Hepatitis C Antiviral Therapy
Policy Number: C12049-A

CRITERIA EFFECTIVE DATES:

ORIGINAL EFFECTIVE DATE	LAST REVIEWED DATE	NEXT REVIEW DATE
10/2014	10/9/2019	10/9/2020
J CODE	**TYPE OF CRITERIA**	**LAST P&T APPROVAL/VERSION**
NA	RxPA	Q4 2019 20191030C12049-A

PRODUCTS AFFECTED: EPCLUSA (sofosbuvir/velpatasvir), MAVYRET (glecaprevir and pibrentasvir), ZEPATIER (elbasvir and grazoprevir tablet), DAKLINZA (daclatasvir), HARVONI® (ledipasvir/sofosbuvir) tablets, SOVALDI (sofosbuvir), VOSEVI (sofosbuvir, velpatasvir, voxilaprevir), COPEGUS (ribavirin), MODERIBA PAK (ribavirin), REBETOL (ribavirin), RIBAPAK® (ribavirin), RIBASPHERE® (ribavirin) 400mg, 600mg, VIEKIRA PAK (paritaprevir/ritonavir/ombitasvir and dasabuvir), Ledipasvir-Sofosbuvir TABS 90-400MG, Sofosbuvir-Velpatasvir TABS 400-100MG DAKLINZA is planned for a cease in distribution from the manufacturer June 2019

DRUG CLASS:
Hepatitis C Agents

ROUTE OF ADMINISTRATION:
Oral

PLACE OF SERVICE:
Specialty Pharmacy

AVAILABLE DOSAGE FORMS: Daklinza TABS 30MG, Daklinza TABS 60MG, Epclusa TABS 400-100MG, Harvoni TABS 90-400MG, 45-200MG, 45/200MG PELLETS, 33.75MG/150MG PELLETS, Ledipasvir-Sofosbuvir TABS 90-400MG, Mavyret TABS 100-40MG, Moderiba 1200 Dose Pack TABS 600MG, Moderiba TABS 200MG, Rebetol SOLN 40MG/ML Ribasphere CAPS 200MG, Ribasphere RibaPak TABS 400MG, Ribasphere RibaPak TABS 600MG Ribasphere RibaPak TBPK 200 & 400MG, Ribasphere RibaPak TBPK 400 & 600MG, Ribasphere TABS 200MG, Ribasphere TABS 400MG, Ribasphere TABS 600MG, Ribavirin CAPS 200MG Ribavirin TABS 200MG, Sofosbuvir-Velpatasvir TABS 400-100MG, Sovaldi TABS 400MG, 200MG, 200MG PELLETS, 150MG PELLETS, Viekira Pak TBPK 12.5-75-50 &250MG, Vosevi TABS 400-100-100MG, Zepatier TABS 50-100MG

FDA-APPROVED USES:
EPCLUSA (sofosbuvir/velpatasvir): indicated for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection: without cirrhosis or with compensated cirrhosis or with decompensated cirrhosis for use in combination with ribavirin

MAVYRET (glecaprevir and pibrentasvir): indicated for the treatment of adult patients and pediatric patients 12 years and older or weighing at least 45kg with chronic HCV genotype (GT) 1, 2, 3, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) and adult and pediatric patients 12 years and older or weighing at least 45kg, with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both

ZEPATIER (elbasvir and grazoprevir tablet): indicated for treatment of chronic HCV genotype 1 or 4 infection in adults. ZEPATIER is indicated for use with ribavirin in certain patient populations

DAKLINZA (daclatasvir): indicated for use with sofosbuvir, with or without ribavirin, for the treatment of chronic HCV genotype 1 or 3 infection. Limitations of Use: Sustained virologic response (SVR12) rates are reduced in genotype 3 patients with cirrhosis receiving DAKLINZA in combination with sofosbuvir for 12 weeks.
HARVONI® (ledipasvir/sofosbuvir): indicated with or without ribavirin for the treatment of chronic hepatitis C virus (HCV) genotype 1, 4, 5 or 6 infection AND pediatric patients 3 years of age and older with genotype 1, 4, 5, or 6 HCV without cirrhosis or with compensated cirrhosis, genotype 1 infection with decompensated cirrhosis, for use in combination with ribavirin, genotype 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis, for use in combination with ribavirin

SOVALDI (sofosbuvir): indicated for the treatment of: Adult patients with genotype 1, 2, 3 or 4 chronic hepatitis C virus (HCV) infection without cirrhosis or with compensated cirrhosis as a component of a combination antiviral treatment regimen AND Pediatric patients 3-years of age and older with genotype 2 or 3 chronic HCV infection without cirrhosis or with compensated cirrhosis in combination with ribavirin

VOSEVI (sofosbuvir, velpatasvir, voxilaprevir): indicated for the treatment of adult patients with chronic HCV infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have: genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor OR genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor. Additional benefit of VOSEVI over sofosbuvir/velpatasvir was not shown in adults with genotype 1b, 2, 4, 5, or 6 infection previously treated with sofosbuvir without an NS5A inhibitor.

