EVALUATION AND MANAGEMENT OF CHRONIC HEPATITIS C VIRUS (HCV) INFECTION

Federal Bureau of Prisons

Clinical Guidance

MAY 2017

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WHAT'S NEW IN BOP GUIDANCE REGARDING HCV INFECTION?

The major changes included in this May 2017 update to the BOP guidance on chronic HCV infection are based primarily on the April 2017 changes to the* American Association for the Study of Liver Diseases (*AASLD) guidelines, as follows:

- The term *resistance-associated substitutions (RASs)* is now being used instead of *resistance-associated variants (RAVs)*.
- Anti-HBs and anti-HBc, in addition to HBsAg, are recommended for baseline testing of hepatitis B status (see LABORATORY TESTS under *BASELINE EVALUATION*).
- *Ledipasvir/sofosbuvir* once daily for eight weeks is now an AASLD-recommended regimen for treatment in a subgroup of HCV-infected persons who have genotype 1a or 1b, have an HCV viral load <6 million IU/ml, and are treatment-naïve—but who are not black, are not HIV-coinfected, and do not have cirrhosis.
- The treatment of peginterferon + ribavirin treatment-experienced genotype 3 with compensated cirrhosis has been updated as follows (see *APPENDIX 1*):
  - The addition of weight-based ribavirin to the sofosbuvir/velpatasvir regimen is recommended.
  - Elbasvir/grazoprevir + sofosbuvir once daily for 12 weeks is now another AASLD-recommended regimen.
- NS5A resistance testing is recommended for peginterferon + ribavirin treatment-experienced genotype 3 without cirrhosis (see *testing for RASs* under PRETREATMENT ASSESSMENT in Section 7).
  - If the Y93H RAS is present, the addition of weight-based ribavirin to a 12-week regimen of *either* daclatasvir + sofosbuvir *or* sofosbuvir/velpatasvir is recommended (see *APPENDIX 2*).
- Genotypes 5 and 6 have been added to the recommendations for treatment of HCV infection with *decompensated cirrhosis*.
- Treatment recommendations are added for cases of decompensated cirrhosis with a history of *treatment failure* using sofosbuvir or an NS5A inhibitor.
- A urine drug screen is no longer required as part of the *baseline* and *pretreatment* evaluations, and is recommended only if ongoing substance use is suspected or if it is otherwise clinically indicated.

The major changes included in the October 2016 update were as follows:

- The recommendation to test all sentenced inmates for HCV infection is clarified with a language change from a "voluntary" to an "opt out" strategy. See *Screening Criteria* in Section 2.
- *BOP Priority Criteria for HCV Treatment* have been revised and condensed into three categories: high, intermediate, and low priority. (See Section 5.)
- Pretreatment patient education—rather than informed consent—is now recommended for topics that include, but are not limited to: how to take the medication, the importance of adherence, monitoring and follow up, and potential medication side effects. When ribavirin is used, specific counseling about the risks and recommendations related to pregnancy should be provided. (See *Pregnancy* in Section 8.)
- Sofosbuvir/velpatasvir (Epclusa®), the newest FDA-approved direct acting antiviral (DAA) for HCV infection, has been incorporated into HCV treatment recommendations. It is FDA-approved for treatment of all HCV genotypes and replaces sofosbuvir + ribavirin for the treatment of genotypes 2 and 3. (See *sofosbuvir/velpatasvir* description in Section 6 and in *Appendix 9*.)
- The new formulation of paritaprevir/ritonavir/ombitasivir/dasabuvir (Viekira XR™) has been substituted for the original formulation as Viekira Pak®**.** Viekira XR is now preferred over Viekira Pak for use in the BOP.

- Pegylated interferon (PEG-IFN) has been eliminated from all recommended and alternative regimens except for cases of HCV genotypes 2, 3, 5, or 6 with a GFR <30 and an urgent need for treatment. (See discussion o*f chronic kidney disease* in Section 8.)
- For HBV/HCV coinfection, starting treatment for HBV infection is recommended prior to or at the same time as treatment for HCV when criteria for treatment of HBV are met. When HBV treatment criteria are not met, monitoring HBV DNA levels monthly during HCV treatment is recommended. (See *HBV Coinfection* in Section 8.)
- The Appendices have been revised as necessary to reflect the above changes, including the order in which the Appendices occur.

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1. PURPOSE AND OVERVIEW

The Federal Bureau of Prisons (BOP) Clinical Guidance on *Evaluation and Management of Chronic Hepatitis C Virus (HCV) Infection* provides the most current BOP recommendations for the treatment of chronic HCV infection in the federal inmate population.

In light of the rapidly changing HCV treatment landscape, review of the most recent recommendations on the AASLD/IDSA/IAS-USA website★ is recommended. BOP Central Office Medical staff will continue to monitor these guidelines and provide revised guidance as necessary.

➜ *Be sure to consult the BOP Health Management Resources website to determine the date of the most recent update to this document: http://www.bop.gov/resources/health_care_mngmt.jsp.*

★ *The HCV website (www.hcvguidelines.org) is provided by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA), in collaboration with the International Antiviral Society–USA (IAS–USA). See the References section in this document for a complete citation.*

In general, the BOP promotes a modified test-and-treat strategy for HCV infection. The BOP-recommended approach to evaluation and management of HCV includes five basic steps.

STEP 1: Test for HCV infection with anti-HCV (HCV Ab) test.

➜ *See Section 2, Screening for HCV Infection.*

- All sentenced inmates
- Diagnostic evaluation of other conditions
- Upon inmate request

STEP 2: Perform a baseline evaluation of inmates who are anti-HCV positive.

➜ *See Section 3, Initial Evaluation of Anti-HCV Positive Inmates.*

- Targeted history and physical exam
- Lab tests – CBC, PT/INR, liver panel, serum creatinine and eGFR, hepatitis B serology (HBsAg, anti-HBs, anti-HBc), HIV Ab, quantitative HCV RNA viral load with reflex testing for HCV genotype

STEP 3: Assess for hepatic cirrhosis/compensation *and* BOP priority criteria for treatment, if HCV RNA is detectable.

- Assess for hepatic cirrhosis/compensation: Calculate APRI score if no obvious cirrhosis; Calculate CTP score if cirrhosis is known or suspected (➜ *Section 4*).
- Assess for BOP priority criteria for treatment of HCV (➜ *Section 5*).

STEP 4: Perform a pretreatment assessment, if priority criteria for treatment are met.

- Determine the most appropriate DAA regimen(s)
  - DAA regimen selection is based on HCV genotype, cirrhosis, compensation, and drug interactions (➜ *Appendix 1 and Appendix 2*).
  - Refer to AASLD HCV guidelines, DHHS antiretroviral guidelines, and manufacturers' prescribing information for specific drug interactions (➜ *References*).
- Obtain pretreatment labs within 90 days of starting treatment (➜ *Appendix 11*).
- Submit Nonformulary Request (NFR) for Hepatitis C Treatment Algorithm; if approved, submit NFR(s) for specific DAA medication(s) (➜ *Appendix 14*).
- Provide preventive health care for patients with cirrhosis.

STEP 5: Monitor patient during and after treatment.

- Start treatment with approved DAA regimen.
- Follow monitoring schedule described in *Appendix 11*.

2. SCREENING FOR HCV INFECTION

INMATE HISTORY AND PATIENT EDUCATION

A health history should be obtained from all newly incarcerated BOP inmates. In addition, these inmates should be provided with educational information regarding prevention and transmission, risk factors, testing, and medical management of HCV infection, in accordance with BOP policy. Health education efforts should make use of the BOP peer-oriented video on infectious diseases, *Staying Alive*, located in Section 5: A–Z Topics on the HSD Infection Control website, http://sallyport.bop.gov/co/hsd/infectious_disease/index.jsp#.

SCREENING CRITERIA

Testing for HCV infection is recommended for (a) all sentenced inmates, (b) all inmates with certain clinical conditions, and (c) all inmates who request testing.

a. RISK FACTORS FOR SENTENCED INMATES

An OPT OUT strategy of voluntary testing for HCV infection at the prevention baseline visit is recommended for all sentenced inmates. An "opt out" approach involves an informed refusal of testing, rather than informed consent (or "opt in") for testing. After informing a patient of the indications and plan for testing, the particular test is ordered and performed—unless the patient declines it. Testing is considered voluntary in that it is good clinical practice, but is not required by policy or law.

The AASLD, CDC, and USPSTF recommend risk factor-based and birth cohort screening for HCV infection. The incarcerated population is reported to have higher prevalence rates of HCV than the general population and is identified by the AASLD and USPSTF as a risk factor for which screening is recommended.

Other well-described risk factors, which should be considered when recommending HCV testing to sentenced inmates, include:

- Ever injected illegal drugs or shared equipment (including intranasal use of illicit drugs)
- Received tattoos or body piercings while in jail or prison, or from any unregulated source
- HIV or chronic hepatitis B virus (HBV) infection
- Received a blood transfusion or an organ transplant before 1992, or received clotting factor transfusion prior to 1987
- History of percutaneous exposure to blood
- Ever received hemodialysis
- Born to a mother who had HCV infection at the time of delivery
- Born between 1945 and 1965

b. CLINICAL CONDITIONS FOR ANY INMATE

HCV testing is recommended for all inmates with the following clinical conditions, regardless of sentencing status:

- A reported history of HCV infection without prior medical records to confirm the diagnosis

- Chronic hemodialysis – screen alanine aminotransferase (ALT) monthly and anti-HCV semiannually
- Elevated ALT levels of unknown etiology
- Evidence of extrahepatic manifestations of HCV – mixed cryoglobulinemia, membranoproliferative glomerulonephritis, porphyria cutanea tarda, vasculitis

SCREENING METHOD

The preferred screening test for HCV infection is an immunoassay that measures the presence of antibodies to HCV antigens, referred to as *HCV Ab* or *anti-HCV*. The presence of these antibodies only indicates a history of exposure to the HCV virus, but does not distinguish between active and resolved infection.

SCREENING OF NONSENTENCED INMATES

Unless clinically indicated (see the ***clinical conditions*** listed under *Screening Criteria* above), screening should ordinarily not be pursued for asymptomatic, highly mobile, nonsentenced inmates. Referrals to community HCV testing sites should be made when appropriate.

➔ **EXCEPTION:** *Long-term inmates in BOP detention facilities should be screened for HCV infection in accordance with the guidelines for sentenced inmates.*

REFUSAL OF TESTING

Sentenced inmates who decline testing at the baseline visit, should be counseled about and offered HCV testing during periodic preventive health visits.

➔ *A treatment refusal form is recommended for every testing and treatment refusal.*

3. INITIAL EVALUATION OF ANTI-HCV POSITIVE INMATES

Initial evaluation of anti-HCV positive inmates includes **(a)** a baseline history and physical examination, **(b)** lab tests, and **(c)** calculation of the APRI score to determine fibrosis. The inmate should also be evaluated to assess the need for **(d)** preventive health interventions such as vaccines and screenings for other conditions, as well as counseled with **(e)** information on HCV infection.

Determining whether the patient meets BOP priority criteria for treatment is an important part of the initial evaluation of anti-HCV positive inmates:

➔ *If cirrhosis is present, see Section 4, Assess for Hepatic Cirrhosis and Decompensation, to determine whether the liver disease is compensated or decompensated.*

➔ *Section 5, BOP Priority Criteria for Treatment, lists the clinical scenarios that will be used in the BOP to prioritize inmates for treatment.*

BASELINE EVALUATION

A baseline clinician evaluation should be conducted for all inmates who are anti-HCV positive. At minimum, this evaluation should include the following elements:

a. TARGETED HISTORY AND PHYSICAL EXAMINATION:

- Evaluate for signs and symptoms of liver disease, quantify prior alcohol consumption, and determine risk behaviors for acquiring HCV infection (see the section on risk factors under *Screening Criteria* above). Attempt to estimate the earliest possible date of infection, including when risk factors for exposures started and stopped, e.g., the time period in which the inmate engaged in injection drug use.
- Evaluate for other possible causes of liver disease, especially alcoholism, nonalcoholic steatohepatitis (NASH), iron overload, and autoimmune hepatitis.
- Inquire about prior treatment for HCV infection, specific medications used, dosages and duration of treatment, and outcomes, if known.

b. LABORATORY TESTS:

Recommended baseline laboratory tests are listed in *Appendix 11* and include the following:

- Complete blood count (CBC); prothrombin time (PT) with International Normalization Ratio (INR); liver panel (albumin, total and direct bilirubin, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and alkaline phosphatase); serum creatinine; and calculated glomerular filtration rate (GFR).
  - ➔ *Unexplained abnormalities should prompt additional diagnostic evaluations, as clinically indicated, to determine the underlying cause, e.g., low hemoglobin/platelet count or GFR.*
- Hepatitis B serology (HBsAg, anti-HBs, and anti-HBc) and HIV antibody (anti-HIV or HIV Ab).
  - ➔ *Refer to the relevant BOP Clincal Guidance for management of a positive HBsAg or HIV Ab test.*
- Quantitative HCV RNA viral load testing, sensitive to $\leq$ 25 IU/ml, with reflex testing for HCV genotype, to determine if the inmate has active HCV infection and identify the HCV genotype.
  - ➔ *Undetectable levels of HCV RNA indicate resolved infection or a false positive HCV Ab test.*
- Unless otherwise clinically indicated, testing for other causes of liver disease—e.g., antinuclear antibody (ANA), ferritin, iron saturation, ceruloplasmin—are not routinely ordered in the evaluation of a positive HCV Ab test.
- A urine drug screen is not required as part of the baseline evaluation, and is recommended only if ongoing substance use is suspected or if it is otherwise clinically indicated.

c. CALCULATION OF THE AST TO PLATELET RATIO INDEX (APRI) TO ASSESS THE DEGREE OF FIBROSIS:

- The APRI score, a calculation based on results from two blood tests—the AST (aspartate aminotransferase) and the platelet count— is a less invasive and less expensive means of assessing fibrosis than a liver biopsy.
- The formula for calculating the APRI score is [(AST/AST ULN) x 100] / platelet count (10^9/L).
  - ➔ *A calculator is available at: http://www.hepatitisc.uw.edu/page/clinical-calculators/apri*
- If a person is known to have cirrhosis, the APRI is irrelevant and unnecessary.

d. PREVENTIVE HEALTH MEASURES:

All inmates who are anti-HCV positive should be evaluated to assess the need for the preventive health interventions, including the following:

- **Hepatitis B vaccine:** Indicated for susceptible inmates with chronic HCV infection. For foreign-born inmates, consider prescreening for hepatitis B immunity prior to vaccination.
  - *Inmates with evidence of liver disease should be priority candidates for hepatitis B vaccination.*
- **Hepatitis A vaccine:** Indicated for susceptible inmates with chronic HCV. For foreign-born inmates, consider prescreening for hepatitis A immunity prior to vaccination.
- **Influenza vaccine:** Offer to all HCV-infected inmates annually.
  - *Inmates with cirrhosis are high priority for influenza vaccine.*

e. PATIENT EDUCATION:

Inmates diagnosed with chronic HCV infection should be counseled by a health care provider regarding the natural history of the infection, potential treatment options, and specific measures to prevent transmitting HCV infection to others (both during incarceration and upon release).

4. ASSESS FOR HEPATIC CIRRHOSIS AND DECOMPENSATION

Cirrhosis is a condition of chronic liver disease marked by inflammation, degeneration of hepatocytes, and replacement with fibrotic scar tissue. The natural history of HCV is such that 50–80% of HCV infections become chronic. Progression of chronic HCV infection to fibrosis and cirrhosis may take years in some patients and decades in others—or, in some cases, may not occur at all. Most complications from HCV infection occur in people with cirrhosis.

- Patients with advanced hepatic fibrosis (primarily stage 3) have a 10% per year rate of progressing to cirrhosis (stage 4).
- Those with cirrhosis have a 4% per year rate of developing decompensated cirrhosis, and a 3% per year rate of developing hepatocellular carcinoma.

The Child-Turcotte-Pugh (CTP) score is a useful tool in determining the severity of cirrhosis and in distinguishing between compensated and decompensated liver disease. See the discussion below under Assessing Hepatic Compensation.

ASSESSING FOR HEPATIC CIRRHOSIS

Assessing for cirrhosis is important for prioritizing inmates for treatment of HCV and in determining the need for additional health care interventions. Cirrhosis may be diagnosed in several ways:

- **Symptoms and signs that support the diagnosis of cirrhosis may include:** Low albumin or platelets, elevated bilirubin or INR, ascites, esophageal varices, and hepatic encephalopathy. However, isolated lab abnormalities may require additional diagnostic evaluation to determine the etiology.

- **The APRI score is the BOP-preferred method for non-invasive assessment of hepatic fibrosis and cirrhosis:**
  - **An APRI score ≥ 2.0 may be used to predict the presence of cirrhosis.** At this cutoff, the APRI score has a sensitivity of 48%, but a specificity of 94%, for predicting cirrhosis. Inmates with an APRI score ≥ 2.0 should have an abdominal ultrasound performed to identify other findings consistent with cirrhosis (see *abdominal imaging studies* below in this list). Lower APRI scores have different sensitivities and specificities for cirrhosis. For example, an APRI score ≥ 1 has a sensitivity of 77% and a specificity of 75% for predicting cirrhosis.
    - ➔ *An APRI score is not necessary for diagnosing cirrhosis if cirrhosis has been diagnosed by other means.*
  - **The APRI may also be used to predict the presence of significant fibrosis (stages 2 to 4, out of 4).** Using a cutoff of ≥ 1.5, the sensitivity is 37% and specificity is 95% for significant fibrosis.
  - **The APRI score may be invalidated in cases of splenectomy.**
- **Liver biopsy is no longer required** unless otherwise clinically indicated. However, the presence of cirrhosis on a prior liver biopsy may be used to meet the BOP criteria for HCV treatment.
- **Abdominal imaging studies** such as ultrasound or CT scan may identify findings consistent with or suggestive of the following: ***cirrhosis*** (nodular contour of the liver), ***portal hypertension*** (ascites, splenomegaly, varices), or ***hepatocellular carcinoma*** (HCC). Abdominal ultrasound is routinely performed in cases of known or suspected cirrhosis, and as clinically indicated on a case-by-case basis.

