

# Exhibit A



**Medication Policy Manual**

**Policy No:** dru366

**Topic:** Harvoni®, ledipasvir-sofosbuvir

**Date of Origin:** October 14, 2014

**Committee Approval Date:** December 11, 2015

**Next Review Date:** February 2016

**Effective Date:** November 12, 2015

#### **IMPORTANT REMINDER**

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

#### **Description**

Ledipasvir-sofosbuvir (Harvoni) is an oral direct-acting antiviral combination medication used for the treatment of chronic genotype 1, 4, 5, and 6 hepatitis C virus (HCV) infection.

## Policy/Criteria

I. Most contracts require prior authorization approval of ledipasvir-sofosbuvir prior to coverage. Ledipasvir-sofosbuvir may be considered medically necessary when criteria A and B below are met.

A. There is a diagnosis of chronic genotype 1, 4, 5, or 6 hepatitis C virus (HCV) infection and criterion 1, 2, 3, 4, or 5 below is met:

1. There is documentation that the member has cryoglobulinemia with end-organ manifestations (e.g. vasculitis).

OR

2. There is documentation that the member has proteinuria, nephrotic syndrome, or glomerulonephritis.

OR

3. The member definitively has advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4), as documented by liver biopsy or non-invasive markers of liver fibrosis (for example an ultrasound, CT scan, FIB-4 score).

OR

4. The member definitively has moderate fibrosis (Metavir F2) as documented by liver biopsy or non-invasive markers of liver fibrosis (for example an ultrasound, CT scan, FIB-4 score) and one of the following comorbid conditions:

a. Co-infection with human immunodeficiency virus (HIV) or hepatitis B virus (HBV) infection

b. Nonalcoholic steatohepatitis (NASH)

OR

5. There is documentation that the member has received a liver transplant and criteria a and b below are met:

a. Ledipasvir-sofosbuvir (Harvoni) will be used in combination with ribavirin.

b. The member has mild to advanced liver fibrosis (Metavir F1, F2, or F3), as documented by liver biopsy or non-invasive markers of liver fibrosis (for example an ultrasound, CT scan, FIB-4 score).

AND

B. There is documentation that the member has had no alcohol abuse or intravenous (IV) drug use in the previous six months.

II. Administration, Quantity Limitations, and Authorization Period

A. OmedaRx considers ledipasvir-sofosbuvir to be a self-administered medication.

B. When prior authorization is approved, ledipasvir-sofosbuvir may be authorized up to #28 ledipasvir 90 mg-sofosbuvir 400 mg tablets per 28 days as follows:

1. **HCV genotype 1: All treatment-naive members and treatment-experienced members without cirrhosis (Metavir F2 or F3): 12 weeks total (one treatment course)**

2. **HCV Genotype 1: Treatment-experienced members with cirrhosis (Metavir F4):**
  - a. **Initial authorization:** 12 weeks
  - b. **Reauthorization:** an additional 12 weeks may be authorized when there is documentation of HCV RNA below the lower limit of quantification after 8 or more weeks of treatment and documentation that ribavirin is contraindicated or not tolerated.
3. **HCV Genotype 4, 5, and 6: All treatment-naïve and treatment-experienced members with or without cirrhosis:** 12 weeks total (one treatment course)
4. **Members who have received a liver transplant:** 12 weeks total (one treatment course)

**III.** Ledipasvir-sofosbuvir is considered investigational when used:

- A. As retreatment when there has been relapse after, or no response to, a prior treatment course with sofosbuvir or ledipasvir-sofosbuvir.
- B. In combination with daclatasvir, peginterferon, simeprevir or sofosbuvir.

**Position Statement**

- Ledipasvir-sofosbuvir (Harvoni) is an oral combination hepatitis C virus (HCV) NS5A inhibitor (ledipasvir) and HCV polymerase inhibitor (sofosbuvir) that is used for the treatment of adult with chronic genotype 1, 4, 5, or 6 HCV infection.
- Ledipasvir-sofosbuvir (Harvoni) has been shown to be safe and effective for treating chronic HCV infection in treatment-naïve patients, as well as in patients who relapsed after or did not respond to prior treatment with peginterferon and ribavirin or a protease inhibitor-based (e.g. boceprevir or telaprevir) triple therapy regimen. There is currently no published, phase III data supporting the efficacy of ledipasvir-sofosbuvir in patients who have failed prior therapy with a sofosbuvir-containing regimen.
- The safety and efficacy of ledipasvir-sofosbuvir in combination with other direct-acting antivirals (e.g. daclatasvir, simeprevir, sofosbuvir, or telaprevir) have not been established.
- The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) clinical practice guidelines state that patients at the highest risk for severe complications are those with advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4), those who have received a liver transplant, those with HIV or HBV coinfection, those with coexistent liver disease (e.g. nonalcoholic steatohepatitis), those who have Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (e.g. vasculitis), and those with proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis.

