**SCHEDULING STATUS**

**S4**

## 1. NAME OF THE MEDICINE

HARVONI (90 mg ledipasvir and 400 mg sofosbuvir) Film-Coated Tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 90 mg ledipasvir and 400 mg sofosbuvir.

Harvoni contains sugar (165 mg lactose per tablet).

For full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.

White, diamond-shaped, biconvex, film-coated tablets with “GSI” debossed on one side and “7985” on the other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Harvoni is indicated for the treatment of chronic hepatitis C (CHC) in adults and in adolescents aged 12 to < 18 years (see sections 4.2, 4.4 and 5.1).

## 4.2 Posology and method of administration

Harvoni treatment should be initiated and monitored by a medical practitioner experienced in the management of patients with CHC.

**Posology**

*Adults and adolescents aged 12 to < 18 years*

The recommended dose of Harvoni is one tablet once daily with or without food (see section 5.2).

Table 1 below provides the recommended treatment durations for treatment-naïve and treatment-experienced patients infected with genotype 1, 3, 4, 5, or 6 CHC, with and without cirrhosis.

**Table 1: Recommended treatment duration for Harvoni and the recommended use of co-administered ribavirin for certain subgroups**

| **Patient population** (including HIV co-infected patients) | **Treatment and duration** |
|---|---|
| *Adult and Adolescent patients 12 years of age or older with genotype 1, 4, 5 or 6 CHC* | |
| Patients without cirrhosis | Harvoni for 12 weeks.<br>- Harvoni for 8 weeks may be considered in previously untreated genotype 1-infected patients. |
| Patients with compensated cirrhosis | Harvoni + ribavirin[A] for 12 weeks<br>or<br>Harvoni (without ribavirin) for 24 weeks.<br>- Harvoni (without ribavirin) for 12 weeks may be considered for patients deemed at low risk for clinical disease progression and who have subsequent retreatment options (see section 4.4). |

| **Patient population**<br>(including HIV co-infected patients) | **Treatment and duration** |
|---|---|
| Patients who are post-liver transplant without cirrhosis or with compensated cirrhosis | Harvoni + ribavirin[A] for 12 weeks.<br>- Harvoni (without ribavirin) for 12 weeks (in patients without cirrhosis) or 24 weeks (in patients with cirrhosis) may be considered for patients who are ineligible for or intolerant to ribavirin. |
| Patients with decompensated cirrhosis irrespective of transplant status | Harvoni + ribavirin[B] for 12 weeks<br>- Harvoni (without ribavirin) for 24 weeks may be considered in patients who are ineligible for or intolerant to ribavirin. |
| *Adult and Adolescent patients 12 years of age or older with genotype 3 CHC* | |
| Patients with compensated cirrhosis and/or prior treatment failure | Harvoni + ribavirin[A] for 24 weeks (see section 4.4). |

A Adults: weight based ribavirin (<75 kg = 1, 000 mg and ≥ 75 kg = 1 200 mg), administered orally in two divided doses with food. Adolescents: for ribavirin dosing recommendations, see Table 3 below.
B For ribavirin dosing recommendations in patients with decompensated cirrhosis, see Table 2 below.

**Table 2: Guidance for ribavirin dosing when administered with Harvoni to patients with decompensated cirrhosis**

| Patient | Ribavirin Dose* |
|---|---|
| Child-Pugh-Turcotte (CPT) Class B cirrhosis pre-transplant | 1,000 mg per day for patients < 75 kg and 1,200 mg for those weighing ≥ 75 kg |
| CPT Class C cirrhosis pre-transplant<br><br>CPT Class B or C cirrhosis post-transplant | Starting dose of 600 mg, which can be titrated up to a maximum of 1,000/1,200 mg (1,000 mg for patients weighing < 75 kg and 1,200 mg for patients weighing ≥ 75 kg) if well tolerated. If the starting dose is not well tolerated, the dose should be reduced as clinically indicated based on haemoglobin levels |

* If a more normalized dose of ribavirin (by weight and renal function) cannot be reached for reasons of tolerability, 24 weeks of Harvoni + ribavirin should be considered in order to minimise the risk for relapse.

**When ribavirin is added to Harvoni, refer also to the Professional Information for Human Medicines of ribavirin.**

In adolescent patients aged 12 to < 18 years the following ribavirin dosing is recommended where ribavirin is divided into two daily doses and given with food:

**Table 3: Guidance for ribavirin dosing when administered with Harvoni to adolescents aged 12 to < 18 years.**

| Body weight kg | Ribavirin Dose* |
|---|---|
| < 47 | 15 mg/kg/day |
| 47-49 | 600 mg/day |
| 50-65 | 800 mg/day |
| 66-74 | 1000 mg/day |
| > or = 75 | 1200 mg/day |

* Ribavirin administered orally in two divided doses with food.

*Dose modification of ribavirin in adults taking 1,000-1,200 mg daily*

If Harvoni is used in combination with ribavirin and a patient has a serious adverse reaction potentially related to ribavirin, the ribavirin dose should be modified or discontinued, if appropriate, until the adverse reaction abates or decreases in severity. Table 4 provides guidelines for dose modifications and discontinuation based on the patient's haemoglobin concentration and cardiac status.

**Table 4: Ribavirin dose modification guideline for co-administration with Harvoni in adults**

| **Laboratory values** | **Reduce ribavirin dose to 600 mg/day if:** | **Discontinue ribavirin if:** |
|---|---|---|
| Haemoglobin in patients with no cardiac disease | < 10 g/dL | < 8.5 g/dL |
| Haemoglobin in patients with history of stable cardiac disease | ≥ 2 g/dL decrease in haemoglobin during any 4-week treatment period | < 12 g/dL despite 4 weeks at reduced dose |

Once ribavirin has been withheld due to either a laboratory abnormality or clinical manifestation, an attempt may be made to restart ribavirin at 600 mg daily and further increase the dose to 800 mg daily. However, it is not recommended that ribavirin be increased to the originally assigned dose (1,000 mg to 1,200 mg daily).

Addition of ribavirin to Harvoni is recommended for liver transplant recipients. It can also be considered for those treatment-experienced patients with compensated cirrhosis who are at high risk of clinical disease progression.

Harvoni in combination with ribavirin for 12 weeks is recommended.

**Concomitant Ribavirin Dose**

When Harvoni is used in combination with ribavirin, the daily dose of ribavirin is 1,000 mg for patients weighing <75 kg and 1,200 mg for those weighing ≥75 kg, except for patients with decompensated

cirrhosis who should receive 600 mg. Ribavirin is administered orally in two divided doses with food. Refer to ribavirin prescribing information for ribavirin dose modifications.

**Special populations**

*Paediatric population*

The safety and efficacy of Harvoni in paediatric patients aged <12 years have not yet been established. No data on paediatric patients aged < 12 years are available.

*Elderly*

No dose adjustment is warranted for elderly patients (see section 5.2).

*Renal Impairment*

No dose adjustment of Harvoni is required for patients with renal impairment, including end stage renal disease (ESRD) requiring dialysis (see section 5.2).

*Hepatic Impairment*

No dose adjustment of Harvoni is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B or C) (see section 5.2). Safety and efficacy of Harvoni have been established in adult patients with decompensated cirrhosis.

**Method of administration**

The film-coated tablet is for oral use. Patients should be instructed to swallow the tablet whole. The film-coated tablet should not be chewed or crushed, due to the bitter taste of the active substance (see section 4.5).

Patients should be instructed that if vomiting occurs within 5 hours of dosing an additional tablet should be taken. If vomiting occurs more than 5 hours after dosing, no further dose is needed.

If a dose is missed and it is within 18 hours of the normal time, patients should be instructed to take the tablet as soon as possible and then patients should take the next dose at the usual time. If it is after 18 hours then patients should be instructed to wait and take the next dose at the usual time. Patients should be instructed not to take a double dose.

## 4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

- Pregnancy and lactation with or without ribavirin
- Concomitant use of Harvoni and amiodarone (in patients with or without symptomatic bradydysrhythmias or patients with or without treatment with beta adrenergic blockers)
- Co-administration with rosuvastatin (see section 4.5).

Concomitant use with potent P-gp inducers

Medicines that are potent P glycoprotein (P-gp) inducers in the intestine (rifampicin, rifabutin, St. John's wort *[Hypericum perforatum]*, carbamazepine, phenobarbital and phenytoin). Co-administration will significantly decrease ledipasvir and sofosbuvir plasma concentrations and could result in loss of efficacy of Harvoni (see section 4.5).

The medical practitioner to consult the professional information of ribavirin for further contraindications.

## 4.4 Special warnings and precautions for use

Harvoni should not be administered concomitantly with other medicines containing sofosbuvir.

Symptomatic bradycardia when co-administered with amiodarone

Post-marketing cases of symptomatic bradycardia, as well as fatal cardiac arrest and cases requiring pacemaker intervention, have been reported when amiodarone is co-administered with Harvoni. Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with

co-administration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this effect is unknown.

Co-administration of amiodarone with Harvoni is contraindicated. Amiodarone should only be used in patients on treatment with Harvoni if no safer appropriate alternative is available, the alternative has failed or cannot be tolerated.