ASSESSING HEPATIC COMPENSATION

Assessing hepatic compensation is important for determining the most appropriate HCV treatment regimen to be used. The recommended HCV treatment regimen may differ depending on whether the cirrhosis is compensated or decompensated.

The **CTP SCORE** is a useful tool to help determine the severity of cirrhosis and is used by the AASLD to distinguish between compensated and decompensated liver disease in patients with known or suspected cirrhosis. (See the table on the next page.)

➔ *CTP calculators are readily available on the Internet and are not reproduced in these guidelines: http://www.hepatitisc.uw.edu/page/clinical-calculators/ctp*

The CTP score includes five parameters (albumin, bilirubin, INR, ascites, and hepatic encephalopathy), each of which is given a score of 1, 2, or 3. The sum of the five scores is the CTP score, which is classified as shown in the table below (see also *Notes* that follow):

CTP SCORE	CTP CLASS	HEPATIC COMPENSATION
5–6	Class A	Compensated cirrhosis
7–9	Class B	Decompensated cirrhosis
≥ 10	Class C	

NOTES:

*A CTP score of **5** or **6** is considered to be compensated cirrhosis, while a score of **7** or greater is considered decompensated.*

- *Warfarin anticoagulation will invalidate CTP calculations if the INR is 1.7 or higher.*
- *It is recommended that cases of decompensated cirrhosis be managed in consultation with a clinician experienced in the treatment of this condition because the dosages of DAA medications are not well-established with severe hepatic impairment.*
- *Inmates with CTP Class C decompensated cirrhosis may have a reduced life expectancy and should be considered for Reduction In Sentence/Compassionate Release in accordance with current policy (PS 5050.49) and procedures.*

ADDITIONAL INTERVENTIONS FOR INMATES WITH CIRRHOSIS:

- **Pneumococcal vaccine:** Offer to all HCV-infected inmates with cirrhosis who are 19 through 64 years of age
  - *See the BOP Clinical Guidance on Preventive Health Care Screening*.
- **Hepatocellular carcinoma (HCC) screening:** Liver ultrasound is recommended every six months for patients with both cirrhosis *and* chronic HCV infection.
- **Esophageal varices screening:** Screening for esophageal and gastric varices with esophagogastroduodenoscopy (EGD) is recommended for patients diagnosed with cirrhosis.

Other healthcare interventions recommended for patients with cirrhosis may include:

- Nonselective beta blockers for prevention of variceal bleeding in patients with esophageal varices.
- Antibiotic prophylaxis if risk factors are present for spontaneous bacterial peritonitis.
- Optimized diuretic therapy for ascites.
- Lactulose and rifaximin therapy for encephalopathy.

In general, NSAIDs should be avoided in advanced liver disease/cirrhosis, and metformin should be avoided in decompensated cirrhosis. The detailed management of cirrhosis is beyond the scope of these guidelines. Other resources should be consulted for more specific recommendations related to this condition.

5. BOP PRIORITY CRITERIA FOR HCV TREATMENT

Determining whether BOP priority criteria for treatment are met is an important part of the initial evaluation and ongoing management of inmates with chronic HCV infection. Although all patients with chronic HCV infection may benefit from treatment, certain cases are at higher risk for complications or disease progression and require more urgent consideration for treatment. The BOP has established priority criteria to ensure that those with the greatest need are identified and treated first. The BOP Medical Director will provide periodic guidance on specific strategies for implementing these priority levels.

PRIORITY LEVEL 1 – HIGH PRIORITY FOR TREATMENT *

- **ADVANCED HEPATIC FIBROSIS**
  - APRI ≥ 2.0, ***OR***
  - Metavir or Batts/Ludwig stage 3 or 4 on liver biopsy, ***OR***
  - Known or suspected cirrhosis
- **LIVER TRANSPLANT RECIPIENTS**
- **HEPATOCELLULAR CARCINOMA (HCC)**
- **COMORBID MEDICAL CONDITIONS ASSOCIATED WITH HCV, INCLUDING:**
  - Cryoglobulinemia with renal disease or vasculitis
  - Certain types of lymphomas or hematologic malignancies
  - Porphyria cutanea tarda
- **IMMUNOSUPPRESSANT MEDICATION FOR A COMORBID MEDICAL CONDITION**
  - Some immusuppressant medications (e.g., certain chemotherapy agents and tumor necrosis factor inhibitors) may be needed to treat a comorbid medical condition, but are not recommended for use when infection is present. Although data are insufficient and current guidelines are inconsistent regarding treatment of HCV infection in this setting, such cases will be considered for prioritized treatment of HCV on an individual basis.
- **CONTINUITY OF CARE FOR THOSE ALREADY STARTED ON TREATMENT**, including inmates who are newly incarcerated in the BOP.

PRIORITY LEVEL 2 – INTERMEDIATE PRIORITY FOR TREATMENT *

- **EVIDENCE FOR PROGRESSIVE FIBROSIS**
  - APRI score ≥ 1.0
  - Stage 2 fibrosis on liver biopsy
- **COMORBID MEDICAL CONDITIONS** associated with more rapid progression of fibrosis
  - Coinfection with HBV or HIV
  - Comorbid liver diseases (e.g., autoimmune hepatitis, hemochromatosis, steatohepatitis)
  - Diabetes mellitus
- **CHRONIC KIDNEY DISEASE (CKD)** with GFR ≤ 59 mL/min per 1.73 m^2

PRIORITY LEVEL 3 – LOW PRIORITY FOR TREATMENT *

- Stage 0 to stage 1 fibrosis on liver biopsy
- APRI < 1
- All other cases of HCV infection meeting the eligibility critera for treatment, as noted below under *Other Criteria for Treatment*.

*** EXCEPTIONS to the above criteria for PRIORITY LEVELS 1–3 will be made on an individual basis and will be determined primarily by a compelling or urgent need for treatment, such as evidence for rapid progression of fibrosis, or deteriorating health status from other comorbidities.**

OTHER CRITERIA FOR TREATMENT

In addition to meeting the above criteria for Priority Levels 1–3, inmates being considered for treatment of HCV infection should:

- Have no contraindications to, or signicifant drug interactions with, any component of the treatment regimen.
- Not be pregnant, especially for any regimen that would require ribavirin or interferon.
- Have sufficient time remaining on their sentence in the BOP to complete a course of treatment.
  - *Inmates with high priority criteria (**PRIORITY LEVEL 1**), but insufficient time remaining in BOP custody, may be considered for treatment if they will have access to medications and health care providers for continuity of care at the time of release.*
- Have a life expectancy > 18 months.
- Demonstrate a willingness and an ability to adhere to a rigorous treatment regimen and to abstain from high-risk activities while incarcerated.
  - *Inmates with with evidence for ongoing high-risk behaviors, e.g., injection drug use, are considered for HCV treatment on an individual basis. Referral for evaluation and treatment of substance abuse is recommended.*

6. RECOMMENDED TREATMENT REGIMENS

Recommendations for preferred HCV treatment regimens continue to evolve, but still depend on several factors:

- **HCV GENOTYPE**
- **PRIOR HCV TREATMENT HISTORY**
- **COMPENSATED VS. DECOMPENSATED LIVER DISEASE**
- **DRUG-DRUG INTERACTIONS**

- **SPECIAL CONSIDERATIONS:** Certain conditions require special consideration when selecting an HCV treatment regimen, including decompensated cirrhosis, chronic kidney disease, solid organ transplant recipients, and pregnancy. These conditions are addressed in *Section 8*.
- **COST:** The cost of direct acting antiviral regimens can vary widely. When more than one regimen is appropriate for an individual case, the most cost-effective regimen is recommended, taking into consideration all the factors listed in the box above.

DIRECT ACTING ANTIVIRAL MEDICATIONS (DAAS)

As the name implies, these antiviral medications for HCV infection act directly on some part of the virus, usually the replication mechanism. Currently, there are three classes of HCV DAAs: polymerase inhibitors (-buvir), protease inhibitors (-previr), and NS5A replication complex inhibitors (-asvir).

- ***DAAs cannot be used as monotherapy; they must be used in combination with at least one other DAA or with ribavirin, and in some cases with peginterferon, depending on the clinical scenario.***
- ***The most commonly recommended regimens are briefly described below.*** *More detailed information about the regimens and the individual medications—including indications, contraindications, dosing and duration, and drug interactions—may be found in the Appendices*.

DACLATASVIR + SOFOSBUVIR

➔ *See Appendix 3 for more detailed information on daclatasvir. See Appendix 5 for more about sofosbuvir.*

- **USE:** Once-daily daclatasvir coadministered with 400 mg of sofosbuvir once daily, with or without food, is FDA-approved for the treatment of **HCV genotype 1 and 3**.
  - AASLD also recommends this combination as an option for treatment of **HCV genotype 2** in various clinical scenarios, and for **genotypes 4, 5, and 6 with decompensated cirrhosis**.
  - If there are no contraindications, ribavirin is added to the regimen in decompensated cirrhosis and in some HCV treatment-experienced cases.
- **DOSING:** The usual dose of daclatasivir is 60 mg once daily, with or without food.
  - Dosage adjustment is required with strong CYP3A inhibitors (30 mg once daily) and with moderate CYP3A inducers (90 mg once daily).
    - ➔ *Daclatasvir is contraindicated with strong CYP3A inducers (e.g., carbamazepine, phenytoin, and rimamycin antimycobacterials) and is not recommended with amiodarone*.
  - When coadministered with antiretrovirals for HIV infection: The dose of daclatasvir is decreased to 30 mg with indinavir, nelfinavir, saquinavir, ritonavir-boosted atazanavir, or any cobicistat-containing regimen except darunavir; the dose of daclatasvir is increased to 90 mg with efavirenz, etravirine, or nevirapine.
- **DURATION:** The usual duration of treatment is 12 weeks in patients with no cirrhosis,
  - Response rates are diminished in cirrhosis; the optimal duration for treatment of HCV with cirrhosis is not well-established, but AASLD recommends longer treatment durations of 16 to 24 weeks, depending on the clinical scenario.

ELBASVIR/GRAZOPREVIR (ZEPATIER™)

➔ *See Appendix 6 for more detailed information on elbasvir/grazoprevir. See Appendix 10 for information on ribavirin.*

- **FORMULATION/USE:** A coformulation of 50 mg of elbasvir (an HCV NS5A inhibitor) and 100 mg of grazoprevir (an HCV NS3 protease inhibitor) is FDA-approved for treatment of **HCV genotypes 1 and 4**.
  - ➔ *In HCV genotype 1a, NS5A resistance testing is recommended prior to treatment.*
- **DOSING AND DURATION:** The usual dose and duration is one tablet orally once daily, with or without food, for 12 weeks.
  - 16 weeks is recommended for **HCV genotype 1a** with baseline NS5A polymorphisms or for **HCV genotype 4** treatment-experienced with peginterferon + ribivarin.
  - Weight-based ribavirin is added to elbasvir/grazoprevir for: **HCV genotype 1a** with baseline NS5A polymorphisms; **HCV genotype 1a or 1b** treatment-experienced with PEG-peginterferon + ribivarin + HCV protease inhibitor; or **HCV genotype 4** treatment-experienced with peginterferon + ribivarin.
  - No dosage adjustment is required for decreased renal function or hemodialysis, although the ribavirin dose must be adjusted for GFR < 50.

- **CONTRAINDICATIONS AND USE NOT RECOMMENDED :**
  - Elbasvir/grazoprevir is contraindicated in decompensated cirrhosis (CTP score ≥ 7), or with certain medications.
  - Contraindicated medications include phenytoin, carbamazepine, rifampin, efavirenz, HIV protease inhibitors (atazanavir, darunavir, lopinavir, saquinavir, and tipranavir), and cyclosporine.
  - Elbasvir/grazoprevir is not recommended with moderate CYP3A inducers or with strong CYP3A inhibitors.

LEDIPASVIR/SOFOSBUVIR (HARVONI®)

➔ *See Appendix 7 for more detailed information on ledipasvir/sofosbuvir.*

- **FORMULATION/USE:** A coformulation of 90 mg of ledipasvir and 400 mg of sofosbuvir is FDA-approved for treatment of **HCV genotypes 1, 4, 5, and 6**; alone or in combination with ribavirin, without or with cirrhosis, compensated or decompensated.
- **DOSING:** The usual dose is one tablet orally once daily, with or without food, for 12 or 24 weeks, depending on the clinical scenario.
  - AASLD recommends only an 8-week course of treatment in a subgroup of HCV-infected persons who have genotype 1a or 1b, have an HCV viral load <6 million IU/ml, and are treatment-naïve—but who are not black, are not HIV-coinfected, and do not have cirrhosis.
- **USES NOT RECOMMENDED:**
  - Ledipasvir/sofosbuvir is not recommended for use with certain anticonvulsants (e.g., carbamazepine, phenytoin, phenobarbital, or oxcarbazepine), certain rifamycin antimycobacterials (e.g., rifabutin, rifampin, or rifapentine), or the antiarrhythmic, amiodarone.
  - The dose and safety of ledipasvir/sofosbuvir is unknown in severe renal impairment; it is not recommended by AASLD in CKD with GFR < 30 mL/min/1.73m^2.

PARITAPRAVIR/RITONAVIR/OMBITASVIR/DASABUVIR (VIEKIRA XR™)

➔ *See Appendix 8 for more detailed information.*

- **FORMULATION:** This treatment includes three tablets, each coformulated with 50 mg of paritaprevir, 33.33 mg of ritonavir, 8.33 mg of ombitasvir, and 200 mg tablets of dasabuvir.
- **USE:** This is an FDA-approved treatment of **HCV genotype 1**, alone (for genotype 1b) or in combination with ribavirin (for genotype 1a).
  - AASLD also recommends this as a treatment option for HCV genotype 1b with CKD and GFR <30 for whom urgent HCV treatment is needed.
- **DOSING/DURATION:** The usual dose is three tablets once daily with a meal. Duration of treatment is either 12 weeks for genotype 1a without cirrhosis, or genotype 1b with or without compensated cirrhosis; or 24 weeks for genotype 1a with compensated cirrhosis.
- **CONTRAINDICATION:** This treatment is contraindicated for use with decompensated cirrhosis.

SOFOSBUVIR/VELPATASVIR (EPCLUSA®)

➔ *See Appendix 9 for more detailed information.*

- **FORMULATION/USE:** A coformulation of 400 mg of sofosbuvir and 100 mg of velpatasvir is FDA-approved for treatment of **HCV genotypes 1, 2, 3, 4, 5, and 6**, with no cirrhosis or with compensated cirrhosis, or for decompensated cirrhosis in combination with ribavirin.
- **DOSING:** The usual dose is one tablet orally once daily, with or without food, for 12 weeks.
- **USES NOT RECOMMENDED:**
  - Sofosbuvir/velpatasvir is not recommended for use with certain anticonvulsants (e.g., carbamazepine, phenytoin, phenobarbital, or oxcarbazepine), certain rifamycin antimycobacterials (e.g., rifabutin, rifampin, or rifapentine), the antiarrhythmic amiodarone, certain antiretrovirals (efavirenz, or tipranavir/ritonavir), or proton pump inhibitors.
  - The dose and safety of sofosbuvir/velpatasvir is unknown in severe renal impairment; it is not recommended in CKD with GFR < 30 mL/min/1.73m^2.
- **CONTRAINDICATION:** If there are contraindicatons to ribavirin, it should not be used in combination with sofosbuvir/velpatasvir.

SOFOSBUVIR + SIMEPREVIR

➔ *See Appendix 5 for more about sofosbuvir. See Appendix 4 for more information on simprevir.*

- **DOSING/DURATION/USE:** Taken together once daily, 400 mg of sofosbuvir and 150 mg of simeprevir, for 12 weeks in patients with no cirrhosis.
  - When used as an alternative regimen to treat patients with compensated cirrhosis, the duration is extended to 24 weeks, with or without ribavirin.
  - This combination is FDA-approved for treatment of **HCV genotype 1**.
    - ➔ *When used for the treatment of HCV genotype 1a with cirrhosis, a test for HCV NS3 virologic resistance looking for the Q80K polymorphism must be obtained prior to treatment.*

PREFERRED TREATMENT REGIMENS

The **preferred treatment regimens** currently recommended by AASLD/IDSA/IAS-USA are included in this BOP guidance in the following appendices:

- *Appendix 1, Treatment Recommendations for HCV with Compensated Cirrhosis*
- *Appendix 2, Treatment Recommendations for HCV with No Cirrhosis*

➔ *Please refer to the AASLD/IDSA/IAS-USA website (www.hcvguidelines.org) for any updates since April 27, 2017.*

Alternative treatment regimens: The AASLD/IDSA/IAS-USA guidelines include recommendations for some regimens that are not specifically FDA-approved and also describe alternative treatment regimens for situations in which a preferred regimen is not an option. These alternative regimens are not included in this BOP guidance, but can be considered on a case-by-case basis.

POTENTIAL DRUG INTERACTIONS

In addition to the genotype, prior HCV treatment history, and status of hepatic compensation, as noted above, it is essential to review each treatment candidate for potential drug interactions prior to selecting the most appropriate regimen for HCV treatment. Adjustments of the inmate's current medications may be needed prior to starting treatment for HCV. Refer to the appendices at the end of this document for specific drug interactions. Other useful resources for potential drug interactions include the AASLD/IDSA guidelines, the individual manufacturers' prescribing information, and the DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.

REGIMENS NOT RECOMMENDED

Regimens that are not recommended for use include the following:

- Monotherapy with peginterferon, ribavirin, or any of the DAAs.
- Dual therapy with peginterferon and ribavirin, except when urgent HCV treatment is needed for genotypes 2, 3, 5, or 6, with GFR < 30.
  - ➔ *See discussion of chronic kidney disease in Section 8.*
- Triple therapy with peginterferon, ribavirin, and the HCV protease inhibitors boceprevir, simeprevir, or telaprevir.
- HCV protease inhibitors for genotype 2, 3, 5, or 6 (paritaprevir, simeprevir).

