Treatment of Hepatitis C with sofosbuvir/ledipasvir (Harvoni®, Authorized Generic)

Policy # 00455
Original Effective Date: 11/21/2014
Current Effective Date: 11/13/2023

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 ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak™) is addressed separately in medical policy 00462.

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

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.

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

Treatment of Hepatitis C with sofosbuvir/ledipasvir (Harvoni®, Authorized Generic)

Policy # 00455
Original Effective Date: 11/21/2014
Current Effective Date: 11/13/2023

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.*

Branded Harvoni Requests

Chronic Hepatitis C Genotype 1-

1. **Treatment Naïve Patients OR Treatment Experienced Adult Patients [Pegylated Interferon Alfa plus Ribavirin OR telaprevir (Incivek)/boceprevir (Victrelis)/simeprevir (Olysio) plus Pegylated Interferon Alfa plus Ribavirin] OR Treatment Experienced Pediatric Patients (interferon based regimen with or without ribavirin)**

Based on review of available data, the Company may consider sofosbuvir/ledipasvir (Harvoni®)‡ 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 sofosbuvir/ledipasvir (Harvoni) when the following criteria are met:

- Patient has a diagnosis of chronic hepatitis C virus (HCV) genotype 1; AND
- Harvoni is used as monotherapy OR with ribavirin as noted in the chart below; AND
- Patient has NOT received prior therapy with a sofosbuvir containing regimen (e.g., Sovaldi®‡, Harvoni® (or its authorized generic), Epclusa®‡ (or its authorized generic), Vosevi™‡); AND
- Patient meets the following definitions and adheres to the timeframes for treatment:

Adults:

Treatment Status	Cirrhotic/Non Cirrhotic	Length of Therapy
Treatment Naïve	Non-Cirrhotic, HCV RNA <6 million IU/mL (pretreatment) who meet ALL of the following: NO HIV Co-Infection, NON African American, NO presence of IL28B	8 weeks&

	polymorphism CR or TT	
Treatment Naïve	Non-Cirrhotic, HCV RNA <6 million IU/mL (pretreatment) with any of the following: HIV Co-Infection, OR an African American, OR presence of IL28B polymorphism CR or TT	12 weeks
Treatment Naïve	Non-Cirrhotic, HCV RNA ≥ 6 million IU/mL (pretreatment)	12 weeks
Treatment Naïve	Cirrhotic (Compensated, e.g., Child- Pugh A)	12 weeks
Treatment Experienced	Non-Cirrhotic	12 weeks
Treatment Experienced	Cirrhotic (Compensated, e.g., Child- Pugh A) with HIV Co-Infection	24 weeks
Treatment Experienced	Cirrhotic (Compensated, e.g., Child- Pugh A) withOUT HIV Co-Infection	12 weeks^ (Harvoni PLUS Ribavirin)
Treatment Naïve/ Treatment Experienced	Cirrhotic (DEcompensated, e.g., Child-Pugh B or C)	12 weeks (Harvoni PLUS Ribavirin)

[&]*Note that treatment of patients for 8 weeks in this particular scenario is an additional company requirement and failure to adhere to this timeframe will result in a denial of not medically necessary***

[^]*Note that treatment of patients for 12 weeks in combination with ribavirin in this particular scenario is an additional company requirement and failure to adhere to this timeframe will result in a denial of not medically necessary.** The requirement for 12 weeks of therapy of Harvoni plus ribavirin for 12 weeks will be waived if any of the following are present: significant or unstable cardiac disease, prior hypersensitivity to ribavirin, autoimmune hepatitis, hemoglobinopathy (e.g., thalassemia major or sickle cell anemia), baseline hemoglobin below 10g/dL, or a history of significant adverse events with a previous ribavirin containing regimen.*

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Pediatrics (3 years of age and older)

Treatment Status	Cirrhotic/Non Cirrhotic	Length of Therapy
Treatment Naïve	Non-Cirrhotic or Cirrhotic (Compensated, e.g., Child-Pugh A)	12 weeks
Treatment Experienced	Non-Cirrhotic	12 weeks
Treatment Experienced	Cirrhotic (Compensated, e.g., Child-Pugh A)	24 weeks
Treatment Naïve/ Treatment Experienced	Cirrhotic (DEcompensated, e.g., Child-Pugh B or C)	12 weeks (Harvoni PLUS Ribavirin)