VIEKIRA PAK (paritaprevir/ritonavir/ombitasvir and dasabuvir): indicated for the treatment of adult patients with chronic hepatitis C virus (HCV): genotype 1b without cirrhosis or with compensated cirrhosis OR genotype 1a without cirrhosis or with compensated cirrhosis for use in combination with ribavirin

COPEGUS (ribavirin), MODERIBA PAK (ribavirin),REBETOL (ribavirin), RIBAPAK® (ribavirin), RIBASPHERE® (ribavirin) 400mg, 600mg: indicated for the treatment of chronic hepatitis C (CHC) virus infection in combination with PEGASYS in patients 5 years of age and older with compensated liver disease not previously treated with interferon alpha, and in adult CHC patients coinfected with HIV.

COMPENDIAL APPROVED OFF-LABELED USES: None

COVERAGE CRITERIA: INITIAL AUTHORIZATION

DIAGNOSIS:
chronic Hepatitis C Infection

REQUIRED MEDICAL INFORMATION:
FOR ALL INDICATIONS:

1. Documentation of diagnosis of Hepatitis C infection
   AND
2. Documentation requested medication is prescribed in accordance to the current FDA approved labeling and current AASLD guideline recommendation at the dose and duration appropriate for the member
   AND
3. Documentation of HCV genotype and subtype (obtained within the last 3 years) with a confirmed genotype of 1a, 1b, 2, 3, 4, 5, or 6

AND

4. Documentation of HCV RNA (HCV viral load) within past 6 months, HIV status (if positive see HIV CO-INFECTION requirements), Hepatitis B status, ALT/AST within past 6 months and any prior HCV treatment history (if re-retreatment see TREAMENT EXPERIENCED requirements)
   AND
5. (a) Documentation of METAVIR SCORE ≥ F2 confirmed by ONE of the following methods (see Appendix-Non-Invasive Fibrosis Serum Tests and Scores): i) confirmed by liver biopsy OR ii) Ultrasound based transient elastography: (Vibration-controlled transient elastography: Fibroscan® score ≥ 7.1 or FibroScan XL (for members with BMI > 30 kg/m2) OR Acoustic Radiation Force Impulse (ARFI) Imaging ≥ 1.38
   OR
   (b) Severe extrahepatic complications: Type 2 or Type 3 essential mixed cryoglobulinemia with end organ manifestations OR HCV induced renal disease
   OR
   (c) Physical findings consistent with substantial or advanced fibrosis or cirrhosis (Hospitalization within the past 12 months for a condition attributed to hepatic cirrhosis, OR History of hepatic encephalopathy requiring medication management and/or hospitalization within the past 12 months, OR History of portal hypertension as demonstrated by variceal bleeding or radiographic evidence or Transjugular Intrahepatic Portosystemic Shunt (TIPS) procedure)
   OR
   (d) Decompensated liver disease [CTP score 7-12 class B/C and MELD ≤ 20] OR
   (e) hepatocellular carcinoma
   OR
   (f) HIV co-infection OR Hepatitis B co-infection
   OR
   (g) Post solid organ transplant; Awaiting liver transplant HCV infection; or Post-liver transplant (must include date)
   AND
6. FOR REGIMENS THAT INCLUDE RIBAVIRIN: Documentation that member or member's partner is not pregnant, two reliable forms of contraception will be used during therapy, and monthly pregnancy tests will be performed throughout treatment AND Documentation of CBC within last 6 months
   AND
7. Documentation of adherence evaluation including review of any potential barriers to successful completion of HCV therapy including, but not limited to: compliance difficulty, missed appointments, inadequate social support, Sub-therapeutic management of comorbid physical health conditions and severe mental health conditions (e.g., psychotic disorders, bipolar disorder, major depression, PTSD), and all potential drug interactions with concomitant prescription or over-the-counter medications have been addressed (including discontinuation of the interacting drug, dose reduction, or counseling of the member of the risks associated with the use of both medications). Documentation of member's current medication list and potential interactions with plan to manage the interaction(s), if applicable. (Office notes documenting this are sufficient to meet this criteria)
   AND
8. Documentation of a urine drug screen and screen for substance abuse using a validated screening tool administered within the last 30 days confirming negative alcohol/drug/substance abuse.
   AND
9. Documentation of Resistant Associated Substitutions (RASs) analysis that indicates that none of the preferred combinations will likely be effective, if request is for a non-preferred formulary agent. Otherwise all requests for non-preferred agents will be redirected to a preferred agent.
   AND
10. Documentation of the following Resistant Associated Substitutions (RASs) testing

