



# BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

## Treatment of Hepatitis C with a sofosbuvir (Sovaldi) Based Regimen

**Policy #** 00397

Original Effective Date: 01/15/2014  
Current Effective Date: 01/15/2014

*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.*

### 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 a sofosbuvir (Sovaldi) based regimen (including ribavirin or ribavirin + pegylated interferon alfa) 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 the use of a sofosbuvir (Sovaldi) based regimen (including ribavirin or ribavirin + pegylated interferon alfa) when the following criteria are met:

- Sovaldi must NOT be used as monotherapy; AND
- Patient has diagnosis of chronic hepatitis C virus (HCV) Genotypes 1,2,3, or 4, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with hepatitis C virus (HCV)/human immunodeficiency virus (HIV-1) co-infection; AND
  - o Patients with genotype 1 hepatitis C virus (HCV) must receive concurrent therapy with pegylated interferon alfa and ribavirin OR ribavirin alone if they are interferon ineligible; OR
  - o Patients with genotype 2 or 3 hepatitis C virus (HCV) must receive concurrent therapy with ribavirin; OR
  - o Patients with genotype 4 hepatitis C virus (HCV) must receive concurrent therapy with pegylated interferon alfa and ribavirin; OR

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- o Patients with hepatocellular carcinoma awaiting liver transplantation must receive concurrent therapy with ribavirin.

*Note: Authorizations timeframes will be based on the below chart*

HCV Mono-infected and HCV/HIV-1 Co-infected	Drugs	Duration
Genotype 1 or 4	Sovaldi + pegylated interferon alfa + ribavirin	12 weeks
Genotype 1 interferon ineligible	Sovaldi + ribavirin	24 weeks
Genotype 2	Sovaldi + ribavirin	12 weeks
Genotype 3	Sovaldi + ribavirin	24 weeks
Hepatocellular carcinoma	Sovaldi + ribavirin	48 weeks or until liver transplantation, whichever occurs first

### **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 a sofosbuvir (Sovaldi) based regimen (including ribavirin or ribavirin + pegylated interferon alfa) for the treatment of individuals with chronic hepatitis C virus (HCV) when patient selection criteria are not met to be **investigational.\***

Based on review of available data, the Company considers the use of a sofosbuvir (Sovaldi) based regimen (including ribavirin or ribavirin + pegylated interferon alfa) for indications not approved by the U.S. Food and Drug Administration (FDA) to be **investigational.\***

### **Background/Overview**

Sovaldi is a HCV nucleotide analog NS5B polymerase inhibitor indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen. Sovaldi's efficacy has been established in subjects with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection. Sovaldi should be used in combination with ribavirin or in combination with pegylated interferon and ribavirin, depending on the patient scenario.

### **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.



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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®)<sup>†</sup>, a synthetic nucleoside analogue with antiviral activity, has also been investigated as a treatment of hepatitis C. In the past few years, pegylated interferon alfa (Pegasys and Pegintron) and ribavirin have become 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 have improved the arsenal of treatment options for those patients with hepatitis C genotype 1. These protease inhibitors are used in combination with pegylated interferon alfa and ribavirin for a variety of timeframes depending on the patient's hepatitis C treatment status. 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. Sofosbuvir (Sovaldi) 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. Drugs and treatment regimens used for CHC will be part of an ever evolving landscape over the next few years.

### **FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration

Pegasys (peginterferon alfa-2a) was approved by the FDA in 2002. It carries indications for both Hepatitis C and Hepatitis B Virus. Peg-Intron (peginterferon alfa-2b) was approved by the FDA in 2001. It carries an indication for the treatment of hepatitis C. Sovaldi was approved in December of 2013 and is indicated for the treatment of CHC genotype 1-4 as a component of a combination antiviral treatment regimen.

### **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.

The safety and efficacy of Sovaldi was evaluated in five Phase 3 trials in a total of 1,724 HCV mono-infected subjects with genotypes 1 to 6 CHC and one Phase 3 trial in 223 HCV/HIV-1 co-infected subjects with genotype 1, 2 or 3 CHC. Among the five trials in HCV mono-infected subjects, one was conducted in treatment-naïve subjects with genotype 1, 4, 5 or 6 CHC in combination with peginterferon alfa 2a and ribavirin and the other four were conducted in subjects with genotype 2 or 3 CHC in combination with ribavirin, including one in treatment-naïve subjects, one in interferon intolerant, ineligible or unwilling subjects, one in subjects previously treated with an interferon-based regimen, and one in all subjects irrespective of prior treatment history or ability to take interferon. The trial in HCV/HIV-1 co-infected subjects was conducted in combination with ribavirin in treatment-naïve subjects with genotype 1 CHC and all subjects with genotype 2 or 3 CHC irrespective of prior treatment history or ability to take interferon. Subjects in these trials had compensated liver disease including cirrhosis. Sovaldi was administered at a dose of 400 mg once daily. The ribavirin dose was weight-based at 1000-1200 mg daily administered in two



