Product Monograph

INCLUDING PATIENT MEDICATION INFORMATION

PrVOSEVI™

(sofosbuvir/velpatasvir/voxilaprevir) tablets

400 mg/100 mg/100 mg

Antiviral Agent

Gilead Sciences Inc.
Foster City, CA 94404
USA

Gilead Sciences Canada, Inc.
Mississauga, ON L5N 2W3
Canada

www.gilead.ca

Date of Preparation:
August 16, 2017

Submission Control No.: 202324

TABLE OF CONTENTS

VOSEVI™
sofosbuvir/velpatasvir/voxilaprevir

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet 400 mg sofosbuvir 100 mg velpatasvir 100 mg voxilaprevir	lactose monohydrate

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

INDICATIONS AND CLINICAL USE

VOSEVI (sofosbuvir/velpatasvir/voxilaprevir) is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adult patients, without cirrhosis or with compensated cirrhosis, who have:

- genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor;
- genotype 1, 2, 3, or 4 infection and have been previously treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.

Geriatrics (≥ 65 years of age)

The response rates observed for patients 65 years of age and over were similar to those of younger patients across treatment groups. VOSEVI can be administered in geriatric patients (see **ACTION AND CLINICAL PHARMACOLOGY** and **CLINICAL TRIALS**).

Pediatrics (< 18 years of age)

Safety and effectiveness in pediatric patients have not been established.

CONTRAINDICATIONS

VOSEVI 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.

Table 1 lists drugs which are contraindicated with VOSEVI (see **DRUG INTERACTIONS**).

Table 1 Drugs that are Contraindicated with VOSEVI

Drug Class: Drug Name	Effect on Concentration	Mechanism of Action	Clinical Comment
Anticoagulants: dabigatran etexilate	↑ dabigatran	P-gp inhibition	Increased risk of bleeding.
Anticonvulsants: phenobarbital, phenytoin	↓ sofosbuvir ↓ velpatasvir ↓ voxilaprevir	Induction of P-gp and CYP450	Risk of loss of therapeutic effect of VOSEVI.
Antimycobacterials: rifampin	↓ sofosbuvir ↓ velpatasvir ↓ voxilaprevir	Induction of P-gp and CYPs	Risk of loss of therapeutic effect of VOSEVI.
Herbal products: St. John's wort (*Hypericum perforatum*)	↓ sofosbuvir ↓ velpatasvir ↓ voxilaprevir	Induction of P-gp and CYP450	Risk of loss of therapeutic effect of VOSEVI.
HMG-CoA reductase inhibitors: rosuvastatin	↑ rosuvastatin	BCRP and OATP1B inhibition	Increased risk of statin-related myopathy, including rhabdomyolysis.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Potential for Hepatitis B Virus (HBV) Reactivation**

Screen all patients for evidence of current or prior HBV infection before initiating VOSEVI treatment. Cases of HBV reactivation, including those resulting in fulminant hepatitis, hepatic failure, and death, have been reported during HCV treatment and/or post-treatment with regimens containing direct-acting antivirals (DAAs) in patients co-infected with HBV (see **WARNINGS AND PRECAUTIONS**, **Potential for Hepatitis B Virus Reactivation**).

General

Treatment with VOSEVI should be initiated and monitored by a physician experienced in the management of chronic HCV infection.

Data to support the treatment of patients infected with HCV genotype 5 or genotype 6 who have failed prior therapy of an HCV regimen containing an NS5A inhibitor are limited. The indication for treatment of these patients is based on extrapolation of relevant clinical and *in vitro* data (see **CLINICAL TRIALS** and **MICROBIOLOGY**).

No clinical data are available to support the treatment of HCV patients with genotype 5 or genotype 6 infection who have failed prior therapy of an HCV regimen containing sofosbuvir without an NS5A inhibitor (see **CLINICAL TRIALS**).

VOSEVI should not be administered concurrently with other medicinal products containing sofosbuvir.

Use with Potent P-gp Inducers and/or Moderate to Potent Inducers of CYP

Medicinal products that are potent inducers of P-glycoprotein (P-gp) and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 [e.g., St. John's wort (*Hypericum perforatum*), and carbamazepine] may significantly decrease plasma concentrations of sofosbuvir, velpatasvir, or voxilaprevir leading to reduced therapeutic effect of VOSEVI and potential loss of virologic response. These agents should not be used with VOSEVI (see **DRUG INTERACTIONS**).

Cardiovascular

Serious Symptomatic Bradycardia When Coadministered with Amiodarone

Postmarketing cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is coadministered with sofosbuvir in combination with daclatasvir or simeprevir. A fatal cardiac arrest was reported in a patient taking amiodarone who was coadministered a sofosbuvir-containing regimen (HARVONI® [ledipasvir/sofosbuvir]). Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this effect is unknown.

Coadministration of amiodarone with VOSEVI is not recommended. For patients taking amiodarone who have no other alternative, viable treatment options and who will be coadministered VOSEVI:

- Counsel patients about the risk of symptomatic bradycardia.
- Cardiac monitoring in an in-patient setting for the first 48 hours of coadministration is recommended, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment.

Patients who are taking VOSEVI who need to start amiodarone therapy due to no other alternative, viable treatment options should undergo similar cardiac monitoring as outlined above.

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

Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately. Symptoms may include near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pains, confusion, or memory problems (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions** and **DRUG INTERACTIONS**).

Potential for Hepatitis B Virus Reactivation

Cases of HBV reactivation, including those resulting in fulminant hepatitis, hepatic failure, and death have been reported in HCV/HBV co-infected patients who were undergoing, or completed treatment with DAAs. To decrease the risk of HBV reactivation in patients co-infected with HBV, HBV screening should be performed in all patients prior to initiation of HCV treatment. Patients with positive HBV serology (HBsAg positive) and patients with serologic evidence of resolved HBV infection (ie, HBsAg negative and anti-HBc positive) should be monitored and treated according to current clinical practice guidelines to manage potential HBV reactivation (see **WARNINGS AND PRECAUTIONS**, **Monitoring and Laboratory Tests**).

Hepatic

VOSEVI is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C) due to significant increases in the exposures of voxilaprevir in these patients (AUC ↑ 299% and 500% in HCV-negative patients with moderate and severe hepatic impairment, respectively); the safety and efficacy of VOSEVI have not been established in HCV-infected patients with moderate or severe hepatic impairment (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency**).

Gastrointestinal

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

Renal

The safety and efficacy of VOSEVI have not been established in patients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] < 30 mL/min) or end stage renal disease (ESRD) requiring hemodialysis (see **ACTION AND CLINICAL PHARMACOLOGY**).

Sexual Function/Reproduction

There are no data on the effect of sofosbuvir, velpatasvir, or voxilaprevir on human fertility. No effects on fertility were observed in animal studies for sofosbuvir, velpatasvir or voxilaprevir (see **TOXICOLOGY**).

Special Populations

Pregnant Women

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

No effects on pre- or post-natal development were observed in animal reproduction studies at the highest doses of sofosbuvir tested. In the rat and rabbit embryo fetal studies, and the rat pre/post-natal study, exposure to the predominant circulating metabolite GS-331007 at the highest dose was approximately 6-fold, 16-fold, and 7-fold the exposure in humans at the recommended clinical dose, respectively.

No effects on pre- or post-natal development have been observed in animal reproduction studies at the highest doses of velpatasvir tested. In the mouse, rat, and rabbit embryo fetal studies, and rat pre/post-natal study velpatasvir exposure was approximately 23-fold, 4-fold, 0.5-fold, and 3-fold the exposure in humans at the recommended clinical dose, respectively.

No effects on pre- or post-natal development have been observed in animal reproduction studies at the highest doses of voxilaprevir tested. In the rat and rabbit embryo fetal studies, and rat pre/post-natal study voxilaprevir exposure was approximately 141-fold, 4-fold, and 238-fold the exposure in humans at the recommended clinical dose, respectively.

Nursing Women

It is not known whether sofosbuvir, metabolites of sofosbuvir, velpatasvir, or voxilaprevir are excreted in human breast milk. The sofosbuvir predominant circulating metabolite GS-331007 and velpatasvir are present in the milk of lactating rats; they had no clear effect on nursing pups. When administered to lactating rats, voxilaprevir was detected in the plasma of nursing pups. Because a risk to the newborn/infant cannot be excluded, mothers should be instructed not to breastfeed if they are taking VOSEVI.

Pediatrics (< 18 years of age)

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

Geriatrics (≥ 65 years of age)

The response rates observed for patients 65 years of age and over were similar to those of patients < 65 years of age across treatment groups.

Pre-and Post-Liver Transplant Patients

The safety and efficacy of VOSEVI have not been established in patients awaiting liver transplantation or in patients with recurrent HCV infection post-liver transplant.

HCV/HIV Co-infection

The safety and efficacy of VOSEVI have not been established in HCV patients co-infected with Human Immunodeficiency Virus (HIV).

VOSEVI has been shown to increase tenofovir exposure when used together with an HIV regimen containing tenofovir disoproxil fumarate (tenofovir DF). Patients receiving VOSEVI concomitantly with tenofovir DF, particularly those at increased risk for renal dysfunction,

should be monitored for tenofovir-associated adverse reactions. Refer to Product Monographs for tenofovir DF-containing products for recommendations on renal monitoring.

Efavirenz has been shown to significantly decrease the concentration of velpatasvir and is expected to decrease the concentration of voxilaprevir; therefore co-administration of VOSEVI with an efavirenz-containing regimen is not recommended (see **DRUG INTERACTIONS**).

HCV/HBV Co-infection

The safety and efficacy of VOSEVI have not been established in HCV patients co-infected with HBV. HBV reactivation has been reported during treatment and post-treatment with DAAs in patients co-infected with HBV who were not undergoing treatment for HBV infection (see **WARNINGS AND PRECAUTIONS**, **Potential for HBV Reactivation**).

Monitoring and Laboratory Tests

If VOSEVI is administered with amiodarone, close monitoring for bradycardia is recommended (see **WARNINGS AND PRECAUTIONS**, **Cardiovascular**). Refer to the amiodarone Product Monograph.

Clearance of HCV may lead to increased replication of HBV in patients who are co-infected with HCV and HBV. Co-infected patients should be monitored for clinical and laboratory signs (eg, HBsAg, anti-HBc, HBV DNA, serum aminotransferase levels, bilirubin) for hepatitis flare or HBV reactivation during and at post-treatment follow-up as clinically appropriate (see **WARNINGS AND PRECAUTIONS**, **Potential for HBV Reactivation**).

Patients Treated with Vitamin K Antagonists

As liver function may improve during treatment with VOSEVI, a close monitoring of International Normalised Ratio (INR) values is recommended.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The overall safety profile of VOSEVI was established in patients infected with HCV, without cirrhosis or with compensated cirrhosis.

Adverse reactions data for VOSEVI were derived from two Phase 3 clinical trials (POLARIS-1 and POLARIS-4) that evaluated a total of 445 patients with chronic HCV infection, without cirrhosis or with compensated cirrhosis, who received VOSEVI for 12 weeks (see **CLINICAL TRIALS**).

The proportion of patients who permanently discontinued treatment due to adverse events was 0.2% for patients receiving VOSEVI for 12 weeks. Of the 445 patients, 2% had at least one serious adverse event (SAE), with no patients experiencing a treatment-related SAE.

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.

Adverse reactions (adverse events assessed as causally related by the investigator), all grades, observed in ≥ 10% of patients receiving 12 weeks of treatment with VOSEVI in clinical trials include headache (22%), fatigue (18%), diarrhea (13%), and nausea (12%). Of patients receiving VOSEVI who experienced these adverse reactions, 76% of subjects had an adverse reaction of mild (Grade 1) severity.

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

Table 2. Adverse Reactions (Grades 2-4) Reported in ≥ 1% of Patients Receiving 12 Weeks of VOSEVI[a] from the Phase 3 Studies (POLARIS-1, POLARIS-4)

	POLARIS-1		POLARIS-4	
	VOSEVI 12 weeks N = 263	**Placebo 12 weeks N = 152**	**VOSEVI 12 weeks N = 182**	**SOF/VEL 12 weeks N = 151**
Headache	5%	2%	4%	2%
Fatigue	3%	4%	2%	7%
Diarrhea	1%	2%	2%	0
Insomnia	2%	<1%	1%	0
Asthenia	1%	<1%	2%	<1%

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 (< 1%)

Adverse reactions (Grades 2 to 4) occurring in less than 1% of patients receiving 12 weeks of treatment with VOSEVI in clinical trials are listed below in Table 3 by body system.