• Counsel patients about the risk of symptomatic bradycardia

• Cardiac monitoring in an in-patient setting for the first 48 hours of co-administration is recommended, after which outpatient or self-monitoring of the heart rate should occur daily for at least the first 2 weeks of treatment.

Patients who are taking Harvoni who need to start amiodarone therapy because no safer appropriate alternative is available, the alternative has failed or cannot be tolerated should undergo similar cardiac monitoring as outlined above.

Due to amiodarone's long half-life, patients discontinuing amiodarone just prior to starting Harvoni should also undergo similar cardiac monitoring as outlined above.

**Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately.** Symptoms may include near-fainting or fainting, dizziness or light-headedness, malaise, weakness, excessive tiredness, shortness of breath, chest pains, confusion or memory problems.

**Hepatitis B virus reactivation**

**Cases of hepatitis B virus (HBV) reactivation have been reported during treatment with HCV direct acting antivirals, including sofosbuvir-containing regimens. Reactivation may result in fulminating hepatitis, hepatic failure and death. HBV screening by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc), should be performed in all patients before initiation of treatment with Harvoni. HCV/HBV co-infected patients are at risk of HBV reactivation, and should therefore be monitored and managed according to current clinical guidelines.**

Co-administration with other direct-acting antivirals against HCV

In patients who fail treatment with Harvoni (ledipasvir/sofosbuvir), selection of NS5A resistance mutations that substantially reduce the susceptibility to ledipasvir is seen in most cases. Limited data indicate that such NS5A mutations do not revert on long-term follow-up.

Use with moderate P-gp inducers

Medicines that are moderate P-gp inducers in the intestine (e.g. oxcarbazepine) may decrease ledipasvir and sofosbuvir plasma concentrations leading to reduced therapeutic effect of Harvoni. Co-administration of such medicines is not recommended with Harvoni (see section 4.5).

Patients with decompensated cirrhosis and/or who are awaiting liver transplant or have received liver transplant

The efficacy of Harvoni in genotype 5 and genotype 6 HCV-infected patients with decompensated cirrhosis and/or who are awaiting liver transplant or post-liver transplant has not been investigated. The efficacy of Harvoni in liver transplant recipients and/or subjects with decompensated cirrhosis was evaluated in two open-label Phase 2 trials (SOLAR-1 and SOLAR-2) that enrolled 670 subjects with genotype 1 and 4 CHC post-liver transplant and/or with decompensated cirrhosis. Subjects in the two trials were treated with Harvoni + RBV for 12 or 24 weeks.

Use with HIV antiretroviral regimens

Harvoni has been shown to increase tenofovir exposure, especially when used together with an HIV regimen containing tenofovir disoproxil fumarate and a pharmacokinetic enhancer (ritonavir or cobicistat). The safety of tenofovir disoproxil fumarate in the setting of Harvoni and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration of Harvoni with the fixed-dose combination tablet containing elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate or tenofovir disoproxil fumarate given in conjunction with a boosted HIV protease inhibitor (e.g. atazanavir or darunavir) should be considered, particularly in patients at increased risk of renal dysfunction. Patients receiving Harvoni concomitantly with elvitegravir/cobicistat/emtricitabine/tenofovir

disoproxil fumarate or with tenofovir disoproxil fumarate and a boosted HIV protease inhibitor should be monitored for tenofovir-associated adverse reactions.

Refer to tenofovir disoproxil fumarate, emtricitabine/tenofovir disoproxil fumarate, or elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate Professional Information (PIs) for recommendations on renal monitoring.

Use with HMG-CoA reductase inhibitors

Co-administration of Harvoni and HMG-CoA reductase inhibitors (statins) can significantly increase the concentration of the statin, which increases the risk of myopathy and rhabdomyolysis see section 4.5).

Use in diabetic patients

Diabetics may experience improved glucose control, potentially resulting in symptomatic hypoglycaemia, after initiating HCV direct-acting antiviral treatment such as with Harvoni. Glucose levels of diabetic patients initiating direct-acting antiviral therapy should be closely monitored, particularly within the first 3 months, and their diabetic medication modified when necessary. The medical practitioner in charge of the diabetic care of the patient should be informed when direct-acting antiviral therapy is initiated.

**Paediatric population**

Harvoni is not recommended for use in paediatric patients aged <12 years of age because the safety and efficacy have not been established in this population.

Harvoni contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactose deficiency, glucose-galactose malabsorption or fructose intolerance should not take Harvoni.

## 4.5 Interaction with other medicines and other forms of interaction

As Harvoni contains ledipasvir and sofosbuvir, any interactions that have been identified with these active substances individually may occur with Harvoni.

Potential for Harvoni to affect other medicines

Ledipasvir is an *in vitro* inhibitor of drug transporter P-gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of co-administered substrates for these transporters. Ledipasvir is an inhibitor of transporters OATP1B1, OATP1B3, and BSEP at concentrations exceeding those when used as directed. Ledipasvir is not an inhibitor of transporters MRP2, MRP4, OCT2, OAT1, OAT3, MATE1, and OCT1. The drug-drug interaction potential of ledipasvir is primarily limited to the 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 drug transporters P-gp, BCRP, MRP2, BSEP, OATP1B1, OATP1B3, and OCT1, and GS-331007 is not an inhibitor of OAT1, OCT2, and MATE1.

Ledipasvir, sofosbuvir, and GS-331007 are not inhibitors or inducers of CYP or UGT1A1 enzymes.

Potential for other medicines to affect Harvoni

Ledipasvir and sofosbuvir are substrates of drug transporters P-gp and BCRP while GS-331007 is not. Medicines that are potent P-gp inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifampicin, rifabutin 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 section 4.3). Co-administration with medicines that inhibit P-gp and/or BCRP may increase sofosbuvir and ledipasvir plasma concentrations without increasing GS-331007 plasma concentration; Harvoni may be co-administered 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.

Patients treated with vitamin K antagonists

As liver function may change during treatment with ledipasvir and sofosbuvir, frequent monitoring of International Normalised Ratio (INR) values is recommended.

Impact of DAA therapy on drugs metabolised by the liver

The pharmacokinetics of drugs that are metabolised by the liver (e.g. immunosuppressive agents such as calcineurin inhibitors) may be impacted by changes in liver function during DAA therapy, related to clearance of HCV virus.

Interactions between Harvoni and other medicines

Table 5 provides a listing of established or potentially clinically significant interactions (where 90 % confidence interval [CI] of the geometric least-squares mean [GLSM] ratio were within "↔", extended above "↑", or extended below "↓" the predetermined equivalence boundaries). The interactions described are based on studies conducted with either ledipasvir/sofosbuvir or ledipasvir and sofosbuvir as individual agents, or are predicted interactions that may occur with ledipasvir/ sofosbuvir. The table is not all-inclusive.

**Table 5: Interactions between Harvoni and other medicines**

| **Medicine by therapeutic areas** | **Effects on medicine levels. Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b]** | **Recommendation concerning co-administration with Harvoni** |
|---|---|---|
| ***ACID REDUCING MEDICINES*** | | |
| | | Ledipasvir solubility decreases as pH increases. Medicines that increase gastric pH are expected to decrease concentration of ledipasvir. |
| *Antacids* | | |
| e.g. Aluminium or magnesium hydroxide; calcium carbonate | Interaction not studied.<br>*Expected:*<br>↓ Ledipasvir<br>↔ Sofosbuvir<br>↔ GS-331007<br><br>(Increase in gastric pH) | It is recommended to separate antacid and Harvoni administration by 4 hours. |

| **Medicine by therapeutic areas** | **Effects on medicine levels. Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b]** | **Recommendation concerning co-administration with Harvoni** |
|---|---|---|
| *$H_2$-receptor antagonists* | | |
| Famotidine (40 mg single dose)/ ledipasvir (90 mg single dose)[c]/ sofosbuvir (400 mg single dose)[c, d]<br><br>Famotidine dosed simultaneously with Harvoni[d]<br><br>Cimetidine[e]<br>Nizatidine[e]<br>Ranitidine[e] | Ledipasvir<br>↓ $C_{max}$ 0.80 (0.69, 0.93)<br>↔ AUC 0.89 (0.76, 1.06)<br><br>Sofosbuvir<br>↑ $C_{max}$ 1.15 (0.88, 1.50)<br>↔ AUC 1.11 (1.00, 1.24)<br><br>GS-331007<br>↔ $C_{max}$ 1.06 (0.97, 1.14)<br>↔ AUC 1.06 (1.02, 1.11)<br><br>(Increase in gastric pH) | $H_2$-receptor antagonists may be administered simultaneously with or staggered from Harvoni at a dose that does not exceed doses comparable to famotidine 40 mg twice daily. |
| Famotidine (40 mg single dose)/ ledipasvir (90 mg single dose)[c]/ sofosbuvir (400 mg single dose)[c, d] | Ledipasvir<br>↓ $C_{max}$ 0.83 (0.69, 1.00)<br>↔ AUC 0.98 (0.80, 1.20) | |

