after treatment, and outcome are required only if there is documentation of treatment experience		
4. Which regimen is requested?	Document and go to #5	
5. Has the patient been treated with a direct acting antiviral regimen previously?	**Yes:** Go to #6	**No:** Go to #8
6. Did the patient achieve a sustained virological response (SVR) at week 12 or longer following the completion of their last DAA regimen?	**Yes:** Go to #7	**No:** Document as treatment failure and treat as indicated for treatment experienced. Go to #8
7. Is this likely a reinfection, indicated by at least one of the following: a. Does the patient have ongoing risk factors for hepatitis C reinfection (e.g. sexually active men who have sex with me, persons who inject drugs), OR b. Is the hepatitis C infection a different genotype than previous	**Yes:** Document as reinfection. Use regimens recommended for treatment naïve patients. Go to #8	**No:** Document as treatment failure and treat as indicated for treatment experienced. Go to #8
8. Is the prescribed drug: a. Elbasvir/grazoprevir for GT 1a infection; or b. Ledipasvir/sofosbuvir for GT 1a treatment-experienced infection; or c. Sofosbuvir/velpatasvir for GT 3 in cirrhosis or treatment-experienced infection	**Yes:** Go to #9	**No:** Go to #10
9. Has the patient had a baseline NS5a resistance test that documents a resistant variant to one of the agents in #8? NOTE: Baseline NS5A resistance testing is required.	**Yes:** Pass to RPh; deny for appropriateness	**No:** Go to #10 Document test and result
10. Is the prescribed drug regimen a recommended regimen based on the patient's genotype, age, treatment status (retreatment or treatment naïve) and cirrhosis status (see **Table 1 and Table 2**)? Note: Safety and efficacy of DAAs for children <3 years of age has not been established Pediatric dosing available in **Table 3** and **Table 4**	**Yes:** Approve for 8-24 weeks based on duration of treatment indicated for approved regimen Referral will be made for optional case management (patient may choose to opt-in).	**No:** Pass to RPh. Deny; medical appropriateness.

Table 1: Recommended Treatment Regimens for Adults, and Adolescents 12 years of age and older with Hepatitis C virus.

Treatment History	Cirrhosis Status	Recommended Regimen
Treatment Naïve (Genotype 1-6)		
Treatment naïve, confirmed reinfection or prior treatment with PEGylated interferon/ribavirin	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks G/P x 8 weeks
	Compensated cirrhosis	G/P x 8 weeks SOF/VEL x 12 weeks (baseline resistance testing recommended for GT3)
	Decompensated Cirrhosis	SOF/VEL + RBV x 12 weeks SOF/VEL x 24 weeks (if ribavirin ineligible*)
Treatment Experienced (Genotype 1-6)		
Sofosbuvir based regimen treatment failures, including: Sofosbuvir + ribavirin Ledipasvir/sofosbuvir Velpatasvir sofosbuvir	Non-cirrhotic or compensated cirrhosis	SOF/VEL/VOX x 12 weeks G/P x 16 weeks (except GT3)
Elbasvir/grazoprevir treatment failures	Non-cirrhotic or compensated cirrhosis	SOF/VEL/VOX x 12 weeks
Glecaprevir/pibrentasvir treatment failures	Non-cirrhotic or compensated cirrhosis	G/P + SOF + RBV x16 weeks SOF/VEL/VOX x 12 weeks (plus RBV if compensated cirrhosis)
Multiple DAA Treatment Failures, including: Sofosbuvir/velpatasvir/voxilaprevir Glecaprevir/pibrentasvir + sofosbuvir	Non-cirrhotic or compensated cirrhosis	G/P + SOF + RBV x 16-24 weeks SOF/VEL/VOX x 24 weeks
Abbreviations: DAA = direct acting antiviral; EBV/GZR = elbasvir/grazoprevir; G/P = glecaprevir/pebrentasvir; PEG = pegylated interferon; RAV = resistance-associated variant; RBV = ribavirin; SOF = sofosbuvir; SOF/VEL = sofosbuvir/velpatasvir; SOF/VEL/VOX = sofosbuvir/velpatasvir/voxilaprevir		
*Ribavirin ineligible/intolerance may include: 1) neutrophils < 750 mm^3, 3) hemoglobin <10 g/dl, 3) platelets <50,000 cells/mm^3, autoimmune hepatitis or other autoimmune condition, hypersensitivity or allergy to ribavirin		
^ Rarely, genotype assays may indicate the presence of a mixed infection (e.g., genotypes 1a and 2). Treatment data for mixed genotypes with direct-acting antivirals are limited. However, in these cases, a pangenotypic regimen is appropriate.		
Ribavirin-containing regimens are absolutely contraindicated in pregnant women and in the male partners of women who are pregnant. Documented use of two forms of birth control in patients and sex partners for whom a ribavirin containing regimen is chosen is required		
All regimens containing a protease inhibitor (elbasvir, glecaprevir, simeprevir, paritaprevir, voxilaprevir) should not be used in patients with moderate to severe hepatic impairment (CTP B and C)		
There is limited data supporting DAA regimens in treatment-experienced patients with decompensated cirrhosis. These patients should be handled on a case by case basis with the patient, prescriber, and CCO or FFS medical director.		
Definitions of Treatment Candidates ▪ Treatment-naïve: Patients without prior HCV treatment ▪ Treat as treatment-naïve: Patients who discontinued HCV DAA therapy within 4 weeks of initiation or have		