7. MONITORING

➔ *See Appendix 11, Hepatitis C Treatment Monitoring Schedule, for a summary chart of the monitoring recommendations.*

PRETREATMENT ASSESSMENT

Pretreatment assessment should be accomplished within* three months *of the projected start of treatment, and should include the following:

- **Laboratory tests** including CBC, PT/INR, liver panel, serum creatinine, calculated GFR.
  - ➔ *Obtain quatitative HCV RNA viral load and HCV genotype if the most recent results are more than one year old or if not previously performed.*
  - ➔ *When elbasvir/grazoprevir is likely to be used to treat inmates with HCV genotype 1a,* an *NS5A resistance test is recommended as part of the pretreatment lab assessment if there is no decompensated cirrhosis, HIV coinfection, or contraindication for use of elbasvir/grazoprevir.*
  - ➔ *A urine drug screen is not required as part of the pretreatment evaluation, and is recommended only if ongoing substance use is suspected or if it is otherwise clinically indicated.*
- **Calculation of the APRI score** using results from the pretreatment labs. (An APRI score is not needed if there is confirmed cirrhosis.)
- **Calculation of current CTP score** for inmates with known or suspected cirrhosis.
- **Assessment for significant drug-drug interactions.**
- **Assessment for current/prior medication adherence.**

- **Review of incident report history** for high-risk behaviors (alcohol/drug possession/use; tattooing).
- **For ribavirin-containing regimens:** In addition to the above, a pretreatment ECG is recommended for inmates with preexisting coronary heart disease.
- **For interferon-containing regimens:** In addition to the above, pretreatment evaluation should include a WBC with differential, TSH/free T4. Such regimens should also include a mental health evaluation.

Testing for resistance-associated substitutions (RASs) is recommended prior to treatment with the following regimens or situations:

- **Elbasvir/grazoprevir for HCV genotype 1a** (obtain an NS5 resistance assay looking for variants at amino acid positions 28, 30, 31, and 93).
- **Simeprevir + sofosbuvir for HCV genotype 1a with cirrhosis** (obtain NS3 resistance assay, looking for Q80K polymorphism).
- **Treatment failures with simeprevir + sofosbuvir or with regimens containing an NS5 inhibitor** (obtain NS3 and NS5 resistance assays).
- **Peginterferon+ribivarin treatment-experienced HCV genotype 3 without cirrhosis** (obtain NS5A resistance assay).

Prior to starting treatment for HCV infection, PATIENT EDUCATION is recommended—including, but not limited to, how to take the medication, the importance of adherence, monitoring and follow up, and potential medication side effects. When ribavirin is used, specific counseling about the risks and recommendations related to pregnancy should be provided.

ON-TREATMENT MONITORING

On-treatment monitoring should include the following:

- **An outpatient clinic visit at 2 weeks and at 4 weeks** after starting therapy, and monthly thereafter; more frequently as clinically indicated.
- **Labs drawn at 4 weeks** after the start of therapy should include CBC, creatinine, calculated GFR, liver panel, and quantitative HCV viral load sensitive to ≤ 25 IU/ml; others as clinically indicated.
  - **For regimens containing interferon and/or ribavirin:** A CBC should also be drawn 2 weeks after starting therapy, then at 4 weeks, then monthly; more frequently as clinically indicated. Interferon and/or ribavirin dosage adjustments may be required.
    ➔ *See Appendix 12, Management of Hematologic Changes.*
  - **More frequent monitoring of ALT is necessary in certain situations:**
    - **Regimens containing elbasvir/grazoprevir:** An ALT should be drawn at 4 weeks and again at 8 weeks, and as clinically indicated. For 16-week regimens, an ALT should also be drawn at 12 weeks.
    - **Patients with compensated cirrhosis** who are treated with paritaprevir/ritonavir/ ombitasvir, with or without dasabuvir, require more frequent monitoring of ALT.
    - **Increases in the ALT should prompt more frequent monitoring or early discontinuation.** Asymptomatic ALT increases of less than tenfold should be monitored approximately

every 2 weeks. Early discontinuation of HCV treatment is recommended if ALT increases by tenfold—or if less than tenfold , but accompanied by *symptoms* such as weakness, anorexia, nausea, vomiting, or change in stool color, or *signs* including elevations in conjugated bilirubin, alkaline phosphatase, and INR, related to hepatic dysfunction.

- **If the quantitative HCV viral load is detectable after 4 weeks of treatment**, it should be repeated 2 weeks later. Early discontinuation of HCV treatment is recommended only if there is > 1 log increase from the nadir in HCV viral load after 6 weeks or more of treatment.
  - *HCV viral load testing is no longer required at the end of treatment, but should be obtained in all cases that failed to achieve undetectable levels during treatment.*

- **A test for thyroid stimulating hormone (TSH)** is recommended every 12 weeks only for patients receiving regimens containing interferon. For a 12-week regimen, a TSH should be drawn at the end of treatment, in addition to the pretreatment baseline.
- **Pregnancy testing is required prior to treatment with ribavirin-containing regimens**, and then periodically during and after treatment—usually monthly during treatment and for 6 months after completion of treatment.
- **Monitoring of interferon and/or ribavirin-containing regimens** has not changed and is included in *Appendix 11, Hepatitis C Treatment Monitoring Schedule*.
- **Testing for HCV drug-resistant mutations is not routinely recommended at this time.**

POST-TREATMENT MONITORING

- A quantitative HCV RNA viral load assessment is recommended at 12 weeks after completion of treatment; if HCV is undetectable, it defines a sustained virologic response (SVR).
- If the HCV viral load is again undetectable at 6 to 12 months after the end of treatment, the inmate may be removed from the chronic care clinic, so long as he or she has no cirrhosis, complications, or related comorbidities.

Recurrent viremia following an SVR may be due to relapse or reinfection. To help distinguish between the two in such cases, an HCV genotype, along with subtyping for genotype 1, should be obtained.

ONGOING MONITORING

Periodic monitoring is recommended for all those with active infection, including acute HCV infection, HCV treatment failures, relapse of HCV infection or reinfection, and those with chronic HCV infection who are not yet treated.

- **For cases without advanced fibrosis, cirrhosis, or complications**, annual evaluation is appropriate. This evaluation should include a focused review of systems and patient education relevant to HCV, vital signs and a focused physical examination, and lab monitoring (CBC, PT/INR, liver panel, serum creatinine, calculated GFR, and calculation of the APRI score).
- **For patients with cirrhosis or significant comorbidities**, evaluation is recommended at least every six months; more frequently as clinically indicated.

(ONGOING MONITORING continues on next page.)

- **In cases of acute HCV infection**, monitoring for spontaneous clearance of the infection with ALT and quantitative HCV RNA levels every four to eight weeks, for six to twelve months, is recommended. If viremia persists after that time, continue to monitor and manage the case as a chronic infection.

  In most cases of acute HCV infection, treatment may be deferred to allow for spontaneous clearance of viremia. However, in some cases there may be a compelling reason to treat the acute infection in order to prevent severe complications, e.g., HCV infection superimposed on established cirrhosis or advanced fibrosis.

8. SPECIAL CONSIDERATIONS

HCV INFECTION WITH MORE THAN ONE GENOTYPE

Very little data are available to guide the selection of an appropriate regimen when more than one HCV genotype are present at the same time. Until data on effective regimens become available, postponing therapy is reasonable in such cases unless the clinical scenario requires prompt treatment. If treatment is necessary and cannot be safely deferred, a regimen should be selected—in consultation with a BOP Hepatitis Clinical Pharmacy Consultant or Central Office Physician—that is effective against both of the existing genotypes, if possible.

HBV COINFECTION

In patients coinfected with HBV and HCV, HBV reactivation may occur during or after treatment with HCV DAAs. Testing for HBV infection—including HBsAg, anti-HBs, and anti-HBc, as well as HBV DNA levels in those with a reactive HBsAg—is recommended for all patients being considered for treatment of HCV infection.

- **If criteria for treatment of HBV are met**, it is recommended that HBV treatment be started prior to or at the same time as HCV treatment, and monitored according to HBV treatment guidance.
- **If criteria for treatment of HBV infection are NOT met**, monitoring of HBV DNA every four weeks during HCV treatment is recommended.

HIV COINFECTION

In general, HCV medication regimens are the same for HIV coinfected patients as for HIV-negative patients. Data indicate that currently recommended HCV regimens are equally effective for HCV mono-infection and coinfection with HIV. However, an alternative HCV regimen or an alternative antiretroviral medication regimen may be necessary due to potential drug interactions between the HCV DAAs and certain antiretrovirals.

- **DACLATASVIR** doses are decreased to 30 mg daily when coadministered with indinavir, nelfinavir, saquinavir, or ritonavir-boosted atazanavir, or with any cobicistat-containing regimens except darunavir. Daclatasvir doses are increased to 90 mg daily when coadministered with efavirenz, etravirine, or nevirapine.
- **ELBASVIR/GRAZOPREVIR** is not recommended for use with efavirenz or etravirine, any of the HIV protease inhibitors, or elvitegravir boosted with cobicistat.

- **LEDIPASVIR/SOFOSBUVIR** may be used with all antiretrovirals except didanosine, zidovudine, tipranavir, or elvitegravir/cobicistat/tenofovir/emtricitabine.
- **PARITAPREVIR/RITONAVIR/OMBITASVIR/DASABUVIR** may be used with all antiretrovirals except efavirenz, rilpivirine, darunavir + ritonavir, or lopinavir/ritonavir.
  - When used with atazanavir, the atazanvir dose is 300 mg once daily; there is no additional boosting with ritonavir.
  - To avoid inducing resistance to HIV-1 protease inhibitors, any HCV/HIV-1 co-infected patients treated with paritaprevir/ritonavir/ombitasvir + dasabuvir should also be on a suppressive antiretroviral drug regimen.
- **SIMEPREVIR** may be used only with abacavir, tenofovir, emtricitabine, lamivudine, rilpivirine, raltegravir (or dolutegravir), maraviroc, and enfuvirtide.
- **SOFOSBUVIR** may be used with all antiretrovirals except didanosine, zidovudine, or tipranavir.
- **VELPATASVIR/SOFOSBUVIR** is not recommended with efavirenz or tipranavir+ritonavir, and must be used with caution when coadministered with tenofovir disoproxyl fumarate.

DECOMPENSATED CIRRHOSIS

Treatment of HCV patients with decompensated cirrhosis should be managed in consultation with an experienced clinician/specialist, with treatment requests considered on a case-by-case basis. HCV treatment recommendations for patients with decompensated cirrhosis apply regardless of eligibility for a liver transplant or the presence of hepatocellular carcinoma. The regimens and other considerations are listed below.

- **HCV GENOTYPE 1, 4, 5, OR 6 WITH DECOMPENSATED CIRRHOSIS:**

  → *See note about the use of ribavirin with this group, following the lists of regimens.*

  The treatment options for HCV genotype 1, 4, 5, or 6 with decompensated cirrhosis, either treatment-naïve or treatment-experienced with peginterferon+ribivarin, are as follows:

  - Ledipasvir/sofosbuvir + low initial dose ribavirin for 12 weeks (or ledipasvir/sofosbuvir for 24 weeks in ribavirin-ineligible cases)
  - Daclatasvir + sofosbuvir + low initial dose ribavirin for 12 weeks (or daclatasvir + sofosbuvir for 24 weeks in ribavirin-ineligible cases)
  - Sofosbuvir/velpatasvir + ribavirin for 12 weeks (or sofosbuvir/velpatasvir for 24 weeks in ribavirin-ineligible cases)

  For cases with a history of treatment failure using a sofosbuvir-based regimen, one of the following two regimens are recommended:

  - Ledipasvir/sofosbuvir + low initial dose ribavirin for 24 weeks.
  - Sofosbuvir/velpatasvir + ribavirin for 24 weeks.

  For cases with a history of treatment failure with a regimen containing an NS5A inhibitor, the following regimen is recommended:

  - Sofosbuvir/velpatasvir + ribavirin for 24 weeks.

*(**DECOMPENSATED CIRRHOSIS** continues on next page.)*

Use of ribavirin for genotypes 1, 4, 5, and 6 with decompensated cirrhosis, in ribavirin-eligible cases*:*

- **When used with ledipasvir/sofosbuvir *or* daclatasvir + sofosbuvir**, the initial dose of ribavirin should be a total daily dose of 600 mg in divided doses twice daily, increasing to a full weight-based regimen as tolerated.
- **For use with sofosbuvir/velpatasvir**, AASLD indicates that a full weight-based ribavirin dose may be started in cases with CTP Class B decompensated cirrhosis, while the low initial dose (described in the above bullet) is used in cases with CTP Class C.

- **HCV GENOTYPE 2 OR 3 WITH DECOMPENSATED CIRRHOSIS:**

The two recommended regimens include:

- Once-daily daclatasvir + once-daily sofosbuvir + low initial dose of ribavirin for 12 weeks
- Once-daily sofosbuvir/velpatasvir + low initial dose of ribavirin for 12 weeks

→ *Ribavirin dosage adjustments may be required for inmates with low GFR or hemoglobin levels.*

- **CONTRAINDICATIONS FOR CTP CLASSES B AND C:**

- Elbasvir/grazoprevir is contraindicated in decompensated cirrhosis with CTP scores ≥ 7 (class B or C).
- Interferon-containing regimens are contraindicated in decompensated cirrhosis.
- The use of paritaprevir/ritonavir/ombitasvir/dasabuvir is contraindicated with severe hepatic impairment (CTP class C) and is not recommended in CTP class B.
- Simeprevir is not recommended for use in decompensated cirrhosis with CTP class B or C.

LIVER TRANSPLANT RECIPIENTS

- **HCV GENOTYPE 1 OR 4 IN LIVER TRANSPLANT RECIPIENTS**

Recommended regimens for HCV genotype 1 or 4 in liver transplant recipients with ongoing or recurrent HCV infection and compensated liver disease, who are either treatment-naïve or treatment-experienced, include two options: **(1)** a ledipasvir/sofosbuvir-based regimen or **(2)** a daclatasvir + sofosbuvir-based regimen—both with or without twice-daily low initial dose ribavirin.

These two options are as follows:

- **Ledipasvir/sofosbuvir once daily + weight based ribavirin twice daily for 12 weeks**
  - Ledipasvir/sofosbuvir for 24 weeks in treatment-naïve patients who are ribavirin-ineligible.
  - Ledipasvir/sofosbuvir once daily + low initial dose ribavirin twice daily for 12 weeks for treatment-naïve or treatment-experienced patient with decompensated cirrhosis.
- **Once-daily daclatasvir + sofosbuvir + low initial dose of ribavirin (twice daily) for 12 weeks**
  - Once-daily daclatasvir + sofosbuvir for 24 weeks in treatment-naïve patients who are ribavirin-ineligible.

→ *Alternative regimens are described in the AASLD guidelines.*

- **HCV GENOTYPE 2 OR 3 IN LIVER TRANSPLANT RECIPIENTS**

  Recommended regimens for HCV genotype 2 or 3 in liver transplant recipients with ongoing HCV infection and compensated liver disease, who are either treatment-naïve or treatment-experienced, include: **(1)** once-daily daclatasvir + sofosbuvir with or without ribavirin or **(2)** sofosbuvir + ribavirin.

  These two options are as follows:

  - **Once-daily daclatasvir + sofosbuvir + low initial dose of ribavirin (twice daily) for 12 weeks**
    - Once-daily daclatasvir + sofosbuvir for 24 weeks in treatment-naïve patients who are ribavirin-ineligible.
  - **Once-daily sofosbuvir + low initial dose ribavirin twice daily for 24 weeks—recommended regimen for genotype 2 only**
    - For genotype 2 with decompensated cirrhosis, once-daily sofosbuvir + low initial dose ribavirin for 24 weeks is a recommended regimen.

CHRONIC KIDNEY DISEASE (CKD)

No dosage adjustment is required for any of the current DAAs when the GFR is ≥ 30. For cases being considered for renal transplantation, consultation with the transplant consultant is recommended regarding timing of HCV treatment relative to transplantation.

- **For patients with CKD and HCV genotype 1 or 4** without cirrhosis or with compensated cirrhosis, treatment-naïve or -experienced, elbasvir/grazoprevir once daily for 12 weeks is a preferred DAA regimen. No dosage adjustments are required. Paritaprevir/ritonavir/ombitasvir + dasabuvir is also an AASLD-recommended treatment option for HCV genotype 1b with CKD and GFR <30.
  - *See discussion of elbasvir/grazoprevir in Section 6, as well as Appendix 6 for specific dosing and duration information.*
  - *See discussion of paritaprevir/ritonavir/ombitasvir/dasabuvir in Section 6, as well as Appendix 8 for specific dosing and duration information.*
- **For patients with GFR < 30 and HCV genotypes 2, 3, 5, or 6** without cirrhosis, for whom renal transplantation is not imminent, but for whom there is an urgent need to treat the HCV infection, peginterferon + low-dose ribavirin may be considered.
- **Ribavirin doses must be decreased with GFRs ≤50.** For GFRs 30–50, ribavirin is dosed 200 mg alternating every other day with 400 mg. For GFR <30, including hemodialysis, the ribavirin dose is 200 mg daily.

PREGNANCY

Data are limited on the reproductive and fetal effects of HCV DAAs in humans. The FDA lists the current HCV DAAs as Pregnancy Category B (i.e., no evidence of risk), based on studies using animal reproduction models. Current guidelines do not address the use of DAAs for treatment of HCV in pregnancy.

Ribavirin (Pregnancy Category X) and is contraindicated. Although interferon is Pregnancy Category C (i.e., risk cannot be ruled out), it is usually combined with ribavirin, which is contraindicated.