Table Definitions (from Harvoni pivotal trials):
Cirrhotic:

- Metavir Stage 4; OR
- Ishak score of 5 or 6; OR
- FibroTest/FibroSure score of more than 0.75; OR
- APRI of greater than 2; OR
- FibroScan results greater than 12.5kPA

Treatment experienced for this section:
Adults: defined as a patient that has failed treatment (e.g., null responder, partial responder, relapser) with either peginterferon alfa plus ribavirin OR an hepatitis C virus (HCV) protease inhibitor [telaprevir (Incivek®)‡, boceprevir (Victrelis®)‡, simeprevir (Olysio®)‡] plus peginterferon alfa plus ribavirin. Note that sofosbuvir (Sovaldi) is NOT a protease inhibitor.

Pediatrics: defined as a patient that has failed treatment (e.g., null responder, partial responder, relapser) with an interferon based regimen with or without ribavirin.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of sofosbuvir/ledipasvir (Harvoni) for an adult treatment naïve, non-cirrhotic, non-human immunodeficiency virus (non-HIV) co-infected patient, non-African American, without the presence of a known IL28B polymorphism CR

or TT, with hepatitis C virus (HCV) ribonucleic acid (RNA) levels <6 million IU/mL for more than 8 weeks of treatment to be **not medically necessary.****

Based on review of available data, the Company considers the use of sofosbuvir/ledipasvir (Harvoni) for a treatment experienced adult, cirrhotic (compensated, e.g., Child-Pugh A), non-human immunodeficiency virus (non-HIV) co-infected patient for 24 weeks of treatment (unless reasoning exists for an inability to take ribavirin) 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 sofosbuvir/ledipasvir (Harvoni) when patient selection criteria are not met for treatment naïve patients OR treatment experienced adult patients [pegylated interferon alfa plus ribavirin OR telaprevir (Incivek)/boceprevir (Victrelis)/simeprevir (Olysio)] plus pegylated interferon alfa plus ribavirin] OR treatment experienced pediatric patients (interferon based regimen with or without ribavirin), with the exception of the criteria denoted above as **not medically necessary**,** to be **investigational.***

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.*

2. <u>Treatment Experienced Patients [sofosbuvir (Sovaldi) plus Ribavirin OR sofosbuvir (Sovaldi) plus Pegylated Interferon Alfa plus Ribavirin OR sofosbuvir (Sovaldi) plus simeprevir (Olysio)]</u>

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

Treatment of Hepatitis C with sofosbuvir/ledipasvir (Harvoni®, Authorized Generic)

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Patient Selection Criteria
Based on review of available data, the Company may consider sofosbuvir/ledipasvir (Harvoni) when the following criteria are met:

- Patient has a diagnosis of chronic hepatitis C virus (HCV) genotype 1; AND
- Harvoni is used in combination with ribavirin ONLY; AND
  *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- Patient has NOT received prior therapy with sofosbuvir/ledipasvir (Harvoni or its authorized generic); AND
- Patient meets the following definitions and adheres to the timeframes for treatment:

Cirrhotic/Non-Cirrhotic	Regimen	Length of Therapy
NON-cirrhotic	Harvoni PLUS Ribavirin	12 weeks
Cirrhotic	Harvoni PLUS Ribavirin	24 weeks

Cirrhotic:

- Metavir Stage 4; OR
- Ishak score of 5 or 6; OR
- FibroTest/FibroSure score of more than 0.75; OR
- APRI of greater than 2; OR
- FibroScan results greater than 12.5kPA

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of sofosbuvir/ledipasvir (Harvoni) without ribavirin in patients that have failed a regimen containing sofosbuvir (Sovaldi) plus ribavirin OR sofosbuvir (Sovaldi) plus pegylated interferon alfa plus ribavirin OR sofosbuvir (Sovaldi) plus simeprevir (Olysio) to be **not medically necessary.****