REQUIRED ONLY FOR REQUESTS WITH THE APPLICABLE DRUG REGIMEN;

a) Zepatier (elbasvir/grazoprevir) : NS5A RAS testing is recommended for genotype 1a-infected, treatment-naive or -experienced patients being considered for elbasvir/grazoprevir

b) Harvoni (sofosbuvir/ledipasvir): NS5A RAS testing can be considered for genotype 1a-infected, treatment-experienced patients without cirrhosis being considered for ledipasvir/sofosbuvir. If >100-fold resistance is present, treatment should include 12 weeks of therapy with weight-based ribavirin, or a different recommended therapy. (AASLD I, A). NS5A RAS testing can be considered for genotype 1a-infected, treatment-experienced patients with cirrhosis being considered for ledipasvir/sofosbuvir. If >100-fold resistance is present, treatment should include 24 weeks of therapy with weight-based ribavirin, or a different recommended therapy used

c) Epclusa (sofosbuvir/velpatasvir): NS5A RAS testing is recommended for genotype 3-infected, treatment-experienced patients (with or without cirrhosis) and treatment-naive patients with cirrhosis being considered for 12 weeks of sofosbuvir/velpatasvir. If Y93H is present, weight-based ribavirin should be added. (AASLD I, A)

d) Daklinza (daclatasvir) plus Sovaldi (sofosbuvir) :NS5A RAS testing is recommended for genotype 3-infected, treatment-experienced patients without cirrhosis being considered for 12 weeks of daclatasvir plus sofosbuvir. Indicate if baseline NS5A Y93H polymorphism is present. If Y93H is present, weight-based ribavirin should be added. (AASLD I, B) NS5A RAS testing is recommended for genotype 3-infected, treatment-naive patients with compensated cirrhosis being considered for 24 weeks of daclatasvir plus sofosbuvir. Indicate if baseline NS5A Y93H polymorphism is present. If Y93H is present, treatment should include weight-based ribavirin, or a different recommended therapy used. (AASLD I, B)

A. CHRONIC HEPATITIS C INFECTION RE-TREATMENT:
1. Documentation of reason(s) for previous failure of DAA therapy (i.e. tolerability, efficacy, etc.) and if the stated reason(s) for the previous treatment failure have been addressed (e.g. re- education and understanding/agreement of treatment plan)
   NOTE: Inadequate compliance to regimen and treatment plan (including office visits, scheduled clinical tests, etc.) or non-adherence to initial/previous HCV regimen as evidenced by medical records and/or pharmacy claims should be noted and addressed
   AND
2. Member adherent to previous HCV therapy as evidenced by pharmacy claims [MOLINA REVIEWER VERIFY]
   AND
3. (a) Documentation of evidence of failure to achieve a SVR or lack of efficacy during treatment: Detectable serum HCV RNA by quantitative assay at 12 or more weeks after completing treatment; or a 10-fold increase of viral load at week 6 of treatment. Laboratory documentation of quantitative viral load required.
   OR
   (b) Evidence of adverse event that required therapy discontinuation: Laboratory results (e.g.: CBC, LFTs, etc.) and/or clinical presentation, AND No improvement of adverse effect after proper clinical management
   AND
4. Requested regimen is the highest-rated regimen per AASLD Guidelines for member's condition [by viral subtype, previous therapy, presence or absence or cirrhosis, and presence or absence of resistance-associated variants (RAVs)]
   AND
5. There is evidence that such re-treatment will improve patient outcomes according to AASLD

guidelines OR at least a Class IIa rating (weight of evidence and/or opinion is in favor of usefulness and efficacy) or higher per AASLD Guidelines
AND

6. Documentation does NOT support any of the following: Inadequate compliance, non- adherence to initial/previous HCV regimen as evidenced by medical record and/or pharmacy claims, Re-infection: Continues to engage in high risk behavior and/or experienced reinfection secondary to high risk behavior, Discontinuation of treatment secondary to alcohol/substance/ drug abuse

B. CHRONIC HEPATITIS C INFECTION, PEDIATRICS:
1. Requested regimen must meet the The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America Present HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis: HCV in Children AND the most recent FDA labeled indications

C. CHRONIC HEPATITIS C INFECTION, HIV COINFECTION:
1. Documentation of diagnosis of HIV-1
AND
2. Documentation of CD4 count > 500 cells/mm3 if member is not taking antiretroviral therapy OR CD4 count > 200 cells/mm3 if member is virologically suppressed (e.g., HIV RNA < 200 copies/mL)
NOTE: see Appendix AASLD recommendations for patients co-infected with HIV and HCV

D. DECOMPENSATED CIRRHOSIS (CHILD PUGH B OR C)
1. Documentation of Decompensated liver disease confirmed by ONE (1) of the following (dated within the past 30 days): [ONE] Child-Turcotte-Pugh Score (CTP): 7-12 class B/C, Model for End-Stage Liver Disease (MELD) ≤ 20, Ascites, hepatic encephalopathy, variceal bleeding or jaundice. NOTE: Mavyret (Glecaprevir-Pibrentasvir) Ombitasvir, Paritaprevir and Ritonavir (Technivie) or Ombitasvir, Paritaprevir and Ritonavir; Dasabuvir tablets (Viekira Pak) will not be authorized for CTP score B or C

E. HEPATOCELLULAR CARCINOMA AWAITING LIVER TRANSPLANT:
1. Documentation of diagnosis of Stage I-III HCC confirmed by image testing: ultrasound, tomography, MRI, laparoscopy or biopsy
NOTE: It is reasonable to treat HCV in a patient with HCC or a history of HCC after the HCC has been treated successfully, with follow-up imaging demonstrating locoregional control. Patients with HCC should be assessed for DAA therapy on a case-by-case basis and, ideally, managed with input from a Tumor Board or specialty care. Patients with extensive or progressive HCC (e.g., vascular invasion or metastatic disease) are less likely to benefit from DAA therapy
AND
2. Member meets all criteria for authorization of a liver transplant as indicated in Molina Healthcare MCP-114: Liver Transplantation Adult & Pediatric

DURATION OF APPROVAL: MOLINA REVIEWER/STAFF: Communicate the following points to the Prescriber upon initial authorization regarding the required criteria for re-authorization of treatment/regimen.