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divided doses when used in combination with Sovaldi, and the peginterferon alfa 2a dose, where applicable, was 180 micrograms per week. Treatment duration was fixed in each trial and was not guided by subjects' HCV RNA levels (no response guided algorithm). Plasma HCV RNA values were measured during the clinical trials using the COBAS TaqMan HCV test (version 2.0), for use with the High Pure System. The assay had a lower limit of quantification (LLOQ) of 25 IU per mL. Sustained virologic response was the primary endpoint which was defined as HCV RNA less than LLOQ at 12 weeks after the end of treatment.

### Treatment Naïve Adults Genotype 1 or 4

NEUTRINO was an open-label, single-arm trial that evaluated 12 weeks of treatment with Sovaldi in combination with peginterferon alfa 2a and ribavirin in treatment-naïve subjects with genotype 1, 4, 5 or 6 HCV infection compared to pre-specified historical control. There were 327 treated subjects in this trial. The response was represented by SVR at 12 weeks, also known as SVR12. Overall SVR12 for the treatment group was 90% and varied by genotype. No patients in the treatment group had a virologic failure while 9% of the subjects experienced a relapse. One percent (1%) of patients were lost to follow-up.

### Treatment Naïve Adults Genotype 2 or 3

FISSION was a randomized, open-label, active-controlled trial that evaluated 12 weeks of treatment with Sovaldi and ribavirin compared to 24 weeks of treatment with peginterferon alfa 2a and ribavirin in treatment-naïve subjects with genotype 2 and 3 HCV. The ribavirin doses used in the Sovaldi + ribavirin and peginterferon alfa 2a + ribavirin arms were weight-based 1000-1200 mg per day and 800 mg per day regardless of weight, respectively. Subjects were randomized in a 1:1 ratio and stratified by cirrhosis (presence vs. absence), HCV genotype (2 vs. 3) and baseline HCV RNA level (< 6 log<sub>10</sub> IU/mL vs. ≥ 6 log<sub>10</sub> IU/mL). Subjects with genotype 2 or 3 HCV were enrolled in an approximately 1:3 ratio. There were 256 members in the Sovaldi + ribavirin group and 243 members in the peginterferon alfa 2a + ribavirin group. The response was represented by SVR at 12 weeks, also known as SVR12. Overall SVR12 for the 2 genotypes combined was 67% in each of the groups. For genotype 2, 95% of patients in the Sovaldi + ribavirin group achieved an SVR 12 vs. 78% in the peginterferon alfa 2a + ribavirin group. For genotype 3, 56% of patients in the Sovaldi + ribavirin group achieved an SVR 12 vs. 63% in the peginterferon alfa 2a + ribavirin group. There was a less than 1% virologic failure rate in the Sovaldi + ribavirin group vs. a 7% rate in the peginterferon alfa 2a + ribavirin group. The relapse rate for the Sovaldi + ribavirin group was 5% vs. 15% in the peginterferon alfa 2a + ribavirin group in patients with genotype 2 HCV. In patients with genotype 3 HCV, there was a 40% relapse rate in the Sovaldi + ribavirin group vs. 24% in the peginterferon alfa 2a + ribavirin group. Breakouts for cirrhosis patients are located in the package insert.

### Interferon Intolerant, Ineligible, or Unwilling Adults with Genotype 2 or 3

POSITRON was a randomized, double-blinded, placebo-controlled trial that evaluated 12 weeks of treatment with Sovaldi and ribavirin (N = 207) compared to placebo (N = 71) in subjects who are interferon intolerant, ineligible or unwilling. Subjects were randomized in 3:1 ratio and stratified by cirrhosis (presence vs. absence). The response was represented by SVR at 12 weeks, also known as SVR12. The overall SVR12 for the treated group was 78%. This breaks down to 93% SVR 12 in genotype 2 patients and 61% SVR in genotype 3 patients. There were no virologic failures in the treated group. The relapse rate for the treated group was 5% in those with genotype 2 and 38% in those with genotype 3. None of the patients in



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the placebo group achieved SVR12. More data regarding a cirrhosis breakout and interferon classification is available in the package insert.

