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Drug Class Literature Scan: Hepatitis C, Direct-Acting Antivirals

Date of Review: October 2024

Date of Last Review: October 2021 Lit Scan, April 2022 Policy Proposal

Literature Search: 08/31/21 – 08/07/2024

Current Status of PDL Class:

See **Appendix 1**.

Plain Language Summary:

- Hepatitis C virus (HCV) is a disease of the liver spread through blood contact, most commonly from sharing drug needles or other items contaminated with blood. If left untreated, chronic HCV can cause liver cancer and other diseases of the liver.
- Direct acting antivirals (DAAs) are medications taken by mouth for 8-12 weeks for the treatment of chronic HCV. They are highly effective at eliminating HCV and are generally well tolerated. These medications do not provide lifelong protection from HCV like a vaccine would.
- The purpose of this review is to look for any new published data comparing DAAs for the treatment of HCV.
- There are two preferred DAAs on the preferred drug list (glecaprevir/pibrentasvir [Mavret] and sofosbuvir/velpatasvir [Epclusa]) and these medications can be prescribed without additional documentation for patients who have never been treated for HCV before and without decompensated cirrhosis, which is a serious liver condition that happens when the liver cannot work anymore due to severe damage.

Conclusions:

- There is no new high-quality evidence from randomized controlled trials (RCTs) evaluating DAA regimens on long term clinical outcomes, including mortality, progression to cirrhosis or decompensation, and hepatocellular carcinoma.
- There is no new high-quality evidence evaluating comparative efficacy or safety between the different DAA regimens in the treatment of chronic or acute HCV.
- There is low quality evidence that grazoprevir/elbasvir results in a higher end-of-treatment response compared to placebo (relative risk [RR] 174.99; 95% confidence interval [CI] 11.03 to 2775.78) in patients with HCV and chronic kidney disease [CKD] on dialysis.¹
- There is low quality evidence that glecaprevir/pibrentasvir is effective at achieving sustained virologic response (SVR) rates in pediatric patients aged 3 to 18 years old (96% - 100%) in low quality open-label studies with no comparator.² There is insufficient evidence evaluating sofosbuvir/velpatasvir in pediatric patients with HCV.²
- Due to inferior SVR rates and its safety profile, treatment with pegylated interferon plus ribavirin is no longer recommended for the treatment of HCV.³

Recommendations:

- No changes based on clinical data recommended at this time.
- Retire pegylated interferon prior authorization criteria.
- After evaluation of comparative costs in executive session, no changes were made.

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Summary of Prior Reviews and Current Policy

- There is high quality evidence that DAA regimens result in pooled SVR rates between 95.5% to 98.8% across genotypes in the treatment of chronic HCV and high quality evidence of low rates of serious adverse events (1.9%; relative risk [RR] 1.90; 95% confidence interval [CI] 0.73 to 4.95) and withdrawals due to adverse events (0.4%).⁴
- There is insufficient direct evidence from randomized controlled trials (RCTs) that DAA therapy improves long term clinical outcomes. There is low quality evidence from observational data that SVR is associated with a decreased risk of all-cause mortality (hazard ratio [HR] 0.40; 95% CI 0.28 to 0.56, I² 52.1%), liver-related mortality (HR 0.11; 95% CI 0.04 to 0.27), cirrhosis (HR 0.36; 95% CI 0.33 to 0.4) and hepatocellular carcinoma (HR 0.29; 95% CI 0.23 to 0.38) after adjustment for potential confounders.⁴
- There are still several limitations in the current evidence for the treatment of chronic HCV:
 - There is still insufficient evidence for the optimal treatment of patients who have had a virologic failure to a previous DAA. Risk of DAA resistance is a major concern in this population.
 - There is still a lack of head-to-head trials for most DAA regimens
 - Trials often exclude patients with chronic hepatitis B virus (HBV), human immunodeficiency virus (HIV), cancer, hepatocellular carcinoma (HCC), decompensated cirrhosis, severe psychiatric, cardiac, pulmonary, or renal comorbidities.
 - There is insufficient evidence to evaluate the use of DAAs in the treatment of acute HCV infection
- The Oregon Drug Use Review/Pharmacy & Therapeutics (P&T) Committee initially prioritized treatment for the fee-for-service population to patients in greatest need of treatment. Limited real-world experience and data, consideration for the number of patients waiting for treatment, limited provider expertise, and the limited number of alternative treatment options in cases of treatment resistance and patient comorbidities all played a role in prioritizing treatment. As more treatment options become available, real-world experience increases, and the community standard evolves, the P&T Committee has expanded treatment in a stepwise fashion to patients with less severe disease.
- Prior authorization criteria was removed for all preferred DAA regimens for treatment-naïve patients with HCV in 2022. PA is required for: retreatment of HCV, non-preferred DAAs, and for uses not FDA approved (**Appendix 1**).

