Treatment of Hepatitis C with sofosbuvir/velpatasvir (Epclusa®)

Policy # 00514
Original Effective Date: 08/17/2016
Current Effective Date: 08/23/2017

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 sofosbuvir/ledipasvir (Harvon®) is addressed separately in medical policy 00455.

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™) PLUS sofosbuvir (Sovaldi®) is addressed separately in medical policy 00479.
Note: Treatment of Hepatitis C with elbasvir and grazoprevir (Zepatier™) is addressed separately in medical policy 00509.
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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.

Based on review of available data, the Company may consider sofosbuvir/velpatasvir (Epclusa®) for the treatment of individuals with chronic hepatitis C virus (HCV) to be eligible for coverage.

Genotypes 1, 4, 5, and 6

Patient Selection Criteria

Based on review of available data, the Company may consider sofosbuvir/velpatasvir (Epclusa) for the treatment of HCV when the following criteria are met:

- Patient has a diagnosis of chronic hepatitis C virus (HCV) genotypes 1, 4, 5, or 6; AND
- Patient has NOT failed prior therapy with drugs such as elabasvir/grazoprevir (Zepatier™), sofosbuvir/ledipasvir (Harvoni®), ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak®), daclatasvir (Daklinza™), or ombitasvir, paritaprevir, ritonavir (Technivie®); AND
- There is clinical evidence or patient history suggesting that ledipasvir/sofosbuvir (Harvoni) will be ineffective or will cause an adverse reaction to the patient; AND

Note that this criterion is an additional company requirement. Failure to meet this criterion will result in a denial of not medically necessary.**

- Epclusa (if approved) will be used as follows:

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Recommended Treatment Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients without cirrhosis</td>
<td>Epclusa for 12 weeks</td>
</tr>
<tr>
<td>Patients with compensated cirrhosis (Child Pugh A)</td>
<td>Epclusa PLUS ribavirin for 12 weeks</td>
</tr>
</tbody>
</table>

Note that in situations where ledipasvir/sofosbuvir (Harvoni) will be a longer regimen than sofosbuvir/velpatasvir (Epclusa) OR where ledipasvir/sofosbuvir (Harvoni) would be combined with ribavirin where a sofosbuvir/velpatasvir (Epclusa) regimen would not, the requirement for ledipasvir/sofosbuvir (Harvoni) will be overridden. This situation includes:

- Treatment experienced (peginterferon/ribavirin, peginterferon/ribavirin/protease inhibitor[Invicke, Victrelis, Olysio]) WITH compensated cirrhosis
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When Services Are Considered Not Medically Necessary
Based on review of available data, the Company considers the use of sofosbuvir/velpatasvir (Epclusa) WITHOUT evidence that ledipasvir/sofosbuvir (Harvoni) in patients with genotype 1, 4, 5, or 6 HCV 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 sofosbuvir/velpatasvir (Epclusa) when patient selection criteria are not met (with the exception of the criterion denoted above as **not medically necessary**) to be investigational.*

Genotypes 2 and 3
Patient Selection Criteria
Based on review of available data, the Company may consider sofosbuvir/velpatasvir (Epclusa) for the treatment of hepatitis C virus (HCV) when the following criteria are met:
- Patient has a diagnosis of chronic hepatitis C virus (HCV) genotypes 2 or 3; AND
- Epclusa (if approved) will be used as follows:

<table>
<thead>
<tr>
<th>Tx Naive</th>
<th>Patient Population</th>
<th>Recommended Treatment Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients without cirrhosis</td>
<td>Epclusa for 12 weeks</td>
<td></td>
</tr>
<tr>
<td>Patients with compensated cirrhosis (Child Pugh A)</td>
<td>Epclusa PLUS ribavirin for 12 weeks</td>
<td></td>
</tr>
<tr>
<td>Patients with decompensated cirrhosis (Child Pugh B and C)</td>
<td>Epclusa PLUS ribavirin for 12 weeks</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tx Experienced</th>
<th>Patient Population</th>
<th>Recommended Treatment Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 2, pegylated interferon/ribavirin failures, without cirrhosis or with compensated cirrhosis (Child Pugh A)</td>
<td>Epclusa for 12 weeks</td>
<td></td>
</tr>
<tr>
<td>Genotype 2, Sovaldi PLUS ribavirin failures, with compensated cirrhosis (Child Pugh A) or without cirrhosis</td>
<td>Epclusa PLUS ribavirin for 12 weeks</td>
<td></td>
</tr>
<tr>
<td>Genotype 3, pegylated interferon/ribavirin failures, without cirrhosis</td>
<td>Epclusa for 12 weeks</td>
<td></td>
</tr>
<tr>
<td>Genotype 3, pegylated interferon/ribavirin failures, with compensated cirrhosis</td>
<td>Epclusa PLUS ribavirin for 12 weeks</td>
<td></td>
</tr>
</tbody>
</table>

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| Compensated cirrhosis (Child Pugh A) | Epclusa PLUS ribavirin for 12 weeks
| Genotype 3, Sovaldi PLUS ribavirin failures, WITH compensated cirrhosis (Child Pugh A) or without compensated cirrhosis | Epclusa PLUS ribavirin for 12 weeks
| Genotype 2 or 3 patients with DEcompensated cirrhosis (Child Pugh B/C) | Epclusa PLUS ribavirin for 12 weeks

*These regimens are considered “off-label” however they are mentioned in the AASLD (American Association for the Study of Liver Diseases) Hepatitis C Guidelines. If the requirements for the addition of ribavirin is not met, these will be denied as not medically necessary** as they are a requirement beyond the package insert.