Table 3. Adverse Reactions (Grades 2-4) Reported in < 1% of Patients Receiving 12 Weeks of VOSEVI[a] from the Pooled Phase 3 Studies (POLARIS-1, POLARIS-4)

Body System	**VOSEVI 12 Weeks**
Gastrointestinal Disorders	Abdominal discomfort, abdominal pain, abdominal pain upper, eructation, flatulence, functional gastrointestinal disorder, gastroesophageal reflux disease, nausea
General Disorders and Administration Site Conditions	Chills, energy increased, influenza like illness, thirst
Infections and Infestations	Subcutaneous abscess

Body System	VOSEVI 12 Weeks
Injury, Poisoning and Procedural Complications	Ligament sprain
Metabolism and Nutrition Disorders	Decreased appetite, gout
Musculoskeletal and Connective Tissue Disorders	Arthralgia, myalgia, polyarthritis
Nervous System Disorders	Disturbance in attention, dizziness, dizziness postural, migraine, somnolence
Respiratory, Thoracic and Mediastinal Disorders	Cough, rhinorrhea
Skin and Subcutaneous Tissue Disorders	Dry skin, night sweats, pruritus, rash maculo-papular, vitiligo
Vascular Disorders	Hot flush

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

For information on the safety profile of sofosbuvir in combination with velpatasvir, consult the EPCLUSA Product Monograph.

Abnormal Hematologic and Clinical Chemistry Findings

The frequency of treatment-emergent laboratory abnormalities (Grades 2 to 4) occurring in at least 1% of patients receiving 12 weeks of treatment with VOSEVI are described in Table 4.

Table 4. Laboratory Abnormalities (Grades 2-4) Reported in ≥ 1% of Patients Receiving 12 Weeks of VOSEVI from the Phase 3 Studies (POLARIS-1, POLARIS-4)

Laboratory Abnormality Parameters	POLARIS-1		POLARIS-4	
	VOSEVI 12 weeks N = 263	Placebo 12 weeks N = 152	VOSEVI 12 weeks N = 182	SOF/VEL 12 weeks N = 151
Chemistry				
ALT (> 2.5 x ULN)	<1%	5%	2%	0%
AST (> 2.5 x ULN)	<1%	9%	2%	0%
Creatine Kinase (≥ 6 x ULN)	2%	2%	2%	1%
Hyperbilirubinemia (> 1.5 x ULN)	3%	3%	3%	1%
Hyperglycemia (> 8.91 mmol/L)	11%	16%	15%	15%
Lipase (> 1.5 x ULN)	7%	5%	10%	4%
Hematology				

Lymphocytes (< 600/mm^3)	<1%	3%	2%	<1%
Neutrophils (< 1000/ mm^3)	1%	<1%	1%	2%
Platelets (< 100 x 10^9/L)	6%	6%	5%	6%

ULN = Upper Limit of Normal

Total bilirubin

In the Phase 3 trials, increases in total bilirubin less than or equal to 1.5 × ULN were observed in 4% of patients without cirrhosis and 10% of patients with compensated cirrhosis, due to inhibition of OATP1B1 and OATP1B3 by voxilaprevir. Total bilirubin levels decreased after completing VOSEVI treatment. No patients experienced jaundice.

Post-Market Adverse Drug Reactions

In addition to adverse reactions from clinical studies, the following adverse reactions have been identified during postapproval use of sofosbuvir-containing regimens. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac Disorders

Serious symptomatic bradycardia when amiodarone is coadministered with sofosbuvir in combination with another HCV DAA (see **WARNINGS AND PRECAUTIONS, Cardiovascular** and **DRUG INTERACTIONS**).

Skin and Subcutaneous Tissue Disorders

Skin rashes (sometimes with blisters or angioedema-like swelling) and angioedema.

DRUG INTERACTIONS

Overview

As VOSEVI contains sofosbuvir, velpatasvir, and voxilaprevir, any interactions that have been identified with these agents individually may occur with VOSEVI.

After oral administration of VOSEVI, sofosbuvir is rapidly absorbed and subject to extensive first-pass hepatic extraction. In clinical pharmacology studies, both sofosbuvir and the primary circulating metabolite GS-331007 (dephosphorylated nucleotide metabolite) were monitored for purposes of pharmacokinetic analyses.

Drug-Drug Interactions

Potential for VOSEVI to Affect Other Drugs

Sofosbuvir and GS-331007 are not relevant inhibitors of efflux drug transporters P-gp, BCRP, renal efflux transporter MRP2, hepatic efflux transporter BSEP, hepatic uptake transporters OATP1B1, OATP1B3, OCT1, and GS-331007 is not an inhibitor of renal uptake transporters OAT1, OCT2 and renal efflux transporter MATE1. Sofosbuvir and GS-331007 are not inhibitors or inducers of CYP or UGT1A1 enzymes.

Velpatasvir is an inhibitor of drug transporters P-gp, breast cancer resistance protein (BCRP), OATP1B1, OATP1B3, and OATP2B1, and its involvement in drug interactions with these transporters is primarily limited to the process of absorption. At clinically relevant concentrations, velpatasvir is not an inhibitor of hepatic transporters OATP1A2 or OCT1, renal transporters OCT2, OAT1, OAT3 or MATE1, or CYP or UGT1A1 enzymes.

Voxilaprevir is an inhibitor of drug transporters P-gp, BCRP, OATP1B1 and OATP1B3, and its involvement in drugs interactions with these transporters is primarily limited to the process of absorption. Coadministration of VOSEVI with drugs that are substrates of these transporters may alter the exposure of such drugs. At clinically relevant concentrations, voxilaprevir is not an inhibitor of hepatic transporter OCT1, renal transporters OCT2, OAT1, OAT3 or MATE1, or CYP or UGT1A1 enzymes.

Potential for Other Drugs to Affect VOSEVI

Sofosbuvir, velpatasvir, and voxilaprevir are substrates of efflux drug transporters P-gp and BCRP while GS-331007 is not. GS-331007 is not a substrate for renal transporters including organic anion transporter OAT1 or OAT3, or organic cation transporter OCT2. Voxilaprevir, and to a lesser extent velpatasvir, are also substrates of OATP1B1 and OATP1B3. *In vitro*, slow metabolic turnover of velpatasvir primarily by CYP2B6, CYP2C8, and CYP3A4 and of voxilaprevir primarily by CYP3A4 was observed.

Drugs that are potent inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., St. John's wort or carbamazepine) may significantly decrease plasma concentrations of sofosbuvir, velpatasvir, and/or voxilaprevir leading to reduced therapeutic effect of VOSEVI. Coadministration of VOSEVI with phenobarbital, phenytoin, rifampin and St. John's wort are contraindicated and coadministration with carbamazepine is not recommended (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

Coadministration with drugs that inhibit P-gp and/or BCRP may increase sofosbuvir, velpatasvir, and/or voxilaprevir plasma concentrations without increasing GS-331007 plasma concentration. Coadministration with drugs that inhibit OATP may increase voxilaprevir plasma concentrations. Drugs that inhibit CYP2B6, CYP2C8, or CYP3A4 may increase plasma concentration of velpatasvir and/or voxilaprevir. VOSEVI may be coadministered with P-gp, BCRP, and CYP inhibitors. The use of potent inhibitors of OATP with VOSEVI is not recommended.

Table 5 provides a listing of established or potentially clinically significant drug interactions. The drug interactions described are based on studies conducted with either VOSEVI, the components of VOSEVI (sofosbuvir, velpatasvir, and voxilaprevir) as individual agents, or are predicted drug interactions that may occur with VOSEVI. The table is not all-inclusive (see **ACTION AND CLINICAL PHARMACOLOGY**).

Table 5. Established and Other Potentially Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Effect/Recommendation
Acid Reducing Agents:		
	↓ velpatasvir	Velpatasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of velpatasvir.
Antacids (e.g., aluminum and magnesium hydroxide)		It is recommended to separate antacid and VOSEVI administration by 4 hours.
H_2-receptor antagonists (e.g., famotidine)[c]		H_2-receptor antagonists may be administered simultaneously with or staggered from VOSEVI at a dose that does not exceed doses comparable with famotidine 40 mg twice daily.
Proton-pump inhibitors (e.g., omeprazole)[c]		Proton-pump inhibitor doses comparable with omeprazole 20 mg can be administered with VOSEVI.
Antiarrhythmics:		
amiodarone	Effect on amiodarone, sofosbuvir, velpatasvir, and voxilaprevir concentrations unknown	Coadministration of amiodarone with VOSEVI may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Coadministration of amiodarone with VOSEVI is not recommended; if coadministration is required, cardiac monitoring is recommended (see **WARNINGS AND PRECAUTIONS, Cardiovascular** and **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).
digoxin[c]	↑ digoxin	Coadministration of VOSEVI with digoxin may increase the concentration of digoxin. Caution is warranted and therapeutic concentration monitoring of digoxin is recommended when coadministered with VOSEVI.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Effect/Recommendation
Anticoagulants:		
dabigatran etexilate[c]	↑ dabigatran	Coadministration of VOSEVI with dabigatran etexilate is contraindicated. Coadministration of VOSEVI with dabigatran etexilate may increase the concentration of dabigatran which may increase the risk of bleeding.
vitamin K antagonists	vitamin K antagonist ↔	As liver function may improve during treatment with VOSEVI, a close monitoring of INR values is recommended.
Anticonvulsants:		
carbamazepine phenytoin phenobarbital oxcarbazepine	↓ sofosbuvir ↓ velpatasvir ↓ voxilaprevir	Coadministration of VOSEVI with phenytoin or phenobarbital is contraindicated. Coadministration of VOSEVI with carbamazepine or oxcarbazepine is not recommended. Coadministration of these anticonvulsants with VOSEVI may significantly decrease the concentration of sofosbuvir, velpatasvir and voxilaprevir, and may lead to loss of therapeutic effect of VOSEVI.
Antimycobacterials:		
rifabutin rifampin[c] rifapentine*	↓ sofosbuvir ↓ velpatasvir ↓ voxilaprevir	Coadministration of VOSEVI with rifampin is contraindicated. Coadministration of VOSEVI with rifabutin or rifapentine is not recommended. Coadministration of these antimicrobials with VOSEVI may significantly decrease the concentrations of sofosbuvir, velpatasvir and voxilaprevir, and may lead to loss of therapeutic effect of VOSEVI.
Antiretrovirals:		
atazanavir[c] lopinavir	↑ voxilaprevir	Coadministration of VOSEVI with atazanavir- or lopinavir-containing regimens is not recommended. Coadministration of these antiretrovirals with VOSEVI has been shown to substantially increase the plasma concentration of voxilaprevir, the safety of which has not been established.
efavirenz[c]	↓ velpatasvir ↓ voxilaprevir	Coadministration of VOSEVI with efavirenz-containing regimens is not recommended. Coadministration of efavirenz with VOSEVI may significantly decrease the concentrations of velpatasvir and voxilaprevir, and may lead to loss of therapeutic effect of VOSEVI.
tenofovir disoproxil fumarate (tenofovir DF)[c]	↑ tenofovir	Monitor for tenofovir-associated adverse reactions in patients receiving VOSEVI concomitantly with a regimen containing tenofovir DF. Refer to the Product Monographs for tenofovir DF-containing products for recommendations on renal monitoring.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Effect/Recommendation
HMG-CoA Reductase Inhibitors:		
atorvastatin	↑ atorvastatin	Coadministration of VOSEVI with atorvastatin may increase the concentration of atorvastatin which is associated with increased risk of myopathy, including rhabdomyolysis. Atorvastatin may be administered with VOSEVI at a dose that does not exceed atorvastatin 10 mg. Monitoring for signs and symptoms of myopathy, including rhabdomyolysis, during concomitant use of atorvastatin with VOSEVI may be warranted.
fluvastatin lovastatin simvastatin	↑ fluvastatin ↑ lovastatin ↑ simvastatin	Coadministration of VOSEVI with fluvastatin, lovastatin, and simvastatin may increase the concentrations of these statins which is associated with increased risk of myopathy, including rhabdomyolysis. Use the lowest approved statin dose. If higher doses are needed, use the lowest necessary statin dose based on a risk/benefit assessment. Monitoring for signs and symptoms of myopathy, including rhabdomyolysis, during concomitant use of statins with VOSEVI may be warranted.
pravastatin[c]	↑ pravastatin	Coadministration of VOSEVI with pravastatin has been shown to increase the concentration of pravastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Pravastatin may be administered with VOSEVI at a dose that does not exceed pravastatin 40 mg. Monitoring for signs and symptoms of myopathy, including rhabdomyolysis, during concomitant use of pravastatin with VOSEVI may be warranted.
rosuvastatin[c]	↑ rosuvastatin	Coadministration of VOSEVI with rosuvastatin is contraindicated. Coadministration of VOSEVI with rosuvastatin may significantly increase the concentration of rosuvastatin which is associated with increased risk of myopathy, including rhabdomyolysis.
Immunosuppressants:		
cyclosporine[c]	↑ voxilaprevir	Coadministration of VOSEVI with cyclosporine is not recommended. Coadministration of voxilaprevir with cyclosporine has been shown to substantially increase the plasma concentration of voxilaprevir, the safety of which has not been established.
Oral Contraceptives:		
ethinyl estradiol-containing drugs	↔	Coadministration of VOSEVI with ethinyl estradiol-containing drugs may increase the risk of ALT elevation. Monitoring of ALT may be considered.

