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 ----------

Indications and Usage (1)	11/2015
Dosage and Administration (2.1)	11/2015
Contraindications (4)	11/2015
Warnings and Precautions (5.1)	03/2015
Warnings and Precautions (5.3)	11/2015

----------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 virus (HCV) genotype 1, 4, 5 or 6 infection (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)

	Patient Population	Duration
Genotype 1	Treatment-naïve with or without cirrhosis	12 weeks
	Treatment-experienced without cirrhosis	12 weeks
	Treatment-experienced with cirrhosis	24 weeks
Genotype 4, 5, or 6	Treatment-naïve and treatment-experienced, with or without cirrhosis	12 weeks

- HCV/HIV-1 co-infection: For patients with HCV/HIV-1 co-infection, follow the dosage recommendations in the table above (2.1)
- A dosage 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----------

If used in combination with ribavirin, all contraindications to ribavirin also apply to HARVONI combination therapy (4)

----------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 is not recommended (5.4)

----------ADVERSE REACTIONS----------

The most common adverse reactions (incidence greater than or equal to 10%, all grades) observed with treatment with HARVONI were fatigue, headache and asthenia (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: 11/2015

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 patients with chronic hepatitis C virus (HCV) genotype 1, 4, 5, or 6 infection *[see Dosage and Administration (2) and Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

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 shows the recommended HARVONI treatment duration based on patient population.

For patients with HCV/HIV-1 co-infection, follow the dosage recommendations in Table 1 *[see Clinical Studies (14)].* Refer to *Drug Interactions (7)* for dosage recommendations for concomitant HIV-1 antiviral drugs.

Table 1 Recommended Treatment Duration for HARVONI in Patients with Genotype 1, 4, 5 or 6 HCV

	Patient Population	Recommended Treatment Duration
Genotype 1	Treatment-naïve with or without cirrhosis	12 weeks*
	Treatment-experienced** without cirrhosis	12 weeks
	Treatment-experienced** with cirrhosis	24 weeks†
Genotype 4, 5 or 6	Treatment-naïve and treatment-experienced**, with or without cirrhosis	12 weeks

* HARVONI for 8 weeks can be considered in treatment-naïve genotype 1 patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL *[see Clinical Studies (14.2)]*.

**Treatment-experienced patients include those who have failed a peginterferon alfa + ribavirin based regimen with or without an HCV protease inhibitor.

† HARVONI+ribavirin for 12 weeks can be considered in treatment-experienced genotype 1 patients with cirrhosis who are eligible for ribavirin *[see Clinical Studies (14.2)]*. The daily dosage of ribavirin is weight-based (1000 mg for patients <75 kg and 1200 mg for those ≥75 kg) administered orally in two divided doses with food. Refer to the ribavirin prescribing information.

2.2 Severe Renal Impairment and End Stage Renal Disease

No dosage recommendation can be given for patients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] less than 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

If HARVONI is administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen. Refer to the ribavirin prescribing information for a list of contraindications for ribavirin *[see Dosage and Administration (2.1)]*.

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 Use with 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 Risks Associated with Ribavirin Combination Treatment

If HARVONI is administered with ribavirin, the warnings and precautions for ribavirin, in particular the pregnancy avoidance warning, apply to this combination regimen. Refer to the ribavirin prescribing information for a full list of the warnings and precautions for ribavirin *[see Dosage and Administration (2.1)].*

5.4 Related Products Not Recommended

The use of HARVONI with other products containing sofosbuvir is not recommended.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in labeling:

- Serious Symptomatic Bradycardia When Coadministered with Amiodarone *[see Warnings and Precautions (5.1)].*

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.

If HARVONI is administered with ribavirin, refer to the prescribing information for ribavirin for a description of ribavirin-associated adverse reactions.

The safety assessment of HARVONI was based on pooled data from three randomized, open-label Phase 3 clinical trials (ION-3, ION-1 and ION-2) of subjects with genotype 1 HCV with compensated liver disease (with and without cirrhosis) including 215, 539, and 326 subjects who received HARVONI once daily by mouth 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%, less than 1%, and 1% for subjects receiving HARVONI for 8, 12, and 24 weeks, respectively.

The most common adverse reactions (at least 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 at least 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%

The safety assessment of HARVONI was also based on pooled data from three open-label trials (Study 1119, ION-4 and ELECTRON-2) in 118 subjects with chronic HCV genotype 4, 5 or 6 infection with compensated liver disease (with or without cirrhosis) *[see Clinical Studies (14.3)]*. The subjects received HARVONI once daily by mouth for 12 weeks. The safety profile in subjects with chronic HCV genotype 4, 5 or 6 infection with compensated liver disease was similar to that observed in subjects with chronic HCV genotype 1 infection with compensated liver disease. The most common adverse reactions occurring in at least 10% of subjects were asthenia (18%), headache (14%) and fatigue (10%).

Adverse Reactions in Subjects with Cirrhosis

The safety assessment of HARVONI with or without ribavirin was based on a randomized, double-blind and placebo-controlled trial in treatment-experienced genotype 1 subjects with compensated cirrhosis and was compared to placebo in the SIRIUS trial. Subjects were randomized to receive 24 weeks of HARVONI once daily by mouth without ribavirin or 12 weeks of placebo followed by 12 weeks of HARVONI once daily by mouth + ribavirin *[see Clinical Studies (14.2)]*. Table 3 presents the adverse reactions, as defined above, that occurred with at least 5% greater frequency in subjects treated with 24 weeks of HARVONI or 12 weeks of HARVONI + ribavirin, compared to those reported for 12 weeks of placebo. The majority of the adverse reactions presented in Table 3 were Grade 1 or 2 in severity.

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