# Product Monograph

# PrHARVONI™

# (Ledipasvir/Sofosbuvir) Tablets

# 90 mg/400 mg

# Antiviral Agent

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**HARVONI**
Ledipasvir/Sofosbuvir

# PART I: HEALTH PROFESSIONAL INFORMATION

## SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedicinal Ingredients |
|---|---|---|
| oral | tablet<br>90 mg ledipasvir/400 mg sofosbuvir | lactose monohydrate |

*For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

## INDICATIONS AND CLINICAL USE

HARVONI (ledipasvir/sofosbuvir) is indicated for the treatment of chronic hepatitis C virus (CHC) genotype 1 infection in adults.

### Geriatrics (> 65 years of age)

Clinical studies of HARVONI included 117 patients aged 65 and over. The response rates observed for patients over 65 years of age were similar to that of younger patients across treatment groups. HARVONI can be administered in geriatric patients (see **ACTION AND CLINICAL PHARMACOLOGY**).

### Pediatrics (< 18 years of age)

Safety and effectiveness in pediatric patients have not been established (see **WARNINGS AND PRECAUTIONS**).

## CONTRAINDICATIONS

HARVONI is contraindicated in patients with known hypersensitivity to any of the components of the product. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

## WARNINGS AND PRECAUTIONS

### General

Treatment with HARVONI should be initiated and monitored by a physician experienced in the management of chronic hepatitis C (CHC).

The safety and efficacy of HARVONI in combination with other anti-HCV medicines has not been studied. The sustained virologic response (SVR) of HARVONI is reduced in treatment-experienced patients with HCV containing certain NS5A baseline mutations (see **MICROBIOLOGY**).

The safety and efficacy of HARVONI have not been studied in patients who have failed previous therapy with HARVONI.

**Use with Potent P-gp Inducers**

Medicinal products that are potent P-glycoprotein (P-gp) inducers [e.g. rifampin, St. John's wort (*Hypercium perforatum*)] may significantly decrease ledipasvir and sofosbuvir plasma concentration leading to reduced therapeutic effect of HARVONI and potential loss of virologic response. Rifampin and St. John's wort should not be used with HARVONI (see **DRUG INTERACTIONS**).

**Patients with Other HCV Genotypes**

The safety and efficacy of HARVONI have not been studied in patients infected with HCV genotype 2, 4, 5 or 6 and has not been fully established in patients infected with genotype 3 (see **CLINICAL TRIALS**).

**Use with Certain HIV Antiretroviral Regimens**

HARVONI has been shown to increase tenofovir exposure when used together with an HIV regimen containing tenofovir disoproxil fumarate (tenofovir DF) and a pharmacokinetic enhancer (ritonavir or cobicistat) (see **DRUG INTERACTIONS**). The safety of tenofovir in the setting of HARVONI and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with coadministration of HARVONI with STRIBILD® (elvitegravir/cobicistat/emtricitabine/tenofovir DF) or with tenofovir DF given in conjunction with a boosted HIV protease inhibitor (e.g atazanavir or darunavir) should be considered, particularly in patients at increased risk for renal dysfunction. Patients receiving HARVONI concomitantly with STRIBILD or with tenofovir DF and a boosted HIV protease inhibitor should be monitored for tenofovir-associated adverse reactions. Refer to STRIBILD, TRUVADA® or VIREAD® Product Monographs for recommendations on renal monitoring.

**Coadministration with Related Products**

HARVONI should not be administered concurrently with other medicinal products containing sofosbuvir (SOVALDI®).

## Hepatic

Hepatic impairment studies have been conducted with the individual drugs, ledipasvir and sofosbuvir. HARVONI can be administered in patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C) (see **ACTION AND CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**). Safety and efficacy of HARVONI have not been established in patients with decompensated cirrhosis.

## Gastrointestinal

HARVONI contains lactose. This medicine is not recommended for patients with rare hereditary problems of galactose intolerance (severe lactase deficiency or glucose-galactose malabsorption).

## Renal

Renal impairment studies have been conducted with the individual drugs, ledipasvir and sofosbuvir. HARVONI can be administered in patients with mild or moderate renal impairment. The safety of HARVONI has not been established in patients with severe renal impairment (eGFR < 30 mL/min/1.73m$^2$) or end stage renal disease (ESRD) requiring hemodialysis (see **ACTION AND CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

## Special Populations

### Pregnant Women

Pregnancy should be avoided while taking HARVONI as there are no data on the use of HARVONI in pregnant women. HARVONI should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Patients should be advised to notify their health care provider immediately in the event of a pregnancy.

In the rat and rabbit, at ledipasvir AUC exposures 5- and 2-fold higher, respectively, than the human exposure at 90 mg dose, no effects on fetal development were observed (see **TOXICOLOGY**).

In the ledipasvir rat pre- and postnatal study, at a maternally toxic dose, the developing rat offspring exhibited mean decreased body weight and body weight gain when exposed in utero (via maternal dosing) and during lactation (via maternal milk) at a maternal exposure approximately 4 times the exposure in humans at the recommended clinical dose. There were no effects on survival, physical and behavioral development, and reproductive performance in the offspring at maternal exposures similar to the exposure in humans at the recommended clinical dose (see **TOXICOLOGY**).

No effects on fetal development were observed in rats and rabbits at the highest doses of sofosbuvir tested. In the rat and rabbit, exposure to the predominant circulating metabolite GS-331007 at the highest dose was approximately 6-fold and 16-fold the exposure in humans at the recommended clinical dose, respectively (see **TOXICOLOGY**).

**Nursing Women**

It is not known whether ledipasvir, sofosbuvir and its metabolites are excreted in human breast milk. A risk to the newborn/infant cannot be excluded; therefore, nursing should be discontinued before treatment with HARVONI.

When administered to lactating rats, ledipasvir was detected in the plasma of suckling rats likely due to excretion of ledipasvir via milk. Ledipasvir plasma AUC ratio in the suckling rats to the lactating female rats was 0.26 on Lactation Day 10. Ledipasvir had no effects on the nursing pups.

Excretion of sofosbuvir in milk was studied in postpartum female rats after a single oral dose. The milk:plasma concentration ratios in the female rats were 0.1 at 1 hour post-dose and 0.8 at 24 hours post-dose. The predominant circulating metabolite GS-331007 was the primary component observed in the milk of lactating rats, and the metabolite had no effect on the nursing pups.

**Pediatrics (< 18 years of age)**

The safety and efficacy of HARVONI in pediatric patients have not been established.

**Geriatrics (> 65 years of age)**

Clinical studies of HARVONI included 117 patients aged 65 and over. The response rates observed for patients over 65 years of age were similar to that of younger patients across treatment groups. HARVONI can be administered in geriatric patients.

## ADVERSE REACTIONS

### Adverse Drug Reaction Overview

The overall safety profile of HARVONI was established in patients infected with HCV genotype 1 who were treatment-naïve or who failed prior treatments (PEG-IFN/RBV or PI + PEG-IFN/RBV) and included a portion of patients with compensated cirrhosis.

The safety assessment of HARVONI is based on pooled data of 1080 patients from three Phase 3 clinical trials including 215, 539 and 326 patients who received HARVONI for 8, 12 and 24 weeks, respectively.

The proportion of patients who permanently discontinued treatment due to adverse events was 0%, <1% and 1% for patients receiving HARVONI for 8, 12 and 24 weeks, respectively. The proportion of Grade 3 adverse events considered related to study drug by site

investigators was 0% and 0.4% for 8 and 12 weeks, respectively; no Grade 4 adverse events were reported.

No adverse drug reactions specific to HARVONI have been identified.

## Clinical Trial Adverse Drug Reactions

*Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

The adverse reactions (Grades 2 to 4) observed in ≥ 2% of patients receiving 8, 12 or 24 weeks treatment with HARVONI in clinical trials are listed in Table 1.

**Table 1. Adverse Reactions (Grades 2 – 4) Reported in ≥ 2% of Patients Receiving 8, 12, or 24 Weeks of HARVONI[a] from the Pooled Phase 3 Studies (ION-1, ION-2, ION-3)**

| | HARVONI 8 weeks | HARVONI 12 weeks | HARVONI 24 weeks |
|---|---|---|---|
| | N = 215 | N = 539 | N = 326 |
| Headache | 3% | 4% | 4% |
| Fatigue | 2% | 2% | 5% |

a. Frequencies of adverse reactions are based on treatment-emergent adverse events, considered related to study drug by site investigators.

## Less Common Clinical Trial Adverse Drug Reactions (< 2%)

Adverse reactions (Grades 2 to 4) occurring in less than 2% of patients receiving 8, 12 or 24 weeks treatment with HARVONI in clinical trials are listed below by body system:

**Table 2. Adverse Reactions (Grades 2 – 4) Reported in < 2% of Patients Receiving 8, 12 or 24 Weeks of HARVONI[a] from the Pooled Phase 3 Studies (ION-1, ION-2, ION-3)**

| Body System | HARVONI 8, 12 or 24 Weeks[b] |
|---|---|
| **Blood And Lymphatic System Disorders** | Factor VIII inhibition |
| **Cardiac Disorders** | Palpitations |
| **Eye Disorders** | Visual impairment |
| **Gastrointestinal Disorders** | Abdominal discomfort, abdominal distension, abdominal pain, abdominal pain upper, constipation, diarrhoea, dyspepsia, gastrooesophageal reflux disease, mesenteric vein thrombosis, nausea, oral discomfort, vomiting |
| **General Disorders And Administration Site Conditions** | Asthenia, feeling abnormal, irritability, edema |
| **Hepatobiliary Disorders** | Hepatitis acute |
| **Infections And Infestations** | Conjunctivitis infective, salpingitis, sinusitis |
| **Injury, Poisoning And Procedural Complications** | Contusion, ligament sprain, meniscus injury, muscle strain |
| **Metabolism and Nutrition Disorders** | Abnormal loss of weight, decreased appetite, gout |
| **Musculoskeletal and Connective Tissue Disorders** | Arthralgia, joint effusion, muscle spasms, muscular weakness |
| **Nervous System Disorders** | Disturbance in attention, dizziness, memory impairment, migraine, migraine with aura, parosmia, somnolence |
| **Psychiatric Disorders** | Affect lability, aggression, anxiety, depressed mood, depression, emotional disorder, insomnia, libido decreased, sleep disorder |
| **Renal And Urinary Disorders** | Urinary retention |
| **Reproductive System and Breast Disorders** | Erectile dysfunction, metrorrhagia |
| **Respiratory, Thoracic and Mediastinal Disorders** | Oropharyngeal pain, sinus congestion |
| **Skin And Subcutaneous Tissue Disorders** | Acne, alopecia, hyperhidrosis, prurigo, pruritus, rash |
| **Vascular Disorders** | Hemorrhage, hypertension |

a. Frequencies of adverse reactions are based on treatment-emergent adverse events, considered related to study drug by site investigators.

b. Note: adverse events have not been distinguished by whether they occurred during 8, 12 or 24 weeks of therapy.

## Abnormal Hematologic and Clinical Chemistry Findings

### Laboratory Abnormalities

The frequency of treatment-emergent laboratory abnormalities (Grades 2-4) occurring in at least 2% of patients receiving 8, 12 or 24 Weeks of Treatment with HARVONI are described in Table 3.

**Table 3. Laboratory Abnormalities (Grades 2-4) Reported in ≥ 2% of Patients Receiving 8, 12 or 24 Weeks of HARVONI from the Pooled Phase 3 Studies (ION-1, ION-2, ION-3)**

| Laboratory Abnormality Parameters | HARVONI 8 weeks | HARVONI 12 weeks | HARVONI 24 weeks |
|---|---|---|---|
| | N = 215 | N = 538* | N = 325* |
| Neutrophils (<1.0 x $10^9$/L) | < 1% | < 1% | 3% |
| Platelets (< 100 x $10^9$/L) | 0 | 2% | 5% |
| Lipase (> 1.5 x ULN) | 4% | 6% | 9% |
| Serum glucose (Hyperglycemia) (> 160 mg/dL) | 9% | 10% | 12% |
| Serum glucose (Hypoglycemia) (< 55 mg/dL) | < 1% | 2% | 2% |
| Total Bilirubin (> 1.5 x ULN) | 3% | < 1% | 2% |

* One patient was dosed but did not have any post-baseline lab values and was therefore excluded from the analysis.

ULN = Upper Limit of Normal

All patients with grades 2 to 4 elevations in lipase were asymptomatic, and the elevations were generally transient, with no treatment emergent clinical events of pancreatitis.

All patients with Grade 3 or 4 increased serum glucose had either a medical history of diabetes or glucose intolerance (HbA1c > 6.0%) at screening.

## DRUG INTERACTIONS

### Overview

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. Hydrolytic prodrug cleavage and sequential phosphorylation steps result in formation of the pharmacologically active uridine nucleoside analog triphosphate. Dephosphorylation of nucleotide metabolites results in conversion to the predominant circulating metabolite GS-331007 that accounts for approximately 85% of total systemic exposure. In clinical pharmacology studies, both sofosbuvir and GS-331007 were monitored for purposes of pharmacokinetic analyses.

## Drug-Drug Interactions

### Potential for HARVONI to Affect Other Drugs

Ledipasvir is a weak inhibitor of intestinal efflux 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 hepatic uptake transporters OATP1B1, OATP1B3 and hepatic efflux transporter BSEP only at concentrations exceeding those achieved in clinic. Ledipasvir is not an inhibitor of renal efflux transporters MRP2, MRP4, MATE1, renal uptake transporters OCT2, OAT1, OAT3, and hepatic uptake transport OCT1. Ledipasvir inhibits UGT1A1 only at concentrations exceeding those achieved in the clinic. The drug-drug interaction potential of ledipasvir is primarily limited to the process of intestinal absorption.

Sofosbuvir and GS-331007 are not relevant inhibitors of drug transporters P-gp, BCRP, MRP2, BSEP, OATP1B1, OATP1B3, OCT1 and GS-331007 is not an inhibitor of OAT1, OCT2 and MATE1 (see **DETAILED PHARMACOLOGY**).

Sofosbuvir and GS-331007 are not inhibitors or inducers of CYP or UGT1A1 enzymes.