Treatment of Hepatitis C with sofosbuvir/ledipasvir (Harvoni®, Authorized Generic)

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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 sofosbuvir/ledipasvir (Harvoni) when patient selection criteria are not met for treatment experienced patients [sofosbuvir (Sovaldi) plus ribavirin OR sofosbuvir (Sovaldi) plus pegylated interferon alfa plus ribavirin OR sofosbuvir (Sovaldi) plus simeprevir (Olysio)], with the exception of the criterion denoted above as **not medically necessary**,** to be **investigational.***

3. **Sofosbuvir/ledipasvir (Harvoni, Authorized Generic) Failures OR paritaprevir/ ritonavir / ombitasvir / dasabuvir (ViekiraPak/XR) Failures OR daclatasvir (Daklinza) Failures OR elbasvir/grazoprevir (Zepatier) OR sofosbuvir/velpatasvir (Epclusa, Authorized Generic) Failures OR glecaprevir/pibrentasvir (Mayvret) Failures OR sofosbuvir/velpatasvir/voxilaprevir (Vosevi) Failures**

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 sofosbuvir/ledipasvir (Harvoni) for the treatment of individuals that have failed therapy with sofosbuvir/ledipasvir (Harvoni, Authorized Generic) OR paritaprevir/ritonavir/ombitasvir/dasabuvir (ViekiraPak/XR™)‡ OR daclatasvir (Daklinza™)‡ OR elbasvir/grazoprevir (Zepatier™)‡ OR sofosbuvir/velpatasvir (Epclusa, Authorized Generic) OR glecaprevir/pibrentasvir (Mayvret™)‡ OR sofosbuvir/velpatasvir/voxilaprevir (Vosevi) to be **investigational.***

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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.*

Chronic Hepatitis C Genotypes 4, 5, or 6 –
Treatment Naïve/Treatment Experienced, With or WithOUT Cirrhosis

Based on review of available data, the Company may consider sofosbuvir/ledipasvir (Harvoni) 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 sofosbuvir/ledipasvir (Harvoni) when the following criteria are met:

- Patient has a diagnosis of chronic hepatitis C virus (HCV) genotypes 4, 5, or 6; AND
- Patient does NOT have decompensated cirrhosis; AND
- Harvoni is used as monotherapy (no concomitant use of ribavirin or a pegylated interferon or other hepatitis C virus [HCV] antiviral medications); AND
- Patient has NOT received prior therapy with a sofosbuvir containing regimen (e.g., Sovaldi, Harvoni (or its authorized generic), Epclusa (or its authorized generic), Vosevi); AND
- Patient meets the following definitions and adheres to the timeframes for treatment:

Adults OR Pediatrics (3 years of age and older)

Patient Scenario	Drug	Length of Therapy
Treatment naïve and treatment experienced, with or withOUT cirrhosis	Harvoni	12 weeks

Treatment experienced for this section:

Adults: defined as a patient that has failed treatment (e.g., null responder, partial responder, relapser) with either peginterferon alfa plus ribavirin OR an hepatitis C virus (HCV) protease inhibitor [telaprevir (Incivek), boceprevir (Victrelis), simeprevir (Olysio)] plus peginterferon alfa plus ribavirin. Note that sofosbuvir (Sovaldi) is NOT a protease inhibitor.

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Pediatrics: defined as a patient that has failed treatment (e.g., null responder, partial responder, relapser) with an interferon based regimen with or without ribavirin.

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 sofosbuvir/ledipasvir (Harvoni) when patient selection criteria are not met for genotypes 4, 5, or 6 to be **investigational.***

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 Genotypes 1 or 4 Post Liver Transplant-

Based on review of available data, the Company may consider sofosbuvir/ledipasvir (Harvoni) 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 sofosbuvir/ledipasvir (Harvoni) when the following criteria are met:

- Patient has a diagnosis of chronic hepatitis C virus (HCV) genotype 1 or genotype 4; AND
- Patient has recurrent hepatitis C virus (HCV) post liver transplantation; AND
- Patient meets the following definitions and adheres to the timeframes for treatment:

