BlueCross BlueShield of Alabama

Hepatitis C Second Generation Antivirals Prior Authorization - Through Preferred Agent(s) Criteria Program Summary

This program applies to Commerical, GenPlus, NetResults A series, SourceRx and Health Insurance Marketplace formularies.

OBJECTIVE

The intent of the Hepatitis C Second Generation Antivirals Prior Authorization (PA) program is to appropriately select patients for therapy according to the Food and Drug Administration (FDA) approved product labeling and/or clinical guidelines and/or clinical studies. The PA process will evaluate the use of these agents when there is supporting clinical evidence for their use. Patients must be abstinent of illicit drug and/or alcohol abuse and/or high risk sexual practices for at least 12 months or must be actively participating in a recovery program and will not continue to actively abuse illicit drugs, abuse alcohol, or participate in high risk sexual practices. Patients re-infected with hepatitis C due to liver transplant will be considered for coverage when all other criteria is also met. A preferred agent may be approved for use once all criteria have been met; a non-preferred agent may be approved if the patient is currently treated with the non-preferred agent or the prescriber has provided documentation in support of use of the non-preferred agent over the preferred agent.

TARGET AGENTS

Preferred Agent

Epclusa® (sofosbuvir/velpatasvir) (co-preferred for genotype 1, 2, 3, 4, 5 and 6)
Harvoni® (ledipasvir/sofosbuvir) (co-preferred for genotype 1, 4, 5, and 6)
Mavyret™ (glecaprevir/pibrentasvir) (co-preferred for genotype 1, 2, 3, 4, 5, and 6)
Vosevi™ (sofosbuvir/velpatasvir/voxilaprevir) (co-preferred for genotype 1, 2, 3, 4, 5, and 6)

Non-Preferred Agent

Technivie™ (ombitasvir/paritaprevir/ritonavir)
Viekira Pak™ (ombitasvir/paritaprevir/ritonavir + dasabuvir)
Viekira XR™ (dasabuvir/ombitasvir/paritaprevir/ritonavir)
Zepatier™ (elbasvir/grazoprevir)

New to Market Hepatitis C Target Agents (This section will be populated when there are new recently FDA approved hepatitis C agents)

Brand (generic)	GPI	Multisource Code
Epclusa®(sofosbuvir/velpatasvir)		
400 mg sofosbuvir/100 mg velpatasvir	12359902650330	M, N, O, or Y
Harvoni® (ledipasvir/sofosbuvir)		
90 mg ledipasvir/ 400 mg sofosbuvir	12359902400320	M, N, O, or Y
Mavyret™ (glecaprevir/pibrentasvir)		
100 mg glacaprevir/40 mg pibrentasvir	12359902350320	M, N, O, or Y
Technivie™ (ombitasvir/paritaprevir/ritonavir)		
12.5/75/50 mg ombitasvir/ paritaprevir/ritonavir	12359903600320	M, N, O, or Y
Viekira PAK™ (ombitasvir/paritaprevir/ritonavir + dasabuvir)		
12.5/75/50 mg ombitasvir/	1235990460B720	M, N, O or Y

paritaprevir/ritonavir + 250 mg dasabuvir		
Viekira XR™ (ombitasvir/paritaprevir/ritonavir/dasabuvir)		
200 mg/8.33 mg/50 mg/33.33 mg dasabuvir/ombitasvir/paritaprevir/ritonavir	12359904607530	M, N, O or Y
Vosevi™ (sofosbuvir/velpatasvir/voxilaprevir)		
400 mg sofosbuvir/100 mg velpatasvir/100 mg voxilaprevir	12359903800330	M, N, O, or Y
Zepatier™ (elbasvir/grazoprevir)		
50 mg elbasvir/100 mg grazoprevir	12359902300320	M, N, O, or Y

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Non-Preferred Agent(s) will be approved when the drug specific criteria below and ONE of the following additional criteria are met:

1. The patient is currently being treated with the non-preferred agent
   OR
2. The patient has an FDA labeled contraindication or hypersensitivity to the preferred agent(s)
   OR
3. The prescriber has submitted documentation in support of the use of the non-preferred agent, over the preferred agent(s)

Length of approval: Up to the duration of treatment as determined below

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Epclusa will be approved when ALL of the following criteria are met:

1. The patient has a diagnosis of chronic hepatitis C genotype 1, 2, 3, 4, 5, or 6
   AND
2. The prescriber has screened the patient for current or prior hepatitis B viral (HBV) infection and will monitor the patient for HBV flare-up or reactivation during and after treatment with the requested agent
   AND
3. The requested agent is being prescribed by a specialist (e.g. gastroenterologist, hepatologist, or infectious disease) or in consultation with a specialist
   AND
4. The patient does not have any FDA labeled contraindications to the requested agent
   AND
5. ONE of the following:
   a. The patient has no known history of illicit drug and/or alcohol abuse and/or high risk sexual practices
      OR
   b. The patient has a history of illicit drug and/or alcohol abuse and/or high risk sexual practices and ONE of the following:
      i. The patient has abstained from the use of illicit drugs, alcohol abuse, and/or high risk sexual practices for the past 12 months or for a length of time at the discretion of the provider to determine readiness for treatment
         OR
      ii. The patient is actively participating in a recovery program and will not continue to actively abuse illicit drugs, abuse alcohol, or participate in high risk sexual practices

   AND
6. ONE of the following:
   a. Therapy is not being requested for treatment of a patient re-infected with hepatitis C
      OR
   b. Therapy is being requested for a patient re-infected with hepatitis C following liver transplantation

   AND

7. ONE of the following:
    a. The patient is treatment naïve
    OR
    b. The patient was previously treated (i.e. treatment experienced) with ONLY peg-interferon and ribavirin with or without an HCV protease inhibitor

