HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use HARVONI® safely and effectively. See full prescribing information for HARVONI.

HARVONI® (ledipasvir and sofosbuvir) tablets, for oral use
Initial U.S. Approval: 2014

----------RECENT MAJOR CHANGES ----------
Warnings and Precautions (5.1) 03/2015

----------INDICATIONS AND USAGE----------
HARVONI is a fixed-dose combination of ledipasvir, a hepatitis C virus (HCV) NS5A inhibitor, and sofosbuvir, an HCV nucleotide analog NS5B polymerase inhibitor, and is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended dosage: One tablet (90 mg of ledipasvir and 400 mg of sofosbuvir) taken orally once daily with or without food (2.1)
- Recommended treatment duration (2.1):
  - Treatment-naïve with or without cirrhosis: 12 weeks
  - Treatment-experienced without cirrhosis: 12 weeks
  - Treatment-experienced with cirrhosis: 24 weeks
- A dose recommendation cannot be made for patients with severe renal impairment or end stage renal disease (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 90 mg ledipasvir and 400 mg sofosbuvir (3)

----------CONTRAINDICATIONS----------
None

----------WARNINGS AND PRECAUTIONS----------
- Bradycardia with amiodarone coadministration: Serious symptomatic bradycardia may occur in patients taking amiodarone, particularly in patients also receiving beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with HARVONI is not recommended. In patients without alternative, viable treatment options, cardiac monitoring is recommended. (5.1, 6.2, 7.2)
- Use with other drugs containing sofosbuvir, including SOVALDI, is not recommended (5.3)

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence greater than or equal to 10%, all grades) observed with treatment with HARVONI for 8, 12, or 24 weeks are fatigue and headache (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Coadministration with amiodarone may result in serious symptomatic bradycardia. Use of HARVONI with amiodarone is not recommended (5.1, 6.2, 7.2)
- P-gp inducers (e.g., rifampin, St. John's wort): May alter concentrations of ledipasvir and sofosbuvir. Use of HARVONI with P-gp inducers is not recommended (5.2, 7, 12.3)
- Consult the full prescribing information prior to use for potential drug interactions (5.1, 5.2, 7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

HARVONI is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage in Adults

HARVONI is a two-drug fixed-dose combination product that contains 90 mg of ledipasvir and 400 mg of sofosbuvir in a single tablet. The recommended dosage of HARVONI is one tablet taken orally once daily with or without food *[see Clinical Pharmacology (12.3)]*.

Duration of Treatment

Relapse rates are affected by baseline host and viral factors and differ between treatment durations for certain subgroups *[see Clinical Studies (14)].*

Table 1 below provides the recommended HARVONI treatment durations for treatment-naïve and treatment-experienced patients and those with and without cirrhosis *[see Clinical Studies (14)].*

Table 1 Recommended Treatment Duration for HARVONI in Patients with CHC Genotype 1

Patient Population	Recommended Treatment Duration
Treatment-naïve with or without cirrhosis	12 weeks*
Treatment-experienced** without cirrhosis	12 weeks
Treatment-experienced** with cirrhosis	24 weeks

* HARVONI for 8 weeks can be considered in treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL *[see Clinical Studies (14)]*.

**Treatment-experienced patients who have failed treatment with either peginterferon alfa + ribavirin or an HCV protease inhibitor + peginterferon alfa + ribavirin.

2.2 Severe Renal Impairment and End Stage Renal Disease

No dose recommendation can be given for patients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] <30 mL/min/1.73m^2) or with end stage renal disease (ESRD) due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

HARVONI is available as an orange colored, diamond shaped, film-coated tablet debossed with “GSI” on one side and “7985” on the other side of the tablet. Each tablet contains 90 mg ledipasvir and 400 mg sofosbuvir.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Serious Symptomatic Bradycardia When Coadministered with Amiodarone

Postmarketing cases of symptomatic bradycardia, as well as fatal cardiac arrest and cases requiring pacemaker intervention, have been reported when amiodarone is coadministered with HARVONI. Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this effect is unknown.

