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

Date of Review: October 2021

Date of Last Review: June 2020
Literature Search: 05/01/20 – 08/31/21

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

Conclusions:

- There is high quality evidence that direct acting antiviral (DAA) regimens result in pooled sustained virologic response (SVR) rates between 95.5% to 98.9% across genotypes in the treatment of chronic hepatitis C virus (HCV). [1]
- There is high quality evidence that DAA regimens have 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%).[1]
- There is insufficient evidence evaluating the effects of HCV screening versus no screening on clinical outcomes.[1]
- 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, I^2 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.[1]
- There is low quality evidence that sofosbuvir/velpatasvir (SOF/VEL) and glecaprevir/pibrentasvir (G/P) are effective in treatment of chronic HCV in pediatric patients between 3 and 6 years of age with SVR rates of 83% to 95%. Higher discontinuations due to adverse events with SOF/VEL (17%) were observed.
- There is insufficient evidence to determine optimal DAA regimen and duration for the treatment of recently acquired HCV. There is low quality evidence that shortened durations of DAA's may result in comparable SVR rates to standard durations based on inconsistent data from mostly open-label, single arm studies excluding persons who inject drugs (PWID). There is low quality evidence that 6 weeks SOF/VEL is not non-inferior to 12 weeks in recently acquired HCV (SVR12 81.7% vs. 90.5%, respectively). [2]
- Considerations in the treatment of recently acquired HCV include potential for spontaneous clearance, risk factors for rapid progression of liver disease, risk factors for disease transmission, and potential for loss to follow up.

Recommendations:

- Update prior authorization criteria and treatment table (**Appendix 6**) to include new pediatric indications and clerical updates.
- Consider approval for acute HCV based on further analysis.
- After review comparative costs in executive session, brand name Epclusa was made non-preferred.

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Summary of Prior Reviews and Current Policy

- There is high quality evidence that all 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 nonstructural protein 5A (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.
- 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 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), human immunodeficiency virus (HIV), cancer, hepatocellular carcinoma (HCC), decompensated cirrhosis, severe psychiatric, cardiac, pulmonary, or renal comorbidities, and severe alcohol or substance abuse.
    - 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.
- 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 RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. Trials evaluating treatment of acute, or recently acquired HCV, were also 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.

New Systematic Reviews:

After review, 2 systematic reviews were excluded due to poor quality[3], wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical)[4].

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1. A systematic review update was prepared by the Agency for Healthcare Research and Quality (AHRQ) for the U.S. Preventive Services Task Force on screening for HCV infection in adolescents and adults.[1] The purpose was to systematically review the evidence on HCV screening in asymptomatic individuals. After a complete literature search and review of studies, 97 studies were included. Overall, most DAA trials were not randomized and did not have a non-DAA comparison group. The primary outcome in almost all studies was SVR and there was limited data in adolescents. Direct evidence on the benefits of HCV screening is unavailable and direct evidence on the effects of DAA therapy on clinical outcomes remains limited but suggests improved long-term outcomes.

   No study directly assessed effects of HCV Screening versus no screening on clinical outcomes including HCV-related mortality or quality of life. No study was identified assessing the effects of prenatal HCV screening on risk of vertical transmission or comparing different methods for HCV screening on clinical outcomes. In terms of efficacy, high strength evidence from 49 trials found DAA regimens resulted in pooled SVR rates between 95.5% to 98.9% across genotypes with low rates of serious adverse events (1.9%; RR 1.90; 95% CI 0.73 to 4.95) and withdrawal due to adverse events (0.4%).[1] The most common reported adverse events were fatigue (18.4%), headache (18.7%), nausea (11.1%), diarrhea (8.7%), and insomnia (8.1%).[1] Seven trials reported similar SVR rates in adolescents (fair strength of evidence). Low strength evidence found that DAA treatment in adults improves quality of life and found no short-term mortality (<1 year). However, trials of DAAs were not designed to assess effects on long-term clinical outcomes. Therefore, cohort studies were included that assessed the association between SVR versus no SVR and effects on clinical outcomes. Fair strength evidence supports a SVR was associated with decreased risk of all-cause mortality (HR 0.40; 95% CI 0.28 to 0.56, I^2 52.1%), liver 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.[1] There is insufficient evidence evaluating DAAs on reducing the risk of mother-to-infant transmission.