| **Medicine by therapeutic areas** | **Effects on medicine levels. Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b]** | **Recommendation concerning co-administration with Harvoni** |
|---|---|---|
| Famotidine dosed 12 hours prior to Harvoni[d] | Sofosbuvir<br>↔ $C_{max}$ 1.00 (0.76, 1.32)<br>↔ AUC 0.95 (0.82, 1.10)<br><br>GS-331007<br>↔ $C_{max}$ 1.13 (1.07, 1.20)<br>↔ AUC 1.06 (1.01, 1.12)<br><br>(Increase in gastric pH) | |
| *Proton pump inhibitors* | | |
| Omeprazole (20 mg once daily)/ ledipasvir (90 mg single dose)[c]/ sofosbuvir (400 mg single dose)[c]<br><br>Omeprazole dosed simultaneously with Harvoni | Ledipasvir<br>↓ $C_{max}$ 0.89 (0.61, 1.30)<br>↓ AUC 0.96 (0.66, 1.39)<br><br>Sofosbuvir<br>↔ $C_{max}$ 1.12 (0.88, 1.42)<br>↔ AUC 1.00 (0.80, 1.25)<br><br>GS-331007 | Proton pump inhibitor doses comparable to omeprazole 20 mg can be administered simultaneously with Harvoni. Proton pump inhibitors should not be taken before Harvoni. |

| **Medicine by therapeutic areas** | **Effects on medicine levels. Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b]** | **Recommendation concerning co-administration with Harvoni** |
|---|---|---|
| Lansoprazole[e]<br>Rabeprazole[e]<br>Pantoprazole[e]<br>Esomeprazole[e] | ↔ $C_{max}$ 1.14 (1.01, 1.29)<br>↔ AUC 1.03 (0.96, 1.12)<br><br>(Increase in gastric pH) | |

| **Medicine by therapeutic areas** | **Effects on medicine levels.**<br>**Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b]** | **Recommendation concerning co-administration with Harvoni** |
|---|---|---|
| ***ANTIDYSRHYTHMIC MEDICINES*** | | |
| Amiodarone | Interaction not studied. | **Use only if no other alternative is available.** Close monitoring is recommended if this medicine is administered with Harvoni. |
| Digoxin | Interaction not studied.<br>*Expected:*<br>↑ Digoxin<br>↔ Ledipasvir<br>↔ Sofosbuvir<br>↔ GS-331007<br><br>(Inhibition of P-gp) | Co-administration of Harvoni with digoxin may increase the concentration of digoxin. Caution is warranted and therapeutic concentration monitoring of digoxin is recommended when co-administered with Harvoni. |
| ***ANTICOAGULANTS*** | | |
| Dabigatran etexilate | Interaction not studied.<br>*Expected:*<br>↑ Dabigatran<br>↔ Ledipasvir<br>↔ Sofosbuvir<br>↔ GS-331007<br><br>(Inhibition of P-gp) | Clinical monitoring, looking for signs of bleeding and anaemia, is recommended when dabigatran etexilate is co-administered with Harvoni. A coagulation test helps to identify patients with an increased bleeding risk due to increased dabigatran exposure. |

| **Medicine by therapeutic areas** | **Effects on medicine levels.**<br>**Mean ratio (90 % confidence interval)**<br>**for AUC, $C_{max}$, $C_{min}$[a, b]** | **Recommendation concerning co-administration with Harvoni** |
|---|---|---|
| Vitamin K antagonists | Interaction not studied | Close monitoring of INR is recommended with all vitamin K antagonists. This is due to liver function changes during treatment with Harvoni. |
| ***ANTICONVULSANTS*** | | |
| Carbamazepine<br>Phenytoin<br>Phenobarbital | Interaction not studied.<br>*Expected:*<br>↓ Ledipasvir<br>↓ Sofosbuvir<br>↔ GS-331007<br>(Induction of P-gp) | Harvoni is contra-indicated with carbamazepine, phenobarbital and phenytoin, potent intestinal P-gp inducers (see section 4.3). |
| Oxcarbazepine | Interaction not studied<br>*Expected:*<br>↓ Ledipasvir<br>↓ Sofosbuvir<br>↔ GS-331007<br>(Induction of P-gp) | Co-administration of Harvoni with oxcarbazepine is expected to decrease the concentration of ledipasvir and sofosbuvir leading to reduced therapeutic effect of Harvoni. Such co-administration is not recommended (see section 4.4). |

| Medicine by therapeutic areas | Effects on medicine levels.<br>Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b] | Recommendation concerning co-administration with Harvoni |
|---|---|---|
| ***ANTIMYCOBACTERIALS*** | | |
| Rifampicin (600 mg once daily)/ ledipasvir (90 mg single dose)[d] | Interaction not studied.<br>*Expected:*<br>Rifampicin<br>↔ $C_{max}$<br>↔ AUC<br>↔ $C_{min}$<br><br>*Observed:*<br>Ledipasvir<br>↓ $C_{max}$ 0.65 (0.56, 0.76)<br>↓ AUC 0.41 (0.36, 0.48)<br><br>(Induction of P-gp) | Harvoni is contra-indicated with rifampicin, a potent intestinal P-gp inducer (see section 4.3). |
| Rifampicin (600 mg once daily)/ sofosbuvir (400 mg single dose)[d] | Interaction not studied.<br>*Expected:*<br>Rifampicin<br>↔ $C_{max}$<br>↔ AUC<br>↔ $C_{min}$<br>*Observed:*<br>Sofosbuvir | |

| Medicine by therapeutic areas | Effects on medicine levels. Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b] | Recommendation concerning co-administration with Harvoni |
|---|---|---|
| | ↓ $C_{max}$ 0.23 (0.19, 0.29)<br>↓ AUC 0.28 (0.24, 0.32)<br>GS-331007<br>↔ $C_{max}$ 1.23 (1.14, 1.34)<br>↔ AUC 0.95 (0.88, 1.03)<br>(Induction of P-gp) | |
| Rifabutin<br>Rifapentine | Interaction not studied.<br>*Expected:*<br>↓ Sofosbuvir<br>↓ Ledipasvir<br>↔ GS-331007<br>(Induction of P-gp) | Harvoni is contra-indicated with rifabutin, a potent intestinal P-gp inducer (see section 4.3).<br>Co-administration of Harvoni with rifapentine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of Harvoni. Such co-administration is not recommended. |
| ***SEDATIVES/HYPNOTICS*** | | |
| Midazolam (2.5 mg single dose)/ ledipasvir (90 mg single dose)<br><br>Ledipasvir (90 mg once | Observed:<br>Midazolam<br>↔ Cmax 1.07 (1.00, 1.14)<br>↔ AUC 0.99 (0.95, 1.04) | No dose adjustment of Harvoni or midazolam is required. |

| Medicine by therapeutic areas | Effects on medicine levels. Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b] | Recommendation concerning co-administration with Harvoni |
|---|---|---|
| daily) | (Inhibition of CYP3A)<br>Midazolam<br>↔ Cmax 0.95 (0.87, 1.04)<br>↔ AUC 0.89 (0.84, 0.95)<br>(Induction of CYP3A)<br>Expected:<br>↔ Sofosbuvir<br>↔ GS-331007 | |
| ***HCV MEDICINES*** | | |
| Simeprevir (150 mg once daily)/ ledipasvir (30 mg once daily) | Simeprevir<br>↑ $C_{max}$ 2.61 (2.39, 2.86)<br>↑ AUC 2.69 (2.44, 2.96)<br><br>Ledipasvir<br>↑ $C_{max}$ 1.81 (1.69, 2.94)<br>↑ AUC 1.92 (1.77, 2.07) | Concentrations of ledipasvir, sofosbuvir and simeprevir are increased when simeprevir is co-administered with Harvoni.<br>Co-administration is not recommended. |
| Simeprevir [h] | Simeprevir<br>↔ $C_{max}$ 0.96 (0.71, 1.30)<br>↔ AUC 0.94 (0.67, 1.33) | |

| Medicine by therapeutic areas | Effects on medicine levels. Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b] | Recommendation concerning co-administration with Harvoni |
|---|---|---|
| | Sofosbuvir<br>↑ $C_{max}$ 1.91 (1.26, 2.90)<br>↑ AUC 3.16 (2.25, 4.44)<br><br>GS-331007<br>↓ $C_{max}$ 0.69 (0.52, 0.93)<br>↔ AUC 1.09 (0.87, 1.37) | |
| ***HIV ANTIVIRAL MEDICINES: REVERSE TRANSCIPTASE INHIBITORS*** | | |
| Efavirenz/ emtricitabine/ tenofovir disoproxil fumarate (600 mg/ 200 mg/ 300 mg/ once daily)/ ledipasvir (90 mg once daily)[c]/ sofosbuvir (400 mg once daily)[c, d] | Efavirenz<br>↔ $C_{max}$ 0.87 (0.79, 0.97)<br>↔ AUC 0.90 (0.84,0.96)<br>↔ $C_{min}$ 0.91 (0.83, 0.99)<br>Emtricitabine<br>↔ $C_{max}$ 1.08 (0.97, 1.21)<br>↔ AUC 1.05 (0.98,1.11)<br>↔ $C_{min}$ 1.04 (0.98, 1.11)<br>Tenofovir<br>↑ $C_{max}$ 1.79 (1.56, 2.04)<br>↑ AUC 1.98 (1.77, 2.23)<br>↑ $C_{min}$ 2.63 (2.32, 2.97) | No dose adjustment of Harvoni or efavirenz/ emtricitabine/ tenofovir disoproxil fumarate is required. |