### Potential for Other Drugs to Affect HARVONI

Ledipasvir and sofosbuvir are substrates of efflux drug transporters P-gp and BCRP while GS-331007 is not. Drugs that are potent P-gp inducers in the intestine (e.g. rifampin or St. John's wort) may decrease ledipasvir and sofosbuvir plasma concentrations leading to reduced therapeutic effect of HARVONI and potential loss of virologic response, and should not be used with HARVONI (see **WARNINGS AND PRECAUTIONS**). Coadministration with drugs that inhibit P-gp and/or BCRP may increase sofosbuvir and ledipasvir 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 uptake 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 ledispavir 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.

Table 4 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. The table is not all-inclusive (see **ACTION AND CLINICAL PHARMACOLOGY**).

## Table 4. Established and Potentially Significant[a] Drug Interactions

| 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 can be administered simultaneously with HARVONI. Proton-pump inhibitors should not be taken before HARVONI. |
| **Antiarrhythmics:** digoxin | ↑ digoxin | Coadministration of HARVONI with digoxin may result in increased plasma concentration of digoxin due to intestinal inhibition of P-gp by LDV. Caution is warranted and therapeutic concentration monitoring of digoxin is recommended to obtain the desired clinical effect 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] | ↓ ledipasvir<br>↓ sofosbuvir<br>↓ GS-331007 | Coadministration of HARVONI with rifabutin is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended. HARVONI should not be used with rifampin, a potent intestinal P-gp inducer (see **WARNINGS AND PRECAUTIONS, General, Use with Potent P-gp Inducers**) |

| Concomitant Drug Class: Drug Name | Effect on Concentration[b] | Clinical Comment |
|---|---|---|
| **Antiretrovirals:**<br>Regimens containing tenofovir disoproxil fumarate (DF)<br>Efavirenz/ emtricitabine/ tenofovir disoproxil fumarate | ↑ 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 Product Monograph for recommendations on renal monitoring. |
| Regimens containing tenofovir disoproxil fumarate (DF) and a pharmacokinetic enhancer | | The safety of tenofovir in the setting of HARVONI and a pharmacokinetic enhancer (ritonavir or cobicistat) has not been established.<br>The potential risks and benefits associated with coadministration of HARVONI with STRIBILD or with tenofovir DF given in conjunction with a boosted HIV protease inhibitor should be considered, particularly in patients at increased risk for renal dysfunction. Patients receiving HARVONI concomitantly with STRIBILD or tenofovir DF and a boosted HIV protease inhibitor should be monitored for tenofovir-associated adverse reactions |
| atazanavir/ritonavir + emtricitabine/tenofovir DF[c]<br>darunavir/ritonavir + emtricitabine/tenofovir DF[c] | | When given with tenofovir DF used in conjunction with atazanavir/ritonavir or darunavir/ritonavir, HARVONI increased the concentration of tenofovir. |
| lopinavir/ritonavir + emtricitabine/tenofovir DF | | When given with tenofovir DF used in conjunction with lopinavir/ritonavir, HARVONI is expected to increase the concentration of tenofovir. |
| elvitegravir/cobicistat/ emtricitabine/tenofovir DF | | When given with STRIBILD, HARVONI is expected to increase the concentration of tenofovir.<br><br>Refer to VIREAD, TRUVADA or STRIBILD Product Monograph for recommendations on renal monitoring. |
| Other HIV Antiretrovirals<br>tipranavir/ritonavir | ↓ ledipasvir<br>↓ sofosbuvir<br>↓ 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:**<br>simeprevir[c] | ↑ ledipasvir<br>↑ simeprevir | Concentrations of ledipasvir and simeprevir are increased significantly when simeprevir is coadministered with ledipasvir. The safety and efficacy of HARVONI in combination with simeprevir have not been established. |

| Concomitant Drug Class: Drug Name | Effect on Concentration[b] | Clinical Comment |
|---|---|---|
| **HMG-CoA Reductase Inhibitors**<br>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. ↑ = increase, ↓ = decrease.
c These interactions have been studied in healthy adults.

## 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: abacavir, atazanavir/ritonavir, cyclosporine, darunavir/ritonavir, emtricitabine, efavirenz, lamivudine, methadone, oral contraceptives, pravastatin, raltegravir, rilpivirine, tacrolimus, tenofovir disoproxil fumarate or verapamil. For use of HARVONI with certain HIV regimens containing tenofovir DF, see **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS**, Table 4.

### Assessment of Drug Interactions

The drug interaction studies described were conducted with HARVONI, or components of HARVONI (ledipasvir or sofosbuvir).

The effects of coadministered drugs on the exposure of ledipasvir, sofosbuvir and GS-331007 are shown in Table 5. The effects of ledipasvir or sofosbuvir on the exposure of coadministered drugs are shown in Table 6.

**Table 5. 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 | $C_{min}$ |
| **Anti-HCV Drugs** | | | | | | | | |
| Simeprevir[h] | 150 once daily | 30 once daily[g] | ND | 22 | ledipasvir | 1.81 (1.69, 2.94) | 1.92 (1.77, 2.07) | NA |
| **Anti-HIV Drugs** | | | | | | | | |
| Abacavir/ lamivudine | 600/300 once daily | 90 single dose | 400 single dose | 13 | ledipasvir | 1.10 (1.01, 1.19) | 1.18 (1.10, 1.28) | 1.26 (1.17, 1.36) |
| | | | | | sofosbuvir | 1.08 (0.85, 1.35) | 1.21 (1.09, 1.35) | NA |
| | | | | | GS-331007 | 1.00 (0.94, 1.07) | 1.05 (1.01, 1.09) | 1.08 (1.01, 1.14) |
| 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) |
| Atazanavir/ ritonavir + emtricitabine/ tenofovir DF | 300/100/200/300 once daily simultaneously with HARVONI[b] | 90 once daily | 400 once daily | 24 | ledipasvir | 1.68 (1.54, 1.84) | 1.96 (1.74, 2.21) | 2.18 (1.91, 2.50) |
| | | | | | sofosbuvir | 1.01 (0.88, 1.15) | 1.11 (1.02, 1.21) | NA |
| | | | | | GS-331007 | 1.17 (1.12, 1.23) | 1.31 (1.25, 1.36) | 1.42 (1.34, 1.49) |
| Darunavir/ ritonavir[h] | 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 |
| Darunavir/ ritonavir + emtricitabine/ tenofovir disoproxil fumarate | 800/100/200/300 once daily simultaneously with HARVONI[b] | 90 once daily | 400 once daily | 24 | ledipasvir | 1.11 (0.99, 1.24) | 1.12 (1.00, 1.25) | 1.17 (1.04, 1.31) |
| | | | | | sofosbuvir | 0.63 (0.52, 0.75) | 0.73 (0.65, 0.82) | NA |
| | | | | | GS-331007 | 1.10 (1.04, 1.16) | 1.20 (1.16, 1.24) | 1.26 (1.20, 1.32) |

| 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 | $C_{min}$ |
| Efavirenz/ emtricitabine/ tenofovir disoproxil fumarate[c] | 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[d] | 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) |
| Emtricitabine/ rilpivirine/ tenofovir disoproxil fumarate[e] | 200/25/300 once daily | 90 once daily | 400 once daily | 15 | ledipasvir | 1.01 (0.95, 1.07) | 1.08 (1.02, 1.15) | 1.16 (1.08, 1.25) |
| | | | | | sofosbuvir | 1.05 (0.93, 1.20) | 1.10 (1.01, 1.21) | NA |
| | | | | | GS-331007 | 1.06 (1.01, 1.11) | 1.15 (1.11, 1.19) | 1.18 (1.13, 1.24) |
| Raltegravir[h] | 400 twice daily | 90 once daily | ND | 28 | ledipasvir | 0.92 (0.85, 1.00) | 0.91 (0.84, 1.00) | 0.89 (0.81, 0.98) |
| | | ND | 400 single dose | 19 | sofosbuvir | 0.87 (0.71, 1.08) | 0.95 (0.82, 1.09) | NA |
| | | | | | GS-331007 | 1.09 (0.99, 1.19) | 1.02 (0.97, 1.08) | NA |
| **Anti-infectives** | | | | | | | | |
| Rifampin[f,h] | 600 once daily | 90 single dose | ND | 31 | ledipasvir | 0.65 (0.56, 0.76) | 0.41 (0.36, 0.48) | NA |
| **H2-Receptor Antagonists** | | | | | | | | |
| 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 |

| Co-administered Drug | Dose of Co-administered Drug (mg) | Ledipasvir Dose (mg) | Sofosbuvir 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 | $C_{min}$ |
| | | | | | GS-331007 | 1.13 (1.07, 1.20) | 1.06 (1.01, 1.12) | NA |
| **Immunosuppressants** | | | | | | | | |
| Cyclosporine[h] | 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 |
| Tacrolimus[h] | 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 |
| **Opiate Agonist** | | | | | | | | |
| Methadone[h] | 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 |
| **Proton Pump Inhibitors** | | | | | | | | |
| 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 |

NA = not available/not applicable, ND = not dosed.

a All interaction studies conducted in healthy volunteers.

b Staggered administration (12 hours apart) of atazanavir/ritonavir+emtricitabine/tenofovir DF or darunavir/ritonavir+emtricibatine/tenofovir DF and HARVONI provided similar results.

c Administered as ATRIPLA®.

d This study was conducted to support the use of STRIBILD.

e Administered as COMPLERA®.

f This study was conducted in the presence of two other investigational HCV direct-acting agents.

g Ledipasvir dose administered in this study is 30 mg which is lower than the ledipasvir dose of 90 mg when administered as HARVONI.

h These studies have not been performed with HARVONI; they were conducted with either ledipasvir or sofosbuvir administered as single agents.

**Table 6. 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 | $C_{min}$ |
| **Anti-HCV** | | | | | | | |
| Simeprevir[f] | 150 once daily | 30 once daily[e] | ND | 22 | 2.61 (2.39, 2.86) | 2.69 (2.44, 2.96) | NA |
| **Anti-HIV** | | | | | | | |
| Abacavir /lamivudine | Abacavir 600 once daily | 90 single dose | 400 single dose | 15 | 0.92 (0.87, 0.97) | 0.90 (0.85, 0.94) | NA |
| | Lamivudine 300 once daily | | | | 0.93 (0.87, 1.00) | 0.94 (0.90, 0.98) | 1.12 (1.05, 1.20) |
| Atazanavir/ ritonavir[g] | 300/100 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) |
| Atazanavir/ ritonavir + emtricitabine/ tenofovir disoproxil fumarate[g] simultaneously with HARVONI[h] | Atazanavir 300 once daily[i] | 90 once daily | 400 once daily | 24 | 1.07 (0.99, 1.14) | 1.27 (1.18, 1.37) | 1.63 (1.45, 1.84) |
| | Emtricitabine 200 once daily[i] | | | | 0.98 (0.94, 1.02) | 1.00 (0.97, 1.04) | 1.04 (0.96, 1.12) |
| | Tenofovir disoproxil fumarate 300 once daily[i] | | | | 1.47 (1.37, 1.58) | 1.35 (1.29, 1.42) | 1.47 (1.38, 1.57) |
| Darunavir (boosted by ritonavir[f,g]) | 800/100 once daily | 90 once daily | ND | 23 | 1.02 (0.88, 1.19) | 0.96 (0.84, 1.11) | 0.97 (0.86, 1.10) |
| | | ND | 400 single dose | 18 | 0.97 (0.94, 1.01) | 0.97 (0.94, 1.00) | 0.86 (0.78, 0.96) |
| Darunavir/ ritonavir + emtricitabine/ tenofovir disoproxil fumarate simultaneously with HARVONI[h] | darunavir 800 once daily[j] | 90 once daily | 400 once daily | 24 | 1.01 (0.96, 1.06) | 1.04 (0.99, 1.08) | 1.08 (0.98, 1.20) |
| | emtricitabine 200 once daily[j] | | | | 1.02 (0.96, 1.08) | 1.04 (1.00, 1.08) | 1.03 (0.97, 1.10) |
| | tenofovir disoproxil fumarate 300 once daily[j] | | | | 1.64 (1.54, 1.74) | 1.50 (1.42, 1.59) | 1.59 (1.49, 1.70) |
| Efavirenz/ emtricitabine/ tenofovir disoproxil fumarate[b] | efavirenz 600 once daily | 90 once daily | 400 once daily | 15 | 0.87 (0.79, 0.97) | 0.90 (0.84, 0.96) | 0.91 (0.83, 0.99) |
| | emtricitabine 200 once daily | | | | 1.08 (0.97, 1.21) | 1.05 (0.98, 1.11) | 1.04 (0.98, 1.11) |

| 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 | $C_{min}$ |
| | tenofovir disoproxil fumarate 300 once daily | | | | 1.79 (1.56, 2.04) | 1.98 (1.77, 2.23) | 2.63 (2.32, 2.97) |
| Elvitegravir + cobicistat[c] | 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) |
| Emtricitabine/ rilpivirine/ tenofovir disoproxil fumarate[d] | emtricitabine once 200 daily | 90 once daily | 400 once daily | 14 | 1.02 (0.98, 1.06) | 1.05 (1.02, 1.08) | 1.06 (0.97, 1.15) |
| | rilpivirine 25 once daily | | | | 0.97 (0.88, 1.07) | 1.02 (0.94, 1.11) | 1.12 (1.03, 1.21) |
| | tenofovir disoproxil fumarate 300 once daily | | | | 1.32 (1.25, 1.39) | 1.40 (1.31, 1.50) | 1.91 (1.74, 2.10) |
| Raltegravir[f] | 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) |
| **Estrogen-based Contraceptives** | | | | | | | |
| Norelgestromin | Norgestimate 0.180/0.215/0.250/ ethinyl estradiol 0.025 once daily[f] | 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) |

| 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 | $C_{min}$ |
| **Immunosuppressants** | | | | | | | |
| Cyclosporine[f] | 600 single dose | ND | 400 single dose | 19 | 1.06 (0.94, 1.18) | 0.98 (0.85, 1.14) | NA |
| Tacrolimus[f] | 5 single dose | ND | 400 single dose | 16 | 0.73 (0.59, 0.90) | 1.09 (0.84, 1.40) | NA |
| **Opiate Agonists** | | | | | | | |
| R-Methadone[f] | 30 to 130 daily | ND | 400 once daily | 14 | 0.99 (0.85, 1.16) | 1.01 (0.85, 1.21) | 0.94 (0.77, 1.14) |
| S-Methadone[f] | | | | | 0.95 (0.79, 1.13) | 0.95 (0.77, 1.17) | 0.95 (0.74, 1.22) |

NA = not available/not applicable, ND = not dosed.

a All interaction studies conducted in healthy volunteers.

b Administered as ATRIPLA.

c This study was conducted to support the use of STRIBILD.

d Administered as COMPLERA.

e Ledipasvir dose administered in this study was 30 mg which is lower than the ledipasvir dose of 90 mg when administered as HARVONI.

f These studies have not been performed with HARVONI; they were conducted with either ledipasvir or sofosbuvir administered as single agents.

g Ledipasvir leads to moderate increases of ritonavir plasma exposures.

h Staggered administration (12 hours apart) of atazanavir/ritonavir+emtricitabine/tenofovir DF or darunavir/ritonavir+emtricitabine/tenofovir DF and HARVONI provided similar results.

i Administered as atazanavir/ritonavir+emtricitabine/tenofovir DF.

j Administered as darunavir/ritonavir+emtricitabine/tenofovir DF.