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Scottish Intercollegiate Guidelines Network (SIGN), and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews of randomized trials and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. Observational studies or systematic reviews of observational studies will only be included for meaningful clinical outcomes (e.g. mortality) when higher quality data is lacking and for safety outcomes of interest.

New Systematic Reviews:

- A Cochrane Collaboration systematic review evaluated interventions for HCV in patients with chronic kidney disease (CDK) on dialysis.¹ Randomized controlled trials, quasi-RCTs, and the first period of randomized cross-over studies were included. Studies including patients with HIV or hepatitis B co-infection and HCV-related manifestations other than liver disease were excluded. ¹ Studies with interferon, pegylated interferon, ribavirin, and DAAs were included. Only studies including DAAs will be discussed further. The primary outcomes were death and HCV relapse. A total of 13 RCTs (n=997) were included. ¹ Only two studies included evaluated DAAs; one study included grazoprevir/elbasvir (low risk of bias) and another study included telaprevir in combination with pegylated interferon (unclear risk of bias). Telaprevir was discontinued from the U.S. market in 2014. There was low certainty evidence that grazoprevir/elbasvir resulted in a higher end-of-treatment response (undetectable HCV RNA at the end of treatment) compared to placebo (RR 174.99; 95% CI 11.03 to 2775.78) in patients with HCV on dialysis. ¹ The evidence was insufficient to evaluate other clinical outcomes, including SVR12 (undetectable HCV RNA 12 weeks after the end of treatment). ¹
- A systematic review and meta-analysis assessed the impact of DAAs on disease progression, hepatocellular carcinoma, and mortality in chronic HCV. ⁵ Randomized, non-randomized, and observational cohort studies comparing DAAs to a control were included. A total of 49 studies were included with median follow-up periods of 6 to 86 months. Most of the included studies were observational studies and strong conclusions of causation cannot be made. Based on six studies (n=58,957), those treated with a DAA had a reduced risk of mortality compared to those without (HR 0.44; 95% CI 0.38-0.52). There was also a decrease in progression to decompensated liver disease based on three studies (HR 0.54; 95% CI 0.28-0.76). When comparing SVR to non-responders, achieving SVR also reduced the risk of mortality (HR 0.33; 95% CI 0.23-0.46) and hepatic decompensation (HR 0.11; 95% CI 0.05-0.24).
- There is a safety warning regarding the risk of liver failure with use of DAA regimens that include a protease inhibitor, including glecaprevir/pibrentasvir. A systematic review and meta-analysis were performed to quantify the risk of drug-induced liver injury (DILI) by glecaprevir/pibrentasvir in the treatment of chronic HCV.⁶ Studies that did not include SVR12 or liver-injury labs were excluded. Studies with patients with HIV or hepatitis B co-infection, posttransplant patients were also excluded. The primary outcome was DILI, defined as total bilirubin greater than 3 times the upper limit of normal (ULN) (grade 3 adverse event). Secondary outcomes included alanine transaminase (ALT) or aspartate transaminase (AST) more than 5 times the ULN. A total of nine studies were included in the analysis (n=7650). Most of these trials were open-label and three had high risk of bias. The most common grade 3 adverse event was an elevation of total bilirubin (RR 0.003; 95% CI 0.00-0.002; p=0.993), but the absolute rate was low (< 1%). Grade 3 elevations in ALT and AST were also minimal. ⁶ The risk of grade 3 hyperbilirubinemia was higher in those with cirrhosis compared to without cirrhosis (RR 2.7; 95% CI 1.182-6.276). ⁶ There was no significant difference based on treatment duration or between different genotypes.
- A rapid review was published from the Canadian Journal of Health Technologies (CADTH) summarizing the clinical effectiveness of glecaprevir/pibrentasvir and sofosbuvir/velpatasvir for the treatment of HCV in pediatric patients aged 3 to less than 18 years and weighing at least 12 kg.² Outcomes of interest included SVR, treatment failure, relapse, mortality, quality of life and safety. After review of initial citations, only 3 publications of 2 studies were included. Both studies included glecaprevir/pibrentasvir (n=152) and there were no relevant studies of sofosbuvir/velpatasvir in pediatric patients. Both studies were prospective, nonrandomized, open-label, single arm studies with significant limitations, including lack of a comparator and lack of blinding. In adolescents aged 12 to 17 years, glecaprevir/pibrentasvir resulted in high SVR rates of 96% and 100% and in patients 3 to 11 years, the overall SVR12 rate was 96%.² There were no cases of severe adverse events, discontinuations due to adverse events, or significant liver-related toxicities in either study.