AND

8. The dose is within the FDA labeled dose

AND

9. The requested agent will be used in a treatment regimen AND length of therapy recommended for the patient's genotype as noted in Table 1 (FDA labeling)

Length of approval: Up to the duration of treatment as determined in Table 1

Table 1: Epclusa Treatment Recommendations based on FDA labeling

Genotype	Patient population*	Treatment	Duration
1, 2, 3, 4, 5, or 6	Patients without cirrhosis or with compensated cirrhosis (Child-Pugh A)	Epclusa	12 weeks
	Patients with decompensated cirrhosis (Child-Pugh B and C)	Epclusa + ribavirin	12 weeks

* HCV/HIV-1 co-infection: For patients with HCV/HIV-1 co-infection, follow the Epclusa dosage recommendations in the table 1 above

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Harvoni will be approved when ALL of the following criteria are met:

1. The patient has a diagnosis of chronic hepatitis C genotype 1, 4, 5, or 6

AND

2. The prescriber has provided the patient's baseline HCV RNA level if the patient has genotype 1

AND

3. The prescriber has screened the patient for current or prior hepatitis B viral (HBV) infection and will monitor the patient for HBV flare-up or reactivation during and after treatment with the requested agent

AND

4. The requested agent is being prescribed by a specialist (e.g. gastroenterologist, hepatologist, or infectious disease) or in consultation with a specialist

AND

5. The patient does not have any FDA labeled contraindications to the requested agent

AND

6. ONE of the following:
    a. The patient has no known history of illicit drug and/or alcohol abuse and/or high risk sexual practices
    OR
    b. The patient has a history of illicit drug and/or alcohol abuse and/or high risk sexual practices and ONE of the following:
        i. The patient has abstained from the use of illicit drugs, alcohol abuse, and/or high risk sexual practices for the past 12 months or for a length of time at the discretion of the provider to determine readiness for treatment
        OR
        ii. The patient is actively participating in a recovery program and will not continue to actively abuse illicit drugs, abuse alcohol, or participate in high risk sexual practices

AND

7. ONE of the following:
    a. Therapy is not being requested for treatment of a patient re-infected with hepatitis C
    OR
    b. Therapy is being requested for a patient re-infected with hepatitis C following liver transplantation

AND

8. ONE of the following:
    a. The patient is treatment naïve
    OR
    The patient was previously treated (i.e. treatment experienced) with peg-interferon and ribavirin with or without an HCV protease inhibitor

AND

9. The dose is within the FDA labeled dose

AND

10. The requested agent will be used in a treatment regimen AND length of therapy recommended for the patient's genotype as noted in Table 2 and 3 (FDA labeling)

Length of approval: Up to the duration of treatment as determined in Tables 2 and/or 3

Table 2: Harvoni Treatment Recommendations based on FDA labeling

Genotype	Adult Patient Population^	Treatment	Treatment Duration
1	Treatment-naïve with initial viral load of < 6 M IU/mL and without cirrhosis, HIV infection, history of liver transplantation and/or are not black or African-American	Harvoni	8 weeks*
	Treatment-naïve without cirrhosis* or with compensated cirrhosis (Child-Pugh A)	Harvoni	12 weeks
	Treatment-experienced** without cirrhosis	Harvoni	12 weeks
	Treatment-experienced** with compensated cirrhosis (Child-Pugh A) and eligible for ribavirin	Harvoni + ribavirin	12 weeks†
	Treatment-experienced** with compensated cirrhosis (Child-Pugh A) and ineligible for ribavirin£	Harvoni	24 weeks
	Treatment-naïve and treatment-experienced** with decompensated cirrhosis (Child-Pugh B or C)	Harvoni + ribavirin	12 weeks
1 or 4	Treatment-naïve and treatment-experienced** liver transplant recipients without cirrhosis, or with compensated cirrhosis (Child-Pugh A)	Harvoni + ribavirin	12 weeks
4, 5, or 6	Treatment-naïve and treatment-experienced** without cirrhosis or with compensated cirrhosis (Child-Pugh A)	Harvoni	12 weeks

Table 3: Harvoni Treatment Recommendations based on FDA labeling

Genotype	Pediatric Patients ≥ 12 years	Treatment	Treatment Duration

	of Age or Weighing at Least 35 Kg^		
1	Treatment-naïve without cirrhosis or with compensated cirrhosis (Child-Pugh A)	Harvoni	12 weeks
	Treatment-experienced[¥] without cirrhosis	Harvoni	12 weeks
	Treatment-experienced[¥] with compensated cirrhosis (Child-Pugh A)	Harvoni	24 weeks
4, 5, or 6	Treatment-naïve and treatment experienced[¥], without cirrhosis or with compensated cirrhosis (Child-Pugh A)	Harvoni	12 weeks

^HCV/HIV co-infected patients: Follow the dosage recommendation in the tables above unless otherwise noted.
*8 weeks may be considered in treatment naïve patients without cirrhosis, without HIV infection, or without history of liver transplantation who have pre-treatment HCV RNA < 6 million IU/mL. For this patient population Prime is requiring 8 weeks of therapy.
**Treatment-experienced - patients who have failed therapy with either peg-interferon + ribavirin or a HCV protease inhibitor + peginterferon + ribavirin.
[†] Harvoni + ribavirin for 12 weeks can be considered in treatment-experienced HCV genotype 1 patients with cirrhosis who are eligible for ribavirin. For this patient population Prime will require treatment with Harvoni in combination with ribavirin for 12 weeks unless the patient is ineligible to receive ribavirin.
[£]Ribavirin ineligible - patients with history of intolerance, contraindication, or hypersensitivity to ribavirin
[¥]Treatment-experienced patients who have failed an interferon based regimen with or without ribavirin

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Mavyret will be approved when ALL of the following criteria are met:

