RXADVANCE
2 Park Central Drive
Southborough, MA 01772

Clinical Policy Title:	elbasvir/grazoprevir
Policy Number:	RxA.572
Drug(s) Applied:	Zepatier®
Original Policy Date:	03/06/2020
Last Review Date:	12/07/2020
Line of Business Policy Applies to:	All lines of business

Background

Elbasvir/grazoprevir (Zepatier®) is a fixed-dose combination product containing elbasvir, a hepatitis C virus (HCV) NS5A inhibitor, and grazoprevir, an HCV NS3/4A protease inhibitor. It is indicated for treatment of chronic HCV genotype 1 or 4 infection in adults. It is indicated for use with ribavirin in certain patient populations.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
elbasvir/grazoprevir (Zepatier®)	Genotype 1a: Treatment-naïve or pegIFN/RBV-experienced with or without compensated cirrhosis without baseline NS5A polymorphisms at amino acid positions 28, 30, 31, or 93	One tablet PO Once daily for 12 weeks	One tablet(grazoprevir 100 mg/ elbasvir 50 mg) per day
	Genotype 1a: Treatment-naïve or PegIFN/RBV experienced with or without compensated cirrhosis with baseline NS5A polymorphisms at amino acid positions 28, 30, 31, or 93	One tablet PO Once daily plus weight-based RBV for 16 weeks	One tablet(grazoprevir 100 mg/ elbasvir 50 mg) per day
	Genotype 1b: Treatment-naïve or PegIFN/RBV experienced with or without compensated cirrhosis	One tablet PO Once daily for 12 weeks	One tablet (grazoprevir 100 mg/ elbasvir 50 mg) per day
	Genotype 1a or 1b: pegIFN/RBV/NS3 PI*‡ experienced with or without compensated cirrhosis without baseline NS5A	One tablet PO Once daily plus weight-based RBV for 12 weeks	One tablet(grazoprevir 100 mg/ elbasvir 50 mg) per day

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	polymorphisms at amino acid positions 28, 30, 31, or 93		
	Genotype 1a or 1b: pegIFN/RBV/NS3 PI*‡ experienced with or without compensated cirrhosis with baseline NS5A polymorphisms at amino acid positions 28, 30, 31, or 93	One tablet PO Once daily plus weight-based RBV for 16 weeks	One tablet (grazoprevir 100 mg/ elbasvir 50 mg) per day
elbasvir/grazoprevir (Zepatier®)	Genotype 3‡:pegIFN/RBV-experienced with compensated cirrhosis	One tablet PO Once daily plus sofosbuvir 400 mg for 12 weeks	One tablet (grazoprevir 100 mg/ elbasvir 50 mg) per day
	Genotype 4:Treatment-naïve with or without compensated cirrhosis	One tablet PO Once daily for 12 weeks	One tablet (grazoprevir 100 mg/ elbasvir 50 mg) per day
	Genotype 4:PegIFN/RBV-experienced with or without compensated cirrhosis with virologic relapse/failure	Virologic relapse after prior pegIFN/RBV therapy: One tablet PO Once daily for 12 weeks Virologic failure while on pegIFN/RBV therapy: One tablet PO Once daily plus weight-based RBV for 16 weeks	One tablet(grazoprevir 100 mg/ elbasvir 50 mg) per day

AASLD/IDSA treatment guidelines for chronic hepatitis C infection are updated at irregular intervals; refer to the most updated AASLD/IDSA guideline for most accurate treatment regimen.
** NS3 protease inhibitor = telaprevir, boceprevir, or simeprevir ǂ Off-label, AASLD-IDSA guideline-supported dosing regimen*

Dosage Forms

- Tablet: grazoprevir 100 mg with elbasvir 50 mg

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

I. Initial Approval Criteria

A. Chronic Hepatitis C Infection (must meet all):

1. Diagnosis of chronic HCV infection as evidenced by detectable serum HCV RNA levels by quantitative assay in the last 6 months;
2. If ribavirin is given in combination, member meets one of the following (a, b, c, or d)*:
   a. Genotype 1a with baseline NS5A resistance-associated substitutions/polymorphisms who are (up to 16 weeks of therapy may be approved):
      i. Treatment-naïve; or
      ii. Failed prior treatment with PegIFN and RBV without an HCV protease inhibitor (e.g., boceprevir, simeprevir or telaprevir);
   b. Genotype 1a without baseline NS5A resistance-associated substitutions/polymorphisms who failed prior treatment with PegIFN and RBV with an HCV protease inhibitor (e.g., boceprevir, simeprevir or telaprevir) (up to 12 weeks of therapy may be approved);
   c. Genotype 1b who failed prior treatment with PegIFN and RBV without an HCV protease inhibitor (e.g., boceprevir, simeprevir or telaprevir) (up to 12 weeks of therapy may be approved); or
   d. Genotype 4 who failed prior treatment with PegIFN and RBV (up to 16 weeks of therapy may be approved)

