Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

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

Date of Review: September 2019

Date of Last Review: September 2018
Literature Search: 08/2018 – 08/2019

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:
- There is insufficient evidence to evaluate the use of direct acting antivirals (DAAs) in the treatment of acute HCV infection.[1]
- There is no new comparative data demonstrating superior efficacy or safety of one DAA over another in the treatment of chronic hepatitis C (CHC) in decreasing mortality, hepatocellular carcinoma (HCC) or complications of liver disease.
- There is low to insufficient evidence that glecaprevir and pibrentasvir (G/P) is safe and effective in pediatric patients ages 12 to 17 with CHC without cirrhosis in achieving sustained virologic response (SVR).

Recommendations:
- Approve updated prior authorization (PA) criteria (**Appendix 5**).
- After review of comparative costs in executive session, designate elbasvir /grazoprevir as non-preferred.

Summary of Prior Reviews and Current Policy
- There is low quality evidence that all of the DAA regimens are effective in achieving a SVR rate of greater than or equal to 90%. SVR rates differ between patients based on disease severity, genotype, and baseline NS5a resistant amino acid variants (RAVs). Relapse may be reduced with baseline NS5A polymorphism screening.
- The regimens that have been studied in patients with cirrhosis include mostly Child-Pugh A and B. There are very limited data in Child-Pugh C.
- From the only comparative data available, there is low quality evidence that 12 weeks sofosbuvir/velpatasvir (SOF/VEL) may be modestly superior to 12 weeks SOF + ribavirin (RBV) in patients with genotype (GT) 2 (SVR 99% vs. 95%, respectively; absolute difference 5.2%; 95% CI, 0.2-10.3%; p=0.02). Treatment with 12 weeks of SOF/VEL may also be superior to 24 weeks of SOF + RBV in patients with GT 3 (SVR 95% vs. 80%; respectively; absolute difference 14.8%; 95% CI 9.6-20%; p<0.001).
- There are still several limitations in the current evidence for the treatment of CHC:
  - There is still insufficient evidence for the optimal treatment of patients who have had a virologic failure to a previous NS5A or NS5B inhibitor. 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. In some populations, data on DAAs are limited to open-label, uncontrolled, or historically controlled trials.

Author: Megan Herink, PharmD

- Trials often exclude patients with chronic hepatitis B virus (HBV), HIV, cancer, hepatocellular carcinoma (HCC), decompensated cirrhosis, severe psychiatric, cardiac, pulmonary, or renal comorbidities, and severe alcohol or substance abuse. When decompensated cirrhosis is included, there are very little data in patients with Child-Pugh class C.
- There is no direct, randomized prospective evidence that treatment with antiviral therapy for CHC leads to improved long-term clinical outcomes in incidence of HCC, liver transplantation, or mortality.

- 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 step-wise fashion to patients with less severe disease.
- Current drug policies in place approve treatment for all patients with CHC, regardless of fibrosis severity or history of substance use disorder.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing any medication in **Table 1** on clinically relevant outcomes to active controls, or placebo if needed, was conducted. Non-randomized data will be considered if clinically important outcomes including mortality and HCC are included. 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, 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 and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Table 1. Direct-acting Antiviral Regimens for Chronic Hepatitis C.

Drug Brand Name	Generic name	Indications	Decompensated Cirrhosis	Mechanism of Action	Duration
Daklinza™ and Solvaldi®	Daclatasvir + sofosbuvir	CHC GT 1 or GT 3	GT 1, 3 with RBV	NS5A inhibitor with NS5B inhibitor	12 weeks
Epclusa®	Sofosbuvir/velpatasvir	CHC GT 1-6	GT 1-6, with RBV	NS5B inhibitor/NS5A inhibitor	12 weeks
Harvoni®	Ledipasvir/sofosbuvir	CHC GT 1; GT 4; GT 5; GT 6	GT 1 with RBV	NS5A inhibitor/ NS5B inhibitor	8 - 24 weeks
Mavyret™	Glecaprevir/pibrentasvir	CHC GT 1-6 without cirrhosis or compensated cirrhosis and GT 1 previously treated with a NS5A	Contraindicated	NS3/4A protease inhibitor/NS5A inhibitor	8-16 weeks

