CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212477Orig1s000

LABELING

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
HARVONI® (ledipasvir and sofosbuvir) oral pellets
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 ----------

Indications and Usage (1)	8/2019
Dosage and Administration	
Recommended Treatment Regimen and Duration in Patients 3 Years of Age and Older with Genotype 1, 4, 5, or 6 HCV (2.2)	8/2019
Recommended Dosage in Pediatric Patients 3 Years of Age and Older (2.4)	8/2019
Preparation and Administration of Oral Pellets (2.5)	8/2019

----------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) in adults and pediatric patients 3 years of age and older:

- Genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis
- Genotype 1 infection with decompensated cirrhosis, in combination with ribavirin
- Genotype 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis, in combination with r bavirin. (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 treatment regimen and duration in patients 3 years of age and older: (2.2)

HCV Genotype	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

- Recommended dosage in adults: One tablet (90 mg of ledipasvir and 400 mg of sofosbuvir) taken orally once daily with or without food. (2.3)
- Recommended dosage in pediatric patients 3 years and older: Recommended dosage of HARVONI in pediatric patients 3 years of age and older is based on weight. Refer to Table 2 of the full prescribing information for specific dosing guidelines based on body weight. (2.4)
- HCV/HIV-1 coinfection: For adult and pediatric patients with HCV/HIV-1 coinfection, follow the dosage recommendations in the tables in the full prescribing information. (2.3, 2.4)
- If used in combination with ribavirin, follow the recommendations for r bavirin dosing and dosage modifications. (2.3, 2.4)
- A dosage recommendation cannot be made for patients with severe renal impairment or end stage renal disease. (2.6)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 90 mg of ledipasvir and 400 mg of sofosbuvir; 45 mg of ledipasvir and 200 mg of sofosbuvir. (3)
- Oral Pellets: 45 mg of ledipasvir and 200 mg of sofosbuvir; 33.75 mg of ledipasvir and 150 mg of 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)

----------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)
- Frequent monitoring of international normalized ratio (INR) values is recommended in patients receiving warfarin. (7.1)
- 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: 08/2019

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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 for the treatment of adults and pediatric patients 3 years of age and older with chronic hepatitis C virus (HCV) *[see Dosage and Administration (2.2 and 2.3) and Clinical Studies (14)]*:

- genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis
- genotype 1 infection with decompensated cirrhosis, for use in combination with ribavirin
- genotype 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis, for use in combination with ribavirin

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 Treatment Regimen and Duration in Patients 3 Years of Age and Older with Genotype 1, 4, 5, or 6 HCV

Table 1 shows the recommended HARVONI treatment regimen and duration based on patient population. Relapse rates are affected by baseline host and viral factors and differ between treatment durations for certain subgroups *[see Clinical Studies (14)].*

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 3 Years of Age and Older with Genotype 1, 4, 5, or 6 HCV

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

a. 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)]*.
b. Treatment-experienced adult and pediatric subjects have failed a peginterferon alfa +/- ribavirin based regimen with or without an HCV protease inhibitor.
c. HARVONI + ribavirin for 12 weeks can be considered in treatment-experienced genotype 1 patients with cirrhosis who are eligible for ribavirin *[see Dosage and Administration (2.3 and 2.4) and Clinical Studies (14.2)]*.
d. See *Dosage and Administration 2.3 and 2.4* for ribavirin dosage recommendations.

2.3 Recommended Dosage in Adults

The recommended dosage of HARVONI in adults with genotype 1, 4, 5, or 6 HCV is one tablet (90 mg ledipasvir and 400 mg sofosbuvir) taken orally once daily with or without food *[see Clinical Pharmacology (12.3)]*.

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.

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.

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

2.4 Recommended Dosage in Pediatric Patients 3 Years of Age and Older

The recommended dosage of HARVONI in pediatric patients 3 years of age and older with genotype 1, 4, 5, or 6 HCV using HARVONI tablets or oral pellets is based on weight (Table 2). Table 3 provides the weight-based dosage of ribavirin when used in

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