New Guidelines:

1. <u>US Department of Health and Human Services/Centers for Disease Control (CDC) and Prevention[5]</u>

The CDC released recommendations for hepatitis C screening among adults based on a comprehensive systematic review of the literature.[5] The following recommendations were included:

- Universal hepatitis C screening:
  - At least once in a lifetime for all adults aged ≥ 18 years
  - For all pregnant women during each pregnancy
- One-time hepatitis C testing for all persons with recognized risk factors or exposure
  - Persons with HIV
  - Persons who ever injected drugs or shared needles, syringes, or other equipment
  - Persons who ever received hemodialysis
  - Persistently abnormal ALT levels
  - Prior recipients of transfusions or organ transplants before July 1992
  - Health care personnel after needle sticks or mucosal exposures

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- Children born to mothers with HCV infection
- Routine periodic testing for persons with ongoing risk factors
  - Persons who currently inject drugs and share needles, syringes, or other drug equipment
  - Persons receiving maintenance hemodialysis

2. US Preventive Services Task Force (USPSTF): Screening for Hepatitis C Virus Infection in Adolescents and Adults[6]

Consistent with CDC guidelines, USPSTF recommends with moderate certainty that screening for HCV infection in adults aged 18 to 79 years has substantial net benefit (B recommendation). USPSTF also suggests screening persons younger than 18 years and older than 79 years who are at high risk for infection. Recommendations were based on the AHRQ systematic review described earlier in this report.[1]

Additional Guidelines for Clinical Context:

1. Veterans Affairs (VA) National Hepatitis C Resource Center[7]

Guidelines from the VA National Hepatitis C Resource Center were updated in March 2021.[7] The following updates are included in the guideline:

- Universal HCV testing for adults and required testing for patients with ongoing risk exposure
- Eight weeks of G/P in all HCV genotypes who are treatment-naïve with compensated cirrhosis
- Treatment updated to include SOF-based therapy in patients with chronic kidney disease, including those on hemodialysis
- Selection for HCV treatment should include patients who become reinfected with HCV after initially achieving SVR
- Patients with acute HCV infection can be treated with DAAs upon initial diagnosis without awaiting spontaneous resolution if appropriate

Additional treatment recommendations are included in **Table 1**.

2. American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA)[8]

Guidelines from the AASLD/IDSA were updated in January 2021.[8] The following updates are included in the guideline:

- Recommendations for universal, routine and opt out testing consistent with the CDC and USPTSF
- End stage renal disease removed as a contraindication to simplified treatment
- Reorganization of recommendations away from genotype based since most patients will be candidates for a pangenotypic regimen and will not require genotyping
- Updates to treatment of HCV in children based on FDA expanded pediatric indications
- Recommendations for the treatment of acute HCV infection
  - HCV treatment should be initiated without awaiting spontaneous resolution
  - Counseling recommended to avoid hepatotoxic drugs, alcohol consumption, and to reduce the risk of HCV transmission to others
  - The same DAA regimens recommended for chronic HCV infection are recommended for acute infection

AASLD/IDSA recommendations for treating hepatitis C are included in **Table 1**

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3. European Association for the Study of the Liver (EASL)[9]
    - All treatment naïve and treatment experienced patients with recently acquired or chronic HCV infection must be offered treatment without delay
    - Urgent treatment should be considered in:
        - Patients with significant fibrosis or cirrhosis or with extrahepatic manifestations
        - HCV recurrence after liver transplantation
        - Patients at risk of rapid evolution of liver disease (HBV and HIV coinfections)
        - Individuals at risk of transmitting HCV (persons who inject drugs, men who have sex with men, women of childbearing age who wish to get pregnant, incarcerated individuals)
    - The presence of viremia must be demonstrated prior to initiating therapy
    - Patients with recently acquired hepatitis C should be treated with SOF/VEL or G/P for 8 weeks. SVR should be assessed 12 and 24 weeks after treatment, because late relapses have been reported.
    - There is no indication for antiviral therapy as post-exposure prophylaxis in the absence of documented HCV transmission