| Medicine by therapeutic areas | Effects on medicine levels. Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b] | Recommendation concerning co-administration with Harvoni |
|---|---|---|
| | Ledipasvir<br>↓ $C_{max}$ 0.66 (0.59, 0.75)<br>↓ AUC 0.66 (0.59, 0.75)<br>↓ $C_{min}$ 0.66 (0.57, 0.76)<br>Sofosbuvir<br>↔ $C_{max}$ 1.03 (0.87, 1.23)<br>↔ AUC 0.94 (0.81,1.10)<br>GS-331007<br>↔ $C_{max}$ 0.86 (0.76, 0.96)<br>↔ AUC 0.90 (0.83, .97)<br>↔ $C_{min}$ 1.07 (1.02, 1.13) | |
| Emtricitabine/ rilpivirine/ tenofovir disoproxil fumarate (200 mg/ 25 mg/ 300 mg once daily)/ ledipasvir (90 mg once daily)[c]/ sofosbuvir (400 mg once daily)[c, d] | Emtricitabine<br>↔ $C_{max}$ 1.02 (0.98, 1.06)<br>↔ AUC 1.05 (1.02,1.08)<br>↔ $C_{min}$ 1.06 (0.97, 1.15)<br>Rilpivirine<br>↔ $C_{max}$ 0.97 (0.88, 1.07)<br>↔ AUC 1.02 (0.94,1.11)<br>↔ $C_{min}$ 1.12 (1.03, 1.21)<br>Tenofovir<br>↔ $C_{max}$ 1.32 (1.25, 1.39)<br>↑ AUC 1.40 (1.31, 1.50)<br>↑ $C_{min}$ 1.91 (1.74, 2.10) | No dose adjustment of Harvoni or emtricitabine/ rilpivirine/ tenofovir disoproxil fumarate is required. |

| Medicine by therapeutic areas | Effects on medicine levels. Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b] | Recommendation concerning co-administration with Harvoni |
|---|---|---|
| | Ledipasvir<br>↔ $C_{max}$ 1.01 (0.95, 1.07)<br>↔ AUC 1.08 (1.02,1.15)<br>↔ $C_{min}$ 1.16 (1.08, 1.25)<br>Sofosbuvir<br>↔ $C_{max}$ 1.05 (0.93, 1.20)<br>↔ AUC 1.10 (1.01,1.21)<br>GS-331007<br>↔ $C_{max}$ 1.06 (1.01, 1.11)<br>↔ AUC 1.15 (1.11, 1.19)<br>↔ $C_{min}$ 1.18 (1.13, 1.24) | |
| Abacavir/ lamivudine (600 mg/ 300 mg once daily)/ ledipasvir (90 mg once daily)[c]/ sofosbuvir (400 mg once daily)[c, d] | Abacavir<br>↔ $C_{max}$ 0.92 (0.87, 0.97)<br>↔ AUC 0.90 (0.85,0.94)<br>Lamivudine<br>↔ $C_{max}$ 0.93 (0.87, 1.00)<br>↔ AUC 0.94 (0.90,0.98)<br>↔ $C_{min}$ 1.12 (1.05, 1.20)<br>Ledipasvir<br>↔ $C_{max}$ 1.10 (1.01, 1.19)<br>↔ AUC 1.18 (1.10,1.28)<br>↔ $C_{min}$ 1.26 (1.17, 1.36) | No dose adjustment of Harvoni or abacavir/ lamivudine is required. |

| Medicine by therapeutic areas | Effects on medicine levels. Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b] | Recommendation concerning co-administration with Harvoni |
|---|---|---|
| | Sofosbuvir<br>↔ $C_{max}$ 1.08 (0.85, 1.35)<br>↔ AUC 1.21 (1.09,1.35)<br>GS-331007<br>↔ $C_{max}$ 1.00 (0.94, 1.07)<br>↔ AUC 1.05 (1.01,1.09)<br>↔ $C_{min}$ 1.08 (1.01, 1.14) | |

| Medicine by therapeutic areas | Effects on medicine levels. Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b] | Recommendation concerning co-administration with Harvoni |
|---|---|---|
| ***HIV ANTIVIRAL MEDICINES: HIV PROTEASE INHIBITORS*** | | |
| Atazanavir boosted with ritonavir (300 mg/ 100 mg once daily)/ ledipasvir (90 mg once daily)[c]/ sofosbuvir (400 mg once daily)[c, d] | Atazanavir<br>↔ $C_{max}$ 1.07 (1.00, 1.15)<br>↔ AUC 1.33 (1.25, 1.42)<br>↑ $C_{min}$ 1.75 (1.58, 1.93)<br>Ledipasvir<br>↑ $C_{max}$ 1.98 (1.78, 2.20)<br>↑ AUC 2.13 (1.89, 2.40)<br>↑ $C_{min}$ 2.36 (2.08, 2.67)<br>Sofosbuvir<br>↔ $C_{max}$ 0.96 (0.88, 1.05)<br>↔ AUC 1.08 (1.02, 1.15)<br>GS-331007<br>↔ $C_{max}$ 1.13 (1.08, 1.19)<br>↔ AUC 1.23 (1.18,1.29)<br>↔ $C_{min}$ 1.28 (1.21, 1.36) | No dose adjustment of Harvoni or atazanavir (ritonavir boosted) is required.<br><br>For the combination of tenofovir/emtricitabine + atazanavir/ritonavir, please see below. |
| Atazanavir boosted with ritonavir (300 mg/ 100 mg once daily) | Atazanavir<br>↔ $C_{max}$ 1.07 (0.99, 1.14)<br>↔ AUC 1.27 (1.18,1.37)<br>↑ $C_{min}$ 1.63 (1.45, 1.84) | When given with tenofovir disoproxil fumarate used in conjunction with atazanavir/ritonavir, Harvoni increased the concentration of tenofovir. |

| Medicine by therapeutic areas | Effects on medicine levels. Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b] | Recommendation concerning co-administration with Harvoni |
|---|---|---|
| + emtricitabine/ tenofovir disoproxil fumarate (200 mg/ 300 mg once daily)/ ledipasvir (90 mg once daily)[c]/ sofosbuvir (400 mg once daily)[c, d]<br><br>Dosed simultaneously[f] | Ritonavir<br>↔ $C_{max}$ 0.86 (0.79, 0.93)<br>↔ AUC 0.97 (0.89,1.05)<br>↑ $C_{min}$ 1.45 (1.27, 1.64)<br>Emtricitabine<br>↔ $C_{max}$ 0.98 (0.94, 1.02)<br>↔ AUC 1.00 (0.97,1.04)<br>↔ $C_{min}$ 1.04 (0.96, 1.12)<br>Tenofovir<br>↑ $C_{max}$ 1.47 (1.37, 1.58)<br>↔ AUC 1.35 (1.29,1.42)<br>↑ $C_{min}$ 1.47 (1.38, 1.57)<br>Ledipasvir<br>↑ $C_{max}$ 1.68 (1.54, 1.84)<br>↑ AUC 1.96 (1.74, 2.21)<br>↑ $C_{min}$ 2.18 (1.91, 2.50)<br>Sofosbuvir<br>↔ $C_{max}$ 1.01 (0.88, 1.15)<br>↔ AUC 1.11 (1.02,1.21)<br>↑ $C_{min}$ 1.42 (1.34, 1.49) | The safety of tenofovir disoproxil fumarate in the setting of Harvoni and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established.<br><br>The combination should be used with caution with frequent renal monitoring, if other alternatives are not available.<br><br>Atazanavir concentrations are also increased, with a risk for an increase in bilirubin levels/icterus. That risk is even higher if ribavirin is used as part of the HCV treatment. |
| | GS-331007<br>↔ Cmax 1.17 (1.12, 1.23) | |

| Medicine by therapeutic areas | Effects on medicine levels.<br>Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b] | Recommendation concerning co-administration with Harvoni |
|---|---|---|
| | ↔ AUC 1.31 (1.25, 1.36)<br>↑ Cmin 1.42 (1.34, 1.49) | |

| Medicine by therapeutic areas | Effects on medicine levels. Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b] | Recommendation concerning co-administration with Harvoni |
|---|---|---|
| Darunavir boosted with ritonavir (800 mg/ 100 mg once daily)/ ledipasvir (90 mg once daily)[d] | Darunavir<br>↔ $C_{max}$ 1.02 (0.88, 1.19)<br>↔ AUC 0.96 (0.84, 1.11)<br>↔ $C_{min}$ 0.97 (0.86, 1.10)<br><br>Ledipasvir<br>↑ $C_{max}$ 1.45 (1.34, 1.56)<br>↑ AUC 1.39 (1.28, 1.49)<br>↑ $C_{min}$ 1.39 (1.29, 1.51) | No dose adjustment of Harvoni or darunavir (ritonavir boosted) is required.<br><br>For the combination of tenofovir/emtricitabine + darunavir/ritonavir, please see below. |
| Darunavir boosted with ritonavir (800 mg/ 100 mg once daily)/ sofosbuvir (400 mg once daily) | Darunavir<br>↔ $C_{max}$ 0.97 (0.94, 1.01)<br>↔ AUC 0.97 (0.94, 1.00)<br>↔ $C_{min}$ 0.86 (0.78, 0.96)<br><br>Sofosbuvir<br>↑ $C_{max}$ 1.45 (1.10, 1.92)<br>↑ AUC 1.34 (1.12, 1.59)<br><br>GS-331007<br>↔ $C_{max}$ 0.97 (0.90, 1.05) | |