confirmed reinfection after achieving SVR following HCV treatment ▪ Treatment-experienced: Patients who received more than 4 weeks of HCV DAA therapy.

Table 2: Recommended Treatment Regimens for Children Ages 3-12 Years of Age with Hepatitis C virus.

Treatment History	Cirrhosis Status	Recommended Regimen
Treatment Naïve Genotype 1-6		
Treatment naïve, confirmed reinfection or prior treatment with PEGylated interferon/ribavirin	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks G/P x 8 weeks
	Decompensated cirrhosis	SOF/VEL + RBV x 12 weeks
Treatment Experienced with DAA Regimen		
Note: Efficacy and safety extremely limited in treatment experienced to other DAAs in this population. Can consider recommended treatment regimens in adults if FDA approved for pediatric use. Recommend consulting with hepatologist.		
Abbreviations: DAA = direct acting antiviral; G/P = glecaprevir/pebrentasvir; RBV = ribavirin; SOF = sofosbuvir; SOF/VEL = sofosbuvir/velpatasvir		
All regimens containing a protease inhibitor (elbasvir, glecaprevir, simeprevir, paritaprevir, voxilaprevir) should not be used in patients with moderate to severe hepatic impairment (CTP B and C)		
There is limited data supporting DAA regimens in treatment-experienced patients with decompensated cirrhosis. These patients should be handled on a case by case basis with the patient, prescriber, and CCO or FFS medical director.		

Table 3: Recommended dosage of sofosbuvir/velpatasvir in pediatric patients 3 years of age and older:

Body Weight	Dosing of sofosbuvir/velpatasvir
Less than 17 kg	One 150 mg/37.5 mg pellet packet once daily
17 kg to less than 30 kg	One 200 mg/50 mg pellet packet OR tablet once daily
At least 30 kg	Two 200 mg/50 mg pellet packets once daily OR one 400 mg/100 mg tablet once daily

Table 4: Recommended dosage of glecaprevir/pibrentasvir in pediatric patients 3 years of age and older:

Body Weight	Dosing of sofosbuvir/velpatasvir
Less than 20 kg	Three 50 mg/20 mg pellet packets once daily
20 kg to less than 30 kg	Four 50 mg/20 mg pellet packets once daily
30 kg to less than 45 kg	Five 50 mg/20 mg pellet packets once daily
45 kg and greater OR 12 years of age and older	Three 100 mg/40 mg tablets once daily

I. Appendices/General Information

Appendix A: 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
Epclusa*	Velpatasvir	Sofosbuvir			

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

**Combination drugs*

Appendix B: 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.
- 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

- AASLD-IDSA simplified treatment recommendations: In their October 2022 HCV guidance, AASLD-IDSA updated treatment recommendations to recommend two simplified regimens for adults with hepatitis C (*any genotype*) who do not have cirrhosis and have not previously received hepatitis C treatment: either Mavyret x8 weeks or Epclusa x12 weeks. With the advent of pangenotypic HCV treatment regimens, HCV genotyping is no longer required prior to treatment initiation for all individuals. In those with evidence of cirrhosis and/or past unsuccessful HCV treatment, treatment regimens may differ by genotype and thus pretreatment genotyping is recommended. For noncirrhotic treatment-naive patients, although genotyping may impact the preferred treatment approach, it is not required if a pangenotypic regimen is used.