*Drug not marketed in Canada

a. This table is not all inclusive.

b. ↑ = increase, ↓ = decrease, ↔ = no effect.
c These interactions have been studied in healthy adults.

Drugs without Clinically Significant Interactions with VOSEVI

Based on drug interaction studies conducted with the components of VOSEVI (sofosbuvir, velpatasvir, and/or voxilaprevir) or VOSEVI, no clinically significant drug interactions have been either observed or are expected when VOSEVI is combined with the following drugs: cobicistat, darunavir, dolutegravir, elvitegravir, emtricitabine, gemfibrozil, ketoconazole, methadone, raltegravir, rilpivirine, ritonavir, tacrolimus, tenofovir alafenamide, or voriconazole (see **DRUG INTERACTIONS**, **Assessment of Drug Interactions**).

Assessment of Drug Interactions

The effects of coadministered drugs on the exposure of sofosbuvir, GS-331007, velpatasvir, and voxilaprevir are shown in Table 6. The effects of sofosbuvir, velpatasvir, voxilaprevir, sofosbuvir/velpatasvir, or VOSEVI on the exposure of coadministered drugs are shown in Table 7.

Table 6. Drug Interactions: Changes in Pharmacokinetic Parameters for Sofosbuvir and the Predominant Circulating Metabolite GS-331007, Velpatasvir, and Voxilaprevir in the Presence of the Coadministered Drug[a]

Co-administered Drug		Sofosbuvir (SOF)/ Velpatasvir (VEL)/ Voxilaprevir (VOX)		N	Mean Ratio (90% CI) of Sofosbuvir, GS-331007, Velpatasvir, and Voxilaprevir PK with/without Coadministered Drug No Effect=1.00			
Drug	Dosage (mg)	Active Component	Dosage (mg)		Component	C_{max}	AUC	C_{min}
Acid Reducing Agents								
Famotidine	40 single dose simultaneously with VOSEVI	SOF/VEL/ VOX	400/100/100 single dose	35	sofosbuvir	0.96 (0.85, 1.09)	0.94 (0.88, 1.00)	NA
					GS-331007	1.08 (1.03, 1.12)	1.04 (1.02, 1.06)	NA
					velpatasvir	0.91 (0.83, 1.00)	0.90 (0.79, 1.01)	NA
					voxilaprevir	0.90 (0.81, 1.00)	0.98 (0.90, 1.06)	NA
	40 single dose 12 hours prior to VOSEVI	SOF/VEL/ VOX	400/100/100 single dose	36	sofosbuvir	0.93 (0.82, 1.05)	0.87 (0.82, 0.92)	NA
					GS-331007	1.14 (1.10, 1.19)	1.01 (0.99, 1.03)	NA
					velpatasvir	0.87 (0.79, 0.95)	0.85 (0.75, 0.96)	NA
					voxilaprevir	0.90 (0.81, 1.01)	0.94 (0.87, 1.03)	NA

Co-administered Drug		Sofosbuvir (SOF)/ Velpatasvir (VEL)/ Voxilaprevir (VOX)		N	Mean Ratio (90% CI) of Sofosbuvir, GS-331007, Velpatasvir, and Voxilaprevir PK with/without Coadministered Drug No Effect=1.00			
Drug	**Dosage (mg)**	**Active Component**	**Dosage (mg)**		**Component**	**C_{max}**	**AUC**	**C_{min}**
Omeprazole	20 once daily 2 hours prior to VOSEVI	SOF/VEL/ VOX	400/100/100 single dose	34	sofosbuvir	0.77 (0.65, 0.91)	0.73 (0.67, 0.79)	NA
					GS-331007	1.27 (1.20, 1.34)	0.97 (0.94, 1.01)	NA
					velpatasvir	0.43 (0.38, 0.49)	0.46 (0.41, 0.52)	NA
					voxilaprevir	0.76 (0.69, 0.85)	0.80 (0.74, 0.87)	NA
	20 once daily 4 hours after VOSEVI	SOF/VEL/ VOX	400/100/100 single dose	34	sofosbuvir	0.94 (0.83, 1.06)	0.82 (0.77, 0.87)	NA
					GS-331007	1.19 (1.13, 1.26)	0.99 (0.97, 1.01)	NA
					velpatasvir	0.49 (0.43, 0.55)	0.49 (0.43, 0.55)	NA
					voxilaprevir	1.08 (0.96, 1.22)	0.95 (0.88, 1.03)	NA
Antifungal Agent								
Ketoconazole	200 twice daily	VEL	100 single dose	12	velpatasvir	1.29 (1.02, 1.64)	1.71 (1.35, 2.18)	NA
Voriconazole	200 twice daily	VOX	100 single dose	24	voxilaprevir	1.13 (0.98, 1.31)	1.84 (1.66, 2.03)	NA
Antihyperlipidemic Agent								
Gemfibrozil	600 twice daily	VOX	100 single dose	24	voxilaprevir	0.98 (0.85, 1.13)	1.11 (1.01, 1.23)	NA
Antimycobacterials								
Rifampin	600 once daily	SOF	400 single dose	17	sofosbuvir	0.23 (0.19, 0.29)	0.28 (0.24, 0.32)	NA
					GS-331007	1.23 (1.14, 1.34)	0.95 (0.88, 1.03)	NA
		VEL	100 single dose	12	velpatasvir	0.29 (0.23, 0.37)	0.18 (0.15, 0.22)	NA
		VOX	100 single dose		voxilaprevir	0.91 (0.76, 1.10)	0.27 (0.23, 0.31)	NA
	600 single dose	VEL	100 single dose	12	velpatasvir	1.28 (1.05, 1.56)	1.46 (1.17, 1.83)	NA
		VOX	100 single dose	24	voxilaprevir	11.10 (8.23, 14.98)	7.91 (6.20, 10.09)	NA

Co-administered Drug		Sofosbuvir (SOF)/ Velpatasvir (VEL)/ Voxilaprevir (VOX)		N	Mean Ratio (90% CI) of Sofosbuvir, GS-331007, Velpatasvir, and Voxilaprevir PK with/without Coadministered Drug No Effect=1.00			
Drug	Dosage (mg)	Active Component	Dosage (mg)		Component	C_{max}	AUC	C_{min}
HIV Antiretrovirals								
Atazanavir + ritonavir	300 + 100 single dose	SOF/VEL/ VOX	400/100/100 single dose	15	sofosbuvir	1.29 (1.09, 1.52)	1.40 (1.25, 1.57)	NA
					GS-331007	1.05 (0.99, 1.12)	1.25 (1.16, 1.36)	NA
					velpatasvir	1.29 (1.07, 1.56)	1.93 (1.58, 2.36)	NA
					voxilaprevir	4.42 (3.65, 5.35)	4.31 (3.76, 4.93)	NA
Darunavir + ritonavir + emtricitabine/ tenofovir DF	800 + 100 + 200/300 once daily	SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily	29	sofosbuvir	0.70 (0.62, 0.78)	0.78 (0.73, 0.83)	NA
					GS-331007	1.06 (1.01, 1.10)	1.15 (1.12, 1.19)	NA
					velpatasvir	0.78 (0.73, 0.84)	0.95 (0.88, 1.02)	1.16 (1.07, 1.26)
					voxilaprevir	1.72 (1.51, 1.97)	2.43 (2.15, 2.75)	4.00 (3.44, 4.65)
Dolutegravir	50 once daily	SOF/VEL	400/100 once daily	24	sofosbuvir	0.88 (0.80, 0.98)	0.92 (0.85, 0.99)	NA
					GS-331007	1.01 (0.93, 1.10)	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)
					velpatasvir	0.94 (0.86, 1.02)	0.91 (0.84, 0.98)	0.88 (0.82, 0.94)
Efavirenz/ emtricitabine/ tenofovir DF[b]	600/200/300 once daily	SOF/VEL	400/100 once daily	14	sofosbuvir	1.38 (1.14, 1.67)	0.97 (0.83, 1.14)	NA
					GS-331007	0.86 (0.80, 0.93)	0.90 (0.85, 0.96)	1.01 (0.95, 1.07)
					velpatasvir	0.53 (0.43, 0.64)	0.47 (0.39, 0.57)	0.43 (0.36, 0.52)
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide[c]	150/150/200/ 10 once daily	SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily	29	sofosbuvir	1.27 (1.09, 1.48)	1.22 (1.12, 1.32)	NA
					GS-331007	1.28 (1.25, 1.32)	1.43 (1.39, 1.47)	NA
					velpatasvir	0.96 (0.89, 1.04)	1.16 (1.06, 1.27)	1.46 (1.30, 1.64)
					voxilaprevir	1.92 (1.63, 2.26)	2.71 (2.30, 3.19)	4.50 (3.68, 5.50)
Emtricitabine/ rilpivirine/ tenofovir alafenamide[d]	200/25/25once daily	SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily	30	sofosbuvir	0.95 (0.86, 1.05)	1.01 (0.97, 1.06)	NA
					GS-331007	1.02 (0.98, 1.06)	1.04 (1.01, 1.06)	NA
					velpatasvir	1.05 (0.96, 1.16)	1.01 (0.94, 1.07)	1.01 (0.95, 1.09)
					voxilaprevir	0.96 (0.84, 1.11)	0.94 (0.84, 1.05)	1.02 (0.92, 1.12)

Co-administered Drug		Sofosbuvir (SOF)/ Velpatasvir (VEL)/ Voxilaprevir (VOX)		N	Mean Ratio (90% CI) of Sofosbuvir, GS-331007, Velpatasvir, and Voxilaprevir PK with/without Coadministered Drug No Effect=1.00			
Drug	Dosage (mg)	Active Component	Dosage (mg)		Component	C_{max}	AUC	C_{min}
Raltegravir + emtricitabine/ tenofovir DF	400 twice daily+200/300 once daily	SOF/VEL	400/100 once daily	30	sofosbuvir	1.09 (0.97, 1.23)	1.16 (1.07, 1.25)	NA
					GS-331007	0.95 (0.91, 0.98)	1.03 (1.00, 1.06)	1.08 (1.04, 1.13)
					velpatasvir	0.97 (0.87, 1.08)	0.98 (0.88, 1.10)	0.97 (0.87, 1.07)
Immunosuppressants								
Cyclosporine	600 single dose	SOF	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
		VEL	100 single dose	12	velpatasvir	1.56 (1.22, 2.01)	2.03 (1.51, 2.71)	NA
		VOX	100 single dose	25	voxilaprevir	19.02 (14.12, 25.62)	9.39 (7.37, 11.96)	NA
Tacrolimus	5 single dose	SOF	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 Agonists								
Methadone	30 to 130 daily	SOF	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

NA = not available/not applicable

a. All interaction studies conducted in healthy volunteers.

b. Administered as ATRIPLA® (efavirenz/emtricitabine/tenofovir DF fixed-dose combination).

c. Administered as GENVOYA® (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fixed-dose single tablet regimen).

d. Administered as ODEFSEY™ (emtricitabine/rilpivirine/tenofovir alafenamide fixed-dose single tablet regimen).