- Women of childbearing potential who are being considered for an HCV regimen that includes ribavirin should be counseled on the adverse fetal effects of ribavirin. They should be advised not to become pregnant during treatment with ribavirin *and* for six months after the treatment has ended. They should also be advised that the same risks apply if a male sex partner is being treated with ribavirin.
  - *A negative pregnancy test should be documented prior to starting treatment with ribavirin, monthly during treatment, and for six months after treatment.*
- Men being treated with ribavirin should also be counseled on the adverse fetal effects of ribavirin. They should be advised not to cause pregnancy in their female sex partners during treatment with ribavirin *and* for six months after the treatment has ended.

REFERENCES

AASLD/IDSA/IAS-USA. Recommendations for testing, managing, and treating hepatitis C. *http://www.hcvguidelines.org/*. Updated April 27, 2017. Accessed May 2017.

➔ *Please refer to the AASLD/IDSA/IAS-USA website (www.hcvguidelines.org) for any updates since* April 27, 2017*.*

Note about the website: *To provide healthcare professionals with timely guidance as new therapies are available and integrated into HCV regimens, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA, in collaboration with the International Antiviral Society–USA (IAS–USA), have developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C management.*

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. *https://aidsinfo.nih.gov/guidelines*. Updated July 14, 2016. Accessed October 2016

GLOSSARY OF ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
ALT	alanine aminotransferase
ANA	antinuclear antibody
APRI	AST to Platelet Ratio Index
AST	aspartate aminotransferase
CBC	complete blood count
CTP score	Child-Turcotte-Pugh score
DAA	direct acting antiviral medication
DCV	daclatasvir
EGD	esophagogastroduodenoscopy
EBR	elbasvir
GFR	glomerular filtration rate
GZR	grazoprevir
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV Ab or anti-HIV	HIV antibody
IAS–USA	International Antiviral Society–USA
IDSA	Infectious Diseases Society of America
INR	International Normalization Ratio
LDV	ledipasvir
NASH	nonalcoholic steatohepatitis
PEG-IFN	pegylated interferon, peginterferon
PI	protease inhibitor
PrO	paritaprevir/ritonavir/ombitasvir
PrOD	paritaprevir/ritonavir/ombitasvir/dasabuvir
PT	prothrombin time
RAS	resistance-associated substitution
RBV	ribavirin
SOF	sofosbuvir
SMV	simprevir
SVR	sustained virologic response
TSH	thyroid stimulating hormone
ULN	upper limit of normal
VEL	velpatasvir

APPENDIX 1. TREATMENT RECOMMENDATIONS FOR HCV W/ COMPENSATED CIRRHOSIS[A,B,C,D]

CONDITION	TREATMENT OPTIONS BY HCV GENOTYPE[E]				
	1a[F,G]	1b[G]	2	3	4[F]
Treatment-Naïve	▸ **EBR/GZR:** 12 wks ▸ **LDV/SOF:** 12 wks ▸ **SOF/VEL:** 12 wks	▸ **EBR/GZR:** 12 wks ▸ **LDV/SOF:** 12 wks ▸ **PrOD:** 12 wks ▸ **SOF/VEL:** 12 wks	▸ **SOF/VEL:** 12 wks	▸ **DCV + SOF +/- RBV:** 24 wks ▸ **SOF/VEL:** 12 wks	▸ **EBR/GZR**: 12 wks ▸ **LDV/SOF:** 12 wks ▸ **PrO + RBV:** 12 wks ▸ **SOF/VEL:** 12 wks
Treatment-Experienced w/ PEG-IFN + RBV[F]	▸ **EBR/GZR:** 12 wks ▸ **LDV/SOF + RBV:** 12 wks ▸ **SOF/VEL:** 12 wks	▸ **EBR/GZR:** 12 wks ▸ **LDV/SOF + RBV:** 12 wks ▸ **PrOD:** 12 wks ▸ **SOF/VEL:** 12 wks	▸ **SOF/VEL:** 12 wks	▸ **SOF/VEL+ RBV:** 12 wks ▸ **EBR/GZR + SOF:** 12 weeks	▸ **EBR/GZR:** 12 wks ▸ **LDV/SOF + RBV:** 12 wks ▸ **PrO+RBV:** 12 wks ▸ **SOF/VEL:** 12 wks
Treatment-Experienced w/ PI + PEG-IFN + RBV	▸ **DCV + SOF +/- RBV:** 24 wks ▸ **EBR/GZR + RBV:** 12 wks ▸ **LDV/SOF:** 24 wks ▸ **LDV/SOF + RBV:** 12 wks ▸ **SOF/VEL:** 12 wks		NA	NA	NA
Treatment-Experienced w/ SOF + RBV (+/- PEG-IFN in genotype 1)	▸ **LDV/SOF +RBV:** 24 wks		▸ **SOF/VEL + RBV:** 12 wks ▸ **DCV + SOF +/- RBV:** 24 wks	▸ **SOF/VEL + RBV:** 12 wks ▸ **DCV + SOF + RBV:** 24 wks	NA

NOTES:

A. All regimens in this appendix are identified as *Recommended* in the AASLD guidelines. Alternative regimens may be appropriate in some cases, but are not included in this table. Some AASLD recommended regimens are not FDA-approved, but are based on available evidence.

B. Choice of regimen is determined by HCV genotype, treatment history, and presence of cirrhosis; it is also influenced by potential drug interactions and cost.

C. Compensated cirrhosis = **CTP class A (CTP score ≤6)**. (See *Section 4, Assess for Hepatic Cirrhosis and Decompensation*.)

Decompensated cirrhosis = **CTP Class B or C (CTP score ≥7).** Manage in consultation w/ specialist. Treatment requests considered on a case-by-case basis. (See discussion of decompensated cirrhosis under *Section 8, Special Considerations*.)

D. Recommendations in this table may not be appropriate in decompensated cirrhosis, chronic kidney disease with GFR < 30, or liver transplant recipients. Refer to the specific sections in this guidance for treatment of HCV in these settings.

E. Genotypes 5 and 6, with or without cirrhosis: LDV/SOF or SOF/VEL once daily for 12 weeks is recommended for treatment-naïve patients or patients who previously failed treatment with PEG-IFN + RBV.

F. EBR/GZR alone is NOT to be used in the following cases (treatment with EBR/GZR + RBV for a duration of 16 weeks may be considered)**:**

- **Genotype 1a with certain NS5A RASs:** A regimen of EBR/GZR alone is recommended only for cases with no RASs on NS5A resistance testing. HCV virologic resistance testing is required prior to treatment. Refer to the AASLD guideline on monitoring for the specific substitutions associated with resistance.
- **Genotype 4** patients with prior on-treatment failure with PEG-IFN + RBV.

G. Genotype 1 (a or b) with cirrhosis and treatment-experienced with SMV+SOF or an NS5A inhibitor. Treatment decisions are based on results of NS3/4A and NS5A resistance tests.

MEDICATIONS:

DCV = daclatasvir; ***EBR/GZR***=elbasvir/grazoprevir; ***LDV/SOF*** = ledipasvir/sofosbuvir (Harvoni ®);
PEG-IFN = pegylated interferon (peginterferon); ***PI*** = protease inhibitor (boceprevir, telaprevir, simeprevir);
PrO = paritaprevir/ritonavir/ombitasvir; ***PrOD*** = paritapravir/ritonavir/ ombitasvir/dasabuvir (Viekira XR™);
RBV = ribavirin; ***SMV*** = simprevir; ***SOF*** = sofosbuvir; ***SOF/VEL*** = sofosbuvir/velpatasvir (Epclusa®)

➜ See *Appendices 3–10* for more specific information on each medication.

APPENDIX 2. TREATMENT RECOMMENDATIONS FOR HCV WITH NO CIRRHOSIS[A,B,C,D]

CONDITION	TREATMENT OPTIONS BY HCV GENOTYPE[E]				
	1a[F,G,H]	1b[G,H]	2	3[I]	4[F]
Treatment- Naïve OR Treatment-Experienced w/ PEG-IFN + RBV	▸ **DCV + SOF:** 12 wks ▸ **EBR/GZR:** 12 wks ▸ **LDV/SOF:** 12 wks ▸ **PrOD + RBV:** 12 wks ▸ **SOF + SMV:** 12 wks ▸ **SOF/VEL:** 12 wks	▸ **DCV + SOF:** 12 wks ▸ **EBR/GZR:** 12 wks ▸ **LDV/SOF:** 12 wks ▸ **PrOD:** 12 wks ▸ **SOF + SMV:** 12 wks ▸ **SOF/VEL:** 12 wks	▸ **SOF/VEL:** 12 wks	▸ **DCV + SOF:** 12 wks ▸ **SOF/VEL:** 12 wks	▸ **EBR/GZR:** 12 wks ▸ **LDV/SOF:** 12 wks ▸ **PrO + RBV:** 12 wks ▸ **SOF/VEL:** 12 wks
Treatment Experienced w/ PI + PEG-IFN + RBV	▸ **DCV + SOF:** 12 wks ▸ **EBR/GZR + RBV:** 12 wks ▸ **LDV/SOF:**12 wks ▸ **SOF/VEL:** 12 wks		NA	NA	NA
Treatment-Experienced w/ SOF +RBV (+/- PEG-IFN in genotype 1)	▸ **LDV/SOF + RBV:** 12 wks		▸ **DCV + SOF +/- RBV:** 24 wks ▸ **SOF/VEL:** 12 wks	▸ **SOF/VEL+RBV:** 12 wks ▸ **DCV + SOF + RBV:** 24 wks	NA

NOTES:

A. **All regimens in this appendix are identified as *Recommended* in the AASLD guidelines.** Alternative regimens may be appropriate in some cases, but are not included in this table. Some AASLD recommended regimens are not FDA-approved, but are based on available evidence.

B. **Choice of regimen** is determined by HCV genotype, treatment history, and presence of cirrhosis; it is also influenced by potential drug interactions and cost.

C. **Compensated cirrhosis** = **CTP class A (CTP score ≤6)**. (See *Section 4, Assess for Hepatic Cirrhosis and Decompensation*.)

Decompensated cirrhosis = **CTP Class B or C (CTP score ≥7).** Manage in consultation w/ specialist. Treatment requests considered on a case-by-case basis. (See discussion of decompensated cirrhosis under *Section 8, Special Considerations*.)

D. **Recommendations in this table may not be appropriate in decompensated cirrhosis, chronic kidney disease with GFR < 30, or liver transplant recipients.** Refer to the specific sections in this CPG for treatment of HCV in these settings.

E. **Genotypes 5 and 6, with or without cirrhosis:** LDV/SOF or SOF/VEL once daily for 12 weeks is recommended for treatment-naïve patients or patients who previously failed treatment with PEG-IFN + RBV.

F. **EBR/GZR alone is NOT to be used in the following cases** (treatment with EBR/GZR + RBV for a duration of 16 weeks may be considered)**:**

- **Genotype 1a with certain NS5A RASs.** A regimen of EBR/GZR alone is recommended only for cases with no RASs on NS5A resistance testing. HCV virologic resistance testing is required prior to treatment. Refer to the AASLD guideline on monitoring for the specific substitutions associated with resistance.
- **Genotype 4** patients with prior on-treatment failure with PEG-IFN + RBV.

G. **Genotypes 1a and 1b:** Unless there is an urgency to treat, deferral of treatment is recommended for genotype 1 treatment failures with SMV + SOF, or NS5A-containing regimens.

H. **An 8-week regimen with LDV/SOF** is AASLD-recommended for persons infected with HCV genotype 1a or 1b, who have an HCV viral load <6 million IU/ml and are treatment-naïve—but who are not black or HIV-coinfected, and do not have cirrhosis.

I. **NS5A resistance testing** is recommended for PEG-IFN + RBV treatment-experienced genotype 3 without cirrhosis. If the Y93H RAS is present, the addition of weight-based RBV to a regimen of either DCV + SOF or SOF/VEL is recommended.

MEDICATIONS:

DCV = daclatasvir; ***EBR/GZR***=elbasvir/grazoprevir; ***LDV/SOF*** = ledipasvir/sofosbuvir (Harvoni ®);
PEG-IFN = pegylated interferon (peginterferon); ***PI*** = protease inhibitor (boceprevir, telaprevir, simeprevir);
PrO = paritaprevir/ritonavir/ombitasvir; ***PrOD*** = paritapravir/ritonavir/ ombitasvir/dasabuvir (Viekira XR™);
RBV = ribavirin; ***SMV*** = simprevir; ***SOF*** = sofosbuvir; ***SOF/VEL*** = sofosbuvir/velpatasvir (Epclusa®)

→ See *Appendices 3–10* for more specific information on each medication.

APPENDIX 3. NS5A INHIBITOR DRUG INFORMATION: DACLATASVIR

DACLATASVIR (DAKLINZA™) DRUG INFORMATION

DESCRIPTION

- Daclatasvir is an oral direct-acting antiviral (DAA) agent against the Hepatitis C virus. Daclatasvir is an inhibitor of the HCV NS5A protein, which is required for viral replication.
- Daclatasvir is indicated for use with sofosbuvir for the treatment of chronic HCV genotype 1 or genotype 3 infection. AASLD includes in their recommended regimens, daclatasvir + sofosbuvir for treatment-naïve HCV genotype 2 infection who cannot tolerate ribavirin (RBV).

➔ ***Daclatasvir should not be used alone as monotherapy for hepatitis C.***

Limitations of Use: Sustained virologic response (SVR) rates are reduced in patients with cirrhosis.

FORMULATIONS

Daclatasvir is manufactured as 30 mg and 60 mg tablets that are packaged in 28-count bottles.

STANDARD DOSING

The recommended dose for daclatasvir is 60 mg taken by mouth once daily, with or without food, in combination with sofosbuvir. Take a missed dose as soon as it is realized, but do not take more than one tablet daily. Daclatasvir should not be used alone as monotherapy for hepatitis C and is used in combination with sofosbuvir as described below. If sofosbuvir is permanently discontinued in a patient receiving daclatasvir in combination with sofosbuvir, then daclatasvir should also be discontinued.

➔ *Refer to Appendix 5 for dosing of sofosbuvir, and Appendix 10 for dosing of ribavirin.*

➔ ***Total treatment duration** is as specified below and is NOT guided by on-treatment HCV RNA response. The optimal duration of daclatasvir and sofosbuvir for patients with cirrhosis has not been established.*

HCV GENOTYPE 1 TREATMENT REGIMENS:

- **For treatment-naïve or treatment-experienced with PEG-IFN + RBV:**
  Without cirrhosis or with compensated cirrhosis = DCV + SOF for 12 weeks
  With decompensated cirrhosis or post-transplant = DCV+ SOF + RBV for 12 weeks
- **For prior treatment failures with PEG-IFN + RBV + PI:**
  Without cirrhosis = DCV + SOF for 12 weeks
  With cirrhosis or post-transplant = DCV + SOF +/- RBV for 24 weeks

HCV GENOTYPE 2 TREATMENT REGIMENS:

- **For treatment-naïve (those who cannot tolerate RBV):**
  Without cirrhosis = Daclatasvir + SOF for 12 weeks
  Cirrhosis = Daclatasvir + SOF for 24 weeks
  Coinfection with HIV = same as listed above for monoinfection
- **For prior treatment failures on SOF + RBV (and PEG-IFN-ineligible):**
  With or without cirrhosis = Daclatasvir + SOF +/- RBV for 24 weeks

HCV GENOTYPE 3 TREATMENT REGIMENS:

- **For treatment-naïve:**
  Without cirrhosis = Daclatasvir + SOF for 12 weeks
  Cirrhosis = Daclatasvir + SOF +/- weight based RBV for 24 weeks
  Coinfection with HIV = same as listed above for monoinfection
- **For prior treatment failures with PEG-IFN + RBV:**
  Without cirrhosis = Daclatasvir + SOF for 12 weeks
  Cirrhosis (and are IFN-ineligible) = Daclatasvir + SOF + weight based RBV for 24 weeks
  Coinfection with HIV = same as listed above for monoinfection
- **For prior treatment failures with SOF + RBV:**
  With or without cirrhosis = Daclatasvir + SOF +/- RBV for 24 weeks

DOSING IN CERTAIN CLINICAL CIRCUMSTANCES

Renal or hepatic impairment: There is no dose modification for toxicity or renal/hepatic insufficiency. Treatment with daclatasvir in decompensated cirrhosis or liver transplant may differ from compensated liver disease and should be managed in consultation with an experienced clinician or consultant.