Table 1: Recommended treatment regimens from clinical guidelines

Genotype	Treatment History	Cirrhosis Status	Veterans Affairs Guidelines[7]	AASLD/IDSA Guidelines[8]
1	***Naïve***	***Non-cirrhotic or compensated cirrhosis (CTP A)***	G/P x 8 weeks SOF/VEL x 12 weeks EBR/GZR x 12 weeks ** LDV/SOF x 8-12 weeks (8 weeks if HCV RNA <6 million IU/ml, non-cirrhotic, and HCV-monoinfected)	G/P x 8 weeks SOF/VEL x 12 weeks EBR/GZR x 12 weeks ** LDV/SOF x 8-12 weeks (8 weeks if HCV RNA <6 million IU/ml, non-cirrhotic, and HCV-monoinfected)
		Decompensated Cirrhosis	LDV/SOF + RBV x 12 weeks SOF/VEL + RBV x 12 weeks	LDV/SOF + RBV x 12 weeks SOF/VEL + RBV x 12 weeks
1	***Experienced (Prior NS3A/4A inhibitor)***	***Non-cirrhotic or compensated cirrhosis***	G/P x 12 weeks (SOF naïve only) SOF/VEL x 12 weeks (SOF naïve only)	G/P + SOF + RBV x 16 weeks (G/P failure only) SOF/VEL/VOX x 12 weeks
1	***Experienced (prior NS5A-containing regimen)***	***Non-cirrhotic or compensated cirrhosis***	SOF/VEL/VOX x 12 weeks G/P x 16 weeks (if failed NS5A inhibitor without NS3A/4A inhibitor)	SOF/VEL/VOX x 12 weeks G/P x 16 weeks (if failed NS5A inhibitor without NS3A/4A inhibitor)
2	***Naïve***	***Non-cirrhotic or compensated cirrhosis***	SOF/VEL x 12 weeks G/P x 8 weeks (consider 12 weeks if poor prognostic factors)	G/P x 8 weeks SOF/VEL x 12 weeks
		Decompensated	SOF/VEL + RBV x 12 weeks	SOF/VEL + RBV x 12 weeks
2	***Experienced (Prior NS3A/4A inhibitor)***	***Non-cirrhotic or compensated cirrhosis***	NA	G/P + SOF + RBV x 16 weeks (G/P failure only) SOF/VEL/VOX x 12 weeks
2	***Experienced (NS5A-experienced)***	***Non-cirrhotic or compensated cirrhosis***	SOF/VEL/VOX x 12 weeks	SOF/VEL/VOX x 12 weeks
2	***Experienced (SOF + RBV)***	***Non-cirrhotic or Compensated Cirrhotic***	SOF/VEL x 12 weeks G/P x 8-12 weeks	G/P x 16 weeks (if no NS3A/4A protease inhibitor) SOF/VEL/VOX x 12 weeks

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3	***Naïve***	***Non-cirrhotic or compensated cirrhosis***	G/P x 8 weeks (consider 12 weeks if poor prognostic factors) SOF/VEL X 12 weeks (without baseline NS5A RAS Y93H)	G/P x 8 weeks SOF/VEL X 12 weeks (without baseline NS5A RAS Y93H)
		Decompensated Cirrhosis	SOF/VEL + RBV X 12 weeks	SOF/VEL + RBV x 12 weeks
3	***Experienced (NS5A or SOF)***	***Non-cirrhotic or Compensated Cirrhotic***	SOF/VEL/VOX x 12 weeks	SOF/VEL/VOX x 12 weeks G/P x 16 weeks (if failed NS5A inhibitor without NS3A/4A inhibitor)
4	***Naïve***	***Non-cirrhotic or Compensated Cirrhosis***	SOF/VEL x 12 weeks G/P x 8 weeks EBV/GZR x 12 weeks LDV/SOF x 12 weeks	G/P x 8 weeks SOF/VEL x 12 weeks EBR/GZR x 12 weeks LDV/SOF x 12 weeks
		Decompensated Cirrhosis	LDV/SOF + RBV x 12 weeks SOF/VEL + RBV x 12 weeks	LDV/SOF + RBV x 12 weeks SOF/VEL + RBV x 12 weeks
4	***Experienced (prior sofosbuvir)***	***Non-cirrhotic or compensated cirrhosis***	G/P x 8-12 weeks SOF/VEL x 12 weeks	G/P x 16 weeks (if no NS3A/4A protease inhibitor) SOF/VEL/VOX x 12 weeks
4	***Experienced (prior NS5A-containing regimen)***	***Non-cirrhotic or compensated cirrhosis***	SOF/VEL/VOX x 12 weeks	SOF/VEL/VOX x 12 weeks G/P x 16 weeks (if failed NS5A inhibitor without NS3A/4A inhibitor)
4	***Experienced (Prior NS3A/4A inhibitor)***	***Non-cirrhotic or compensated cirrhosis***	NA	G/P + SOF + RBV x 16 weeks (G/P failure only) SOF/VEL/VOX x 12 weeks
1-6	***Experienced (Multiple DAA regimens)***	***Non-cirrhotic or compensated cirrhosis***	NA	G/P + SOF + RBV x 16 weeks (up to 24 weeks in difficult cases) SOF/VEL/VOX x 24 weeks
Abbreviations: EBR/GZR (elbasvir/grazoprevir); G/P (glecaprevir/pibrentasvir); LDV/SOF (ledipasvir/sofosbuvir); SOF/VEL (sofosbuvir/velpatasvir); SOF (sofosbuvir); SOF/VEL/VOX (sofosbuvir/velpatasvir/voxilaprevir)				