1. The patient has a diagnosis of chronic hepatitis C genotype 1, 2, 3, 4, 5, or 6
   AND
2. The prescriber has screened the patient for current or prior hepatitis B viral (HBV) infection and will monitor the patient for HBV flare-up or reactivation during and after treatment with the requested agent
   AND
3. The requested agent is being prescribed by a specialist (e.g. gastroenterologist, hepatologist, or infectious disease) or in consultation with a specialist
   AND
4. The patient does not have any FDA labeled contraindications to the requested agent
   AND
5. ONE of the following:
   a. The patient has no known history of illicit drug and/or alcohol abuse and/or high risk sexual practices
      OR
   b. The patient has a history of illicit drug and/or alcohol abuse and/or high risk sexual practices and ONE of the following:
      i. The patient has abstained from the use of illicit drugs, alcohol abuse, and/or high risk sexual practices for the past 12 months or for a length of time at the discretion of the provider to determine readiness for treatment
         OR
      ii. The patient is actively participating in a recovery program and will not continue to actively abuse illicit drugs, abuse alcohol, or participate in high risk sexual practices

   AND
6. ONE of the following:
   a. Therapy is not being requested for treatment of a patient re-infected with hepatitis C
      OR
   b. Therapy is being requested for a patient re-infected with hepatitis C following liver transplantation

   AND

7. The patient has not been previously treated with the requested agent
   AND
8. The dose is within the FDA labeled dose
   AND
9. The requested agent will be used in a treatment regimen AND length of therapy recommended for the patient's genotype as noted in Table 4 (FDA labeling)

Length of approval: Up to the duration of treatment as determined in Table 4

Table 4: **Mavyret Treatment Recommendations based on FDA labeling**

Genotype	Patient Population*	Treatment	Treatment Duration	
			No Cirrhosis	Compensated Cirrhosis (Child-Pugh A)
1, 2, 3, 4, 5, or 6	Treatment naïve	Mavyret	8 weeks	12 weeks
1	Treatment experienced with an NS5A inhibitor[1] but without prior treatment with an NS3/4A protease inhibitor (PI)	Mavyret	16 weeks	16 weeks
1	Treatment experienced with an NS3/4A protease inhibitor[2] but without prior treatment with an NS5A inhibitor	Mavyret	12 weeks	12 weeks
1, 2, 4, 5, or 6	Treatment experienced with PRS[3]	Mavyret	8 weeks	12 weeks
3	Treatment experienced with PRS[3]	Mavyret	16 weeks	16 weeks

*Follow the dosage recommendations above for HCV/HIV co infected patient and in patients with any degree of kidney impairment (including those on hemodialysis)
1. Examples of HCV NS5A inhibitors include daclatasvir, elbasvir, ledipasvir, ombitasvir, velpatasvir.
2. Examples of NS3/4A protease inhibitors include simeprevir, boceprevir, telaprevir
3. PRS=Prior treatment experience with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor.

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Technivie (ombitasvir/paritaprevir/ritonavir) will be approved when ALL of the following criteria are met:
1. The patient has a diagnosis of compensated chronic hepatitis C, genotype 4
   AND
2. The prescriber has screened the patient for current or prior hepatitis B viral (HBV) infection and will monitor the patient for HBV flare-up or reactivation during and after treatment with the requested agent
   AND
3. The requested agent is being prescribed by a specialist (e.g. gastroenterologist, hepatologist, or infectious disease) or in consultation with a specialist
   AND
4. The patient does not have any FDA labeled contraindications to the requested agent
   AND
5. ONE of the following:
   a. The patient has no known history of illicit drug and/or alcohol abuse and/or high risk sexual practices
      OR
   b. The patient has a history of illicit drug and/or alcohol abuse and/or high risk sexual practices and ONE of the following:
      i. The patient has abstained from the use of illicit drugs, alcohol abuse, and/or high risk sexual practices for the past 12 months or for a length of time at the discretion of the provider to determine readiness for treatment
         OR

ii. The patient is actively participating in a recovery program and will not continue to actively abuse illicit drugs, abuse alcohol, or participate in high risk sexual practices

AND

6. ONE of the following:
   a. Therapy is not being requested for treatment of a patient re-infected with hepatitis C
      OR
   b. Therapy is being requested for a patient re-infected with hepatitis C following liver transplantation

AND

7. ONE of the following:
   a. The patient is treatment naïve
      OR
   b. The patient was previously treated (i.e. treatment experienced) with ONLY peg-interferon and ribavirin

AND

8. The dose is within the FDA labeled dose

AND

9. The requested agent will be used in a treatment regimen AND length of therapy recommended for the patient's genotype as noted in Table 5 (FDA labeling)

Length of approval: Up to the duration of treatment as determined by Table 5

Table 5: Technivie Treatment Recommendations based on FDA labeling

Patient population	Treatment	Treatment Duration
Genotype 4 without cirrhosis and the patient ribavirin eligible	Technivie + ribavirin	12 weeks
Genotype 4, treatment naïve, without cirrhosis and the patient ribavirin ineligible*	Technivie	12 weeks
Genotype 4 with compensated cirrhosis	Technivie + ribavirin	12 weeks

*Ribavirin ineligible - patients with history of intolerance, contraindication, or hypersensitivity to ribavirin

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Viekira PAK or Viekira XR will be approved when ALL of the following criteria are met:

1. The patient has a diagnosis of compensated chronic hepatitis C genotype 1

AND

2. The prescriber has provided the patient's subtype

AND

3. The prescriber has screened the patient for current or prior hepatitis B viral (HBV) infection and will monitor the patient for HBV flare-up or reactivation during and after treatment with the requested agent

AND

4. The requested agent is being prescribed by a specialist (e.g. gastroenterologist, hepatologist, or infectious disease) or in consultation with a specialist