DACLATASVIR (DAKLINZA™) DRUG INFORMATION

CONTRAINDICATIONS

- Any hypersensitivity to daclatasvir or a component thereof.
- When daclatasvir is administered with sofosbuvir and/or ribavirin, then contraindications to sofosbuvir and/or ribavirin also apply.
- Daclatasvir is contraindicated in patients with moderate or severe hepatic impairment (CTP B or C) due to the expected significantly increased grazoprevir plasma concentration and the increased risk of ALT elevations.
- Daclatasvir is contraindicated with strong inducers of CYP 3A, which could lower exposure to and potentially lead to loss of efficacy of daclatasvir
- Concomitant usage with:
  - Anticonvulsants (carbamazepine, phenytoin)
  - Antimycobacterial (rifampin)
  - Herbal products (St. John's Wort)

NOT RECOMMENDED

The following medications are not recommended with the co-administration of daclatasvir:

- Antiarrhythmic (amiodarone); co-administration of amiodarone with daclatasvir and sofosbuvir may result in serious symptomatic bradycardia; if coadmininstration is required, cardiac monitoring is recommended.
- Anticoagulant (dabigatran); not recommended in specific renal impairment groups, depending on the indication. Please see dabigatran prescribing information for specific recommendations

USE WITH CAUTION

- ***Dacatasvir is a substrate of CYP3A.*** Co-administration of DCV with moderate CYP3A inducers or strong CYP3A inhibitors should be used with caution; recommended dosage modification of daclatasvir with CYP3A inducers and inhibitors is listed below.
- ***Daclatasvir inhibits breast cancer resistance protein (BCRP), OATP1B1/3, and P-glycoprotein (P-gp) transporters.*** Coadministration of daclatasvir with drugs that are substrates for BCRP, OATP1B1/3, and P-gp transport may result in increased plasma concentrations of such drugs.
- ***The following medications may pose a risk for potential interaction with daclatasvir that may require close monitoring, alteration of drug dosage, or timing of administration:***
  - ***Strong CYP3A inhibitors and certain HIV medications: DCV dose should be reduced to 30 mg once daily.***
  - HIV protease inhibitors: Atazanavir with ritonavir, indinavir, nelfinavir, saquinavir
  - HIV cobicistat-containing regimens: Atazanavir/cobicistat, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumurate
  - Antifungals: Itraconazole, ketoconazole, posaconazole, voriconazole
  - Antibacterials: Clarithromycin, telithromycin
  - Antidepressant: Nefazodone
  - ***Moderate CYP3A inducers and certain HIV medications: DCV dose should be increased to 90 mg once daily.***
  - HIV Non-nucleoside reverse transcriptase inhibitors (NNRTIs): Efavirenz, etravirine, nevirapine
  - Antibacterial: Nafcillin
  - Antidepressant: Modafinil
  - Antihypertensive: Bosentan
  - Antimycobacterial: Rifapentine
  - Steroids: Dexamethasone
  - ***Antiarrhythmic: Digoxin***
    - **Patients already receiving digoxin prior to initiating DCV** should measure serum digoxin concentrations before initiating DCV; reduce digoxin concentration by decreasing digoxin dosage by approximately 15% to 30% or by modifying the dosing frequency and continue monitoring
    - **Patients already receiving DCV initiating digoxin** should initiate with lowest appropriate digoxin dose and monitor digoxin concentrations; adjust digoxin dose if necessary and continue monitoring digoxin
  - ***HMG-CoA reductase inhibitors:*** **Monitor for HMG-CoA reductase inhibitor associated adverse events such as myopathy.** Includes atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin
  - ***Bupenorphine or buprenorphine/naloxone:*** **Clinical monitoring for buprenorphine associated adverse events is recommended.**

DACLATASVIR (DAKLINZA™) DRUG INFORMATION

MOST COMMON SIDE EFFECTS

- ***Flu-like symptoms:*** Fatigue and headache
- ***Gastrointestinal effects:*** Nausea
- ***Hematologic effects:*** Anemia (those on ribavirin containing regimens)

LAB ABNORMALITIES

- ***Hyperbilirubinemia:*** Bilirubin elevations of greater than 2.5 times the upper limit of normal (ULN).
- ***ALT elevations***: Transient, asymptomatic ALT elevations of >5x ULN in those with cirrhosis. Watch for warning signs of liver inflammation such as fatigue, weakness, lack of appetite, nausea and vomiting, jaundice, and discolored feces.

Appendix 3—*page 3 of 3*

APPENDIX 4. HCV PROTEASE INHIBITOR DRUG INFORMATION: SIMEPREVIR

SIMEPREVIR (OLYSIO™) DRUG INFORMATION

DESCRIPTION

Simeprevir is an oral direct-acting antiviral (DAA) agent against the hepatitis C virus. Simeprevir is an inhibitor of the HCV NS3/4A protease, which is essential for viral replication. Simeprevir is indicated for the treatment of chronic HCV genotype 1 monoinfection as a component of a combination antiviral treatment regimen. In addition to this FDA-approved indication, the AASLD-IDSA guidance also recommends use of simeprevir as part of an alternative regimen for HCV treatment in the setting of HIV co-infection or ineligibility for peginterferon.

- ***Simeprevir should not be used alone as monotherapy.***
- ***Screening patients with HCV genotype 1a infection for the presence of virus with the NS3 Q80K polymorphism at baseline is strongly recommended.*** Alternative therapy should be considered for patients infected with HCV genotype 1a containing the Q80K polymorphism.

FORMULATIONS

Simeprevir is manufactured as a 150 mg strength hard gelatin capsule that is packaged into 28-count bottles.

STANDARD DOSING

DOSING:

The dose for simeprevir is one 150 mg capsule taken orally once daily with food. The type of food does not affect exposure to simeprevir. The capsule should be swallowed whole. For a missed dose within 12 hours of the usual dosing time, the patient should take the missed dose of simeprevir with food as soon as possible. If missed dose is > 12 hours past usual dosing time, skip that missed dose and resume usual dosing of simeprevir with food at the regularly scheduled time.

- ***Patients of East Asian ancestry exhibit higher simeprevir exposures.*** *In clinical trials, higher simeprevir exposures have been associated with increased frequency of adverse reactions, including rash and photosensitivity. There are insufficient safety data to recommend an appropriate dose for patients of East Asian ancestry. The risks and benefits of simeprevir should be carefully considered prior to use in patients of East Asian ancestry.*

DURATION:

Recommended treatment duration for HCV genotype 1 (treatment-naïve or treatment-experienced):

- **Without cirrhosis:** Simeprevir with sofosbuvir for 12 weeks
- **With cirrhosis:** Simeprevir with sofosbuvir for 24 weeks

Notes:

- Treatment-experienced patients include those who failed prior interferon-based therapy.
- For dosage instructions for other antiviral drugs used in combination with simeprevir, see their respective appendices in these guidelines.
- Although simeprevir is approved for treatment of HCV genotype 1 with both peginterferon alfa and ribavirin, it has a limited role in current treatment guidance. ***For patients prescribed this regimen, consultation with an experienced clinician is recommended.***

SIMEPREVIR (OLYSIO™) DRUG INFORMATION

DOSING IN CERTAIN CLINICAL CIRCUMSTANCES

Renal or Hepatic Impairment:

- There is no dose modification for toxicity or renal/hepatic insufficiency.
- Although the safety and efficacy of simeprevir have not been studied in HCV-infected patients with a GFR < 30, renal elimination is minimal and no dosage adjustment is required for renal impairment. Simeprevir should not be used in patients on hemodialysis.
- Safety and efficacy of simeprevir have not been studied in HCV-infected patients with moderate or severe hepatic impairment. The combination of peginterferon and ribavirin is contraindicated in patients with moderate or severe hepatic impairment. Potential risks and benefits of simeprevir should be carefully considered prior to use in patients with moderate or severe haptic impairment.

CONTRAINDICATIONS

- Any hypersensitivity to simeprevir or a component thereof.
- All contraindications to peginterferon alfa and ribavirin, since simeprevir must be administered with peginterferon and ribavirin.
- Pregnant women and men whose female partners are pregnant, because ribavirin may cause birth defects and/or fetal death
- Concomitant usage with:
  - *Anticonvulsant* (carbamazepine, oxcarbazepine, phenobarbital, phenytoin)
  - *Antibiotics* (erythromycin, clarithromycin, telithromycin)
  - *Antifungals* (itraconazole, ketoconazole, posaconazole, fluconazole, voriconazole)
  - *Antimycobacterials* (rifampin, rifabutin, rifapentine)
  - *Corticosteroids* (systemic dexamethasone)
  - *Cyclosporine* (increased simeprevir concentrations)
  - Gastrointestinal products (cisapride)
  - *Herbal products* (milk thistle, St. John's Wort)
  - *HIV products* (all HIV protease inhibitors, boosted or unboosted; any cobicistatc-containing regimen; and the following NNRTIs: efavirenz, delavirdine, etravirine, and nevirapine)

NOT RECOMMENDED

- Coadministration of amiodarone is not recommended. Serious symptomatic bradycardia, as well as fatal cardiac arrest and cases requiring pacemaker intervention have been reported when sofosbuvir in combination with another DAA, including simeprevir, is coadministred with amiodarone.
- Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease, may be at increased risk for symptomatic bradycardia. If coadministration is necessary, counseling on bradycardia risk and cardiac monitoring is recommended.

SIMEPREVIR (OLYSIO™) DRUG INFORMATION

USE WITH CAUTION

Simeprevir mildly inhibits CYP1A2 activity and intestinal cytochrome P450 3A (CYP3A4) activity, but does not affect hepatic CYP3A4 activity. Coadministration of simeprevir with drugs that are primarily metabolized by CYP3A4 may result in increased plasma concentrations of such drugs. Coadministration of simeprevir with substances that are moderate or strong inducers or inhibitors of CYP3A is not recommended, as this may lead to significantly lower or higher exposure to simeprevir.

Simeprevir inhibits OATP1B1/3 and P-glycoprotein (P-gp) transporters. Coadministration of simeprevir with drugs that are substrates for OATP1B1/3 and P-gp transport may result in increased plasma concentrations of such drugs.

The following medications may pose a risk for potential interaction with simeprevir that may require close monitoring. *However, except those medications noted with an asterisk (*), they do not require alteration of drug dosage, or timing of administration. (See the* ***NOTES*** *that follow the list.):*

- ***Antiarrhythmics*** (amiodarone, digoxin, disopyramide, flecainide, mexiletine, propafenone, quinidine)
- ***Anticoagulant*** (warfarin)
- ***Calcium Channel Blockers*** (amlodipine, diltiazem, felodipine, nicardipine, nifedipine, nisoldipine, verapamil)
- ***HMG Co-A Reductase Inhibitors**** (atorvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin)
- ***Immunosuppressants*** (cyclosporine, sirolimus, tacrolimus)
- ***Phosphodiesterase Type 5 (PDE-5) Inhibitors**** (sildenafil, tadalafil, vardenafil)
- ***Sedatives/Anxiolytics*** (oral midazolam or triazolam)

*** NOTES:**

The interaction between simeprevir and these medications was evaluated in clinical trials. The following dose adjustment of HMG Co-A reductase inhibitors and PDE-5 inhibitors may be necessary:

- *Atorvastatin:* Use the lowest necessary dose of atorvastatin (do not exceed 40 mg).
- *Rosuvastatin:* Initiate rosuvastatin therapy with 5 mg once daily; do not exceed 10 mg daily.
- *Simvastatin:* Titrate simvastatin dose carefully and use the lowest necessary dose of simvastatin and monitor for safety when co-administering with simeprevir.
- *Lovastatin, pitavastatin, and pravastatin:* Concomitant use of simeprevir with these statins has not been studied. Titrate statin dose carefully and use the lowest necessary dose of statin while monitoring for safety.
- *PDE-5 Inhibitors:* When used to treat chronic pulmonary arterial hypertension, consider starting with the lowest dose of PDE-5 inhibitor and increase as needed, with clinical monitoring as appropriate. No dose adjustment is necessary if using PDE-5 for erectile dysfunction.

SIMEPREVIR (OLYSIO™) DRUG INFORMATION

SIDE EFFECTS

- ***Dermatologic effects:***
  - *Photosensitivity:* Serious photosensitivity reactions have been observed during combination therapy with simeprevir, peginterferon alfa, and ribavirin. Photosensitivity may present as an exaggerated sunburn reaction, usually affecting areas exposed to light. Manifestations may include burning, erythema, exudation, blistering, and edema. Use sun protection measures and limit sun exposure. Consider discontinuation if a photosensitivity reaction occurs.
  - *Rash:* Rash occurs most frequently in the first 4 weeks of treatment with a simeprevir-based regimen, but can occur at any time during treatment. Most rashes are mild to moderate and should be followed for possible progression of rash, including the development of mucosal signs (e.g., oral lesions, conjunctivitis) or systemic symptoms. If the rash becomes severe, discontinue simeprevir. Patients should be monitored until the rash has resolved.
  - Pruritus
- ***Gastrointestinal effects:*** Nausea
- ***Musculoskeletal effects:*** Myalgia
- ***Pulmonary effects:*** Dyspnea
- ***Other effects:***
  - *Hyperbilirubinemia:* Elevations in bilirubin were predominately mild to moderate in severity, and included elevation of both direct and indirect bilirubin. Elevations in bilirubin occurred early after treatment initiation, peaking by treatment week 2, and were rapidly reversible upon cessation of simeprevir. Bilirubin elevations were generally not associated with elevations in liver transaminases.

APPENDIX 5. HCV POLYMERASE INHIBITOR DRUG INFORMATION: SOFOSBUVIR

SOFOSBUVIR (SOVALDI™) DRUG INFORMATION

DESCRIPTION

Sofosbuvir is an oral direct-acting antiviral (DAA) agent against the hepatitis C virus (HCV). Sofosbuvir is a prodrug that is metabolized to a nucleotide analogue inhibitor of the HCV NS5B RNA-dependent RNA polymerase. Sofosbuvir is indicated as one component of a combination antiviral regimen for the treatment of HCV monoinfection or coinfection with HIV.

➔ ***Sofosbuvir should not be used alone as monotherapy for hepatitis C.***

FORMULATIONS

Sofosbuvir is manufactured as a 400 mg oral film-coated tablet that is packaged in 28-count bottles.

STANDARD DOSING

The dose for sofosbuvir is 400 mg once daily with or without food. Patients should take a missed dose as soon as it is realized, but should not take more than 1 tablet daily. Sofosbuvir does not have a snack or fat content requirement.

Sofosbuvir is recommended by the AASLD for use in combination with daclatasvir or simeprevir, or coformulated with either ledipasvir or velpatasvir. Although sofosbuvir is FDA-approved for use in combination with ribavirin, with or without pegylated interferon, these regimens are no longer identified as preferred regimens by the AASLD. Refer to *Appendix 1*, *Appendix 2*, and *Section 8, Special Considerations*, for the preferred regimens for each clinical scenario.

DOSING IN CERTAIN CLINICAL CIRCUMSTANCES

Renal or Hepatic Impairment: There is no dose modification for toxicity or renal/hepatic insufficiency. Sofosbuvir should not be used in patients with GFRs less than 30 mL/min. Treatment with sofosbuvir in decompensated cirrhosis or liver transplant may differ from compensated liver disease and should be managed in consultation with an experienced clinician or consultant.

CONTRAINDICATIONS

- Any hypersensitivity to sofosbuvir or a component thereof.
- All contraindications to peginterferon alfa and ribavirin when those medications are part of the HCV treatment regimen.
- Ribavirin causes birth defects and is contraindicated in pregnant women and men whose female partners are pregnant.
- Use of HIV medications didanosine, zidovudine, and tipranavir.
- Concomitant usage with modafinil, oxcarbazepine, rifabutin, rifampin, rifapentine, or St. John's Wort.

NOT RECOMMENDED

Coadministration of amiodarone with sofosbuvir in combination with another direct acting antiviral (DAA) is not recommended. Symptomatic bradycardia, as well as fatal cardiac arrest and cases requiring pacemaker intervention have been observed when sofosbuvir is taken in combination with another DAA and amiodarone—particularly in patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease. If amiodarone must be used in combination with sofosbuvir and another DAA, cardiac monitoring is recommended .

SOFOSBUVIR (SOVALDI™) DRUG INFORMATION

USE WITH CAUTION

Sofosbuvir is a substrate of permeability glycoprotein (P-gp) drug transporter and breast cancer resistance protein (BCRP). ***The following medications may pose a risk for potential interaction with sofosbuvir that may require close monitoring, alteration of drug dosage, or timing of administration:***

- ***Antiepileptics*** (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone
- ***Antifungals*** (itraconazole, ketoconazole)
- ***Antihypertensives*** (carvedilol, nicardipine, prazosin, propranolol, verapamil)
- ***Biologics*** (crizotinib, lapatinib, gefitinib, nilotinib, sunitinib, vandetanib, vemurafenib)
- ***HIV drugs*** (darunavir, ritonavir*, saquinavir, lopinavir, nelfinavir, tenofovir)
- ***Immunosuppressants*** (dexamethasone, doxorubicin, cyclosporine*, tacrolimus*, vinblastine)
- ***Other drugs and foods*** (amiodarone, atorvastatin, clarithromycin, cobicistat, dipyridamole, dronedarone, eltrombopag, erythromycin, grapefruit juice, ivacaftor, lomitapide, mefloquine, nefazodone, progesterone, quinidine, quinine, ranolazine, reserpine, tamoxifen, ulipristal)

* *The interaction between sofosbuvir and the medication marked above with an asterisk (*) was evaluated in clinical trials and no adjustment of either drug should be necessary.*

SIDE EFFECTS

- ***Dermatologic effects:*** Pruritus
- ***Flu-like symptoms*****:** Fatigue and headache
- **Gastrointestinal effects:** Nausea, decreased appetite, and diarrhea
- ***Hematologic effects:***
  - ***Anemia:*** The addition of sofosbuvir to peginterferon alfa and ribavirin (PEG-IFN/RBV) is associated with an additional decrease in hemoglobin concentrations.
  - ***Neutropenia:*** The addition of sofosbuvir to PEG-IFN/RBV is associated with an additional decrease in neutrophil counts. Decreases in neutrophil counts may require dose reduction or discontinuation of PEG-IFN/RBV. No dose adjustment should be made to sofosbuvir. If RBV is discontinued, sofosbuvir should be discontinued and not restarted.

Appendix 5—*page 2 of 2*

APPENDIX 6. HCV NS5A INHIBITOR/HCV NS3/4A PROTEASE INHIBITOR DRUG INFORMATION: ELBASVIR/GRAZOPREVIR

ELBASVIR/GRAZOPREVIR (ZEPATIER®) DRUG INFORMATION (2 PAGES)

DESCRIPTION

Elbasvir/Grazoprevir (EBR/GZR) are oral direct-acting antiviral (DAA) agents indicated for the treatment of chronic HCV genotype 1 and genotype 4 infection. Elbasvir is an inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly. Grazoprevir is a HCV NS3/4A protease inhibitor.

FORMULATIONS

Elbasvir/Grazoprevir is manufactured as a fixed-dose combination (50 mg elbasvir/100 mg grazoprevir), oral film-coated, oval-shaped single tablet, packaged into a carton with two 14-count blister packs (total of 28 tablets).

STANDARD DOSING

The dose for elbasvir/grazoprevir is one 50 mg/100 mg tablet once daily with or without food. Patients should take a missed dose as soon as it is realized, but not take more than 1 tablet daily. Elbasvir/grazoprevir can be used alone as monotherapy, or in conjunction with ribavirin, for HCV genotypes 1 and 4 infection, as described below.