New Indications and formulations:

1. The FDA labeling of SOF/VEL (Epclusa) was expanded in June 2021 to include pediatric patients 3 years of age or older with chronic HCV (genotypes 1-6).[10] A new formulation of oral pellet was approved for pediatric patients and is the only formulation available for patients weighting less than 17 kg. Approval was based on a phase 2, open-label, clinical trial that enrolled 41 children 3 years to less than 6 years of age. [10, 11] Overall, 83% of patients achieved SVR12 (34/41).[11] The seven patients who did not achieve SVR12, discontinued treatment within the first 20 days. Vomiting (15%) and spitting up the drug (10%) occurred more commonly in patients less than 6 years of age. This study was sponsored by Gilead Sciences and remains unpublished.

2. The FDA labeling for G/P (Mavyret) was also expanded to include pediatric patients 3 years of age and older in June 2021 and the oral pellet formulation was approved for pediatric patients.[12] This is the only formulation available for patients weighing less than 45 kg. Approval was based on part 2 of the DORA study, a phase 2/3, nonrandomized, open-label study in children 3 to 12 years of age given the pellet formulation of G/P for 8 to 12 weeks, depending on the presence of cirrhosis and geographical location (n=80).[13] Part one was a pharmacokinetic analysis. Most subjects were treatment naïve (98%) with genotype 1 HCV (73%). The overall SVR rate was 96% (77/80; 95% CI 90-99%).[13] In those ages 3 to 6 years old, 95% achieved SVR (23/24) at a dose of 50/20 mg. There were two discontinuations due to adverse effects. The most common adverse effects were headache (14%), vomiting (14%), and diarrhea (10%).[13]

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New FDA Safety Alerts:

Table 2. Description of New FDA Safety Alerts[14]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Elbasvir/grazoprevir	Zepatier	12/2019	Warnings and Precautions	Risk of hepatic decompensation/failure in patients with evidence of advanced liver disease. Contraindicated in patients with moderate or severe hepatic impairment or those with any history of hepatic decompensation due to the risk of hepatic decompensation

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Appendix 1: Current Preferred Drug List

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

Direct Acting Antiviral Abbreviations: **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **G/P** (glecaprevir/pibrentasvir): Mavyret®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; SOF**/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®; **SOF/VEL/VOX** (sofosbuvir/velpatasvir/voxilaprevir): Vosevi®

