Treatment of Hepatitis C with elbasvir and grazoprevir (Zepatier®)

Policy # 00509
Original Effective Date: 05/18/2016
Current Effective Date: 12/14/2020

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Treatment of Hepatitis C with Dual Therapy (Ribavirin Plus Pegylated Interferon Alfa) is addressed separately in medical policy 00374.

Note: Pegylated Interferons (Pegasys®, PegIntron®)‡ for Other (Non-Hepatitis C) Uses is addressed separately in medical policy 00375.

Note: Treatment of Hepatitis C with a sofosbuvir (Sovaldi®)‡ Based Regimen is addressed separately in medical policy 00397.

Note: Treatment of Hepatitis C with sofosbuvir/ledipasvir (Harvoni®‡, Authorized Generic) is addressed separately in medical policy 00455.

Note: Treatment of Hepatitis C with ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak™/Viekira XR™)‡ is addressed separately in medical policy 00462.

Note: Treatment of Hepatitis C with ombitasvir, paritaprevir, and ritonavir (Technivie®)‡ is addressed separately in medical policy 00478.

Note: Treatment of Hepatitis C with daclatasvir (Daklinza™)‡ and sofosbuvir (Sovaldi®)‡ is addressed separately in medical policy 00479.

Note: Treatment of Hepatitis C with sofosbuvir/velpatasvir (Epclusa®‡, Authorized Generic) is addressed separately in medical policy 00514.

Note: Treatment of Hepatitis C with glecaprevir/pibrentasvir (Mavyret™)‡ is addressed separately in medical policy 00593.

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Note: Treatment of Hepatitis C with sofosbuvir/velpatasvir/voxilaprevir (Vosevi™)‡ is addressed separately in medical policy 00594.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Chronic Hepatitis C Virus

Based on review of available data, the Company may consider elbasvir and grazoprevir (Zepatier®)‡ for the treatment of individuals with chronic hepatitis C virus (HCV) to be **eligible for coverage.****

Patient Selection Criteria

Based on review of available data, the Company may consider elbasvir and grazoprevir (Zepatier) when the following criteria are met:

- Patient has a diagnosis of chronic hepatitis C virus (HCV) genotype 1 OR genotype 4; AND
- Patient is 18 years of age or older; AND
- Patient has NOT failed prior therapy with drugs such as elabasvir/grazoprevir (Zepatier), sofusbuvir/velpatasvir (Epclusa, Authorized Generic), sofusbuvir/velpatasvir/voxilaprevir (Vosevi), sofosbuvir/ledipasvir (Harvoni, Authorized Generic), ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak/Viekira XR), daclatasvir (Daklinza), sofosbuvir (Sovaldi), glecaprevir/pibrentasvir (Mavyret), ombitasvir, paritaprevir, ritonavir (Technivie); AND
- Patient does NOT have moderate to severe hepatic impairment (Child-Pugh B or C); AND
- There is clinical evidence or patient history that suggests the use of sofosbuvir/velpatasvir (Epclusa), sofosbuvir/ledipasvir (Harvoni), or glecaprevir/pibrentasvir (Mavyret) will be ineffective or will cause an adverse reaction to the patient; AND
  *Note that failure to meet this criterion, which is an additional company requirement, will result in a denial of not medically necessary***
- Patient meets the following definitions and adheres to the timeframes for treatment (including concomitant medications):

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Patient Population	Drugs	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 PLUS ribavirin	16 weeks
Genotype 1b: Treatment naïve or PegIFN/RBV experienced ^	Zepatier	12 weeks
Genotype 1a or 1b: PegIFN/RBV/PI-experienced*	Zepatier PLUS ribavirin	12 weeks
Genotype 4: Treatment naïve	Zepatier	12 weeks
Genotype 4: PegIFN/RBV-experienced^	Zepatier PLUS ribavirin	16 weeks

^:Pegylated interferon + ribavirin
&:Polymorphisms at amino acid positions 28, 30, 31, or 93
*:Pegylated interferon + ribavirin + HCV NS3/4A protease inhibitor [telaprevir (Incivek®)‡, boceprevir (Victrelis®)‡, simeprevir (Olysio®)‡]