AND

5. The patient does not have any FDA contraindications to the requested agent

AND

6. ONE of the following:
   a. The patient has no known history of illicit drug and/or alcohol abuse and/or high risk sexual practices
      OR
   b. The patient has a history of illicit drug and/or alcohol abuse and/or high risk sexual practices and ONE of the following:

i. The patient has abstained from the use of illicit drugs, alcohol abuse, and/or high risk sexual practices for the past 12 months or for a length of time at the discretion of the provider to determine readiness for treatment
OR
ii. The patient is actively participating in a recovery program and will not continue to actively abuse illicit drugs, abuse alcohol, or participate in high risk sexual practices

AND

7. ONE of the following:
   a. Therapy is not being requested for treatment of a patient re-infected with hepatitis C
   OR
   b. Therapy is being requested for a patient re-infected with hepatitis C following liver transplantation

AND

8. ONE of the following:
   a. The patient is treatment naïve
   OR
   b. The patient was previously treated (i.e. treatment experienced) with ONLY peg-interferon and ribavirin

AND

9. The dose is within the FDA labeled dose

AND

10. The requested agent will be used in a treatment regimen AND length of therapy recommended for the patient's genotype as noted in Table 6 (FDA labeling)

Length of approval: Up to the duration as determined in Table 6

Table 6: Viekira PAK and Viekira XR Treatment Recommendations based on FDA labeling

Patient Population	Treatment*	Duration
Genotype 1a, without cirrhosis	Viekira PAK + ribavirin OR Viekira XR + ribavirin	12 weeks
Genotype 1a, with compensated cirrhosis	Viekira PAK + ribavirin OR Viekira XR + ribavirin	24 weeks**
Genotype 1b, with or without compensated cirrhosis	Viekira PAK OR Viekira XR	12 weeks
Genotype 1a or 1b post liver transplant with normal hepatic function (i.e. Metavir ≤2)	Viekira PAK + ribavirin OR Viekira XR + ribavirin	24 weeks

*HCV/HIV-1 co-infection, follow recommendations in table above
**Viekira PAK or Viekira XR with RBV for 12 weeks may be considered for some patients based on prior treatment history. The SVR12 rate difference between 24 and 12 weeks of treatment was +6% with differences varying by pretreatment history.

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Vosevi will be approved when ALL of the following criteria are met:

1. The patient has a diagnosis of chronic hepatitis C genotype 1, 2, 3, 4, 5, or 6
   AND
2. If genotype 1, the prescriber has provided the patient's subtype
   AND
3. The prescriber has screened the patient for current or prior hepatitis B viral (HBV) infection and will monitor the patient for HBV flare-up or reactivation during and after treatment with the requested agent
   AND
4. The requested agent is being prescribed by a specialist (e.g. gastroenterologist, hepatologist, or infectious disease) or in consultation with a specialist
   AND

5. The patient does not have any FDA labeled contraindications to the requested agent
   AND
6. ONE of the following:
   a. The patient has no known history of illicit drug and/or alcohol abuse and/or high risk sexual practices
      OR
   b. The patient has a history of illicit drug and/or alcohol abuse and/or high risk sexual practices and ONE of the following:
      i. The patient has abstained from the use of illicit drugs, alcohol abuse, and/or high risk sexual practices for the past 12 months or for a length of time at the discretion of the provider to determine readiness for treatment
         OR
      ii. The patient is actively participating in a recovery program and will not continue to actively abuse illicit drugs, abuse alcohol, or participate in high risk sexual practices

   AND
7. ONE of the following:
   a. Therapy is not being requested for treatment of a patient re-infected with hepatitis C
      OR
   b. Therapy is being requested for a patient re-infected with hepatitis C following liver transplantation

   AND
8. BOTH of the following:
   a. The patient is not treatment naïve **AND**
   b. The patient has not been previously treated with the requested agent

   AND
9. The dose is within the FDA labeled dose
   AND
10. The requested agent will be used in a treatment regimen AND length of therapy recommended for the patient's genotype as noted in Table 7 (FDA labeling)

Length of approval: Up to the duration of treatment as determined in Table 7

Table 7: **Vosevi Treatment Recommendations based on FDA labeling**

Patient Population	Patients Previously Treated with an HCV Regimen Containing:	Treatment Duration
Genotype 1,2,3,4,5, or 6 without cirrhosis or with compensated cirrhosis (Child Pugh A)	An NS5A inhibitor[a]	12 weeks
Genotype 1a or 3 without cirrhosis or with compensated cirrhosis (Child Pugh A)	Sofosbuvir without an NS5A inhibitor[b]	12 weeks

a Examples of HCV NS5A inhibitors include daclatasvir, elbasvir, ledipasvir, ombitasvir, velpatasvir
b Sofosbuvir with or without any of the following: peginterferon alfa/ribavirin, ribavirin, HCV NS3/4A protease inhibitor (simeprevir)

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Zepatier will be approved when ALL of the following criteria are met:
1. The patient has a diagnosis of compensated chronic hepatitis C genotype 1 or 4
   AND
2. BOTH of the following:
   a. If genotype 1, the prescriber has provided the patient's subtype
      AND
   b. If the subtype 1a, the prescriber has tested the patient for NS5A polymorphisms

   AND
3. The prescriber has screened the patient for current or prior hepatitis B viral (HBV) infection and will monitor the patient for HBV flare-up or reactivation during and after treatment with the requested agent

AND

4. The requested agent is being prescribed by a specialist (e.g. gastroenterologist, hepatologist, or infectious disease) or in consultation with a specialist
   AND
5. The patient does not have any FDA labeled contraindications to the requested agent
   AND
6. ONE of the following:
   a. The patient has no known history of illicit drug and/or alcohol abuse and/or high risk sexual practices
      OR
   b. The patient has a history of illicit drug and/or alcohol abuse and/or high risk sexual practices and ONE of the following:
      i. The patient has abstained from the use of illicit drugs, alcohol abuse, and/or high risk sexual practices for the past 12 months or for a length of time at the discretion of the provider to determine readiness for treatment
         OR
      ii. The patient is actively participating in a recovery program and will not continue to actively abuse illicit drugs, abuse alcohol, or participate in high risk sexual practices

