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Drug Class Literature Scan: Hepatitis C Direct Acting Antivirals

Date of Review: June 2020

Date of Last Review: September 2019
Literature Search: 08/01/2019 – 02/25/2020

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

Conclusions:
- There is low quality evidence that ledipasvir/sofosbuvir (LDV/SOF) results in sustained virologic response at 12 weeks after treatment (SVR12) of 98% (124/126) in pediatric patients ages 3 to 11 with chronic hepatitis C virus (HCV) genotype (GT) 1.
- There is low quality evidence that SOF plus ribavirin is efficacious in pediatric patients ages 3 to 11 with chronic HCV GT 2 or 3 infection with 98% (53/54) of patients achieving SVR12.
- There is low quality evidence that velpatasvir/sofosbuvir (VEL/SOF) results in SVR12 rates of 93% (66/71) in pediatric patients ages 6 to <12 years of age with chronic HCV GTs 1, 2, 3, and 4.
- There is low quality evidence of no serious treatment emergent adverse events in the pediatric population greater than 3 years of age and insufficient data to evaluate long-term safety.
- There is insufficient evidence to evaluate efficacy and safety of LDV/SOF or SOF in those with GT 4, 5 and 6, in pediatric patients with cirrhosis and in treatment experienced patients.
- There is no new comparative evidence evaluating long-term efficacy and safety of direct acting antivirals (DAAs) in chronic hepatitis C.

Recommendations:
- Amend prior authorization criteria to include new FDA approved indications in pediatric patients and removal of the pregnancy test requirement.
- Allow for future updating of the *Table of Recommended Treatment Regimens* to accommodate any expanded or new FDA-indications for current recommended regimens and to add guidance for patients have contraindications or intolerances to ribavirin.

Summary of Prior Reviews and Current Policy
- There is low quality evidence that all of the direct acting antiviral (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).
- 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).

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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.
  - 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 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, 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.

New Systematic Reviews:

After review, two systematic reviews were excluded due to poor quality.[1,2]

New Guidelines:

After review, one guideline update was excluded due to poor quality.[3]

New Indications:

1. The FDA approved sofosbuvir (SOF) (Solvadi®) and ledipasvir/sofosbuvir (LDV/SOF) (Harvoni®) for pediatric patients with HCV aged 3 years to younger than 12 years without cirrhosis or with compensated cirrhosis with GT 1, 4, 5 or 6. Prior to this, agents were approved for patients ages 12 years of age and older, and the only option for patients younger than 12 years was pegylated interferon plus ribavirin. Approval of LDV/SOF was based on a multicenter, open-label, phase 2, non-comparative, single-arm study evaluating the safety and efficacy of LDV/SOF 45 mg/200 mg for 12 or 24 weeks in treatment-naïve (or interferon-experienced) children 3 to less than 12 years old with HCV genotype (GT) 1, 3 or 4 infection (n=126).[4,5] Patients were excluded if they had decompensated liver disease, acute hepatitis A, hepatitis B or human immunodeficiency virus (HIV), serum creatinine greater than 1.5 mg/dl, evidence of malignancy, significant cardiovascular, pulmonary or neurological disease, or psychiatric illness. All patients received 12 weeks of therapy, except interferon-experienced patients with cirrhosis, who received 24 weeks. Those with GT 3 and interferon treatment experience received ribavirin in addition to LDV/SOF. However, since LDV/SOF is not approved for treatment of GT 3, the efficacy in this group was not taken into consideration.[6] Although there were no pediatric patients with GT 5 or 6, FDA approved it based on pharmacokinetic data and efficacy data in adults.[6]

   The majority of patients were treatment naïve, GT 1 (95%), without cirrhosis and were perinatally infected. Only two patients (ages 8 and 11) had compensated cirrhosis. In those ages 6 to 11, 99% (91/92) of patients achieved sustained virologic response at 12 weeks after treatment (SVR12).[4] In those ages 3 to less than 6, 97% (33/34) of patients achieved SVR12.[5] The most common adverse events in those 6 to 11 were headache (18%), fatigue (15%), vomiting (15%), and cough (15%).[4] The most common adverse events in those ages 3 to 6 were vomiting (24%), cough (21%), and pyrexia (21%).[5] Only one patient in either group discontinued treatment due to an adverse event (abnormal drug taste and vomiting).