| Medicine by therapeutic areas | Effects on medicine levels. Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b] | Recommendation concerning co-administration with Harvoni |
|---|---|---|
| | ↔ AUC 1.24 (1.18, 1.30) | |

| Medicine by therapeutic areas | Effects on medicine levels.<br>Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b] | Recommendation concerning co-administration with Harvoni |
|---|---|---|
| Darunavir boosted with ritonavir (800 mg/ 100 mg once daily)<br>+ emtricitabine/ tenofovir disoproxil fumarate (200 mg/ 300 mg once daily)/ ledipasvir (90 mg once daily)[c]/ sofosbuvir (400 mg once daily)[c, d]<br><br>Dosed simultaneously[f] | Darunavir<br>↔ $C_{max}$ 1.01 (0.96, 1.06)<br>↔ AUC 1.04 (0.99, 1.08)<br>↔ $C_{min}$ 1.08 (0.98, 1.20)<br>Ritonavir<br>↔ $C_{max}$ 1.17 (1.01, 1.35)<br>↔ AUC 1.25 (1.15, 1.36)<br>↑ $C_{min}$ 1.48 (1.34, 1.63)<br>Emtricitabine<br>↔ $C_{max}$ 1.02 (0.96, 1.08)<br>↔ AUC 1.04 (1.00, 1.08)<br>↔ $C_{min}$ 1.03 (0.97, 1.10)<br>Tenofovir<br>↑ $C_{max}$ 1.64 (1.54, 1.74)<br>↑ AUC 1.50 (1.42, 1.59)<br>↑ $C_{min}$ 1.59 (1.49, 1.70)<br>Ledipasvir<br>↔ $C_{max}$ 1.11 (0.99, 1.24)<br>↔ AUC 1.12 (1.00, 1.25)<br>↔ $C_{min}$ 1.17 (1.04, 1.31)<br>Sofosbuvir<br>↓ $C_{max}$ 0.63 (0.52, 0.75)<br>↓ AUC 0.73 (0.65, 0.82)<br>GS-331007<br>↔ $C_{max}$ 1.10 (1.04, 1.16) | When given with darunavir/ritonavir used in conjunction with tenofovir disoproxil fumarate, Harvoni increased the concentration of tenofovir.<br><br>The safety of tenofovir disoproxil fumarate in the setting of Harvoni and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established.<br><br>The combination should be used with caution with frequent renal monitoring, if other alternatives are not available. |

| Medicine by therapeutic areas | Effects on medicine levels. Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b] | Recommendation concerning co-administration with Harvoni |
|---|---|---|
| | ↔ AUC 1.20 (1.16, 1.24)<br>↔ $C_{min}$ 1.26 (1.20, 1.32) | |

| **Medicine by therapeutic areas** | **Effects on medicine levels.**<br>**Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b]** | **Recommendation concerning co-administration with Harvoni** |
|---|---|---|
| Lopinavir boosted with ritonavir + emtricitabine/ tenofovir disoproxil fumarate | Interaction not studied.<br>*Expected:*<br>↑ Lopinavir<br>↑ Ritonavir<br><br>↔ Emtricitabine<br>↑ Tenofovir<br><br>↑ Ledipasvir<br>↔ Sofosbuvir<br>↔ GS-331007 | When given with lopinavir/ritonavir used in conjunction with tenofovir disoproxil fumarate, Harvoni is expected to increase the concentration of tenofovir.<br><br>The safety of tenofovir disoproxil fumarate in the setting of Harvoni and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established.<br><br>The combination should be used with caution with frequent renal monitoring, if other alternatives are not available (see section 4.4). |
| Tipranavir boosted with ritonavir | Interaction not studied.<br>*Expected:*<br>↓ Ledipasvir<br>↓ Sofosbuvir<br>↔ GS-331007<br><br>(Induction of P-gp) | Co-administration of Harvoni with tipranavir (ritonavir boosted) is expected to decrease the concentration of ledipasvir, leading to reduced therapeutic effect of Harvoni.<br>Co-administration is not recommended. |

| Medicine by therapeutic areas | Effects on medicine levels. Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b] | Recommendation concerning co-administration with Harvoni |
|---|---|---|
| ***HIV ANTIVIRAL MEDICINES: INTEGRASE INHIBITORS*** | | |
| Raltegravir (400 mg twice daily)/ ledipasvir (90 mg once daily)[d] | Raltegravir<br>↓ $C_{max}$ 0.82 (0.66, 1.02)<br>↔ AUC 0.85 (0.70, 1.02)<br>↑ $C_{min}$ 1.15 (0.90, 1.46)<br><br>Ledipasvir<br>↔ $C_{max}$ 0.92 (0.85, 1.00)<br>↔ AUC 0.91 (0.84, 1.00)<br>↔ $C_{min}$ 0.89 (0.81, 0.98) | No dose adjustment of Harvoni or raltegravir is required. |
| Raltegravir (400 mg twice daily)/ sofosbuvir (400 mg once daily)[d] | Raltegravir<br>↓ $C_{max}$ 0.57 (0.44, 0.75)<br>↓ AUC 0.73 (0.59, 0.91)<br>↔ $C_{min}$ 0.95 (0.81, 1.12)<br><br>Sofosbuvir<br>↔ $C_{max}$ 0.87 (0.71, 1.08)<br>↔ AUC 0.95 (0.82, 1.09) | |

| **Medicine by therapeutic areas** | **Effects on medicine levels.**<br>**Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b]** | **Recommendation concerning co-administration with Harvoni** |
|---|---|---|
| | GS-331007<br>↔ $C_{max}$ 1.09 (0.99, 1.19)<br>↔ AUC 1.02 (0.97, 1.08) | |
| Elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil fumarate (150 mg/ 150 mg/ 200 mg/ 300 mg once daily)/ ledipasvir (90 mg once daily)[c]/ sofosbuvir (400 mg once daily)[c] | Interaction not studied.<br>*Expected:*<br>↔ Emtricitabine<br>↑ Tenofovir<br><br>*Observed:*<br>Elvitegravir<br>↔ $C_{max}$ 0.88 (0.82, 0.95)<br>↔ AUC 1.02 (0.95, 1.09)<br>↑ $C_{min}$ 1.36 (1.23, 1.49)<br><br>Cobicistat<br>↔ $C_{max}$ 1.25 (1.18, 1.32)<br>↑ AUC 1.59 (1.49, 1.70)<br>↑ $C_{min}$ 4.25 (3.47, 5.22)<br><br>Ledipasvir<br>↑ $C_{max}$ 1.63 (1.51, 1.75)<br>↑ AUC 1.78 (1.64, 1.94)<br>↑ $C_{min}$ 1.91 (1.76, 2.08)<br><br>Sofosbuvir<br>↑ $C_{max}$ 1.33 (1.14, 1.56)<br>↑ AUC 1.36 (1.21, 1.52) | When given with elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil fumarate, Harvoni is expected to increase the concentration of tenofovir.<br><br>The safety of tenofovir disoproxil fumarate in the setting of Harvoni and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established.<br><br>The combination should be used with caution with frequent renal monitoring, if other alternatives are not available (see section 4.4). |

| Medicine by therapeutic areas | Effects on medicine levels. Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b] | Recommendation concerning co-administration with Harvoni |
|---|---|---|
| | GS-331007<br>↑ $C_{max}$ 1.33 (1.22, 1.44)<br>↑ AUC 1.44 (1.41, 1.48)<br>↑ $C_{min}$ 1.53 (1.47, 1.59) | |

| **Medicine by therapeutic areas** | **Effects on medicine levels. Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b]** | **Recommendation concerning co-administration with Harvoni** |
|---|---|---|
| Dolutegravir | Interaction not studied.<br>*Expected:*<br>↔ Dolutegravir<br>↔ Ledipasvir<br>↔ Sofosbuvir<br>↔ GS-331007 | No dose adjustment required. |
| ***HERBAL SUPPLEMENTS*** | | |
| St. John's wort | Interaction not studied.<br>*Expected:*<br>↓ Ledipasvir<br>↓ Sofosbuvir<br>↔ GS-331007<br><br>(Induction of P-gp) | Harvoni is contraindicated with St. John's wort, a potent P-gp inducer (see section 4.3). |
| ***HMG-CoA REDUCTASE INHIBITORS*** | | |
| Rosuvastatin[g] | ↑ Rosuvastatin<br><br>(Inhibition of drug transporters OATP and BCRP) | Co-administration of Harvoni with rosuvastatin may significantly increase the concentration of rosuvastatin (several fold-increase in AUC) which is associated with increased risk of myopathy, including rhabdomyolysis.<br>Co-administration of Harvoni with rosuvastatin is contra-indicated (see section 4.3). |