   AND
7. ONE of the following:
   a. Therapy is not being requested for treatment of a patient re-infected with hepatitis C
      OR
   b. Therapy is being requested for a patient re-infected with hepatitis C following liver transplantation

   AND
8. ONE of the following:
   a. The patient is treatment naïve
      OR
   b. The patient was previously treated (i.e. treatment experienced) with ONLY peg-interferon and ribavirin with or without an HCV protease inhibitor

   AND
9. The dose is within the FDA labeled dose
   AND
10. The requested agent will be used in a treatment regimen AND length of therapy recommended for the patient's genotype as noted in Table 8 (FDA labeling)

Length of approval: Up to the duration of treatment as determined in Table 8

Table 8: Zepatier Treatment Recommendations based on FDA labeling

Patient Population^,£	Treatment	Duration
Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced without baseline NS5A polymorphisms†	Zepatier	12 weeks
Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced with baseline NS5A polymorphisms†	Zepatier + ribavirin	16 weeks
Genotype 1b: Treatment-naïve or PegIFN/RBV-experienced	Zepatier	12 weeks
Genotype 1a or 1b: PegIFN/RBV/protease inhibitor-experienced	Zepatier + ribavirin	12 weeks
Genotype 4: Treatment-naive	Zepatier	12 weeks
Genotype 4: PegIFN/RBV-experienced	Zepatier + ribavirin	16 weeks

†Polymorphisms at amino acid positions 28, 30, 31, or 93

^Genotype 1a: Testing for the presence of virus with NS5A resistance-associated polymorphisms is recommended.

£ HCV/HIV co-infection and/or cirrhosis: follow dosage recommendations in the table above

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

New to market chronic Hepatitis C agents will be approved when ALL of the following criteria are met:

1. The patient has an FDA approved diagnosis for the requested agent
   AND
2. BOTH of the following:
   a. FDA labeling for the requested agent requires patients are tested for hepatitis B viral (HBV) infection prior to starting treatment with the requested agent
      AND
   b. The prescriber has screened the patient for current or prior HBV and will monitor the patient for HBV flare-up or reactivation during and after treatment with the requested agent
3. The requested agent is FDA approved for treatment of the patient's genotype
   AND
4. The patient does not have any FDA labeled contraindications to the requested agent
   AND
5. The requested agent is being prescribed by a specialist (e.g. gastroenterologist, hepatologist, or infectious disease) or in consultation with a specialist
   AND
6. ONE of the following:
   a. The patient has no known history of illicit drug and/or alcohol abuse and/or high risk sexual practices
      OR
   b. The patient has a history of illicit drug and/or alcohol abuse and/or high risk sexual practices and ONE of the following:
      i. The patient has abstained from the use of illicit drugs, alcohol abuse, and/or high risk sexual practices for the past 12 months or for a length of time at the discretion of the provider to determine readiness for treatment
         OR
      ii. The patient is actively participating in a recovery program and will not continue to actively abuse illicit drugs, abuse alcohol, or participate in high risk sexual practices

   AND
7. ONE of the following:
   a. Therapy is not being requested for treatment of a patient re-infected with hepatitis C
      OR
   b. Therapy is being requested for a patient re-infected with hepatitis C following liver transplantation

   AND
8. The dose is within the FDA labeled dose
   AND
9. The requested agent will be used in a treatment regimen AND length of therapy recommended for the patient's diagnosis, and genotype as noted in Table 9 (FDA labeling)

Length of approval: Up to the duration of treatment as determined in Table 9

Table 9: Treatment Recommendations based on FDA labeling

Agent(s)	FDA approved indication(s)	Genotype	Treatment Regimen	FDA labeled dose	Treatment Duration

HCV/HIV-1 co-infection and patients with any degree of renal impairment: Follow the Mavyret dosage recommendations in the table above

1 In clinical trials, subjects were treated with prior regimens containing ledipasvir and sofosbuvir or daclatasvir with pegylated infeterferon and ribavirin

2 In clinical trials, subjects were treated with prior regimens containing simeprevir and sofosbuvir, or simeprevir, boceprevir, or telaprevir with pegylated interferon and ribavirin

3 PRS-Pegylated interferon, ribavirin, and sofosbuvir

* Vosevi is not FDA indicated for treatment naïve patients

a. HCV NS5A inhibitors include but are not limited to daclatasvir, elbasvir, ledipasvir, ombitasvir, or velpatasvir.

b. Sofosbuvir with or without any of the following: peginterferon alfa/ribavirin, ribavirin, HCV NS3/4A protease inhibitor (boceprevir, simeprevir or telaprevir).

Contraindications:

Agent(s)	Contraindication(s)
Epclusa® (sofosbuvir/velpatasvir)	Epclusa and ribavirin combination regimen is contraindicated in patients for whom ribavirin is contraindicated
Harvoni® (ledipasvir/sofosbuvir)	If used in combination with ribavirin, all contraindications to ribavirin also apply to Harvoni combination therapy.
Mavyret™ (glecaprevir/pibrentasvir)	Patients with severe hepatic impairment (Child-Pugh C) Coadministration with atazanavir or rifampin
Technivie™ (paritaprevir/ritonavir/ombitasvir)	Patients with moderate to severe hepatic impairment [decompensated cirrhosis (Child-Pugh B or C)]. Co-administration with drugs that are: highly dependent on CYP3A for clearance; moderate and strong inducers of CYP3A. Known hypersensitivity to ritonavir (e.g. toxic epidermal necrolysis, Steven-Johnson syndrome). The contraindications to ribavirin also apply to this combination regimen (Technivie + ribavirin).
Viekira PAK™ (paritaprevir/ritonavir/ombitasvir + dasabuvir) and **Viekira XR™** (dasabuvir/ombitasvir/paritaprevir/ritonavir)	Patients with moderate to severe hepatic impairment [decompensated cirrhosis (Child-Pugh B or C)]. Known hypersensitivity to ritonavir (e.g. toxic epidermal necrolysis, Steven-Johnson syndrome). Co-administration with drugs that are: highly dependent on CYP3A for clearance; moderate or strong inducers of CYP3A and strong inducers of CYP2C8; and strong inhibitors of CYP2C8. If Viekira or Viekira XR is administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen.
Vosevi™ (sofosbuvir/velpatasvir/voxilaprevir)	Coadministration with rifampin
Zepatier™ (elbasvir/grazoprevir)	Patients with moderate or severe hepatic impairment [decompensated cirrhosis (Child-Pugh B or C)]. Organic anion transporting polypeptides 1B1/3 (OATP1B1/3) inhibitors, strong CYP3A inducers, and efavirenz. If Zepatier is administered with ribavirin, the contraindications to ribavirin also apply.