IF PREFERRED HCV treatment AND regimen is 8 weeks or less, therapy may be authorized up to 8 weeks on initial authorization WITHOUT requirement of 4 week HCV RNA level.

FOR ANY OTHER TREATMENT AND REGIMEN: Prescriber agrees to submit, within 6 weeks after beginning treatment, a HCV RNA level drawn at 4 weeks of therapy to determine response to therapy. Prescriber also agrees to submit a HCV RNA level at 12 weeks post treatment and 24 weeks post treatment.

If at any point the patient's viral load is undetectable, the prescriber is not required to submit any subsequent test. Prescriber's failure to submit a lab report in a timely fashion due to patient's non-cooperation may result in denial of re-treatment, should that situation arise. However, situations beyond the control of the prescriber or the patient will not result in a denial of re-treatment under this criteria.

If HCV RNA is detectable at week 4 of treatment, repeat quantitative HCV RNA viral load testing is recommended after 2 additional weeks of treatment (treatment week 6). If quantitative HCV viral load has increased by >10-fold (>1 log10 IU/mL) on repeat testing at week 6 (or thereafter), discontinuation of HCV treatment is recommended.

Requests for authorization past 6 weeks will NOT be authorized in members who have not achieved a 2-log decrease in HCV RNA after 4 weeks of requested HCV therapy [MOLINA REVIEWER/STAFF: Consult updated AASLD guidelines* and Medical Director for exceptions on a case-by-case basis]

*If HCV RNA is detectable at week 4 of treatment, repeat quantitative HCV RNA viral load testing is recommended after 2 additional weeks of treatment (treatment week 6). If quantitative HCV viral load has increased by >10-fold (>1 log10 IU/mL) on repeat testing at week 6 (or thereafter), discontinuation of HCV treatment is recommended. III, C (AASLD, May 2018)

Prescriber to submit laboratory results to Molina Healthcare for review as soon as available

QUANTITY: Therapy start date must be verified with patient and/or prescriber before the second fill is dispensed. UPDATE Q2 P&T- MAX QUANTITY IS A 28 DAYS SUPPLY PER DISPENSE. THE NUMBER OF DISPENSES ARE ALLOWED UP TO APPROVED DURATION.

PRESCRIBER REQUIREMENTS:
PRE- OR POST SOLID ORGAN TRANSPLANT (E.G. HEART, KIDNEY, and LIVER) RECURRENT HCV INFECTION AFTER LIVER TRANSPLANT ONLY: Prescribed by or in consultation with a board-certified physician affiliated with a transplant center and is ONE of the following specialist:
physician or advanced practice provider within a gastroenterology, hepatology, infectious disease or transplant specialty practice

CHRONIC HEPATITIS C INFECTION, HIV COINFECTION: Prescribed by or in consultation with a board-certified physician or advanced practice provider infectious disease specialty practice.

ALL OTHER INDICATIONS: Prescribed by or in consultation with a board-certified physician or advanced practice provider within a gastroenterology, hepatology, infectious disease or transplant specialty practice.

AGE RESTRICTIONS: 18 years of age or older with the exceptions found under CHRONIC HEPATITIS C INFECTION, PEDIATRICS section

GENDER: Male and female

CONTINUATION OF THERAPY:
A. FOR ALL INDICATIONS:
   1. Documentation of HCV RNA quantitative viral load performed at following week 4 of treatment that shows a 2-log decrease in viral load at week 4 to continue treatment after the initial authorization period. Requests for renewal will NOT be authorized in members who have not achieved a 2-log decrease in HCV RNA after 4 weeks of requested HCV therapy [MOLINA REVIEWER/STAFF: Consult updated AASLD guidelines† and Medical Director for exceptions on a case-by-case basis]
      AND
   2. [IF APPLICABLE] After 12 weeks (for treatment durations longer than 12 weeks): HCV RNA undetectable (< 25 IU/mL) AND

3. Member must be at least 85% compliant to the prescribed HCV regimen as confirmed by the Prescriber and verified by medication fill history (review Rx history and dispensing for compliance)

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION: Clinically-significant medical disorder(s) or medical/psychiatric/social comorbidities likely to result in non-compliance. A short life expectancy due to co-morbid conditions that cannot be remediated by HCV therapy, liver transplantation, or another directed therapy (AASLD, September 2017)

Members identified having any barriers to treatment mentioned in RMI are not appropriate candidates for therapy until issues have been resolved, or acknowledgement of actions taken by prescriber or another provider involved in the member's care to address those barriers

Pregnancy: Currently pregnant or planning on becoming pregnant in the next six months, treatment during pregnancy is not recommended due to the lack of safety and efficacy data. (AASLD, September 2017).The safety and efficacy of DAA therapy in pregnant or lactating women have not been established for any of the currently FDA-approved agents. During pregnancy, these drugs should be used only if the benefits outweigh the risks to the fetus.