Patient Scenario	Patient Type	Length of Therapy
Recurrent hepatitis C virus (HCV) Post-Liver Transplant	Patient is treatment naïve OR treatment experienced for *recurrent hepatitis C virus* (cirrhotic or non-	12 weeks (Harvoni Plus Ribavirin)

	cirrhotic) and is able to receive ribavirin.	
Recurrent hepatitis C virus (HCV) Post-Liver Transplant	Patient is treatment naïve for *recurrent hepatitis C virus* (cirrhotic or non-cirrhotic) and is intolerant to or ineligible to receive ribavirin.	24 weeks

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 sofosbuvir/ledipasvir (Harvoni) when patient selection criteria are not met for post liver transplant patients to be **investigational.***

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.*

Harvoni Quantity Coverage

Based on review of available data, the Company may consider a quantity override for the "non-standard" dosage forms (e.g., dosage forms other than the 90 mg/400 mg tablets) of sofosbuvir/ledipasvir (Harvoni) for the treatment of pediatric patients with chronic hepatitis C virus (HCV) to be **eligible for coverage.****

Patient Selection Criteria

Based on review of available data, the Company may consider a quantity override for the "non-standard" dosage forms (e.g., dosage forms other than the 90 mg/400 mg tablets) of sofosbuvir/ledipasvir (Harvoni) for pediatric patients when the following criterion is met:

- A valid clinical reason exists as to why the patient cannot take ONE unit of a dosage form daily versus TWO units of a dosage form daily.

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When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers use of the "non-standard" dosage forms (e.g., dosage forms other than the 90 mg/400 mg tablets) of sofosbuvir/ledipasvir (Harvoni) for the treatment of pediatric patients with chronic hepatitis C virus (HCV) when NO valid clinical reason exists as to why the patient cannot take ONE unit of a dosage form daily versus TWO units of a dosage form daily 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 on available data, the Company considers use of the "non-standard" dosage forms (e.g., dosage forms other than the 90 mg/400 mg tablets) of sofosbuvir/ledipasvir (Harvoni) in adults to be **investigational.***

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.*

ledipasvir/sofosbuvir Authorized Generic Requests

Based on review of available data, the Company may consider the sofosbuvir/ledipasvir authorized generic 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 sofosbuvir/ledipasvir authorized generic when the following criteria are met:

- Patient meets the criteria for ledipasvir/sofosbuvir (Harvoni) approval; AND
- There is clinical evidence or patient history that suggests the use of the clinically applicable preferred products [i.e., sofosbuvir/velpatasvir (Epclusa), sofosbuvir/ledipasvir (Harvoni)] be ineffective or will cause an adverse reaction to the patient.

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*(Note that failure to meet this criterion, which is an additional company requirement, will result in a denial of not medically necessary**)*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers use of the sofosbuvir/ledipasvir authorized generic when there is an absence of clinical evidence or patient history that suggests the use of the clinically applicable preferred products [i.e., sofosbuvir/velpatasvir (Epclusa), sofosbuvir/ledipasvir (Harvoni)] will be ineffective or will cause an adverse reaction to the patient to be **not medically necessary.****

Based on review of available data, the Company considers use of the sofosbuvir/ledipasvir authorized generic when the criteria for the parent drug, Harvoni, would have been denied as **not medically necessary**** 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 on available data, the Company considers use of the sofosbuvir/ledipasvir authorized generic when the criteria for the parent drug, Harvoni, would have been denied as **investigational*** to be **investigational.***

Background/Overview

Harvoni is a combination of two products: sofosbuvir and ledipasvir. Sofosbuvir is an HCV nucleotide analog NS5B polymerase inhibitor, and ledipasvir is an HCV NS5A inhibitor. Both of these moieties inhibit viral replication. Harvoni is taken as a once daily product, with or without food. When first launched, the package insert did not support use with any additional medications for the treatment of HCV. Now, in some instances, ribavirin is an add on therapy with Harvoni. This drug is currently approved for use in genotypes 1, 4, 5, or 6 in both adults and pediatric patients. In early 2019, Asegua Therapeutics, a subsidiary of Gilead, launched an authorized generic of Harvoni, which carries the same indications. The ingredients in this product are identical to Harvoni.

