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: 3/2015

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.

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 (5.2)]*.

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, 5.2) 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: amiodarone	Effect on amiodarone, ledipasvir, and sofosbuvir concentrations unknown	Coadministration of amiodarone with HARVONI may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Coadministration of amiodarone with HARVONI is not recommended; if coadministration is required, cardiac monitoring is recommended *[see Warnings and Precautions (5.1), Adverse Reactions (6.2)]*
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 ↓ sofosbuvir ↓ 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	↓ ledipasvir ↓ sofosbuvir	Coadministration of HARVONI with rifabutin or rifapentine is expected to decrease the concentration of ledipasvir

rifampin[c] rifapentine	↓ GS-331007	and sofosbuvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended. Coadministration of HARVONI with rifampin, a P-gp inducer, is not recommended *[see Warnings and Precautions (5.2)].*
HIV Antiretrovirals:		
efavirenz, emtricitabine, tenofovir disoproxil fumarate (DF)	↑ tenofovir	Monitor for tenofovir-associated adverse reactions in patients receiving HARVONI concomitantly with the combination of efavirenz, emtricitabine and tenofovir DF. Refer to VIREAD, TRUVADA, or ATRIPLA prescribing information for recommendations on renal monitoring.
Regimens containing tenofovir DF and a HIV protease inhibitor/ritonavir • atazanavir/ritonavir + emtricitabine/tenofovir DF[c] • darunavir/ritonavir + emtricitabine/tenofovir DF[c] • lopinavir/ritonavir + emtricitabine/tenofovir DF	↑ tenofovir	The safety of increased tenofovir concentrations in the setting of HARVONI and a HIV protease inhibitor/ritonavir has not been established. Consider alternative HCV or antiretroviral therapy to avoid increases in tenofovir exposures. If coadministration is necessary, monitor for tenofovir-associated adverse reactions. Refer to VIREAD or TRUVADA prescribing information for recommendations on renal monitoring.
elvitegravir, cobicistat, emtricitabine, tenofovir DF	↑ tenofovir	The safety of increased tenofovir concentrations in the setting of HARVONI and the combination of elvitegravir, cobicistat, emtricitabine and tenofovir DF has not been established. Coadministration is not recommended.
tipranavir/ritonavir	↓ ledipasvir ↓ sofosbuvir ↓ GS-331007	Coadministration of HARVONI with tipranavir/ritonavir is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended.
HCV Products: simeprevir[c]	↑ ledipasvir ↑ simeprevir	Concentrations of ledipasvir and simeprevir are increased when simeprevir is coadministered with ledipasvir. Coadministration of HARVONI with simeprevir is not recommended.
Herbal Supplements: St. John's wort *(Hypericum perforatum)*	↓ ledipasvir ↓ sofosbuvir ↓ GS-331007	Coadministration of HARVONI with St. John's wort, a P-gp inducer is not recommended *[see Warnings and Precautions (5.2)].*
HMG-CoA Reductase Inhibitors: rosuvastatin	↑ rosuvastatin	Coadministration of HARVONI with rosuvastatin may significantly increase the concentration of rosuvastatin which is associated with increased risk of myopathy, including rhabdomyolysis. Coadministration of HARVONI with rosuvastatin is not recommended.

a. This table is not all inclusive.
b. ↓ = decrease, ↑ = increase
c. These interactions have been studied in healthy adults.

7.3 Drugs without Clinically Significant Interactions with HARVONI

Based on drug interaction studies conducted with the components of HARVONI (ledipasvir or sofosbuvir) or HARVONI, no clinically significant drug interactions have been either observed or are expected when HARVONI is used with the following drugs

individually *[see Clinical Pharmacology (12.3)]:* abacavir, atazanavir/ritonavir, cyclosporine, darunavir/ritonavir, efavirenz, emtricitabine, lamivudine, methadone, oral contraceptives, pravastatin, raltegravir, rilpivirine, tacrolimus, tenofovir disoproxil fumarate, or verapamil. See Table 3 for use of HARVONI with certain HIV antiretroviral regimens *[see Drug Interactions (7.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies with HARVONI in pregnant women. Because animal reproduction studies are not always predictive of human response, HARVONI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

Ledipasvir: No effects on fetal development have been observed in rats and rabbits at the highest doses tested. In the rat and rabbit, AUC exposure to ledipasvir was approximately 4- and 2-fold, respectively, the exposure in humans at the recommended clinical dose.

Sofosbuvir: No effects on fetal development have been observed in rats and rabbits at the highest doses tested. In the rat and rabbit, AUC exposure to the predominant circulating metabolite GS-331007 increased over the course of gestation from approximately 3- to 6-fold and 7- to 17-fold the exposure in humans at the recommended clinical dose, respectively.

8.3 Nursing Mothers

It is not known whether HARVONI and its metabolites are present in human breast milk. When administered to lactating rats, ledipasvir was detected in the plasma of suckling rats likely due to the presence of ledipasvir in milk. Ledipasvir had no clear effects on the nursing pups. The predominant circulating metabolite of sofosbuvir (GS-331007) was the primary component observed in the milk of lactating rats, without effect on nursing pups. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HARVONI and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of HARVONI have not been established in pediatric patients.

8.5 Geriatric Use
Clinical trials of HARVONI included 117 subjects aged 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment of HARVONI is warranted in geriatric patients *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment
No dosage adjustment of HARVONI is required for patients with mild or moderate renal impairment. The safety and efficacy of HARVONI have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) or ESRD requiring hemodialysis. No dosage recommendation can be given for patients with severe renal impairment or ESRD *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment
No dosage adjustment of HARVONI is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C). Safety and efficacy of HARVONI have not been established in patients with decompensated cirrhosis *[see Clinical Pharmacology (12.3)].*

10 OVERDOSAGE
No specific antidote is available for overdose with HARVONI. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with HARVONI consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient. Hemodialysis is unlikely to result in significant removal of ledipasvir since ledipasvir is highly bound to plasma protein. Hemodialysis can efficiently remove the predominant circulating metabolite of sofosbuvir, GS-331007, with an extraction ratio of 53%.

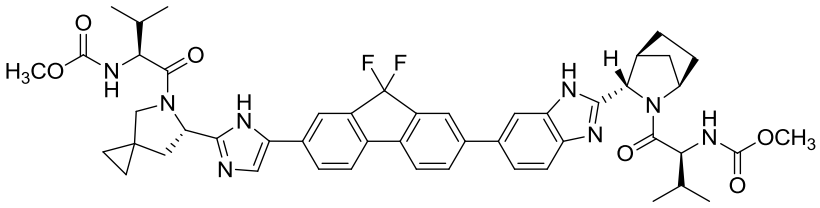
11 DESCRIPTION
HARVONI is a fixed-dose combination tablet containing ledipasvir and sofosbuvir for oral administration. Ledipasvir is an HCV NS5A inhibitor and sofosbuvir is a nucleotide analog inhibitor of HCV NS5B polymerase.