After review, 7 systematic reviews were excluded due to poor quality⁷, wrong study design of included trials (e.g., observational),⁸⁻¹⁷ comparator (e.g., no control or placebo-controlled)¹⁸, or outcome studied (e.g., non-clinical).

New Guidelines:

High Quality Guidelines: None Identified

Additional Guidelines for Clinical Context:

1. American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA)³
Guidelines from the AASLD/IDSA were updated in October 2022.³ The following updates are included in the guideline:
 - Continued emphasis on universal HCV screening
 - Removal of HIV as a contraindication to the simplified treatment approach
 - Removal of 12-week glecaprevir/pibrentasvir recommendation for HIV with cirrhosis.
 - Guidance for patients with incomplete adherence based on limited data and expert consensus
 - Medication interruptions before receiving 28 days of DAA therapy:
 - Missed ≤ 7 days
 - Restart immediately and complete originally planned duration
 - Missed ≥ 8 days
 - Restart immediately. Obtain HCV RNA test and if positive, extend DAA duration for an additional 4 weeks
 - Medication interruptions after receiving 28 days of DAA therapy:
 - Missed ≤ 7 days
 - Restart immediately and complete originally planned duration
 - Missed 8-20 consecutive days
 - Restart immediately. Obtain HCV RNA test and if positive, extend DAA duration for an additional 4 weeks
 - Missed ≥ 21 days
 - Stop DAA treatment and assess for SVR12.

Guidelines recommend a simplified treatment regimen for adults with chronic HCV who are treatment naïve, without cirrhosis or with compensated cirrhosis. The following are excluded from the simplified regimen: **previously treated, hepatitis B coinfection, compensated cirrhosis with end stage renal disease, decompensated cirrhosis, current pregnancy, hepatocellular carcinoma, and prior liver transplantation.**

Table 1: Recommended DAA regimens as part of the simplified treatment algorithm (treatment naïve without decompensated cirrhosis):

DAA regimen	Duration	Genotypes	Preferred or Alternative	Additional Info
Glecaprevir/pibrentasvir	8 weeks	1-6	Preferred	
Sofosbuvir/velpatasvir	12 weeks	1-6	Preferred	If GT 3 and compensated cirrhosis, NS5A RAS testing is recommended.
Ledipasvir/sofosbuvir	12 weeks	1, 4, 5, 6	Alternative	8 weeks for GT 1 without cirrhosis
Elbasvir/grazoprevir	12 weeks	1b, 4	Alternative	If GT 1a, NS5A RAS testing is recommended
Abbreviations: GT = genotype; NS5A = hepatitis C virus nonstructural protein 5A; RAS = resistance-associated substitution				

New Formulations:

None

New Indications:

- The FDA labeling of elbasvir and grazoprevir (Zepatier) was expanded in December 2021 to include adolescent patients 12 years of age and older or weighing at least 30 kg with chronic HCV genotype 1 or 4 infection.¹⁹ Previously, it was only approved for adults. Approval was based on an open-label phase 2b pharmacokinetic study in 22 patients 12-18 years of age with GT 1 or 4 HCV without cirrhosis. The median age was 13.5 years and 64% were treatment naïve.²⁰ All participants achieved SVR12, and pharmacokinetic analysis found steady state area under the curve within comparability bounds for adults. The most common adverse events were headache (13.6%), fatigue (4.5%) and nausea (9.1%). There were no severe adverse events or discontinuations due to adverse events.