FDA APPROVED INDICATIONS AND DOSAGE [1,2,3,4,7,8,10,11]

Medication	Indications	Dose and Interval
Epclusa (sofosbuvir/velpatasvir)	Treatment of chronic hepatitis C genotype 1, 2, 3, 4, 5, or 6 infection: - without cirrhosis or with compensated cirrhosis with decompensated cirrhosis (use in combination with ribavirin)	1 tablet orally once daily containing 400 mg of sofosbuvir and 100 mg of velpatasvir for 12 weeks
Harvoni (ledipasvir-sofosbuvir)	Treatment, with or without ribavirin, of adults with chronic hepatitis C, genotype 1, 4, 5, or 6 infection Treatment of pediatric patients 12 years of age or older or weighing at least 35 kg with chronic hepatitis C, genotype 1, 4, 5, or 6 without or with compensated cirrhosis	1 tablet orally once daily containing 90 mg of ledipasvir and 400 mg of sofosbuvir for up to 24 weeks
Mavyret (glecaprevir/pibrentasvir)	Treatment of adult patients within chronic hepatitis C genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis (Child Pugh A) Treatment of adult patients within chronic hepatitis C 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	3 tablets orally once daily for up to 16 weeks
Technivie (ombitasvir/paritaprevir/ritonavir)	Treatment, in combination with ribavirin, of chronic hepatitis C genotype 4 without cirrhosis or with compensated cirrhosis	Two ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets once daily (in the morning) for 12 weeks
Viekira Pak (paritaprevir/ritonavir/ombitasvir and dasabuvir)	Treatment of adult patients with chronic hepatitis C virus: - genotype 1b with or without compensated cirrhosis - genotype 1a with or without compensated cirrhosis. Use in combination with ribavirin for genotype 1a	Two ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening) for up to 24 weeks
Viekira XR (dasabuvir/ombitasvir/paritaprevir/ritonavir)	Treatment of adult patients with chronic hepatitis C virus: - genotype 1b with or without compensated cirrhosis - genotype 1a with or without compensated cirrhosis. Use in combination with ribavirin for genotype 1a	3 tablets taken once daily for up to 24 weeks
Vosevi (sofosbuvir/velpatasvir/voxilaprevir)	Treatment of adult patients with HCV infection without cirrhosis or compensated cirrhosis (Child-Pugh A) who have: - genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated	1 tablet taken once daily for 12 weeks

	with an HCV regimen containing an NS5A inhibitor - genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor	
Zepatier (elbasvir/grazoprevir)	Treatment, with or without ribavirin, of chronic hepatitis C genotype 1 or 4 infection	1 tablet (50 mg elbasvir and 100 mg grazoprevir) once daily for up to 16 weeks

Disease Background[5,6]
Hepatitis C is an infection of the liver caused by the Hepatitis C virus (HCV) and is one of the leading causes of chronic liver disease in the United States. According to the Centers for Disease Control and Prevention (CDC), there were an estimated 3.5 million people infected with hepatitis C as of 2015. Hepatitis C infection can either be acute or chronic. Acute HCV infection is defined as presenting within 6 months following exposure to the virus. The infection is defined as chronic if the virus is present beyond 6 months following exposure. 70% to 80% of those infected with HCV will go on to develop chronic HCV infection.

Persons at high risk for contracting HCV infection include intravenous drug users, recipients of donated blood, blood products, and organs (now rare in the United States due to stringent blood screening), babies born to HCV infected mothers, and persons with HIV infection.

Hepatitis C infection is asymptomatic in the early stages of the disease. However, with disease progression, patients may develop mild to severe chronic liver disease including cirrhosis and liver cancer. The goal of therapy is to eradicate the virus and prevent liver damage including cirrhosis. Direct acting antivirals (DAAs) are currently the mainstay of treatment for chronic HCV infection. Certain DAAs may be used as monotherapy while others require use in combination with other agents including peg-interferon, ribavirin and other DAAs.

The American Association of the Study of Liver Disease (AASLD) and the Infectious Disease Society of America (IDSA) have developed guidelines to aid in the management of hepatitis C. The guidelines address issues ranging from testing and linkage to care to the optimal treatment regimen based on patient situations.

AASLD/IDSA guidelines on when and in whom to treat[5]
The goal of therapy is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure. According to the AASLD/IDSA guidelines, treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Treatment should be initiated early because delaying therapy may decrease the benefits of eradicating the hepatitis C viral infection.

Treatment recommendations for patients who have failed therapy with the newer DAAs is limited. AASLD/IDSA recommend ledipasvir/sofosbuvir plus ribavirin for 24 weeks for those who have cirrhosis and have failed sofosbuvir plus ribavirin with or without peg-interferon. Deferral of treatment is recommended, pending availability of data, for patients who have failed other DAAs (not including protease inhibitors). If the decision is made to treat urgently, resistance testing should guide selections of the appropriate therapy for treatment.