### **Previously Treated Adults with Genotype 2 or 3**

FUSION was a randomized, double-blinded trial that evaluated 12 or 16 weeks of treatment with Sovaldi and ribavirin in subjects who did not achieve SVR with prior interferon-based treatment (relapsers and nonresponders). Subjects were randomized in a 1:1 ratio and stratified by cirrhosis (presence vs. absence) and HCV genotype (2 vs. 3). There were 103 patients in the 12 week treatment group and 98 patients in the 16 week treatment group. The response was represented by SVR at 12 weeks, also known as SVR12. The overall SVR12 was 71% in the group treated for 16 weeks vs. 50% in the group treated for 12 weeks. For genotype 2, the SVR12 was 89% in the 16 week treatment group vs. 82% in the 12 week treatment group. For genotype 3, the SVR12 was 62% in the 16 week treatment group vs. 30% in the 12 week treatment group. There were no virologic failures in either group. The relapse rate was 11% in the 16 week treatment group vs. 18% in the 12 week treatment group in genotype 2 patients. In genotype 3 patients, the relapse rate was 38% in the 16 week treatment group vs. 66% in the 12 week treatment group. More data regarding a cirrhosis breakout and interferon classification is available in the package insert.

### **Treatment Naïve and Previously Treated Adults with Genotype 2 or 3**

The VALENCE trial evaluated Sovaldi in combination with weight-based ribavirin for the treatment of genotype 2 or 3 HCV infection in treatment-naïve subjects or subjects who did not achieve SVR with prior interferon-based treatment, including subjects with compensated cirrhosis. The original trial design was a 4 to 1 randomization to Sovaldi + ribavirin for 12 weeks or placebo. Based on emerging data, this trial was unblinded and all genotype 2 HCV-infected subjects continued the original planned treatment and received Sovaldi + ribavirin for 12 weeks, and duration of treatment with Sovaldi + ribavirin in genotype 3 HCV-infected subjects was extended to 24 weeks. Eleven genotype 3 subjects had already completed SOVALDI + ribavirin for 12 weeks at the time of the amendment. The response was represented by SVR at 12 weeks, also known as SVR12. There were 73 patients in the 12 week treatment group (genotype 2) vs. 250 patients in the 24 week treatment group (genotype 3). The overall SVR12 was 93% in the 12 week genotype 2 group vs. 84% in the 24 week genotype 3 group. There were no virologic failures in the 12 week genotype 2 group and 1 in the 24 week genotype 3 group. The relapse rate was 14% in the 24 week genotype 3 group vs. 7% in the 12 week genotype 2 group.

### **Subjects Co-infected with HCV and HIV-1**

Sovaldi was studied in an open-label clinical trial (Study PHOTON-1) evaluating the safety and efficacy of 12 or 24 weeks of treatment with Sovaldi and ribavirin in subjects with genotype 1, 2 or 3 CHC co-infected with HIV-1. Genotype 2 and 3 subjects were either HCV treatment-naïve or experienced, whereas genotype 1 subjects were all treatment-naïve. Subjects received 400 mg SOVALDI and weight-based ribavirin (1000 mg for subjects weighing < 75 kg or 1200 mg for subjects weighing ≥ 75kg) daily for 12 or 24 weeks based on genotype and prior treatment history. Subjects were either not on antiretroviral therapy with a CD4+ cell count > 500 cells/mm<sup>3</sup> or had virologically suppressed HIV-1 with a CD4+ cell count > 200 cells/mm<sup>3</sup>. There were 114 patients with genotype 1, 26 patients with genotype 2, and 13 patients with genotype 3. The response was represented by SVR at 12 weeks, also known as SVR12. The overall SVR12 rates were as follows for genotypes 1, 2, and 3, respectively: 76%, 88%, and 92%. There was virologic failure in 1% of



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genotype 1 patients and 4% of genotype 2 patients. Twenty-two percent (22%) of patients with genotype 2 relapsed vs. none in the genotype 2 group vs. 8% in the genotype 3 group.

### Treatment

The most recent AASLD (American Association for the Study of Liver Diseases) guidelines do not address the most recent approvals of the new Hepatitis C medications such as Sovaldi.

### References

1. The Centers for Disease Control and Prevention. Hepatitis C for health care professionals. Last updated: March 14, 2011. Available at: <http://www.cdc.gov/hepatitis/HCV/index.htm>.
2. Sovaldi™ tablets [package insert]. Foster City, CA: Gilead Sciences, Inc.; Revised December 2013.

### Policy History

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01/09/2014 Medical Policy Committee review

01/15/2014 Medical Policy Implementation Committee approval. New policy.

Next Scheduled Review Date: 01/2015

\*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.

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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