## Drug-Food Interactions

The response rates in Phase 3 trials were similar in HCV-infected patients who received HARVONI with food or without food. HARVONI can be administered without regard to 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 did not substantially affect the sofosbuvir $C_{max}$ and $AUC_{inf}$. The exposures of GS-331007 and ledipasvir were not altered in the presence of either meal type. (see **DOSAGE AND ADMINISTRATION, ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics** and **DETAILED PHARMACOLOGY).**

## Drug-Herb Interactions

St. John's wort should not be used with HARVONI.

Coadministration of St. John's wort, a potent intestinal P-gp inducer, may decrease ledipasvir and sofosbuvir plasma concentrations, which may result in loss of therapeutic effect. See **WARNINGS AND PRECAUTIONS**, **General, Use with Potent Pgp Inducers**.

## Drug-Laboratory Interactions

Interactions of HARVONI with laboratory tests have not been established.

# DOSAGE AND ADMINISTRATION

## Dosing Considerations

The treatment duration of HARVONI is fixed and is not guided by a patient's HCV RNA levels (i.e., no response guided therapy).

## Recommended Dose and Dosage Adjustment

HARVONI is a fixed dose single tablet regimen. No dosage adjustments are possible for HARVONI.

The recommended dose of HARVONI is one tablet of 90 mg/400 mg ledipasvir/sofosbuvir, taken orally, once daily with or without food (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

The recommended dose and treatment duration for HARVONI is provided in Table 7.

**Table 7. Recommended Dose and Treatment Duration for HARVONI**

| | Fixed Duration | HARVONI Dose (daily) |
|---|---|---|
| Treatment-naïve[a] genotype 1 patients without cirrhosis | 12[b] weeks | 90 mg ledipasvir/400 mg sofosbuvir (one tablet) |
| Treatment-naïve[a] genotype 1 patients with cirrhosis[c] | 12 weeks | |
| Treatment-experienced[d] genotype 1 patients without cirrhosis | 12 weeks | |
| Treatment-experienced[d] genotype 1 patients with cirrhosis | 24 weeks | |

a. Treatment-naïve is defined as no prior exposure to any interferon, RBV, or other approved or experimental HCV-specific direct-acting antiviral agent at the time of treatment initiation.
b. 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 TRIALS**).
c. Cirrhosis is defined as any one of the following: Liver biopsy showing cirrhosis (eg, Metavir score = 4 or Ishak score ≥ 5); or Fibroscan (in countries where locally approved) showing cirrhosis or results > 12.5 kPa; or FibroTest® score of > 0.75 and an aspartate aminotransferase (AST): platelet ratio index (APRI) of > 2.
d. Treatment-experienced is defined as those who failed prior therapy with an interferon-based regimen, including regimens containing an HCV protease inhibitor.

## Special Populations

### Pediatrics (<18 Years of age)

HARVONI is not indicated for use in pediatric patients < 18 years of age.

### Geriatrics (> 65 years of age)

HARVONI can be administered in elderly patients (see **ACTION AND CLINICAL PHARMACOLOGY**).

### Renal Impairment

Renal impairment studies have been conducted with the individual drugs, ledipasvir and sofosbuvir. HARVONI can be administered in patients with mild or moderate renal impairment. The safety of HARVONI has not been established in patients with severe renal impairment (eGFR < 30 mL/min/1.73m$^2$) or end stage renal disease (ESRD) requiring hemodialysis (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

### Hepatic Impairment

Hepatic impairment studies have been conducted with the individual drugs, ledipasvir and sofosbuvir. HARVONI can be administered in patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C) (see **WARNINGS AND PRECAUTIONS** and

**ACTION AND CLINICAL PHARMACOLOGY**). Safety and efficacy of HARVONI have not been established in patients with decompensated cirrhosis.

**Missed Dose**

If a patient misses a dose of HARVONI within 18 hours of the time it is usually taken, the patient should take HARVONI as soon as possible, and then take the next dose of HARVONI at the regularly scheduled time.

If a patient misses a dose of HARVONI and it is after 18 hours of the time it is usually taken, the patient should not take the missed dose, but resume the usual dosing schedule. A double dose of HARVONI must not be taken.

If a patient vomits less than 5 hours after taking a dose of HARVONI, the patient should take another dose of HARVONI. If a patient vomits more than 5 hours after taking a dose of HARVONI, the patient should take the next dose at the regularly scheduled time.

## OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

No specific antidote is available for overdose with HARVONI. If overdose occurs the patient must be monitored for evidence of toxicity. Hemodialysis is unlikely to result in significant removal of ledipasvir since ledipasvir is highly bound to plasma protein. Hemodialysis can efficiently remove (53% extraction ratio) the predominant circulating metabolite GS-331007.

Administration of activated charcoal may also be used to aid in the removal of unabsorbed active substance. General supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient are recommended.

The highest documented doses of ledipasvir and sofosbuvir were 120 mg twice daily for 10 days and a single dose of 1200 mg, respectively. In these trials, there were no untoward effects observed at this dose level, and adverse events were similar in frequency and severity to those reported in the placebo groups. The effects of higher doses/exposures are not known.

## ACTION AND CLINICAL PHARMACOLOGY

**Description**

Ledipasvir is an HCV NS5A inhibitor. Sofosbuvir is a nucleotide analog pan-genotypic NS5B polymerase inhibitor.

**Mechanism of Action**

**HARVONI**

HARVONI is a fixed-dose single tablet regimen of ledipasvir and sofosbuvir.

Both sofosbuvir and ledipasvir exhibit high potency and specificity as individual agents against HCV as compounds that target the HCV NS5B and NS5A proteins, respectively. Both compounds display low cytotoxicity in a number of distinct cell lines and display no significant antiviral activity against other viruses tested. *In vitro* combination studies using both sofosbuvir and ledipasvir showed an additive effect as measured by *in vitro* cell based genotype 1a and 1b HCV replicon assays. As individual components, both sofosbuvir and ledispasvir showed additive to synergistic activity with all other anti-HCV agents.

### Ledipasvir

Ledipasvir is a direct acting anti-viral agent that inhibits HCV RNA replication and virion production by targeting the HCV NS5A protein. The NS5A protein is thought to play multiple roles in mediating viral replication, host-cell interactions, and viral pathogenesis. As a nonstructural (NS) protein with no apparent enzymatic activity, NS5A functions through interaction with other viral and cellular proteins. The protein NS5A protein is critical for HCV viability and the rapid viral load (HCV RNA) decline produced by NS5A inhibitors has been postulated to be due to inhibition of viral replication (as with NS3 and NS5B inhibitors) and additional inhibition of virion assembly or secretion from infected cells. The HCV NS5A protein is phosphorylated on multiple sites by host cell kinases and interacts with host cell membranes. While no known enzymatic function has been ascribed to NS5A, it is an essential component of the HCV replicase. *In vitro* resistance selection and cross-resistance studies also indicate ledipasvir targets NS5A as its mode of action.

### Sofosbuvir

Sofosbuvir is a pan-genotypic polymerase inhibitor of the HCV NS5B RNA-dependent RNA polymerase (RdRp). HCV NS5B is the essential initiating and catalytic subunit of the membrane-associated multiprotein complex that mediates HCV RNA replication and is critical for the viral replication cycle. There is no human homolog for HCV NS5B RdRp. Sofosbuvir is a monophosphorylated pyrimidine nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203). Incorporation of GS-461203 into nascent RNA strongly reduces the efficiency of further RNA elongation by RdRp, resulting in premature termination of RNA synthesis. The stopping of viral replication leads to a rapid decline of HCV viral load and clearing of HCV levels in the body.

## Pharmacodynamics

### Effect on Electrocardiogram

The thorough QT studies have been conducted with the individual drugs, ledipasvir and sofosbuvir.

The effect of ledipasvir 120 mg twice daily 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.

The effects of sofosbuvir at the therapeutic dose (400 mg) and 3-fold above therapeutic dose (1200 mg) on QTc interval were evaluated in a randomized, single-dose, placebo-, and active-controlled (moxifloxacin 400 mg) four period crossover thorough QT trial in 59 healthy subjects.

These trials demonstrated a lack of effect of ledipasvir or sofosbuvir on prolongation of the QTcF interval. The upper bounds of the two-sided 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc based on Fridericia correction method (QTcF) were below 10 ms.

## Pharmacokinetics

Ledipasvir AUC is dose proportional over the dose range of 3 to 100 mg. Sofosbuvir and GS-331007 AUCs are near dose proportional over the dose range of 200 mg to 1200 mg.

The pharmacokinetic properties of ledipasvir, sofosbuvir and the predominant circulating metabolite GS-331007 have been evaluated in healthy adult subjects and in patients with chronic hepatitis C following oral administration of HARVONI.

The pharmacokinetics of HARVONI are shown in Table 8.

**Table 8. Summary of Once-Daily Administration of HARVONI in Healthy Adult Subjects and HCV-Infected Patients**

| PK Parameters | Healthy Subjects[a] HARVONI N=192 Geometric Mean (Range) | | | HCV-Infected Patients[b] HARVONI N=2113 Geometric Mean (Range) | | |
|---|---|---|---|---|---|---|
| | LDV[c] | SOF | GS-331007 | LDV | SOF[d] | GS-331007 |
| $AUC_{0-24}$ (ng·h/mL) | 9600 (1160, 36800) | 1170 (505, 2470) | 11400 (5660, 21300) | 7290 (416, 49100) | 1320 (511, 6690) | 12000 (1790, 32000) |
| $C_{max}$ (ng/mL) | 476 (56.9, 1590) | 563 (156, 1290) | 826 (492, 1730) | 323 (19.6, 1910) | 618 (87.7, 2540) | 707 (83.1, 1690) |
| $C_{min}$ (ng/mL) | 283 (33.5, 1180) | ND | ND | 211 (13.4, 1550) | ND | ND |

a. Population PK analysis from Phase 1 studies.
b. Population PK analysis from Phase 2 and 3 studies.
c. N=191, one subject did not have estimable PK parameters for LDV
d. N=1542; 571 subjects did not have estimable PK parameters for SOF
ND: not determined

Relative to healthy subjects, ledipasvir $AUC_{0-24}$ and $C_{max}$ were 24% lower and 32% lower, respectively in HCV-infected patients. Sofosbuvir and GS-331007 $AUC_{0-24}$ and $C_{max}$ were similar in healthy adult subjects and patients with HCV infection.

Based on population PK analyses, age, race, BMI, treatment status (treatment-naive or treatment-experienced), presence of RBV in the treatment regimen, or the presence or absence of cirrhosis had no clinically relevant effects on the exposure of SOF, GS-331007, or LDV.

## Absorption

The pharmacokinetic properties of ledipasvir, sofosbuvir and the predominant circulating metabolite GS-331007 have been evaluated in healthy adult subjects and in patients with chronic hepatitis C. Following oral administration of HARVONI, ledipasvir median peak concentrations were observed 4.0 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.

### *Effects of Food*

The response rates in Phase 3 trials were similar in HCV-infected patients who received HARVONI with food or without 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 did not alter the exposures of ledipasvir or GS-331007. Either meal type did not substantially affect the sofosbuvir $C_{max}$ and $AUC_{inf}$. 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, indicating radioactivity exclusion from erythocytes.

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, CYP 2C19, CYP2D6 and CYP3A4. Evidence of slow oxidative metabolism via an unknown mechanism has been observed. Following a single dose of 90 mg [$^{14}$C]-LDV, 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 biosysthesis pathway. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity *in vitro*.

**Excretion**

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 suggest 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. This 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.

**Special Populations and Conditions**

**Pediatrics (< 18 years of age)**

The pharmacokinetics of ledipasvir, sofosbuvir and GS-331007 in pediatric patients have not been established.

**Geriatrics (> 65 years of age)**

Population pharmacokinetic analysis in HCV-infected patients 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 or GS-331007. Clinical studies of HARVONI included 117 patients aged 65 and over. The response rates observed for patients ≥65 years of age were similar to that of patients <65 years of age, across treatment groups.

**Gender**

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 patients across the Phase 3 studies. No clinically relevant pharmacokinetic differences have been observed between men and women for sofosbuvir and GS-331007.

### Race

No clinically relevant pharmacokinetic differences due to race have been identified for ledipasvir, sofosbuvir or GS-331007.

### Hepatic Insufficiency

Hepatic impairment studies have been conducted with the individual drugs, ledipasvir and sofosbuvir. Data from these studies support the use of HARVONI in 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 **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

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 ($AUC_{inf}$) was similar in subjects with severe hepatic impairment and matched control subjects with normal hepatic function. Mild or moderate hepatic impairment is not expected to alter HARVONI pharmacokinetics. No dose adjustment of ledipasvir is recommended for patients with mild, moderate and severe hepatic impairment. Population pharmacokinetics analysis in HCV-infected patients indicated that compensated cirrhosis had no clinically relevant effect on the exposure of ledipasvir.