New FDA Safety Alerts:

None

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23. Sulkowski MS, Moon JS, Sherman KE, et al. A Pragmatic, Randomized Controlled Trial of Oral Antivirals for the Treatment of Chronic Hepatitis C: The PRIORITIZE Study. *Hepatology (Baltimore, Md)*. Dec 2021;74(6):2952-2964. doi:10.1002/hep.32053

Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
glecaprevir/pibrentasvir	MAVYRET	ORAL	TABLET	Y
sofosbuvir/velpatasvir	SOFOSBUVIR-VELPATASVIR	ORAL	TABLET	Y
sofosbuvir/velpatasvir	EPCLUSA	ORAL	PELET PACK	N
ledipasvir/sofosbuvir	HARVONI	ORAL	PELET PACK	N
glecaprevir/pibrentasvir	MAVYRET	ORAL	PELET PACK	N
sofosbuvir	SOVALDI	ORAL	PELET PACK	N
sofosbuvir/velpatasvir	EPCLUSA	ORAL	TABLET	N
ledipasvir/sofosbuvir	HARVONI	ORAL	TABLET	N
ledipasvir/sofosbuvir	LEDIPASVIR-SOFOSBUVIR	ORAL	TABLET	N
sofosbuvir	SOVALDI	ORAL	TABLET	N
sofosbuvir/velpatas/voxilaprev	VOSEVI	ORAL	TABLET	N
elbasvir/grazoprevir	ZEPATIER	ORAL	TABLET	N

Appendix 2: New Comparative Clinical Trials

A total of 18 citations were manually reviewed from the initial literature search. After further review, 15 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining 3 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Matthews, et al. ²¹	SOF/VEL 6 weeks vs. SOF/VEL 12 weeks	Recent HCV infection (n=196)	SVR12	<u>SVR12:</u> 6 weeks: 81.7%; 95% CI 84.1 – 96.3 12 weeks: 90.5%; 95% CI 82.8 – 95.6 Diff: -8.81; 95% CI -18.6 to 1.0*; p=0.08 <i>*Did not meet non-inferiority margin (lower bound of 12%)</i>	- open label - limited to recent HCV infection (≤ 12 months) - excluded HBV coinfection - mostly white males
El-Kassass, et al. ²²	SOF/VEL/VOX (Group A) vs. SOF/VEL/VOX + RBV (Group B)	Retreatment of chronic HCV after DAA failure (n=315)	SVR12	<u>SVR12:</u> Group A: 87.3% (138/158) Group B: 87.9% (138/157) Diff: NS <u>Adverse Events</u> Group A: 55 (39%) Group B: 77 (55%) P=0.002	- open label - 10.8% loss to follow up before SVR12 - previous DAA regimen no longer standard of care (daclatasvir) - differences in fibrosis severity between groups at baseline
Sulkowski, et al. ²³	LDV/SOF vs. EBR/GZR	Adults with chronic HCV GT 1a or 1b (n=1609)	SVR12	<u>SVR12:</u> LDV/SOF: 97.4%; 95% CI 95.5 – 99.2 EBR/GZR: 95.2%; 95% CI 92.8 – 97.6 Diff: 2.2%; 95% CI -0.5% to 4.7%* <i>*Within the prespecified equivalence range</i>	- open label - 16% rate of loss to follow up in both groups - limited to GT1 - Does not include pangenotypic first line DAA regimens
Abbreviations: CI = confidence interval; DAA = direct acting antiviral; Diff = difference; EBR = elbasvir; GZR = grazoprevir; HBV = hepatitis B virus; GT = genotype; HCV = hepatitis C virus; LDV = ledipasvir; NS = nonsignificant; RCT = randomized clinical trial; RBV = ribavirin; SOF = sofosbuvir; SVR12: sustained virologic response 12 weeks after end of treatment; VEL = velpatasvir; VOX = voxilaprevir					

Appendix 3: Abstracts of Comparative Clinical Trials

1. Matthews GV, Bhagani S, Van der Valk M, et al. Sofosbuvir/velpatasvir for 12 vs. 6 weeks for the treatment of recently acquired hepatitis C infection. *J Hepatol.* 2021 Oct;75(4):829-839. doi: 10.1016/j.jhep.2021.04.056. Epub 2021 May 21. PMID: 34023350; PMCID: PMC9831671.