Each tablet contains 90 mg ledipasvir and 400 mg sofosbuvir. The tablets include the following inactive ingredients: colloidal silicon dioxide, copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing the following inactive ingredients: FD&C yellow #6/sunset yellow FCF aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Ledipasvir: The IUPAC name for ledipasvir is Methyl [(2*S*)-1-{(6*S*)-6-[5-(9,9-difluoro-7-{2-[(1*R*,3*S*,4*S*)-2-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-

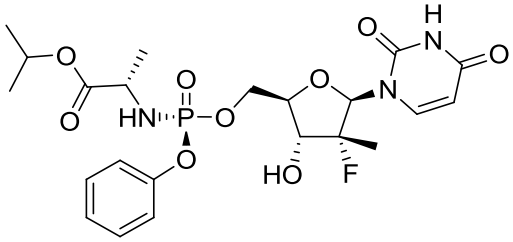
azabicyclo[2.2.1]hept-3-yl]-1*H*-benzimidazol-6-yl}-9*H*-fluoren-2-yl)-1*H*-imidazol-2-yl]-5-azaspiro[2.4]hept-5-yl}-3-methyl-1-oxobutan-2-yl]carbamate.

It has a molecular formula of $C_{49}H_{54}F_2N_8O_6$ and a molecular weight of 889.00. It has the following structural formula:



Ledipasvir is practically insoluble (<0.1 mg/mL) across the pH range of 3.0–7.5 and is slightly soluble below pH 2.3 (1.1 mg/mL).

Sofosbuvir: The IUPAC name for sofosbuvir is (*S*)-Isopropyl 2-((*S*)-(((2*R*,3*R*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)-(phenoxy)phosphorylamino)propanoate. It has a molecular formula of $C_{22}H_{29}FN_3O_9P$ and a molecular weight of 529.45. It has the following structural formula:



Sofosbuvir is a white to off-white crystalline solid with a solubility of ≥2 mg/mL across the pH range of 2–7.7 at 37°C and is slightly soluble in water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

HARVONI is a fixed-dose combination of ledipasvir and sofosbuvir which are direct-acting antiviral agents against the hepatitis C virus *[see Microbiology (12.4)].*

12.2 Pharmacodynamics

Cardiac Electrophysiology

Thorough QT studies have been conducted for ledipasvir and sofosbuvir.

The effect of ledipasvir 120 mg twice daily (2.67 times the maximum recommended dosage) for 10 days on QTc interval was evaluated in a randomized, multiple-dose, placebo-, and active-controlled (moxifloxacin 400 mg) three period crossover thorough QT trial in 59 healthy subjects. At the dose of 120 mg twice daily (2.67 times the maximum recommended dosage), ledipasvir does not prolong QTc interval to any clinically relevant extent.

The effect of sofosbuvir 400 mg (maximum recommended dosage) and 1200 mg (three times the maximum recommended dosage) on QTc interval was evaluated in a randomized, single-dose, placebo-, and active-controlled (moxifloxacin 400 mg) four period crossover thorough QT trial in 59 healthy subjects. At a dose three times the maximum recommended dose, sofosbuvir does not prolong QTc to any clinically relevant extent.

12.3 Pharmacokinetics

Absorption

The pharmacokinetic properties of ledipasvir, sofosbuvir, and the predominant circulating metabolite GS-331007 have been evaluated in healthy adult subjects and in subjects with chronic hepatitis C. Following oral administration of HARVONI, ledipasvir median peak concentrations were observed 4 to 4.5 hours post-dose. Sofosbuvir was absorbed quickly and the peak median plasma concentration was observed ~0.8 to 1 hour post-dose. Median peak plasma concentration of GS-331007 was observed between 3.5 to 4 hours post-dose.

Based on the population pharmacokinetic analysis in HCV-infected subjects, geometric mean steady-state AUC_{0-24} for ledipasvir (N=2113), sofosbuvir (N=1542), and GS-331007 (N=2113) were 7290, 1320, and 12,000 ng•hr/mL, respectively. Steady-state C_{max} for ledipasvir, sofosbuvir, and GS-331007 were 323, 618, and 707 ng/mL, respectively. Sofosbuvir and GS-331007 AUC_{0-24} and C_{max} were similar in healthy adult subjects and subjects with HCV infection. Relative to healthy subjects (N=191), ledipasvir AUC_{0-24} and C_{max} were 24% lower and 32% lower, respectively, in HCV-infected subjects.

Effect of Food

Relative to fasting conditions, the administration of a single dose of HARVONI with a moderate fat (~600 kcal, 25% to 30% fat) or high fat (~1000 kcal, 50% fat) meal increased sofosbuvir AUC_{0-inf} by approximately 2-fold, but did not significantly affect sofosbuvir C_{max}. The exposures of GS-331007 and ledipasvir were not altered in the presence of either meal type. The response rates in Phase 3 trials were similar in HCV-infected subjects who received HARVONI with food or without food. HARVONI can be administered without regard to food.

Distribution

Ledipasvir is >99.8% bound to human plasma proteins. After a single 90 mg dose of [^{14}C]-ledipasvir in healthy subjects, the blood to plasma ratio of ^{14}C-radioactivity ranged between 0.51 and 0.66.

Sofosbuvir is approximately 61–65% bound to human plasma proteins and the binding is independent of drug concentration over the range of 1 μg/mL to 20 μg/mL. Protein binding of GS-331007 was minimal in human plasma. After a single 400 mg dose of [^{14}C]-sofosbuvir in healthy subjects, the blood to plasma ratio of ^{14}C-radioactivity was approximately 0.7.

Metabolism

In vitro, no detectable metabolism of ledipasvir was observed by human CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Evidence of slow oxidative metabolism via an unknown mechanism has been observed. Following a single dose of 90 mg [^{14}C]-ledipasvir, systemic exposure was almost exclusively to the parent drug (>98%). Unchanged ledipasvir is the major species present in feces.

Sofosbuvir is extensively metabolized in the liver to form the pharmacologically active nucleoside analog triphosphate GS-461203. The metabolic activation pathway involves sequential hydrolysis of the carboxyl ester moiety catalyzed by human cathepsin A (CatA) or carboxylesterase 1 (CES1) and phosphoramidate cleavage by histidine triad nucleotide-binding protein 1 (HINT1) followed by phosphorylation by the pyrimidine nucleotide biosynthesis pathway. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity in vitro. After a single 400 mg oral dose of [^{14}C]-sofosbuvir, GS-331007 accounted for approximately >90% of total systemic exposure.

Elimination

Following a single 90 mg oral dose of [^{14}C]-ledipasvir, mean total recovery of the [^{14}C]-radioactivity in feces and urine was approximately 87%, with most of the radioactive dose recovered from feces (approximately 86%). Unchanged ledipasvir excreted in feces accounted for a mean of 70% of the administered dose and the oxidative metabolite M19 accounted for 2.2% of the dose. These data indicate that biliary excretion of unchanged ledipasvir is a major route of elimination, with renal excretion being a minor pathway (approximately 1%). The median terminal half-life of ledipasvir following administration of HARVONI was 47 hours.

Following a single 400 mg oral dose of [^{14}C]-sofosbuvir, mean total recovery of the dose was greater than 92%, consisting of approximately 80%, 14%, and 2.5% recovered in urine, feces, and expired air, respectively. The majority of the sofosbuvir dose recovered in urine was GS-331007 (78%) while 3.5% was recovered as sofosbuvir. These data indicate that renal clearance is the major elimination pathway for GS-331007. The median terminal half-lives of sofosbuvir and GS-331007 following administration of HARVONI were 0.5 and 27 hours, respectively.