- Given the high cost of oral medications for HCV infection and the lack of overall affordability to the health care system, at this time coverage is limited to patient population at the highest risk for severe complications as described above.
- The duration of therapy for most patients is 12 weeks. The prescribing information lists 24 weeks of therapy as an option in treatment-experienced patients with HCV genotype 1 and cirrhosis; however, 12-weeks of sofosbuvir-ledipasvir in combination with ribavirin produces similar rates of SVR, thus it provides a better value for members. Twenty-four weeks of therapy may be considered in treatment-experienced cirrhotics with HCV genotype who have a documented intolerance to contraindication to ribavirin.
- The primary endpoint evaluated in most HCV clinical trials is rate of viral cure, defined as a sustained virologic response (SVR) 12 weeks following the completion of therapy. Although SVR is measured by a series of HCV RNA levels and is considered a surrogate endpoint, it is accepted as a measure of efficacy for the treatment of HCV.
- Ledipasvir-sofosbuvir (Harvoni) has been evaluated in liver transplant recipients with HCV infection. Reported treatment success rates among patients with cirrhosis ranged from 60-96%, with higher success rates in patients with less severe cirrhosis (Child-Turcotte-Pugh A score) and lower success rates in patients with more severe cirrhosis (Child-Turcotte-Pugh C score). Additional clinical trial data is needed in post-transplant cirrhotic patients to confirm efficacy and the appropriate treatment duration.
- Chronic and excessive alcohol intake can cause damage to the liver in addition to damage caused by the hepatitis C virus and injection drug use is a common way that the hepatitis C virus is spread; therefore, patients must be free of drugs and alcohol in order to have the best chance at treatment success with ledipasvir-sofosbuvir (Harvoni).
- The duration of treatment with ledipasvir-sofosbuvir (Harvoni) is based on treatment history and presence or absence of cirrhosis.
- The dose of ledipasvir-sofosbuvir (Harvoni) is 90 mg-400 mg by mouth once daily for a total of 12 to 24 weeks based on the prescribing information and AASLD/IDSA treatment guidelines.
- In clinical trials with ledipasvir-sofosbuvir (Harvoni), 99-100% of treatment-experienced patients had HCV RNA below the lower limit of quantification by week 4 of treatment. HCV RNA below the lower limit of quantification by week 4 of treatment indicates preliminary efficacy of the regimen, as well as adherence to the regimen. Ledipasvir-sofosbuvir (Harvoni) is currently being studied in a variety of HCV clinical settings. While there is limited evidence in several non-FDA approved settings the evidence is considered preliminary and investigational.

### *Clinical Efficacy*

#### HCV Genotype 1: Treatment-Naïve Patients

Ledipasvir-sofosbuvir (Harvoni) has been shown to produce high viral cure rates in treatment-naïve patients with chronic genotype 1 hepatitis C virus (HCV) infection.

- Two published fair confidence trials (ION-1 and ION-3) evaluated ledipasvir-sofosbuvir in treatment-naïve patients. <sup>[1,2]</sup> ION-1 included cirrhotic patients, whereas ION-3 did not.

- In ION-1, patients were treated with ledipasvir-sofosbuvir for 12 or 24 weeks, with or without ribavirin. [1] In ION-3, patients were treated with ledipasvir-sofosbuvir for 8 weeks, with or without ribavirin, or with ledipasvir-sofosbuvir without ribavirin for 12 weeks. [2]
- Both trials included a fair number of historically difficult to treat patients including those with a non-CC IL28B genotype (70-73%), black patients (12-19%), and those with HCV genotype 1a (67-80%). In ION-1, 16% of patients had cirrhosis of the liver.

The following overall SVR rates were reported in ION-1 and ION-3:	8 weeks	12 weeks	24 weeks
<b>ledipasvir-sofosbuvir</b>	94%	95-99%	98%
<b>ledipasvir-sofosbuvir + ribavirin</b>	93%	97%	99%

- \* In both studies, SVR rates were not significantly different between groups regardless of concomitant ribavirin therapy, cirrhosis status, or HCV genotype 1 subtype (1a vs 1b). [1,2]
- \* Less than 1% of patients in ION-1 and ION-3 had virologic breakthrough (on-treatment failure).
- \* Relapse occurred in < 1% of ION-1 study patients and in 4% of ION-3 patients. Among patients who relapsed in ION-3, the majority (87%) received 8 weeks of therapy vs 12 weeks of therapy. [1,2]

#### HCV Genotype 1: Treatment-Experienced Patients

Ledipasvir-sofosbuvir (Harvoni) has been shown to produce high viral cure rates in treatment-experienced patients with chronic genotype 1 HCV infection.