Background & aims: Shortened duration therapy for acute and recent HCV infection has been shown to be highly effective in several small non-randomised studies with direct-acting antiviral regimens; however, large randomised studies are lacking.

Methods: REACT was an NIH-funded multicentre international, open-label, randomised, phase IV non-inferiority trial examining the efficacy of short course (6-week) vs. standard course (12-week) therapy with sofosbuvir-velpatasvir for recent HCV infection (estimated duration of infection \leq 12 months). Randomisation occurred at week 6. The primary endpoint was sustained virological response 12 weeks after treatment end (SVR12) in the intention-to treat (ITT) population. A total of 250 participants were due to be enrolled, but on advice of the data safety and monitoring board the study was halted early.

Results: The primary analysis population consisted of 188 randomised participants at termination of study enrolment; short arm (n = 93), standard arm (n = 95). Ninety-seven percent were male and 69% HIV positive. ITT SVR12 was 76/93, 81.7% (95% CI 72.4-89.0) in the short arm and 86/95, 90.5% (95% CI 82.7-95.6) in the standard arm. The difference between the arms was -8.8 (95% CI -18.6 to 1.0). In modified ITT analysis, wherein non-virological reasons for failure were excluded (death, reinfection, loss to follow-up), SVR12 was 76/85, 89.4% (95% CI 80.8-95.0) in the short arm and 86/88, 97.7% in the standard arm (95% CI 92.0-99.7; difference -8.3%, p = 0.025).

Conclusions: In this randomised study in recent HCV infection, a 6-week course of sofosbuvir-velpatasvir did not meet the criteria for non-inferiority to standard 12-week therapy.

2. El-Kassas M, Emadeldeen M, Hassany M, et al. A randomized-controlled trial of SOF/VEL/VOX with or without ribavirin for retreatment of chronic hepatitis C. *J Hepatol.* 2023 Aug;79(2):314-320. doi: 10.1016/j.jhep.2023.04.011. Epub 2023 Apr 23. PMID: 37088312.

Background & aims: The combination of sofosbuvir, velpatasvir and voxilaprevir (SOF/VEL/VOX) is recommended for the retreatment of patients with HCV infection in whom previous direct-acting antiviral (DAA) treatment failed. However, whether ribavirin further increases the therapeutic efficacy of SOF/VEL/VOX retreatment remains unclear. We aimed to test this hypothesis in a randomized-controlled trial.

Methods: We randomly assigned 315 patients with DAA treatment failure from five Egyptian sites into two groups. Group A (n = 158) received SOF/VEL/VOX for 12 weeks, and group B (n = 157) received SOF/VEL/VOX + weight-based ribavirin for 12 weeks. Therapeutic efficacy was defined as

SVR12 (sustained virologic response 12 weeks after treatment end). Safety and tolerability were evaluated by monitoring treatment-related adverse events (AEs) and laboratory abnormalities.

Results: Males comprised 53.9% of group A and 57.1% of group B ($p = 0.58$); mean ages were 51.8 and 47.3 years in group A and B, respectively. Seventeen patients in each group were lost to follow-up. SVR12 rates were 87.3% (138/158) by intention-to-treat analysis and 97.8% (138/141) by per-protocol analysis in group A; and 87.9% (138/157) and 98.5% (138/140), respectively, in group B ($p = n.s.$ for intention-to-treat and per-protocol analyses). Both regimens were well-tolerated, with no deaths and only one serious AE (anemia) in group B, which required ribavirin discontinuation. Fifty-five patients in group A vs. 77 in group B experienced any AE ($p = 0.002$).

Conclusion: This randomized-controlled trial showed equal, high efficacy of both regimens for the retreatment of previous DAA failures, although ribavirin was associated with more AEs. Therefore SOF/VEL/VOX monotherapy should be the preferred retreatment strategy. CLINICALTRIALS

3. Sulkowski MS, Moon JS, Sherman KE, Morelli G, et al. A Pragmatic, Randomized Controlled Trial of Oral Antivirals for the Treatment of Chronic Hepatitis C: The PRIORITIZE Study. *Hepatology*. 2021 Dec;74(6):2952-2964. doi: 10.1002/hep.32053. Epub 2021 Aug 26. PMID: 34255381; PMCID: PMC8639765.