Specific Populations

Patients with Renal Impairment: The pharmacokinetics of ledipasvir were studied with a single dose of 90 mg ledipasvir in HCV negative subjects with severe renal impairment (eGFR <30 mL/min by Cockcroft-Gault). No clinically relevant differences in ledipasvir pharmacokinetics were observed between healthy subjects and subjects with severe renal impairment.

The pharmacokinetics of sofosbuvir were studied in HCV negative subjects with mild (eGFR ≥50 and <80 mL/min/1.73m^2), moderate (eGFR ≥30 and <50 mL/min/1.73m^2), severe renal impairment (eGFR <30 mL/min/1.73m^2), and subjects with ESRD requiring hemodialysis following a single 400 mg dose of sofosbuvir. Relative to subjects with normal renal function (eGFR >80 mL/min/1.73m^2), the sofosbuvir $AUC_{0\text{-inf}}$ was 61%, 107%, and 171% higher in mild, moderate, and severe renal impairment, while the GS-331007 $AUC_{0\text{-inf}}$ was 55%, 88%, and 451% higher, respectively. In subjects with ESRD, relative to subjects with normal renal function, sofosbuvir and GS-331007 $AUC_{0\text{-inf}}$ was 28% and 1280% higher when sofosbuvir was dosed 1 hour before hemodialysis compared with 60% and 2070% higher when sofosbuvir was dosed 1 hour after hemodialysis, respectively. A 4 hour hemodialysis session removed approximately 18% of administered dose *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)].*

Race: Population pharmacokinetics analysis in HCV-infected subjects indicated that race had no clinically relevant effect on the exposure of ledipasvir, sofosbuvir, and GS-331007.

Gender: Population pharmacokinetics analysis in HCV-infected subjects indicated that gender had no clinically relevant effect on the exposure of sofosbuvir and GS-331007. AUC and C_{max} of ledipasvir were 77% and 58% higher, respectively, in females than males; however, the relationship between gender and ledipasvir exposures was not considered clinically relevant, as high response rates (SVR >90%) were achieved in male and female subjects across the Phase 3 studies and the safety profiles are similar in females and males.

Pediatric Patients: The pharmacokinetics of ledipasvir or sofosbuvir in pediatric patients has not been established *[see Use in Specific Populations (8.4)]*.

Geriatric Patients: Population pharmacokinetic analysis in HCV-infected subjects showed that within the age range (18 to 80 years) analyzed, age did not have a clinically relevant effect on the exposure to ledipasvir, sofosbuvir, and GS-331007 *[see Use in Specific Populations (8.5)]*.

Patients with Hepatic Impairment: The pharmacokinetics of ledipasvir were studied with a single dose of 90 mg ledipasvir in HCV negative subjects with severe hepatic impairment (Child-Pugh Class C). Ledipasvir plasma exposure ($AUC_{0\text{-inf}}$) was similar in subjects with severe hepatic impairment and control subjects with normal hepatic function. Population pharmacokinetics analysis in HCV-infected subjects indicated

that cirrhosis had no clinically relevant effect on the exposure of ledipasvir *[see Use in Specific Populations (8.7)]*.

The pharmacokinetics of sofosbuvir were studied following 7-day dosing of 400 mg sofosbuvir in HCV-infected subjects with moderate and severe hepatic impairment (Child-Pugh Class B and C). Relative to subjects with normal hepatic function, the sofosbuvir AUC_{0-24} were 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 AUC_{0-24} were 18% and 9% higher, respectively. Population pharmacokinetics analysis in HCV-infected subjects indicated that cirrhosis had no clinically relevant effect on the exposure of sofosbuvir and GS-331007 *[see Use in Specific Populations (8.7)]*.

Drug Interaction Studies

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 (5.2)]*. Coadministration with drugs that inhibit P-gp and/or BCRP may increase ledipasvir and sofosbuvir plasma concentrations without increasing GS-331007 plasma concentration; HARVONI may be coadministered with P-gp and/or BCRP inhibitors. Neither ledipasvir nor sofosbuvir is a substrate for hepatic uptake transporters OCT1, OATP1B1, or OATP1B3. GS-331007 is not a substrate for renal transporters, including organic anion transporter OAT1 or OAT3, or organic cation transporter OCT2.

Ledipasvir is subject to slow oxidative metabolism via an unknown mechanism. In vitro, no detectable metabolism of ledipasvir by CYP enzymes has been observed. Biliary excretion of unchanged ledipasvir is a major route of elimination. Sofosbuvir is not a substrate for CYP and UGT1A1 enzymes. Clinically significant drug interactions with HARVONI mediated by CYP or UGT1A1 enzymes are not expected.

The effects of coadministered drugs on the exposure of ledipasvir, sofosbuvir, and GS-331007 are shown in Table 4 *[see Drug Interactions (7.2)].*

Table 4 Drug Interactions: Changes in Pharmacokinetic Parameters for Ledipasvir, Sofosbuvir, and the Predominant Circulating Metabolite GS-331007 in the Presence of the Coadministered Drug[a]

Co-administered Drug	Dose of Co-administered Drug (mg)	Ledi-pasvir Dose (mg)	Sofos-buvir Dose (mg)	N	Mean Ratio (90% CI) of Ledipasvir, Sofosbuvir, and GS-331007 PK With/Without Coadministered Drug No Effect=1.00			
						C_{max}	AUC	C_{min}
Atazanavir/ ritonavir	300/100 once daily	90 once daily	400 once daily	30	ledipasvir	1.98 (1.78, 2.20)	2.13 (1.89, 2.40)	2.36 (2.08, 2.67)
					sofosbuvir	0.96 (0.88, 1.05)	1.08 (1.02, 1.15)	NA
					GS-331007	1.13 (1.08, 1.19)	1.23 (1.18, 1.29)	1.28 (1.21, 1.36)
Cyclosporine	600 single dose	ND	400 single dose	19	sofosbuvir	2.54 (1.87, 3.45)	4.53 (3.26, 6.30)	NA
					GS-331007	0.60 (0.53, 0.69)	1.04 (0.90, 1.20)	NA
Darunavir/ ritonavir	800/100 once daily	90 once daily	ND	23	ledipasvir	1.45 (1.34, 1.56)	1.39 (1.28, 1.49)	1.39 (1.29, 1.51)
		ND	400 single dose	18	sofosbuvir	1.45 (1.10, 1.92)	1.34 (1.12, 1.59)	NA
					GS-331007	0.97 (0.90, 1.05)	1.24 (1.18, 1.30)	NA
Efavirenz/ emtricitabine/ tenofovir DF[b]	600/200/300 once daily	90 once daily	400 once daily	14	ledipasvir	0.66 (0.59, 0.75)	0.66 (0.59, 0.75)	0.66 (0.57, 0.76)
					sofosbuvir	1.03 (0.87, 1.23)	0.94 (0.81, 1.10)	NA
					GS-331007	0.86 (0.76, 0.96)	0.90 (0.83, 0.97)	1.07 (1.02, 1.13)
Elvitegravir/ cobicistat	150/150 once daily	90 once daily	400 once daily	29	ledipasvir	1.63 (1.51, 1.75)	1.78 (1.64, 1.94)	1.91 (1.76, 2.08)
					sofosbuvir	1.33 (1.14, 1.56)	1.36 (1.21, 1.52)	NA
					GS-331007	1.33 (1.22, 1.44)	1.44 (1.41, 1.48)	1.53 (1.47, 1.59)
Famotidine	40 single dose simultaneously with HARVONI	90 single dose	400 single dose	12	ledipasvir	0.80 (0.69, 0.93)	0.89 (0.76, 1.06)	NA
					sofosbuvir	1.15 (0.88, 1.50)	1.11 (1.00, 1.24)	NA
					GS-331007	1.06 (0.97, 1.14)	1.06 (1.02, 1.11)	NA
	40 single dose 12 hours prior to HARVONI			12	ledipasvir	0.83 (0.69, 1.00)	0.98 (0.80, 1.20)	NA
					sofosbuvir	1.00 (0.76, 1.32)	0.95 (0.82, 1.10)	NA
					GS-331007	1.13 (1.07, 1.20)	1.06 (1.01, 1.12)	NA
Methadone	30 to 130 daily	ND	400 once daily	14	sofosbuvir	0.95 (0.68, 1.33)	1.30 (1.00, 1.69)	NA
					GS-331007	0.73 (0.65, 0.83)	1.04 (0.89, 1.22)	NA