Table 7. Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Sofosbuvir, Velpatasvir, Voxilaprevir, or VOSEVI[a]

Co-administered Drug		Sofosbuvir (SOF)/ Velpatasvir (VEL)/ Voxilaprevir (VOX)		N	Mean Ratio (90% CI) of Coadministered Drug PK with/without Sofosbuvir, Velpatasvir, Voxilaprevir, or VOSEVI No Effect=1.00		
Drug	Dosage (mg)	Active Component	Dosage (mg)		C_{max}	AUC	C_{min}
Antiarrhythmics							
Digoxin	0.25 single dose	VEL	100 once daily	21	1.88 (1.71, 2.08)	1.34 (1.13, 1.60)	NA

Co-administered Drug		Sofosbuvir (SOF)/ Velpatasvir (VEL)/ Voxilaprevir (VOX)		N	Mean Ratio (90% CI) of Coadministered Drug PK with/without Sofosbuvir, Velpatasvir, Voxilaprevir, or VOSEVI No Effect=1.00		
Drug	Dosage (mg)	Active Component	Dosage (mg)		C_{max}	AUC	C_{min}
Anticoagulant							
Dabigatran etexilate	75 single dose	SOF/VEL/ VOX + VOX	400/100/100 + 100 single dose	36	2.87 (2.61, 3.15)	2.61 (2.41, 2.82)	NA
HIV Antiretrovirals							
Darunavir + ritonavir + emtricitabine/ tenofovir DF[b]	darunavir 800 once daily	SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily	29	0.89 (0.85, 0.94)	0.86 (0.81, 0.91)	0.66 (0.58, 0.74)
	ritonavir 100 once daily				1.60 (1.47, 1.75)	1.45 (1.35, 1.57)	0.80 (0.72, 0.89)
	emtricitabine 200 once daily				0.88 (0.82, 0.94)	0.99 (0.96, 1.03)	1.20 (1.15, 1.26)
	tenofovir DF 300 once daily				1.48 (1.36, 1.61)	1.39 (1.32, 1.46)	1.47 (1.38, 1.56)
Dolutegravir	50 once daily	SOF/VEL	400/100 once daily	24	1.06 (1.01, 1.11)	1.06 (1.01, 1.13)	1.04 (0.98, 1.10)
Efavirenz/ emtricitabine/ tenofovir DF[c]	efavirenz 600 once daily	SOF/VEL	400/100 once daily	15	0.81 (0.74, 0.89)	0.85 (0.80, 0.91)	0.90 (0.85, 0.95)
	emtricitabine 200 once daily				1.07 (0.98, 1.18)	1.07 (1.00, 1.14)	1.10 (0.97, 1.25)
	tenofovir DF 300 once daily				1.77 (1.53, 2.04)	1.81 (1.68, 1.94)	2.21 (2.00, 2.43)
Elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide[d]	elvitegravir 150 once daily	SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily	29	0.79 (0.75, 0.85)	0.94 (0.88, 1.00)	1.32 (1.17, 1.49)
	cobicistat 150 once daily				1.23 (1.18, 1.28)	1.50 (1.44, 1.58)	3.50 (3.01, 4.07)
	emtricitabine 200 once daily				0.87 (0.84, 0.91)	0.96 (0.94, 0.99)	1.14 (1.09, 1.20)
	tenofovir alafenamide 10 once daily				0.79 (0.68, 0.92)	0.93 (0.85, 1.01)	NA
Emtricitabine/ rilpivirine/tenofovir alafenamide[e]	emtricitabine 200 once daily	SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily	30	0.88 (0.83, 0.93)	0.93 (0.90, 0.96)	1.07 (1.01, 1.14)
	rilpivirine 25 once daily				0.79 (0.74, 0.84)	0.80 (0.76, 0.85)	0.82 (0.77, 0.87)
	tenofovir alafenamide 25 once daily				1.32 (1.17, 1.48)	1.52 (1.43, 1.61)	NA
Raltegravir + emtricitabine/ tenofovir DF	emtricitabine 200 once daily	SOF/VEL	400/100 once daily	30	1.08 (1.04, 1.12)	1.05 (1.03, 1.07)	1.02 (0.97, 1.08)
	tenofovir DF 300 once daily				1.46 (1.39, 1.54)	1.40 (1.34, 1.45)	1.70 (1.61, 1.79)
	raltegravir 400 twice daily				1.03 (0.74, 1.43)	0.97 (0.73, 1.28)	0.79 (0.42, 1.48)

Co-administered Drug		Sofosbuvir (SOF)/ Velpatasvir (VEL)/ Voxilaprevir (VOX)		N	Mean Ratio (90% CI) of Coadministered Drug PK with/without Sofosbuvir, Velpatasvir, Voxilaprevir, or VOSEVI No Effect=1.00		
Drug	Dosage (mg)	Active Component	Dosage (mg)		C_{max}	AUC	C_{min}
HMG-COA Reductase Inhibitors							
Pravastatin	pravastatin 40 single dose	SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily	19	1.89 (1.53, 2.34)	2.16 (1.79, 2.60)	NA
Rosuvastatin	rosuvastatin 10 single dose	SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily	19	18.88 (16.23, 21.96)	7.39 (6.68, 8.18)	NA
Immunosuppressants							
Cyclosporine	600 single dose	SOF	400 single dose	19	1.06 (0.94, 1.18)	0.98 (0.85, 1.14)	NA
		VEL	100 single dose	12	0.92 (0.82, 1.02)	0.88 (0.78, 1.00)	NA
		VOX	100 single dose	24	0.95 (0.88, 1.03)	0.94 (0.84, 1.06)	NA
Tacrolimus	5 single dose	SOF	400 once daily	16	0.73 (0.59, 0.90)	1.09 (0.84, 1.40)	NA
Oral Contraceptives							
Norelgestromin	norgestimate 0.180/0.215/0.250/ ethinyl estradiol 0.025 once daily	SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily	15	1.08 (0.98, 1.19)	1.07 (1.03, 1.12)	1.14 (1.07, 1.21)
Norgestrel					1.15 (1.08, 1.22)	1.15 (1.06, 1.25)	1.22 (1.11, 1.33)
Ethinyl estradiol					1.21 (1.06, 1.38)	1.05 (0.97, 1.15)	0.93 (0.83, 1.04)
Opiate Agonists							
R-Methadone	30 to 130 daily	SOF	400 once daily	14	0.99 (0.85, 1.16)	1.01 (0.85, 1.21)	0.94 (0.77, 1.14)
S-Methadone		SOF	400 once daily	14	0.95 (0.79, 1.13)	0.95 (0.77, 1.17)	0.95 (0.74, 1.22)

NA = not available/not applicable

a. All interaction studies conducted in healthy volunteers.

b. Comparison based on exposures when administered as darunavir + ritonavir + emtricitabine/tenofovir DF.

c. Administered as ATRIPLA (efavirenz/emtricitabine/tenofovir DF fixed-dose combination).

d. Administered as GENVOYA (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fixed-dose single tablet regimen).

e. Administered as ODEFSEY (emtricitabine/rilpivirine/tenofovir alafenamide fixed-dose single tablet regimen).

Drug-Food Interactions

VOSEVI should be taken with food. Food increases the bioavailability of VOSEVI (see **DOSAGE AND ADMINISTRATION**, **Recommended Dose and Dosage Adjustment** and **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics**).

Drug-Herb Interactions

Coadministration of VOSEVI with St. John's wort is contraindicated.

Coadministration of St. John's wort, a potent P-gp and CYP inducer, may decrease sofosbuvir, velpatasvir, and voxilaprevir plasma concentrations, which may result in loss of therapeutic effect. See **WARNINGS AND PRECAUTIONS**, **General, Use with Potent P-gp Inducers and/or Moderate to Potent Inducers of CYP**.

Drug-Laboratory Interactions

Interactions of VOSEVI with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

VOSEVI is a single tablet regimen. No dosage adjustments are possible for VOSEVI.

The recommended dose of VOSEVI is one tablet of 400 mg/100 mg/100 mg sofosbuvir/velpatasvir/voxilaprevir, taken orally, once daily with food (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**, ***Effects of Food***).

The recommended dose and treatment duration for VOSEVI is provided in Table 8.

Table 8. Recommended Treatment Regimen

Genotype	Patients Previously Treated with an HCV Regimen Containing:	VOSEVI Duration
1, 2, 3, 4, 5, or 6	An NS5A inhibitor[a]	12 weeks
1, 2, 3, or 4	Sofosbuvir without an NS5A inhibitor[b]	12 weeks

a. In clinical trials, prior NS5A inhibitor experience included daclatasvir, elbasvir, ledipasvir, ombitasvir, or velpatasvir.

b. In clinical trials, prior treatment experience included sofosbuvir with or without any of the following: peginterferon alfa/ribavirin, ribavirin, HCV NS3/4A protease inhibitor (boceprevir, simeprevir or telaprevir).

Special Populations

Pediatrics (< 18 Years of age)

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

Geriatrics (≥ 65 years of age)

No dose adjustment is warranted for elderly patients (see **ACTION AND CLINICAL PHARMACOLOGY**).

Hepatic Impairment

VOSEVI is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C). No dose adjustment of VOSEVI is required for patients with mild hepatic impairment (Child-Pugh A) (see **ACTION AND CLINICAL PHARMACOLOGY**).

Renal Impairment

The safety and efficacy of VOSEVI has not been established in patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2) or ESRD requiring hemodialysis. No dose adjustment of VOSEVI is required for patients with mild or moderate renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY**).

Missed Dose

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

If a patient misses a dose of VOSEVI 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 VOSEVI must not be taken.

If a patient vomits less than 4 hours after taking a dose of VOSEVI, the patient should take another dose of VOSEVI. If a patient vomits more than 4 hours after taking a dose of VOSEVI, 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.

Administration of activated charcoal may 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.

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

The highest documented doses of sofosbuvir, velpatasvir, and voxilaprevir were single doses of 1200 mg, 500 mg, and 900 mg, respectively. In healthy volunteer studies with sofosbuvir and velpatasvir, there were no untoward effects observed at these dose levels, and adverse events were similar in frequency and severity to those reported in the placebo groups. The most common adverse events in subjects receiving voxilaprevir 900 mg were diarrhea (34%), vomiting (19%), and nausea (17%). The effects of higher doses/exposures are not known.

ACTION AND CLINICAL PHARMACOLOGY

Description

VOSEVI is a pan-genotypic single tablet regimen of sofosbuvir, velpatasvir, and voxilaprevir.

Sofosbuvir is a nucleotide analog pan-genotypic NS5B polymerase inhibitor. Velpatasvir is a pan-genotypic HCV NS5A inhibitor. Voxilaprevir is a pan-genotypic inhibitor of the NS3/4A protease.

Mechanism of Action

VOSEVI

Sofosbuvir, velpatasvir and voxilaprevir exhibit high potency and specificity as individual agents against HCV as compounds that target the HCV NS5B, NS5A, and NS3/4A proteins, respectively. Sofosbuvir, velpatasvir, and voxilaprevir individually displayed potent and broad inhibitory activity against HCV genotypes 1-6. *In vitro* combination of sofosbuvir and velpatasvir, sofosbuvir and voxilaprevir, or velpatasvir and voxilaprevir exhibited an additive antiviral interaction. No antiviral antagonism or exacerbated cellular toxicity was observed in either of the 2-drug combinations.

Sofosbuvir

Sofosbuvir is a pan-genotypic polymerase inhibitor of the HCV NS5B RNA-dependent RNA polymerase. Sofosbuvir is a monophosphorylated pyrimidine nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203).

Velpatasvir

Velpatasvir is a pan-genotypic HCV inhibitor targeting the HCV NS5A protein, which is essential for both RNA replication and the assembly of HCV virions. *In vitro* resistance selection and cross-resistance studies indicate velpatasvir targets NS5A as its mode of action.

Voxilaprevir

Voxilaprevir is a pan-genotypic inhibitor of the HCV NS3/4A protease. Voxilaprevir acts as a noncovalent, reversible inhibitor of the NS3/4A protease.

Pharmacodynamics

Effect on Electrocardiogram

Administration of supratherapeutic doses of sofosbuvir (1200 mg), velpatasvir (500 mg), or voxilaprevir (900 mg) (as individual drugs) demonstrated a lack of effect on QTc interval.

Pharmacokinetics

Sofosbuvir and GS-331007 AUCs are near dose proportional over the dose range of 200 mg to 1200 mg. Velpatasvir AUC increases in a greater than proportional manner from 5 to 50 mg and in a less than proportional manner from 50 to 450 mg, indicating velpatasvir absorption is solubility limited. Voxilaprevir (studied under fed conditions) AUC increases in a greater than proportional manner over the dose range of 100 to 900 mg.

The pharmacokinetic properties of the components of VOSEVI are provided in Table 9. The multiple dose pharmacokinetic parameters of sofosbuvir and its metabolite, GS-331007, velpatasvir, and voxilaprevir are provided in Table 10.