   Limitations to this study include lack of generalizability as there was only one patient with cirrhosis and only 4 patients had genotype 3 or 4. Additionally, there was no comparator, it was open-label and funding was provided by Gilead Sciences. Finally, many of the authors had significant conflicts of interest. Treatment options for pediatric patients who are DAA treatment experienced remains unknown.

   LDV/SOF was also approved for pediatric patients with HCV GT 1 who have decompensated cirrhosis (Child-Pugh B or C) and for pediatric patients with HCV GT 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis. This approval was based on submitted pharmacokinetic data demonstrating similar LDF/SOF exposure as adults.[6]

2. SOF in combination with ribavirin was also FDA approved for pediatric patients 3 years of age and older with GT 2 or 3 chronic hepatitis C without cirrhosis or with compensated cirrhosis based on one phase 2 open-label study.[7] Treatment was administered for 12 weeks in those with GT 2 and 24 weeks in GT 3. A total of 54 patients were enrolled at 28 sites in Australia, Belgium, Germany, Italy, New Zealand, United Kingdom and the United States. Nineteen patients (35%) had GT 2 and 36 had GT 3 (67%). All but one patient was treatment naïve, and none of the patients had documented cirrhosis. All 41 of the patients aged 6 to less than 12 achieved SVR 12 (100%), and 12 of the 13 (92%) patients aged 3 to less than 6 years achieved SVR12.[7] Among patients aged 6 to less than 12 years, the most commonly reported adverse events were vomiting (32%) and headache (29%). Among the patients aged 3 to less than 6 years, the most common adverse events were vomiting (46%) and diarrhea (39%). Only one patient discontinued treatment due to an adverse event.

   Limitations inherent to this study are similar to the above. Additionally, this was a small study including only GT 2 and 3 with minimal patients who were treatment experienced or who had cirrhosis. It remains unknown if those factors would impact SVR12 rates in this patient population. Additionally, this therapy requires the addition of weight-based ribavirin. Currently, SOF with ribavirin is the only FDA approved DAA regimen for children 3 through 11

years with GT 2 or 3 infection. However, recent clinical trials have evaluated SOF/VEL and glecaprevir/pibrentasvir (GLE/PIB) which would offer pangenotypic options without the need for ribavirin. Current HCV guidance panel recommends awaiting approval of these regimens unless there is an urgent or compelling need for immediate treatment in this subgroup.[8]

3. In November 2019, the FDA approved sofosbuvir-containing regimens, including LDV/SOF (Harvoni®), velpatasvir/sofosbuvir (VEL/SOF) (Epclusa®) and sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) (Vosevi®) for adults with severe renal impairment, including those who are on dialysis. None of these therapies require dosage adjustment for any degree of renal impairment. This approval was based on studies demonstrating efficacy and safety in LDV/SOF and VEL/SOF in patients with severe renal impairment.[9,10] Most patients (80%) experienced side effects similar to what is seen in other clinical trials, including fatigue, headache, nausea, vomiting and insomnia. There were no adverse effects associated with renal dysfunction observed in these short-term, single arm studies. The pharmacokinetics of VOX have not been studied in patients with patients with end stage renal disease.

4. In September 2019, the FDA approved GLE/PIB for those with compensated cirrhosis for 8 weeks. Previously, treatment in those was compensated cirrhosis required 12 weeks. Approval was based on the EXPEDITION-1 trial.[11] This was a single-arm, open-label phase IIIb trial conducted at 94 sites that evaluated patients 18 years of age or older, with chronic HCV GT 1-6 (n=343). Patients were HCV treatment-naïve and had documented cirrhosis. Patients with decompensated cirrhosis, HIV, and HBV were excluded from the trial. The majority of patients were male (63%), white (83%) and had GT 1 infection (67%). Overall, the SVR12 rate was 97.7% (335/343; 95% CI 96.1-99.3).[11] There was one patient with GT 3 who experienced relapse. Overall, 46% of patients experienced treatment-emergent adverse events. The most common were fatigue (9%), pruritis (8%), headache (8%), and nausea (6%). No patient discontinued treatment because of an adverse event. No liver-related toxicities or cases of drug-induced liver injury were observed. This study was open label, single arm and was funded and designed by AbbVie pharmaceuticals.