Omeprazole	20 once daily simultaneously with HARVONI	90 single dose	400 single dose	16	ledipasvir	0.89 (0.61, 1.30)	0.96 (0.66, 1.39)	NA
					sofosbuvir	1.12 (0.88, 1.42)	1.00 (0.80, 1.25)	NA
					GS-331007	1.14 (1.01, 1.29)	1.03 (0.96, 1.12)	NA
	20 once daily 2 hours prior to ledipasvir	30 single dose	ND	17	ledipasvir	0.52 (0.41, 0.66)	0.58 (0.48, 0.71)	NA
Rifampin[c]	600 once daily	90 single dose	ND	31	ledipasvir	0.65 (0.56, 0.76)	0.41 (0.36, 0.48)	NA
Simeprevir	150 once daily	30 once daily	ND	22	ledipasvir	1.81 (1.69, 2.94)	1.92 (1.77, 2.07)	NA
Tacrolimus	5 single dose	ND	400 single dose	16	sofosbuvir	0.97 (0.65, 1.43)	1.13 (0.81, 1.57)	NA
					GS-331007	0.97 (0.83, 1.14)	1.00 (0.87, 1.13)	NA

NA = not available/not applicable, ND = not dosed.
a. All interaction studies conducted in healthy volunteers.
b. Administered as ATRIPLA® (efavirenz, emtricitabine, tenofovir DF).
c. This study was conducted in the presence of two other investigational HCV direct-acting agents.

No effect on the pharmacokinetic parameters of ledipasvir, sofosbuvir, and GS-331007 was observed with the combination of abacavir and lamivudine, or emtricitabine, rilpivirine, and tenofovir DF, or raltegravir.

Ledipasvir is an inhibitor of drug transporter P-gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of coadministered substrates for these transporters. Ledipasvir is an inhibitor of transporters OATP1B1, OATP1B3, and BSEP only at concentrations exceeding those achieved in clinic. Ledipasvir is not an inhibitor of transporters MRP2, MRP4, OCT2, OAT1, OAT3, MATE1, and OCT1. The drug-drug interaction potential of ledipasvir is primarily limited to the intestinal inhibition of P-gp and BCRP. Clinically relevant transporter inhibition by ledipasvir in the systemic circulation is not expected due to its high protein binding. Sofosbuvir and GS-331007 are not inhibitors of drug transporters P-gp, BCRP, MRP2, BSEP, OATP1B1, OATP1B3, and OCT1, and GS-331007 is not an inhibitor of OAT1, OCT2, and MATE1. Ledipasvir, sofosbuvir, and GS-331007 are not inhibitors or inducers of CYP or UGT1A1 enzymes.

The effects of ledipasvir or sofosbuvir on the exposure of coadministered drugs are shown in Table 5 *[see Drug Interactions (7.2)].*

Table 5 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Ledipasvir, Sofosbuvir, or HARVONI[a]

Co-administered Drug	Dose of Co-administered Drug (mg)	Ledi-pasvir Dose (mg)	Sofos-buvir Dose (mg)	N	Mean Ratio (90% CI) of Coadministered Drug PK With/Without Ledipasvir, Sofosbuvir, or HARVONI No Effect=1.00		
					C_{max}	AUC	C_{min}
Atazanavir/ ritonavir	atazanavir 300 once daily	90 once daily	400 once daily	30	1.07 (1.00, 1.15)	1.33 (1.25, 1.42)	1.75 (1.58, 1.93)
	ritonavir 100 once daily				0.93 (0.84, 1.02)	1.05 (0.98, 1.11)	1.56 (1.42, 1.71)
Elvitegravir/ cobicistat	elvitegravir 150 once daily	90 once daily	400 once daily	29	0.88 (0.82, 0.95)	1.02 (0.95, 1.09)	1.36 (1.23, 1.49)
	cobicistat 150 once daily				1.25 (1.18, 1.32)	1.59 (1.49, 1.70)	4.25 (3.47, 5.22)
Norelgestromin	norgestimate 0.180/0.215/0.25/ ethinyl estradiol 0.025 once daily	90 once daily	ND	15	1.02 (0.89, 1.16)	1.03 (0.90, 1.18)	1.09 (0.91, 1.31)
		ND	400 once daily		1.07 (0.94, 1.22)	1.06 (0.92, 1.21)	1.07 (0.89, 1.28)
Norgestrel		90 once daily	ND		1.03 (0.87, 1.23)	0.99 (0.82, 1.20)	1.00 (0.81, 1.23)
		ND	400 once daily		1.18 (0.99, 1.41)	1.19 (0.98, 1.45)	1.23 (1.00, 1.51)
Ethinyl estradiol		90 once daily	ND		1.40 (1.18, 1.66)	1.20 (1.04, 1.39)	0.98 (0.79, 1.22)
		ND	400 once daily		1.15 (0.97, 1.36)	1.09 (0.94, 1.26)	0.99 (0.80, 1.23)
Raltegravir	400 twice daily	90 once daily	ND	28	0.82 (0.66, 1.02)	0.85 (0.70, 1.02)	1.15 (0.90, 1.46)
		ND	400 single dose	19	0.57 (0.44, 0.75)	0.73 (0.59, 0.91)	0.95 (0.81, 1.12)
Simeprevir	150 once daily	30 once daily	ND	22	2.61 (2.39, 2.86)	2.69 (2.44, 2.96)	NA
Tacrolimus	5 single dose	ND	400 single dose	16	0.73 (0.59, 0.90)	1.09 (0.84, 1.40)	NA
Tenofovir DF	300 once daily[b]	90 once daily	400 once daily	15	1.79 (1.56, 2.04)	1.98 (1.77, 2.23)	2.63 (2.32, 2.97)
	300 once daily[c]			14	1.32 (1.25, 1.39)	1.40 (1.31, 1.50)	1.91 (1.74, 2.10)

NA = not available/not applicable, ND = not dosed.
a. All interaction studies conducted in healthy volunteers.
b. Administered as ATRIPLA (efavirenz, emtricitabine, tenofovir DF).
c. Administered as COMPLERA® (emtricitabine, rilpivirine, tenofovir DF).