AASLD recommends awaiting availability of pangenotypic agents for the management of patients with mixed genotypes. Patients who are co-infected with HCV and either hepatitis B or HIV should be treated as those mono-infected with HCV.

Elbasvir/grazoprevir[4]
Elbasvir/grazoprevir is a combination regimen of an NS5A replication inhibitor (elbasvir) and an NS3/4A protease inhibitor (grazoprevir). Its efficacy was evaluated in several phase 2 and 3 clinical trials. All the trials had a primary end point of sustained virologic response at 12 weeks (SVR12) following completion of treatment.

Efficacy of this combination in treatment naïve patients with HCV genotype 1 with or without cirrhosis was evaluated in the C-EDGE TN and C-EDGE COINFECTION trials. Subjects in both trials received elbasvir/grazoprevir for 12 weeks. SVR12 was 95% in both trials. There were no significant differences in SVR12 between cirrhotic and non-cirrhotic patients. The C-EDGE TE trial evaluated efficacy of this combination in treatment experienced HCV genotype 1 patients with or without cirrhosis who had previously failed peginterferon plus ribavirin. Subjects received elbasvir/grazoprevir monotherapy for 12 weeks or elbasvir/grazoprevir with ribavirin for 16 weeks. SVR12 rates in the two treatment groups were 94% and 97% respectively. Efficacy in HCV genotype 1 patients with or without cirrhosis who had previously failed peginterferon, ribavirin, plus a protease inhibitor was evaluated in the C-SALVAGE trial. This was an open label, single arm trial. All subjects received elbasvir/grazoprevir plus ribavirin for 12 weeks. Overall SVR12 was 96%.

Efficacy of this combination in patients with HCV genotype 1 with or without cirrhosis and who had Chronic Kidney Disease (CKD) stage 4 (eGFR 15-29 mL/min/1.73 m^2) or CKD Stage 5 (eGFR <15 mL/min/1.73 m^2), including patients on hemodialysis was evaluated in the C-SURFER trial. Patients were randomized to receive either elbasvir/grazoprevir for 12 weeks or placebo for 12 weeks followed by 12 weeks of elbasvir/grazoprevir (deferred treatment group). Overal SVR12 was 99%. There were no significant differences with regard to safety in the elbasvir/grazoprevir group versus placebo group.

These trials found that presence of NS5A amino acid polymorphisms in patients with HCV genotype 1a was associated with reduced efficacy of elbasvir/grazoprevir regardless of treatment history or cirrhosis status. It is recommended to test for NS5A polymorphisms in HCV genotype 1a patients prior to starting treatment with this combination. If the polymorphism is present, addition of ribavirin to the treatment regimen and extension of the duration of treatment to 16 weeks is recommended.

Efficacy of this combination in HCV genotype 4 patients was evaluated in the C-SCAPE, C-EDGE TE, C-EDGE TN, and C-EDGE COINFECTION trials. Treatment naïve patients in these trials received elbasvir/grazoprevir for 12 weeks while those who were treatment experienced received elbasvir/grazoprevir plus ribavirin for 12 to 16 weeks. SVR12 in the treatment naïve and treatment experienced patients was 97% and 100% respectively.

The most common adverse events observed with elbasvir/grazoprevir were fatigue, headache, and nausea. This combination is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B or C). Use in combination with strong CPY3A inducers, efavirenz, or organic anion transporting polypeptides 1B1/3 (OATP1B1/3) inhibitors is contraindicated.

Glecaprevir/pibrentasvir[11]
Glecaprevir/pibrentasvir is a combination of an NS3/4A protease inhibitor and an NS5A inhibitor. Its safety and efficacy have been demonstrated in treatment naïve patients with HCV genotype 1, 2, 3, 4, 5 or 6 without cirrhosis or with compensated cirrhosis. Its safety and efficacy has also been demonstrated in patients who have previously been treated with a regimen containing an NS5A inhibitor or an NS3/4A protease inhibitor but not both. Patients with prior treatment with both an NS5A inhibitor and NS3/4A inhibitor were at an increased risk of virologic failure when retreated with glecaprevir/pibrentasvir.

The most common adverse events associated with glecaprevir/pibrentasvir are headache and fatigue.

Ledipasvir/sofosbuvir[1]
Ledipasvir/sofosbuvir is a combination of an NS5A inhibitor and nucleotide analog NS5B polymerase inhibitor. Its efficacy was evaluated in several phase 2 and 3 clinical trials. These trials enrolled a broad

range of patient populations including treatment naïve and treatment experienced patients, those without cirrhosis and with cirrhosis (compensated and decompensated), post-liver transplant patients, as well as those with HIV/HCV co-infection. All the trials had a primary end point of sustained virologic response at 12 weeks (SVR12) following completion of treatment. Overall SVR12 was greater than 90% for the various patient populations. The treatment duration of this agent varies from 8 weeks to 24 weeks. Per the FDA labeling, treatment naïve patients with HCV genotype 1 with RNA of less than 6 million can be successfully treated with 8 weeks of ledipasvir/sofosbuvir. This duration of treatment is not recommended in patients with cirrhosis, HIV, are post-liver transplantation, and/or black or African-American. Treatment experienced patients with cirrhosis may be treated with ledipasvir/sofosbuvir alone for 24 weeks or in combination with ribavirin for 12 weeks. These two regimens are equally efficacious with SVR12 of 96% and 97% respectively.[1]

The most common side effects associated with ledipasvir/sofosbuvir are fatigue, headache, and asthenia.