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Various dosage forms now exist for Harvoni. There are tablets containing 90 mg/400 mg and tablets containing 45 mg/200 mg. There are also 45 mg/200 mg packets of pellets and 33.75 mg/150 mg packets of pellets. Refer to the package insert for specific dosing based on age and body weight. However, note that the 90 mg/400 mg tablets are intended for adults and certain pediatric populations. The "non-standard" dosage forms (dosage forms other than the 90 mg/400 mg tablets) are intended for pediatric patients only. In some instances, the package insert recommends taking two lower strength dosage forms to equal one higher strength dosage form, which is already commercially available. These requests will be reviewed for clinical reasoning as to why one dosage form unit cannot be used versus the two units.

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.

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

Harvoni 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.

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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Harvoni was FDA approved in October of 2014 for the treatment of chronic HCV genotype 1 in adults. In November of 2015, Harvoni was approved for the treatment of chronic HCV genotypes 4, 5, and 6. An option for 12 weeks of therapy with ribavirin was also included in the package insert. Harvoni was also approved for HIV/HCV co-infection during the last package insert update. Harvoni's indications were once again updated in February of 2016 to include patients that are post liver transplant as well as those with decompensated cirrhosis. In 2017, Harvoni was approved for the treatment of pediatric patients 12 years of age and older or at least 35kg with genotypes 1, 4, 5, or 6 without cirrhosis or with compensated cirrhosis. The authorized generic of Harvoni was launched in early 2019 with identical indications. In November of 2019, the age in the package insert was lowered to 3 years of age or older.

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, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Treatment Naïve Genotype 1 Adults without Cirrhosis

ION-3 was a randomized, open label trial that evaluated treatment naïve genotype 1 subjects without cirrhosis. Subjects received either Harvoni for 8 weeks, Harvoni for 12 weeks, or Harvoni plus ribavirin for 8 weeks. Treatment with ribavirin did not increase response rates for patients. The sustained virologic response (SVR) for the 8 week treatment group was 94% vs. 96% in the 12 week treatment group. The relapse rate in the 8 week group was 5% vs. 1% in the 12 week group. In those patients without cirrhosis that had a baseline HCV RNA <6 million IU/mL, the SVR was 97% with the 8 week treatment of Harvoni vs. 96% with the 12 week treatment of Harvoni. This finding led to the wording regarding 8 weeks of therapy in the package insert. The relapse rates of those with <6 million IU/mL of HCV RNA were the same at 2% in both the 8 and 12 week groups. The July 2016 update from AASLD recommended against use of the 8 week regimen in those that have any of the following: HIV coinfection, are African American, have a known IL28B polymorphism CT or TT.

Treatment Naïve Genotype 1 Adults with or Without Cirrhosis
ION-1 was a randomized, open label trial that evaluated 12 and 24 weeks of treatment in those patients that are treatment naïve with or without cirrhosis. Subjects either received 12 weeks of Harvoni, 12 weeks of Harvoni plus ribavirin, 24 weeks of Harvoni, or 24 weeks of Harvoni plus ribavirin. SVR rates for the 24 week population where not available for the interim analysis. Use of ribavirin was not shown to increase the SVR. In the 12 week patient population, there was a 99% SVR at 12 weeks with a <1% relapse rate and no virologic failure. When broken down for cirrhotic/non-cirrhotic cohorts, there was a 99% SVR in those without cirrhosis and a 94% SVR in those with cirrhosis.