Coadministration of amiodarone with HARVONI is not recommended. For patients taking amiodarone who have no other alternative, viable treatment options and who will be coadministered HARVONI:

- Counsel patients about the risk of serious symptomatic bradycardia
- Cardiac monitoring in an in-patient setting for the first 48 hours of coadministration is recommended, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment.

Patients who are taking HARVONI who need to start amiodarone therapy due to no other alternative, viable treatment options should undergo similar cardiac monitoring as outlined above.

Due to amiodarone's long half-life, patients discontinuing amiodarone just prior to starting HARVONI should also undergo similar cardiac monitoring as outlined above.

Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately. Symptoms may include near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pains, confusion or memory problems *[See Adverse Reactions (6.2), Drug Interactions (7.2)]*.

5.2 Risk of Reduced Therapeutic Effect Due to P-gp Inducers

The concomitant use of HARVONI and P-gp inducers (e.g., rifampin, St. John's wort) may significantly decrease ledipasvir and sofosbuvir plasma concentrations and may lead to a reduced therapeutic effect of HARVONI. Therefore, the use of HARVONI with P-gp inducers (e.g., rifampin or St. John's wort) is not recommended *[see Drug Interactions (7.2)]*.

5.3 Related Products Not Recommended

The use of HARVONI with other products containing sofosbuvir (SOVALDI®) is not recommended.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety assessment of HARVONI was based on pooled data from three Phase 3 clinical trials of subjects with genotype 1 chronic hepatitis C (CHC) with compensated liver disease (with and without cirrhosis) including 215, 539, and 326 subjects who received HARVONI for 8, 12 and 24 weeks, respectively *[see Clinical Studies (14)].*

The proportion of subjects who permanently discontinued treatment due to adverse events was 0%, <1%, and 1% for subjects receiving HARVONI for 8, 12, and 24 weeks, respectively.

The most common adverse reactions (≥10%) were fatigue and headache in subjects treated with 8, 12, or 24 weeks of HARVONI.

Table 2 lists adverse reactions (adverse events assessed as causally related by the investigator, all grades) observed in ≥5% of subjects receiving 8, 12, or 24 weeks treatment with HARVONI in clinical trials. The majority of adverse reactions presented in Table 2 occurred at severity of grade 1. The side-by-side tabulation is to simplify presentation; direct comparison across trials should not be made due to differing trial designs.

Table 2 Adverse Reactions (All Grades) Reported in ≥5% of Subjects Receiving 8, 12, or 24 Weeks of Treatment with HARVONI

	HARVONI 8 weeks	**HARVONI 12 weeks**	**HARVONI 24 weeks**
	N=215	N=539	N=326
Fatigue	16%	13%	18%
Headache	11%	14%	17%
Nausea	6%	7%	9%
Diarrhea	4%	3%	7%
Insomnia	3%	5%	6%

Laboratory Abnormalities

Bilirubin Elevations: Bilirubin elevations of greater than 1.5xULN were observed in 3%, <1%, and 2% of subjects treated with HARVONI for 8, 12, and 24 weeks, respectively.

Lipase Elevations: Transient, asymptomatic lipase elevations of greater than 3xULN were observed in <1%, 2%, and 3% of subjects treated with HARVONI for 8, 12, and 24 weeks, respectively.

Creatine Kinase: Creatine kinase was not assessed in Phase 3 trials of HARVONI. Isolated, asymptomatic creatine kinase elevations (Grade 3 or 4) have been previously reported in subjects treated with sofosbuvir in combination with ribavirin or peginterferon/ribavirin in other clinical trials.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of HARVONI. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac Disorders

Serious symptomatic bradycardia has been reported in patients taking amiodarone who initiate treatment with HARVONI *[See Warnings and Precautions (5.1), Drug Interactions (7.2)]*

7 DRUG INTERACTIONS

7.1 Potential for Drug Interaction

As HARVONI contains ledipasvir and sofosbuvir, any interactions that have been identified with these agents individually may occur with HARVONI.

After oral administration of HARVONI, sofosbuvir is rapidly absorbed and subject to extensive first-pass hepatic extraction. In clinical pharmacology studies, both sofosbuvir and the inactive metabolite GS-331007 were monitored for purposes of pharmacokinetic analyses.

Ledipasvir is an inhibitor of the drug transporters P-gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of coadministered substrates for these transporters.

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