Table 9 Pharmacokinetic Properties of the Components of VOSEVI

			Sofosbuvir	Velpatasvir	Voxilaprevir
Absorption					
T_{max} (h)			2	4	4
Effect of food (relative to fasting)[a]	Low fat, low calorie[b]	AUC_T	↑ 119%	↑ 181%	↑ 131%
		C_{max}	↑ 73%	↑ 187%	↑ 147%
	Moderate fat, moderate calorie[b]	AUC_T	↑ 146%	↑ 142%	↑ 223%
		C_{max}	↑ 76	↑ 146%	↑ 259%
	High fat, high calorie[c]	AUC_T	↑ 64%	↑ 41%	↑ 542%
		C_{max}	↑ 9	↑ 37%	↑ 679%
Distribution					
% Bound to human plasma proteins			61–65	>99	>99
Blood-to-plasma ratio			0.7	0.5-0.7	0.5-0.8
Metabolism					
Metabolism			Cathepsin A CES1 HINT1	CYP2B6 CYP2C8 CYP3A4	CYP3A4
Elimination					
Major route of elimination			SOF: metabolism GS-331007[d]: glomerular filtration and active tubular secretion	Biliary excretion as parent (77%)	Biliary excretion as parent (40%)
$t_{1/2}$ (h)[e]			SOF: 0.5 GS-331007[d]: 29	17	33
% Of dose excreted in urine[f]			80[e]	0.4	0
% Of dose excreted in feces[f]			14	94	94

CES1 = carboxylesterase 1; HINT1 = histidine triad nucleotide-binding protein 1.

a. Values refer to % increase in geometric mean exposures.
b. Single dose concomitant administration of sofosbuvir/velpatasvir 400 mg/100 mg fixed-dose combination tablet + voxilaprevir 100 mg tablet.
c. Single dose administration of VOSEVI.
d. GS-331007 is the primary circulating nucleoside metabolite of SOF.
e. $t_{1/2}$ values refer to median terminal plasma half-life.
f. Single dose administration of [^{14}C] SOF, [^{14}C] VEL, [^{14}C] VOX in mass balance studies.
g. Predominantly as GS-331007.

Table 10 Multiple Dose Pharmacokinetic Parameters of Sofosbuvir and its Metabolite, GS-331007, Velpatasvir, and Voxilaprevir Following Oral Administration in HCV-Infected Adults

Parameter Mean (%CV)	Sofosbuvir[a]	GS-331007[b]	Velpatasvir[c]	Voxilaprevir[d]
C_{max} (nanogram per mL)	678 (35.4)	744 (28.3)	311 (56.1)	192 (85.8)
AUC_{tau} (nanogram•hr per mL)	1665 (30.1)	12834 (29.0)	4041 (48.6)	2577 (73.7)
C_{trough} (nanogram per mL)	NA	NA	51 (64.7)	47 (82.0)

CV = Coefficient of Variation; NA = Not Applicable.
a. From Population PK analysis, N = 1038.
b. From Population PK analysis, N = 1593.
c. From Population PK analysis, N = 1595.
d. From Population PK analysis, N = 1591.

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, velpatasvir AUC_{0-24} and C_{max} were 41% lower and 39% lower, respectively, in HCV-infected subjects. Relative to healthy subjects, voxilaprevir AUC_{0-24} and C_{max} were both 260% higher in HCV-infected subjects. Age, sex, race, BMI, or the presence or absence of cirrhosis had no clinically relevant effects on the exposure of sofosbuvir, GS-331007, velpatasvir, or voxilaprevir.

Absorption

Following oral administration of VOSEVI, sofosbuvir median peak plasma concentration was observed 2 hours post-dose. Median peak plasma concentration of GS-331007, velpatasvir, and voxilaprevir were observed 4 hours post-dose.

Effects of Food

The bioavailability of sofosbuvir, velpatasvir and voxilaprevir increased following single dose administration of VOSEVI with a high fat, high calorie meal or concomitant administration of a sofosbuvir/velpatasvir fixed dose combination tablet + voxilaprevir tablet with a low fat, low calorie or a moderate fat, moderate calorie meal (Table 9).

Distribution

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.

Velpatasvir is > 99% bound to human plasma proteins and binding is independent of drug concentration over the range of 0.09 μg/mL to 1.8 μg/mL. After a single 100 mg dose of [^{14}C]-velpatasvir in healthy subjects, the blood to plasma ratio of [^{14}C]-radioactivity ranged between 0.5 and 0.7.

Voxilaprevir is approximately > 99% bound to human plasma proteins. After a single 100 mg dose of [^{14}C]-voxilaprevir in healthy male subjects, the blood to plasma ratio of [^{14}C]-radioactivity ranged between 0.5 and 0.8.

Metabolism

Sofosbuvir is extensively metabolized in the liver to form the pharmacologically active nucleoside analog triphosphate, GS-461203. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity *in vitro*. After a single 400 mg oral dose of [^{14}C]-sofosbuvir, GS-331007 accounted for greater than 90% of total systemic exposure.

Velpatasvir is primarily a substrate of CYP2B6, CYP2C8, and CYP3A4 with slow turnover. Following a single dose of 100 mg [^{14}C]-velpatasvir to healthy human male subjects, the majority (> 98%) of radioactivity in plasma was the parent drug. Unchanged velpatasvir is the major species present in feces.

Voxilaprevir is primarily a substrate of CYP3A4 with slow turnover. Following a single dose of 100 mg [^{14}C]-voxilaprevir, the majority (approximately 91%) of radioactivity in plasma was parent drug. Hydrolyzed- and dehydrogenated-voxilaprevir were the major metabolites identified in human plasma. Unchanged voxilaprevir is the major species present in feces.

Excretion

Sofosbuvir is primarily eliminated in the urine as GS-331007. The median terminal half-lives of sofosbuvir and GS-331007 following administration of VOSEVI were 0.5 and 29 hours, respectively.

Biliary excretion of parent drug was the major route of elimination for velpatasvir. The median terminal half-life of velpatasvir following administration of VOSEVI was approximately 17 hours.

Biliary excretion of parent drug was the major route of elimination for voxilaprevir. The median terminal half-life of voxilaprevir following administration of VOSEVI was approximately 33 hours.

Special Populations and Conditions

Pediatrics (< 18 years of age)

The pharmacokinetics of VOSEVI in pediatric patients have not been established.

Geriatrics (≥ 65 years of age)

Based on population pharmacokinetic analyses, age did not have a clinically relevant effect on the exposure to sofosbuvir, GS-331007, velpatasvir, or voxilaprevir. Clinical trials of VOSEVI included 74 subjects aged 65 and over (17% of the total number of subjects in the POLARIS-1 and POLARIS-4 Phase 3 clinical trials). The response rates observed for patients ≥ 65 years of age were similar to those of patients < 65 years of age, across treatment groups.

Gender

No clinically relevant pharmacokinetic differences due to gender have been identified for sofosbuvir, GS-331007, velpatasvir, or voxilaprevir.

Race

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

Hepatic Insufficiency

Hepatic impairment studies were conducted with the individual drugs, sofosbuvir, velpatasvir, and voxilaprevir.

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 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, respectively, 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. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (Child-Pugh A) had no clinically relevant effect on the exposure of sofosbuvir and GS-331007.

The pharmacokinetics of velpatasvir were studied with a single dose of 100 mg velpatasvir in HCV negative subjects with moderate and severe hepatic impairment (Child-Pugh B and C). Velpatasvir plasma exposure (AUC_{inf}) was similar in subjects with moderate hepatic impairment, severe hepatic impairment, and control subjects with normal hepatic function. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (Child-Pugh A) had no clinically relevant effect on the exposure of velpatasvir.

The pharmacokinetics of voxilaprevir were studied with a single dose of 100 mg voxilaprevir in HCV negative subjects with moderate and severe hepatic impairment (Child-Pugh B and C). Relative to subjects with normal hepatic function, the voxilaprevir AUC_{inf} was 299% and 500% higher in subjects with moderate and severe hepatic impairment, respectively. Population pharmacokinetic analysis in HCV-infected patients indicated that patients with cirrhosis (Child-Pugh A) had 73% higher exposure of voxilaprevir than those without cirrhosis.

Renal Insufficiency

Renal impairment studies have been conducted with the individual drugs, sofosbuvir, velpatasvir, and voxilaprevir.

The pharmacokinetics of sofosbuvir were studied in HCV negative subjects with mild (eGFR ≥ 50 and < 80 mL/min/1.73m^2), moderate (eGFR ≥ 30 and < 50 mL/min/1.73m^2), severe renal impairment (eGFR < 30 mL/min/1.73m^2) and subjects with ESRD requiring hemodialysis following a single 400 mg dose of sofosbuvir. Relative to subjects with normal renal function (eGFR > 80 mL/min/1.73m^2), the sofosbuvir AUC_{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 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.

Exposure of velpatasvir is not significantly impacted in the setting of severe renal impairment. The pharmacokinetics of velpatasvir were studied with a single dose of 100 mg velpatasvir in HCV negative subjects with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault). Velpatasvir AUC and C_{max} were approximately 50% and 11% higher, respectively, in subjects with severe renal impairment compared to control subjects with normal renal function; these differences are not considered clinically relevant.

The pharmacokinetics of voxilaprevir were studied with a single dose of 100 mg voxilaprevir in HCV negative subjects with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault). Voxilaprevir AUC and C_{max} were approximately 71% and 45% higher, respectively, in subjects with severe renal impairment compared to control subjects with normal renal function; these differences are not considered clinically significant.

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

VOSEVI is a single tablet regimen containing sofosbuvir, velpatasvir, and voxilaprevir for oral administration.

Each tablet contains 400 mg of sofosbuvir, 100 mg of velpatasvir, and 100 mg of voxilaprevir. 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: ferrosoferric oxide, iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

VOSEVI is available as a beige-colored, capsule-shaped, film-coated tablet debossed with "GSI" on one side and "3" on the other side of the tablet. Each bottle contains 28 tablets, a polyester coil and silica gel desiccant and is closed with a child-resistant closure.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

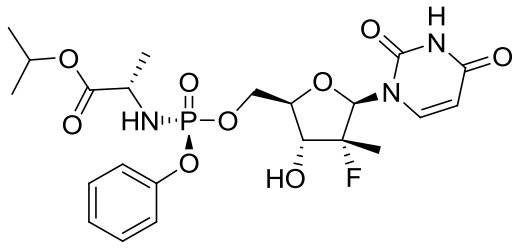
Common name: **sofosbuvir**

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.

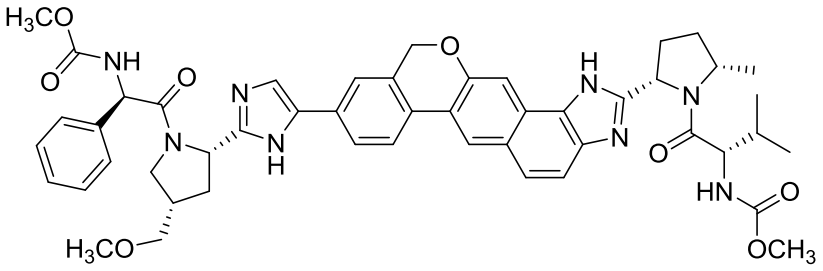
Common name: **velpatasvir**

Chemical name: Methyl {(1*R*)-2-[(2*S*,4*S*)-2-(5-{2-[(2*S*,5*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

Molecular formula: $C_{49}H_{54}N_8O_8$

Molecular mass: 883.00

Structural formula:



Physicochemical properties:

Appearance — Velpatasvir is a white to tan or yellow solid.

Solubility — Velpatasvir is practically insoluble (< 0.1 mg/mL) above pH 5, slightly soluble (3.6 mg/mL) at pH 2.0, and soluble (> 36 mg/mL) at pH 1.2.