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, sofosbuvir $AUC_{0-24}$ was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 $AUC_{0-24}$ was 18% and 9% higher, respectively. No dose adjustment of sofosbuvir is recommended for patients with mild, moderate and severe hepatic impairment. Population pharmacokinetics analysis in HCV-infected patients indicated that compensated cirrhosis had no clinically relevant effect on the exposure of sofosbuvir and GS-331007.

### Renal Insufficiency

Renal impairment studies have been conducted with the individual drugs, ledipasvir and sofosbuvir. Data from these studies support the use of HARVONI in patients with mild or moderate renal impairment. The safety of HARVONI has not been established in patients with severe renal impairment (eGFR < 30 mL/min/1.73m$^2$) or end stage renal disease (ESRD) requiring hemodialysis (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION)**.

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) and matched control subjects with normal renal function (eGFR ≥ 90 mL/min by Cockcroft-Gault). No clinically relevant differences in ledipasvir pharmacokinetics were observed between healthy subjects and subjects with severe renal impairment. No dose adjustment of ledipasvir is required for patients with mild, moderate or severe renal impairment. An evaluation of ledipasvir pharmacokinetics in subjects with ESRD has not

been conducted.

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. An increase in plasma exposure of sofosbuvir and its 2 metabolites of approximately 2-fold or less was observed in subjects with mild and moderate renal impairment compared with subjects with normal renal function. No dose adjustment is required for patients with mild or moderate renal impairment.

Hemodialysis can efficiently remove (53% extraction ratio) the predominant circulating metabolite GS-331007. Following a single 400 mg dose of sofosbuvir, a 4 hour hemodialysis session removed approximately 18% of administered dose. The safety and efficacy of sofosbuvir has not been assessed in patients with severe renal impairment or ESRD (see **WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION** and **DETAILED PHARMACOLOGY**).

## STORAGE AND STABILITY

Store below 30 °C (86 °F).

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

## SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

HARVONI is a fixed-dose single tablet regimen containing ledipasvir and sofosbuvir for oral administration.

Each tablet contains 90 mg ledipasvir and 400 mg of 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: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and FD&C Yellow #6/sunset yellow FCF aluminum lake.

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 bottle contains 28 tablets, a silica gel desiccant, polyester coil and closed with a child resistant closure.

# PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

### Drug Substance

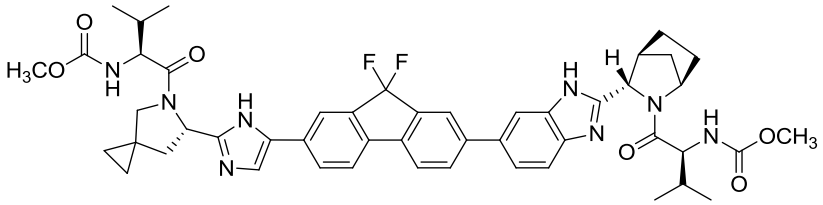
**Proper name:** **ledipasvir**

Chemical name: 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

Molecular formula: $C_{49}H_{54}F_2N_8O_6$

Molecular mass: 889.00

Structural formula:



Physicochemical properties:

Solubility: 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).

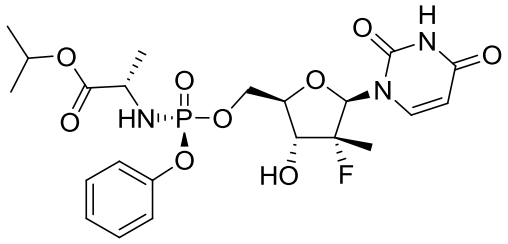
**Proper name:** **sofosbuvir**

Chemical name: (*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

Molecular formula: $C_{22}H_{29}FN_3O_9P$

Molecular mass: 529.45

Structural formula:



Physicochemical properties:

| | |
|---|---|
| Appearance | Sofosbuvir is a white to off-white crystalline solid. |
| Solubility | Sofosbuvir is slightly soluble in water. |

## CLINICAL TRIALS

The efficacy of HARVONI was evaluated in three Phase 3 trials with data available for a total of 1518 patients with genotype 1 chronic hepatitis C (CHC). Patients in these trials had compensated liver disease. All three Phase 3 trials evaluated efficacy of HARVONI with or without ribavirin.

The demographics and baseline characteristics for the patients in studies ION-3, ION-1 and ION-2 were well balanced across the treatment groups as summarized in Table 10, Table 14, and Table 18, respectively.

Treatment duration was fixed in each trial.

Sustained virologic response (SVR) was the primary endpoint to determine the HCV cure rate which was defined as HCV RNA less than Lower Limit of Quantitation (LLOQ) at 12 weeks after the cessation of treatment.

### Clinical Trials in Treatment-Naïve Patients without Cirrhosis [ION-3 (Study 0108)]

#### Trial Design

The trial design of Study ION-3 is described in Table 9.

**Table 9. Summary of Trial Design in Treatment Naïve[a] Patients without Cirrhosis (ION-3)**

| Trial Design | Dosage and Route of Administration | Treatment Regimen | Total Duration |
|---|---|---|---|
| Phase 3, randomized, open label, multicentre | HARVONI (90 mg/400 mg), QD, PO +/- RBV 1000 or 1200 mg/day, BID, PO | HARVONI | 8 weeks |
| | | HARVONI + RBV | 8 weeks |
| | | HARVONI | 12 weeks |

RBV = ribavirin; PO = orally; QD = once a day; BID = twice a day

a. Patients were treatment naïve (defined as no prior exposure to any interferon, RBV, or other approved or experimental HCV-specific direct-acting antiviral agent at the time of enrollment), non-cirrhotic, with genotype 1 CHC. Patients were randomized in a 1:1:1 ratio to one of the three treatment groups and stratified by HCV genotype (1a vs. 1b).

## Demographics and Other Baseline Characteristics

Demographic characteristics for patients in ION-3 are provided in Table 10.

**Table 10. Demographic and Other Baseline Characteristics of HCV Treatment-Naïve Patients without Cirrhosis (ION-3)**

| Characteristics | HARVONI 8 Weeks N= 215 n (%) | HARVONI + RBV 8 Weeks N = 216 n (%) | HARVONI 12 Weeks N = 216 n (%) | Total N = 647 n (%) |
|---|---|---|---|---|
| **Age (years)** | | | | |
| Mean (range) | 53 (20-75) | 51 (21-75) | 53 (20-71) | 52 (20-75) |
| **Gender** | | | | |
| Male | 130 (60) | 117 (54) | 128 (59) | 375 (58) |
| Female | 85 (40) | 99 (46) | 88 (41) | 272 (42) |
| **Race** | | | | |
| White | 164 (76) | 176 (82) | 167 (77) | 507 (78) |
| Black | 45 (21) | 36 (17) | 42 (19) | 123 (19) |
| Asian | 5 (2) | 2 (1) | 3 (1) | 10 (2) |
| Other | 1 (1) | 2 (1) | 4 (2) | 7 (1) |
| **BMI** | | | | |
| $< 30$ kg/m$^2$ | 151 (70) | 152 (70) | 159 (74) | 462 (71) |
| $> 30$ kg/m$^2$ | 64 (30) | 64 (30) | 57 (26) | 185 (29) |
| **Viral Load** | | | | |
| HCV RNA $Log_{10}$ IU/mL | 6.5 ± 0.8 | 6.4 ± 0.7 | 6.4 ± 0.8 | 6.4 ± 0.7 |
| < 800,000 copies/mL | 34 (15) | 45 (21) | 44 (20) | 123 (19) |
| ≥ 800,000 copies/mL | 181 (84) | 171 (79) | 172 (80) | 524 (81) |
| **HCV genotype** | | | | |
| 1a | 171 (80) | 172 (80) | 172 (80) | 515 (80) |
| 1b | 43 (20) | 44 (20) | 44 (20) | 131 (20) |
| 1 (no confirmed subtype) | 1 (< 1) | | | 1 (< 1) |
| **IL28B** | | | | |
| CC | 56 (26) | 60 (28) | 56 (26) | 172 (27) |
| Non-CC | 159 (74) | 156 (72) | 160 (74) | 475 (73) |

| Characteristics | HARVONI 8 Weeks N= 215 n (%) | HARVONI + RBV 8 Weeks N = 216 n (%) | HARVONI 12 Weeks N = 216 n (%) | Total N = 647 n (%) |
|---|---|---|---|---|
| **Interferon Eligible Status** | | | | |
| Eligible | 202 (94) | 203 (94) | 201 (93) | 606(94) |

## Study Results

The response rates for the treatment groups in the ION-3 trial are presented in Table 11. All treatment groups met the primary efficacy endpoint. The 8-week treatment of HARVONI without ribavirin was noninferior to the 8-week treatment of HARVONI with ribavirin (treatment difference 0.9%; 95% confidence interval: -3.9% to 5.7%) and the 12-week treatment of HARVONI (treatment difference -1.4%; 97.5% confidence interval: -6.4% to 3.6%). Among patients with a baseline HCV RNA <6 million IU/mL, the SVR rates were similar between 8-week and 12-week treatments of HARVONI. Among patients with a baseline HCV RNA ≥6 million IU/mL, patients treated for 8 weeks had a numerically lower SVR rate compared to those treated for 12 weeks.

**Table 11. Virologic Outcome in HCV Treatment-Naïve Patients without Cirrhosis (ION-3)**

| | HARVONI 8 Weeks N = 215 % (n/N) | HARVONI+ RBV 8 Weeks N = 216 % (n/N) | HARVONI 12 Weeks N = 216 % (n/N) |
|---|---|---|---|
| **Overall SVR12[a]** | 94 (202/215) | 93 (201/216) | 95 (206/216) |
| 95% CI[b] | 89.9 to 96.7 | 88.8 to 96.1 | 91.7 to 97.8 |
| HCV RNA <6 million IU/mL at BL | 97 (119/123) | 96 (133/138) | 96 (126/131) |
| HCV RNA ≥ 6 million IU/mL at BL | 90 (83/92) | 87 (68/78) | 94 (80/85) |
| **HCV RNA <LLOQ[c] by Visits** | | | |
| HCV RNA < LLOQ at treatment week 4 | 100 (215/215) | 99 (211/213) | 100 (216/216) |
| HCV RNA < LLOQ at treatment week 12 (end of treatment) | N/A | N/A | 99 (210/211) |
| **Outcome for patients without SVR** | | | |
| Overall Virologic Failure | 5 (11/215) | 4 (9/214) | 1 (3/216) |
| On-Treatment Virologic Failure | 0/215 | 0/216 | 0/216 |
| Overall Relapse[d] | 5 (11/215) | 4 (9/214) | 1 (3/216) |
| HCV RNA <6 million IU/mL at BL | 2 (2/123) | 2 (3/137) | 2 (2/131) |
| HCV RNA ≥ 6 million IU/mL at BL | 10 (9/92) | 8 (6/77) | 1 (1/85) |
| Lost to Follow Up | <1 (1/215) | 2 (5/216) | 2 (5/216) |
| Other[e] | <1 (1/215) | <1 (1/216) | 1 (2/216) |
| **Death** | 0 | 0 | 0 |
| **Discontinuation** | | | |
| Due to AE | 0 | <1 (1/216) | 1 (2/216) |
| Due to Other[f] | 0 | 1 (2/216) | 1 (3/216) |

BL = baseline; N/A = not applicable

a SVR12= Sustained virologic response, defined as HCV RNA less than LLOQ (Lower Limit of Quantitation, 25 IU/mL) at 12 weeks after the cessation of treatment.

b The exact 95% CI for the proportion of within treatment group was based on the Clopper-Pearson method.

c Number of patients reporting HCV RNA less than LLOQ detected + the number of patients with HCV RNA less than LLOQ TND (target not detected). 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 per mL.

d The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.

e Other includes patients who did not achieve SVR and did not meet virologic failure criteria (excluding lost to follow-up).

f Other includes patients who did not complete study treatment due to lost to follow up and non-compliance with study drug.

Subgroup analyses were performed for the primary efficacy endpoint (SVR12) for selected subgroups. Response rates for some of these subgroups are presented in Table 12.

**Table 12. Sustained Virologic Response (SVR) for Selected Baseline Subgroups of Treatment-Naïve Patients without Cirrhosis (ION-3)**

| Study Outcomes | HARVONI 8-Weeks N=215 % (n/N) | HARVONI + RBV 8-Weeks N=216 % (n/N) | HARVONI 12-Weeks N=216 % (n/N) |
|---|---|---|---|
| **Genotype[a]** | | | |
| 1a | 93 (159/171) | 92 (159/172) | 95 (163/172) |
| 1b | 98 (42/43) | 95 (42/44) | 98 (43/44) |
| **Viral Load[a] (HCV RNA $Log_{10}$ IU/ml)** | | | |
| < 800,000 | 97 (33/34) | 96 (43/45) | 96 (42/44) |
| ≥ 800,000 | 93 (169/181) | 92 (158/171) | 95 (164/172) |
| **IL28B[a]** | | | |
| CC | 96 (54/56) | 95 (57/60) | 96 (54/56) |
| Non-CC | 93 (148/159) | 92 (144/156) | 95 (152/160) |
| **BMI[a]** | | | |
| < 30 $Kg/m^2$ | 93 (141/151) | 91 (139/152) | 95 (151/159) |
| ≥ 30 $Kg/m^2$ | 95 (61/64) | 97 (62/64) | 97 (55/57) |
| **Interferon eligible patients[a]** | | | |
| Eligible | 94 (190/202) | 93 (188/203) | 96 (192/201) |

a The results were within the 90% CI for all treatment groups.

Host and viral factors that have been traditionally predictive of or associated with lower rates of SVR (eg, African-American race, high BMI, genotype 1a, non-CC IL28B allele) had no impact on SVR12 rates.

## Clinical Trials in Treatment-Naïve Patients with or without Cirrhosis [ION-1 (Study 0102)]

### Trial Design

The trial design of Study ION-1 is described in Table 13.