Previously Treated Genotype 1 Adults with or without Cirrhosis
ION-2 was a randomized, open label trial that evaluated 12 and 24 weeks of treatment in previously treated adult patients with or without cirrhosis. Subjects either received 12 weeks of Harvoni, 12 weeks of Harvoni plus ribavirin, 24 weeks of Harvoni, or 24 weeks of Harvoni plus ribavirin. Ribavirin did not make a difference in SVRs between the groups. Overall, there was a 94% SVR in the 12 week Harvoni group and a 99% SVR in the 24 week Harvoni group. There were no virologic failures in either group, but there was a 6% relapse rate in the 12 week group. When broken further down into cirrhotics/non-cirrhotics, there was a 100% SVR in those taking 24 weeks of Harvoni in those with cirrhosis. There was a 86% SVR in those with cirrhosis that took only 12 weeks of Harvoni. In those patients without cirrhosis, the SVRs were 99% in the 24 week group and 95% in the 12 week group. Cirrhotics in ION-2 were defined as those who had Metavir Stage 4; Ishak score of 5 or 6, FibroTest score of more than 0.75 AND APRI of greater than 2 or FibroScan results greater than 12.5kPA. “Treatment experienced” did not include those subjects that stopped a regimen due to adverse events.

Previously Treated Genotype 1 Adults with Cirrhosis
SIRIUS was a randomized, double blind and placebo controlled trial that evaluated Harvoni plus ribavirin for 12 weeks vs. Harvoni alone for 24 weeks in genotype 1 HCV infected subjects with compensated cirrhosis who failed prior therapy with a pegylated interferon plus ribavirin regimen followed by a pegylated interferon plus ribavirin plus HCV protease inhibitor regimen. The SVR12 was 96% (74/77) and 97% (75/77) in subjects treated with Harvoni plus ribavirin for 12 weeks and Harvoni alone for 24 weeks, respectively.

Genotype 4
Harvoni was administered for 12 weeks to treatment naïve and previously treated subjects with genotype 4 HCV infection in two studies (Study 1119 and ION-4). Study 1119 enrolled 44 subjects that were treatment naïve or previously treated, with or without cirrhosis. ION-4 enrolled 4 treatment naïve and 4 previously treated subjects without cirrhosis that were co-infected with HIV. In Study 1119, the overall SVR12 rate was 93% (41/44). SVR12 was similar based on prior HCV treatment history and cirrhosis status. In ION 4, the SVR 12 was 100% (8/8).

Genotype 5
Harvoni was administered for 12 weeks to 41 treatment naïve or previously treated subjects with genotype 5 HCV infection, with or without cirrhosis (in the 1119 trial). The overall SVR 12 was 93% (38/41). The SVR12 was similar based upon prior HCV treatment history and cirrhosis status.

Genotype 6
In the ELECTRON-2 trial, Harvoni was administered for 12 weeks to 25 treatment naïve or previously treated subjects with genotype 6 HCV infection, with or without cirrhosis. The overall SVR12 was 96% (24/25). SVR12 was similar based upon prior HCV treatment history and cirrhosis status. The single subject that relapsed discontinued the study early (near week 8).

Liver Transplant Recipients and/or Subjects with Decompensated Cirrhosis
SOLAR-1 and SOLAR-2 were two open label trials that evaluated 12 and 24 weeks of treatment with Harvoni in combination with ribavirin in treatment naïve and previously treated subjects with genotype 1 and 4 infection who had undergone liver transplantation and/or who had compensated liver disease. Subject were randomized to either 12 or 24 weeks of Harvoni plus ribavirin. The results were similar in the 12 and 24 week groups. In the pre-transplant population, the SVR12 ranged from 87-88%. In the post-transplant setting, the SVR12 was 95% for those with F0-F3, 98% for those Child-Pugh A, 89% for those Child-Pugh B, and 57% for those Child-Pugh C. In genotype 4 HCV post-transplant subjects without cirrhosis or with compensated cirrhosis treated with Harvoni plus ribavirin for 12 weeks (N=12), the SVR12 rate was similar to rates reported with genotype 1; no subjects relapsed. Available data in subjects with genotype 4 HCV who had decompensated cirrhosis (pre- and post-liver transplantation) were insufficient for dosing recommendations, therefore these results are not presented.

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Original Effective Date: 11/21/2014
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Pediatric Subjects
The efficacy of 12 weeks of Harvoni was evaluated in genotype 1 HCV treatment naïve and experienced pediatric subjects 12 years and older without cirrhosis or with compensated cirrhosis. The SVR12 was 98% overall (98% in treatment naïve and 100% in treatment experienced subjects.