Background and aims: Multiple direct-acting antiviral (DAA) regimens are available to treat HCV genotype 1 infection. However, comparative effectiveness from randomized controlled trials of DAA regimens is unavailable.

Approach and results: We conducted a pragmatic randomized controlled trial ([NCT02786537](#)) to compare the effectiveness of DAAs for HCV genotype 1a or 1b on viral response, safety, tolerability, and medication nonadherence. Adults with compensated liver disease, HCV genotype 1, not pregnant or breastfeeding, and with health insurance likely to cover ledipasvir/sofosbuvir (LDV/SOF) were recruited from 34 US viral hepatitis clinics. Participants were randomized (\pm ribavirin) to LDV/SOF, elbasvir/grazoprevir (EBR/GZR), and paritaprevir/ritonavir/ombitasvir+dasabuvir (PrOD; treatment arm stopped early). Primary outcomes included sustained viral response at 12 weeks (SVR12), clinician-recorded adverse events, patient-reported symptoms, and medication nonadherence. Between June 2016 and March 2018, 1,609 participants were randomized. Among 1,128 participants who received ≥ 1 dose of EBR/GZR or LDV/SOF (\pm ribavirin), SVR12 was 95.2% (95% CI, 92.8%-97.6%) and 97.4% (95% CI, 95.5%-99.2%), respectively, with a difference estimate of 2.2% (-0.5% to 4.7%), falling within the "equivalence" interval (-5% to 5%). While most (56%) participants experienced adverse events, few were serious (4.2%) or severe (1.8%). In the absence of ribavirin, discontinuations due to adverse events were rare. Patient-reported symptoms and medication nonadherence were similar. Study limitations were dropout due to insurance denial and loss to follow-up after treatment, limiting the ability to measure SVR12.

Conclusions: This pragmatic trial demonstrated high SVR12 for participants treated with EBR/GZR and LDV/SOF with few adverse effects. Overall, the two regimens were equivalent in effectiveness. The results support current HCV guidelines that do not distinguish between ribavirin-free EBR/GZR and LDV/SOF

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to August 7, 2024>

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1      glecaprevir.mp. 552
2      pibrentasvir.mp.      532
3      mavyret.mp.  21
4      sofosbuvir.mp. or SOFOSBUVIR/3824
5      velpatasvir.mp. 680
6      voxilaprevir.mp.      168
7      vosevi.mp.  19
8      epclusa.mp.  46
9      ledipasvir.mp. 1367
10     harvoni.mp.  84
11     antiviral agents.mp. or Antiviral Agents/ 108551
12     direct acting antivirals.mp.      4567
13     protease inhibitors.mp. or Protease Inhibitors/ 47845
14     ribavirin.mp. or RIBAVIRIN/      18358
15     ns5a inhibitors.mp.  326
16     ns5b inhibitor.mp.  110
17     Hepatitis C, Chronic/ or Hepatitis C/      72150
18     acute hepatitis c.mp.  1163
19     1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16      159467
20     17 or 18      72285
21     19 and 20      24529
22     limit 21 to (english language and humans and yr="2021 -Current" and (clinical trial, phase iii or comparative study or controlled clinical trial or guideline
or meta analysis or randomized controlled trial or "systematic review")) 153
23     from 22 keep 1,7-8,10-11,13,16,20,23,26,37,39,43,53,57,64-65,70,75,78,88,99-100,104,106,110,113,116,123,131-133,135,140-142      36
24     from 23 keep 8-12,14-17,19-23,29-31,34      18
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Appendix 5: Key Inclusion Criteria

Population	Hepatitis C virus
Intervention	Direct acting antivirals
Comparator	Direct acting antivirals or placebo
Outcomes	Sustained virologic response, hepatocellular carcinoma, liver transplant, cirrhosis, decompensated cirrhosis, all-cause mortality
Timing	Not applicable
Setting	Not applicable

Hepatitis C Direct-Acting Antivirals

Goals:

- Approve use of cost-effective treatments supported by the medical evidence.
- Provide consistent patient evaluations across 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

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 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.