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of elbasvir and grazoprevir (Zepatier) in the absence of clinical evidence or patient history that suggests the use of sofosbuvir/velpatasvir (Epclusa), sofosbuvir/ledipasvir (Harvoni), or glecaprevir/pibrentasvir (Mavyret) will be ineffective or will cause an adverse reaction to the patient to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of elbasvir and grazoprevir (Zepatier) when patient selection criteria are not met (with the exception of the criteria denoted above as **not medically necessary****) to be **investigational.***

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Background/Overview

Zepatier is a fixed dose combination product containing elbasvir 50 mg, a HCV NS5A inhibitor, and grazoprevir 100 mg, an HCV NS3/4A protease inhibitor, and is indicated to be taken, with or without ribavirin, for the treatment of chronic HCV genotypes 1 or 4 infection in adults. The elbasvir portion of the drug inhibits viral replication and virion assembly. The grazoprevir portion of the drug inhibits viral replication as well by preventing proteolytic cleavage from occurring. It is recommended that patients with genotype 1a HCV be tested for NS5A resistance associated polymorphisms. The results of this test determine the treatment duration for these patients. Zepatier is taken one tablet once daily (with or without ribavirin depending on the clinical situation) for 12-16 weeks (depending on the clinical situation). Zepatier is contraindicated in Child-Pugh B or C moderate to severe hepatic impairment due to the expected significantly increased grazoprevir plasma concentration and the increased risk of alanine aminotransferase (ALT) elevations.

Hepatitis C

Hepatitis C is the most common blood borne pathogen. In the US, there are approximately 3.2 million people chronically infected with hepatitis C. Hepatitis C, a single-stranded ribonucleic acid (RNA) virus, is genetically complex with several recognized genotypes. Genotypes 1, 2, and 3 are the most frequently encountered genotypes worldwide. Type 1a is most frequently found in Northern Europe and North America, while 1b is most common in Japan and Southern and Eastern Europe. Genotypes 4 and 5 are most commonly found in Africa, while genotype 6 is common in Asia.

Drug regimens have evolved quite a bit over the past few years in this class. It is beyond the scope of this policy to delve into the entire timeline of approvals, however a brief overview will provide an idea of the evolution of these drugs. The earlier regimens contained ribavirin and interferon/pegylated interferons. The next wave of products brought NS3/4A protease inhibitors to market such as Incivek and Victrelis. After that, an NS5B polymerase inhibitor was approved (Sovaldi). Following the release of Sovaldi, a drug was approved that contained a combination NS5A inhibitor and NS5B polymerase inhibitor combination (Harvoni). Drugs approved up until that point in time mainly treated genotype 1 hepatitis C virus. After these drugs were approved, a multitude of other drugs were approved (Viekira/XR, Zepatier, Daklinza, etc). As drugs continue to be FDA approved in this space, the range of genotypes that can be treated increases. The latest wave of drugs includes pangenotypic products such as Eplcusa, Mavyret, and Vosevi. For more information on

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each individual drug, please see the product's package insert or refer to their respective medical policy.

Zepatier has been integrated into the American Association for the Study of Liver Diseases (AASLD) guidelines in various scenarios for the treatment of HCV, however it should be noted that these guidelines are receiving constant updates as new products are approved.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Zepatier was approved in January of 2016 for the treatment (with or without ribavirin) of adults with HCV genotypes 1 or 4.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Treatment Naïve Subjects with Genotype 1 HCV
The efficacy of Zepatier in treatment naïve subjects with genotype 1 HCV with or without cirrhosis was demonstrated in 2 trials (C-EDGE TN and C-EDGE COINFECTION). C-EDGE TN included treatment naïve subjects with genotype 1 or 4 infection with or without cirrhosis. Subjects were randomized to Zepatier for 12 weeks or placebo for 12 weeks followed by open label Zepatier for 12 weeks. C-EDGE COINFECTION included treatment naïve HCV/HIV-1 co-infected subjects with genotype 1 or 4 infection with or without cirrhosis. Subjects in this trial received 12 weeks of Zepatier. The overall sustained virologic response (SVR) for those with genotype 1 HCV was 95% in both trials.

