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

WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV

See full prescribing information for complete boxed warning.

Hepatitis B virus (HBV) reactivation has been reported, in some cases resulting in fulminant hepatitis, hepatic failure, and death. (5.1)

----------RECENT MAJOR CHANGES ----------

Boxed Warning	02/2017
Indications and Usage (1)	02/2016
Dosage and Administration (2.1)	02/2017
Dosage and Administration (2.2)	02/2016
Warnings and Precautions (5.1)	02/2017

----------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 with or without ribavirin for the treatment of chronic hepatitis C virus (HCV) genotype 1, 4, 5 or 6 infection (1)

----------DOSAGE AND ADMINISTRATION----------

- Testing Prior to the Initiation of Therapy: Test all patients for HBV infection by measuring HBsAg and anti-HBc. (2.1)
- Recommended dosage: One tablet (90 mg of ledipasvir and 400 mg of sofosbuvir) taken orally once daily with or without food (2.2)
- Recommended treatment regimen and duration: (2.2)

	Patient Population	Regimen and Duration
Genotype 1	Treatment-naïve without cirrhosis or with compensated cirrhosis (Child-Pugh A)	HARVONI 12 weeks
	Treatment-experienced without cirrhosis	HARVONI 12 weeks
	Treatment-experienced with compensated cirrhosis (Child-Pugh A)	HARVONI 24 weeks
	Treatment-naïve and treatment-experienced with decompensated cirrhosis (Child-Pugh B or C)	HARVONI + ribavirin 12 weeks
Genotype 1 or 4	Treatment-naïve and treatment-experienced liver transplant recipients without cirrhosis, or with compensated cirrhosis (Child-Pugh A)	HARVONI + ribavirin 12 weeks
Genotype 4, 5, or 6	Treatment-naïve and treatment-experienced without cirrhosis or with compensated cirrhosis (Child-Pugh A)	HARVONI 12 weeks

follow the dosage recommendations in the table above (2.2)

- If used in combination with ribavirin, follow the recommendations for ribavirin dosing and dosage modifications (2.2)
- A dosage recommendation cannot be made for patients with severe renal impairment or end stage renal disease (2.3)

----------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----------

- Risk of Hepatitis B Virus Reactivation: Test all patients for evidence of current or prior HBV infection before initiation of HCV treatment. Monitor HCV/HBV coinfected patients for HBV reactivation and hepatitis flare during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated. (5.1)
- 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. (5.2, 6.2, 7.2)
- Use with other drugs containing sofosbuvir is not recommended (5.5)

----------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 (5.2, 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 (5.3, 7, 12.3)
- Consult the full prescribing information prior to use for potential drug interactions (5.2, 5.3, 7, 12.3)

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

Revised: 02/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV

Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with HARVONI. HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct acting antivirals and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV coinfected patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated *[see Warnings and Precautions (5.1)].*

1 INDICATIONS AND USAGE

HARVONI is indicated with or without ribavirin 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 Testing Prior to the Initiation of Therapy

Test all patients for evidence of current or prior HBV infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) before initiating HCV treatment with HARVONI *[see Warnings and Precautions (5.1)]*.

2.2 Recommended Dosage

The recommended dosage of HARVONI is one tablet taken orally once daily with or without food *[see Clinical Pharmacology (12.3)]*.

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 regimen and duration based on patient population.

For patients with HCV/HIV-1 coinfection, 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 Regimen and Duration for HARVONI in Patients with Genotype 1, 4, 5 or 6 HCV

	Patient Population	Treatment Regimen and Duration
Genotype 1	Treatment-naïve without cirrhosis or with compensated cirrhosis (Child-	HARVONI 12 weeks*

	Pugh A)	
	Treatment-experienced** without cirrhosis	HARVONI 12 weeks
	Treatment-experienced** with compensated cirrhosis (Child-Pugh A)	HARVONI 24 weeks†
	Treatment-naïve and treatment-experienced** with decompensated cirrhosis (Child-Pugh B or C)	HARVONI + ribavirin‡ 12 weeks
Genotype 1 or 4	Treatment-naïve and treatment-experienced** liver transplant recipients without cirrhosis, or with compensated cirrhosis (Child-Pugh A)	HARVONI + ribavirin§ 12 weeks
Genotype 4, 5 or 6	Treatment-naïve and treatment-experienced**, without cirrhosis or with compensated cirrhosis (Child-Pugh A)	HARVONI 12 weeks

* HARVONI for 8 weeks can be considered in treatment-naïve genotype 1 patients without cirrhosis who have pretreatment 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)]*. See footnote § for ribavirin dosage recommendations.

‡ In patients with decompensated cirrhosis, the starting dosage of ribavirin is 600 mg and can be titrated up to 1000 mg for patients <75 kg and 1200 mg for those ≥75 kg in two divided doses with food. If the starting dosage of ribavirin is not well tolerated, the dosage should be reduced as clinically indicated based on hemoglobin levels.

§ 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.

For further information on ribavirin dosing and dosage modifications, refer to the ribavirin prescribing information *[see Clinical Studies (14.5)]*.

2.3 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/1.73 m^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 (2.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Hepatitis B Virus Reactivation in Patients Coinfected with HCV and HBV

Hepatitis B virus (HBV) reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct acting antivirals, and who were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Cases have been reported in patients who are HBsAg positive and also in patients with serologic evidence of resolved HBV infection (i.e., HBsAg negative and anti-HBc positive). HBV reactivation has also been reported in patients receiving certain immunosuppressants or chemotherapeutic agents; the risk of HBV reactivation associated with treatment with HCV direct-acting antivirals may be increased in these patients.

HBV reactivation is characterized as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level. In patients with resolved HBV infection, reappearance of HBsAg can occur. Reactivation of HBV replication may be accompanied by hepatitis, i.e., increases in aminotransferase levels and, in severe cases, increases in bilirubin levels, liver failure, and death can occur.

Test all patients for evidence of current or prior HBV infection by measuring HBsAg and anti-HBc before initiating HCV treatment with HARVONI. In patients with serologic evidence of HBV infection, monitor for clinical and laboratory signs of hepatitis flare or HBV reactivation during HCV treatment with HARVONI and during post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.

5.2 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

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