- The ION-2 study evaluated ledipasvir-sofosbuvir in treatment experienced patients, including prior relapsers, partial responders, and null responders. [3]
- Patients were treated with ledipasvir-sofosbuvir (Harvoni) for 12 or 24 weeks, with or without ribavirin. [3]
- ION-2 included a fair number of historically difficult to treat patients including those with a non-CC IL28B genotype (88%), cirrhotics (20%), black patients (14-22%), and those with HCV genotype 1a (78-79%).
- The following overall SVR rates were reported in ION-2:

	12 weeks	24 weeks
<b>ledipasvir-sofosbuvir</b>	94%	99%
<b>ledipasvir-sofosbuvir + ribavirin</b>	96%	99%

- \* SVR rates were not significantly different between groups regardless of concomitant ribavirin therapy, HCV genotype 1 subtype (1a vs 1b), prior treatment response (relapse vs non-response), and prior treatment history (peginterferon and ribavirin vs protease inhibitor-based triple therapy). [3]
  - \* Significantly more patients with cirrhosis who were treated for 24 weeks achieved SVR as compared to those who were treated for 12 weeks (100% vs 82-86%, respectively; P = 0.007). [3]
  - \* Less than 1% of patients in ION-2 had virologic breakthrough (on-treatment failure). [3]
  - \* Relapse occurred in 2.5% of ION-2 study patients, all of whom were treated for 12 weeks. [3]
- The SIRIUS study evaluated patients with HCV genotype 1 and compensated cirrhosis who had not achieved SVR after successive treatments with pegylated interferon and protease-inhibitor regimens. [4] Patients were randomly assigned to received ledipasvir-sofosbuvir (Harvoni) plus ribavirin for 12 weeks or ledipasvir-sofosbuvir for 24 weeks. In total, 77 patients were randomized to each treatment group. The following overall SVR rates were reported in SIRIUS:

<b>Regimen</b>	<b>Duration</b>	<b>SVR</b>
<b>ledipasvir-sofosbuvir</b>	24 weeks	96%
<b>ledipasvir-sofosbuvir + ribavirin</b>	12 weeks	97%

#### HCV Genotype 4

Ledipasvir-sofosbuvir (Harvoni) has been shown to produce high viral cure rates in treatment-experienced patients with chronic genotype 4 HCV infection.

- Study 1119 evaluated treatment-naïve and treatment-experienced patients with HCV genotype 4, including patients with cirrhosis. All patients received sofosbuvir-ledipasvir (Harvoni) for 12 weeks. The overall SVR12 rate was 93% (41/44). Rates of SVR were similar regardless of prior HCV treatment history and cirrhosis status.
- The ION-4 study included HIV-HCV coinfecting patients with HCV genotype 1 or 4. Although the study only included eight patients with HCV Genotype 4, all achieved an SVR.

#### HCV Genotypes 5 and 6

Ledipasvir-sofosbuvir (Harvoni) has been shown to produce high viral cure rates in treatment-experienced patients with chronic genotype 5 or 6 HCV infection.

- Study 1119 evaluated treatment-naïve or previously-treated subjects with HCV genotype 5, with or without cirrhosis. All patients received sofosbuvir-ledipasvir (Harvoni) for 12 weeks. The overall SVR12 was 93% (38/41). Rates of SVR12 were similar regardless of prior HCV treatment history and cirrhosis status. [5]

- The ELECTRON-2 trial evaluated treatment-naïve or treatment-experienced patients with HCV genotype 6, with or without cirrhosis. The overall SVR12 was 96% (24/25). Rates of SVR12 were similar regardless of prior HCV treatment history and cirrhosis status. [6]

HIV-HCV Co-infection

Ledipasvir-sofosbuvir (Harvoni) has been shown to produce high viral cure rates in patients with HIV/HCV coinfection.