Appendix C: Incomplete Adherence and AASLD-IDSA Recommended Management of Treatment Interruptions

- There are minimal data regarding the outcome of patients who have incomplete adherence to direct-acting antiviral (DAA) therapy or the threshold level of adherence below which the incidence of sustained virologic response at 12 weeks (SVR12) is significantly reduced. In general, a treatment interruption of < 7 days is unlikely to impact SVR12.
- There are few data on which to base recommendations regarding how to manage patients who have discontinued DAAs for several days to weeks. The below recommendations are applicable to treatment-naive patients with HCV, without cirrhosis or with compensated cirrhosis*, receiving either Mavyret or Epclusa*. Patients with prior DAA treatment, or receiving other DAA treatment regimens, or other populations (e.g., patients who are posttransplant or have decompensated cirrhosis) should be managed in consultation with an expert.
  - Interruptions during the first 28 days of DAA therapy:
    - If missed ≤ 7 days, restart DAA therapy immediately and complete therapy for originally planned duration (8 or 12 weeks).
    - If missed ≥ 8 days, restart DAA therapy immediately and obtain HCV RNA test as soon as possible. If HCV RNA is negative, complete originally planned DAA treatment course (8 or 12 weeks). Recommendation to extend DAA treatment for an additional 4 weeks for patients with genotype 3 and/or cirrhosis. If HCV RNA is positive or not obtained, extend DAA treatment for an additional 4 weeks.
  - Interruptions after receiving ≥ 28 days of DAA therapy:
    - If missed ≤ 7 days, restart DAA therapy immediately and complete therapy for originally planned duration (8 or 12 weeks).
    - If missed 8-20 consecutive days, restart DAA therapy immediately and obtain HCV RNA test as soon as possible. If HCV RNA is negative, complete originally planned DAA treatment course (8 or 12 weeks). Recommendation to extend DAA treatment for an additional 4 weeks for patients with genotype 3 and/or cirrhosis. If HCV RNA is positive or not obtained, stop treatment and retreat according to the recommendations in the AASLD-IDSA Retreatment Section.
    - If missed ≥ 21 consecutive days, stop DAA treatment and assess for SVR12. If SVR12 not achieved, retreat according to the recommendations in the AASLD-IDSA Retreatment Section.

II. References

1. Hepatitis C Direct-Acting Antivirals. Oregon Health Plan Current Drug Use Criteria. Available at: http://orpdl.org/drugs/index.php. Accessed June 28, 2024.
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 December 19, 2023. Available at: https://www.hcvguidelines.org/. Accessed June 28, 2024.
3. Bourliere M, et al. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection. NEJM 2017;376:2134-46.
4. Epclusa Prescribing Information. Foster City, CA: Gilead Sciences, Inc.; April 2022. Available at: https://hcp.epclusa.com/. Accessed June 28, 2024.
5. Zepatier Prescribing Information. Whitehouse Station, NJ: Merck and Company, Inc.; May 2022. Available at: http://www.merck.com/product/usa/pi_circulars/z/zepatier/zepatier_pi.pdf. Accessed June 28, 2024.
6. Viekira Pak Prescribing Information. North Chicago, IL: Abbvie Pharmaceuticals Corp; December 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/206619s020lbl.pdf /. Accessed June 28, 2024
7. Harvoni Prescribing Information. Foster City, CA: Gilead Sciences, Inc.; March 2020. Available at: http://www.harvoni.com. Accessed June 28, 2024.

8. Sovaldi Prescribing Information. Foster City, CA: Gilead Sciences, Inc.; March 2020. Available at: https://www.gilead.com/-/media/8c41933bdd5d4e4691af495f40aa6016.ashxhttp://www.sovaldi.com/. Accessed June 28, 2024.
9. Vosevi Prescribing Information. Foster City, CA: Gilead Sciences, Inc.; November 2019. Available at: www.vosevi.com. Accessed June 28, 2024.
10. Mavyret Prescribing Information. North Chicago, IL: AbbVie Inc.;October 2023. Available at: https://www.rxabbvie.com/pdf/mavyret_pi.pdf. Accessed June 28, 2024.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created: adapted from previously approved policy TCHP.PHAR.1801 Hepatitis C Direct Acting Antivirals.	12.20.21	01.06.22
Policy revised for 1/1/2023 implementation to align with OHA FFS coverage criteria; PA for preferred regiments to no longer be required for treatment naïve patients; participating in Case Management no longer a requirement for coverage	12.14.22	01.05.23
1Q 2024 annual review: no significant changes; references reviewed and updated.	12.28.23	02.20.24
Removed qualifier of "chronic" from HCV criteria as AASLD-IDSA recommends treatment of both acute and chronic HCV; added Appendix C for guidance on incomplete adherence and AASLD-IDSA recommended management of treatment interruptions; references reviewed and updated.	06.28.24	09.17.24

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.

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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.