**Table 13. Summary of Trial Design in Treatment Naïve[a] Patients with or without Cirrhosis (ION-1)**

| Trial Design | Dosage and Route of Administration | Treatment Regimen | Total Duration |
|---|---|---|---|
| Phase 3, ongoing, randomized, open label, multicentre | HARVONI (90 mg/400 mg), QD, PO +/- RBV 1000 or 1200 mg/day, BID, PO | HARVONI | 12 weeks |
| | | HARVONI + RBV | 12 weeks |
| | | HARVONI | 24 weeks |
| | | HARVONI + RBV | 24 weeks |

RBV = ribavirin; PO = orally; QD = once a day; BID = twice a day

a. Patients were treatment naïve (defined as no prior exposure to any interferon, RBV, or other approved or experimental HCV-specific direct-acting antiviral agent at the time of enrollment), with genotype 1 CHC, including those with cirrhosis. Patients were randomized in a 1:1:1:1 ratio to one of the four treatment groups and stratified by the presence or absence of cirrhosis and HCV genotype (1a vs. 1b).

## Demographic and Baseline Characteristics

Demographic characteristics for patients in ION-1 are provided in Table 14.

**Table 14. Demographic and Other Baseline Characteristics of HCV Treatment-Naïve Patients with or without Cirrhosis (ION-1)**

| Characteristics | HARVONI 12 Weeks N = 214 n (%) | HARVONI + RBV 12 Weeks N = 217 n (%) | HARVONI 24 Weeks N = 217 n (%) | HARVONI + RBV 24 Weeks N = 217 n (%) | Total N= 865 n (%) |
|---|---|---|---|---|---|
| **Age (years)** | | | | | |
| Mean (range) | 52 (18–75) | 52 (18-78) | 53 (22-80) | 54 (24-77) | 52 (18-80) |
| **Gender** | | | | | |
| Male | 127 (59) | 128 (59) | 139 (64) | 119 (55) | 513 (59) |
| Female | 87 (41) | 89 (41) | 78 (36) | 98 (45) | 352 (41) |
| **Race** | | | | | |
| White | 187 (87) | 188 (87) | 177 (82) | 183 (84) | 735 (85) |
| Black | 24 (11) | 26 (12) | 32 (15) | 26 (12) | 108 (13) |
| Asian | 1 (1) | 0 | 5 (2) | 5 (2) | 11 (1) |
| Other | 2 (1) | 3 (1) | 3 (1) | 3 (1) | 11 (1) |
| **BMI** | | | | | |
| < 30 kg/$m^2$ | 176 (82) | 171 (79) | 168 (77) | 177 (82) | 692 (80) |
| > 30 kg/$m^2$ | 38 (18) | 46 (21) | 49 (23) | 40 (18) | 173 (20) |
| **Viral Load** | | | | | |
| HCV RNA $Log_{10}$ IU/mL | 6.4 ± 0.7 | 6.4 ± 0.6 | 6.3 ± 0.7 | 6.3 ± 0.7 | 6.4 ± 0.7 |
| < 800,000 copies/mL | 45 (21) | 44 (20) | 49 (23) | 44 (20) | 182 (21) |
| ≥ 800,000 copies/mL | 169 (80) | 173 (80) | 168 (77) | 173 (79) | 683 (79) |

| Characteristics | HARVONI 12 Weeks N = 214 n (%) | HARVONI + RBV 12 Weeks N = 217 n (%) | HARVONI 24 Weeks N = 217 n (%) | HARVONI + RBV 24 Weeks N = 217 n (%) | Total N= 865 n (%) |
|---|---|---|---|---|---|
| **HCV genotype** | | | | | |
| 1a | 144 (67) | 148 (68) | 146 (67) | 143 (66) | 581 (67) |
| 1b | 66 (31) | 68 (31) | 68 (31) | 71 (33) | 273 (32) |
| 1 (no confirmed subtype) | 1 (< 1) | 1 (< 1) | 1 (< 1) | 1 (< 1) | 4 (< 1) |
| **IL28B** | | | | | |
| CC | 55 (26) | 76 (35) | 52 (24) | 73 (34) | 256 (30) |
| Non-CC | 159 (74) | 141 (65) | 165 (76) | 144 (66) | 609 (70) |
| **Interferon Eligible Status** | | | | | |
| Eligible | 200 (93) | 197 (91) | 198 (91) | 203 (94) | 798 (92) |
| **Cirrhosis** | | | | | |
| Yes | 34 (16) | 33 (15) | 33 (15) | 36 (17) | 136 (16) |
| No | 178 (83) | 182 (84) | 184 (85) | 181 (83) | 726 (84) |

## Study Results

The response rates for the treatment groups of HARVONI with or without ribavirin for 12 weeks in the ION-1 trial are presented in Table 15. The interim primary endpoint analysis for SVR included all patients enrolled in the 12-week treatment groups (N = 431). The 12-week treatment groups met the primary efficacy endpoint. SVR rates for all patients enrolled in the 24 week treatment groups (N= 434) were not available at the time of interim analysis. However, a total of 197 patients had both posttreatment Week 12 and 24 data available for a concordance analysis (47 patients in the HARVONI 12 Week treatment group, 51 patients in the HARVONI+RBV 12 Week treatment group, 49 patients in the HARVONI 24 Week treatment group, and 50 patients in the HARVONI+RBV 24 Week treatment group). Each of the 197 patients who achieved SVR12 also achieved SVR24, resulting in a positive predictive value of 100.0% for all groups.

**Table 15. Virologic Outcome in HCV Adult Treatment-Naïve Patients with or without Cirrhosis (ION-1)**

| | HARVONI 12 Weeks N = 214 % (n/N) | HARVONI + RBV 12 Weeks N = 217 % (n/N) |
|---|---|---|
| **SVR12[a]** | 98 (209/214) | 97 (211/217) |
| 95% CI[b] | 94.6 to 99.2 | 94.1 to 99.0 |
| **HCV RNA < LLOQ[c] by visit** | | |
| HCV RNA <LLOQ[c] at treatment week 4 | 100 (213/213) | 99 (215/217) |
| HCV RNA <LLOQ[c] at treatment week 12 (end of treatment for 12 week group) | 100 (213/213) | 100 (214/214) |
| **Outcome for patients without SVR** | | |
| Overall Virologic Failure | <1 (1/214) | 0/217 |
| On-Treatment Virologic Failure | 0/214 | 0/217 |
| Relapse[d] | <1 (1/213) | 0/217 |
| Lost to Follow Up | 1 (2/214) | 1 (2/217) |
| Other[e] | 1 (2/214) | 1 (3/217) |
| **Death** | 0 | 0 |
| **Discontinuation** | | |
| Due to AE | 0 | 0 |
| Due to Other[f] | 1 (2/214) | 2 (4/217) |

N/A = Not Applicable

a SVR12 = Sustained virologic response, defined as HCV RNA less than LLOQ at 12 weeks (Lower Limit of Quantitation, 25 IU/mL) after the cessation of treatment.

b The exact 95% CI for the proportion of within treatment group was based on the Clopper-Pearson method.

c Number of patients reporting HCV RNA less than LLOQ detected + the number of patients with HCV RNA less than LLOQ TND (target not detected).

d The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.

e Other includes patients who did not achieve SVR and did not meet virologic failure criteria (excluding lost to follow-up).

f Other includes patients who did not complete study treatment due to lost to follow up, withdrew consent, protocol violation, lack of efficacy and pregnancy.

g SVR rates for all patients enrolled in the 24 week treatment groups (N=434) were not available at the time of the interim study report. Therefore data has only been included for patients who had both posttreatment Week 12 and 24 data available at the time of interim analysis.

Subgroup analyses were performed for the primary efficacy endpoint (SVR12) for selected subgroups. Response rates for some of these subgroups are presented in Table 16.

**Table 16. Sustained Virologic Response (SVR) for Selected Baseline Subgroups of Treatment-Naïve Patients with or without Cirrhosis (ION-1)**

| Study Outcomes | HARVONI 12-Weeks N=214 % (n/N) | HARVONI + RBV 12-Weeks N=217 % (n/N) |
|---|---|---|
| **Genotype**[a] | | |
| 1a | 97 (139/144) | 97 (143/148) |
| 1b | 100 (66/66) | 99 (67/68) |
| **Viral Load**[a] **(HCV RNA $Log_{10}$ IU/ml)** | | |
| < 800,000 | 98 (44/45) | 93 (41/44) |
| ≥ 800,000 | 98 (165/169) | 98 (170/173) |
| **IL28B**[a] | | |
| CC | 100 (55/55) | 97 (74/76) |
| Non-CC | 97 (154/159) | 97 (137/141) |
| **Cirrhosis** | | |
| Yes | 94 (32/34) | 100 (33/33) |
| No | 98 (177/180) | 97 (178/184) |
| **BMI** | | |
| < 30 $Kg/m^2$ | 98 (172/176) | 97 (166/171) |
| ≥ 30 $Kg/m^2$ | 97 (37/38) | 98 (45/46) |

a The exact 95% confidence interval (CI) for the proportion within treatment group and subgroup is based on the Clopper-Pearson method. The results were within the 90% CI for all treatment groups.

Host and viral factors that have been traditionally predictive of or associated with lower rates of SVR (eg, African-American race, cirrhosis, high BMI, genotype 1a, high viral load, non-CC IL28B allele) had no impact on SVR12 rates.

## Clinical Trials in Treatment Experienced Patients with or without Cirrhosis [ION-2 (Study 0109)]

### Trial Design

The trial design of Study ION-2 is described in Table 17.

**Table 17. Summary of Trial Design in Treatment Experienced[a] Patients with or without Cirrhosis (ION-2)**

| Trial Design | Dosage and Route of Administration | Treatment Regimen | Total Duration |
|---|---|---|---|
| Phase 3, randomized, open label, multicentre | HARVONI (90 mg/400 mg), QD, PO<br><br>RBV 1000 or 1200 mg/day, BID, PO | HARVONI | 12 weeks |
| | | HARVONI + RBV | 12 weeks |
| | | HARVONI | 24 weeks |
| | | HARVONI + RBV | 24 weeks |

RBV = ribavirin; PO = orally; QD = once a day; BID = twice a day

a Patients were treatment experienced (those who failed prior therapy with an interferon-based regimen, including regimens containing an HCV protease inhibitor) genotype 1 CHC, with or without cirrhosis. Patients were randomized in a 1:1:1:1 ratio to one of the four treatment groups and 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 Other Baseline Characteristics

Demographic characteristics for patients in ION-2 are provided in Table 18.

**Table 18. Demographic and Other Baseline Characteristics of HCV Treatment-Experienced Patients with or without Cirrhosis (ION-2)**

| Characteristics | HARVONI 12 Weeks N = 109 n (%) | HARVONI + RBV 12 Weeks N = 111 n (%) | HARVONI 24 Weeks N = 109 n (%) | HARVONI + RBV 24 Weeks N = 111 n (%) | Total N = 440 n (%) |
|---|---|---|---|---|---|
| **Age (years)** | | | | | |
| Mean (range) | 56 (24–67) | 57 (27-75) | 56 (25-68) | 55 (28-70) | 56 (24-75) |
| **Gender** | | | | | |
| Male | 74 (68) | 71 (64) | 74 (68) | 68 (61) | 287 (65) |
| Female | 35 (32) | 40 (36) | 35 (32) | 43 (39) | 153 (35) |
| **Race** | | | | | |
| White | 84 (77) | 94 (85) | 91 (83) | 89 (80) | 358 (81) |
| Black | 24 (22) | 16 (14) | 17 (16) | 20 (18) | 77 (18) |
| Asian | 1 (1) | 0 | 0 | 0 | 1 (<1) |
| Other | 0 | 1 (1) | 1 (1) | 2 (2) | 4 (1) |
| **BMI** | | | | | |
| < 30 kg/$m^2$ | 66 (61) | 74 (67) | 75 (69) | 82 (74) | 297 (68) |
| > 30 kg/$m^2$ | 43 (39) | 37 (33) | 34 (31) | 29 (26) | 143 (32) |
| **Viral Load** | | | | | |
| HCV RNA Log10 IU/mL | 6.5 ± 0.4 | 6.4 ± 0.5 | 6.4 ± 0.6 | 6.5 ± 0.6 | 6.5 ± 0.5 |
| < 800,000 copies/mL | 6 (5) | 13 (12) | 16 (15) | 15 (13) | 50 (11) |
| ≥ 800,000 copies/mL | 103 (95) | 98 (88) | 93 (85) | 96 (87) | 390 (89) |
| **HCV genotype** | | | | | |
| 1a | 86 (79) | 88 (79) | 85 (78) | 88 (79) | 347 (79) |
| 1b | 23 (21) | 23 (21) | 24 (22) | 23 (21) | 93 (21) |
| **IL28B** | | | | | |
| CC | 10 (9) | 11 (10) | 16 (15) | 18 (16) | 55 (13) |
| Non-CC | 99 (91) | 100 (90) | 93 (85) | 93 (84) | 385 (88) |
| **Cirrhosis** | | | | | |
| Yes | 22 (20) | 22 (20) | 22 (20) | 22 (20) | 88 (20) |
| No | 87 (80) | 88 (79) | 86 (79) | 89 (80) | 350 (80) |
| **Response to Prior HCV Treatment** | | | | | |
| Peg-IFN +RBV | 43 (39) | 47 (42) | 58 (53) | 59 (53) | 207 (47) |
| Relapse/ Breakthrough[b] | 21 (49) | 23 (49) | 25 (43) | 32 (54) | 101 (49) |
| Non-Responder[c] | 22 (51) | 24 (51) | 33 (57) | 27 (49) | 106 (51) |
| Null | 17 (77) | 12 (50) | 19 (58) | 16 (59) | 64 (60) |
| Partial | 5 (23) | 12 (50) | 14 (42) | 11 (41) | 42 (40) |
| PI+ Peg-IFN +RBV | 66 (61) | 64 (58) | 50 (46) | 51 (46) | 231 (53) |
| Relapse/ Breakthrough[b] | 39 (59) | 42 (66) | 35 (70) | 28 (55) | 144 (62) |
| Non-Responder[c] | 27 (41) | 22 (34) | 15 (30) | 23 (45) | 87 (38) |

a Relapse/Breakthrough: Patient achieved undetectable HCV RNA levels (HCV RNA < LLOQ) during treatment or within 4 weeks of the end of treatment, but did not achieve SVR.

b Non-Responder: Patient did not achieve undetectable HCV RNA levels (HCV RNA ≥ LLOQ) while on treatment.