➔ *Refer to Appendix 10 for ribavirin dosing information.*

HCV-1 and HCV-4 treatment regimens with or without cirrhosis:

Treatment-naïve HCV-4 *OR* HCV-1b *OR* HCV-1a★ *without* baseline NS5A polymorphisms:
- EBR/GZR for 12 weeks

Treatment-experienced (to PEG-IFN/RBV) HCV-1b *OR* HCV-1a★ *without* baseline NS5A polymorphisms:
- EBR/GZR for 12 weeks

Treatment-experienced (to PEG-IFN/RBV/HCV protease inhibitor) HCV-1a★ *OR* HCV-1b:
- EBR/GZR + ribavirin for 12 weeks

HCV-1a★ *with* baseline NS5A polymorphisms:
- EBR/GZR + ribavirin for 16 weeks

Treatment-experienced (to PEG-IFN/RBV) HCV-4:
- EBR/GZR + ribavirin for 16 weeks

★ ***NS5A resistance testing in HCV -1a patients prior to the initiation of therapy*** is recommended to determine appropriate dosage regimen and duration. Those HCV-1a patients with NS5A resistance-associated polymorphisms should receive a longer duration (16 weeks) of treatment with a regimen that includes ribavirin. Clinical studies have shown that those HCV-1a with NS5A polymorphisms had a lower sustained virologic response (SVR12) with only 12 weeks of treatment without ribavirin than those with no baseline NS5A resistance.

Total treatment duration is as specified above and is not guided by on-treatment HCV RNA response. Treatment regimen and duration do not differ between HCV mono-infection and HIV/HCV co-infection.

DOSING IN CERTAIN CLINICAL CIRCUMSTANCES/USE IN SPECIFIC POPULATIONS

Renal Impairment: There is no dosage adjustment required for patients with any degree of renal impairment, including those on hemodialysis. For those on EBR/GZR with ribavirin regimens, refer to ribavirin prescribing information for the correct ribavirin dosage for patients with a CrCl ≤ 50mL/min.

Hepatic Impairment: No dose adjustment required for patients with mild hepatic impairment (CTP class A). Elbasvir/grasoprevir is contraindicated in patients with moderate or severe hepatic impairment (CTP B or C) due to the expected significantly increased grazoprevir plasma concentration and the increased risk of ALT elevations. Safety and efficacy of EBR/GZR has not been established in patients awaiting liver transplant or in liver transplant recipients.

Pregnancy: (Category B) There are no adequate and well-controlled studies with EBR/GZR in pregnant women. Because animal reproduction studies are not always predictive of human response, EBR/GZR should be used during pregnancy only if potential benefit outweighs potential risk to the fetus. (See more discussion under *Pregnancy* in *Section 8*.)

Nursing Mothers: It is not known whether EBR/GZR and its metabolites are present in human breast milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EBR/GZR and any potential adverse effects on the breastfed child from the drug or from underlying maternal condition.

ELBASVIR/GRAZOPREVIR (ZEPATIER®) DRUG INFORMATION (2 PAGES)

CONTRAINDICATIONS

- Any hypersensitivity to elbasvir or grasoprevir or a component thereof.
- If Elbasvir/grazoprevir is administered with ribavirin, then contraindications to ribavirin also apply.
- Elbasvir/grasoprevir is contraindicated in patients with moderate or severe hepatic impairment (CTP B or C) due to the expected significantly increased grazoprevir plasma concentration and the increased risk of ALT elevations.
- Elbasvir/grazoprevir is contraindicated with organic anion transporting polypeptides 1B1/3 (OATP1B1/3) inhibitors and strong inducers of CYP 3A.
- Concomitant usage with:
  - *Anticonvulsant:* carbamazepine, phenytoin
  - *Antimycobacterials*: rifampin
  - *Immunosuppressant*: cyclosporine
  - *Herbal products*: St. John's Wort
  - *HIV medications (Protease Inhibitors:* atazanavir, darunavir, lopinavir, saquinavir, and tipranavir; *NNRTI:* efavirenz)

NOT RECOMMENDED

Elbasvir and grazoprevir are substrates of CYP3A and P-gp(to a lesser extent). Co-administration of EBR/GZR with moderate CYP3A inducers or strong CYP3A inhibitors is not recommended. Specifically, the following medications are not recommended with the co-administration of elbasvir/grazoprevir:

- *Antibiotic:* nafcillin
- *Antifungal*: ketoconazole
- *Endothelian antagonist:* bosentan
- *HIV medications*: etravirine, or any cobicistat based regimens to include elvitegravir/cobicistat/emtricitabine/tenofovir(TDF or TAF).
- *Wakefulness-promoting agent:* modafinil

USE WITH CAUTION

The following medications may pose a risk for potential interaction with elbasvir/grasoprevir that may require close monitoring, alteration of drug dosage, or timing of administration:

- ***HMG-CoA Reductase Inhibitors:*** Co-administration of EBR/GZR with statins may increase the concentration of the statin. The lowest necessary dose should be used when co-administered with EBR/GZR. Statin-associated adverse events such as myopathy should be closely monitored.
  - *Atorvastatin:* Do not exceed daily dose of 20 mg atorvastatin.
  - *Rosuvastatin:* Do not exceed a daily dose of 10 mg rosuvastatin.
  - *Fluvastatin, lovastatin, simvastatin:* Lowest necessary dose should be used; monitor for statin-associated adverse events.
- ***Tacrolimus*:** Therapeutic concentration of *tacrolimus* should be monitored, as EBR/GZR can cause increase in concentration of tacrolimus. Frequent monitoring of renal function and tacrolimus-associated adverse events is recommended.

SIDE EFFECTS

- ***Flu-like symptoms:*** Fatigue, headache, and insomnia
- ***Gastrointestinal effects:*** Nausea and diarrhea

LAB ABNORMALITIES

- ***Hyperbilirubinemia:*** Bilirubin elevations of greater than 2.5 times the upper limit of normal (ULN).
- ***ALT elevations:*** Late (at or after treatment week 8), transient, asymptomatic ALT elevations of >5x ULN. Watch for warning signs of liver inflammation such as fatigue, weakness, lack of appetite, nausea and vomiting, jaundice and discolored feces.
- ***Decreased hemoglobin:*** In clinical trials, decreases(mean changes from baseline) in Hgb of -0.3g/dL up to -2.2g/dL for those on treatment with elbasvir/grazoprevir without ribavirin for 12 weeks, or with ribavirin for 16 weeks, respectively.

Appendix 6—*page 2 of 2*

APPENDIX 7. HCV NS5A INHIBITOR/HCV NS5B POLYMERASE INHIBITOR DRUG INFORMATION: LEDIPASVIR/SOFOSBUVIR

LEDIPASVIR/SOFOSBUVIR (HARVONI®) DRUG INFORMATION

DESCRIPTION

Ledipasvir/sofosbuvir (LDV/SOF) are oral direct-acting antiviral (DAA) agents against the hepatitis C genotype 1, 4, 5 or 6 virus. Ledipasvir is an inhibitor of the HCV NS5A protein, which is required for viral replication. Sofosbuvir is a prodrug that is metabolized to a nucleotide analogue inhibitor of the HCV NS5B RNA-dependent RNA polymerase. Ledipasvir/sofosbuvir is indicated for the treatment of chronic hepatitis C infection in monoinfected (HCV) or coinfected (HCV/HIV-1) genotype 1, 4, 5, or 6 infection.

FORMULATIONS

Ledipasvir/sofosbuvir is manufactured as a fixed-dose combination (90 mg ledipasvir/400 mg sofosbuvir), oral film-coated, diamond shaped single tablet that is packaged in 28-count bottles.

STANDARD DOSING

The dose for ledipasvir/sofosbuvir is one 400 mg/90 mg tablet once daily with or without food. Patients should take a missed dose as soon as it is realized, but not take more than 1 tablet daily. Ledipasvir/sofosbuvir does not have a snack or fat content requirement. Ledipasvir/sofosbuvir can be used for hepatitis C genotype 1, 4, 5, or 6 infection as described below:

HCV-1 TREATMENT REGIMENS:

Treatment-naïve without cirrhosis:
- An 8-week regimen with LDV/SOF is AASLD-recommended for persons infected with HCV genotype 1a or 1b, who have an HCV viral load <6 million IU/ml and are treatment-naïve—but who are not black or HIV-coinfected, and do not have cirrhosis.

Treatment-naïve with or without cirrhosis:
- LDV/SOF for 12 weeks

Treatment-experienced (to PEG-IFN/RBV or PEG-IFN/RBV/HCV Protease Inhibitor) without cirrhosis:
- LDV/SOF for 12 weeks

Treatment-experienced (to PEG-IFN/RBV or PEG-IFN/RBV/HCV Protease Inhibitor) with cirrhosis:
- LDV/SOF + ribavirin for 12 weeks ***OR***
- LDV/SOF for 24 weeks (for those ineligible for ribavirin)

HCV-4, 5, OR 6 TREATMENT REGIMENS:

Treatment-naïve or treatment-experienced (to PEG-IFN/RBV or PEG-IFN/RBV/HCV PI) with or without cirrhosis:
- LDV/SOF for 12 weeks

Total treatment duration is as specified above and is **not** guided by on-treatment HCV RNA response. Treatment regimen and duration does not differ between HCV mono-infection and HCV/HIV-1 co-infection.

DOSING IN CERTAIN CLINICAL CIRCUMSTANCES/USE IN SPECIFIC POPULATIONS

Renal Impairment: There is no dosage adjustment required for patients with mild or moderate renal impairment. No dose modification recommendation is given for patients with severe renal impairment (GFRs <30 mL/min) or with end-stage renal disease (ESRD) due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite. ***Sofosbuvir should not be used in patients with GFRs <30 mL/min.*** The safety and efficacy of LDV/SOF have not been established in patients with severe renal impairment or ESRD requiring hemodialysis.

Hepatic Impairment: No dose adjustment required for patients with mild, moderate, or severe hepatic impairment (CTP class A, B, or C). Safety and efficacy of treatment with ledipasvir/sofosbuvir in decompensated cirrhosis has not been established.

Pregnancy: Category B—There are no adequate and well-controlled studies with LDV/SOF in pregnant women. Because animal reproduction studies are not always predictive of human response, LDV/SOF should be used during pregnancy only if potential benefit outweighs potential risk to the fetus. (See more discussion under *Pregnancy*.)

Nursing Mothers: It is not known whether LDV/SOF and its metabolites are present in human breast milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LDV/SOF and any potential adverse effects on the breastfed child from the drug or from underlying maternal condition.

LEDIPASVIR/SOFOSBUVIR (HARVONI®) DRUG INFORMATION

CONTRAINDICATIONS.

No contraindications.

NOT RECOMMENDED

- Ledipasvir and sofosbuvir are substrates of permeability glycoprotein (P-gp) drug transporter and breast cancer resistance protein (BCRP). The concomitant use of LDV/SOF and P-gp inducers may significantly decrease ledipasvir and sofosbuvir plasma concentrations and lead to a reduced therapeutic effect of LDV/SOF. Therefore, use of LDV/SOF with P-gp inducers is not recommended.
- Coadministration of amiodarone is not recommended. Symptomatic bradycardia, as well as fatal cardiac arrest and cases requiring pacemaker intervention, have been observed when LDV/SOF is coadministred with amiodarone. Patients taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease, may be at increased risk for symptomatic bradycardia. If coadministration is necessary, counseling on bradycardia risk and cardiac monitoring is recommended.
- Concomitant usage with carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, or St. John's Wort is not recommended.
- Coadministration of LDV/SOF with other products containing sofosbuvir is not recommended.
- Coadministration with simeprevir is not recommended.
- If any hypersensitivity to ledipasvir, sofosbuvir, or a component thereof, then LDV/SOF should not be used.
- Coadministration not recommended with HMG-CoA Reductase Inhibitors such as rosuvastatin
- Coadministration not recommended with these HIV medications: tipranavir/ritonavir, STRIBILD™ (elvitegravir, cobicistat, emtricitabine, tenofovir DF).

USE WITH CAUTION

The following medications may pose a risk for potential interaction with ledipasvir/sofosbuvir that may require close monitoring, alteration of drug dosage, or timing of administration:

- ***Acid-Reducing Agents:*** Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of ledipasvir.
  - *Antacids (e.g., aluminum and magnesium hydroxide):* Separate antacid and LDV/SOF administration by 4 hours.
  - *H2 blockers (e.g., famotidine)* may be administered simultaneously with or 12 hours apart from LDV/SOF at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
  - *Proton pump inhibitors (e.g., omeprazole)*—Doses comparable to omeprazole 20 mg or lower can be administered simultaneously with LDV/SOF under fasted conditions.
- ***Antiarrhythmics*:** Therapeutic concentration of *digoxin* should be monitored, as LDV/SOF can cause increase in concentration of digoxin.
- ***HIV drugs:***
  - *Tenofovir disoproxil fumarate (DF),emtricitabine, efavirenz*: Monitor for tenofovir-associated adverse reactions; refer to Viread, Truvada, or ATRIPLA prescribing information for recommendations on renal monitoring.
  - *Regimens containing tenofovir DF and a boosted (with ritonavir) HIV protease inhibitor (eg, atazanavir/ritonavir + emtricitabine/tenofovir DF, darunavir/ritonavir + emtricitabine/tenofovir DF, lopinavir/ritonavir + emtricitabine/tenofovir DF)*: Consider alternative HCV or antiretroviral therapy to avoid increases in tenofovir exposures. If coadministration is necessary, monitor for tenofovir-associated adverse reactions. Recommend renal monitoring.

SIDE EFFECTS

- ***Flu-like symptoms:*** Fatigue, headache, and insomnia
- ***Gastrointestinal effects:*** Nausea and diarrhea

LAB ABNORMALITIES

- ***Hyperbilirubinemia****:* Bilirubin elevations of greater than 1.5 times the upper limit of normal (ULN).
- ***Lipase elevations:*** Transient, asymptomatic lipase elevations of >3x ULN.
- ***Creatinine kinase****:* Creatinine kinase was not assessed in Phase 3 trials of LDV/SOF. Isolated, asymptomatic creatinine kinase elevations (grade 3 or 4) have been previously reported in subjects treated with sofosbuvir in combination with ribavirin or peginterferon/ribavirin in other clinical trials.

APPENDIX 8. HCV NS3/4A PROTEASE INHIBITOR/NS5A INHIBITOR/HCV NS5B POLYMERASE INHIBITOR DRUG INFORMATION: PARITAPREVIR/RITONAVIR/OMBITASVIR/DASABUVIR

PARITAPREVIR/RITONAVIR/OMBITASVIR/DASABUVIR (VIEKIRA XR™) INFORMATION

DESCRIPTION

Paritaprevir/ritonavir/ombitasvir/dasabuvir combines three oral direct-acting antiviral (DAA) agents against the hepatitis C genotype 1 virus. **This combination is indicated for the treatment of chronic HCV genotype 1 infection.**

- **PARITAPREVIR** is an inhibitor of the HCV NS3/4A protease, which is necessary for the proteolytic cleavage of the HCV-encoded polyprotein and is essential for viral replication.
- **RITONAVIR** inhibits cytochrome P-450 and is used to increase the levels of paritaprevir.
- **OMBITASVIR** is an inhibitor of the HCV NS5A protein, which is required for viral replication and virion assembly.
- **DASABUVIR** is a non-nucleoside inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication.

FORMULATIONS

VIEKIRA XR is a fixed-dose combination of *paritaprevir 50 mg/ritonavir 33.33 mg/ ombitasvir 8.33 mg/dasabuvir 200 mg* **(PrOD)**. Pale yellow, oblong, film-coated extended-release tablet. Viekira XR is dispensed in a monthly carton for a total of 28 days of therapy. Each monthly carton contains four weekly cartons. Each weekly carton contains seven daily dose packs. Each child-resistant, daily dose pack contains three tablets.

TECHNIVIE™—a separate formulation indicated for HCV genotype 4 patients without cirrhosis—consists of a fixed-dose, co-formulated tablet of *paritaprevir (75 mg)/ritonavir (50 mg)/ombitasvir (12.5 mg)* **(PrO).**

VIEKIRA PAK® was the original formulation approved for treatment of HCV genotype 1, but the Viekira XR is now preferred over Viekira Pak for use in the BOP. Viekira Pak is manufactured as daily-dose packs of a fixed-dose combination of two *paritaprevir (75 mg)/ritonavir (50 mg) /ombitasvir (12.5 mg)* pink-colored, film-coated, oblong-shaped tablets *and* two *dasabuvir (250 mg)* beige-colored, film-coated, oval-shaped tablets—a total of four tablets. It is supplied as a monthly carton containing four weekly cartons, each containing seven daily dose packs of four tablets; each pack indicates which tablets need to be taken in the morning and evening.

STANDARD DOSING

STANDARD DOSE:

- **VIEKIRA XR:** Three extended-release tablets with food once a day. Tablets need to be taken with food, but should be swallowed whole —do not split, crush, or chew.
- **TECHNIVIE:** Two tablets with food once daily, plus weight-based ribavirin for 12 weeks. Technivie may be administered without ribavirin for those treatment-naïve HCV-4 cirrhotics who cannot take or tolerate ribavirin.

MISSED DOSES:

- **VIEKIRA XR:** No specific guidance is available regarding missed doses of Viekira XR. Persons taking Viekira XR should be instructed not to miss or skip any doses
- **TECHNIVIE:** A missed dose of Technivie can be taken within 12 hours of the prescribed dose. If more than 12 hours has passed since Technivie is usually taken, the missed dose should NOT be taken; the patient should take the next dose as per the usual dosing schedule.

NOTES:

- Viekira XR does not have a specified calorie or fat content requirement.
- Viekira XR can be used with or without ribavirin for hepatitis C genotype 1 infection, as described below in *HCV-1a Treatment Regimens* and *HCV-1b Treatment Regimens*.
- Follow genotype 1a regimens in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.
- For HIV/HCV coinfected patients, use same regimen as HCV monoinfected patient.
- Paritaprevir/ritonavir/ombitasvir + dasabuvir is an AASLD-recommended treatment option for HCV genotype 1b with CKD and GFR <30.