| Medicine by therapeutic areas | Effects on medicine levels. Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b] | Recommendation concerning co-administration with Harvoni |
|---|---|---|
| Pravastatin[g] | ↑ Pravastatin | Co-administration of Harvoni with pravastatin may significantly increase the concentration of pravastatin which is associated with increased risk of myopathy. Clinical and biochemical control is recommended in these patients and a dose adjustment may be needed (see section 4.4). |
| Other statins | *Expected:* ↑ Statins | Interactions cannot be excluded with other HMG-CoA reductase inhibitors. When co-administered with Harvoni, a reduced dose of statins should be considered and careful monitoring for statin adverse reactions should be undertaken (see section 4.4). |
| ***NARCOTIC ANALGESICS*** | | |
| Methadone | Interaction not studied. *Expected:* ↔ Ledipasvir | No dose adjustment of Harvoni or methadone is required. |
| Methadone (Methadone maintenance therapy [30 to 130 mg/daily])/ sofosbuvir (400 mg once daily)[d] | R-methadone ↔ $C_{max}$ 0.99 (0.85, 1.16) ↔ AUC 1.01 (0.85, 1.21) ↔ $C_{min}$ 0.94 (0.77, 1.14) | |

| Medicine by therapeutic areas | Effects on medicine levels. Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b] | Recommendation concerning co-administration with Harvoni |
|---|---|---|
| | S-methadone<br>↔ $C_{max}$ 0.95 (0.79, 1.13)<br>↔ AUC 0.95 (0.77, 1.17)<br>↔ $C_{min}$ 0.95 (0.74, 1.22)<br><br>Sofosbuvir<br>↓ $C_{max}$ 0.95 (0.68, 1.33)<br>↑ AUC 1.30 (1.00, 1.69)<br><br>GS-331007<br>↓ $C_{max}$ 0.73 (0.65, 0.83)<br>↔ AUC 1.04 (0.89, 1.22) | |
| ***IMMUNOSUPPRESSANTS*** | | |
| Ciclosporin[g] | Interaction not studied.<br>*Expected:*<br>↑ Ledipasvir<br>↔ Ciclosporin | No dose adjustment of Harvoni or ciclosporin is required at initiation of co-administration. Afterwards, close monitoring and potential dose adjustment of ciclosporin may be required. |
| Ciclosporin | Ciclosporin<br>↔ $C_{max}$ 1.06 (0.94, 1.18) | |

| **Medicine by therapeutic areas** | **Effects on medicine levels.**<br>**Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b]** | **Recommendation concerning co-administration with Harvoni** |
|---|---|---|
| (600 mg single dose)/ sofosbuvir (400 mg single dose)[h] | ↔ AUC 0.98 (0.85, 1.14)<br><br>Sofosbuvir<br>↑ $C_{max}$ 2.54 (1.87, 3.45)<br>↑ AUC 4.53 (3.26, 6.30)<br><br>GS-331007<br>↓ $C_{max}$ 0.60 (0.53, 0.69)<br>↔ AUC 1.04 (0.90, 1.20) | |
| Tacrolimus | Interaction not studied.<br>*Expected:*<br>↔ Ledipasvir | No dose adjustment of Harvoni or tacrolimus is required at initiation of co-administration. Afterwards, close monitoring and potential Dose adjustment of tacrolimus may be required. |
| Tacrolimus<br>(5 mg single dose)/ sofosbuvir (400 mg single dose)[h] | Tacrolimus<br>↓ $C_{max}$ 0.73 (0.59, 0.90)<br>↑ AUC 1.09 (0.84, 1.40)<br><br>Sofosbuvir<br>↓ $C_{max}$ 0.97 (0.65, 1.43)<br>↑ AUC 1.13 (0.81, 1.57) | |

| Medicine by therapeutic areas | Effects on medicine levels. Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b] | Recommendation concerning co-administration with Harvoni |
|---|---|---|
| | GS-331007<br>↔ $C_{max}$ 0.97 (0.83, 1.14)<br>↔ AUC 1.00 (0.87, 1.13) | |
| ***ORAL CONTRACEPTIVES*** | | |
| Norgestimate/ ethinyl estradiol (norgestimate 0.180 mg/ 0.215 mg/ 0.25 mg/ ethinyl estradiol 0.025 mg)/ ledipasvir (90 mg once daily)[d] | Norelgestromin<br>↔ $C_{max}$ 1.02 (0.89, 1.16)<br>↔ AUC 1.03 (0.90, 1.18)<br>↔ $C_{min}$ 1.09 (0.91, 1.31)<br><br>Norgestrel<br>↔ $C_{max}$ 1.03 (0.87, 1.23)<br>↔ AUC 0.99 (0.82, 1.20)<br>↔ $C_{min}$ 1.00 (0.81, 1.23)<br><br>Ethinyl estradiol<br>↑ $C_{max}$ 1.40 (1.18, 1.66)<br>↔ AUC 1.20 (1.04, 1.39)<br>↔ $C_{min}$ 0.98 (0.79, 1.22) | No dose adjustment of oral contraceptives is required. |

| **Medicine by therapeutic areas** | **Effects on medicine levels. Mean ratio (90 % confidence interval) for AUC, $C_{max}$, $C_{min}$[a, b]** | **Recommendation concerning co-administration with Harvoni** |
|---|---|---|
| Norgestimate/ ethinyl estradiol (norgestimate 0.180 mg/ 0.215 mg/ 0.25 mg/ ethinyl estradiol 0.025 mg)/ sofosbuvir (400 mg once daily)[d] | Norelgestromin<br>↔ $C_{max}$ 1.07 (0.94, 1.22)<br>↔ AUC 1.06 (0.92, 1.21)<br>↔ $C_{min}$ 1.07 (0.89, 1.28)<br><br>Norgestrel<br>↔ $C_{max}$ 1.18 (0.99, 1.41)<br>↑ AUC 1.19 (0.98, 1.45)<br>↑ $C_{min}$ 1.23 (1.00, 1.51)<br><br>Ethinyl estradiol<br>↔ $C_{max}$ 1.15 (0.97, 1.36)<br>↔ AUC 1.09 (0.94, 1.26)<br>↔ $C_{min}$ 0.99 (0.80, 1.23) | |

a. Mean ratio (90 % CI) of co-administered drug pharmacokinetics of study medicinal products alone or in combination. No effect = 1.00.

b. All interaction studies conducted in healthy volunteers.

c. Administered as Harvoni.

d. Lack of pharmacokinetics interaction bounds 70-143 %.

e. These are drugs within class where similar interactions could be predicted.

f. Staggered administration (12 hours apart) of atazanavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate or darunavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate and Harvoni provided similar results.

g. This study was conducted in the presence of another two direct-acting antiviral agents.

h. Bioequivalence/Equivalence boundary 80-125 %.

Medicines without Clinically Significant Interactions with Harvoni

Based on medicine interaction studies conducted with the components of Harvoni (ledipasvir or sofosbuvir) or Harvoni, no clinically significant medicines interactions have been either observed or are expected when Harvoni is combined with the following medicines : abacavir, atazanavir/ritonavir, carbamazepine, cyclosporine, darunavir/ritonavir, dolutegravir, efavirenz, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, emtricitabine, lamivudine, methadone, midazolam, oral contraceptives, oxcarbazepine, pravastatin, raltegravir, rilpivirine, tacrolimus, or verapamil.

## 4.6 Fertility, pregnancy and lactation

**Safety and/or efficacy has not been established (see section 4.3).**

**Women of childbearing potential / contraception in males and females**

Harvoni in combination with ribavirin must not be used in pregnancy. When Harvoni is used in combination with ribavirin, extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Women of childbearing potential or their male partners must use an effective form of contraception during treatment and for 6 months after the treatment has concluded as recommended in the Professional Information for ribavirin

Refer to the Professional Information for Human Medicines for ribavirin for additional information.

**Pregnancy**

Harvoni should not be used during pregnancy.

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of ledipasvir, sofosbuvir or Harvoni in pregnant women.

Animal studies do not indicate direct harmful effects with respect to reproductive toxicity. No significant effects on foetal development have been observed with ledipasvir or sofosbuvir in rats and rabbits. However, it has not been possible to fully estimate exposure margins achieved for sofosbuvir in the rat relative to the exposure in humans at the recommended clinical dose.

**Breastfeeding**

It is unknown whether ledipasvir or sofosbuvir and its metabolites are excreted in human milk.

Available pharmacokinetic data in animals has shown excretion of ledipasvir and metabolites of sofosbuvir in milk.

A risk to the newborns/infants cannot be excluded. **Therefore, women on treatment with Harvoni should not breastfeed their babies.**

**Fertility**

No human data on the effect of Harvoni on fertility are available. Animal studies do not indicate harmful effects of ledipasvir or sofosbuvir on fertility.

**If ribavirin is co administered with Harvoni, the contra-indications regarding use of ribavirin during pregnancy and breast-feeding apply (see also the Professional Information for Human Medicines for ribavirin).**

## 4.7 Effects on ability to drive and use machines

Harvoni may affect the ability to drive and use machines.

Patients should not drive or use machines until they know how Harvoni affects them.

Headache, fatigue and other side effects may impair the patient's ability to drive or use machines.