Approval Criteria		
<p>3. Has <u>all</u> the following pre-treatment testing been documented:</p> <ul style="list-style-type: none"> a. Genotype testing in past 3 years is required if the patient has decompensated cirrhosis, <u>prior treatment experience</u> with a DAA regimen, and if prescribed a regimen which is not pan-genotypic b. History of previous HCV treatment, viral load after treatment, and outcome are required only if there is documentation of treatment experience 	<p>Yes: Record results of each test and go to #4</p>	<p>No: Pass to RPh. Request updated testing.</p>
<p>4. Which regimen is requested?</p>	<p>Document and go to #5</p>	
<p>5. Has the patient been treated with a direct acting antiviral regimen previously?</p>	<p>Yes: Go to #6</p>	<p>No: Go to #8</p>
<p>6. Did the patient achieve a sustained virological response (SVR) at week 12 or longer following the completion of their last DAA regimen?</p>	<p>Yes: Go to #7</p>	<p>No: Document as treatment failure and treat as indicated for treatment experienced. Go to #8</p>
<p>7. Is this likely a reinfection, indicated by at least one of the following:</p> <ul style="list-style-type: none"> a. Does the patient have ongoing risk factors for hepatitis C reinfection (e.g. sexually active men who have sex with men, persons who inject drugs), OR b. Is the hepatitis C infection a different genotype than previous 	<p>Yes: Document as reinfection. Use regimens recommended for treatment naïve patients. Go to #8</p>	<p>No: Document as treatment failure and treat as indicated for treatment experienced. Go to #8</p>
<p>8. Is the prescribed drug:</p> <ul style="list-style-type: none"> a) Elbasvir/grazoprevir for GT 1a infection; <u>or</u> b) Ledipasvir/sofosbuvir for GT 1a <u>treatment-experienced</u> infection; <u>or</u> c) Sofosbuvir/velpatasvir for GT 3 in <u>cirrhosis</u> <u>or</u> <u>treatment-experienced</u> infection 	<p>Yes: Go to #9</p>	<p>No: Go to #10</p>

Approval Criteria		
<p>9. Has the patient had a baseline NS5a resistance test that documents a resistant variant to one of the agents in #10?</p> <p>Note: Baseline NS5A resistance testing is required.</p>	<p>Yes: Pass to RPh; deny for appropriateness</p>	<p>No: Go to #10</p> <p>Document test and result.</p>
<p>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)?</p> <p>Note: Safety and efficacy of DAAs for children < 3 years of age have not been established Pediatric dosing available in Table 3 & Table 4</p>	<p>Yes: Approve for 8-24 weeks based on duration of treatment indicated for approved regimen</p> <p>Referral will be made for optional case management (patient may choose to opt-in).</p>	<p>No: Pass to RPh. Deny; medical appropriateness.</p>

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)		
<u>Sofosbuvir based regimen treatment failures, including:</u> Sofosbuvir + ribavirin Ledipasvir/sofosbuvir Velpatasvir/sofosbuvir	Non-cirrhotic or compensated cirrhosis	SOF/VEL/VOX x12 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 x 16 weeks SOF/VEL/VOX x 12 weeks (plus RBV if compensated cirrhosis)
<u>Multiple DAA Treatment Failures, including:</u> 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 and pibrentasvir; 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 , 2) hemoglobin < 10 g/dl, 3) platelets <50,000 cells/mm ³ , autoimmune hepatitis or other autoimmune condition, hypersensitivity or allergy to ribavirin		
^ Rarely, genotyping 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 and pibrentasvir; 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 glecaprevir/pibrentasvir
Less than 20 kg	Three 50mg/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 100mg/40 mg tablets once daily

P&T Review: 10/24 (MH); 4/22; 10/21; 6/20; 9/19; 1/19; 11/18; 9/18; 1/18; 9/17; 9/16; 1/16; 5/15; 3/15; 1/15; 9/14; 1/14
 Implementation: 1/1/23; 7/1/20; 1/1/20; 3/1/2019; 1/1/2019; 3/1/2018; 1/1/2018; 2/12/16; 4/15; 1/15