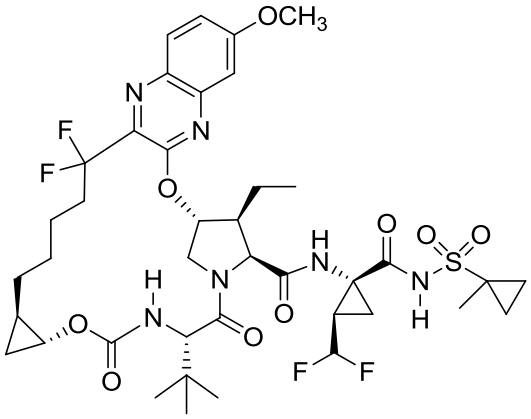
Common name: **voxilaprevir**

Chemical name: (1*aR*,5*S*,8*S*,9*S*,10*R*,22a*R*)-5-*tert*-butyl-*N*-{(1*R*,2*R*)-2-(difluoromethyl)-1-[(1-methylcyclopropanesulfonyl) carbamoyl]cyclopropyl}-9-ethyl-18,18-difluoro-14-methoxy-3,6-dioxo-1,1*a*,3,4,5,6,9,10,18,19,20,21,22,22*a*-tetradecahydro-8*H*-7,10-methanocyclopropa[18,19][1,10,3,6] dioxadiazacyclononadecino[11,12-*b*]quinoxaline-8-carboxamide

Molecular formula: $C_{40}H_{52}F_4N_6O_9S$ (on solvate-free basis)

Molecular mass: 868.9 (on solvate-free basis)

Structural formula:



Voxilaprevir drug substance is produced from the crystallization, isolation, and drying of the voxilaprevir ethyl acetate solvate.

Physicochemical properties:

Appearance	Voxilaprevir is a white to light brown solid.
Solubility	Voxilaprevir is slightly hygroscopic to hygroscopic. Voxilaprevir is practically insoluble (less than 0.1 mg/mL) below pH 6.8.

CLINICAL TRIALS

The efficacy of VOSEVI was evaluated in two Phase 3 trials with data available for a total of 445 DAA-experienced patients with genotype 1 to 6 HCV infection without cirrhosis or with compensated cirrhosis.

Sustained virologic response (SVR12), defined as HCV RNA less than lower limit of quantification (LLOQ) at 12 weeks after the cessation of treatment, was the primary endpoint to determine the HCV cure rate. Serum HCV RNA values were measured during the clinical trials using the COBAS AmpliPrep/COBAS Taqman HCV test (version 2.0) with a LLOQ of 15 IU per mL.

NS5A Inhibitor-Experienced Adults (POLARIS-1)

Trial Design

The trial design of POLARIS-1 is described in Table 11. Patients with genotype 1 HCV infection were randomized in a 1:1 to each group. Randomization was stratified by the presence or absence of cirrhosis. Patients with all other HCV genotypes were enrolled into the VOSEVI 12-week group.

Table 11. Summary of Trial Design in NS5A Inhibitor-Experienced Patients with Genotypes 1, 2, 3, 4, 5, 6 HCV Infection Without Cirrhosis or with Compensated Cirrhosis (POLARIS-1)

Trial Design	Dosage and Route of Administration	Treatment Regimen	Total Duration
Phase 3, randomized, double-blind, placebo-controlled, multicentre	VOSEVI (400 mg/100 mg/100 mg), QD, PO or Placebo, QD, PO	VOSEVI	12 weeks
		Placebo	12 weeks

PO = orally; QD = once a day

Demographics and Other Baseline Characteristics

The demographics and baseline characteristics for the patients in study POLARIS-1 were generally balanced across the treatment groups and are summarized in Table 12. In the POLARIS-1 trial, prior DAA regimens contained the following NS5A inhibitors: ledipasvir (51%), daclatasvir (27%), ombitasvir (11%), velpatasvir (7%), and elbasvir (3%).

Table 12. Demographic and Other Baseline Characteristics of NS5A Inhibitor-Experienced Patients with Genotypes 1, 2, 3, 4, 5, 6 HCV Infection Without Cirrhosis or with Compensated Cirrhosis (POLARIS-1)

Characteristics	VOSEVI 12 Weeks N = 263	Placebo 12 Weeks N = 152
Age (years)		
Mean (range)	58 (27-84)	59 (29-80)
Gender, n (%)		
Male	200 (76)	121 (80)
Female	63 (24)	31 (20)
Race, n (%*)		
White	211 (80)	124 (82)
Black	38 (14)	22 (14)
Asian	8 (3)	6 (4)
Native Hawaiian or Pacific Islander	3 (1)	0
Not disclosed	1 (<1)	0
American Indian or Alaska Native	1 (<1)	0
Other	1 (< 1)	0
BMI, n (%)		
< 30 kg/m^2	179 (68)	100 (66)
≥ 30 kg/m^2	84 (32)	52 (34)
Viral Load		
HCV RNA Log_{10} IU/mL, mean ± SD	6.3 ± 0.7	6.3 ± 0.6
< 800,000 copies/mL, n (%)	73 (28)	36 (24)
≥ 800,000 copies/mL, n (%)	190 (72)	116 (76)
HCV genotype, n (%*)		
1	150 (57)	150 (99)
1a	101 (38)	117 (77)
1b	45 (17)	31 (20)
1 Other	4 (1)	2 (1)
2	5 (2)	0
3	78 (30)	0
4	22 (8)	0
5	1 (<1)	0
6	6 (2)	2 (1)
Unknown	1 (<1)	0
IL28B, n (%*)		
CC	47 (18)	27 (18)
Non-CC	216 (82)	125 (82)
Cirrhosis, n (%*)		
Yes (compensated)	121 (46)	51 (34)
No	142 (54)	101 (66)

Characteristics	VOSEVI 12 Weeks N = 263	Placebo 12 Weeks N = 152
Prior HCV Treatment, n (%)		
DAA-Experienced	263 (100)	152 (100)
NS5A ± DAA(s)	262 (100)	151 (99)
NS5A + NS5B	161 (61)	81 (53)
NS5A + NS3 ± NS5B	83 (32)	61 (40)
NS5A ± Others	18 (7)	9 (6)
Others	1 (<1)	1 (1)

DAA = direct-acting antiviral; SD = standard deviation
*Total percentage may not add to 100% due to rounding.

Study Results

The response rates for the VOSEVI treatment group by HCV genotype in the POLARIS-1 trial are presented in Table 13. Overall, the SVR12 in NS5A inhibitor-experienced patients with genotypes 1, 2, 3, 4, 5, 6 HCV infection with compensated cirrhosis or without cirrhosis was 96%. Treatment with VOSEVI for 12 weeks in POLARIS-1 was statistically superior relative to the pre-specified performance goal of 85% ($p < 0.001$). No patient in the placebo group achieved SVR.

Table 13. SVR12 and Virologic Outcome in NS5A Inhibitor-Experienced Patients with Genotypes 1, 2, 3, 4, 5, 6 HCV Infection Without Cirrhosis or with Compensated Cirrhosis (POLARIS-1)

	VOSEVI 12 Weeks (N=263)								
	Total (all GTs)[a] (N=263)	GT-1			GT-2 (N=5)	GT-3 (N=78)	GT-4 (N=22)	GT-5 (N=1)	GT-6 (N=6)
		GT-1a (N=101)	GT-1b (N=45)	Total[b] (N=150)					
SVR12	96% (253/263)	96% (97/101)	100% (45/45)	97% (146/150)	100% (5/5)	95% (74/78)	91% (20/22)	100% (1/1)	100% (6/6)
Outcome for Patients without SVR									
On-Treatment Virologic Failure[c]	<1% (1/263)	1% (1/101)	0/45	1% (1/150)	0/5	0/78	0/22	0/1	0/6
Relapse[d]	2% (6/261)	1% (1/100)	0/45	1% (1/149)	0/5	5% (4/78)	5% (1/21)	0/1	0/6
Other[e]	1% (3/263)	2% (2/101)	0/45	1% (2/150)	0/5	0/78	5% (1/22)	0/1	0/6

GT = genotype; SVR12 = Sustained virologic response, defined as HCV RNA less than LLOQ (Lower Limit of Quantitation, 15 IU/mL) at 12 weeks after the cessation of treatment.

a. One patient with undetermined genotype achieved SVR12.
b. Four patients had GT-1 subtypes other than GT-1a or GT-1b; all 4 patients achieved SVR12.
c. Pharmacokinetic data for the 1 patient with on-treatment virologic failure was consistent with non-adherence.
d. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.
e. Other includes patients with missing data and those who discontinued treatment prior to virologic suppression.

Subgroup analyses were performed for the primary efficacy endpoint (SVR12) for selected subgroups. High SVR12 rates were achieved in all subgroups, regardless of the presence of cirrhosis (Table 14) or prior DAA class combinations or specific DAA combinations.

Table 14. SVR12 for NS5A Inhibitor-Experienced Patients with Genotypes 1, 2, 3, 4, 5, 6 HCV Infection Without Cirrhosis or With Compensated Cirrhosis (POLARIS-1)

	VOSEVI 12 Weeks N = 263									
	All GTs[a] (N=263) % (n/N)	GT-1				GT-2 (N=5) % (n/N)	GT-3 (N=78) % (n/N)	GT-4 (N=22) % (n/N)	GT-5 (N=1) % (n/N)	GT-6 (N=6) % (n/N)
		GT-1a (N=101) % (n/N)	GT-1b (N=45) % (n/N)	GT-1 Other (N=4) % (n/N)	GT-1 Total (N=150) % (n/N)					
Cirrhosis	93 (113/121)	94 (31/33)	100 (16/16)	100 (2/2)	96 (49/51)	0/0	93 (52/56)	86 (12/14)	0/0	0/0
No Cirrhosis	99 (140/142)	97 (66/68)	100 (29/29)	100 (2/2)	98 (97/99)	100 (5/5)	100 (22/22)	100 (8/8)	100 (1/1)	100 (6/6)

GT = genotype
a. One patient with undetermined genotype without cirrhosis achieved SVR12.

DAA-Experienced Adults Who Had Not Received an NS5A Inhibitor (POLARIS-4)

Trial Design

The trial design of POLARIS-4 is described in Table 15. Patients with genotype 1, 2, or 3 HCV infection were randomized 1:1 to each group. Randomization was stratified by HCV genotype and by the presence or absence of cirrhosis. Patients with genotype 4 HCV infection were enrolled to the VOSEVI 12-week group. Patients whose only DAA exposure was a NS3/4A protease inhibitor were excluded.

Table 15. Summary of Trial Design in DAA-Experienced Patients with Genotype 1, 2, 3, or 4 HCV Infection Without Cirrhosis or With Compensated Cirrhosis who had Not Received an NS5A Inhibitor (POLARIS-4)

Trial Design	Dosage and Route of Administration	Treatment Regimen	Total Duration
Phase 3, randomized, open label, multicentre	VOSEVI (400 mg/100 mg/100 mg), QD, PO or SOF/VEL (400 mg/100 mg), QD, PO	VOSEVI	12 weeks
		SOF/VEL	12 weeks

PO = orally; QD = once a day; SOF = sofosbuvir; VEL = velpatasvir; VOX = voxilaprevir

Demographic and Baseline Characteristics

The demographics and baseline characteristics for the patients in study POLARIS-4 were balanced across the treatment groups and are summarized in Table 16. In the POLARIS-4 trial, prior DAA regimens contained sofosbuvir (85%) with the following: peginterferon alfa and ribavirin or ribavirin (69%), HCV NS3/4A protease inhibitor (boceprevir, simeprevir, or telaprevir; 15%) and investigational DAA (<1%). Of the 15% of subjects without prior sofosbuvir exposure, most received investigational HCV DAAs or approved HCV NS3/4A protease inhibitors, with or without peginterferon alfa and ribavirin.

Table 16. Demographic and Other Baseline Characteristics of DAA-Experienced Patients with Genotype 1, 2, 3, or 4 HCV Infection Without Cirrhosis or With Compensated Cirrhosis who had Not Received an NS5A Inhibitor (POLARIS-4)

Characteristics	VOSEVI 12 Weeks N = 182	SOF/VEL 12 Weeks N = 151
Age (years)		
Mean (range)	57 (24-85)	57 (24-80)
Gender, n (%*)		
Male	143 (79)	114 (75)
Female	39 (21)	37 (24)
Race, n (%*)		
White	160 (88)	131 (87)
Black	16 (9)	13 (9)
Asian	2 (1)	4 (3)
Other	2 (1)	1 (1)
American Indian or Alaska Native	2 (1)	0
Native Hawaiian or Pacific Islander	0	2 (1)
BMI, n (%)		
< 30 kg/m^2	120 (66)	98 (65)
≥ 30 kg/m^2	62 (34)	53 (35)
Viral Load		
HCV RNA Log_{10} IU/mL, mean ± SD	6.3 ± 0.6	6.3 ± 0.7
< 800,000 copies/mL, n (%)	46 (25)	38 (25)
≥ 800,000 copies/mL, n (%)	136 (75)	113 (75)
HCV genotype, n (%)		
1	78 (43)	66 (44)
1a	54 (30)	44 (29)
1b	24 (13)	22 (15)
2 (no confirmed subtype)	31 (17)	33 (22)
3	54 (30)	52 (34)
4	19 (10)	0/0
IL28B, n (%)		
CC	33 (18)	29 (19)
Non-CC	149 (82)	122 (81)
Cirrhosis, n (%)		
Yes (compensated)	84 (46)	69 (46)
No	98 (54)	82 (54)

Characteristics	VOSEVI 12 Weeks N = 182	SOF/VEL 12 Weeks N = 151
Prior HCV Treatment Experience, n (%*)		
DAA-Naïve	0	1 (<1)
DAA-Experienced	182 (100)	150 (99)
NS5B only	134 (74)	109 (72)
NS5B + NS3	46 (25)	38 (25)
Others	2 (1)	3 (2)

SD = standard deviation
*Total percentage may not add to 100% due to rounding.