## 4.8 Undesirable effects

Summary of the safety profile

The safety assessment of Harvoni is based on pooled data from three Phase 3 clinical studies including 215, 539 and 326 patients who received Harvoni for 8, 12 and 24 weeks, respectively; and 216, 328 and 328 patients who received Harvoni + ribavirin combination therapy for 8, 12 and 24 weeks, respectively. These studies did not include any control group not receiving Harvoni. Further data include a double-blind comparison of the safety of Harvoni (12 weeks) and placebo in 155 cirrhotic patients.

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; and < 1 %, 0 %, and 2 % for patients receiving Harvoni + ribavirin combination therapy for 8, 12 and 24 weeks, respectively.

In clinical studies, fatigue, headache, and nausea were the most common (incidence ≥10 %) treatment emergent adverse events reported in subjects treated with 8 or 12 weeks of Harvoni. The type of treatment emergent adverse events observed during 24 weeks of treatment with Harvoni was consistent

with those observed during 8 or 12 weeks of treatment but the frequency of adverse events is generally higher in the 24 week treatment group than the 8 or 12 week treatment groups.

When Harvoni was studied with ribavirin, the most frequent adverse drug reactions to the Harvoni and ribavirin combination therapy were consistent with the known safety profile of ribavirin, without increasing the frequency or severity of the expected adverse drug reactions.

No adverse drug reactions specific to Harvoni were identified from the clinical trials conducted in subjects with genotype 2, 3, 4, 5, or 6 CHC.

The following adverse drug reactions have been identified with Harvoni (Table 6). The adverse reactions are listed below by body system organ class and frequency. Frequencies are defined as follows: very common (≥ 1/10) and common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) or very rare (< 1/10,000).

**Table 6: Adverse drug reactions identified with Harvoni**

| **Frequency** | **Adverse drug reaction** |
|---|---|
| ***Nervous system disorders:*** | |
| Very common | headache |
| ***Skin and subcutaneous tissue disorders:*** | |
| Common | rash |
| Not known | angioedema |
| ***General disorders:*** | |
| Very common | fatigue |

Other special population(s)

Liver transplant recipients and/or Subjects with decompensated Cirrhosis

No adverse drug reactions specific to Harvoni were identified from two open-label trials (SOLAR-1 and SOLAR-2) in which liver transplant recipients and/or subjects with decompensated cirrhosis received Harvoni with ribavirin for 12 or 24 weeks (N=670). The adverse events observed were consistent with expected clinical sequelae of liver transplantation and/or decompensated liver disease, or the known toxicity profile of ribavirin.

Decreases in hemoglobin to < 10 mg/dL and < 8,5 mg/dL during treatment were experienced by 39 % and 13 % of subjects treated with Harvoni and ribavirin, respectively. Ribavirin was discontinued in 15 % of the subjects.

Due to improved organ function, 7 % of liver transplant recipients had a dose modification of their immunosuppressive medicines.

Subjects with severe renal impairment

No adverse reactions specific to Harvoni were identified from an open-label trial (Study GS-US-334-0154) in which subjects with genotype 1 CHC and severe renal impairment received Harvoni for 12 weeks (N=18). The adverse events observed were consistent with expected clinical sequelae of severe renal impairment.

No adverse reactions specific to Harvoni were identified from an open-label clinical trial (Study GS-US-337-4063) in which a total of 95 subjects with genotype 1, 2, 4, 5, or 6 CHC and ESRD requiring dialysis received Harvoni for 8 (n=45), 12 (n=31), or 24 (n=19) weeks. The adverse events observed were consistent with expected clinical sequelae of ESRD.

Paediatric Population

The safety information of Harvoni in adolescents aged 12 to < 18 years is limited and based on data from a Phase 2, open-label clinical study that enrolled 100 patients with genotype 1 HCV infection who were treated with ledipasvir/sofosbuvir for 12 weeks. The adverse reactions observed were consistent with those observed in clinical studies of ledipasvir/sofosbuvir in adults (see table 6).

Post-marketing Experience

In addition to adverse reactions from clinical studies, the following adverse reactions were also identified during post approval use of Harvoni. Because these reactions were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Description of selected adverse reactions

*Cardiac dysrhythmias*

Symptomatic bradycardia when amiodarone is co-administered with Harvoni) (see section 4.4 and 4.5).

*Skin and subcutaneous tissue disorders*

Frequency not known: Steven-Johnson syndrome

*Reporting of suspected adverse reactions*

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

## 4.9 Overdose

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacological Classification: A 20.2.8 Antiviral Agents

Pharmacotherapeutic group: Direct-acting antiviral, ATC code: J05AP51

Mechanism of action

Ledipasvir is an HCV inhibitor targeting the HCV NS5A protein, which is essential for both RNA replication and the assembly of HCV virions. Biochemical confirmation of NS5A inhibition by ledipasvir is not currently possible as NS5A has no enzymatic function. *In vitro* resistance selection and cross-resistance studies indicate ledipasvir targets NS5A as its mode of action.

Sofosbuvir is a pan-genotypic inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analogue triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator.

In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a, and 4a with an IC50 value ranging from 0,7 to 2,6 µm.

GS-461203 (the active metabolite of sofosbuvir) is neither an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

Patients with renal impairment

Study 0154 was an open-label clinical trial that evaluated 12 weeks of treatment with ledipasvir/sofosbuvir in 18 genotype 1 HCV- infected patients with severe renal impairment without dialysis. At baseline, two patients (11 %) had cirrhosis and the mean eGFR was 24.9 ml/min (range: 9.0-39.6). The SVR rate was 100 % (18/18).

Study 4063 was an open-label three-arm clinical trial that evaluated 8, 12, and 24 weeks of treatment with ledipasvir/sofosbuvir in a total of 95 patients with genotype 1 (72 %), 2 (22 %), 4 (2 %), 5 (1 %), or 6 (2 %) CHC and ESRD requiring dialysis: 45 treatment-naïve genotype 1 HCV-infected patients without

cirrhosis received ledipasvir/sofosbuvir for 8 weeks; 31 treatment-experienced genotype 1 HCV-infected patients and treatment-naïve or treatment-experienced patients with genotype 2, 5, and 6 infection without cirrhosis received ledipasvir/sofosbuvir for 12 weeks; and 19 genotype 1, 2, and 4 HCV-infected patients with compensated cirrhosis received ledipasvir/sofosbuvir for 24 weeks. Of the 95 total subjects, at baseline, 20 % of patients had cirrhosis, 22 % were treatment experienced, 21 % had received a kidney transplant, 92 % were on hemodialysis, and 8 % were on peritoneal dialysis; mean duration on dialysis was 11.5 years (range: 0.2 to 43.0 years). The SVR rates for the 8, 12, and 24 week ledipasvir/sofosbuvir treatment groups were 93 % (42/45), 100 % (31/31), and 79 % (15/19), respectively. Of the 7 patients who did not achieve SVR12, none experienced virologic failure or relapsed.

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 EC50 greater than 1 000-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, the ability of the active triphosphate of sofosbuvir (GS-461203) to inhibit recombinant NS5B polymerase from genotypes 1b, 2a, 3a, and 4a expressing the S282T substitution

was reduced compared to its ability to inhibit wild-type recombinant NS5B polymerase, as indicated by a 8-24-fold increase in $IC_{50}$.

Cross-resistance

Ledipasvir was fully active against the sofosbuvir resistance-associated substitution S282T in NS5B while all ledipasvir resistance-associated substitutions in NS5A were fully susceptible to sofosbuvir.
Both sofosbuvir and ledipasvir were fully active against substitutions associated with resistance to other classes of direct acting antivirals with different mechanisms of actions, such as NS5B non-nucleoside inhibitors and NS3 protease inhibitors.
NS5A substitutions conferring resistance to ledipasvir may reduce the antiviral activity of other NS5A inhibitors.

## 5.2 Pharmacokinetic properties

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 ledipasvir/sofosbuvir, ledipasvir median peak concentrations were observed 4,0 to 4,5 hours post-dose. The peak median plasma concentration of sofosbuvir was observed ~ 0,8 to 1 hour post-oral dosing. Median peak plasma concentration of GS-331007 was observed between 3,5 to 4 hours post-dose.
Based on the population pharmacokinetic analysis in HCV-infected subjects, geometric mean steady-state AUC0-24 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 AUC0-24 and $C_{max}$ were 24 % lower and 32 % lower, respectively in HCV-infected subjects.
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 1,200 mg.

Effects of food

Relative to fasting conditions, the administration of a single dose of ledipasvir/sofosbuvir with a moderate fat (~600 kcal, 25 % to 30 % fat) or high fat (~1 000 kcal, 50 % fat) meal did not substantially affect the sofosbuvir $C_{max}$ and $AUC_{0\text{-}inf}$. The exposures of the sofosbuvir metabolite, GS-331007 and ledipasvir were not altered in the presence of either meal type. The response rates in Phase 3 trials were similar in HCV-infected subjects who received ledipasvir/sofosbuvir with food or without food. Harvoni can be administered without regard to food.