		inhibitor or an NS3/4a protease inhibitor			
Vosevi®	sofosbuvir/velpatasvir/voxilaprevir	CHC GT 1-6 TE with NS5A inhibitor; GT 1a or 3 TE with sofosbuvir and without an NS5A inhibitor	Contraindicated	NS5B inhibitor/NS5A inhibitor/NS3 protease inhibitor	12 weeks
Zepatier®	Elbasvir / grazoprevir	CHC GT 1; GT 4	Contraindicated	NS3/4A protease inhibitor/ NS5A inhibitor	12 or 16 weeks
Abbreviations: CHC = chronic hepatitis C; GT = genotype, RBV: ribavirin; TE: treatment-experienced					

New Systematic Reviews:
After review, 5 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

A Cochrane Collaboration systematic review was published in December 2018 to assess the comparative benefits and harms of pharmacologic interventions in the treatment of acute HCV, as it remains controversial if any intervention is beneficial in acute HCV infection.[1] Randomized trials evaluating interferons as well as DAAs were included. Overall, 13 trials met inclusion criteria (n=488). However, none of the trials compared DAAs versus other interventions. At this time, there is insufficient evidence to evaluate the use of DAAs in the treatment of acute HCV infection.

New Guidelines:
None Identified

New Formulations:
None Identified

New FDA Safety Alerts:
None Identified

New Indications:
In April 2019, the FDA approved Mavyret™ (glecaprevir and pibrentasvir [G/P]) to treat all six genotypes in pediatric patients ages 12 to 17 who weigh at least 45 kg without cirrhosis or with compensated cirrhosis.[2] Approval was based on one, unpublished, open-label study designed to assess the pharmacokinetics, safety and efficacy of G/P 300 mg/120 mg once daily for 8, 12 or 16 weeks in patients ages 12 to 17 with CHC without cirrhosis. The primary outcome was area under the curve and SVR12 was a secondary endpoint. The majority of patients (79%) had HCV GT 1, and 77% were treatment-naïve.[2] The overall SVR12 rate was 100% (47/47).[2] This data remains unpublished and cannot be fully assessed for risk of bias. Approval in patients with compensated cirrhosis and GTs 5 or 6 was based on comparable exposure of G/P between adolescents and adults.

References:

1. Kalafateli M, Buzzetti E, Thorburn D, Davidson BR, Tsochatzis E, Gurusamy KS. Pharmacological interventions for acute hepatitis C infection. *The Cochrane database of systematic reviews.* 2018;12:Cd011644.
2. Mavyret (glecaprevir and pibrentasvir) Prescribing Information. Abbvie Pharmaceuticals. 4/2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209394s006lbl.pdf.
3. Lok AS, Sulkowski MS, Kort JJ, et al. Efficacy of Glecaprevir and Pibrentasvir in Patients with Genotype 1 Hepatitis C Virus Infection with Treatment Failure after NS5A Inhibitor Plus Sofosbuvir Therapy. *Gastroenterology.* 2019.
4. Esteban R, Pineda JA, Calleja JL, et al. Efficacy of Sofosbuvir and Velpatasvir, With and Without Ribavirin, in Patients With Hepatitis C Virus Genotype 3 Infection and Cirrhosis. *Gastroenterology.* 2018;155(4):1120-1127.e1124.
5. Asselah T, Lee SS, Yao BB, et al. Efficacy and safety of glecaprevir/pibrentasvir in patients with chronic hepatitis C virus genotype 5 or 6 infection (ENDURANCE-5,6): an open-label, multicentre, phase 3b trial. *The lancet Gastroenterology & hepatology.* 2019;4(1):45-51.
6. Carrat F, Fontaine H, Dorival C, et al. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. *Lancet (London, England).* 2019;393(10179):1453-1464.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
elbasvir/grazoprevir	ZEPATIER	TABLET	Y
glecaprevir/pibrentasvir	MAVYRET	TABLET	Y
sofosbuvir/velpatas/voxilaprev	VOSEVI	TABLET	Y
sofosbuvir/velpatasvir	EPCLUSA	TABLET	Y
sofosbuvir/velpatasvir	SOFOSBUVIR-VELPATASVIR	TABLET	Y
daclatasvir dihydrochloride	DAKLINZA	TABLET	N
ledipasvir/sofosbuvir	HARVONI	TABLET	N
ledipasvir/sofosbuvir	LEDIPASVIR-SOFOSBUVIR	TABLET	N
ombita/paritap/riton/dasabuvir	VIEKIRA PAK	TAB DS PK	N
sofosbuvir	SOVALDI	TABLET	N