## Study Results

The response rates for the treatment groups in study ION-2 are presented in Table 19. All treatment groups met the primary efficacy endpoint. A total of 98 patients in the HARVONI 12 Week treatment arm and 107 patients in the HARVONI+RBV 12 Week treatment arm had both posttreatment Week 12 and 24 data available for a concordance analysis. Each of the 205 patients who achieved SVR12 also achieved SVR24, resulting in a positive predictive value of 100.0% in both groups.

**Table 19. Virologic Outcome in Treatment-Experienced HCV Patients with or without Cirrhosis (ION-2)**

| | HARVONI 12 Weeks N=109 % (n/N) | HARVONI +RBV 12 Weeks N=111 % (n/N) | HARVONI 24 Weeks N=109 % (n/N) | HARVONI +RBV 24 Weeks N=111 % (n/N) |
|---|---|---|---|---|
| **SVR12[a]** | 94 (102/109) | 96 (107/111) | 99 (108/109) | 99 (110/111) |
| 95% CI[b] | 87.2 to 97.4 | 91.0 to 99.0 | 95.0 to 100.0 | 95.1 to 100.0 |
| **SVR24[c]** | 94 (102/109) | 96 (107/111) | 99 (108/109) | 99 (110/111) |
| **HCV RNA <LLOQ[d] by Visit** | | | | |
| HCV RNA <LLOQ[d] at treatment week 4 | 100 (109/109) | 99 (110/111) | 99 (108/109) | 99 (110/111) |
| HCV RNA <LLOQ[d] at treatment week 12 (end of treatment for 12 week group) | 99 (108/109)[e] | 100 (111/111) | 100 (109/109) | 100 (110/110) |
| HCV RNA <LLOQ[d] at treatment week 24 (end of treatment) | N/A | N/A | 100 (107/107) | 100 (110/110) |
| **Outcome for patients without SVR** | | | | |
| Overall Virologic Failure | 6 (7/109) | 4 (4/111) | 0/109 | 1 (1/111) |
| On-Treatment Virologic Failure | 0/109 | 0/111 | 0/109 | 1 (1/111)[f] |
| Relapse[g] | 6 (7/108) | 4 (4/111) | 0/109 | 0/110 |
| Lost to Follow Up | 0/109 | 0/111 | 0/109 | 0/111 |
| Other[h] | 0/109 | 0/111 | 1 (1/109) | 0/111 |
| **Death** | 0 | 0 | 0 | 0 |
| **Discontinuation** | | | | |
| Due to AE | 0 | 0 | 0 | 0 |
| Due to Other[i] | 0 | 0 | 2 (2/109) | 1 (1/111) |

N/A = not available

a SVR12, Sustained virologic response, defined as HCV RNA less than LLOQ (Lower Limit of Quantitation, 25 IU/mL) at 12 weeks after the cessation of treatment.

b The exact 95% CI for the proportion of within treatment group was based on the Clopper-Pearson method.

c SVR24, defined as HCV RNA less than LLOQ (25 IU/mL) at 24 weeks after cessation of treatment.

d Number of patients reporting HCV RNA less than LLOQ detected + the number of patients with HCV RNA less than LLOQ TND (target not detected).

e The one patient who did not achieve HCV RNA <LLOQ at the last on treatment visit achieved SVR12.

f This patient was discontinued after 6 weeks of treatment due to lack of efficacy (rebound) and never achieved HCV RNA <LLOQ. Plasma concentrations of GS-331007 and LDV at weeks 2, 4 and 6 were indicative of noncompliance with the study drug at or around these study visits.

g The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.

h Other includes patients who did not achieve SVR and did not meet virologic failure criteria (excluding lost to follow-up).

i Other includes patients who did not complete study treatment due to protocol violation and lack of efficacy.

Response rates for selected subgroups are presented in Table 20.

**Table 20. Sustained Virologic Response (SVR) for Selected Baseline Subgroups of Treatment-Experienced Patients with or without Cirrhosis (ION-2)**

| Study Outcomes | HARVONI 12 Weeks N=109 % (n/N) | HARVONI +RBV 12 Weeks N=111 % (n/N) | HARVONI 24 Weeks N=109 % (n/N) | HARVONI +RBV 24 Weeks N=111 % (n/N) |
|---|---|---|---|---|
| **Genotype[a]** | | | | |
| 1a | 95 (82/86) | 95 (84/88) | 99 (84/85) | 99 (87/88) |
| 1b | 87 (20/23) | 100 (23/23) | 100 (24/24) | 100 (23/23) |
| **Viral Load[a] (HCV RNA $Log_{10}$ IU/ml)** | | | | |
| < 800,000 | 83 (5/6) | 100 (13/13) | 100 (16/16) | 100 (15/15) |
| ≥ 800,000 | 94 (97/103) | 96 (94/98) | 99 (92/93) | 99 (95/96) |
| **Cirrhosis[a]** | | | | |
| Yes | 86 (19/22) | 82 (18/22) | 100 (22/22) | 100 (22/22) |
| No | 95 (83/87) | 100 (89/89) | 99 (86/87) | 99 (88/89) |
| **IL28B[a]** | | | | |
| CC | 100 (10/10) | 100 (11/11) | 100 (16/16) | 94 (17/18) |
| Non-CC | 93 (92/99) | 96 (96/100) | 99 (92/93) | 100 (93/93) |
| **BMI[a]** | | | | |
| < 30 $Kg/m^2$ | 92 (61/66) | 96 (71/74) | 99 (74/75) | 99 (81/82) |
| ≥ 30 $Kg/m^2$ | 95 (41/43) | 97 (36/37) | 100 (34/34) | 100 (29/29) |
| **Response to Prior HCV Therapy[a]** | | | | |
| Relapse/ Breakthrough | 95 (57/60) | 97 (63/65) | 100 (60/60) | 98 (59/60) |
| Non-Responder | 92 (45/49) | 96 (44/46) | 98 (48/49) | 100 (51/51) |
| **Prior HCV Therapy[a]** | | | | |
| PI + PEG-IFN + RBV | 94 (62/66) | 97 (62/64) | 98 (49/50) | 100 (51/51) |
| PEG-IFN + RBV | 93 (40/43) | 96 (45/47) | 100 (58/58) | 98 (58/59) |
| **Cirrhosis by Prior HCV Therapy[a]** | | | | |
| PI + PEG-IFN + RBV | | | | |
| Yes | 86 (12/14) | 85 (11/13) | 100 (14/14) | 100 (13/13) |
| No | 96 (50/52) | 100 (51/51) | 97 (35/36) | 100 (38/38) |
| PEG-IFN + RBV | | | | |
| Yes | 88 (7/8) | 78 (7/9) | 100 (8/8) | 100 (9/9) |
| No | 94 (33/35) | 100 (38/38) | 100 (50/50) | 98 (49/50) |

a The exact 95% confidence interval (CI) for the proportion within treatment group and subgroup is based on the Clopper-Pearson method. The results were within the 90% CI for all treatment groups.

Host and viral factors that have been traditionally predictive of or associated with lower rates of SVR (eg, African-American race, high BMI, genotype 1a, high viral load, non-CC IL28B allele) had no impact on SVR12 rates. Treatment-experienced patients with cirrhosis who received 12 weeks of treatment showed numerically lower SVR rates compared with treatment-experienced patients with cirrhosis who received 24 weeks of treatment (±RBV).

**Patients with Other HCV Genotypes**

In a Phase 2 open-label trial, the safety and efficacy of HARVONI were evaluated with or without ribavirin in 51 treatment-naive patients with genotype 3 HCV infection, with or without cirrhosis. Patients were treated with HARVONI (N=25) or HARVONI + RBV (N=26) for 12 weeks. SVR rates were 64% (16/25) and 100% (26/26) in the HARVONI and HARVONI + RBV treatment groups, respectively. The safety of HARVONI with or without ribavirin was comparable to that observed in patients with genotype 1 HCV infection treated with HARVONI with or without ribavirin in Phase 3 clinical trials.

The safety and efficacy of HARVONI has not been fully established in patients infected with genotype 3.

## DETAILED PHARMACOLOGY

### Pharmacodynamics

#### Effect on Electrocardiogram

Thorough QT studies have been conducted for ledipasvir and sofosbuvir.

The effect of ledipasvir 120 mg twice daily 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. The effects of sofosbuvir at the therapeutic dose (400 mg) and 3-fold above therapeutic dose (1200 mg) on QTc interval were evaluated in a randomized, single-dose, placebo-, and active-controlled (moxifloxacin 400 mg) four period crossover thorough QT trial in 59 healthy subjects.

The results from both studies showed the expected effect of the single dose of moxifloxacin (positive control) on the QTc interval, indicating that the study had appropriate assay sensitivity; the lower bound of the 2 sided 90% confidence interval was > 5 msec at more than 1 time point.

Evaluation of the baseline-adjusted mean differences between ledipasvir 120 mg BID, sofosbuvir 400 mg or 1200-mg doses and placebo and their associated 2-sided 90% confidence intervals demonstrated a lack of effect of ledipasvir or sofosbuvir on prolongation of the QTcF interval (primary PD endpoint). The upper bounds of the 90% confidence intervals were < 10 msec at all time points after dosing. Consistent with the results using the QTcF correction formula, the upper bounds of the 2-sided 90% confidence intervals were

< 10 msec for ledipasvir and both doses of sofosbuvir at all time points using other correction methods.

Ledipasvir $AUC_{0-24}$ and $C_{max}$ were 3.7- fold and 4.2-fold higher, respectively, than the mean exposure (based on population PK exposures) achieved in Phase 2 and 3 studies following administration of HARVONI. The mean exposures of GS-331007 ($AUC_{0-24}$ and $C_{max}$) and sofosbuvir ($AUC_{0-24}$ and $C_{max}$) at the supratherapeutic dose (sofosbuvir 1200 mg) were approximately 2.2-, 2.9-, 1.8-, and 3.4-fold higher, respectively, than the mean exposures (based on population PK exposures) achieved following administration of HARVONI.

**Safety Pharmacology**

The effects of ledipasvir on the central nervous, cardiovascular and respiratory systems were examined in a core battery of safety pharmacology studies. The studies did not reveal any concerns for cardiovascular, respiratory, or CNS effects.

The effects of sofosbuvir (evaluated as GS-9851, a 1:1 diastereomeric mixture of sofosbuvir and its stereoisomer) on the central nervous, cardiovascular, and respiratory systems were examined in a core battery of safety pharmacology studies. The studies presented have not identified any undesirable pharmacodynamic effect of sofosbuvir on physiological function at therapeutic dose level.

**Pharmacokinetics**

Ledipasvir AUC is dose proportional over the dose range of 3 to 100 mg. Sofosbuvir and GS-331007 AUCs are near dose proportional over the dose range of 200 mg to 1200 mg.

Based on the population pharmacokinetic analysis in HCV-infected patients, 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.

**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 4.0 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.

### *Effects of Food*

The response rates in Phase 3 trials were similar in HCV-infected patients who received HARVONI with food or without food.

A study conducted in 28 healthy subjects showed that relative to fasting conditions, for GS-331007, an approximately 18% to 30% lower $C_{max}$ was observed upon administration of HARVONI with food, with no change in AUC (90% CIs of the Geometric Mean Ratios (GMRs) were contained within 80-125%). The decrease in GS-331007 $C_{max}$ was not considered clinically significant. Similar LDV plasma exposures (AUC and $C_{max}$) were achieved upon administration of HARVONI under fasted or fed conditions (90% CIs of the GMRs were contained within 70-143%).

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 slowed the rate of absorption of SOF (high or moderate fat meal versus fasted; prolonged $T_{max}$: 2.0-2.25 hours versus 1.0 hours) but did not substantially affect the sofosbuvir $C_{max}$ and $AUC_{inf}$ as evidenced by < 30% higher $C_{max}$ and < 2-fold higher mean AUC.

HARVONI can be administered without regard to food.

### Distribution

Ledipasvir is >99.8% bound to human plasma proteins. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment. After a single 90 mg dose of [$^{14}$C]-ledipasvir in 8 healthy adult male subjects, the blood to plasma ratio of $^{14}$C-radioactivity ranged between 0.51 and 0.66, indicating that total radioactivity was excluded from erythrocytes. [$^{14}$C]-ledipasvir-derived radioactivity was absorbed and widely distributed to tissues (e.g., alimentary canal, liver, kidney, pancreas, adrenal gland, and brown fat) of male mice and rats after a single oral dose. Low levels of [$^{14}$C]-ledipasvir-derived radioactivity were observed in the CNS, bone, eye and testes. Plasma LDV exposure in nursing pups of postpartum female rats orally administered LDV illustrates transfer into milk.

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 (< 10%) in human plasma. After a single 400 mg dose of [$^{14}$C]-sofosbuvir in healthy male subjects, the blood to plasma ratio of $^{14}$C-radioactivity was approximately 0.7.

After a single 400 mg dose of [$^{14}$C]-sofosbuvir in 7 healthy adult male subjects, derived radioactivity was absorbed and widely distributed to tissues (e.g., alimentary canal, lymphatic system, excretory system) of male rats and pregnant, non-pregnant, and postpartum female rats after a single oral dose. Drug-derived radioactivity was transferred through the placenta of females and was found in amniotic fluid and absorbed into fetuses. Low levels of [$^{14}$C]-sofosbuvir-derived radioactivity were observed in the CNS, bone, eye, testes, and white adipose. Fetal blood and brain levels of drug-related material were higher

than those observed in dams. Levels of drug-derived radioactivity were quantifiable in the milk collected from postpartum females. Levels of drug-derived radioactivity were transferred into nursing pups and were detectable in the liver and gastrointestinal (GI)/stomach contents. See **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Nursing Women.**

**Metabolism**

*In vitro*, no detectable metabolism of ledipasvir was observed by human CYP1A2, CYP2C8, CYP2C9, CYP 2C19, 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 to 8 healthy adult male subjects, the systemic exposure was almost exclusively due to the parent drug (> 98%) with 1.1% and 0.75% attributed to unidentified metabolites (M1 and M12, respectively). 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 biosysthesis pathway. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity *in vitro*.