No effect on the pharmacokinetic parameters of the following coadministered drugs was observed with ledipasvir or sofosbuvir: abacavir, cyclosporine, darunavir/ritonavir, efavirenz, emtricitabine, lamivudine, methadone, or rilpivirine.

12.4 Microbiology

Mechanism of Action

Ledipasvir is an inhibitor of the HCV NS5A protein, which is required for viral replication. Resistance selection in cell culture and cross-resistance studies indicate ledipasvir targets NS5A as its mode of action.

Sofosbuvir is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is required for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotypes 1b, 2a, 3a and 4a with IC_{50} values ranging from 0.7 to 2.6 μM. GS-461203 is neither an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

Antiviral Activity

In HCV replicon assays, the EC_{50} values of ledipasvir against full-length replicons from genotypes 1a and 1b were 0.031 nM and 0.004 nM, respectively. The median EC_{50} values of ledipasvir against chimeric replicons encoding NS5A sequences from clinical isolates were 0.018 nM for genotype 1a (range 0.009–0.085 nM; N=30) and 0.006 nM for genotype 1b (range 0.004–0.007 nM; N=3). Ledipasvir has less antiviral activity compared to genotype 1 against genotypes 4a, 5a, and 6a, with EC_{50} values of 0.39 nM, 0.15 nM, and 1.1 nM, respectively. Ledipasvir has substantially lower activity against genotypes 2a, 2b, 3a, and 6e with EC_{50} values of 21–249 nM, 16–530 nM, 168 nM, and 264 nM, respectively.

In HCV replicon assays, the EC_{50} values of sofosbuvir against full-length replicons from genotypes 1a, 1b, 2a, 3a, and 4a, and chimeric 1b replicons encoding NS5B from genotypes 2b, 5a, or 6a ranged from 14–110 nM. The median EC_{50} value of sofosbuvir against chimeric replicons encoding NS5B sequences from clinical isolates was 62 nM for genotype 1a (range 29–128 nM; N=67), 102 nM for genotype 1b (range 45–170 nM; N=29), 29 nM for genotype 2 (range 14–81 nM; N=15), and 81 nM for genotype 3a (range 24–181 nM; N=106). In replication competent virus assays, the EC_{50} values of sofosbuvir against genotypes 1a and 2a were 30 nM and 20 nM, respectively. Evaluation of sofosbuvir in combination with ledipasvir showed no antagonistic effect in reducing HCV RNA levels in replicon cells.

Resistance

In Cell Culture

HCV replicons with reduced susceptibility to ledipasvir have been selected in cell culture for genotypes 1a and 1b. Reduced susceptibility to ledipasvir was associated with the primary NS5A amino acid substitution Y93H in both genotypes 1a and 1b. Additionally, a Q30E substitution emerged in genotype 1a replicons. Site-directed mutagenesis of the Y93H in both genotypes 1a and 1b, as well as the Q30E substitution in genotype 1a, conferred high levels of reduced susceptibility to ledipasvir (fold change in EC_{50} greater than 1000-fold).

HCV replicons with reduced susceptibility to sofosbuvir have been selected in cell culture for multiple genotypes including 1b, 2a, 2b, 3a, 4a, 5a, and 6a. Reduced susceptibility to sofosbuvir was associated with the primary NS5B substitution S282T in all replicon genotypes examined. Site-directed mutagenesis of the S282T substitution in replicons of 8 genotypes conferred 2- to 18-fold reduced susceptibility to sofosbuvir.

In Clinical Trials
In a pooled analysis of subjects who received HARVONI in Phase 3 trials, 37 subjects (29 with genotype 1a and 8 with genotype 1b) qualified for resistance analysis due to virologic failure (35 with virologic relapse, 2 with breakthrough on-treatment due to documented non-adherence). Post-baseline NS5A and NS5B deep sequencing data (assay cutoff of 1%) were available for 37/37 and 36/37 subjects' viruses, respectively.

Of the 29 genotype 1a virologic failure subjects, 55% (16/29) of subjects had virus with emergent NS5A resistance-associated substitutions K24R, M28T/V, Q30R/H/K/L, L31M, or Y93H/N at failure. Five of these 16 subjects also had baseline NS5A polymorphisms at resistance-associated amino acid positions. The most common substitutions detected at failure were Q30R, Y93H or N, and L31M.

Of the 8 genotype 1b virologic failure subjects, 88% (7/8) had virus with emergent NS5A resistance-associated substitutions L31V/M/I or Y93H at failure. Three of these 7 subjects also had baseline NS5A polymorphisms at resistance-associated positions. The most common substitution detected at failure was Y93H.

At failure, 38% (14/37) of virologic failure subjects had 2 or more NS5A substitutions at resistance-associated positions.

In phenotypic analyses, post-baseline isolates from subjects who harbored NS5A resistance-associated substitutions at failure showed 20- to >243-fold reduced susceptibility to ledipasvir.

Treatment-emergent NS5B substitutions L159 (n=1) and V321 (n=2) previously associated with sofosbuvir failure were detected in the Phase 3 trials. In addition, NS5B substitutions at highly conserved positions D61G (n=3), A112T (n=2), E237G (n=2), and S473T (n=1) were detected at low frequency by next generation sequencing in treatment failure subjects infected with HCV GT1a. The D61G substitution was previously described in subjects infected with HCV GT1a in a liver pre-transplant trial. The clinical significance of these substitutions is currently unknown.

The sofosbuvir-associated resistance substitution S282T in NS5B was not detected in any failure isolate from the Phase 3 trials. NS5B substitutions S282T, L320V/I, and V321I in combination with NS5A substitutions L31M, Y93H, and Q30L were

detected in one subject at failure following 8 weeks of treatment with HARVONI in a Phase 2 trial.

Cross Resistance

Ledipasvir was fully active against the sofosbuvir resistance-associated substitution S282T in NS5B while all ledipasvir resistance-associated substitutions in NS5A were fully susceptible to sofosbuvir. Both sofosbuvir and ledipasvir were fully active against substitutions associated with resistance to other classes of direct-acting antivirals with different mechanisms of actions, such as NS5B non-nucleoside inhibitors and NS3 protease inhibitors. NS5A substitutions conferring resistance to ledipasvir may reduce the antiviral activity of other NS5A inhibitors. The efficacy of ledipasvir/sofosbuvir has not been established in patients who have previously failed treatment with other regimens that include an NS5A inhibitor.

Persistence of Resistance-Associated Substitutions

No data are available on the persistence of ledipasvir or sofosbuvir resistance-associated substitutions. NS5A resistance-associated substitutions for other NS5A inhibitors have been found to persist for >1 year in some patients.

Effect of Baseline HCV Polymorphisms on Treatment Response

Analyses were conducted to explore the association between pre-existing baseline NS5A polymorphisms at resistance-associated positions and relapse rates. In the pooled analysis of the Phase 3 trials, 23% (370/1589) of subjects' virus had baseline NS5A polymorphisms at resistance-associated positions (any change from reference at NS5A amino acid positions 24, 28, 30, 31, 58, 92, or 93) identified by population or deep sequencing.