Harvoni was evaluated in 90 subjects 6 years to <12 years of age with HCV genotype 1 or 4 infection. Among these subjects, 72 (80%) were treatment-naïve and 18 (20%) were treatment-experienced. Eighty-nine of the subjects (87 with genotype 1 HCV infection and 2 with genotype 4 HCV infection) were treated with Harvoni for 12 weeks, 1 subject with genotype 1 HCV infection was treated with Harvoni for 24 weeks. The SVR12 rate was 99% (86/87) in subjects with genotype 1 HCV infection, and 100% (2/2) in subjects with genotype 4 HCV infection. The one genotype 1 subject treated with Harvoni for 24 weeks also achieved SVR12. The one subject (genotype 1) who did not achieve SVR12 and relapsed had been treated with Harvoni for 12 weeks.

Harvoni was evaluated in 34 subjects 3 years to <6 years of age with HCV genotype 1 (N = 33) or genotype 4 (N = 1) infection. All of the subjects were treatment-naïve and treated with Harvoni for 12 weeks. The SVR12 rate was 97% (32/33) in subjects with genotype 1 HCV infection, and the one subject with genotype 4 HCV infection also achieved SVR12. One subject prematurely discontinued study treatment due to an adverse event.

References

1. Harvoni. Express Scripts Prior Authorization Document. Updated September 2017.
2. Harvoni [package insert]. Gilead Sciences, Inc. Updated March 2020.
3. Recommendations for Testing, Managing, and Treating Hepatitis C. American Association for the Study of liver diseases. Updated January 2021.
4. Ledipasvir/Sofosbuvir [package insert]. Asegua Therapeutics. Foster City, California. Updated March 2020.

Policy History

Original Effective Date: 11/21/2014
Current Effective Date: 11/13/2023
11/06/2014 Medical Policy Committee review
11/21/2014 Medical Policy Implementation Committee approval. New Policy

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02/05/2015	Medical Policy Committee review
02/18/2015	Medical Policy Implementation Committee approval. Removed any mention of F3/F4. Updated background info. Clarified that patient should NOT have decompensated cirrhosis.
08/06/2015	Medical Policy Committee review
08/19/2015	Medical Policy Implementation Committee approval. Reflected changes in the AASLD guidelines regarding Sovaldi failures and Harvoni/ViekiraPak failures.
12/03/2015	Medical Policy Committee review
12/16/2015	Medical Policy Implementation Committee approval. Added indications for genotypes 4,5,6. Added requirement to use Harvoni plus RBV for 12 weeks in those that are treatment experienced, cirrhotic, non-HIV infected patients. Updated background, FDA, and rationale sections to support changes.
03/03/2016	Medical Policy Committee review
03/16/2016	Medical Policy Implementation Committee approval. Updated new package insert indications (specifically for decompensated cirrhosis and post-transplant patients).
08/04/2016	Medical Policy Committee review
08/17/2016	Medical Policy Implementation Committee approval. Included references to the Zepatier and Epclusa policies. Also integrated more opt outs to the 8 week therapy to include African Americans and those with the presence of IL28B polymorphism CR or TT. HIV co-infection was already included as an opt out.
08/03/2017	Medical Policy Committee review
08/23/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/02/2017	Medical Policy Committee review
11/15/2017	Medical Policy Implementation Committee approval. Incorporated the pediatric indication into the policy.
11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/01/2019	Medical Policy Committee review
08/14/2019	Medical Policy Implementation Committee approval. Added “Authorized Generic” to the title and to the policy. Added criteria for the authorized generic product.
12/05/2019	Medical Policy Committee review

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12/11/2019	Medical Policy Implementation Committee approval. Updated criteria to reflect a change in age down to 3 years of age. Added information about non-standard dosage forms as well as quantity information/coverage.
12/03/2020	Medical Policy Committee review
12/09/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/07/2021	Medical Policy Committee review
10/13/2021	Medical Policy Implementation Committee approval. Removed Mavyret as an option to use prior to the authorized generic of Harvoni.
10/06/2022	Medical Policy Committee review
10/11/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/05/2023	Medical Policy Committee review
10/11/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 10/2024

*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 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.

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**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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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.