   *Chart note documentation and copies of lab results are required
3. In the absence of concomitant ribavirin, member meets one of the following (a, b, c, or d)*:
   a. Genotype 1a without baseline NS5A resistance-associated substitutions/polymorphisms who failed prior treatment with PegIFN and RBV with an HCV protease inhibitor (e.g., boceprevir, simeprevir or telaprevir) (up to 12 weeks of therapy may be approved)
   b. Genotype 1b who are (up to 12 weeks of therapy may be approved):
      i. Treatment-naïve; or
      ii. Failed prior treatment with PegIFN and RBV without an HCV protease inhibitor (e.g., boceprevir, simeprevir or telaprevir);
   c. Genotype 4 who are (up to 12 weeks of therapy may be approved):
      i. Treatment naïve; or
      ii. Failed prior treatment with PegIFN and RBV;
   d. Genotype 3 with compensated cirrhosis who failed PegIFN and RBV, in combination with sofosbuvir (off-label) (up to 12 weeks of therapy may be approved);

   *Chart note documentation and copies of lab results are required
4. If cirrhosis is present, confirmation of Child-Pugh A status;
5. Prescribed by or in consultation with a gastroenterologist, hepatologist or infectious disease specialist;
6. Age 18 years of age or older;
7. Life expectancy is 12 months or longer with HCV treatment;
8. Member agrees to participate in a medication adherence program meeting both of the following components (a and b):
   a. Medication adherence monitored by pharmacy claims data or member report;
   b. Member's risk for non-adherence identified by adherence program or member/prescribing physician follow-up at least every 4 weeks;
9. Prescribed regimen is consistent with an FDA or AASLD-IDSA recommended regimen (see Dosing Information);
10. Dose does not exceed Zepatier® (elbasvir/grazoprevir) 50 mg/100 mg (1 tablet) per day.

Approval Duration
Commercial: See length of duration permitted in criteria 2 and 3.
Medicaid: See length of duration permitted in criteria 2 and 3.
*(*Approved duration should be consistent with a regimen in Dosing Information)*

II. Continued Therapy Approval

A. Chronic Hepatitis C Infection (must meet all):

1. Member meets one of the following (a orb):
   a. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy
   b. Must meet both of the following (i and ii):
      i. Documentation supports that member is currently receiving Zepatier for chronic HCV infection and has recently completed at least three quarters of the full regimen with Zepatier;
      ii. Confirmed HCV genotype as outlined in initial approval criteria;
2. Member is responding positively to therapy;
3. Dose does not exceed Zepatier® (elbasvir/grazoprevir) 50 mg/100 mg (1 tablet) per day.

Approval Duration
Commercial: See total length of duration permitted in initial criteria 2 and 3.
Medicaid: See total length of duration permitted in initial criteria 2 and 3.
*(*Approved duration should be consistent with a regimen in Dosing Information)*

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
AASLD: American Association for the Study of Liver Diseases
FDA: Food and Drug Administration
HBV: hepatitis B virus HCV: hepatitis C virus
HIV: human immunodeficiency virus
IDSA: Infectious Diseases Society of America
NS3/4A, NS5A/B: nonstructural protein
PegIFN: pegylated interferon
RBV: ribavirin
RNA: ribonucleic acid

APPENDIX B: Therapeutic Alternatives
- Not applicable

APPENDIX C: Contraindications/Boxed Warnings
- Contraindication(s):
  - Patients with moderate or severe hepatic impairment (Child-Pugh B or C) due to the expected significantly increased grazoprevir plasma concentration and the increased risk of alanine aminotransferase (ALT) elevations
  - With inhibitors of organic anion transporting polypeptides 1B1/3 (OATP1B1/3) that are known or expected to significantly increase grazoprevir plasma concentrations, strong CYP3A inducers, and efavirenz
  - If Zepatier® is administered with RBV, the contraindications to RBV also apply.