In treatment-naïve subjects whose virus had baseline NS5A polymorphisms at resistance-associated positions in Studies ION-1 and ION-3, relapse rates were 6% (3/48) after 8 weeks and 1% (1/113) after 12 weeks of treatment with HARVONI. Relapse rates among subjects without baseline NS5A polymorphisms at resistance-associated positions were 5% (8/167) after 8 weeks and 1% (3/306) after 12 weeks treatment with HARVONI.

In treatment-experienced subjects whose virus had baseline NS5A polymorphisms at resistance-associated positions, relapse rates were 22% (5/23) after 12 weeks and 0% (0/19) after 24 weeks of treatment with HARVONI.

The specific baseline NS5A resistance-associated polymorphisms observed among subjects with relapse were M28T/V, Q30H, Q30R, L31M, H58P, Y93H, and Y93N in genotype 1a, and L28M, A92T, and Y93H in genotype 1b. Subjects with multiple NS5A polymorphisms at resistance-associated positions appeared to have higher relapse rates.

SVR was achieved in all 24 subjects (N=20 with L159F+C316N; N=1 with L159F; and N=3 with N142T) who had baseline polymorphisms associated with resistance to NS5B nucleoside inhibitors. The sofosbuvir resistance-associated substitution S282T was not

detected in the baseline NS5B sequence of any subject in Phase 3 trials by population or deep sequencing.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Ledipasvir: Ledipasvir was not genotoxic in a battery of in vitro or in vivo assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes, and in vivo rat micronucleus assays.

Carcinogenicity studies of ledipasvir in mice and rats are ongoing.

Sofosbuvir: Sofosbuvir was not genotoxic in a battery of in vitro or in vivo assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and in vivo mouse micronucleus assays.

Two-year carcinogenicity studies in mice and rats were conducted with sofosbuvir. Mice were administered doses of up to 200 mg/kg/day in males and 600 mg/kg/day in females, while rats were administered doses of up to 750 mg/kg/day in males and females. No increase in the incidence of drug-related neoplasms were observed at the highest doses tested in mice and rats, resulting in AUC exposure to the predominant circulating metabolite GS-331007 of approximately 4- and 18-fold (in mice) and 8- and 10-fold (in rats), in males and females respectively, the exposure in humans at the recommended clinical dose.

Impairment of Fertility

Ledipasvir: Ledipasvir had no adverse effects on mating and fertility. In female rats, the mean number of corpora lutea and implantation sites were reduced slightly at maternal exposures approximately 3-fold the exposure in humans at the recommended clinical dose. At the highest dose levels without effects, AUC exposure to ledipasvir was approximately 5- and 2-fold, in males and females, respectively, the exposure in humans at the recommended clinical dose.

Sofosbuvir: Sofosbuvir had no effects on embryo-fetal viability or on fertility when evaluated in rats. At the highest dose tested, AUC exposure to the predominant circulating metabolite GS-331007 was approximately 5-fold the exposure in humans at the recommended clinical dose.

13.2 Animal Toxicology and/or Pharmacology

Sofosbuvir: Heart degeneration and inflammation were observed in rats following GS-9851 (a stereoisomeric mixture containing approximately 50% sofosbuvir) doses of 2,000 mg/kg/day for up to 5 days. At this dose, AUC exposure to the predominant circulating metabolite GS-331007 is approximately 17-fold higher than human exposure at the recommended clinical dose. No heart degeneration or inflammation was observed in mice, rats, or dogs in studies up to 3 months, 6 months, or 9 months at GS-331007

AUC exposures approximately 24-, 5-, or 17-fold higher, respectively, than human exposure at the recommended clinical dose. In addition, no heart degeneration or inflammation was observed in rats following sofosbuvir doses of up to 750 mg/kg/day in the 2-year carcinogenicity study at GS-331007 AUC exposure approximately 9-fold the exposure in humans at the recommended clinical dose.

14 CLINICAL STUDIES

14.1 Overview of Clinical Trials

The efficacy of HARVONI was evaluated in three Phase 3 trials of 1518 subjects with genotype 1 chronic hepatitis C (CHC) with compensated liver disease:

- Study ION-3: noncirrhotic treatment-naïve subjects *[see Clinical Studies (14.2)]*,
- Study ION-1: cirrhotic and noncirrhotic treatment-naïve subjects *[see Clinical Studies (14.2)]*, and
- Study ION-2: cirrhotic and noncirrhotic subjects who failed prior therapy with an interferon-based regimen, including regimens containing an HCV protease inhibitor *[see Clinical Studies (14.3)].*

All three Phase 3 trials evaluated efficacy of HARVONI (one fixed-dose tablet of 90 mg of ledipasvir and 400 mg of sofosbuvir administered once daily) with or without ribavirin. Treatment duration was fixed in each trial. Serum HCV RNA values were measured during the clinical trials using the COBAS TaqMan HCV test (version 2.0), for use with the High Pure System. The assay had a lower limit of quantification (LLOQ) of 25 IU/mL.

Sustained virologic response (SVR) was the primary endpoint and was defined as HCV RNA less than LLOQ at 12 weeks after the cessation of treatment. Relapse was a secondary endpoint, which was defined as HCV RNA greater than or equal to LLOQ with 2 consecutive values or last available post-treatment measurement during the post-treatment period after achieving HCV RNA less than LLOQ at end of treatment.

14.2 Clinical Trials in Treatment-Naïve Subjects

Treatment-Naïve Adults without Cirrhosis ─ ION-3 (Study 0108)

ION-3 was a randomized, open-label trial in treatment-naïve non-cirrhotic subjects with genotype 1 CHC. Subjects were randomized in a 1:1:1 ratio to one of the following three treatment groups and stratified by HCV genotype (1a vs 1b): HARVONI for 8 weeks, HARVONI for 12 weeks, or HARVONI + ribavirin for 8 weeks.

Demographics and baseline characteristics were balanced across the treatment groups. Of the 647 treated subjects, the median age was 55 years (range: 20 to 75); 58% of the subjects were male; 78% were White; 19% were Black; 6% were Hispanic or Latino; mean body mass index was 28 kg/m^2 (range: 18 to 56 kg/m^2); 81% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; 80% had genotype 1a HCV infection; 73% had non-C/C IL28B alleles (CT or TT).

Table 6 presents the response rates for the HARVONI treatment groups in the ION-3 trial after 8 and 12 weeks of HARVONI treatment. Ribavirin was not shown to increase the response rates observed with HARVONI. Therefore, the HARVONI + ribavirin arm is not presented in Table 6.

Table 6 Study ION-3: Response Rates after 8 and 12 Weeks of Treatment in Treatment-Naïve Non-Cirrhotic Subjects with Genotype 1 CHC

	HARVONI 8 Weeks (N=215)	**HARVONI 12 Weeks (N=216)**
SVR	94% (202/215)	96% (208/216)
Outcome for Subjects without SVR		
On-Treatment Virologic Failure	0/215	0/216
Relapse[a]	5% (11/215)	1% (3/216)
Other[b]	1% (2/215)	2% (5/216)
SVR by Genotype[c]		
Genotype 1a	93% (159/171)	96% (165/172)
Genotype 1b	98% (42/43)	98% (43/44)

a. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment.
b. Other includes subjects who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).
c. One subject without a confirmed subtype for genotype 1 infection was excluded from this subgroup analysis.