Severe end organ disease and is not eligible for solid organ transplant. Clinically-significant illness or any other major medical disorder that may interfere with a patient's ability to complete a course of treatment. Individuals who in the professional judgment of the primary treating clinician would not achieve a long-term clinical benefit from HCV treatment, with conditions such as those: Multisystem organ failure, Receiving palliative care or are enrolled in hospice, Presence of significant pulmonary or cardiac disease, Malignancy outside of the liver not meeting oncologic criteria for cure, Decompensated liver disease with CTP score > 12 or MELD > 20, OR Model For End-Stage Liver Disease (MELD) ≤ 20 and ONE (1) of the following: [ONE] Cardiopulmonary disease that cannot be correct and is a prohibitive risk for surgery, Malignancy outside of the liver not meeting oncologic criteria for cure, Hepatocellular carcinoma with metastatic spread or not listed for liver transplant, Intrahepatic cholangiocarcinoma, Hemangiosarcoma

OTHER SPECIAL CONSIDERATIONS: None

BACKGROUND:

Risk of Hepatitis B infection reactivation with HCV Direct Acting Antivirals (DAA)

In October of 2016, the FDA issued a safety alert concerning risk of reactivation of hepatitis B viral (HBV) infection in patients treated with HCV direct acting antivirals (DAA). At the time of the alert, the FDA had identified 24 cases of HBV infection reactivation in patients who had been treated with a HCV DAA. In a few of these cases, the HBV reactivation resulted in serious liver problems or death. As a result, the FDA has required labeling for all HCV DAAs to include a boxed warning for HBV infection reactivation. In addition, the FDA has recommended that all patients be screened for evidence of current or prior HBV infection before starting treatment with HCV DAAs and be monitored for HBV reactivation during and after treatment with a HCV DAA.

APPENDIX:

Measure of Fibrosis and Inflammation

Histologic scoring systems for chronic liver disease are used to characterize and predict disease progression, to determine prognosis, to guide treatment strategies, and to provide standards in clinical trials. Commonly used scoring systems for chronic hepatitis include:The METAVIR score, The Ishak score (modified Knodell score). These scoring systems include descriptions of both necroinflammatory activity and the degree of fibrosis. An important difference among the scoring systems is in the staging of fibrosis. Scoring systems that include more stages for describing fibrosis are better able to document small changes in fibrosis over time.

Non-Invasive Fibrosis Serum Tests and Scores					
Metavir Score	**Biopsy**	**Fibroscan**	**Elastography (ARFI/pSWE)**	**Fibrosure/ Fibrosure-Actitest**	**APRI‡**
F4	F4	> 12.5 kPa	> 2.34 m/s	> 0.75	> 2.0 *Likely cirrhosis*
F3	F3	9.6 – 12.4	2.01 – 2.33 m/s	0.58 – 0.74	>1.5 and ≤ 2 *Likely significant fibrosis, cirrhosis possible*
F2	F2	7.1 – 9.5	1.38 – 2.0 m/s	0.49 – 0.57	> 0.5 and ≤ 1.5 *Significant fibrosis or cirrhosis possible*
F1/0	F1/0	< 7.0 kPa	< 1.37 m/s	< 0.48	APRI > 0.3 and ≤ 0.5 *Unlikely cirrhosis, significant fibrosis possible* APRI ≤ 0.3 *Unlikely cirrhosis or significant fibrosis*

METAVIR score

The METAVIR fibrosis scoring system is the most commonly used method to stage and grade hepatic fibrosis and it assigns a score from F0 to F4 based on a liver biopsy. The METAVIR score is a semi-quantitative classification system that consists of an activity score and a fibrosis score (represented by a two letter and two number coding system): The activity score is graded according to the intensity of necroinflammatory lesions (A0 = no activity, A1 = mild activity, A2 = moderate activity, A3 = severe activity). The fibrosis score is assessed on a five-point scale (F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = few septa, F3 = numerous septa without cirrhosis, F4 = cirrhosis).

Reference: The French METAVIR Cooperative Study Group. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. Hepatology 1994; 29:15.

Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology 1996; 24:289.

Ishak score (modified Knodell score)

The Ishak score is a modification of the Knodell score that includes six stages of fibrosis. This permits documentation of small changes in fibrosis compared with the standard Knodell fibrosis score, which has only four stages. Like the METAVIR score, the grades for necroinflammation are categorized separately from the stage of fibrosis. (0=no fibrosis, 1=fibrous expansion of some portal areas ± short fibrous septa, 2= fibrous expansion of most portal areas ± short fibrous septa,
3=fibrous expansion of most portal areas with occasional portal to portal bridging, 4= fibrous expansion of most portal areas with marked bridging, 5= marked bridging with occasional nodules,
6= cirrhosis)

Comparison Between FibroScan Measurement and METAVIR Stage	
METAVIR Stage FibroScan Measurement (kPa)	**METAVIR Stage Equivalent**
7.0	Stage F2