In a human mass balance study conducted with sofosbuvir administered as a single agent at a 400 mg oral dose of [$^{14}$C]-sofosbuvir in healthy male subjects (n=7), sofosbuvir and GS-331007 accounted for approximately 4% and >90% of drug related material (sum of molecular weight-adjusted AUC of sofosbuvir and its metabolites) systemic exposure, respectively.

**Excretion**

Following a single 90 mg oral dose of [$^{14}$C]-ledipasvir to 8 healthy adult male subjects, the mean cumulative urinary and fecal recovery of the [$^{14}$C]-radioactivity was approximately 87%, with most of the radioactive dose recovered in the feces (approximately 86%). The major component excreted in feces was unchanged ledipasvir, accounting for a mean of 70% of the administered dose; the oxidative metabolite M19 accounted for 2.2% of the dose. These data suggest 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 in healthy male subjects (n=7), 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. Renal clearance is the major elimination pathway for GS-331007. Consistent with substantial elimination of GS-331007 in the urine, clinically significant changes in

GS-331007 PK were noted with declining renal function. The median terminal half-life of sofosbuvir and GS-331007 following administration of HARVONI were 0.5 and 27 hours respectively.

## Special Populations and Conditions

### Hepatic Insufficiency

Hepatic impairment studies have been conducted with the individual drugs, ledipasvir and sofosbuvir. Data from these studies support the use of HARVONI in 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 **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

The pharmacokinetics of ledipasvir was studied with a single dose of 90 mg ledipasvir in 10 HCV negative subjects with normal hepatic function and 10 HCV negative matched control subjects with severe hepatic impairment (Child Pugh Class C). Similar $AUC_{inf}$, a modestly lower (approximately 35%) $C_{max}$ and prolonged terminal $t_{1/2}$ (median 84.25 hrs vs 45.72 hrs) observed in subjects with severe hepatic impairment as compared to subjects with normal hepatic function. A reduction in $C_{max}$ in the absence of a change in AUC was not deemed clinically important. Mild and moderate hepatic impairment is not expected to meaningfully alter the pharmacokinetics of ledipasvir. No dose adjustment of ledipasvir is recommended for patients with mild, moderate and severe hepatic impairment. The effect of decompensated cirrhosis on ledipasvir pharmacokinetics has not been specifically evaluated. Population pharmacokinetics analysis in HCV-infected patients indicated that compensated cirrhosis had no clinically relevant effect on the exposure of ledipasvir (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

The pharmacokinetics of sofosbuvir was studied following 7-day dosing of 400 mg sofosbuvir in HCV-infected patients with moderate and severe hepatic impairment (Child-Pugh Class B and C). Relative to subjects with normal hepatic function, the sofosbuvir $AUC_{0-24}$ was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 $AUC_{0-24}$ was 18% and 9% higher, respectively. Mild hepatic impairment is not expected to meaningfully alter the pharmacokinetics of sofosbuvir and GS-331007. No dose adjustment of sofosbuvir is recommended for patients with mild, moderate and severe hepatic impairment. The effect of decompensated cirrhosis on sofosbuvir pharmacokinetics has not been specifically evaluated. Population pharmacokinetics analysis in HCV-infected patients indicated that compensated cirrhosis had no clinically relevant effect on the exposure of sofosbuvir and GS-331007 (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

### Renal Insufficiency

Renal impairment studies have been conducted with the individual drugs, ledipasvir and sofosbuvir. Data from these studies support the use of HARVONI in patients with mild or moderate renal impairment. The safety of HARVONI has not been established in patients

with severe renal impairment (eGFR < 30 mL/min/1.73m$^2$) or ESRD requiring hemodialysis (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION)**.

The pharmacokinetics of ledipasvir were studied with a single dose of 90 mg ledipasvir in 10 HCV negative subjects with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault) and 10 matched control subjects with normal renal function (eGFR ≥ 90 mL/min by Cockcroft-Gault). No clinically relevant differences in ledipasvir pharmacokinetics were observed between healthy subjects and subjects with severe renal impairment. An evaluation of lediapasvir pharmacokinetics in subjects with ESRD has not been conducted. No dose adjustment of ledipasvir is required for patients with mild, moderate or 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 end stage renal disease (ESRD) requiring hemodialysis following a single 400 mg dose of sofosbuvir (N=6/group). Relative to subjects with normal renal function (eGFR > 80 mL/min/1.73m$^2$), the sofosbuvir $AUC_{inf}$ was 61%, 107% and 171% higher in mild, moderate and severe renal impairment, while the GS-331007 $AUC_{inf}$ was 55%, 88% and 451% higher, respectively. In subjects with ESRD, sofosbuvir $AUC_{inf}$ was 28% higher when sofosbuvir was dosed 1 hour before hemodialysis compared with 60% higher when dosed 1 hour after hemodialysis. The $AUC_{inf}$ of GS-331007 in subjects with ESRD administered sofosbuvir 1 hour before or 1 hour after hemodialysis was at least 10-fold and 20-fold higher, respectively, compared to normal subjects.

Hemodialysis is required for the elimination of GS-331007 (extraction ratio 53%) in subjects with ESRD; following a single 400 mg dose of sofosbuvir, a 4 hour hemodialysis removed approximately 18% of administered dose. No dose adjustment of sofosbuvir is required for patients with mild or moderate renal impairment. The safety of HARVONI has not been assessed in patients with severe renal impairment or ESRD (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

**Drug-Drug Interactions**

As HARVONI contains ledipasvir and sofosbuvir, any interactions that have been identified with these agents individually may occur with HARVONI.

**Potential for HARVONI to Affect Other Drugs**

Ledipasvir is an inhibitor of intestinal efflux 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 hepatic uptake transporters OATP1B1, OATP1B3 and hepatic efflux transporter BSEP only at concentrations exceeding those achieved in clinic. Ledipasvir is not an inhibitor of renal efflux transporters MRP2, MRP4, MATE1, renal uptake transporters OCT2, OAT1, OAT3, and hepatic uptake transporter OCT1. The drug-drug interaction potential of ledipasvir is primarily limited to the process of intestinal absorption. 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 efflux transporters drug transporters P-gp, BCRP, renal efflux transporter MRP2, hepatic efflux transporter BSEP, hepatic uptake transporters OATP1B1, OATP1B3 and OCT1 and GS-331007 is not an inhibitor of renal uptake transporters OAT1, OCT2, and renal efflux transporter MATE1.

Ledipasvir inhibits UGT1A1 only at concentrations exceeding those achieved in the clinic.

Sofosbuvir and GS-331007 are not inhibitors or inducers of CYP or UGT1A1 enzymes.

**Potential for Other Drugs to Affect HARVONI**

Ledipasvir and sofosbuvir are substrates of efflux drug transporters P-gp and BCRP while GS-331007 is not. Drugs that are potent P-gp inducers in the intestine (e.g. rifampin or St. John's wort) may decrease ledipasvir and sofosbuvir plasma concentrations leading to reduced therapeutic effect of HARVONI and should not be used with HARVONI (see **WARNINGS AND PRECAUTIONS, Use with Potent P-gp Inducers**). Coadministration with drugs that inhibit P-gp and/or BCRP may increase sofosbuvir and ledipasvir 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 ledispavir 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.

Based on these data, ledipasvir, sofosbuvir and its metabolites are predicted to have low liability to cause clinically significant drug interactions through human CYP or drug transporters. The fact that ledipasvir and sofosbuvir are substrates of Pgp and BCRP suggests that they may be susceptible to modest changes in PK that can occur via Pgp and/or BCRP transporter-based drug interactions. Clinical studies were conducted to evaluate the effect of drugs that can affect or be affected by ledipasvir, sofosbuvir and GS-331007 during co-administration (see **DRUG INTERACTIONS)**.

## MICROBIOLOGY

### Antiviral Activity in Cell Culture

In HCV replicon assays, the $EC_{50}$ values of ledipasvir against full-length replicons from genotype 1a and 1b were 0.031 nM and 0.004 nM, respectively. The median $EC_{50}$ of ledipasvir against chimeric replicons encoding NS5A sequences from clinical isolates was 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 μM; N=3). Ledipasvir has $EC_{50}$ values of 21 nM in genotype 2a and 16 nM against the genotype 2b replicons that have leucine at amino acid position 31 (L31) in NS5A, but has a significantly reduced activity against the genotype 2a replicon ($EC_{50}$ = 249 nM) and the genotype 2b replicon ($EC_{50}$ = 530 nM) that both have methionine at position 31 (M31) as well as genotype 3 replicons ($EC_{50}$ = 168 nM). In addition, ledipasvir is active against genotypes 4a, 5a, and 6a, with $EC_{50}$ values of 0.39 nM, 0.15 nM and 1.1 nM, respectively. The presence of 40% human serum reduced anti-HCV activity of ledipasvir by 12-fold against genotype 1a HCV replicon.

Sofosbuvir exhibits pan-genotypic anti-HCV activity In HCV replicon assays, the $EC_{50}$ values of sofosbuvir against full-length replicons from genotype 1a, 1b, 2a, 3a and 4a, and chimeric 1b replicons encoding NS5B from genotype 2b, 5a or 6a ranged from 0.014 to 0.11 μM. The median $EC_{50}$ value of sofosbuvir against chimeric replicons encoding NS5B sequences from clinical isolates was 0.062 μM for genotype 1a (range 0.029-0.128 μM; N=67), 0.102 μM for genotype 1b (range 0.045-0.170 μM; N=29), 0.029 μM for genotype 2 (range 0.014-0.081 μM; N=15) and 0.081μM for genotype 3a (range 0.024-0.181 μM; N=106). In infectious virus assays, the $EC_{50}$ values of sofosbuvir against genotype 1a and 2a were 0.03 and 0.02 μM, respectively. The presence of 40% human serum had no effect on the anti-HCV activity of sofosbuvir.

Since there is about 65% homology of the HCV NS5B polymerase across HCV genotypes, and since GS-461203 binds to a highly conserved region of RdRp, sofosbuvir is a pan-genotypic inhibitor of the HCV NS5B with a high barrier to resistance. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a and 4a with an IC50 value ranging from 0.7 to 2.6 μM. GS-461203 is not an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

Evaluation of sofosbuvir in combination with ledipasvir showed no antagonistic effect in reducing HCV RNA levels in replicon cells.

## Antiviral Activity *in vivo*

In patients taking HARVONI, an average HCV RNA viral load decline of -4.5 ($log_{10}$ IU/ml) was observed by Week 1 of treatment.

## Resistance

### In Cell Culture

HCV replicons with reduced susceptibility to ledipasvir have been selected in cell culture for genotype 1a and 1b. Reduced susceptibility to ledipasvir was associated with the primary NS5A substitution Y93H in both genotype 1a and 1b. Additionally a Q30E substitution emerged in genotype 1a replicons. Site-directed mutagenesis of the Y93H in both genotype 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 and reduced the replication viral capacity by 89% to 99% compared to the corresponding wild-type. In biochemical assays, recombinant NS5B polymerase from genotypes 1b, 2a, 3a and 4a expressing the S282T substitution showed reduced susceptibility to GS-461203 compared to respective wild-types.

**In Clinical Trials**

In a pooled analysis of patients who received HARVONI in Phase 3 trials, 37 (2.3%) patients (29 with genotype 1a and 8 with genotype 1b) qualified for resistance analysis due to virologic failure or early study drug discontinuation and having HCV RNA > 1000 IU/ml. Post-baseline NS5A and NS5B deep sequencing data (assay cutoff of 1%) were available for 37/37 and 36/37 patients, respectively.

NS5A resistance-associated variants (RAVs) were observed in post-baseline isolates from 29/37 patients not achieving SVR. Of the 29 genotype 1a patients who qualified for resistance testing, 22/29 (76%) patients harbored one or more NS5A RAVs at positions K24, M28, Q30, L31, S38 and Y93 at failure, while the remaining 7/29 patients had no NS5A RAVs detected at failure. The most common variants were Q30R (36.4%), Y93H (27.3%) L31M (22.7%), Y93N (18.2%), Q30H (13.6%) and M28T (9.1%). Of the 8 genotype 1b patients who qualified for resistance testing, 7/8 (88%) harbored one or more NS5A RAVs at positions L31 and Y93 at failure, while 1/8 patients had no NS5A RAVs at failure. The most common variant was Y93H (85.7%). Among the 8 patients who had no NS5A RAVs at failure, 7 patients received 8 weeks of treatment (N=3 with HARVONI; N=4 with HARVONI + RBV) and 1 patient received HARVONI for 12 weeks. In phenotypic analyses, post-baseline isolates from patients who harbored NS5A RAVs at failure showed 20- to >243-fold reduced susceptibility to ledipasvir.

The sofosbuvir-associated resistance substitution S282T in NS5B was not detected in any failure isolate from the Phase 3 trials. However, the NS5B S282T substitution in combination with NS5A substitutions L31M, Y93H and Q30L were detected in one patient at failure following 8 week treatment with HARVONI from a Phase 2 trial [LONESTAR]. This patient was subsequently retreated with HARVONI + RBV for 24 weeks and achieved SVR following retreatment.

<u>Effect of Baseline HCV Resistance Associated Variants on Treatment Outcome</u>

Analyses were conducted to explore the association between pre-existing baseline NS5A resistance-associated variants (RAVs) and treatment outcome. In the pooled analysis of the Phase 3 trials, 256/1618 (16%) patients had baseline NS5A RAVs identified by population or

deep sequencing irrespective of subtype. Of the 256 patients with NS5A RAVs, 235 (91.5%) achieved SVR12 following 8, 12 or 24 weeks of treatment with HARVONI (± RBV). The overall SVR12 rates in patients with baseline NS5A RAVs were 90.6% (174 of 192) for genotype 1a and 95.0% (57 of 60) for genotype 1b.