Distribution

Ledipasvir is > 99,8 % bound to human plasma proteins. After a single 90 mg dose of [$^{14}$C] ledipasvir in healthy subjects, the blood to plasma ratio of [$^{14}$C] radioactivity ranged between 0.51 and 0.66. Sofosbuvir is approximately 61-65 % bound to human plasma proteins and the binding is independent of drug concentration over the range of 1 µg/ml to 20 µg/ml. Protein binding of GS-331007 was minimal in human plasma. After a single 400 mg dose of [$^{14}$C] sofosbuvir in healthy subjects, the blood to plasma ratio of [$^{14}$C] radioactivity was approximately 0,7.

Biotransformation

*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 medicine (> 98 %). Unchanged ledipasvir is the major species present in faeces. Sofosbuvir is extensively metabolised in the liver to form the pharmacologically active nucleoside analogue triphosphate GS-461203. The metabolic activation pathway involves sequential hydrolysis of the carboxyl ester moiety catalysed by human cathepsin A (Cat A) 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*. After a single 400 mg oral dose of [14C]-sofosbuvir, GS-331007 accounted for approximately >90 % of total systemic exposure.

Elimination

Following a single 90 mg oral dose of [$^{14}$C] ledipasvir, mean total recovery of the [$^{14}$C] radioactivity in faeces and urine was 87 %, with most of the radioactive dose recovered from faeces (86 %). Unchanged ledipasvir excreted in faeces 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 in healthy volunteers following administration of ledipasvir/sofosbuvir in the fasted state 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, faeces, 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 ledipasvir/sofosbuvir were 0,5 and 27 hours, respectively.

Pharmacokinetics in special populations

*Gender*

No clinically relevant pharmacokinetic differences due to gender have been identified for sofosbuvir or GS-331007. The AUC and $C_{max}$ of ledipasvir were 77 % and 58 % higher respectively in females than males; however, the relationship between gender and ledipasvir exposures was not considered clinically relevant as high response rates (SVR >90 %) were achieved in male and female subjects across the Phase 3 studies.

*Elderly*

Population pharmacokinetic analysis in HCV infected patients showed that within the age range (18 to 80 years) analysed, age did not have a clinically relevant effect on the exposure to ledipasvir, sofosbuvir or GS-331007.

*Renal impairment*

The pharmacokinetics of ledipasvir were studied with a single dose of 90 mg ledipasvir in HCV negative patients with severe renal impairment (eGFR < 30 ml/min by Cockcroft-Gault). No clinically relevant differences in ledipasvir pharmacokinetics were observed between healthy subjects and patients with severe renal impairment. 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/1,73 $m^2$), moderate (eGFR ≥30 and <50 ml/min/1,73 $m^2$), severe renal impairment (eGFR < 30 ml/min/1,73 $m^2$), and subjects with end stage renal disease (ESRD) requiring haemodialysis following a single 400 mg dose of sofosbuvir. Relative to subjects with normal renal function (eGFR > 80 ml/min/1,73 $m^2$), the sofosbuvir $AUC_{0\text{-}inf}$ was 61 %, 107 %, and 171 % higher in mild, moderate, and severe renal impairment, while the GS-331007 $AUC_{0\text{-}inf}$ was 55 %, 88 %, and 451 % higher, respectively. In subjects with ESRD, sofosbuvir $AUC_{0\text{-}inf}$ was 28 % higher when sofosbuvir was dosed 1 hour before haemodialysis compared with 60 % higher when dosed 1 hour after haemodialysis, respectively. The $AUC_{0\text{-}inf}$ of GS-331007 in subjects with ESRD administered with sofosbuvir 1 hour before or 1 hour after haemodialysis was at least 10-fold and 20-fold higher, respectively. GS-331007 is efficiently removed by haemodialysis with an extraction coefficient of approximately 53 %. Following a single 400 mg dose of sofosbuvir, a 4hour haemodialysis removed 18 % of administered dose.

The pharmacokinetics of ledipasvir, sofosbuvir, and GS-331007 were studied in HCV-infected subjects with ESRD requiring dialysis treated with Harvoni for 8, 12, or 24 weeks. Steady-state $AUC_{tau}$ of ledipasvir, sofosbuvir and GS-331007 were increased by 61 %, 89 %, and 2180 %, respectively, compared to subjects without renal impairment in the ledipasvir/sofosbuvir Phase 2/3 trials. No

exposure-safety relationships were observed in HCV-infected subjects with ESRD requiring dialysis treated with Harvoni. No dose adjustment is required for patients with renal impairment, including ESRD requiring dialysis (see section 5.2).

*Hepatic impairment*

The pharmacokinetics of ledipasvir were studied with a single dose of 90 mg ledipasvir in HCV negative patients with severe hepatic impairment (Child-Pugh class C). Ledipasvir plasma exposure ($AUC_{inf}$) was similar in patients with severe hepatic impairment and control patients with normal hepatic function. Population pharmacokinetics analysis in HCV infected patients indicated that cirrhosis had no clinically relevant effect on the exposure to ledipasvir. No dose adjustment of ledipasvir is recommended for patients with mild, moderate or severe hepatic impairment.

The pharmacokinetics of sofosbuvir were 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 patients 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. Population pharmacokinetics analysis in HCV infected patients indicated that cirrhosis had no clinically relevant effect on the exposure to sofosbuvir and GS-331007. No dose adjustment of sofosbuvir is recommended for patients with mild, moderate and severe hepatic impairment (see section 4.2).

*Paediatric population*

Ledipasvir, sofosbuvir, and GS-331007 exposures in adolescents aged 12 to < 18 years were similar to those in adults from Phase 2/3 studies, following administration of ledipasvir/sofosbuvir (90 mg/400 mg). The pharmacokinetics of ledipasvir, sofosbuvir, and GS-331007 have not been established in paediatric patients aged < 12 years (see section 4.2).

*Body weight*

Body weight did not have a significant effect on sofosbuvir exposure according to a population pharmacokinetic analysis. Exposure to ledipasvir decreases with increasing body weight but the effect is not considered to be clinically relevant.

## 5.3 Preclinical safety data

Ledipasvir

No target organs of toxicity were identified in rat and dog studies with ledipasvir at AUC exposures approximately 7 times the human exposure at the recommended clinical dose.

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 was not carcinogenic in the 6 month rasH2 transgenic mouse study at exposures up to 26 fold higher than human exposure. A carcinogenicity study in rats is ongoing.

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 4 times the exposure in humans at the recommended clinical dose. There were no effects on survival, physical and behavioural development and reproductive

performance in the offspring at maternal exposures similar to the exposure in humans at the recommended clinical dose.

When administered to lactating rats, ledipasvir was detected in plasma of suckling rats likely due to excretion of ledipasvir via milk.

Sofosbuvir

In repeat dose toxicology studies in rat and dog, high doses of the 1:1 diastereomeric mixture caused adverse liver (dog) and heart (rat) effects and gastrointestinal reactions (dog). Exposure to sofosbuvir in rodent studies could not be detected likely due to high esterase activity; however, exposure to the major metabolite GS-331007 at doses which cause adverse effects was 16 times (rat) and 71 times (dog) higher than the clinical exposure at 400 mg sofosbuvir. No liver or heart findings were observed in chronic toxicity studies at exposures 5 times (rat) and 16 times (dog) higher than the clinical exposure. No liver or heart findings were observed in the 2 year carcinogenicity studies at exposures 17 times (mouse) and 9 times (rat) higher than the clinical exposure.

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

Carcinogenicity studies in mice and rats do not indicate any carcinogenicity potential of sofosbuvir administered at doses up to 600 mg/kg/day in mouse and 750 mg/kg/day in rat. Exposure to GS-331007 in these studies was up to 17 times (mouse) and 9 times (rat) higher than the clinical exposure at 400 mg sofosbuvir.

Sofosbuvir had no effects on embryo foetal viability or on fertility in rat and was not teratogenic in rat and rabbit development studies. No adverse effects on behaviour, reproduction or development of offspring in rat were reported. In rabbit studies exposure to sofosbuvir was 6 times the expected clinical exposure. In the rat studies, exposure to sofosbuvir could not be determined but exposure margins based on the major human metabolite was approximately 5 times higher than the clinical exposure at 400 mg sofosbuvir.

Sofosbuvir-derived material was transferred through the placenta in pregnant rats and into the milk of lactating rats.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet core

Copovidone

Microcrystalline cellulose (E460(i))

Croscarmellose sodium

Colloidal silicon dioxide

Magnesium stearate (E470b)

Film-coating

Polyvinyl alcohol (E1203)

Titanium dioxide (E171)

Macrogol (Polyethylene glycol) 3350 (E1521)

Talc (E553b)

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

6 years.

## 6.4 Special precautions for storage

Store at or below 30 °C.

Do not remove the desiccant.

## 6.5 Nature and contents of container

Harvoni tablets are supplied in a 100ml high density polyethylene (HDPE) bottles with a polypropylene child-resistant closure containing 28 film-coated tablets with a silica gel desiccant and polyester coil.

## 6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Gilead Sciences South Africa (Pty) Ltd,

Ground Floor Mac Mac Building

Maxwell Office Park

Magwa Crescent

Waterfall, Midrand

Gauteng, 2090

South Africa

## 8. REGISTRATION NUMBER(S)

51/20.2.8/0369

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01 September 2020

## 10. DATE OF REVISION OF THE TEXT

N/A

Mee Towindo Digitally signed by Mee Towindo
Date: 2024.07.24 16:18:56
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