The treatment difference between the 8-week treatment of HARVONI and 12-week treatment of HARVONI was –2.3% (97.5% confidence interval –7.2% to 2.5%). Among subjects with a baseline HCV RNA <6 million IU/mL, the SVR was 97% (119/123) with 8-week treatment of HARVONI and 96% (126/131) with 12-week treatment of HARVONI.

Relapse rates by baseline viral load are presented in Table 7.

Table 7 Study ION-3: Relapse Rates by Baseline Viral Load after 8 and 12 Weeks of Treatment in Treatment-Naïve Non-Cirrhotic Subjects with Genotype 1 CHC

	HARVONI 8 Weeks (N=215)	HARVONI 12 Weeks (N=216)
Number of Responders at End of Treatment	215	216
Baseline HCV RNA[a]		
HCV RNA <6 million IU/mL	2% (2/123)	2% (2/131)
HCV RNA ≥6 million IU/mL	10% (9/92)	1% (1/85)

a. HCV RNA values were determined using the Roche TaqMan Assay; a subject's HCV RNA may vary from visit to visit.

Treatment-Naïve Adults with or without Cirrhosis ─ ION-1 (Study 0102)

ION-1 was a randomized, open-label trial that evaluated 12 and 24 weeks of treatment with HARVONI with or without ribavirin in 865 treatment-naïve subjects with genotype 1 CHC including those with cirrhosis. Subjects were randomized in a 1:1:1:1 ratio to receive HARVONI for 12 weeks, HARVONI + ribavirin for 12 weeks, HARVONI for 24 weeks, or HARVONI + ribavirin for 24 weeks. Randomization was stratified by the presence or absence of cirrhosis and HCV genotype (1a vs 1b). The interim primary endpoint analysis for SVR included all subjects enrolled in the 12-week treatment groups (N=431). SVR rates for all subjects enrolled in the 24-week treatment groups (N=434) were not available at the time of interim analysis.

Demographics and baseline characteristics were balanced across the treatment groups. Of the 865 treated subjects, the median age was 54 years (range: 18 to 80); 59% of the subjects were male; 85% were White; 12% were Black; 12% were Hispanic or Latino; mean body mass index was 27 kg/m^2 (range: 18 to 48 kg/m^2); 79% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; 67% had genotype 1a HCV infection; 70% had non-C/C IL28B alleles (CT or TT); and 16% had cirrhosis.

Table 8 presents the response rates for the treatment group of HARVONI for 12 weeks in the ION-1 trial. Ribavirin was not shown to increase response rates observed with HARVONI. Therefore, the HARVONI + ribavirin arm is not presented in Table 8.

Table 8 Study ION-1: Response Rates after 12 Weeks of Treatment in Treatment-Naïve Subjects with Genotype 1 CHC with and without Cirrhosis

	HARVONI 12 Weeks (N=214)
SVR[a]	99% (210/213)
Outcome for Subjects without SVR	
On-Treatment Virologic Failure[a]	0/213
Relapse[a,b]	<1% (1/212)
Other[a,c]	1% (2/213)

a. Excluding one subject with genotype 4 infection.
b. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment.
c. Other includes subjects who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

Response rates for selected subgroups are presented in Table 9.

Table 9 Study ION-1: SVR Rates for Selected Subgroups after 12 Weeks of Treatment in Treatment-Naïve Subjects with Genotype 1 CHC with and without Cirrhosis

	HARVONI 12 Weeks (N=214)
Genotype[a]	
Genotype 1a	98% (142/145)
Genotype 1b	100% (67/67)
Cirrhosis[b]	
No	99% (176/177)
Yes	94% (32/34)

a. One subject without a confirmed subtype for genotype 1 infection and one subject with genotype 4 infection were excluded from this subgroup analysis.
b. Subjects with missing cirrhosis status were excluded from this subgroup analysis.

14.3 Clinical Trials in Subjects Who Failed Prior Therapy

Previously-Treated Adults with or without Cirrhosis ─ ION-2 (Study 0109)

ION-2 was a randomized, open-label trial that evaluated 12 and 24 weeks of treatment with HARVONI with or without ribavirin in genotype 1 HCV-infected subjects with or without cirrhosis who failed prior therapy with an interferon-based regimen, including regimens containing an HCV protease inhibitor. Subjects were randomized in a 1:1:1:1 ratio to receive HARVONI for 12 weeks, HARVONI + ribavirin for 12 weeks, HARVONI for 24 weeks, or HARVONI + ribavirin for 24 weeks. Randomization was stratified by the presence or absence of cirrhosis, HCV genotype (1a vs 1b) and response to prior HCV therapy (relapse/breakthrough vs nonresponse).

Demographics and baseline characteristics were balanced across the treatment groups. Of the 440 treated subjects, the median age was 57 years (range: 24 to 75); 65% of the subjects were male; 81% were White; 18% were Black; 9% were Hispanic or Latino; mean body mass index was 28 kg/m^2 (range: 19 to 50 kg/m^2); 89% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; 79% had genotype 1a HCV infection; 88% had non-C/C IL28B alleles (CT or TT); and 20% had cirrhosis. Forty-seven percent (47%) of the subjects failed a prior therapy of pegylated interferon and ribavirin. Among these subjects, 49% were relapse/breakthrough and 51% were non-responder. Fifty-three percent (53%) of the subjects failed a prior therapy of pegylated interferon and ribavirin with an HCV protease inhibitor. Among these subjects, 62% were relapse/breakthrough and 38% were non-responder.

Table 10 presents the response rates for the HARVONI treatment groups in the ION-2 trial. Ribavirin was not shown to increase response rates observed with HARVONI. Therefore, the HARVONI + ribavirin arms are not presented in Table 10.

Table 10 Study ION-2: Response Rates after 12 and 24 Weeks of Treatment in Subjects with Genotype 1 CHC with or without Cirrhosis who Failed Prior Therapy

	HARVONI 12 Weeks (N=109)	**HARVONI 24 Weeks (N=109)**
SVR	94% (102/109)	99% (108/109)
Outcome for Subjects without SVR		
On-Treatment Virologic Failure	0/109	0/109
Relapse[a]	6% (7/108)	0/109
Other[b]	0/109	1% (1/109)

a. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment.
b. Other includes subjects who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

Among the subjects with available SVR12 and SVR24 data (206/218), all subjects who achieved SVR12 in the ION-2 study also achieved SVR24.

Response rates and relapse rates for selected subgroups are presented in Tables 11 and 12.

Table 11 Study ION-2: SVR Rates for Selected Subgroups after 12 and 24 Weeks of Treatment in Subjects with Genotype 1 CHC who Failed Prior Therapy

	HARVONI 12 Weeks (N=109)	HARVONI 24 Weeks (N=109)
Genotype		
Genotype 1a	95% (82/86)	99% (84/85)
Genotype 1b	87% (20/23)	100% (24/24)
Cirrhosis[a]		
No	95% (83/87)	99% (85/86)
Yes	86% (19/22)	100% (22/22)
Prior HCV Therapy		
Peg-IFN + RBV	93% (40/43)	100% (58/58)
HCV protease inhibitor + Peg-IFN + RBV	94% (62/66)	98% (49/50)
Response to Prior HCV Therapy		
Relapse/Breakthrough	95% (57/60)	100% (60/60)
Nonresponder	92% (45/49)	98% (48/49)

a. Subjects with missing cirrhosis status were excluded from this subgroup analysis.