Author: Herink October 2021

Appendix 2: New Comparative Clinical Trials

A total of 7 citations were manually reviewed from the initial literature search. After further review, 4 citations were excluded because of wrong study design[15, 16] (e.g., observational), comparator[17-19] (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trials are summarized in the table below. Full abstracts are included in **Appendix 3**. Additional trials evaluating treatment of acute HCV are included in Table for clinical context.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	
Matthew et al.[2] Open-label, phase IV, randomized, non-inferiority trial	SOF/VEL for 12 weeks vs. SOF/VEL for 6 weeks	Recently acquired acute HCV (n=188)	SVR12	SVR12: 6-week:76/93 (81.7%; 95% CI 72.4-89.0) 12 weeks:86/95 (90.5%; 95% CI 82.8-95.6) Difference: -8.81 (95% CI -18.6 to 1.0) **non-inferiority was not shown*	
Kamal et al.[20]	LDV/SOF for 8 weeks vs. LDV/SOF for 12 weeks	Pediatrics 3-6 years old with chronic HCV GT 4 (n=22)	SVR12	SVR12: 8 weeks: 11/11 (100%) 12 weeks: 11/11 (100%)	
Lok et al.[21] Phase 3b, open-label RCT	<u>Noncirrhotic:</u> G/P x 12 weeks vs. G/P x 16 weeks <u>Cirrhotic:</u> G/P + RBV x 12 weeks vs. G/P + RBV x 16 weeks	Adults with chronic HCV GT 1 and treatment failure to NS5A inhibitor + SOF (n-180)	SVR12	Overall SVR12: 162/177 (91.5%)	
				<u>Noncirrhotic:</u> 12 wks: 70/78 (90%; 95% CI 81-95) 16 wks: 46/49 (94%; 95% CI 83-98)	<u>Cirrhotic:</u> 12 wks: 18/21 (86%;95% CI 65-95) 16 wks: 28/29 (97%;95% CI 83-99)

Abbreviations: CI = confidence interval; G/P = glecaprevir/pibrentasvir; GT = genotype; HCV = hepatitis C virus; RCT = randomized clinical trial; SOF = sofosbuvir; SOF/VEL = sofosbuvir/velpatasvir; SVR12 = sustained virologic response at 12 weeks after treatment end

Table 2: Additional Trials for Clinical Context in Recently Acquired (Acute) Hepatitis C Virus

Study	Comparison	Population	Primary Outcome	Results
Boerekamps, et al.[18] Single arm, open-label, phase 3 b trial	EBR/GZR x 8 weeks	Recently acquired acute HCV (n=146)	SVR12	<u>SVR12:</u> 79/80 (99%; 95% CI 93-100)

Direct Acting Antiviral Abbreviations: **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **G/P** (glecaprevir/pibrentasvir): Mavyret®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; SOF**/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®; **SOF/VEL/VOX** (sofosbuvir/velpatasvir/voxilaprevir): Vosevi®

Martinello, et al[17] Single arm, open label	G/P x 6 weeks	Recently acquired acute HCV (n=30)	SVR12	SVR12: 27/30 (90%; 95% CI 73-98)
Rockstroh, et al.[22] Single arm, open label	LDV/SOF x 6 weeks	Recently acquired acute HCV GT 1 or 4 in patients with HIV coinfection (n=26)	SVR12	SVR12: 20/26 (77%; 95% CI 56-91)
Matthews, et al.[23] Open-label, phase 3 RCT	SOF/VEL x 6 weeks vs. SOF/VEL x 12 weeks	Recently acquired HCV (n=196)	SVR12	SVR12: 6 weeks: 76/93 (81.7%; 95% CI 72.4-89) 12 weeks: 86/95 (90.5%; 95% CI 82.8-95.6) Difference* -8.81; 95% CI -18.6 to 1.0 *Criteria for non-inferiority was not met

Abbreviations: CI = confidence interval; EBR/GZR = elbasvir/grazoprevir; G/P = glecaprevir/pibrentasvir; GT = genotype; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LDV/SOF = ledipasvir/sofosbuvir; SOF/VEL = sofosbuvir/velptasavir; SVR12 = sustained virologic response at 12 weeks after treatment end

Direct Acting Antiviral Abbreviations: **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **G/P** (glecaprevir/pibrentasvir): Mavyret®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; SOF**/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®; **SOF/VEL/VOX** (sofosbuvir/velpatasvir/voxilaprevir): Vosevi®

Appendix 3: Abstracts of Comparative Clinical Trials

1. Matthews G, 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 May 21;S0168-8278(21)00336-6. doi: 10.1016/j.jhep.2021.04.056.

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 ≤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. Kamal E, El-Shabrawi M, El-Khayat H. Effects of sofosbuvir/ledipasvir therapy on chronic hepatitis C virus genotype 4, infected children of 3-6 years of age. Liver Int. 2020 Feb;40(2):319-323.