- ION-4 evaluated ledipasvir-sofosbuvir (Harvoni), without ribavirin, for 12 weeks in 335 patients with HIV/HCV coinfection. SVR rates were similarly high between all treatment groups (96-100%) and rates were consistently high regardless of genotype, prior treatment history (dual therapy or triple therapy), and presence or absence of cirrhosis. [6]
- The following overall SVR rates were reported in ION-4:

<b>Population</b>	<b>SVR12</b>
Genotype 1a	96% (240/250)
Genotype 1b	96% (74/77)
Genotype 4	100% (8/8)

Other Uses

- The safety and efficacy of ledipasvir-sofosbuvir (Harvoni) in combination with other treatments for chronic HCV infection (e.g. peginterferon, boceprevir, simeprevir, telaprevir) have not been established.
- The safety and efficacy of ledipasvir-sofosbuvir (Harvoni) has not been established in patients previously treated with a sofosbuvir-containing regimen. [7]
  - \* Although small pilot studies have evaluated retreatment with ledipasvir-sofosbuvir (Harvoni) in patients who failed a previous sofosbuvir-containing regimen, data from larger well designed trials are needed to establish efficacy in this setting.
  - \* The AASLD/IDSA treatment guidelines acknowledge that clinical trial experience and clinical trial data in this retreatment setting is very limited.

*Clinical guidelines [7]*

- As of October 2015, the Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) clinical guidelines recommend the following regimens for treatment-naïve patients with HCV.



<i>Treatment-naïve patients</i>		
Genotype	Recommended Regimens	Alternative Regimens
1a	<ul style="list-style-type: none"> <li>• Daclatasvir + sofosbuvir x 12 weeks (no cirrhosis) or 24 weeks ± RBV (cirrhosis)</li> <li>• Ledipasvir-sofosbuvir x 12 weeks</li> <li>• Viekira Pak + RBV x 12 weeks (no cirrhosis) or 24 weeks (cirrhosis)</li> <li>• Sofosbuvir + simeprevir ± RBV x 12 weeks (no cirrhosis) or 24 weeks (cirrhosis)</li> </ul>	None listed
1b	<ul style="list-style-type: none"> <li>• Daclatasvir + sofosbuvir x 12 weeks (no cirrhosis) or 24 weeks (cirrhosis)</li> <li>• Ledipasvir-sofosbuvir x 12 weeks</li> <li>• Viekira Pak x 12 weeks</li> <li>• Sofosbuvir + simeprevir ± RBV x 12 weeks (no cirrhosis) or 24 weeks (cirrhosis)</li> </ul>	None listed
2	<ul style="list-style-type: none"> <li>• Daclatasvir + sofosbuvir x 12 weeks</li> <li>• Sofosbuvir + RBV x 12 weeks</li> </ul>	None listed
3	<ul style="list-style-type: none"> <li>• Daclatasvir + sofosbuvir x 12 weeks (no cirrhosis) or 24 weeks ± RBV (cirrhosis)</li> <li>• Sofosbuvir + PEG/RBV x 12 weeks</li> </ul>	Sofosbuvir + RBV x 24 weeks
4	<ul style="list-style-type: none"> <li>• Ledipasvir-sofosbuvir x 12 weeks</li> <li>• Technivie + RBV x 12 weeks</li> <li>• Sofosbuvir + RBV x 24 weeks</li> </ul>	Sofosbuvir + PEG/RBV x 12 weeks
5 or 6	Ledipasvir-sofosbuvir x 12 weeks	Sofosbuvir + PEG/RBV x 12 weeks

Technivie= ombitasvir, paritaprevir, and ritonavir; Viekira Pak = ombitasvir, paritaprevir, and ritonavir plus dasabuvir

- AASLD/IDSA guidelines state that patients with HIV/HCV coinfection should be treated similarly to non-coinfected patients.
- Specific recommendations for treatment-experienced patients are based on HCV genotype, prior treatments received, and cirrhosis status.

#### *Safety* <sup>[5]</sup>

- The most common adverse events reported in clinical trials with ledipasvir-sofosbuvir were headache and fatigue. Less than 1% of patients treated with ledipasvir-sofosbuvir experienced anemia (an adverse event of interest in the treatment of HCV infection).
- Ledipasvir-sofosbuvir (Harvoni) is not associated with CYP 3A drug-drug interactions. It is a substrate of P-gp, so strong P-gp inducers (e.g. rifampin or St. John's Wort) may decrease the plasma concentration of sofosbuvir.
- Post-marketing cases of symptomatic bradycardia have been reported when amiodarone is coadministered with a sofosbuvir-containing regimen in combination with an NS5A inhibitor, such as simeprevir. Co-administration of amiodarone with a sofosbuvir-containing regimen in combination with another direct-acting antiviral for HCV infection is not recommended.

