Drug Monograph

Drug/Drug Class:	**Harvoni™ (ledipasvir/sofosbuvir) tablet/ Hepatitis C**
Prepared for:	MO HealthNet
Prepared by:	Xerox Heritage, LLC

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Harvoni™ is available in a 90/400 mg fixed-dose combination tablet that contains 90 mg of ledipasvir and 400 mg of sofosbuvir respectively. Gilead Sciences, Inc. Foster City, CA 94404
Summary of Findings:	Harvoni™ demonstrated efficacy for both previously untreated and previously treated patients with chronic hepatitis C infections due to HCV genotype 1. In 2 randomized, open-label studies of treatment-naive patients (n=865; n=647), Harvoni™ treatment resulted in sustained virologic responses in 94% after 8 weeks in one study, 95% and 99% after 12 weeks in both studies, and in 98% after 24 weeks in one study. In a randomized, open-label study of treatment-experienced patients (n=440), Harvoni™ treatment resulted in sustained virologic responses in 94% after 12 weeks and in 99% after 24 weeks. Of patients with cirrhosis (n=88), sustained virologic response rates were significantly improved in patients who were treated with 24 weeks of Harvoni™ (95%) compared to 12 weeks of Harvoni™ (86%). In all trials, concomitant ribavirin did not increase response rates but did increase the frequency of adverse events.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☒ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☒ Non-Preferred Agent ☐ Appropriate Indications ☐ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction[5]

Hepatitis C is a contagious liver disease that ranges in severity from a mild illness lasting a few weeks to a serious, lifelong illness that attacks the liver. It results from infection with the Hepatitis C virus (HCV), which is spread primarily through contact with the blood of an infected person. Hepatitis C can be either "acute" or "chronic." An estimated 3.2 million people in the United States have chronic Hepatitis C virus infection. Most people do not know they are infected because they don't look or feel sick.

Dosage Form(s) [1]

Harvoni™ is available in a 90/400 mg fixed-dose combination tablet that contains 90 mg of ledipasvir and 400 mg of sofosbuvir respectively.

Manufacturer [1]

Gilead Sciences, Inc., Foster City, CA 94404

Indication(s) [1]

Harvoni™ is indicated for the treatment of adults with chronic hepatitis C genotype 1 infection.

Clinical Efficacy [1-5] (mechanism of action/pharmacology, comparative efficacy)

Harvoni™ is a combination of ledipasvir, a hepatitis C virus (HCV) NS5A inhibitor, and sofosbuvir, an HCV nucleotide analog NS5B polymerase inhibitor, acts by interfering with viral replication. Sofosbuvir is a prodrug which is metabolized to GS-461203, the active metabolite.

Pharmacokinetics

	Ledispasvir	**Sofosbuvir**
Protein binding	>99.8%	61% to 65%
Metabolism	Minimal via slow oxidation	Liver to active GS-461203, then inactive GS-331007
Excretion	Urine (1%) Feces (86%; 70% unchanged)	Urine (80%; 78% GS-331007) Feces (14%) Expired air (2.5%)
Half-life	47 hours	0.5 hour (parent) 27 hours (GS-331007)

Harvoni™, with or without ribavirin, led to high sustained virologic response rates after 12 and 24 weeks of treatment in previously untreated patients with HCV genotype 1.

STUDY DESIGN	Randomized, open-label, multicenter, phase 3 clinical trial (n=865).
INCLUSION CRITERIA	Treatment-naive adult patients with chronic HCV genotype 1 infection.
EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	All patients (age range, 18 to 80 years) received one combination tablet of Harvoni™ orally once daily and were randomly assigned to 4 groups: Harvoni™ for 12 weeks (n=214), Harvoni™ plus ribavirin (administered twice daily in doses of 1000 mg/day for body weights < 75 kg; 1200 mg/day for body weights of 75 kg or greater) for 12 weeks (n=217), Harvoni™ for 24 weeks (n=217), and Harvoni™ plus ribavirin.for 24 weeks (n=217).
RESULTS	At baseline, cirrhosis was present in 16% of patients. At week 12 following the end of treatment, sustained virologic response rates (primary endpoint) were 99%, 97%, 98%, and 99% in patients who received 12 weeks of Harvoni™ , 12 weeks of Harvoni™ plus ribavirin, 24 weeks of Harvoni™, and 24 weeks of Harvoni™ plus ribavirin, respectively. Three patients had virologic failure.
SAFETY	Commonly reported adverse events included fatigue, headache, nausea, and insomnia, with higher rates reported in the groups that received concomitant ribavirin.

Harvoni™, with or without ribavirin, led to high sustained virologic response rates after 12 and 24 weeks of treatment in previously treated patients with HCV genotype 1, with 24 weeks of treatment providing higher response rates in patients with cirrhosis.

