**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**

**----------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----------**
Use with other drugs containing sofosbuvir, including SOVALDI, is not recommended (5.2)

**----------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----------**
- 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 (5.1, 7, 12.3)
- Consult the full prescribing information prior to use for potential drug interactions (5.1, 7, 12.3)

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

**Revised: 10/2014**

**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 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)]*.

### 5.2 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.

## 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.

Ledipasvir and sofosbuvir are substrates of drug transporters P-gp and BCRP while GS-331007 is not. P-gp inducers (e.g., rifampin or St. John's wort) may decrease ledipasvir and sofosbuvir plasma concentrations, leading to reduced therapeutic effect of HARVONI, and the use with P-gp inducers is not recommended with HARVONI *[see Warnings and Precautions (5.1)]*.

### 7.2 Established and Potentially Significant Drug Interactions

Table 3 provides a listing of established or potentially clinically significant drug interactions. The drug interactions described are based on studies conducted with either HARVONI, the components of HARVONI (ledipasvir and sofosbuvir) as individual agents, or are predicted drug interactions that may occur with HARVONI *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

**Table 3 Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction[a]**

| Concomitant Drug Class: Drug Name | Effect on Concentration[b] | Clinical Comment |
|---|---|---|
| **Acid Reducing Agents:** | ↓ ledipasvir | Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of ledipasvir. |
| Antacids (e.g., aluminum and magnesium hydroxide) | | It is recommended to separate antacid and HARVONI administration by 4 hours. |
| $H_2$-receptor antagonists[c] (e.g., famotidine) | | $H_2$-receptor antagonists may be administered simultaneously with or 12 hours apart from HARVONI at a dose that does not exceed doses comparable to famotidine 40 mg twice daily. |
| Proton-pump inhibitors[c] (e.g., omeprazole) | | Proton-pump inhibitor doses comparable to omeprazole 20 mg or lower can be administered simultaneously with HARVONI under fasted conditions. |
| **Antiarrhythmics:** digoxin | ↑ digoxin | Coadministration of HARVONI with digoxin may increase the concentration of digoxin. Therapeutic concentration monitoring of digoxin is recommended when coadministered with HARVONI. |
| **Anticonvulsants:** carbamazepine phenytoin phenobarbital oxcarbazepine | ↓ ledipasvir<br>↓ sofosbuvir<br>↓ GS-331007 | Coadministration of HARVONI with carbamazepine, phenytoin, phenobarbital, or oxcarbazepine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended. |
| **Antimycobacterials:** rifabutin rifampin[c] rifapentine | ↓ ledipasvir<br>↓ sofosbuvir<br>↓ GS-331007 | Coadministration of HARVONI with rifabutin or rifapentine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended.<br>Coadministration of HARVONI with rifampin, a P-gp inducer, is not recommended *[see Warnings and Precautions (5.1)].* |
| **HIV Antiretrovirals:** | | |

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