Appendix 2: New Clinical Trials

A total of 99 citations were manually reviewed from the initial literature search. After further review, 96 citations were excluded because of wrong study design, 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 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Lok, et al.[3] Open-label RCT, phase 3b	No Cirrhosis 1. G/P x 12 weeks 2. G/P x 16 weeks Compensated Cirrhosis: 3. G/P + RBV x 12 weeks 4. G/P + RBV x 16 weeks	HCV GT 1 with previous treatment failure from sofosbuvir + NS5A inhibitor (n=177)	SVR12	SVR12: 1. 70/78 (90%) 2. 46/49 (94%) 3. 18/21 (86%) 4. 28/29 (97%)
Esteban, et al. [4] Open-label RCT, phase 2	SOF/VEL vs. SOF/VEL + RBV X 12 weeks	Adults with HCV GT 3 and compensated cirrhosis (n=201)	SVR12	SVR12: SOF/VEL: 92/101 (95%; 95% CI 84 to 96) SOF/VEL + RBV: 99/103 (96%; 95% CI 90.4 to 98)

Abbreviations: G/P: glecaprevir/pibrentasvir; GT = genotype; HCV = hepatitis V virus; NS5A = nonstructural protein 5A; RBV = ribavirin; RCT = randomized clinical trial; SOF/VEL = sofosbuvir and velpatasvir; SVR12 = sustained virologic response 12 weeks after treatment

Table 2. Description of Prospective Observational Trials on Clinical Outcomes

Study	Comparison	Population	Primary Outcome	Results	
Carrat et al.[6] Prospective, cohort study	DAA vs. no DAA	Patients with CHC without HIV, HBV, and decompensated cirrhosis (n=9895)	All-cause mortality, hepatocellular carcinoma (HCC), or liver transplantation	All-cause mortality (n per person years) DAA: 129/13,626 No DAA: 89/12,709 HR* 0.48; 95% CI 0.33-0.70 Decompensated Cirrhosis: DAA: 74/13520 No DAA: 32/12,698 HR* 1.14; 95% CI 0.57 to 2.27	HCC: DAA: 187/13,375 No DAA: 71/12,660 HR* 0.66; 95% CI 0.46 to 0.93

Abbreviations: CHC = chronic liver disease; CI = confidence interval; DAA = direct acting antiviral; HBV = hepatitis B virus; HIV = human immunodeficiency virus; HR = hazard ratio; n = number

*Multivariable adjusted HR

Appendix 3: Abstracts of Comparative Clinical Trials

1.Efficacy of Glecaprevir and Pibrentasvir in Patients with Genotype 1 Hepatitis C Virus Infectionwith Treatment Failure after NS5A Inhibitor Plus Sofosbuvir Th erapy Gastroenterology. 2019 Aug 8. pii: S0016-5085(19)41199-2. doi: 10.1053/j.gastro.2019.08.008. [Epub ahead of print]

BACKGROUND/AIMS:
Treatment options are limited for patients with hepatitis C (HCV) infection with treatment failure after sofosbuvir plusan NS5A inhibitor. There are some data for the efficacy of glecaprevir/pibrentasvir (G/P) in these patients. We performed a randomized trial of the safety and efficacy of 12 and 16 weeks of G/P, with or without ribavirin, in patients with HCV genotype 1 infection with treatment failureafter sofosbuvir and an NS5A inhibitor.