Background & aims: Treatment of children aged 3-6 genotype 4 is still limited by the interferon side effects. We aimed in this study to evaluate the effectiveness and safety of sofosbuvir/ledipasvir in children (3-6 years) genotype 4 chronic HCV-infected patients.

Methods: In total, 22 consecutive chronic HCV-infected patients (mean age 4.8 ± 0.9years, 19 males) were included in this prospective study. All patients received sofosbuvir 200 mg/ledipasvir 45 mg in a single oral daily dose. Patients were randomly subdivided into two groups according the duration of treatment into 8 and 12 weeks. All the clinical and laboratory data were collected. All the side effects were recorded from the patients or their parents. Follow-up were made at Week 4, 8 and 12 and 12 weeks after the end of treatment (SVR12).

Results: The overall SVR12 rate was 100%. At Week 4, 9/11 patients in the 12-week group (81.8%; 95% CI: 52.3%-94.7%) achieved virologic negativity, vs 10/11 (90.9%; 95% CI: 62.3%-98.4%) in the 8-week group. At Week 8, 10/11 (90.8%; 95% CI: 62.3%-98.4%) in the 12-week group vs 11/11 (100%; 95% CI: 74.1%-100%) in the 8-week group were virologically negative. The reported side effects were cough, abdominal pain, nausea, vomiting and diarrhoea

Direct Acting Antiviral Abbreviations: **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **G/P** (glecaprevir/pibrentasvir): Mavyret®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; SOF**/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®; **SOF/VEL/VOX** (sofosbuvir/velpatasvir/voxilaprevir): Vosevi®

especially early in the treatment. The main complaint was difficulty in swallowing the tablets in the youngest patient at the beginning of the course of treatment. All patients were compliant to treatment.

Conclusion: Sofosbuvir/ledipasvir combination is safe and tolerable in the chronic infected HCV genotype 4 infected children (3-6 years). The 8-week treatment duration is similarly effective as the 12-week duration.

Direct Acting Antiviral Abbreviations: **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **G/P** (glecaprevir/pibrentasvir): Mavyret®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; SOF**/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®; **SOF/VEL/VOX** (sofosbuvir/velpatasvir/voxilaprevir): Vosevi®

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to August 06, 2021>

1	glecaprevir.mp.	355
2	pibrentasvir.mp.	351
3	mavyret.mp.	12
4	sofosbuvir.mp. or SOFOSBUVIR/	3232
5	velpatasvir.mp.	455
6	voxilaprevir.mp.	124
7	vosevi.mp.	12
8	epclusa.mp.	26
9	daclatasvir.mp.	1296
10	daklinza.mp.	15
11	technivie.mp.	6
12	ombitasvir.mp.	596
13	paritaprevir.mp.	620
14	ritonavir.mp. or RITONAVIR/	8167
15	dasabuvir.mp.	503
16	simeprevir.mp. or SIMEPREVIR/	877
17	ledipasvir.mp.	1209
18	harvoni.mp.	71
19	antiviral agents.mp. or Antiviral Agents/	90918
20	direct acting antivirals.mp.	3417
21	protease inhibitors.mp. or Protease Inhibitors/	45050
22	ribavirin.mp. or RIBAVIRIN/	17498
23	ns5a inhibitors.mp.	296
24	ns5b inhibitor.mp.	107
25	Hepatitis C, Chronic/ or Hepatitis C/	66572
26	hepatocellular carcinoma.mp. or Carcinoma, Hepatocellular/	126466
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	142722
28	25 or 26	185548
29	27 and 28	24357
30	limit 29 to (english language and full text and humans and yr="2020 -Current" and (clinical trial, all or comparative study or controlled clinical trial or meta analysis or randomized controlled trial or "systematic review"))	37
31	from 30 keep 2,4,6-8,10,12,15,18,20-21,27,32,34,37	15
32	from 31 keep 1,3-4,6,8,13-14	7

Direct Acting Antiviral Abbreviations: **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **G/P** (glecaprevir/pibrentasvir): Mavyret®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; SOF**/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®; **SOF/VEL/VOX** (sofosbuvir/velpatasvir/voxilaprevir): Vosevi®