9.5	Stage F3
11.8	Stage F4

AASLD recommendations for patients co-infected with HIV and HCV

HIV/HCV-coinfected patients should be treated and retreated the same as patients without HIV infection, after recognizing and managing interactions with antiretroviral medications (AASLD Class I, Level B)

If antiretroviral regimen alterations cannot be made to accommodate alternative HCV direct-acting antivirals in treatment-naive or -experienced patients, give daclatasvir (see dosing below) plus sofosbuvir 400 mg daily with or without ribavirin for 12 weeks in patients without cirrhosis and 24 weeks in patients with cirrhosis (AASLD Class I, Level B)

Daclatasvir doses are affected by numerous possible drug interactions and requires dose adjustment decrease daclatasvir to 30 mg/day in patients also taking ritonavir-boosted atazanavir (AASLD Class IIa, Level B), increase daclatasvir to 90 mg/day in patients also taking efavirenz or etravirine (AASLD Class IIa, Level B), daclatasvir dose may require adjustment in patients taking cytochrome P450 3A/4 inducers or inhibitors

Antiretroviral drug switches, when needed, should be done in collaboration with HIV practitioner; for HIV antiretroviral and HCV direct-acting antiviral combinations not addressed below, expert consultation is recommended (AASLD Class I, Level A)

Recommendation based on the risks associated with switching from an optimal and effective HIV antiretroviral regimen (including adverse effects and viral breakthrough) and the compatibility of daclatasvir plus sofosbuvir with almost all antiretroviral regimens; daclatasvir dose recommendations based on drug-interaction studies in healthy volunteers without blinding and preliminary results of modeling and simulation study

Treatment Naïve Patient Population

Highlighted cells indicate treatment regimens that may be approved

****Non-highlighted Treatment regimens are approvable in the order listed and will require documentation to support why the higher ranked regimens cannot be used. The below listed regimens are also applicable for the treatment of HCV/HIV coinfection. ***Abbreviations***: Riba – ribavirin, CTP – Child-Turcotte-Pugh

	Gen					
	1a	**1b**	**2**	**3**	**4**	**5,6**
Treatment naïve no cirrhosis	***SOF/VEL AG x12wks OR SOF/LED AG x8wks †***	***SOF/VEL AG x12wks O R***	***SOF/VEL AG*** *x12wks*	***SOF/VEL AG*** *x12wks*	***SOF/VEL AG*** *x12wks*	***SOF/VEL AG*** *x12wks*
	Zepatier+/-Riba x 12-16wks°	*Zepatier x12wks*	Mavyret x8wks	Mavyret x8wks	*Zepatier x12wks*	Mavyret x8wk
	Mavyret x8wks	Mavyret x8wks			Mavyret x8wks	
Treatment naïve compensated cirrhosis	***SOF/VEL AG x12wks***	***SOF/VEL AG x12wks***	***SOF/VEL AG x12wks***	***SOF/VEL AG x12wks***	***SOF/VEL AG x12wks***	***SOF/VEL AG x12wks***
	Zepatier+/-Riba x 12-16wks°	*Zepatier x12wks*	Mavyret x12wks	Mavyret x12wks	*Zepatier x12wks*	Mavyret x12wks
	Mavyret x12wks	Mavyret x12wks		*Vosevi x12wks*$^{\mu}$	Mavyret x12wks	

	SOF/LED AG x12wks	*SOF/LED AG x12wks*				
Treatment naïve decompensated cirrhosis CTP B	***SOF/VEL AG* /Riba x12wks**	***SOF/VEL AG* /Riba x12wks**	***SOF/VEL AG* /Riba x12wks** *Epclusa x24wks**	***SOF/VEL AG* /Riba x12wks** *Epclusa x24wks**	***SOF/VEL AG* /Riba x12wks**	***SOF/VEL AG* /Riba x12wks**
	Harvoni/Riba x12wks	*Harvoni/Riba x12wks*	*Daklinza/Sovaldi/Riba x12wks*	*Daklinza/Sovaldi/Riba x12wks*	*Harvoni/Riba x12wks*	
	*SOF/VEL AG x24wks**	*SOF/VEL AG x24wks**	*Daklinza/Sovaldi/Riba x24wks**	*Daklinza/ Sovaldi/ R iba*	*SOF/VEL AG x24wks**	
Treatment naïve decompensated cirrhosis CTP C	***SOF/VEL AG* /Riba x12wks**	***SOF/VEL AG* /Riba x12wks**	***SOF/VEL AG* /Riba x12wks** *Epclusa x24wks**	***SOF/VEL AG* /Riba x12wks** *Epclusa x24wks**	***SOF/VEL AG* /Riba x12wks**	***SOF/VEL AG* /Riba x12wks**
	SOF/LED AG /Riba x12wks	*SOF/LED AG /Riba x12wks*	*Daklinza/Sovaldi/Riba x12wks*	*Daklinza/Sovaldi/Riba x12wks*	*SOF/LED AG /Riba x12wks*	
	*SOF/VEL AG x24wks**	*SOF/VEL AG x24wks**	*Daklinza/Sovaldi/Riba x24wks**	*Daklinza/ Sovaldi/ R iba*	*SOF/VEL AG x24wks**	

*Must meet criteria for ribavirin intolerant or ribavirin ineligible

†Member must have baseline viral load < 6 million, be treatment naïve, no cirrhosis, non-black, and not have HIV co infection

ºMembers who do not qualify for the highlighted approvable regimen with genotype 1a infection that only qualify for Zepatier require additional testing. Prior to initiation, presence of virus with NS5A resistance associated polymorphisms is required to be submitted. For members with genotype 1a without NS5A resistance- associated polymorphisms, the approvable regimen is Zepatier x 12 weeks. For members with genotype 1a with NS5A resistance-associated polymorphisms, the approvable regimen is Zepatier + Ribavirin x 16 weeks.