- Boxed Warning(s):
  - Risk of hepatitis B virus reactivation in patients coinfected with HCV and HBV

APPENDIX D: General Information

- Hepatitis B Virus Reactivation (HBV) is a Black Box Warning for all direct-acting antiviral drugs for the treatment of HCV. HBV reactivation has been reported when treating HCV for patients co-infected with HBV, leading to fulminant hepatitis, hepatic failure, and death, in some cases. Patients should be monitored for HBV reactivation and hepatitis flare during HCV treatment and post-treatment follow-up, with treatment of HBV infection as clinically indicated.
- For patients infected with HCV Genotype 1a: Testing for the presence of virus with NS5A resistance-associated polymorphisms is recommended. Clinical trial results show decreased efficacy of Zepatier in HCV genotype 1a with presence of NS5A polymorphisms. If baseline NS5A polymorphisms are present for genotype 1a, refer to Section VI on the longer recommended duration of therapy.
- According to the September 2017 AASLD/IDSA HCV guidance updates, Zepatier plus Sovaldi is a recommended treatment option for patients treatment-experienced with pegIFN/RBV with compensated cirrhosis and genotype 3.
- Child-Pugh Score:

	1 Point	2 Points	3 Points
Bilirubin	Less than 2 mg/dL (Less than 34 umol/L)	2-3 mg/dL (34-50 umol/L)	Over 3 mg/dL (Over 50 umol/L)
Albumin	Over 3.5 g/dL (Over 35 g/L)	2.8-3.5 g/dL (28-35 g/L)	Less than 2.8 g/dL (Less than 28 g/L)
INR	Less than 1.7	1.7 - 2.2	Over 2.2
Ascites	None	Mild / medically controlled	Moderate-severe/poorly controlled
Encephalopathy	None	Mild / medically controlled Grade I-II	Moderate-severe/poorly controlled. Grade III-IV

Child-Pugh class is determined by the total number of points: A = 5-6 points; B = 7-9 points; C = 10-15 points.

APPENDIX E: Direct-Acting Antivirals for Treatment of HCV Infection

Brand Name	Drug Class				
	NS5A Inhibitor	Nucleotide Analog NS5B Polymerase Inhibitor	Non-Nucleoside NS5B Palm Polymerase Inhibitor	NS3/4A Protease Inhibitor (PI)	CYP3A Inhibitor
Daklinza	Daclatasvir				
Epclusa*	Velpatasvir	Sofosbuvir			

Harvoni*	Ledipasvir	Sofosbuvir			
Mavyret*	Pibrentasvir			Glecaprevir	
Olysio				Simeprevir	
Sovaldi		Sofosbuvir			
Technivie*	Ombitasvir			Paritaprevir	Ritonavir
Viekira XR/PAK*	Ombitasvir		Dasabuvir	Paritaprevir	Ritonavir
Vosevi*	Velpatasvir	Sofosbuvir		Voxilaprevir	
Zepatier*	Elbasvir			Grazoprevir	

References

1. Zepatier® Prescribing Information. Whitehouse Station, NJ: Merck and Company, Inc.; December 2019. Available at https://www.merck.com/product/usa/pi_circulars/z/zepatier/zepatier_pi.pdf. Accessed October 8, 2020.
2. American Association for the Study of Liver Diseases/ Infectious Disease Society of America (AASLD-IDSA). HCV guidance: recommendations for testing, managing, and treating hepatitis C. Last updated August 27, 2020. Available at: https://www.hcvguidelines.org/. Accessed October 8, 2020.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established	01/2020	03/06/2020
Policy was reviewed: 1. Clinical Policy Title Table was updated. 2. Line of business policy applies was updated to All lines of business. 3. Initial criteria for approval updated specific to genotype. 4. Continued Therapy criteria II.A.1 was rephrased to " Member is currently receiving medication that has been authorized by RxAdvance..." 5. Initial Approval criteria: Commercial and Medicaid approval duration updated. 6. Continued Approval criteria: Commercial and Medicaid approval duration were updated from up to total of 16 weeks to 112 days. 7. References were reviewed and updated.	10/07/2020	12/07/2020