#### *Liver Fibrosis Status* <sup>[7]</sup>

- AASLD/IDSA treatment guidelines recommend an evaluation for advanced liver fibrosis using liver biopsy, imaging, or non-invasive markers for all patients with HCV infection in order to determine the treatment strategy.
  - \* Liver biopsy can provide objective information about the level of liver fibrosis and inflammation, which assists with treatment and monitoring plans. Liver biopsy can be used in conjunction with Metavir or Ishak fibrosis scores to determine the severity of liver fibrosis present. Liver biopsy carries some risk of complication, although this risk is low.
  - \* Non-invasive methods used to estimate liver disease severity include routine blood tests (e.g. serum alanine transaminase, albumin, bilirubin, INR, complete blood counts, and platelets), serum fibrosis marker panels, liver imaging (e.g. ultrasound, CT scan) and liver elastography. These methods may help determine the likelihood of developing future liver complications or distinguish cirrhosis from non-cirrhosis, but may not be sufficient to determine the severity of liver fibrosis.

#### *Dosing Considerations* <sup>[7]</sup>

- The dose of ledipasvir-sofosbuvir is 90 mg-400 mg (one tablet) by mouth once daily with or without food.
- The duration of therapy with ledipasvir-sofosbuvir is dependent on treatment experience and presence or absence of cirrhosis:
  - \* Treatment-naïve patients with or without cirrhosis and treatment-experienced patients without cirrhosis: 12 weeks
  - \* Treatment-experienced patients with HCV genotype 1 and cirrhosis: 12 weeks in combination with ribavirin or 24 weeks.

Appendix 1: Definitions of Member Treatment History	
<b>Treatment-naive</b>	Patients who have never received therapy for the treatment of hepatitis C.
<b>Relapser</b>	Patients who had an undetectable HCV RNA level at the end of prior therapy with peginterferon and ribavirin, but had a subsequent detectable HCV RNA level during the follow-up period.
<b>Partial responder</b>	Patients who had a HCV RNA reduction of $\geq 2 \log_{10}$ after 12 weeks of prior therapy with peginterferon and ribavirin, but still had a detectable HCV RNA level during the treatment period.
<b>Null responder</b>	Patients who had a $< 2 \log_{10}$ reduction in HCV RNA after 12 weeks of prior therapy with peginterferon and ribavirin.

Cross References
Daklinza™, daclatasvir, dru411
Olysio®, simeprevir, dru331
Sovaldi®, sofosbuvir, dru332
Viekira Pak®, paritaprevir/ritonavir-ombitasvir plus dasabuvir, dru387
Technivie™, paritaprevir/ritonavir-ombitasvir, dru412
Medical Policy Lab 47, Multianalyte Assays with Algorithmic Analysis for the Evaluation and Monitoring of Patients with Chronic Liver Disease ( <a href="http://blue.regence.com/trgmedpol/lab/lab47.pdf">http://blue.regence.com/trgmedpol/lab/lab47.pdf</a> )

Codes	Number	Description
N/A		

## References

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2. Kowdley, KV, Gordon, SC, Reddy, KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *The New England journal of medicine*. 2014 May 15;370(20):1879-88. PMID: 24720702
3. Afdhal, N, Reddy, KR, Nelson, DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *The New England journal of medicine*. 2014 Apr 17;370(16):1483-93. PMID: 24725238

4. Bourliere, M, Bronowicki, JP, de Ledinghen, V, et al. Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS). *The Lancet infectious diseases*. 2015 Apr;15(4):397-404. PMID: 25773757
5. Harvoni® [prescribing information]. Foster City, CA: Gilead Sciences; November 2015.
6. Naggie, S, Cooper, C, Saag, M, et al. Ledipasvir and Sofosbuvir for HCV in Patients Coinfected with HIV-1. *The New England journal of medicine*. 2015 Aug 20;373(8):705-13. PMID: 26196665
7. American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA). Recommendations for testing, managing, and treating hepatitis C. [cited 11/18/2015]; Available from: <http://hcvguidelines.org>.

*Revision History*

Revision Date	Revision Summary
12/11/2015	<ul style="list-style-type: none"> <li>• Added coverage criteria for HCV genotypes 4, 5, and 6</li> <li>• Added combination therapy with daclatasvir (Daklinza) as an investigational use</li> <li>• Duration of coverage for treatment-experienced patients with HCV genotype 1 and cirrhosis is now limited to 12 weeks, unless there is documentation of HCV RNA below the lower limit of quantification after 8 or more weeks of treatment <b>and</b> documentation that ribavirin is contraindicated or not tolerated.</li> </ul>