5. In March 2020, FDA approved VEL/SOF (Epclusa®) for children ages 6 and older or weighing at least 37 pounds with any of the six HCV genotypes without cirrhosis or with compensated cirrhosis, and in combination with ribavirin for those with decompensated cirrhosis.[12] Approval was based on an unpublished, phase 2, open-label study in adolescents and children. Following a pharmacokinetic lead in phase, 71 subjects 6 to 12 years of age with GT 1, 2, 3, or 4 HCV were treated with 12 weeks of VEL/SOF. Seventy six percent of individuals were GT 1 and the majority (94%) were treatment naïve. Overall, SVR rates were 93% (66/71).[12] The most common adverse events were fatigue and headache. Data remains unpublished[13] and results are not available on clinicaltrials.gov so further quality appraisal cannot be done at this time. The safety and efficacy in children < 6 years of age has not been established.

New FDA Safety Alerts:
None

References:

1. Li M, Chen J, Fang Z, Li Y, Lin Q. Sofosbuvir-based regimen is safe and effective for hepatitis C infected patients with stage 4-5 chronic kidney disease: a systematic review and meta-analysis. *Virology journal.* 2019;16(1):34.
2. Luo A, Xu P, Wang J, et al. Efficacy and safety of direct-acting antiviral therapy for chronic hepatitis C genotype 6: A meta-analysis. *Medicine.* 2019;98(20):e15626.
3. AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org/full-report/hcv-testing-and-linkage-care. [December 2019].
4. Murray KF, Balistreri WF, Bansal S, et al. Safety and Efficacy of Ledipasvir-Sofosbuvir With or Without Ribavirin for Chronic Hepatitis C in Children Ages 6-11. *Hepatology (Baltimore, Md).* 2018;68(6):2158-2166.
5. Schwarz KB, Rosenthal P, Murray KF, et al. Ledipasvir-Sofosbuvir for 12 Weeks in Children 3 to <6 Years Old With Chronic Hepatitis C. *Hepatology (Baltimore, Md).* 2020;71(2):422-430.
6. FDA Clinical Review: Cross-Discipline Team Leader Review: Ledipasvir/sofosbuvir. Available at: https://www.fda.gov/media/131628/download.
7. Rosenthal P, Schwarz KB, Gonzalez-Peralta RP, et al. Sofosbuvir and Ribavirin Therapy for Children Aged 3 to <12 Years With Hepatitis C Virus Genotype 2 or 3 Infection. *Hepatology (Baltimore, Md).* 2020;71(1):31-43.
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9. Borgia SM, Dearden J, Yoshida EM, et al. Sofosbuvir/velpatasvir for 12 weeks in hepatitis C virus-infected patients with end-stage renal disease undergoing dialysis. *Journal of hepatology.* 2019;71(4):660-665.
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11. Brown RS, Jr., Buti M, Rodrigues L, et al. Glecaprevir/pibrentasvir for 8 weeks in treatment-naïve patients with chronic HCV genotypes 1-6 and compensated cirrhosis: The EXPEDITION-8 trial. *Journal of hepatology.* 2020;72(3):441-449.
12. EPCLUSA (sofosbuvir and velpatasvir) prescribing information. Gilead Sciences, Inc. Foster City, CA. March 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208341s014lbl.pdf.
13. Jonas MM, Romero R, Sokal EM, et al. Safety and efficacy of sofosbuvir/velpatasvir in pediatric patients 6 to <18 years old with chronic hepatitis C infection [abstract 748]. The Liver Meeting. Boston, Massachusetts; 2019.
14. 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;157(6):1506-1517.e1501.

Appendix 1: Current Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	MAVYRET	GLECAPREVIR/PIBRENTASVIR	Y
ORAL	TABLET	VOSEVI	SOFOSBUVIR/VELPTASVIR/VOXILAPREVIR	Y
ORAL	TABLET	EPCLUSA	SOFOSBUVIR/VELPATASVIR	Y
ORAL	TABLET	SOFOSBUVIR/VELPATASVIR	SOFOSBUVIR/VELPATASVIR	Y
ORAL	TABLET	DAKLINZA	DACLATASVIR	N
ORAL	TABLET	ZEPATIER	ELBASVIR/GRAZOPREVIR	N
ORAL	TABLET	HARVONI	LEDIPASVIR/SOFOSBUVIR	N
ORAL	TABLET	LEDIPASVIR/SOFOSBUVIR	LEDIPASVIR/SOFOSOBUVIR	N
ORAL	TABLET DOSE PACK	VIEKIRA PAK	OMBITASVIR/PARITAPREVIR/RITONAVIR + DASABUVIR	N
ORAL	TABLET	SOVALDI	SOFOSBUVIR	N