Study Results

Overall, the SVR12 rate in DAA-experienced patients with genotype 1, 2, 3, 4 HCV infection without cirrhosis or with compensated cirrhosis who had not received an NS5A inhibitor was 98%. Table 17 presents the SVR12 by HCV genotype and virologic outcome for the POLARIS-4 trial. Treatment with VOSEVI for 12 weeks in POLARIS-4 was statistically superior to the SVR12 performance goal of 85% at the pre-specified 0.025 significance level ($p < 0.001$). Treatment with SOF/VEL for 12 weeks was not statistically superior to a performance goal of 85% at the pre-specified 0.025 significance level ($p = 0.092$).

Table 17. SVR12 and Virologic Outcome in DAA-Experienced Patients with Genotype 1, 2, 3, or 4 HCV Infection Without Cirrhosis or With Compensated Cirrhosis who had Not Received an NS5A Inhibitor (POLARIS-4)

	VOSEVI 12 Weeks (N=182)	SOF/VEL 12 Weeks (N=151)
Overall SVR12	98% (178/182)	90% (136/151)
Genotype 1	97% (76/78)	91% (60/66)
Genotype 1a	98% (53/54)	89% (39/44)
Genotype 1b	96% (23/24)	95% (21/22)
Genotype 2	100% (31/31)	97% (32/33)
Genotype 3	94% (52/54)	85% (44/52)
Genotype 4	100% (19/19)	0/0
Outcome for Patients without SVR		
On-Treatment Virologic Failure	0/182	1% (1/151)
Relapse[a]	1% (1/182)	9% (14/150)
Other[b]	2% (3/182)	0/151

SOF = sofosbuvir; VEL = velpatasvir; SVR12 = Sustained virologic response, defined as HCV RNA less than LLOQ (Lower Limit of Quantitation, 15 IU/mL) at 12 weeks after the cessation of treatment.
a. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.
b. Other includes patients with missing data and those who discontinued treatment prior to virologic suppression.

Subgroup analyses were performed for the primary efficacy endpoint (SVR12) for selected subgroups. High SVR12 rates were achieved in all subgroups in the VOSEVI 12-week group, regardless of the presence of cirrhosis (Table 18) or prior DAA class combinations or specific DAA combinations.

Table 18. SVR12 for DAA-Experienced Patients with Genotype 1, 2, 3, or 4 HCV Infection Without Cirrhosis or With Compensated Cirrhosis who had Not Received an NS5A Inhibitor (POLARIS-4)

	VOSEVI 12 Weeks N = 182						
	All GTs (N=182) % (n/N)	GT-1			GT-2 (N=31) % (n/N)	GT-3 (N=54) % (n/N)	GT-4 (N=19) % (n/N)
		GT-1a (N=54) % (n/N)	GT-1b (N=24) % (n/N)	GT-1 Total (N=78) % (n/N)			
Cirrhosis	96 (81/84)	94 (16/17)	100 (11/11)	96 (27/28)	100 (13/13)	97 (30/31)	100 (12/12)
No Cirrhosis	98 (96/98)	100 (37/37)	92 (12/13)	98 (49/50)	100 (18/18)	96 (22/23)	100 (7/7)

NA = not applicable

Overall in the POLARIS-1 and POLARIS-4 studies, the presence of baseline NS3, NS5A, and NS5B NI RAVs did not alter the SVR12 rates for DAA-experienced patients who received 12 weeks of VOSEVI (see **MICROBIOLOGY**).

MICROBIOLOGY

Antiviral Activity in Cell Culture

The EC_{50} values of sofosbuvir, velpatasvir, and voxilaprevir against full-length or chimeric replicons encoding NS5B, NS5A, and NS3 protease sequences from the laboratory strains are presented in Table 19. The EC_{50} values of sofosbuvir, velpatasvir, and voxilaprevir against clinical isolates are presented in Table 20.

Table 19 Activity of Sofosbuvir, Velpatasvir, and Voxilaprevir Against Full Length or Chimeric Laboratory Replicons

Replicon Genotype	Sofosbuvir EC_{50}, nM[a]	Velpatasvir EC_{50}, nM[a]	Voxilaprevir EC_{50}, nM[a]
1a	40	0.014	3.9[e]
1b	110	0.016	3.3[e]
2a	50	0.005-0.016[c]	3.7-4.5[e]
2b	15[b]	0.002-0.006[c]	1.8-6.6[f]
3a	50	0.004	6.1[f]
4a	40	0.009	2.9[e]

Replicon Genotype	Sofosbuvir EC_{50}, nM[a]	Velpatasvir EC_{50}, nM[a]	Voxilaprevir EC_{50}, nM[a]
4d	33	0.004	3.2[e]
5a	15[b]	0.021-0.054[d]	1.9[f]
6a	14-25[b]	0.006-0.009	3.0-4.0[e]
6e	NA	0.130[d]	0.33[f]
6n	NA	NA	2.9[f]

NA = not available

a. Mean value from multiple experiments of same laboratory replicon.

b. Stable chimeric 1b replicons carrying NS5B genes from genotype 2b, 5a or 6a were used for testing.

c. Data from various strains of full length NS5A replicons or chimeric NS5A replicons carrying full-length NS5A genes that contain L31 or M31 polymorphisms.

d. Data from a chimeric NS5A replicon carrying NS5A amino acids 9-184.

e. Stable cell lines expressing Renilla luciferase-encoding replicons.

f. Data obtained from transiently transfected replicons.

Table 20 Activity of Sofosbuvir, Velpatasvir, and Voxilaprevir Against Transient Replicons Containing NS5A, NS5B, or NS3 Protease from Clinical Isolates

	Replicons containing NS5B from clinical isolates		Replicons containing NS5A from clinical isolates		Replicons containing NS3 protease from clinical isolates	
Replicon Genotype	Number of clinical isolates	Median sofosbuvir EC_{50}, nM (range)	Number of clinical isolates	Median velpatasvir EC_{50}, nM (range)	Number of clinical isolates	Median voxilaprevir EC_{50}, nM (range)
1a	67	62 (29-128)	23	0.019 (0.011-0.078)	58	0.59 (0.14-19.16)
1b	29	102 (45-170)	34	0.012 (0.005-0.500)	29	0.50 (0.19-2.87)
2a	1	28	8	0.011 (0.006-0.364)	18	2.8 (1.78-6.72)
2b	14	30 (14-81)	16	0.002 (0.0003-0.007)	43	2.1 (0.92-8.3)
3a	106	81 (24-181)	38	0.005 (0.002-1.871)	32	6.3 (1.3-21.48)
4a	NA	NA	5	0.002 (0.001-0.004)	58	0.52 (0.12-1.7)
4d	NA	NA	10	0.007 (0.004-0.011)	11	0.85 (0.41-1.1)
4r	NA	NA	7	0.003 (0.002-0.006)	1	1.15 NA
5a	NA	NA	42	0.005 (0.001-0.019)	16	1.8 (0.87-5.63)

6a	NA	NA	26	0.007 (0.0005-0.113)	15	2.7 (0.23-7.35)
6e	NA	NA	15	0.024 (0.005-0.433)	12	0.2 (0.12-0.43)

NA = not available

The presence of 40% human serum had no effect on the anti-HCV activity of sofosbuvir, but reduced the anti-HCV activity of velpatasvir and voxilaprevir by 13- and 6.8-fold, respectively, against genotype 1a HCV replicons.

Evaluation of sofosbuvir in combination with velpatasvir or voxilaprevir, as well as the combination of velpatasvir and voxilaprevir, showed no antagonistic effect in reducing HCV RNA levels in replicon cells.

Resistance

In Cell Culture

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 genotype 1 to 6 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 showed reduced susceptibility to GS-461203 compared to respective wild-types.

In vitro selection of HCV replicons with reduced susceptibility to velpatasvir was performed in cell culture for multiple genotypes including 1a, 1b, 2a, 3a, 4a, 5a, and 6a. Variants were selected at NS5A resistance associated positions 24, 28, 30, 31, 32, 58, 92, and 93. The resistance associated variants (RAVs) selected in 2 or more genotypes were F28S, L31I/V, and Y93H. From site-directed mutagenesis studies, NS5A RAVs that showed a > 2.5-fold reduction in velpatasvir susceptibility are listed in Table 21 below. No individual substitutions tested in genotypes 2a, 4a, or 5a conferred a >100-fold reduction in velpatasvir susceptibility. Combinations of variants often showed greater reductions in susceptibility to velpatasvir than single RAVs alone.

Table 21. Phenotypic Change of Genotype 1-6 NS5A Substitutions to Velpatasvir

Genotype	> 2.5-100-fold*	> 100-fold*
1a	M28A/T, Q30E/G/K, L31F/I/M/V, P32L, H58D, Y93C/L/S/T	M28G, A92K, Y93H/N/R/W
1b	Q24K, L31F/I, P58T, Y93H/N/T	A92K
2a	F28S, L31V, C92R, Y93H/N	None

Genotype	> 2.5-100-fold*	> 100-fold*
2b	L28F, P58A, C92S, Y93F	C92T, Y93H/N
3a	A30H/K, L31F/M, P58G	Y93H
4a	L28T, Y93H/N/S	None
5a	L31I	None
6a	F28M/V, L31I/M, T58G/H, A92T, T93A/H/N/S	L31V, P32A/L/Q/R

*Fold change was calculated as the ratio of mutant EC_{50} to wild-type EC_{50}.

HCV genotype 1a, 1b, 2a, 3a, 4a, 5a, and 6a replicon variants with reduced susceptibility to voxilaprevir were selected in cell culture. Variants were selected at NS3 resistance associated positions 41, 156, and 168. The RAVs selected in 2 or more genotypes were Q41H, A156V/T/L, and D168E/H/Y. From site-directed mutagenesis studies, NS3 RAVs that showed a > 2.5-fold reduction in voxilaprevir susceptibility are listed in Table 22 below. No individual substitutions tested in genotypes 5a, or 6a conferred a > 100-fold reduction in voxilaprevir susceptibility. Combinations of variants often showed greater reductions in susceptibility to voxilaprevir than single RAVs alone.

Table 22. Phenotypic Change of Genotype 1-6 NS3 Substitutions to Voxilaprevir

Genotype	> 2.5-100-fold*	> 100-fold*
1a	V36G, Q41R, F43S, R155G/W, D168A/F/I/K/L/R/T/V	A156L/T
1b	V36A/M, S122D, R155W, A156S, D168V/Y, V170A,	A156T/V
2a	F43V, A156T	A156L/V
3a	Q41K, Q80K, L175M	A156T/V
4a	Q41R, D168E/T/V	A156L/T/V
5a	D168A/H/K/R/Y	None
6a	Q41K/R, Y56H, D168A/H	None

*Fold change was calculated as the ratio of mutant EC_{50} to wild-type EC_{50}.

In Clinical Trials

Of the 263 NS5A inhibitor-experienced patients treated with VOSEVI for 12 weeks in POLARIS-1, 7 of 263 (3%) patients (2 with genotype 1, 4 with genotype 3, and 1 with genotype 4) did not achieve SVR12 and qualified for resistance analysis; 6 relapsed and 1 experienced virologic breakthrough with pharmacokinetic data consistent with nonadherence. The patient with genotype 1a and virologic breakthrough developed the NS5A RAVs L31M and Y93H. One patient with genotype 4d who relapsed developed the NS5A RAV Y93H. No NS3, NS5A, or NS5B nucleoside analog (NI) RAVs emerged in the other 5 patients who relapsed.

Of the 182 DAA-experienced patients treated with VOSEVI for 12 weeks in POLARIS-4, 1 of 182 (1%) patients relapsed and qualified for resistance analysis. No NS3, NS5A, or NS5B NI RAVs emerged in this patient infected with genotype 1a HCV.