METHODS:
We performed a phase 3b, open label study of patients with chronic HCV genotype 1 infection who received previous treatmentwith sofosbuvir plus an NS5A inhibitor. Patients without cirrhosis were randomly assigned to groups that received G/P for 12 weeks (n=78, group A) or 16 weeks (n=49, group B). Patients with compensated cirrhosis were randomly assigned to groups that received G/P and ribavirin for 12 weeks (n=21, group C) or G/P for 16 weeks (n=29, group D). The primary endpoint was a sustained virologic response 12 weeks aftertreatment (SVR12). Samples collected at baseline and at time of treatment failure were sequenced for resistance-associated substitutions (RASs) in NS3 and NS5A.

RESULTS:
Of the 177 patients in the 4 groups, 81% were men, 79% had HCV genotype 1a infection, and 44% were black. Proportions of patients with an SVR12 in groups A, B, C, and D were 90%, 94%, 86%, and 97%, respectively. The treatment failed in 13 patients with HCV genotype 1a infection (7.3%), 6 in group A (7.9%), 3 in group B (6.1%), 3 in group C (14.3%), and 1 in group D (3.4%). Most patients had baseline RASs in NS5A. Treatment-emergent RASs in NS3 and NS5A were observed in 9 and 10 patients with treatment failure, respectively. G/P was well tolerated. Ribavirin increased adverse events but did not increase efficacy.

CONCLUSIONS:
In a randomized study of patients with chronic HCV genotype 1 infection who received previous treatment with sofosbuvirplus an NS5A inhibitor, 16 weeks treatment with G/P produced an SVR12 in more than 90% of patients, including those with compensated cirrhosis.

2. Efficacy of Sofosbuvir and Velpatasvir, With and Without Ribavirin, in Patients With Hepatitis C Virus Genotype 3 Infection and Cirrhosis.

Gastroenterology. 2018 Oct;155(4):1120-1127.e4. doi: 10.1053/j.gastro.2018.06.042. Epub 2018 Jun 27.

BACKGROUND & AIMS:
In phase 3 trials and real-world settings, smaller proportions of patients with genotype 3 hepatitis C virus (HCV) infection and cirrhosis have a sustained virologic response 12 weeks after treatment (SVR12) with the combination of sofosbuvir and velpatasvir than in patients without cirrhosis. It is unclear whether adding ribavirin to this treatment regimen increases SVRs in patients with genotype 3 HCV infection and cirrhosis.

METHODS:

We performed a phase 2 trial of 204 patients with genotype 3 HCV infection and compensated cirrhosis (mean age 51 ± 7.4 years) at 29 sites in Spain from August 19, 2016 through April 18, 2017. Patients were assigned to groups given sofosbuvir and velpatasvirfor 12 weeks (n = 101) or sofosbuvir and velpatasvir plus ribavirin for 12 weeks (n = 103). The primary efficacy end point was SVR12.

RESULTS:
The overall rates of SVR12 were 91% (92 of 101; 95% CI 84-96) for the sofosbuvir-velpatasvir group and 96% (99 of 103; 95% CI 90-99) for the sofosbuvir-velpatasvir plus ribavirin group. In the sofosbuvir-velpatasvir group, a smaller proportion of patients with baseline resistance-associated substitutions (RASs) in nonstructural protein 5A (NS5A) achieved an SVR12 (84%) than did patients without (96%). In the sofosbuvir-velpatasvir plus ribavirin group, baseline RASs had less effect on the proportion of patients with an SVR12 (96% for patientswith baseline RASs; 99% for patients without). The most common adverse events (which occurred in ≥10% of patients) were asthenia (12%) in the sofosbuvir-velpatasvir group and asthenia (27%), headache (24%), and insomnia (12%) in the sofosbuvir-velpatasvir plus ribaviringroup.

CONCLUSIONS:
Consistent with findings from previous studies, a high rate of patients (91% and 96%) with genotype 3 HCV infection and compensated cirrhosis achieved an SVR12 with sofosbuvir and velpatasvir, with or without ribavirin. Of patients treated with sofosbuvir and velpatasvir without ribavirin, fewer patients with baseline NS5A RASs achieved an SVR12 compared with patients without baseline NS5A.

3. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. Lancet. 2019 Apr 6;393(10179):1453-1464. doi: 10.1016/S0140-6736(18)32111-1. Epub 2019 Feb 11.

BACKGROUND:
Although direct-acting antivirals have been used extensively to treat patients with chronic hepatitis C virus (HCV) infection, their clinical effectiveness has not been well reported. We compared the incidence of death, hepatocellular carcinoma, and decompensated cirrhosis between patients treated with direct-acting antivirals and those untreated, in the French ANRS CO22 Hepather cohort.

METHODS:
We did a prospective study in adult patients with chronic HCV infection enrolled from 32 expert hepatology centres in France. We excluded patients with chronic hepatitis B, those with a history of decompensated cirrhosis, hepatocellular carcinoma, or liver transplantation, and patients who were treated with interferon-ribavirin with or without first-generation protease inhibitors. Co-primary study outcomes were incidence of all-cause mortality, hepatocellular carcinoma, and decompensated cirrhosis. The association between direct-acting antivirals and these outcomes was quantified using time-dependent Cox proportional hazards models. This study is registered with ClinicalTrials.gov, number NCT01953458.

FINDINGS:
Between Aug 6, 2012, and Dec 31, 2015, 10 166 patients were eligible for the study. 9895 (97%) patients had available follow-up information and were included in analyses. Median follow-up was 33·4 months (IQR 24·0-40·7). Treatment with direct-acting antivirals was initiated during follow-up in 7344 patients, and 2551 patients remained untreated at the final follow-up visit. During follow-up, 218 patients died (129 treated, 89 untreated), 258 reported hepatocellular carcinoma (187 treated, 71 untreated), and 106 had decompensated cirrhosis (74 treated, 32 untreated). Exposure to direct-acting antivirals was associated with increased risk for hepatocellular carcinoma (unadjusted hazard ratio [HR] 2·77, 95% CI 2·07-3·71) and decompensated cirrhosis (3·83, 2·29-6·42). After adjustment for variables (age, sex, body-mass index, geographical origin, infection route, fibrosis score, HCV treatment-naive, HCV genotype, alcohol consumption, diabetes,

arterial hypertension, biological variables, and model for end-stage liver disease score in patients with cirrhosis), exposure to direct-acting antivirals was associated with a decrease in all-cause mortality (adjusted HR 0·48, 95% CI 0·33-0·70) and hepatocellular carcinoma (0·66, 0·46-0·93), and was not associated with decompensated cirrhosis (1·14, 0·57-2·27).

INTERPRETATION:
Treatment with direct-acting antivirals is associated with reduced risk for mortality and hepatocellular carcinoma and should be considered in all patients with chronic HCV infection.

Appendix 4: Medline Search Strategy

▼ **Search History** (32)

# ▲	Searches	Results
1	glecaprevir.mp.	62
2	pibrentasvir.mp.	70
3	mavyret.mp.	3
4	sofosbuvir.mp. or SOFOSBUVIR/	1776
5	velpatasvir.mp.	144
6	voxilaprevir.mp.	40
7	vosevi.mp.	4
8	epclusa.mp.	10
9	daclatasvir.mp.	682
10	daklinza.mp.	10
11	technivie.mp.	3
12	ombitasvir.mp.	340
13	paritaprevir.mp.	329
14	ritonavir.mp. or RITONAVIR/	6059

☐	15	dasabuvir.mp.	295
☐	16	simeprevir.mp. or SIMEPREVIR/	610
☐	17	ledipasvir.mp.	683
☐	18	harvoni.mp.	42
☐	19	antiviral agents.mp. or Antiviral Agents/	77301
☐	20	direct acting antivirals.mp.	1640
☐	21	protease inhibitors.mp. or Protease Inhibitors/	41739
☐	22	ribavirin.mp. or RIBAVIRIN/	14744
☐	23	ns5a inhibitors.mp.	203
☐	24	ns5b inhibitor.mp.	85
☐	25	Hepatitis C, Chronic/ or Hepatitis C/	61515
☐	26	hepatocellular carcinoma.mp. or Carcinoma, Hepatocellular/	94545
☐	27	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 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	122268
☐	28	25 or 26	149285
☐	29	27 and 28	21142
☐	30	limit 29 to (english language and humans and yr="2018 -Current" and (clinical trial, phase iii or clinical trial, phase iv or meta analysis or randomized controlled trial or "systematic review"))	99
☐	31	from 30 keep 5, 7-8, 12, 19-21, 24-26, 42-43...	22
☐	32	from 31 keep 5-10, 12-13, 17-20	12