μ when Y93H RAS is present

Retreatment of Treatment Experienced Patients

Highlighted cells indicate treatment regimens that may be approved

Non-highlighted treatment regimens are approvable in the order listed with submission of documentation and clinical rationale supporting rationale higher ranked regimens cannot be used. The below listed regimens are also applicable for the treatment of HCV/HIV co-infection

	Genotype					
	1a	**1b**	**2**	**3**	**4**	**5/6**
Tx Experienced to Riba/IFN without cirrhosis	**SOF/VEL AG X 12 WKS**	**SOF/VEL AG X 12 WKS**	**SOF/VEL AG X 12 WKS**	**SOF/VE¥ AG X 12 WKS**	**SOF/VEL AG X 12 WKS**	**SOF/VEL AG X 12 WKS**
	Zepatier+/-Riba x 12-16wksº	*Zepatier x12wks*	*Mavyret x 8 wks*	*Mavyret x 16wks*	*Zepatier/Riba x16wks*	*Mavyret x 8 wk*
	Mavyret x 8 wks	*Mavyret x 8 wks*		*Daklinza/Sovaldi ¥ x12wks*	*Mavyret x8wks*	*SOF/LED AG X 12WKS*
Tx Experienced to Riba/IFN with cirrhosis no NS5A polymorphism	**SOF/VEL AG X 12 WKS**	**SOF/VEL AG X 12 WKS** *Mavyret*	**SOF/VEL AG X 12 WKS**	**SOF/VEL AG X 12 WKS** *Zepatier/Riba*	**SOF/VEL AG X 12 WKS**	**SOF/VEL AG X 12 WKS**
	Zepatier x12wks	*Zepatier x12wks*	*12wks*	*Mavyret x 16wks*	*x16wks*	*Mavyret x 12wks*
	Mavyret x 12wks	*Mavyret x 12wks*		*Zepatier/Sovaldi x12wks*	*Mavyret x 12wks*	*SOF/LED AG X 12WKS*
Tx Experienced To Riba/IFN with cirrhosis with NS5A polymorphism	**SOF/VEL AG X 12 WKS**	**NA**	**SOF/VEL AG X 12 WKS**	**SOF/VEL+RIB AG X 12 WKS**	**SOF/VEL AG X 12 WKS**	**SOF/VEL AG X 12 WKS**
	Zepatier/Riba x16wks		*M on 12wks yre*	*Mavyret x 12wks*	*Mavyret x 12wks*	*Mavyret x 12wks*
	Mavyret x 12wks		*t x*	*Zepatier/Sovaldi x12wks*		*SOF/LED AG X 12WKS*
Tx Experienced to Riba/IFN/PI without cirrhosis	**SOF/VEL AG X 12 WKS**	**SOF/VEL AG X 12 WKS**	**N/A**	**N/A**	**N/A**	**N/A**
	Mavyret x 12wks	*Mavyret x 12wks*				
	SOF/LED AG X 12WKS	*SOF/LED AG X 12WKS*				
Tx Experienced to Riba/IFN/PI with cirrhosis	**SOF/VEL AG X 12 WKS**	**SOF/VEL AG X 12 WKS**	**N/A**	**N/A**	**N/A**	**N/A**
	Mavyret x 12wks	*Mavyret x 12wks*				
		Harvoni/Riba x12wks				
Tx Experienced to non-NS5A WITH OR without cirrhosis	**Vosevi x12wks**	**SOF/VEL AG X 12 WKS**	**N/A**	**Vosevi x12wks**	**Vosevi x12wks**	**Vosevi x12wks**
	Mavyret x 12wks	*Mavyret x 12wks*		*Add ribavirin if prior NS5A failure*		
Tx Experienced to NS5A WITH OR without cirrhosis	**Vosevi x12wks**	**Vosevi x12wks**	**N/A**	**Vosevi x12wks**	**Vosevi x12wks**	**Vosevi x12wks**
	Mavyret x16wks (except Viekira/Zepatier prior tx	*Mavyret x16wks (except Viekira/Zepatier prior tx)*		*Add ribavirin if prior NS5A failure*		