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Treatment Experienced Subjects with Genotype 1 HCV

Failures with pegylated interferon/ribavirin

C-EDGE TE studied subjects with genotype 1 or genotype 4 HCV infection, with or without cirrhosis, with or without HCV/HIV-1 coinfection who had failed prior therapy with pegylated interferon and ribavirin. Subjects either received Zepatier for 12 weeks, Zepatier plus ribavirin for 12 weeks, Zepatier for 16 weeks, or Zepatier plus ribavirin for 16 weeks. Treatment outcomes with Zepatier plus ribavirin for 12 weeks or without ribavirin for 16 weeks were not included in the package insert as those regimens are not recommended for this group of patients. Zepatier alone for 12 weeks had an overall SVR or 94% while Zepatier plus ribavirin for 16 weeks had an overall SVR of 97%

Failures with pegylated interferon/ribavirin PLUS an HCV protease inhibitor

C-SALVAGE studied patients with genotype 1 infection, with or without cirrhosis, who failed prior treatment with boceprevir, simeprevir, or telaprevir in combination with pegylated interferon and ribavirin. Patients received Zepatier plus ribavirin for 12 weeks. Overall SVR was achieved in 96% of subjects takin Zepatier plus ribavirin.

Severe Renal Impairment (Including Hemodialysis) with Genotype 1 HCV

C-SURFER studied subjects with genotype 1 HCV infection, with or without cirrhosis, with chronic kidney disease stage 4 or stage 5, including subjects on hemodialysis, who were treatment naïve or who had failed therapy with interferon or pegylated interferon (with or without ribavirin). Patients received either Zepatier once daily for 12 weeks or placebo followed by open label treatment with Zepatier for 12 weeks. The overall SVR in these patients was 94%. It should be noted that this specific patient population does not have a dosing recommendation in the Harvoni package insert.

Genotype 1a Subjects with Polymorphisms

In genotype 1a infected subjects, the presence of one or more HCV NS5A amino acid polymorphisms at position M28, Q30, L31, or Y93 was associated with reduced efficacy of Zepatier for 12 weeks. The overall SVR for those with baseline NS5A polymorphisms (M28, Q30, L31, or Y93) was 70% and in those patients without the baseline NS5A polymorphisms was 98%. In those patients taking 16 weeks of Zepatier plus ribavirin, the SVR was 100%, therefore prompting the appropriate regimen for those with genotype 1a HCV and baseline NS5A polymorphisms to use Zepatier plus ribavirin for 16 weeks.

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Genotype 4 HCV
The efficacy of Zepatier in subjects with genotype 4 HCV infection was demonstrated in C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, and C-SCAPE. Combined, the overall SVR was 97% in the C-SCAPE, C-EDGE TN, and C-EDGE COINFECTION trials (treatment naïve) using Zepatier for 12 weeks. In C-EDGE TE (treatment experienced with pegylated interferon/ribavirin), the overall SVR for those taking Zepatier plus ribavirin for 16 weeks was 100%.

References

1. Zepatier [package insert]. Merck and Company. Whitehouse Station, NJ . January 2016.
2. Recommendations for Testing, Managing, and Treating Hepatitis C. American Association for the Study of liver diseases. Updated September 2017.

Policy History

Original Effective Date: 05/18/2016
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05/05/2016	Medical Policy Committee review
05/18/2016	Medical Policy Implementation Committee approval. New Policy.
05/04/2017	Medical Policy Committee review
05/17/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/02/2017	Medical Policy Committee review
11/15/2017	Medical Policy Implementation Committee approval. Changed from Harvoni first to Epclusa, Harvoni, or Mavyret first.
12/20/2017	Changed trademark symbol to a registration symbol in the title and in the policy.
11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/07/2019	Medical Policy Committee review
11/13/2019	Medical Policy Implementation Committee approval. Updated the policy referral section to include mention of the authorized generics in the policy titles for Harvoni and Epclusa. Removed reference to policy 00457 as it is retired.
11/05/2020	Medical Policy Committee review

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11/11/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 11/2021

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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