Hepatitis C Direct-Acting

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 disease severity, genotype, and patient comorbidities.

Length of Authorization:

- 8-16 weeks

Requires PA:

All direct-acting antivirals for treatment of Hepatitis C

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of chronic Hepatitis C infection (B18.2) as identified through positive detection of HCV viral load?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is expected survival from non-HCV-associated morbidities more than 1 year?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
4. Has <u>all</u> of the following pre-treatment testing been documented: a. Genotype testing in past 3 years is required if the patient has cirrhosis, <u>any</u> prior treatment experience, and if prescribed a regimen which is not pan-genotypic; b. Current HBV status of patient c. Pregnancy test in past 30 days for a woman of child-bearing age; <u>and</u> d. History of previous HCV treatment and outcome e. Presence or absence of cirrhosis as clinically determined (e.g., clinical, laboratory, or radiologic evidence)? Note: Direct-acting antiviral agents can re-activate hepatitis B in some patients. Patients with history of HBV should be monitored carefully during and after treatment for flare-up of hepatitis. Prior to treatment with a DAA, all patients should be tested for HBsAG, HBsAb, and HBcAB status. HIV testing is also recommended, and modification of HIV or HCV treatment regimens may be necessary if there are significant drug-drug interactions.	**Yes:** Record results of each test and go to #5 Note: If the patient has HIV or HBV co-infection, it is highly recommended that a specialist be consulted prior to treatment. Currently treatment is not recommended during pregnancy due to lack of safety and efficacy data	**No**: Pass to RPh. Request updated testing.
5. Which regimen is requested?	Document and go to #6	
6. Does the patient have complications of cirrhosis (ascites, portal hypertension, hepatic encephalopathy, hepatocellular carcinoma, esophageal varices)?	**Yes:** Go to #7 .	**No:** Go to #8

Approval Criteria		
7. Is the regimen prescribed by, OR is the patient in the process of establishing care with or in consultation with a hepatologist, gastroenterologist, or infectious disease specialist?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness. Recommend prescriber document referral to a specialist prior to initiating treatment.
8. Is there attestation that the patient and provider will comply with case management to promote the best possible outcome for the patient and adhere to monitoring requirements required by the Oregon Health Authority, including measuring and reporting of a post-treatment viral load? Case management includes assessment of treatment barriers and offer of patient support to mitigate potential barriers to regimen adherence as well as facilitation of SVR12 evaluation to assess treatment success.	**Yes**: Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is the prescribed drug: a) Elbasvir/grazoprevir for GT 1a infection; or b) Daclatasvir + sofosbuvir for GT 3 infection?	**Yes**: Go to #10	**No:** Go to #11
10. Has the patient had a baseline NS5a resistance test that documents a resistant variant to one of the agents in #16? Note: Baseline NS5A resistance testing is required.	**Yes:** Pass to RPh; deny for appropriateness	**No:** Go to #11 Document test and result.
11. Does the prescribed regimen include a NS3/4a protease inhibitor (elbasvir, glecaprevir, simeprevir, paritaprevir, voxilaprevir)?	**Yes:** Go to #12	**No:** Go to #13

Approval Criteria		
12. Does the patient have moderate-severe hepatic impairment (Child-Pugh B or Child-Pugh C)?	**Yes:** Pass to RPh; deny for appropriateness	**No:** Go to #13
13. Is the prescribed regimen for the retreatment after failure of a DAA due to noncompliance or loss of follow-up?	**Yes:** Pass to RPh; Deny and refer to medical director for review	**No:** Go to #14
14. Is the prescribed drug regimen a recommended regimen based on the patient's genotype, treatment status (retreatment or treatment naïve) and cirrhosis status (see **Table 1**)?	**Yes:** Approve for 8-16 weeks based on duration of treatment indicated for approved regimen	**No:** Pass to RPh. Deny; medical appropriateness.