HCV-1A TREATMENT REGIMENS

- **Without cirrhosis:** Viekira XR + RBV for 12 weeks
- **With (compensated) cirrhosis:** Viekira XR + RBV for 24 weeks (alternative regimen)

PARITAPREVIR/RITONAVIR/OMBITASVIR/DASABUVIR (VIEKIRA XR™) INFORMATION

HCV-1B TREATMENT REGIMENS

- **Without cirrhosis:** Viekira XR for 12 weeks
- **With (compensated) cirrhosis:** Viekira XR for 12 weeks

DOSING IN CERTAIN CLINICAL CIRCUMSTANCES/USE IN SPECIFIC POPULATIONS

Liver Transplant Recipients (those with normal hepatic function and mild fibrosis—Metavir fibrosis ≤2): The dosing is Viekira XR + RBV for 24 weeks. Total treatment duration is as specified above under STANDARD DOSING and is not guided by on-treatment HCV RNA response.

Renal Impairment: No dosage adjustment of Viekira XR is required for patients with mild, moderate, or severe renal impairment including those patients on hemodialysis. For patients that require ribavirin, refer to the ribavirin prescribing information for use in patients with renal impairment (see *Appendix 10*).

Hepatic Impairment: No dose adjustment of Viekira XR is required for patients with mild hepatic impairment (CTP class A). Viekira XR is contraindicated in patients with moderate to severe hepatic impairment (CTP classes B and C).

Pregnancy: Category B—There are no adequate and well-controlled studies with Viekira XR in pregnant women. Because animal reproduction studies are not always predictive of human response, Viekira XR should be used during pregnancy only if potential benefit outweighs potential risk to the fetus. If Viekira XR is administered with ribavirin (which is teratogenic (Category X), the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. (See more discussion under *Pregnancy* in Section 8.)

Nursing Mothers: It is not known whether any components of Viekira XR or their metabolites are present in human breast milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Viekira XR and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

HCV/HIV-1 Coinfected: The ritonavir component of Viekira XR is also an HIV-1 protease inhibitor and can select for HIV-1 protease inhibitor resistance-associated substitutions. Any HCV/HIV-1 co-infected patients treated with Viekira XR should also be on a suppressive antiretroviral drug regimen to reduce the risk of HIV-1 protease inhibitor drug resistance.

CONTRAINDICATIONS

- If Viekira XR is administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen (see *Appendix 10*).
- The use of Viekira XR is contraindicated with moderate to severe hepatic impairment (CTP class B and C)/ decompensated cirrhosis.
- Known hypersensitivity to ritonavir (e.g., toxic epidermal necrolysis [TEN] or Stevens-Johnson syndrome).
- Drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.
- Drugs that are strong inducers of CYP3A and CYP2C8 may lead to reduced efficacy of Viekira XR.
- Drugs that are strong inhibitors of CYP2C8 may increase dasabuvir plasma concentrations and risk of QT prolongation**.**
- Concomitant usage with:
  - *Alpha-adrenergic blocker*—alfuzosin
  - *Anti-anginal—ranolazine*
  - *Anti-arrhythmic*—dronedarone
  - *Anticonvulsants*—carbamazepine, phenytoin, phenobarbital
  - *Anti-gout*--colchicine
  - *Antihyperlipidemicagent/HMG-CoA reductase inhibitor*—gemfibrozil, lovastatin, simvastatin
  - *Antimycobacterial*—rifampin
  - *Ergot derivatives*—ergotamine, dihydroergotamine, ergonovine, methylergonovine
  - *Ethinyl estradiol–containing products* (such as combined oral contraceptives)
  - *GI Motility Agent*--Cisapride
  - *Herbal products*—St. John's Wort
  - *HIV drugs*—efavirenz, ritonavir (Viekira XR is contraindicated to ritonavir ONLY in patients with known hypersensitivity, e.g., toxic epidermal necrolysis [TEN] or Stevens-Johnson syndrome).
  - *Neuroleptics and Anti-psychotic*—pimozide and lurasidone
  - *Phosphodiesterase-5 (PDE5) inhibitors*—sildenafil (only when dosed as Revatio® for the treatment of pulmonary arterial hypertension)
  - *Sedatives/hypnotics*—triazolam, orally administered midazolam

PARITAPREVIR/RITONAVIR/OMBITASVIR/DASABUVIR (VIEKIRA XR™) INFORMATION

NOT RECOMMENDED

The following medications are not recommended for use with Viekira XR:

- *Antifungals*—voriconazole (not recommended unless benefit-to-risk justifies use)
- *HMG-CoA Reductase Inhibitors*—rosuvastatin >10 mg/day, pravastatin >40 mg/day
- *HIV drugs*—darunavir/ritonavir, lopinavir/ritonavir, rilpivirine
- *Long-acting beta agonists (LABA)*—salmeterol (risk of QT prolongation, palpitations, and sinus tachycardia)

USE WITH CAUTION

The following medications may pose a risk for potential interaction with Viekira XR that may require close monitoring, alteration of drug dosage, or timing of administration:

- *ARBs*—valsartan, losartan, candesartan. Decrease the dose of the angiotensin receptor blockers (ARBs) and monitor patients for signs and symptoms of hypotension and/or worsening renal function. If such events occur, consider further dose reduction of the ARB or switching to an alternative to the ARB.
- *Antifungals*—ketoconazole (max daily dose 200 mg)
- *Antiarrhythmics*—amiodarone, bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine. Therapeutic concentration (if available) should be monitored as Viekira XR can cause increase in concentration of the antiarrythmic.
- *Antidiabetics*—metformin. Monitor for signs of onset of lactic acidosis such as respiratory distress, somnolence, and non-specific abdominal distress or worsening renal function. Concomitant metformin use in patients with renal insufficiency or hepatic impairment is not recommended.
- *Antipsychotic*—quetiapine. Before initiating Viekira XR in patients taking quetiapine, consider alternative anti-HCV therapy to avoid increases in quetiapine exposures. If coadministration is necessary, reduce the quetiapine dose to one-sixth of the current dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for the recommendations on adverse reaction monitoring. For initiation of quetiapine in patients taking Viekira XR, refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.
- *Calcium channel blocker*—amlodipine, nifedipine, diltiazem, verapamil. Decrease the dose of the calcium channel blocker (CCB). The dose of amlodipine should be decreased by at least 50%. Clinical monitoring of patients is recommended for edema and/or signs and symptoms of hypotension. If such events occur, consider further dose reduction of the CCB or switching to an alternative to the CCB.
- *Corticosteroids(inhaled/nasal)*—fluticasone. Use with Viekira XR may reduce serum cortisol concentrations; alternative corticosteroids should be considered, particularly for long-term use.
- *Diuretics*—furosemide. Clinical monitoring is recommended; individualize therapy, based on response.
- *HIV drugs*—atazanavir/ritonavir once daily. When coadministered with Viekira XR, atazanavir 300 mg (without ritonavir) should only be given in the morning.
- *Immunosuppressants*—
  - *Cyclosporine*. When initiating therapy with Viekira XR, reduce cyclosporine dose to one-fifth of patient's current cyclosporine dose; measure cyclosporine blood concentrations to determine subsequent dose modifications. Upon completion of Viekira XR, the appropriate time to resume pre-Viekira XR dose of cyclosporine should be guided by assessment of cyclosporine blood concentrations. Frequent assessment of renal function and cyclosporine-related side effects is recommended.
  - *Tacrolimus*. When initiating therapy with Viekira XR, the dose of tacrolimus needs to be reduced; do not administer tacrolimus on the day Viekira XR is initiated. Beginning the day AFTER Viekira XR is initiated, reinstate tacrolimus at a reduced dose, based on tacrolimus blood concentrations. Typical tacrolimus dosing is 0.5 mg every 7 days. Measure tacrolimus blood concentrations and adjust dose or dosing frequency to determine subsequent dose modifications. Upon completion of Viekira XR, the appropriate time to resume pre-Viekira XR dose of tacrolimus should be guided by assessment of tacrolimus blood concentrations. Frequent assessment of renal function and tacrolimus-related side effects is recommended.
- *Muscle Relaxants*—carisoprodol, cyclobenzaprine. May increase the muscle relaxant doses if clinically indicated.
- *Narcotic Analgesics*—
  - *Buprenorphine/naloxone*. Closely monitor for sedation and cognitive effects.
  - *Hydrocodone/acetaminophen*. Reduce the dose of hydrocodone by 50% and monitor patients for respiratory depression and sedation at frequent intervals. Upon completion of Viekira XR therapy, adjust the hydrocodone dose and monitor for signs of opioid withdrawal.
- *Proton Pump Inhibitors*—omeprazole. Avoid use of >40 mg/day; monitor for decreased efficacy of omeprazole.
- *Sedatives/Hypnotics*—
  - *Alprazolam*. Clinical monitoring is recommended; a decrease in alprazolam dose can be considered, based on clinical response;
  - *Diazepam*. May need to increase the dose of diazepam, if clinically indicated.

PARITAPREVIR/RITONAVIR/OMBITASVIR/DASABUVIR (VIEKIRA XR™) INFORMATION

MOST COMMON SIDE EFFECTS

- ***Regimen with Ribavirin (>10%):*** Fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia
- ***Regimen without Ribavirin (≥5%):*** Nausea, pruritus, and insomnia

LAB ABNORMALITIES

- ***Increased risk of ALT elevations:*** Elevations of ALT >5 times the upper limit of normal (ULN) occurred in 1% of subjects in clinical trials. If ALT>10 x ULN at week 4 or later in treatment, consider discontinuation of therapy. Also consider discontinuation of therapy if ALT <10 x ULN, but symptomatic.
- ***Bilirubin elevations:*** In clinical studies, transient elevations of bilirubin >2x ULN were observed in 15% of subjects receiving Viekira XR with ribavirin, compared with 2% of those receiving Viekira XR alone. These elevations usually peaked by study Week 1, and generally resolved with ongoing therapy. Bilirubin elevations were not associated with serum ALT elevations.

  Hepatic decompensation and hepatic failure, including liver transplantation and fatal cases, have been reported with ombitasvir, paritaprevir, ritonavir, and dasabuvir. It typically occurs between 1 and 4 weeks of treatment initiation and is characterized by acute elevation of direct bilirubin—without ALT elevation—and signs and symptoms of hepatic decompensation. In patients with cirrhosis, monitor for clinical signs and symptoms of hepatic decompensation (e.g., ascites, hepatic encephalopathy, variceal hemorrhage) and perform hepatic function testing (including direct bilirubin) at baseline, during the first 4 weeks of treatment initiation, and as indicated thereafter.

  ➔ **Discontinue treatment in patients who develop signs/symptoms of hepatic decompensation.**
- ***Anemia/decreased hemoglobin:*** Across all Phase 3 studies, the mean change from baseline in hemoglobin levels in subjects treated with Viekira XR + RBV was -2.4g/dL; the mean change in those treated with Viekira XR alone was 0.5g/dL. Decreases in hemoglobin levels occurred early in treatment (Week 1-2), with further reductions through Week 3. Hemoglobin values remained low during the remainder of treatment and returned toward baseline levels by post-treatment week 4. No subjects treated with the components of Viekira XR without ribavirin had a hemoglobin level less than 10 g/dL.

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APPENDIX 9. HCV NS5B POLYMERASE INHIBITOR/ HCV NS5A INHIBITOR DRUG INFORMATION: SOFOSBUVIR/VELPATASVIR

SOFOSBUVIR/VELPATASVIR (EPCLUSA®) DRUG INFORMATION (2 PAGES)

DESCRIPTION

Sofosbuvir/velpatasvir (SOF/VEL) are oral direct-acting antiviral (DAA) agents against the hepatitis C genotype 1, 2, 3, 4, 5 or 6 virus. Sofosbuvir is a prodrug that is metabolized to a nucleotide analogue inhibitor of the HCV NS5B RNA-dependent RNA polymerase. Velpatasvir is an inhibitor of the HCV NS5A protein, which is required for viral replication. Sofosbuvir/velpatasvir is indicated for the treatment of chronic hepatitis C infection in genotype 1, 2, 3, 4, 5, or 6 infections in adults without cirrhosis or with compensated cirrhosis, or in combination with ribavirin in patients with decompensated cirrhosis.

FORMULATIONS

Sofosbuvir/velpatasvir is manufactured as a fixed-dose combination (400 mg sofosbuvir /100 mg velpatasvir). The oral tablet is pink, film-coated, diamond-shaped. It is packaged in 28-count bottles.

STANDARD DOSING

The dose for sofosbuvir/velpatasvir is one 400 mg/100 mg tablet once daily with or without food. Patients should take a missed dose as soon as it is realized, but not take more than 1 tablet daily.

HCV-1, 2, 3, 4, 5, 6 TREATMENT REGIMENS:

- **Treatment-naïve/treatment-experienced (to PEG-IFN/RBV) with compensated cirrhosis or without cirrhosis:**
  - SOF/VEL for 12 weeks
- **Treatment-naïve/treatment-experienced (to PEG-IFN/RBV) with decompensated cirrhosis:**
  - SOF/VEL with ribavirin for 12 weeks
  - SOF/VEL for 24 weeks— in genotypes 1 & 4 who are ribavirin-ineligible patients
  - SOF/VEL with ribavirin for 24 weeks— in genotypes 1 & 4 patients who have failed a SOF-based regimen
- **Genotype 1 treatment-experienced (PEG-IFN/RBV/HCV Protease Inhibitor) with compensated cirrhosis or without cirrhosis:**
  - SOF/VEL for 12 weeks
  - SOF/VEL with ribavirin for 24 weeks—if decompensated cirrhosis
- **Genotype 2 and 3 treatment-experienced (to SOF/RBV) with compensated cirrhosis or without cirrhosis:**
  - SOF/VEL with ribavirin for 12 weeks

➔ Total treatment duration is as specified above and is *not* guided by on-treatment HCV RNA response.

➔ Treatment regimen and duration does not differ between HCV mono-infection and HCV/HIV-1 co-infection.

DOSING IN CERTAIN CLINICAL CIRCUMSTANCES/USE IN SPECIFIC POPULATIONS

Renal Impairment: There is no dosage adjustment is required for patients with mild or moderate renal impairment. No dose modification recommendation is given for patients with severe renal impairment (GFRs <30 mL/min) or with end-stage renal disease (ESRD) due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite. ***Sofosbuvir should not be used in patients with GFRs <30 mL/min.*** The safety and efficacy of SOF/VEL have not been established in patients with severe renal impairment or ESRD requiring hemodialysis.

Hepatic Impairment: No dose adjustment is required for patients with mild, moderate, or severe hepatic impairment (CTP class A, B, or C).

Pregnancy: Category B—There are no adequate and well-controlled studies with SOF/VEL in pregnant women. Because animal reproduction studies are not always predictive of human response, SOF/VEL should be used during pregnancy *only* if potential benefit outweighs potential risk to the fetus. (See more discussion under *PREGNANCY* in Section 8.)

Nursing mothers: It is not known whether SOF/VEL and its metabolites are present in human breast milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SOF/VEL and any potential adverse effects on the breastfed child from the drug or from underlying maternal conditions.

SOFOSBUVIR/VELPATASVIR (EPCLUSA®) DRUG INFORMATION (2 PAGES)

CONTRAINDICATIONS

No contraindications.

NOT RECOMMENDED

- Sofosbuvir and velpatasvir are substrates of permeability glycoprotein (P-gp) drug transporter and breast cancer resistance protein (BCRP). The concomitant use of SOF/VEL and P-gp inducers may significantly decrease sofosbuvir and velpatasvir plasma concentrations and lead to a reduced therapeutic effect of SOF/VEL. Therefore, use of SOF/VEL with P-gp inducers is not recommended.
- Coadministration of amiodarone is not recommended. Symptomatic bradycardia, as well as fatal cardiac arrest and cases requiring pacemaker intervention, have been observed when SOF/VEL is coadministred with amiodarone. Patients taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease, may be at increased risk for symptomatic bradycardia. If coadministration is necessary, counseling on bradycardia risk and cardiac monitoring is recommended.
- Risk of reduced therapeutic effect is attributed to concomitant use of SOF/VEL with P-gp Inducers and/or moderate-to-potent Inducers of CYP2B6, CYP2C8 or CYP3A4. Concomitant usage with carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, or St. John's Wort is not recommended as they may significantly decrease sofosbuvir and/or velpatasvir plasma concentrations.
- Coadministration of omeprazole or other proton-pump inhibitors is not recommended. If it is considered medically necessary to coadminister, SOF/VEL should be administered with food and taken 4 hours before taking omeprazole 20 mg. Use with other proton-pump inhibitors has not been studied.
- Coadministration of SOF/VEL with the anticancer drug topotecan is not recommended.
- If any hypersensitivity to velpatasvir, sofosbuvir, or a component thereof, then SOF/VEL should not be used.
- Coadministration is not recommended with the HIV medications efavirenz and tipranavir/ritonavir.

USE WITH CAUTION

The following medications may pose a risk for potential interaction with SOF/VEL that may require close monitoring, alteration of drug dosage, or timing of administration:

- ***Acid-Reducing Agents:*** Velpatasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of velpatasvir.
  - *Antacids (e.g., aluminum and magnesium hydroxide):* Separate antacid and SOF/VEL administration by 4 hours.
  - *H2 blockers (e.g., famotidine)* may be administered simultaneously with or 12 hours apart from SOF/VEL at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
- ***Antiarrhythmics*:** Therapeutic concentration of *digoxin* should be monitored, as SOF/VEL can cause an increase in the concentration of digoxin.
- ***HIV drugs:*** *Tenofovir disoproxil fumarate (DF)*: Monitor for tenofovir-associated adverse reactions; refer to Viread, Truvada, or ATRIPLA prescribing information for recommendations on renal monitoring. Consider alternative HCV or antiretroviral therapy to avoid increases in tenofovir exposures. If coadministration is necessary, monitor for tenofovir-associated adverse reactions. Recommend renal monitoring.
- ***HMG-CoA Reductase Inhibitors:***
  - *Rosuvastatin:* Coadministration of SOF/VEL with rosuvastatin may significantly increase the concentration of rosuvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Rosuvastatin may be administered with SOF/VEL at a dose that does not exceed 10 mg.
  - *Atorvastatin:* Coadministration of SOF/VEL with atorvastatin is expected to increase the concentrations of atorvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Monitor closely for HMG-CoA reductase inhibitor-associated adverse reactions, such as myopathy and rhabdomyolysis.
  - *Pravastatin:* No clinically significant interactions with SOF/VEL have been found.