STUDY DESIGN	Randomized, open-label, multicenter, phase 3 clinical trial (n=440).
INCLUSION CRITERIA	Adult patients with chronic HCV genotype 1 infection who did not experience a sustained virologic response to previous treatment with peginterferon and ribavirin +/- an NS3/4A protease inhibitor.
EXCLUSION CRITERIA	Patients who discontinued previous treatment due to an adverse event.
TREATMENT REGIMEN	All patients (age range, 24 to 75 years) received one combination tablet of Harvoni™ orally once daily and were randomly assigned to 4 groups: Harvoni™ for 12 weeks (n=109), Harvoni™ plus ribavirin (administered twice daily in doses of 1000 mg/day for body weights < 75 kg; 1200

	mg/day for body weights of 75 kg or greater) for 12 weeks (n=111), Harvoni™ for 24 weeks (n=109), and Harvoni™ plus ribavirin for 24 weeks (n=111).
RESULTS	At baseline, cirrhosis was present in 20% of patients and 52% of patients had received prior treatment with a protease inhibitor. At week 12 following the end of treatment, sustained virologic response rates (primary endpoint) were 94%, 96%, 99%, and 99% in patients who received 12 weeks of Harvoni™, 12 weeks of Harvoni™ plus ribavirin, 24 weeks of Harvoni™, and 24 weeks of Harvoni™ plus ribavirin, respectively. Two percent of patients had virologic relapse after the end of treatment but none were in the groups that received 24 weeks of treatment. Of patients with cirrhosis (n=88), sustained virologic response rates were significantly improved in patients who were treated with 24 weeks of Harvoni™ (95%) compared to 12 weeks of Harvoni™ (86%;p=0.007).
SAFETY	Patients who received 24 weeks of Harvoni™ alone had higher rates of adverse events than those who received 12 weeks of Harvoni™ alone (81% vs 67%). Higher rates of adverse events were reported in the groups that received concomitant ribavirin.

Contraindications [(1)]

- None

Warnings and Precautions [(1)]

- Anticonvulsants (eg, carbamazepine, phenytoin, phenobarbital, oxcarbazepine) are not recommended.
- Antimycobacterials (eg, rifabutin, rifampin, rifapentine) are not recommended.
- Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate is not recommended.
- Other products containing sofosbuvir are not recommended.
- P-glycoprotein (P-gp) inducers (eg, rifampin, St. John's wort) are not recommended.
- Rosuvastatin is not recommended.
- Simeprevir is not recommended.
- Tipranavir/ritonavir is not recommended.

Adverse Effects [1]

Most common, ≥ 5%	Harvoni™ (n=326)
Fatigue	18%
Headache	17%
Nausea	9%
Diarrhea	7%
Insomnia	6%

Drug Interactions [1]

- Acid-reducing agents: antacids, H2-receptor antagonists, proton pump inhibitors
- Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- Antimycobacterials: rifabutin, rifampin, rifapentine
- Digoxin
- HIV antiretrovirals: efavirenz, emtricitabine, elvitegravir, cobicistat, tenofovir disoproxil fumarate, tipranavir/ritonavir
- P-glycoprotein inducers, potent: rifampin, St. John's wort
- Rosuvastatin
- Simeprevir

Dosage and Administration [1]

The recommended dose is 1 tablet orally once daily with or without food for 12 to 24 weeks.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST*/ MONTH
Ledipasvir/ Sofosbuvir	Harvoni	Gilead	90 mg/400 mg tablets	1 tablet daily	$31,815

* Maximum Allowable Cost

Conclusion

Harvoni™ is the first oral combination agent approved for the treatment of chronic hepatitis C genotype 1 infection in adults. Ledipasvir and sofosbuvir are 2 antiviral agents that, in combination, demonstrated efficacy for both previously untreated and previously treated patients in clinical trials. In 2 randomized, open-label studies of treatment-naive patients (n=865; n=647), Harvoni™ treatment resulted in sustained virologic responses in 94% after 8 weeks in one study, 95% and

99% after 12 weeks in both studies, and in 98% after 24 weeks in one study. In a randomized, open-label study of treatment-experienced patients (n=440), Harvoni™ treatment resulted in sustained virologic responses in 94% after 12 weeks and in 99% after 24 weeks. Of patients with cirrhosis (n=88), sustained virologic response rates were significantly improved in patients who were treated with 24 weeks of Harvoni™ (95%) compared to 12 weeks of Harvoni™ (86%). In all trials, concomitant ribavirin did not increase response rates but did increase the frequency of adverse events. Harvoni™ was approved under the priority review program at the US Food and Drug Administration (FDA) and received a Breakthrough Therapy designation. It eliminates the need for treatment with interferon and ribavirin. The most common adverse effects in clinical trials were fatigue, headache, nausea, and insomnia.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List as non-preferred.

References

1. Product Information: Harvoni™, ledipasvir/sofosbuvir tablets. Gilead Sciences, Foster City, CA, 10/2014
2. Afdhal N, Zeuzem S, Kwo P et al: Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 2014; 370(20):1889-1898.
3. Kowdley KV, Gordon SC, Reddy KR et al: Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med 2014; 370(20):1879-1888.
4. Afdhal N, Reddy KR, Nelson DR et al: Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med 2014; 370(16):1483-1493.
5. Hepatits C FAQs for the Public. Retrieved March 9, 2015 from http://www.cdc.gov/hepatitis/c/cfaq.htm

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