**Background/Overview**

Epclusa is a fixed dose combination of sofosbuvir 400 mg, a HCV nucleotide analog NS5B polymerase inhibitor, and velpatasvir 100 mg, a HCV NS5A inhibitor, approved for the treatment of adult patients with chronic HCV genotypes 1, 2, 3, 4, 5, or 6 infection. The dosage is 1 tablet per day for 12 weeks of therapy. Depending on the indication, ribavirin may or may not need to be taken concomitantly.

**Hepatitis C**

Hepatitis C is the most common blood borne pathogen. In the US, there are approximately 5.2 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.

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 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 few years, 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 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.
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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 ritonavir 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 (addressed in policy 00509). In mid 2016, Epclusa was approved for the treatment of genotypes 1-6. Given the number of options that don’t have to be given together, Daklinza and Sovaldi taken together offers no advantages for genotype 1 patients. Harvoni will likely remain the workhorse for genotype 1 patients.

The standard for genotype 2 patients over the last few years has been Sovaldi plus ribavirin. Since the approval of Epclusa, this regimen will likely fall out of favor.

A few potential treatment regimens exist for genotype 3 hepatitis C. Pegylated interferon in combination with ribavirin has since fallen out of favor for the treatment of choice for hepatitis C since the explosion of new products in this market. The most recent regimens include Sovaldi plus ribavirin for 24 weeks (on-label, see policy 00397), Daklinza plus Sovaldi (on-label for certain lengths of therapy), Sovaldi plus pegylated interferon plus ribavirin for 12 weeks (off-label, but substantial evidence for those that can tolerate the pegylated interferon, see policy 00397) and Epclusa with or without ribavirin for 12 weeks. With the recent introduction of Epclusa, there is no reason to use the other regimens available for genotype 3 treatment.

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 approved 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 and is likely the treatment of choice for this patient population.

Epclusa 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. Epclusa’s use will fall mainly in the genotype 2 and genotype 3 categories.

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)

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Epclusa was approved in June of 2016 for the treatment of adult patients with chronic HCV genotypes 1, 2, 3, 4, 5, and 6.

Rationale/Source
This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA 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.

With/Without Compensated Cirrhosis
ABSTRAL-1 was a randomized, double-blind, placebo-controlled trial that evaluated 12 weeks of treatment with Epclusa vs. 12 weeks of placebo in subjects with genotype 1, 2, 4, 5, or 6 HCV infection. Subjects in this study either had no cirrhosis or had compensated cirrhosis. The overall SVR12 for all genotypes was 99%. For genotype 1, the SVR was 98%, for genotype 2, 100%, genotype 4, 100%, genotype 5, 97%, and genotype 6 was 100%. In this trial, there were no on-treatment virologic failures and <1% relapses.

ABSTRAL-2 was a randomized, open-label trial that evaluated 12 weeks of therapy with Epclusa versus treatment with Sovaldi plus ribavirin in patients with genotype 2 HCV. This study included those that were both treatment naïve and treatment experienced. This trial also included subjects without cirrhosis or with compensated cirrhosis. The SVR12 in the Epclusa group was 99% versus 94% in the Sovaldi plus ribavirin group. There were no on-treatment virologic failures in either groups. There were no relapses in the Epclusa group versus 5% of the population relapsing in the Sovaldi plus ribavirin group.

ABSTRAL-3 was a randomized, open-label trial that studied 12 weeks of Epclusa versus 24 weeks of Sovaldi plus ribavirin in patients with genotype 3 HCV. There were both treatment naïve and treatment experienced subjects in this trial. This trial also included subjects without cirrhosis or with compensated cirrhosis. The SVR12 in this Epclusa group was 95% versus 80% in the Sovaldi plus ribavirin group. There were no on-treatment virologic failures in the Epclusa group versus <1% in the Sovaldi plus ribavirin group. There was a 4% relapse rate in the Epclusa group versus a 14% rate in the Sovaldi plus ribavirin group.

Just to note, Epclusa did not include studies in the package insert for those that have failed a sofosbuvir containing regimen. Those patients are likely better suited to receive Harvoni per the AASLD guidelines.

DEcompensated Cirrhosis
ABSTRAL-4 was a randomized, open-label trial in subjects with genotypes 1, 2, 3, 4, 5, or 6 with decompensated cirrhosis. Subjects were randomized to Epclusa for 12 weeks or Epclusa plus ribavirin for 12 weeks or Epclusa for 24 weeks. The Epclusa plus ribavirin regimen had numerically higher SVR rates than the other two regimens. The overall SVR12 for all genotypes was 94% with a 3% virologic failure rate.
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References

Policy History
Original Effective Date: 08/17/2016
Current Effective Date: 08/23/2017
08/04/2016 Medical Policy Committee review
08/17/2016 Medical Policy Implementation Committee approval. New Policy.
08/03/2017 Medical Policy Committee review
08/23/2017 Medical Policy Implementation Committee approval. No change to coverage.
Next Scheduled Review Date: 08/2018

*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 U.S. 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.

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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