	Genotype					
	1a	**1b**	**2**	**3**	**4**	**5/6**
Tx Experienced to Riba/IFN/PI decomp cirrhosis CTP B/C	**SOF/VEL AG+RIB AG X 12 WKS**	**SOF/VEL AG+RIB AG X 12 WKS**	**SOF/VEL AG+RIB AG X 12 WKS**	**SOF/VE AG+RIB AG X 12 WKS**	**SOF/VEL AG+RIB AG X 12 WKS**	**SOF/VEL AG+RIB AG X 12 WKS**
	SOF/LED AG+RIB X 12WKS	SOF/LED+RIB X 12WKS	*Daklinza/Sovaldi/Ribax12wks*	Daklinza/Sovaldi/Ribax12wks	SOF/LED AG +RIB X 12 WKS	SOF/LED AG +RIB X 12 WKS
	SOF/VEL AG X 24 WKS*	SOF/VEL AG X 24 WKS	SOF/VEL AG X 24 WKS*	SOF/VEL AG X 24 WKS*	SOF/VEL AG X 24 WKS*	SOF/VEL AG X 24 WKS*
Tx Experienced to Sovaldi or NS5A decomp cirrhosis CTP B/C	**SOF/VEL AG X 24 WKS ADD RIB FOR CTP C**	**SOF/VEL AG X 24 WKS ADD RIB FOR CTP C**	N/A	N/A	**SOF/VEL AG X 24 WKS ADD RIB FOR CTP C**	**SOF/VEL AG X 24 WKS ADD RIB FOR CTP C**
	SOF/LED AG + RIB X 24KS	SOF/LED AG + RIB X 24KS			SOF/LED AG + RIB X 24KS	SOF/LED AG + RIB X 24KS

*Must meet criteria for ribavirin intolerant or ribavirin ineligible
†If previous nonresponder to interferon and ribavirin regimen then 24 weeks is the approvable length of treatment
¥NS5A Polymorphism testing for Y93H is recommended and ribavirin should be included in regimen if present.
ºMembers who do not qualify for the highlighted approvable regimen with genotype 1a infection that only qualify for Zepatier require additional testing. Prior to initiation, presence of virus with NS5A
resistance-associated polymorphisms is required to be submitted. For members with genotype 1a without NS5A resistance-associated polymorphisms, the approvable regimen is Zepatier x 12 weeks. For members with genotype 1a with NS5A resistance-associated polymorphisms, the
approvable regimen is Zepatier + Ribavirin x 16 weeks.

Other TREATMENT Patient Populations (HCC, Post-liver transplant)

Approvable Regimens for the Treatment of Chronic Hepatitis C infection

Highlighted cells indicate treatment regimens that may be approved

Non-highlighted treatment regimens are approvable in the order listed with submission of documentation and clinical rationale supporting rationale higher ranked regimens cannot be used

Abbreviations: HCV – Hepatitis C virus, Riba – ribavirin, HCC – hepatocellular carcinoma, CTP – Child-Turcotte-Pugh

†up to 48 weeks treatment length or until liver transplantation, whichever occurs first

	Genotype					
	1a	**1b**	**2**	**3**	**4**	**5/6**
HCC awaiting liver transplant Milan criteria met with or without cirrhosis	**Sovaldi/Riba x48wks †**	**Sovaldi/Riba x48wks †**	**Sovaldi/Riba x48wks †**	**Sovaldi/Riba x48wks †**	**Sovaldi/Riba x48wks †**	**Sovaldi/Riba x48wks†**
Post-liver transplant HCV reoccurrence	**SOF/LED AG +RIB X 12 WKS**	**SOF/LED AG +RIB X 12 WKS**	**Mavyret x12wks**			
no cirrhosis fibrosis stage ≤ 2 normal LFTs	Mavyret x12wks	Mavyret x12wks	*Daklinza/Sovaldi/Riba x12wks*	*Daklinza/Sovaldi/Riba x12wks*	Mavyret x12wks	Mavyret x12wks
If all of the above bulleted criteria for Post-liver transplant HCV reoccurrence are not present then the below selections are applicable						
Post-liver transplant HCV reoccurrence	**SOF/LED+RIB X 12WKS**	**SOF/LED+RIB X 12WKS**	**Daklinza/Sovaldi/Riba x12wks**	**Daklinza/Sovaldi/Riba x12wks**	**SOF/LED+RIB X 12WKS**	**SOF/LED+RIB X 12WKS**
disease (CTP A)	*Mavyret X 12 wks Daklinza/Sovaldi/ Ribax12wks*	*Mavyret X 12 wks Daklinza/Sovaldi/ Ribax12wks*	*SOF/VEL AG X 12 WKS Mavyret X 12 wks*	*SOF/VEL AG X 12 WKS Mavyret X 12 wks*	*Mavyret X 12 wks Daklinza/Sovaldi/Ribax12wks*	*Mavyret X 12 wks Daklinza/Sovaldi/Ribax12wks*
Post-liver transplant HCV reoccurrence	**SOF/LED+RIB X 12WKS**	**SOF/LED+RIB X 12WKS**	**SOF/VEL AG X 12 WKS**	**SOF/VEL AG X 12 WKS**	**SOF/LED+RIB X 12WKS**	**SOF/LED+RIB X 12WKS**
decompensated cirrhosis (CTP B/C)			**Daklinza/Sovaldi/Riba x12wks**	**Daklinza/Sovaldi/Riba x12wks**		

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