Appendix 2: New Comparative Clinical Trials

A total of 53 citations were manually reviewed from the initial literature search. After further review, 52 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 trial is 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.[14] Phase 3b, open label RCT.	<u>Without Cirrhosis</u> GLE/PIB x 12 weeks (A) vs. GLE/PIB x 16 weeks (B) <u>With Cirrhosis</u> GLE/PIB + RBV x 12 weeks (C) vs. GLE/PIB x 16 weeks (D)	Chronic HCV GT 1 treatment failure with SOF + NS5A inhibitor (n=177)	SVR12	A: 70/78 (90%; 95% CI 81-95%) B: 46/49 (94%; 95% CI 83-98%) C: 18/21 (86%; 95% CI 65-95%) D: 28/29 (97%; 95% CI 83-99%)

Abbreviations: GLE/PIB: glecaprevir/pibrentasvir; GT: genotype; HCV: hepatitis C virus; NS5A: non-structural protein 5A; RBV: ribavirin; RCT = randomized clinical trial; SOF: sofosbuvir; SVR12: sustained virologic response 12 weeks after treatment.

Appendix 3: Abstracts of Comparative Clinical Trials

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 Dec;157(6):1506-1517.e1. doi: 10.1053/j.gastro.2019.08.008. Epub 2019 Aug 8.

BACKGROUND & AIMS:
Treatment options are limited for patients with hepatitis C (HCV) infection with treatment failure after sofosbuvir plus an 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 failure after 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 treatment with 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 end point was a sustained virologic response 12 weeks after treatment. Samples collected at baseline and at time of treatment failure were sequenced for resistance-associated substitutions 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 sustained virologic response 12 weeks after treatment in groups A, B, C, and D were 90%, 94%, 86%, and 97%, respectively. The treatment failed in 13 (7.3%) patients with HCV genotype 1a infection, 6 (7.9%) in group A, 3 (6.1%) in group B, 3 (6.1%) in group C (6.1%), and 1 (3.4%) in group D. Most patients had baseline resistance-associated substitutions in NS5A. Treatment-emergent resistance-associated substitutions 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 sofosbuvir plus an NS5A inhibitor, 16 weeks treatment with G/P produced sustained virologic response 12 weeks after treatment in >90% of patients, including those with compensated cirrhosis. ClinicalTrials.gov, Number: NCT03092375.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to February 25, 2020

▼ **Search History** (33)

# ▲	Searches	Results	Type
1	glecaprevir.mp.	193	Advanced
2	glecaprevir.mp.	193	Advanced
3	pibrentasvir.mp.	203	Advanced
4	mavyret.mp.	10	Advanced
5	sofosbuvir.mp. or SOFOSBUVIR/	2677	Advanced
6	velpatasvir.mp.	294	Advanced
7	voxilaprevir.mp.	91	Advanced
8	vosevi.mp.	11	Advanced
9	epclusa.mp.	16	Advanced
10	daclatasvir.mp.	1123	Advanced
11	daklinza.mp.	15	Advanced
12	technivie.mp.	5	Advanced
13	ombitasvir.mp.	511	Advanced
14	paritaprevir.mp.	501	Advanced
15	ritonavir.mp. or RITONAVIR/	6851	Advanced
16	dasabuvir.mp.	436	Advanced
17	simeprevir.mp. or SIMEPREVIR/	813	Advanced
18	ledipasvir.mp.	1034	Advanced
19	harvoni.mp.	69	Advanced
20	antiviral agents.mp. or Antiviral Agents/	80201	Advanced
21	direct acting antivirals.mp.	2662	Advanced
22	protease inhibitors.mp. or Protease Inhibitors/	43336	Advanced
23	ribavirin.mp. or RIBAVIRIN/	16681	Advanced
24	ns5a inhibitors.mp.	269	Advanced
25	ns5b inhibitor.mp.	108	Advanced