In genotype 1a treatment-naïve patients with NS5A RAVs (M28A, Q30H/R/E, L31M/V/I, H58D, Y93H/N/C), SVR12 rates of 89% (34/38) after 8 weeks and 96% (69/72) after 12 weeks of therapy were observed with HARVONI. All genotype 1b treatment-naive patients with baseline NS5A RAVs (Y93H) achieved SVR12, regardless of treatment duration. Following HARVONI 12-week treatment, one of the 4 treatment-naïve patients who relapsed had L31M mutation at baseline while 11 other patients with L31M at baseline achieved SVR12.

In treatment-experienced patients, a lower SVR rate of 69% (9 of 13) was observed among the small group of patients (n = 13) with NS5A RAVs conferring > 100-fold resistance to ledipasvir and who were treated with HARVONI for 12 weeks. All treatment-experienced patients with NS5A RAVs conferring < 100-fold resistance had SVR12. The group of NS5A RAVs that conferred >100-fold shift and were observed in patients were the following substitutions in genotype 1a (M28A, Q30H/R/E, L31M/V/I, H58D, Y93H/N/C) or in genotype 1b (Y93H). Among treatment-experienced patients who relapsed, the following resistance associated variants were detected at baseline: Q30H/R, L31M and/or Y93H/N.

The sofosbuvir resistance-associated substitution S282T was not detected in the baseline NS5B sequence of any patient in Phase 3 trials by population or deep sequencing. SVR was achieved in all 24 patients (N=20 with L159F+C316N; N=1 with L159F; and N=3 with N142T) who had baseline variants associated with resistance to NS5B nucleoside inhibitors.

## 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. Sofosbuvir retained activity against the NS5B substitutions L159F and L320F associated with resistance to other nucleoside inhibitors. *In vitro* studies demonstrated no cross resistance between sofosbuvir and ledipasvir when tested individually against HCV mutations resistant to other classes of HCV inhibitors. Both sofosbuvir and ledipasvir have been tested against an extensive panel of known resistance-associated variants (RAVs) to other classes of direct acting antivirals with different mechanisms of actions. These included NS3 RAVs affecting HCV protease inhibitors (i.e. Q80K, R155K, A156T and D168E/G/ V in genotype 1a; A156T and D168E/G/V in genotype 1b), and NS5B RAVs known to affect NNIs (ie. L419M/S, R422K and M423I/T in genotypes 1a and 1b) and RBV (T390I and F415Y). No cross-resistance has been observed in these studies, and sofosbuvir and ledipasvir remain highly potent against RAVs affecting inhibitor classes other than their own.

## Cytotoxicity

Sofosbuvir showed little or no cytotoxicity at the highest concentration tested (89 – 100 µM) in human cell lines derived from liver, prostate, lymphoid, or endothelial tissues or primary human cells isolated from the liver, circulating lymphoid cells, or bone marrow, except for Huh-7 cells where 50% cytotoxicity ($CC_{50}$) was observed at 66 µM.

Ledipasvir showed little or no cytotoxicity in multiple cell lines derived from liver, lymphoid or endothelial tissue. The $CC_{50}$ values ranged from 2791 nM to > 50,000 nM in 1b-Rluc-2, Huh-luc, 1a-HRlucP, HepG2, MT4 and SL3 cell lines. Ledipasvir is therefore highly selective in cell-based replicon assays (Selectivity Index [SI] > 837,000-fold).

# TOXICOLOGY

## Repeat-Dose Toxicity

### Ledipasvir

No target organs of toxicity were identified with ledipasvir. Ledipasvir was well tolerated in studies for up to 4 weeks in the mouse, 6 months in the rat and 9 months in the dog. At the respective NOAELs, ledipasvir systemic exposure levels (sexes combined) were approximately 25-, 7-, and 7-fold greater in mice, rats, and dogs, respectively, than those in subjects treated with HARVONI. The only notable changes in the repeat dose toxicity studies were transient decreases in body weight gain and/or food consumption.

### Sofosbuvir

Sofosbuvir or GS-9851, a 1:1 diastereomeric mixture of sofosbuvir and its stereoisomer, were evaluated in repeat-dose oral toxicity studies up to 13 weeks in mice, 26 weeks in rats, and 39 weeks in dogs. The primary target organs identified were the cardiovascular, hepatobiliary, gastrointestinal (GI) and hematopoietic (erythroid) systems. For example, in 7-day toxicity studies with GS-9851, the 1:1 diastereomic mixture of sofosbuvir and its stereoisomer, doses of 2000 mg/kg/day in the rat and 1500 mg/kg/day in the dog resulted (but were not limited to) in increased mucus secretions in the stomach, glycogen depletion, and increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin, with associated histopathologic liver findings in dogs; and heart adverse effects in rats (e.g., multifocal cardiac myofiber degeneration) and dogs (e.g., increased QT/QTc intervals). In general, exposure levels in the 7-day toxicity studies at the adverse dose were at least 16-fold (based on an AUC of GS-331007) higher than human exposure at 400 mg sofosbuvir. Findings in the liver and heart were not observed in long-term studies with GS-9851 or sofosbuvir. In chronic toxicity studies in rats (26 weeks) and dogs (39 weeks), effects included (but were not limited to) GI-related clinical signs (e.g., soft feces and emesis) and a decrease (e.g., approximately 10%) in mean red cell indices that were observed mainly in the high-dose group of dogs. One male dog was euthanized moribund with intestinal hemorrhage. The relationship to sofosbuvir was undetermined. Sofosbuvir was well tolerated for up to 3 months in the mouse, 6 months in the rat, and 9 months in the dog with no clinically-relevant target organ toxicities. At the respective NOAELs, GS-331007 systemic

exposure levels were 2/13- (male/female), 5- (sexes combined), and 7- (sexes combined) in mice, rats, and dogs, respectively, than those in subjects treated with the recommended clinical dose (400 mg).

## Genotoxicity and Carcinogenicity

### 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.

Ledipasvir carcinogenicity studies are ongoing.

### Sofosbuvir

Sofosbuvir, when administered as the diastereomeric mixture GS-9851, was not genotoxic in a bacterial mutagenicity assay, in an *in vitro* chromosome aberration test using human peripheral blood lymphocytes and in an *in vivo* mouse micronucleus assay.

Sofosbuvir was not a carcinogen in the 2-year mouse and rat carcinogenicity studies at GS-331007 exposures up to 17 and 9 times, respectively, higher than human exposure at 400 mg dose.

## Reproductive and Development Toxicity

### Ledipasvir

Ledipasvir had no adverse effects on mating and fertility. In female rats, the mean number of corpora lutea, and implantation sites were slightly reduced at maternal exposures 6-fold the exposure in humans at the recommended clinical dose. At the no observed effect level, AUC exposure to ledipasvir was approximately 7- and 3-fold, in males and females, respectively, the human exposure at the recommended clinical dose.

No teratogenic effects were observed in rat and rabbit developmental toxicity studies with ledipasvir.

In a rat pre- and postnatal study, at a maternally toxic dose, the developing rat offspring exhibited mean decreased body weight and body weight gain when exposed in utero (via maternal dosing) and during lactation (via maternal milk) at a maternal exposure approximately 4 times the exposure in humans at the recommended clinical dose. There were no effects on survival, physical and behavioral development and reproductive performance in the offspring at maternal exposures similar to 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. No teratogenic effects were observed in rat and rabbit developmental toxicity studies with sofosbuvir. Sofosbuvir had no adverse effects on behavior, reproduction, or development of

the offspring in the rat pre- and post-natal development study. At the highest dose tested where no adverse effects were observed, exposure to the predominant circulating metabolite GS-331007 was at least 5-fold the exposure in humans at the recommended clinical dose.

Fertility was normal in the offspring of rats exposed daily from before birth (in utero) through lactation day 20 at daily GS-331007 exposures of approximately 7-fold higher than human exposures at the recommended clinical dose.

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**PART III: CONSUMER INFORMATION**

**PrHARVONI™**
**(Ledipasvir/Sofosbuvir) Tablets**

**This leaflet is part III of a three-part "Product Monograph" published when HARVONI was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about HARVONI. Contact your doctor or pharmacist if you have any questions about the drug.**

## ABOUT THIS MEDICATION

**What the medication is used for:**
HARVONI is used to treat chronic (long term) hepatitis C infection (genotype 1) in adults. Hepatitis C is an infectious disease affecting primarily the liver, caused by the hepatitis C virus (HCV). People with hepatitis C have the virus in their blood and in their liver. It is not known if HARVONI is safe and effective in children under 18 years of age.

**What it does:**
HARVONI has been shown to cure chronic hepatitis C infection in the majority of patients. Cure means the HCV virus is cleared from your blood (remains at an undetectable level) when measured 3 months after finishing all treatment.

HARVONI contains the prescription medicines ledipasvir and sofosbuvir. Ledipasvir is an HCV inhibitor. It works by blocking a protein required for replication and assembly of the HCV virus. Sofosbuvir is a type of medicine called a polymerase inhibitor. It works by blocking a specific step in the replication of the HCV virus. During this specific step, the HCV virus copies its genetic material so that it can create duplicate virus particles. Polymerase inhibitors like sofosbuvir prevent the HCV virus from creating a full copy of its genetic material. When sofosbuvir is used along with the other medicine in this combination, ledipasvir, many steps in the virus replication process can be blocked. This prevents the virus particles from duplicating themselves, allowing your body to clear (remove) the virus from your blood.

**When it should not be used:**
Do not take HARVONI if you:
- are allergic to ledipasvir, sofosbuvir or any of the other ingredients in this product (See "**What the important nonmedicinal ingredients are"**)

**What the medicinal ingredient is:**
ledipasvir, sofosbuvir

**What the important nonmedicinal ingredients are:**
colloidal silicon dioxide, copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The tablets are film-coated with a coating material containing polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and FD&C Yellow #6/sunset yellow FCF aluminum lake.

**What dosage forms it comes in:**
HARVONI is available as tablets. Each tablet contains ledipasvir 90 mg and sofosbuvir 400 mg, as the active ingredients. 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, a silica gel desiccant, polyester coil and closed with a child resistant closure.

## WARNINGS AND PRECAUTIONS

**BEFORE you use HARVONI talk to your doctor, nurse, or pharmacist if you:**
- **have liver problems other than hepatitis C infection**
- **have hepatitis B or HIV**
- **have severe kidney disease or you are on dialysis**
- **have any other medical condition**
- **are pregnant or plan to become pregnant. It is not known if HARVONI can harm your unborn child. Ask your doctor for advice before taking this medicine**
- **are breastfeeding or plan to breastfeed. Do not breastfeed while taking HARVONI.**
- **are taking any medication that is listed in this pamphlet under "Drugs that may interact with HARVONI" (see INTERACTIONS WITH THIS MEDICATION).**
- have a rare hereditary problem of galactose intolerance (severe lactase deficiency or glucose/galactose malabsorption) as this product contains lactose.

Do not take HARVONI with other medicines containing sofosbuvir (e.g., SOVALDI®)

## INTERACTIONS WITH THIS MEDICATION

**Drugs that may interact with HARVONI include:**

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Other medicines may affect how HARVONI works and vice versa.
Especially tell your healthcare provider if you take:
- antacids or buffered medicines
- carbamazepine (Tegretol®)
- digoxin (Lanoxin®, Toloxin®)
- efavirenz/emtricitabine/tenofovir disoproxil fumarate (ATRIPLA®)
- elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (STRIBILD®)
- tenofovir disoproxil fumarate (VIREAD®, TRUVADA®) used together with atazanavir (Reyataz®), darunavir (Prezista®) or lopinavir/ritonavir (Kaletra®)
- medicines for indigestion, heartburn or ulcers such as nizatidine (Axid®), famotidine (Pepcid AC®, Peptic Guard®, Ulcidine®), cimetidine (Tagamet®), ranitidine (Zantac®), esomeprazole (Nexium®), lansoprazole (Prevacid®), omeprazole (Losec®), rabeprazole (Aciphex®) or pantoprazole (Pantoloc®)
- oxcarbazepine (Trileptal®)
- phenytoin (Dilantin®)
- phenobarbital

- rifabutin (Mycobutin®)
- rifampin (Rifadin®, Rifater®, Rofact®)
- rosuvastatin (Crestor®)
- simeprevir (Galexos®)
- St. John's wort *(Hypericum perforatum)* or a product that contains St. John's wort
- tipranavir (Aptivus®) or tipranavir/ritonavir

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.

## PROPER USE OF THIS MEDICATION

**Usual Adult Dose:**
Take 1 tablet once daily with or without food.

HARVONI is normally taken for either 12 or 24 weeks (8 weeks can be considered in certain cases). Your healthcare provider will tell you exactly how long you need to take HARVONI.

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.

If you are taking an antacid, you may need to take HARVONI at a different time than the antacid. Talk to your doctor.

**Overdose:**

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Missed Dose:**
It is important not to miss a dose of HARVONI.

- **If you do miss a dose** of HARVONI and you notice within 18 hours, you must take the tablet as soon as possible. Then take the next dose as usual.
- **If you do miss a dose** of HARVONI and you notice after 18 hours**,** wait and take the next dose at your usual time. Do not take a double dose (two doses close together).

If you are sick (vomit) **less than 5 hours** after taking HARVONI, take another tablet. If you vomit **more than 5 hours** after taking HARVONI you should not take another tablet until your next regularly scheduled tablet.

**Do not** take a double dose to make up for a missed dose.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects of HARVONI include:

- tiredness
- headache
- nausea

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.

***This is not a complete list of side effects. For any unexpected effects while taking HARVONI, contact your doctor or pharmacist.***

## HOW TO STORE IT

Store HARVONI below 30 °C (86 °F).
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 reach and sight of children.

**REPORTING SUSPECTED SIDE EFFECTS**

**You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:**

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- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
- **Health Canada**
  **Postal Locator 0701D**
  **Ottawa, Ontario**
  **K1A 0K9**

**Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.**

***NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.***

## MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at:
www.gilead.ca
or by contacting the sponsor, Gilead Sciences Canada, Inc., at:
1–866–207–4267

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