Treatment of Hepatitis C with elbasvir and grazoprevir (Zepatier)

Policy # 00509
Original Effective Date: 05/18/2016
Current Effective Date: 05/17/2017

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 Triple Therapy (Ribavirin Plus Pegylated Interferon Alfa Plus telaprevir [Incivek®] or boceprevir [Victrelis®])‡ is addressed separately in medical policy 00373.

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 simeprevir (Olysio®)‡ Based Regimen is addressed separately in medical policy 00396.

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

Note: Treatment of Hepatitis C with simeprevir (Olysio®)‡ PLUS sofosbuvir (Sovaldi®)‡ is addressed separately in medical policy 00457.

Note: Treatment of Hepatitis C with ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak®)‡ 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/ledipasvir (Harvoni®) is addressed separately in medical policy 00455.

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.
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**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 elbasvir/grazoprevir (Zepatier), sofosbuvir/ledipasvir (Harvoni)®, ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak)®, daclatasvir (Daklinza™)®, sofosbuvir (Sovaldi®)™, or 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/ledipasvir (Harvoni) will be ineffective or will cause an adverse reaction to the patient (e.g. Stage 4/5 renal failure, including those on dialysis); 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):

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Drugs</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1a: Treatment Naïve or PegIFN/RBV experiencedª without baseline NS5A polymorphismsª</td>
<td>Zepatier</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 1a: Treatment Naïve or PegIFN/RBV experiencedª WITH baseline NS5A polymorphismsª</td>
<td>Zepatier PLUS ribavirin</td>
<td>16 weeks</td>
</tr>
<tr>
<td>Genotype 1b: Treatment naïve or PegIFN/RBV experienced ^</td>
<td>Zepatier</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 1a or 1b: PegIFN/RBV/PI-experienced*</td>
<td>Zepatier PLUS ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 4: Treatment naïve</td>
<td>Zepatier</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 4: PegIFN/RBV-experienced ^</td>
<td>Zepatier PLUS ribavirin</td>
<td>16 weeks</td>
</tr>
</tbody>
</table>

ª: Pegylated interferon + ribavirin
ªª: Polymorphisms at amino acid positions 28, 30, 31, or 93
ª*: Pegylated interferon + ribavirin + HCV NS3/4A protease inhibitor [telaprevir (Incivek®)™, boceprevir (Victrelis®)™, simeprevir (Olysio®)™]
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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/ledipasvir (Harvoni) 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.*

Background/Overview
Zepatier is a fixed dose combination product containing elbasvir 50 mg, a hepatitis C virus (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 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.

Up until the last few years, Interferon alfa has been considered the only effective treatment of hepatitis C. A total of 40% of patients will show an initial response to interferon alfa, but most patients relapse soon after stopping treatment. Ribavirin (Rebetron®), a synthetic nucleoside analogue with antiviral activity, has also been investigated as a treatment of hepatitis C. Up until a few years ago, pegylated interferon alfa (Pegasys and PEGINtron) and ribavirin were the standard treatment in patients with non-genotype 1 infections. The addition of the pegylated moiety improved the pharmacokinetic profile of the drug as well as doubled sustained virologic response (SVR) rates. The standard has since evolved into Sovaldi plus ribavirin for genotype 2 and 3 patients. Now, Daklinza and Sovaldi can be used for genotype 3 HCV patients (representing a ribavirin free regimen). However it should be noted that off-label use of Sovaldi, pegylated
interferon, and ribavirin has substantial evidence in genotype 3 patients. The approval of hepatitis C protease inhibitors such as Victrelis and Incivek improved the arsenal of treatment options for those patients with hepatitis C genotype 1. These protease inhibitors were used in combination with pegylated interferon alfa and ribavirin for a variety of timeframes depending on the patient’s hepatitis C treatment status. With the addition of new medications over the last year, Incivek and Victrelis are falling out of favor for the treatment of HCV. The latest addition to the protease inhibitor family of medications is simeprevir (Olysio). Olysio is indicated for use in combination with pegylated interferon and ribavirin in genotype 1 patients. Another recently released drug, Sovaldi (sofosbuvir), is actually part of a new class of medications in which it is the first approved drug of its kind. Sovaldi is a nucleotide analog NS5B polymerase inhibitor indicated for use in patients with genotypes 1-4 chronic HCV. It is approved for use in combination with pegylated interferon and ribavirin or with ribavirin alone in some situations. With the addition of these new drugs, the majority of SVRs are in the 90% range. Harvoni was recently launched, with desirable SVRs as well. Recently the use of Olysio in combination with Sovaldi was approved by the U.S. Food and Drug Administration (FDA). Even though this combination is mentioned in treatment guidelines, its use will be limited due to the availability of Harvoni. In late 2014, Viekira Pak was launched as well for the treatment of patients with genotype 1 chronic hepatitis C. Viekira Pak contains rifonavir along with a HCV NS5A inhibitor, a NS3/4A protease inhibitor, and a NS5B palm polymerase inhibitor (addressed in policy 00462). Most recently, Daklinza plus Sovaldi has been approved for use in patients with genotype 1 HCV (addressed in policy 00479). Zepatier, a new product from Merck was also recently approved for the treatment of genotype 1 HCV. Drugs and treatment regimens used for CHC will be part of an ever evolving landscape over the next few years.

Genotypes 4-6 are less common in the United States, and have therefore had fewer advances in therapy until recently. As mentioned, above, Sovaldi, pegylated interferon, and ribavirin gained approval in genotype 4 patients upon Sovaldi’s first release. In mid 2015, Technivie gained approval for genotype 4 patients without cirrhosis. Technivie is similar to Viekira Pak, but without the dasabuvir portion of the drug. Harvoni recently gained approval for genotypes 4-6 in December of 2015. Zepatier (a combo NS5A inhibitor and NS3/4A protease inhibitor) was approved in January of 2016 for treatment of adults with genotype 4 HCV.

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. FDA

Zepatier was approved in January of 2016 for the treatment (with or without ribavirin) of adults with hepatitis c virus 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, FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield of Louisiana.
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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.

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 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 naive) 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

Policy History
Original Effective Date: 05/18/2016
Current Effective Date: 05/17/2017
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.
Next Scheduled Review Date: 05/2018

*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 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 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.
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.

‡ Indicated trademarks are the registered trademarks of their respective owners.
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