☐	26	Hepatitis C, Chronic/ or Hepatitis C/	62849	Advanced
☐	27	hepatocellular carcinoma.mp. or Carcinoma, Hepatocellular/	112599	Advanced
☐	28	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 or 25	129678	Advanced
☐	29	26 or 27	168501	Advanced
☐	30	28 and 29	22229	Advanced
☐	31	limit 30 to (english language and humans and yr="2019 -Current" and (clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or meta analysis or practice guideline or randomized controlled trial or "systematic review"))	53	Advanced
☐	32	from 31 keep 4, 11-12, 14, 16-17, 23, 27...	12	Advanced
☐	33	from 32 keep 2, 7-9, 12	5	Advanced

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)? Note: Accurate diagnosis of chronic hepatitis C infection typically includes positive detection of a viral load. Diagnosis should not rely solely on HCV antibody testing.	**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. History of previous HCV treatment and outcome d. 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 needed if there are 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
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.

Approval Criteria		
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
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

Approval Criteria		
14. 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 have not been established	**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 Adults, and Adolescents 12 years of age and older with Chronic Hepatitis C virus.

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 SOF/VEL x 24 weeks (if ribavirin ineligible*)
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 SOF/VEL x 24 weeks (if ribavirin ineligible*)
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 SOF/VEL x 24 weeks (if ribavirin ineligible*)
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 DAA-containing regimen, including NS5A)	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 SOF/VEL x 24 weeks (if ribavirin ineligible*)
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 DAA-containing regimen, including NS5A)	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 SOF/VEL x 24 weeks (if ribavirin ineligible*)
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 SOF/VEL x 24 weeks (if ribavirin ineligible*)

Experienced (prior DAA-containing regimen, including NS5A)	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 * 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 ±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.		
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 2: Recommended Treatment Regimens for children ages 3 - 12 years of age with Chronic Hepatitis C virus.

Treatment History	Cirrhosis Status	Recommended Regimen
Genotype 1		
Treatment naïve or PEG/RBV Treatment Experienced	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks (≥ 6 years) LDV/SOF x 12 weeks (only for 3 - <6 years)
	Decompensated Cirrhosis	SOF/VEL + RBV x 12 week (≥ 6 years) LDV/SOF x 12 weeks + RBV (only for 3 - <6 years)
Treatment Experienced (Prior NS3A/4A inhibitor) Note: Efficacy and safety not established in treatment experienced to other DAAs in this population	Non-cirrhotic	SOF/VEL x 12 weeks(≥ 6 years) LDV/SOF x 12 weeks (only for 3 - <6 years)
	Compensated cirrhosis	SOF/VEL x 12 weeks(≥ 6 years) LDV/SOF x 24 weeks (only for 3 - <6 years)
Genotype 2		
Naïve	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks (≥ 6 years)
	Decompensated (safety and efficacy not established for < 6 years)	SOF/VEL + RBV x 12 weeks (≥ 6 years)
Treatment Experienced (prior PEG/RBV or NS3/4A)	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks(≥ 6 years)

Note: Efficacy and safety not established in treatment experienced to other DAAs in this population	Decompensated (safety and efficacy not established for < 6 years)	SOF/VEL + RBV x 12 weeks (≥ 6 years)
Genotype 3		
Naïve	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks (≥ 6 years)
	Decompensated (safety and efficacy not established for < 6 years)	SOF/VEL + RBV x 12 weeks (≥ 6 years)
Treatment Experienced (prior PEG/RBV or NS3/4A) Note: Efficacy and safety not established in treatment experienced to other DAAs in this population	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks(≥ 6 years)
	Decompensated (safety and efficacy not established for < 6 years)	SOF/VEL + RBV x 12 weeks (≥ 6 years)
Genotype 4, 5, or 6		
Treatment naïve	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks (≥ 6 years) LDV/SOF x 12 weeks (only for 3 - <6 years)
	Decompensated Cirrhosis	SOF/VEL + RBV x 12 week
Treatment Experienced (prior PEG/RBV or NS3/4A) Note: Efficacy and safety not established in treatment experienced to other DAAs in this population	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks (≥ 6 years) LDV/SOF x 12 weeks (only for 3 - <6 years)
	Decompensated cirrhosis	SOF/VEL + RBV x 12 week
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		
^ 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.		
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.		

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