Author: Herink October 2021

Appendix 5: Key Inclusion Criteria

Population	Hepatitis C Virus
Intervention	Direct Acting Antiviral
Comparator	Direct acting antiviral
Outcomes	Sustained virologic response, hepatocellular carcinoma, liver transplant, cirrhosis, decompensated cirrhosis, all-cause mortality
Timing	N/A
Setting	N/A

Direct Acting Antiviral Abbreviations: **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **G/P** (glecaprevir/pibrentasvir): Mavyret®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; SOF**/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®; **SOF/VEL/VOX** (sofosbuvir/velpatasvir/voxilaprevir): Vosevi®

Appendix 6: Prior Authorization Criteria

Hepatitis C Direct-Acting Antivirals

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.

Direct Acting Antiviral Abbreviations: **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **G/P** (glecaprevir/pibrentasvir): Mavyret®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; SOF**/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®; **SOF/VEL/VOX** (sofosbuvir/velpatasvir/voxilaprevir): Vosevi®

Approval Criteria		
4. Has <u>all</u> the following pre-treatment testing been documented: a. Genotype testing in past 3 years is required if the patient has decompensated cirrhosis, prior treatment experience with a DAA regimen, and if prescribed a regimen which is not pan-genotypic 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. Treatment-experienced: Patients who received more than 4 weeks of HCV DAA therapy.	**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.

Direct Acting Antiviral Abbreviations: **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **G/P** (glecaprevir/pibrentasvir): Mavyret®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; SOF**/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®; **SOF/VEL/VOX** (sofosbuvir/velpatasvir/voxilaprevir): Vosevi®

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 OR Is there attestation from the patient and provider that they have opted out of OHA case management? 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. Patients may opt out of OHA case management with attestation that they understand goals and benefits of the program and responsibilities associated with treatment including adherence to treatment and lab tests. Members may rejoin the program at any time.	**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 (glecaprevir, simeprevir, paritaprevir, voxilaprevir)?	**Yes:** Go to #12	**No:** Go to #13

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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, 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 Pediatric dosing available in **Table 3** and **Table 4**	**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 Hepatitis C virus.

Treatment History	Cirrhosis Status	Recommended Regimen
Treatment Naïve (Genotype 1-6)		
Treatment naïve, confirmed reinfection or prior treatment with PEG/RBV	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks G/P x 8 weeks
	Compensated cirrhosis	G/P x 8 weeks SOF/VEL x 12 weeks (baseline resistance testing recommended for GT3)
	Decompensated Cirrhosis	SOF/VEL + RBV x 12 weeks SOF/VEL x 24 weeks (if ribavirin ineligible*)
Treatment Experienced (Genotype 1-6)		
Sofosbuvir based regimen treatment failures, including: Sofosbuvir + ribavirin Ledipasvir/sofosbuvir	Non-cirrhotic or compensated cirrhosis	SOF/VEL/VOX x12 weeks G/P x 16 weeks (except GT3)

Direct Acting Antiviral Abbreviations: **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **G/P** (glecaprevir/pibrentasvir): Mavyret®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; SOF**/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®; **SOF/VEL/VOX** (sofosbuvir/velpatasvir/voxilaprevir): Vosevi®

Velpatasvir/sofosbuvir		
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)
Multiple DAA Treatment Failures, including: sofosbuvir/velpatasvir/voxilaprevir glecaprevir/pibrentasvir + sofosbuvir	Non-cirrhotic or compensated cirrhosis	G/P + SOF + RBV x 16-24 weeks SOF/VEL/VOX x 24 weeks
Abbreviations: DAA = direct acting antiviral; EBV/GZR = elbasvir/grazoprevir; G/P = glecaprevir 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 PEG/RBV	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		

Direct Acting Antiviral Abbreviations: **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **G/P** (glecaprevir/pibrentasvir): Mavyret®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; SOF**/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®; **SOF/VEL/VOX** (sofosbuvir/velpatasvir/voxilaprevir): Vosevi®

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 mg50 mg pellet packet OR tablet once daily
At least 30 kg	Two 200 mg/50 mg pellet packets once daily OR one 400 mg/100 mg tablet once daily

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

Body weight	Dosing of sofosbuvir/velpatasvir
Less than 20 kg	Three 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: *10/21 (MH); 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: *1/1/22; 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*