SOFOSBUVIR/VELPATASVIR (EPCLUSA®) DRUG INFORMATION (2 PAGES)

SIDE EFFECTS

- ***Flu-like symptoms:*** Fatigue, headache, and insomnia
- ***Gastrointestinal effects:*** Nausea and diarrhea

LAB ABNORMALITIES

- ***Hyperbilirubinemia:*** Increases in indirect bilirubin up to 3 mg/dL above baseline were noted among HIV-1/HCV coinfected subjects treated with SOF/VEL and an atazanavir/ritonavir-based antiretroviral regimen. The elevated indirect bilirubin values were not associated with clinical adverse events and all subjects completed 12 weeks of SOF/VEL without dose adjustment or treatment interruption of either SOF/VEL or HIV antiretroviral agents.
- ***Lipase elevations:*** Transient, asymptomatic lipase elevations of >3x ULN.
- ***Creatinine kinase:*** In ASTRAL-1, isolated, asymptomatic creatine kinase elevations greater than or equal to 10xULN were reported in 1% and 0% of subjects treated with SOF/VEL and placebo for 12 weeks, respectively; and in 2% and 1% of subjects treated with SOF/VEL in ASTRAL-2 and ASTRAL-3, respectively. In the Phase 3 trial with decompensated cirrhosis (ASTRAL-4), isolated, asymptomatic creatine kinase elevations greater than or equal to 10xULN were reported in 1% of subjects treated with SOF/VEL with ribavirin for 12 weeks.

APPENDIX 10: RIBAVIRIN DRUG INFORMATION

RIBAVIRIN DRUG INFORMATION

DESCRIPTION

A nucleoside analogue with antiviral activity. Ribavirin is used in conjunction with other antiviral medication for treatment of HCV infection. ***Ribavirin should not be used alone as monotherapy for hepatitis C.***

FORMULATIONS

Several formulations of 200 mg tablets or capsules are available for oral administration, including 2 brand-name versions: Copegus® and Rebetol®. The generic versions are less expensive and equivalent to the branded drugs.

STANDARD DOSING *(in combination with simeprevir or sofosbuvir, with or without peginterferon)*

Ribavirin dosing is based on the patient's weight, regardless of genotype. ***Ribavirin should be taken with food.***

Weight <75 kg (<165 lb)	Weight >75 kg (>165 lb)
Total daily dose of 1,000 mg administered as: • 400 mg orally every morning • 600 mg orally every evening	**Total daily dose of 1,200mg administered as:** • 600 mg orally every morning • 600 mg orally every evening

DOSING IN CERTAIN CLINICAL CIRCUMSTANCES

Renal Dysfunction, Including Hemodialysis:
In patients with moderate renal function impairment (CrCl of 30–50 mL/min), the dose of ribavirin is 200 mg alternating with 400 mg every other day. In severe renal function impairment (CrCl 10–29 mL/min), including hemodialysis, the ribavirin dose is 200 mg/day.

CONTRAINDICATIONS

- Thalassemia or other hemoglobinopathy
- Significant cardiac disease (arrhythmias, angina, CABG, MI) in the past 12 months
- Pregnancy or unwillingness to use contraception in both female patients and in female partners of male patients
- Hemoglobin $\leq$12 g/dL in men or $\leq$11 g/dL in women
- Hypersensitivity to ribavirin

MAJOR SIDE EFFECTS

Has a primary clinical toxicity of *hemolytic anemia*. Since ribavirin-associated anemia has been known to lead to myocardial infarction, it is contraindicated in patients with significant or unstable cardiac disease. *Significant teratogenic effects* have been noted in all animal species exposed to ribavirin. Pregnancy should be prevented during therapy, and for the 6 months after the completion of therapy, *in both female patients and female partners of male patients.*

BLACK BOX WARNINGS

- **Hemolytic Anemia Warning** (primarily in the first 2 weeks of therapy)
- **Pregnancy Warning** (negative pregnancy test is required pretherapy)
- **Respiratory Warning** for patients requiring assisted ventilation

OTHER POSSIBLE SIDE EFFECTS

- *Cardiovascular effects:* Fatal and nonfatal myocardial infarction
- *Dermatologic effects:* Alopecia, pruritus, and rashes
- *Flu-like symptoms:* Myalgia, fatigue, and headache
- *Gastrointestinal effects:* Nausea, anorexia, and vomiting
- *Hematologic:* Neutropenia and thrombocytopenia
- *Hepatic decompensation and death*
- *Hypersensitivity—acute:* Anaphylaxis, angioedema, and bronchoconstriction
- *Pulmonary symptoms:* Dyspnea, pneumonia, and pulmonary infiltrates
- *Teratogen (significant), carthogenesis, and mutagenesis*

Appendix 10—*page 1 of 1*

APPENDIX 11. HEPATITIS C TREATMENT MONITORING SCHEDULE

Evaluation[1]	Baseline (anti-HCV positive)	Pretreatment (Within 90 days of Tx)	On-Treatment Monitoring (by week of treatment)[2]							12 wks post-treatment	6–12 mos post-treatment
			2	4	8	12	16	20	24		
Clinician evaluation	X	X	X	X	X	X	X	X	X	X	X
HIV Ab, HBV Serology[3], Anti-HAV (IgG)	X										
Prothrombin Time / INR	X	X									
CBC	X	X	X	X	*As clinically indicated* [4]						
Serum creatinine + eGFR	X	X		X						X	X
ALT, AST, bilirubin, alkaline, phosphatase, albumin	X	X		X							
APRI & CTP scores[5]	X	X									
HCV RNA, quantitative [6]	X	X		X	*See footnote #6.*					X	X
HCV genotype	X										
Assess for drug-drug interactions & adherence		X	*At each clinician evaluation during treatment.*								
Review incident report history for high risk behavior (alcohol / drug possession / use; tattooing)		X	*If indicated.*								
Urine pregnancy test (if childbearing potential)		X		X	X	X	X	X	X	*monthly x 6 mos*	

1 Conduct further diagnostic evaluations as clinically warranted to identify other potential causes of the patient's liver disease such as hemochromatosis, Wilson's disease, or autoimmune hepatitis (e.g., serum iron, serum copper,ANA/ ESR). If any of these conditions are diagnosed or are strongly suspected, a liver biopsy should be considered prior to treatment.

2 More frequent monitoring may be required if clinically indicated.

3 Recommended baseline testing for hepatitis B status includes HBsAg, anti-HBs, and anti-HBc. If either HBsAb or anti-HBc is positive, obtain an HBV DNA viral load. If criteria for treatment of HBV are met, initiating antiviral therapy for HBV is recommended prior to or at the same time as HCV treatment. If criteria for treatment of chronic HBV infection are not met, monthly HBV DNA viral loads are recommended during treatment for HCV.

4 More frequent monitoring of ALT is necessary in certain situations: 1) Regimens containing elbasvir/grazoprevir: An ALT should be drawn at 4 weeks and again at 8 weeks, and as clinically indicated. For 16-week regimens, an ALT should also be drawn at 12 weeks; **2) Patients with compensated cirrhosis** who are treated with paritaprevir/ritonavir/ ombitasvir, with or without dasabuvir, require more frequent monitoring of ALT; **3) Increases in the ALT should prompt more frequent monitoring or early discontinuation.** Asymptomatic ALT increases of less than tenfold should be monitored approximately every 2 weeks. Early discontinuation of HCV treatment is recommended if ALT increases by tenfold—or if less than tenfold , but accompanied by *symptoms* such as weakness, anorexia, nausea, vomiting, or change in stool color, or *signs* including elevations in conjugated bilirubin, alkaline phosphatase, and INR, related to hepatic dysfunction

5 A CTP score is calculated only for cases with known or suspected cirrhosis.

6 For treatment regimens recommended in this document, the routine schedule of HCV RNA testing includes baseline testing, after 4 weeks on treatment, and 12 weeks after completion of therapy. BOP recommends pretreatment testing of HCV RNA if the most recent test was performed more than 1 year ago. If the quantitative HCV viral load is detectable after 4 weeks of treatment, it should be repeated 2 weeks later. An HCV RNA is no longer necessary at the end of treatment unless undetectable levels were not achieved during treatment. If HCV RNA is undetectable12 weeks after treatment, BOP recommends repeat testing 6 to 12 months after completion of treatment.

➔ **RIBAVIRIN-CONTAINING REGIMENS: A pretreatment ECG is recommended for inmates with preexisting coronary heart disease. A CBC should be obtained two and four weeks after starting treatment, every four weeks while on treatment, and more frequently as clinically indicated.**

APPENDIX 12. MANAGEMENT OF HEMATOLOGIC CHANGES

Note: For patients prescribed a direct-acting antiviral (DAA) for HCV infection (e.g., sofosbuvir or simeprevir), if ribavirin must be discontinued due to hematologic changes, the DAA also may need to be discontinued. Consultation with an experienced clinician is recommended.

HEMOGLOBIN (Hgb)

Value	*Peginterferon/Ribavirin Adjustment and Supportive Treatment*	
10–11 g/dL	☐ ***Peginterferon*** → No change. ☐ ***Ribavirin*** → ► If no or minimal symptoms, then no dose modification. ► If symptomatic, decrease ribavirin by 200 mg/day.	***Candidates for Erythropoietin:*** Rule out other causes of anemia. If anemia persists at 2 weeks after reducing ribavirin—and there is no hypertension—then consider erythropoietin, especially if the patient demonstrates a virologic response. Erythropoietin should be considered primarily for patients who are cirrhotic, post-transplant, HIV/HCV coinfected, or treated with a DAA. ***Dosage:*** Epoetin alfa 40,000 units subcutaneously weekly ***Goal:*** Hemoglobin 12 g/dL ***Note:*** If hemoglobin is <12 g/dL for more than 4 weeks at the reduced/adjusted dose, then discontinue ribavirin.
8.5–10 g/dL	☐ ***Peginterferon*** → ► ***Peginterferon alfa 2a*** (Pegasys) → No change. ► ***Peginterferon alfa 2b*** (PEG-Intron) → Reduce 50% (*see note below*). ☐ ***Ribavirin*** → ↓ to 600 mg daily (200 mg AM & 400 mg PM)	
<8.5 g/dL	☐ ***Peginterferon*** → ► ***Peginterferon alfa 2a*** (Pegasys) → No change. ► ***Peginterferon alfa 2b*** (PEG-Intron) → Discontinue until resolved. ☐ ***Ribavirin*** → Discontinue until resolved.	

ABSOLUTE NEUTROPHIL COUNT (ANC)

Value	*Peginterferon/Ribavirin Adjustment and Supportive Treatment*	
<750	☐ ***Peginterferon*** → ► ***Peginterferon alfa 2a*** (Pegasys) → Reduce dose to 135 microgram/week (75% dose). ► ***Peginterferon alfa 2b*** (PEG-Intron) → Reduce to a 50% dose *(see note below)* ☐ ***Ribavirin*** → No change.	
< 500	☐ ***Peginterferon*** & ***Ribavirin*** → Discontinue both until resolved.	***Granulocyte Colony Stimulating Factor (G-CSF):*** If the patient is responding to treatment and neutropenia persists despite reduced peginterferon dose, consider G-CSF (in consultation with an expert) for patients who are cirrhotic, post-transplant, HIV/HCV coinfected, or treated with a DAA. ***Dosage:*** Filgrastim 300 microgram subcutaneous daily or less frequently. ***Goal:*** ANC >1500

PLATELETS

Value	*Peginterferon/Ribavirin Adjustment and Supportive Treatment*
<50,000	☐ ***Peginterferon*** → ► ***Peginterferon alfa 2a*** (Pegasys) → Reduce dosage to 90 micrograms/week (50% dose) (*see note below*). ► ***Peginterferon alfa 2b*** (PEG-Intron) → Discontinue until resolved. ☐ ***Ribavirin*** → If on PEG-Intron, then discontinue ribavirin.
<30,000	☐ ***Peginterferon*** → Discontinue until resolved. ☐ ***Ribavirin*** → Discontinue until resolved.

Note: While the manufacturer of peginterferon recommends reducing dose to 50%, recent data suggest that lowering the dose to this extent may significantly reduce the likelihood of achieving an SVR. Some experts recommend a 25% dose reduction with close monitoring of hematologic parameters.

APPENDIX 13. RESOURCES—PREVENTION AND TREATMENT OF VIRAL HEPATITIS

HEALTH CARE PROFESSIONALS

- **American Association for the Study of Liver Diseases and Infectious Disease Society of America Hepatitis C Guidelines**
  http://www.hcvguidelines.org
- **Centers for Disease Control and Prevention**
  National Center for Infectious Diseases—Hepatitis Branch
  http://www.cdc.gov/ncidod/diseases/hepatitis/
- **MELD Score Calculator**
  http://optn.transplant.hrsa.gov/converge/resources/MeldPeldCalculator.asp?index=98
- **National Institutes of Health**
  National Institute of Diabetes and Digestive and Kidney Diseases
  http://www.niddk.nih.gov
- **National Clinicians' Post-Exposure Prophylaxis PEPline: (888) 448-4911**
  http://www.nccc.ucsf.edu/
- **U.S. Department of Veterans Affairs National Hepatitis C Program**
  http://www.hepatitis.va.gov/

PATIENT EDUCATION

- **American Liver Foundation (ALF)**
  http://www.liverfoundation.org
- **Centers for Disease Control and Prevention (CDC)**
  http://www.cdc.gov/idu/hepatitis/index.htm
- **Hepatitis Foundation International (HFI)**
  http://www.hepfi.org
- **The National Digestive Diseases Information Clearinghouse (NDDIC)**
  http://www.digestive.niddk.nih.gov/ddiseases/pubs/hepc_ez/index.htm
- **U.S. Department of Veterans Affairs National Hepatitis C Program—For Veterans and the Public**
  http://www.hepatitis.va.gov/patient/index.asp

APPENDIX 14. HEPATITIS C TREATMENT ALGORITHM/NONFORMULARY REQUEST WORKSHEET

The BOP *Hepatitis C Treatment Algorithm/Nonformulary Request Worksheet* is available on the next page.

May 2017 **Hepatitis C Treatment Algorithm/Nonformulary Request Worksheet**

U.S. DEPARTMENT OF JUSTICE FEDERAL BUREAU OF PRISONS

Inmate Name:	**Projected Release Date:**
Register Number:	**Weight (lb.):** (within 90 days of request)
CTP score (if cirrhotic):	**HCV Genotype:** 1a 1b 2 3 4 5 6
APRI score: **APRI date:** APRI = ((AST/ULN AST)/ Plt) x 100	**Liver Biopsy Result / Date:** (amount of fibrosis): ☐ Not Performed ☐ None ☐ Portal ☐ Periportal ☐ Bridging ☐ Cirrhosis Note: For regimens with elbasvir/grazoprevir in the treatment of HCV genotype 1a, an HCV NSSA virologic resistence test is required.

Prior Antiviral Treatment for HCV: ☐ No ☐ Yes If yes, answer the following:

Drug Names and Dosages:

Start Date: Stop Date: Reason stopped:

Prior Treatment Response ☐ SVR ☐ Relapser ☐ Partial Responder ☐ Null Responder

Requested Treatment Regimen: (check all that apply)

☐ Daclatasvir ☐ Sofosbuvir ☐ Simeprevir ☐ Ledipasvir/sofosbuvir (Harvoni®)

☐ Paritapravir/ritonavir/ombitasvir/dasabuvir (Viekira XR™)

☐ Paritaprevir/ritonavir/ombitasvir (Technivie®) ☐ Elbasvir/grazoprevir (Zepatier™)

☐ Sofosbuvir/velpatasvir (Epclusa®) ☐ Ribavirin ☐ Other_____

Medical Clearance:

☐ **Sentenced inmate with sufficient time remaining on sentence to complete a course of treatment prior to halfway house (RRC), home confinement, or GCT/Full Term release.**

☐ **No sanctions for drug or alcohol/intoxicant possession/use, or tattooing within previous 1 year.**

☐ **No documented non-adherence to prior therapy, failure to complete pretreatment evaluation process, or unwillingness to commit or consent to HCV treatment.**

☐ **No contraindications or drug interactions with requested treatment regimen**

☐ **No uncontrolled or unstable medical or mental health conditions.**

☐ **No current pregnancy**

Health Services Staff Name / Signature / Date / Institution

Required Documentation – include copies of the following with this request:

☐ CBC, serum creatinine and eGFR, liver panel, INR (dated within 90 days of request)

☐ HCV RNA viral load (reported as IU/ml) and genotype (dated within 90 days of request)

☐ HIV Ab – if positive, include CD4 and HIV viral load (dated within 90 days of request) and current antiretroviral medication regimen

☐ Hepatitis B serology (sAb and sAg)- if sAg reactive, include eAg, eAb, and HBV DNA viral load

☐ Liver biopsy report (if performed, but not required unless clinically indicated)

☐ For regimens with peginterferon include WBC differential, TSH & free T4 (dated within 90 days of request)and a mental health assessment (dated within 6 months of request)

☐ If cirrhosis or APRI $\geq$ 2(defined by pathology or clinical findings), include abdominal US or CT

☐ Pregnancy test if woman with child-bearing potential (dated within 90 days of request)

PROCEDURE FOR SUBMITTING HCV TREATMENT REQUEST

- Generate a BEMR non-formulary request (NFR) for Hepatitis C Treatment Algorithm.
- Include all information and attach all required documentation from above.
- May scan and attach Hepatitis C Treatment Algorithm Nonformulary Request Worksheet to NFR.