Table 12 Study ION-2: Relapse Rates for Selected Subgroups after 12 and 24 Weeks of Treatment in Subjects with Genotype 1 CHC who Failed Prior Therapy

	HARVONI 12 Weeks (N=109)	HARVONI 24 Weeks (N=109)
Number of Responders at End of Treatment	108	109
Cirrhosis[a]		
No	5% (4/86)[b]	0% (0/86)
Yes	14% (3/22)	0% (0/22)
Presence of Baseline NS5A Resistance-Associated Polymorphisms[c]		
No	2% (2/85)	0% (0/90)
Yes	22% (5/23)	0% (0/19)
IL28B Status		
C/C	0% (0/10)	0% (0/16)
Non-C/C	7% (7/98)	0% (0/93)

a. Subjects with missing cirrhosis status were excluded from this subgroup analysis.
b. These 4 non-cirrhotic relapsers all had baseline NS5A resistance-associated polymorphisms.
c. NS5A resistance-associated polymorphisms include any change at NS5A positions 24, 28, 30, 31, 58, 92, or 93.

16 HOW SUPPLIED/STORAGE AND HANDLING

HARVONI tablets are orange, diamond-shaped, film-coated, debossed with “GSI” on one side and “7985” on the other side of the tablet. Each bottle contains 28 tablets (NDC 61958-1801-1), a silica gel desiccant, polyester coil, and is closed with a child-resistant closure.

Store at room temperature below 30°C (86°F).

- Dispense only in original container.
- Do not use if seal over bottle opening is broken or missing.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Drug Interactions

Inform patients that HARVONI may interact with other drugs. Advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products including St. John’s wort *[see Warnings and Precautions (5.1, 5.2) and Drug Interactions (7)].*

Hepatitis C Virus Transmission

Inform patients that the effect of treatment of hepatitis C infection on transmission is not known, and that appropriate precautions to prevent transmission of the hepatitis C virus during treatment or in the event of treatment failure should be taken.

Administration

Advise patients that HARVONI should be taken once daily on a regular dosing schedule with or without food. If a patient did not take HARVONI at the regular time, it should be taken as soon as they remember on the same day. Resume the usual dosing schedule the next day. Advise the patient not to take more than 1 tablet of HARVONI in a day.

Manufactured and distributed by:
Gilead Sciences, Inc.
Foster City, CA 94404

205834-GS-001

Patient Information

HARVONI® (har-VOE-nee)
(ledipasvir and sofosbuvir)
tablets

Read this Patient Information before you start taking HARVONI and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is HARVONI?

- HARVONI is a prescription medicine used to treat chronic (lasting a long time) hepatitis C genotype 1 infection in adults.
- HARVONI contains the prescription medicines ledipasvir and sofosbuvir (SOVALDI®).

It is not known if HARVONI is safe and effective in children under 18 years of age.

What should I tell my healthcare provider before taking HARVONI?

Before taking HARVONI, tell your healthcare provider if you:

- have liver problems other than hepatitis C infection
- have severe kidney problems or you are on dialysis
- have any other medical condition
- are pregnant or plan to become pregnant. It is not known if HARVONI will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if HARVONI passes into your breast milk.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. HARVONI may affect the way other medicines work, and other medicines may affect how HARVONI works.

You should not take HARVONI if you also take other medicines that contain sofosbuvir (SOVALDI®).

Especially tell your healthcare provider if you take any of the following medicines:

- an antacid that contains aluminum or magnesium hydroxide. If you take an antacid during treatment with HARVONI, take the antacid 4 hours before or 4 hours after you take HARVONI.

- amiodarone (Cordarone®, Nexterone® Pacerone®)
- carbamazepine (Carbatrol®, Epitol®, Equetro®, Tegretol®)
- digoxin (Lanoxin®)
- efavirenz, emtricitabine, tenofovir disoproxil fumarate (ATRIPLA®)
- elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate (STRIBILD®)
- medicines for indigestion, heartburn, or stomach ulcers, such as nizatidine (Axid®), famotidine (Pepcid AC®), cimetidine (Tagamet®), ranitidine (Zantac®), esomeprazole (Nexium®), lansoprazole (Prevacid®), omeprazole (Prilosec®), rabeprazole (Aciphex®), or pantoprazole (Protonix®)
- oxcarbazepine (Trileptal®, Oxtellar XR®)
- phenytoin (Dilantin®, Phenytek®)
- phenobarbital (Luminal®)
- rifabutin (Mycobutin®)
- rifampin (Rifadin®, Rifamate®, Rifater®, Rimactane®)
- rifapentine (Priftin®)
- rosuvastatin (Crestor®)
- simeprevir (Olysio®)
- St. John's wort (*Hypericum perforatum*) or a product that contains St. John's wort
- tipranavir (Aptivus®) used in combination with ritonavir (Norvir®)
- tenofovir disoproxil fumarate (VIREAD®, TRUVADA®) used in combination with atazanavir (Reyataz®) and ritonavir (Norvir®), darunavir (Prezista®) and ritonavir (Norvir®), or used in combination with lopinavir and ritonavir (Kaletra®)

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take HARVONI?

- Take HARVONI exactly as your healthcare provider tells you to take it. Do not change your dose unless your healthcare provider tells you to.
- Do not stop taking HARVONI without first talking with your healthcare provider. If you think there is a reason to stop taking HARVONI, talk to your healthcare provider before doing so.
- Take HARVONI 1 time each day with or without food.
- If you miss a dose of HARVONI, take the missed dose as soon as you remember the same day. Do not take more than 1 tablet of HARVONI in a day. Take your next dose of HARVONI at your regular time the next day.

- If you take too much HARVONI, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of HARVONI?

The most common side effects of HARVONI include:

- tiredness
- headache

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of HARVONI. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store HARVONI?

- Store HARVONI at room temperature below 86°F (30°C).
- Keep HARVONI in its original container.
- Do not use HARVONI if the seal over the bottle opening is broken or missing.

Keep HARVONI and all medicines out of the reach of children.

General information about the safe and effective use of HARVONI

It is not known if treatment with HARVONI will prevent you from infecting another person with the hepatitis C virus during treatment. Talk with your healthcare provider about ways to prevent spreading the hepatitis C virus.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use HARVONI for a condition for which it was not prescribed. Do not give HARVONI to other people, even if they have the same symptoms you have. It may harm them.

If you would like more information about HARVONI, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about HARVONI that is written for health professionals.

For more information, call 1-800-445-3235 or go to www.HARVONI.com.

What are the ingredients in HARVONI?

Active ingredients: ledipasvir and sofosbuvir

Inactive ingredients: colloidal silicon dioxide, copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose.

The tablet film-coat contains: FD&C yellow #6/sunset yellow FCF aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured and distributed by:
Gilead Sciences, Inc.
Foster City, CA 94404

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