Ombitasvir/paritaprevir/ritonavir and dasabuvir[3,8]
Safety and efficacy of this combination was evaluated in 4 pivotal trials including treatment naïve, previous failures, cirrhotics and non-cirrhotic genotype 1 patients. The studies (Sapphire I, Turquoise II, Pearl III and Pearl IV) all had a primary efficacy endpoint of a sustained virologic response (SVR) at 12 weeks after the end of therapy. Sapphire I was conducted in treatment naïve patients without cirrhosis. Turquoise-2 was conducted in treatment naïve and previously treated patients and included cirrhotic patients. Pearl III evaluated treatment naïve genotype 1b patients and Pearl IV evaluated treatment naïve genotype 1a patients. SVR rates in these trials ranged from 90% to 99%. Treatment guidelines recommend that patients that have failed a previous protease inhibitor containing regimen receive ledipasvir/sofosbuvir. Ombitasvir/paritaprevir/ritonavir + dasabuvir is not a recommended regimen in previous protease inhibitor failures due to risk of resistance.

Ombitasvir/paritaprevir/ritonavir[2]
Efficacy and safety of this combination, when used with or without ribavirin, was evaluated in a single clinical trial (PEARL-I). The study enrolled 135 subjects with chronic hepatitis C (HCV) infection genotype 4 without cirrhosis. The subjects were either treatment naïve or had history of virologic failure following treatment with pegylated interferon and ribavirin. The primary end point of the study was sustained virologic response at 12 weeks (SVR 12) following completion of therapy. SVR 12 was 100% for treatment naïve and treatment experienced subjects whose regimen included ribavirin and 91% for treatment naïve patients whose regimen did not include ribavirin. Safety and efficacy of this combination regimen has not been studied in patients previously treated with a direct acting antiviral.

The most common adverse events reported in the trial were asthenia, fatigue, nausea, insomnia, pruritis, and skin reaction. These adverse events were graded as mild in severity.

Sofosbuvir/velpatasvir[7]
Efficacy of this combination agent was evaluated in four phase 3 trials (ASTRAL-1, ASTRAL-2, ASTRAL-3, and ASTRAL-4). All these trials included patients who were either treatment naïve or had previously been treated with an interferon based regimen (peginterferon plus ribavirin with or without a protease inhibitor). The primary endpoint for these trials was sustained virologic response at 12 weeks (SVR 12) following completion of therapy. ASTRAL-1 was a placebo controlled trial that enrolled patients with HCV infection genotype 1, 2, 4, 5, or 6. Overall, the SVR 12 rate was 99% in patients who received sofosbuvir/velpatasvir and 0% in those receiving placebo (95% confidence interval, $p<0.001$) . ASTRAL-2 and ASRTAL-3 were randomized, open label trials evaluating efficacy in patients with HCV genotype 2 or 3 respectively. Those with HCV genotype 2 received either sofosbuvir/velpatasvir for 12 weeks or sofosbuvir plus ribavirin for 12 weeks. The SVR12 rates for the two treatment arms were 99% and 94% respectively. Subjects with HCV genotype 3 were randomized to receive either sofosbuvir/velpatasvir for 12 weeks or sofosbuvir plus ribavirin for 24 weeks. The SVR 12 rates were 95% and 80% respectively. ASTRAL-4 was an open label trial that evaluated efficacy of sofosbuvir/velpatasvir in patients with decompensated cirrhosis. Patients were randomized to receive one of three treatment regimens: sofosbuvir/velpatasvir for 12 weeks, sofosbuvir/velpatasvir for 24 weeks, or sofosbuvir/velpatasvir plus ribavirin for 12 weeks. SVR 12 rates were 83%, 86%, and 94% respectively.

The most common adverse events reported in patients who received sofosbuvir/velpatasvir were headache and fatigue. Those with decompensated cirrhosis who were treated with sofosbuvir/velpatasvir and ribavirin reported fatigue, anemia, nausea, headache, insomnia, and diarrhea as the most common adverse events.

Sofosbuvir/velpatasvir/voxilaprevir[10]
Sofosbuvir/velpatasvir/voxilaprevir is a fixed-dose combination of sofosbuvir, a nucleotide analog NS5B polymerase inhibitor, velpatasvir, an HCV NS5A inhibitor, and voxilaprevir, an HCV NS3/4A protease inhibitor. Efficacy of this combination agent has been demonstrated in patients with HCV genotype 1, 2, 3, 4, 5, or 6 who have previously been treated with a regimen containing an NS5A inhibitor and in patients with genotype 1a or 3 infection who have been previously treated with a regimen containing sofosbuvir without an NS5A inhibitor. Additional benefit of this combination agent over sofosbuvir/velpatasvir has not been shown in patients with genotype 1b, 2, 4, 5, or 6 infection who were previously treated with sofosbuvir without an NS5A inhibitor.

The most common adverse events reported in patients who received sofosbuvir/velpatasvir/voxilaprevir were headache, fatigue, diarrhea, and nausea.

Risk of Hepatitis B infection reactivation with HCV Direct Acting Antivirals[9]
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.

References

1. Harvoni prescribing information. Gilead. April 2017.
2. Technivie prescribing information. Abbvie Inc. February 2017.
3. Viekira prescribing information. Abbvie Inc. February 2017
4. Zepatier prescribing information. Merck. February 2017.
5. AASLD/IDSA HCV Guidance: Recommendations for Testing, Managing, and Testing Hepatitis C. Available at www.hcvguidelines.org. Accessed May 2017.
6. The center for Disease Control and Prevention. Viral Hepatitis Statistics and Surveillance. Available at http://www.cdc.gov/hepatitis/statistics. Accessed June 2016.
7. Epclusa prescribing information. Gilead. August 2017.
8. Viekira XR prescribing information. Abbvie. July 2016.
9. Direct-Acting Antivirals for Hepatitis C: FDA Drug Safety Communication-Risk of Hepatitis B Reactivation. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm523690.htm Accessed November 2016.
10. Vosevi prescribing information. Gilead. July 2017.
11. Mavyret prescribing information. AbbVie. August 2017.