Table 1: Recommended Treatment Regimens for Chronic Hepatitis C.

Treatment History	Cirrhosis Status	Recommended Regimen
Genotype 1		
DAA-Treatment naive	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks G/P x 8 weeks
	Decompensated Cirrhosis	SOF/VEL + RBV x 12 week
Treatment experienced (Prior PEG/RBV)	Non-cirrhotic	SOF/VEL x 12 weeks G/P x 8 weeks
	Compensated cirrhosis	SOF/VEL x 12 weeks G/P x 12 weeks
Treatment Experienced (Prior sofosbuvir)	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks G/P x 12 weeks

Treatment Experienced (Prior NS3A/4A inhibitor)	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks G/P x 12 weeks
Treatment Experienced (prior NS5A-containing regimen)	Non-cirrhotic or compensated cirrhosis	G/P x 16 weeks
Genotype 2		
Naïve	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks G/P x 8 weeks
	Decompensated	SOF/VEL + RBV x 12 weeks
Treatment Experienced (prior PEG/RBV)	Non-cirrhotic	SOF/VEL x 12 weeks G/P x 8 weeks
	Compensated cirrhosis	SOF/VEL x 12 weeks G/P x 12 weeks
Treatment Experienced (SOF + RBV)	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks G/P x 12 weeks
Treatment Experienced (prior NS5A-containing regimen)	Non-cirrhotic or compensated cirrhosis	SOF/VEL/VOX x 12 weeks
Genotype 3		
Naïve	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 (prior PEG/RBV only)	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks G/P x 16 weeks
Treatment Experienced (SOF + RBV)	Non-cirrhotic or compensated cirrhosis	G/P x 16 weeks
Experienced (prior NS5A-containing regimen)	Non-cirrhotic or compensated cirrhosis	SOF/VEL/VOX x 12 weeks
Genotype 4		
Treatment Naïve	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks G/P x 8 weeks
	Decompensated Cirrhosis	SOF/VEL + RBV x 12 week
Treatment Experienced (prior PEG/RBV only)	Non-cirrhotic	SOF/VEL x 12 weeks G/P x 8 weeks
	Compensated cirrhosis	SOF/VEL x 12 weeks G/P x 12 weeks

Treatment Experienced (prior NS5A-containing regimen OR sofosbuvir)	Non-cirrhotic or compensated cirrhosis	SOF/VEL/VOX x 12 weeks
Genotype 5/6		
Treatment Naïve	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 (prior PEG-IFN/RBV only)	Non-cirrhotic	SOF/VEL x 12 weeks G/P x 8 weeks
	Compensated cirrhosis	SOF/VEL x 12 weeks G/P x 12 weeks
	Decompensated cirrhosis	SOF/VEL + RBV x 12 weeks
Experienced (prior NS5A-containing regimen OR sofosbuvir)	Non-cirrhotic or compensated cirrhosis	SOF/VEL/VOX x 12 weeks
Abbreviations: CTP = Child-Turcotte-Pugh; 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 ‡Evidence is insufficient if the addition of RBV may benefit subjects with GT3 and cirrhosis. If RBV is not used with regimen, then baseline RAV testing should be done prior to treatment to rule out the Y93 polymorphism.		
^ 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.		
Regimens other than glecaprevir/pibrentasvir (G/P;) and elbasvir/grazoprevir (EBV/GZR) should not be used in patients with severe renal impairment (GRF < 30 mL/min) or end stage renal disease requiring dialysis.		
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.		

P&T Review: *9/19 (MH); 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: *1/1/20; 3/1/2019; 1/1/2019; 3/1/2018; 1/1/2018; 2/12/16; 4/15; 1/15*