Effect of Baseline HCV Resistance Associated Variants on Treatment Outcome

Analyses were conducted to explore the association between pre-existing baseline NS3 and NS5A RAVs and treatment outcome for patients that had previously been treated with DAA regimens in POLARIS-1 and POLARIS-4. Patients were included in the analysis if they had a known virologic outcome. Of the patients treated with VOSEVI for 12 weeks, 260 of 263 in POLARIS-1 and 179 of 182 in POLARIS-4 were included in the analysis of NS3 and NS5A RAVs. Overall, 205 of 260 (79%) patients from POLARIS-1 and 83 of 179 (46%) patients from POLARIS-4 had HCV with NS3 and/or NS5A RAVs at baseline.

SVR12 rates in patients with or without baseline NS3 and/or NS5A RAVs in the POLARIS-1 and POLARIS-4 trials are shown in Table 23.

Table 23 SVR12 in DAA-Experienced Patients with or without Baseline NS3 or NS5A RAVs by Study

	VOSEVI 12 Weeks	
	POLARIS-1 (N=260)	**POLARIS-4 (N=179)**
No NS3 or NS5A RAVs	98% (42/43)	99% (85/86)
Any NS3 or NS5A RAV	97% (199/205)	100% (83/83)
NS3 Only	100% (9/9)	100% (39/39)
NS5A Only	97% (120/124)	100% (40/40)
NS3 and NS5A	97% (70/72)	100% (4/4)
RAVs Not Determined for Both NS3 and NS5A[a]	100% (12/12)	100% (10/10)

a. Patients with NS3 and/or NS5A gene sequencing failure.

SVR12 was achieved in 18 of 19 (95%) patients who had baseline NS5B NI RAVs in POLARIS-1, including 2 patients that had virus with the S282T NS5B NI RAV in addition to NS5A RAVs at baseline. In POLARIS-4, a total of 14 patients had virus with NS5B NI RAVs at baseline and all achieved SVR12.

Cross Resistance

Voxilaprevir is active *in vitro* against most of the NS3 RAVs that confer resistance to first generation NS3/4A protease inhibitors. Additionally, velpatasvir is active *in vitro* against most of the NS5A RAVs that confer resistance to ledipasvir and daclatasvir. Sofosbuvir, velpatasvir, and voxilaprevir were fully active against substitutions associated with resistance to other classes of DAAs with different mechanisms of actions; e.g., voxilaprevir was fully active against NS5A and NS5B NI RAVs.

TOXICOLOGY

Repeat-Dose Toxicity

Sofosbuvir

Sofosbuvir or GS-9851, a 1:1 diastereomeric mixture of sofosbuvir and its stereoisomer, was evaluated in repeat-dose oral toxicity studies up to 13 weeks in mice, 26 weeks in rats, and 39 weeks in dogs. The primary sofosbuvir target organs identified were the gastrointestinal (GI) and hematopoietic (erythroid) systems. In a 7-day toxicity dog study with GS-9851, a dose of 1500 mg/kg/day resulted in (but were not limited to) increased mucus secretions in the stomach, glycogen depletion, and increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin, with associated histopathologic liver findings and increased QT/QTc intervals in dogs. At the adverse dose, GS-331007 exposure levels in the dog study were at least 69-fold higher than HCV-infected patients treated once daily with VOSEVI. In chronic toxicity studies in rats (26 weeks) and dogs (39 weeks), sofosbuvir 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. In general, exposure levels in the chronic toxicity studies at the no observed adverse effect level were at least 5-fold (based on AUC of GS-331007) higher than HCV-infected patients treated once daily with VOSEVI.

Velpatasvir

Velpatasvir was well tolerated in studies for up to 4 weeks in the mouse, 26 weeks in the rat, and 39 weeks in the dog. No target organs were identified at the highest dose evaluated in each respective repeat dose toxicity study, corresponding to exposure margins of 54-, 3-, and 7-fold greater in mice, rats, and dogs, respectively, than those in HCV-infected patients treated once daily with VOSEVI.

Voxilaprevir

Voxilaprevir was evaluated in repeat-dose oral toxicity studies up to 26 weeks in rats and up to 39 weeks in dogs. The potential target organ/tissues identified for voxilaprevir were the GI tract (rat, dog), hepatobiliary system (rat, dog), hematological system (rat), and renal system (rat, dog). Minimal hematological changes indicative of mild blood loss and an appropriate regenerative response were also observed in the rat. Observed changes were minimal in nature

and considered nonadverse. Voxilaprevir exposures at the no observed adverse effect levels from the chronic repeat-dose toxicity studies in rats and dogs were approximately 244-, and 96-fold higher, respectively, than HCV-infected patients treated once daily with VOSEVI.

Genotoxicity and Carcinogenicity

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 carcinogenic in the 2-year mouse and rat carcinogenicity studies at doses resulting in GS-331007 exposures up to 17-fold in mice and 10-fold in rats, higher than human exposure at 400 mg dose.

Velpatasvir

Velpatasvir 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.

Velpatasvir was not carcinogenic in a 26-week mouse study at exposures up to 42- and 67-fold higher than human exposure in male and female mice, respectively. A carcinogenicity study in rats is ongoing.

Voxilaprevir

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

Carcinogenicity studies for voxilaprevir have not been conducted.

Fertility

Sofosbuvir

Sofosbuvir had no effects on fertility when evaluated in rats at exposures (AUC) to the predominant circulating metabolite GS-331007 of at least 4-fold the exposure in humans at the recommended clinical dose.

Velpatasvir

Velpatasvir had no adverse effects on fertility in rats at AUC exposure 4-fold higher than the human exposure at the recommended clinical dose.

Voxilaprevir

Voxilaprevir had no adverse effects on fertility in rats at AUC exposures 149-fold higher than the human exposure at the recommended clinical dose.

REFERENCES

1. Sovaldi (tablet, 400 mg sofosbuvir), submission control number 202358, Product Monograph, Gilead Sciences Canada, Inc. April 28, 2017

2. Epclusa (tablet, 400 mg sofosbuvir/100 mg velpatasvir), submission control number 202377, Product Monograph, Gilead Sciences Canada, Inc. May 8, 2017

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

VOSEVI™
sofosbuvir/velpatasvir/voxilaprevir tablets

Read this carefully before you start taking **Vosevi**. Read it again every time you get a refill. This leaflet is a summary. It will not tell you everything about this drug. Talk to your doctor about your medical condition and treatment. Ask whether there is any new information about **Vosevi**.

Serious Warnings and Precautions

Hepatitis B activity (eg, inflamed liver) may increase when taking antiviral drugs like **Vosevi**, sometimes leading to liver failure and death. (See the "To help avoid side effects…" section, *Hepatitis B Reactivation*)

What is Vosevi used for?
Vosevi is used to treat chronic (long-lasting) hepatitis C in adults who have:
- genotype 1, 2, 3, 4, 5, or 6 infection and have been previously treated with a type of medicine called an NS5A inhibitor.
- genotype 1, 2, 3 or 4 infection and have been previously treated with sofosbuvir without another medicine called an NS5A inhibitor.

How does Vosevi work?
Vosevi contains three medicines put together into one tablet (pill).

- **Vosevi** blocks the hepatitis C virus from making more copies of itself in the body.
- **Vosevi** cures chronic hepatitis C in most patients. Cure means the virus is no longer in your blood 3 months after finishing the medicine.
- Curing chronic hepatitis C virus can help lower the chance you will have liver problems or die from liver disease.

What are the ingredients in Vosevi?
Each tablet has the following medicines: sofosbuvir, velpatasvir, voxilaprevir
Each tablet has the following ingredients that are not medicines: colloidal silicon dioxide, copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose.
Each tablet is covered with the following ingredients that are not medicines: ferrosoferric oxide, iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Vosevi comes in the following dosage forms:
Vosevi comes in beige tablets. Each tablet contains sofosbuvir (400 mg), velpatasvir (100 mg),

and voxilaprevir (100 mg).

Do not use Vosevi if:
- You are allergic to sofosbuvir (also called **Sovaldi**® when it is used alone), velpatasvir (also called **Epclusa™** when it is used with sofosbuvir), voxilaprevir, or any of the other ingredients in this product. (Read also "**What are the ingredients in Vosevi?**" above.)
- You are taking any of the following medicines or natural substances:
    - dabigatran etexilate (Pradaxa®), a drug used to treat blood clots.
    - rifampin (Rifadin®, Rifater®, Rofact®), a drug used to treat tuberculosis.
    - phenobarbital, a drug used to treat anxiety and to control seizures.
    - phenytoin (Dilantin®), a drug used to control seizures.
    - rosuvastatin (Crestor®), a drug used to treat high cholesterol and to help prevent heart attacks and strokes.
    - St. John's wort (*Hypericum perforatum*), an herbal product used for anxiety or depression.

To help avoid side effects and ensure you take your medicine properly, talk to your doctor before you take Vosevi. Talk about any health problems you may have, including if you:
- have liver problems other than hepatitis C infection.
- have HIV.
- have severe kidney disease or you are on dialysis.
- are taking heart medication such as amiodarone (eg, Cordarone®). Your doctor may monitor your heart function while taking **Vosevi** (see "**The following may interact with Vosevi**").
- were born with the rare problem of not being able to tolerate galactose (severe lack of lactase or cannot absorb glucose or galactose). **Vosevi** has lactose.

Other warnings you should know about:

Hepatitis B Reactivation:

Taking antiviral drugs such as **Vosevi** may increase hepatitis B activity. This can lead to liver problems such as liver failure and death. Contact your doctor if:

- you have never been tested for hepatitis B.
- you know you have a current hepatitis B infection.
- you have had a previous hepatitis B infection.

Your healthcare professional may do blood tests:

- before hepatitis C treatment.
- to see the hepatitis B levels in your blood.
- and may order hepatitis B treatment.

Pregnancy:
- If you are pregnant or plan to become pregnant, talk to your doctor before you take this medicine. The effects of **Vosevi** during pregnancy are not known. Avoid pregnancy while

taking **Vosevi**. Tell your doctor if you become pregnant while taking **Vosevi**.

Breastfeeding:
- If you are breastfeeding or plan to breastfeed, talk to your doctor about the best way to feed your baby. Do not breastfeed while taking **Vosevi**.

Products containing sofosbuvir:
Because **Vosevi** already contains sofosbuvir, do not take **Vosevi** with any other medicines that have sofosbuvir (e.g., **Sovaldi**, **Harvoni**®, **Epclusa**).

Tell your doctor or pharmacist about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Vosevi:
- amiodarone (Cordarone®), a drug used to treat irregular heartbeats.
- atazanavir (Reyataz®), a drug used to treat HIV.
- atorvastatin (Lipitor®), a drug used to treat high cholesterol and to help prevent heart attacks and strokes.
- carbamazepine (Tegretol®), a drug used to treat seizures, nerve pain, and bipolar disorder.
- cyclosporine (Neoral®, Sandimmune® I.V.), a drug used to suppress the immune system.
- digoxin (Lanoxin®, Toloxin®), a drug used to treat congestive heart failure and a certain abnormal heart rhythm (atrial fibrillation).
- efavirenz (Sustiva®, **Atripla**®), a drug used to treat HIV.
- fluvastatin (Lescol®, Lescol® XL), a drug used to treat high cholesterol and to help prevent heart attacks and strokes.
- lopinavir, a drug used to treat HIV.
- lovastatin (Advicor®*, Mevacor®*), a drug used to treat high cholesterol and to help prevent heart attacks and strokes.
- medicines for indigestion, heartburn, or ulcers. Examples are nizatidine (Axid®), famotidine (Pepcid AC®, Peptic Guard®, Ulcidine®), cimetidine (Tagamet®), ranitidine (Zantac®), esomeprazole (Nexium®), lansoprazole (Prevacid®), omeprazole (Losec®), rabeprazole (Aciphex®) and pantoprazole (Pantoloc®) or antacids (like Tums®, Rolaids® or Alka-Seltzer®) that have an ingredient to protect the stomach.
- ethinyl estradiol, a drug in some oral contraceptives used to prevent pregnancy (eg, Alesse®, Apri®, Aviane®, Marvelon®, Seasonale®, Tri-Cyclen®, Yasmin®, Yaz®).
- oxcarbazepine (Trileptal®), a drug used to control seizures.
- pravastatin (Pravachol®), a drug used to treat high cholesterol and to help prevent heart attacks and strokes.
- rifabutin (Mycobutin®), a drug used to treat tuberculosis.
- rifapentine*, a drug used to treat tuberculosis.
- simvastatin (Zocor®), a drug used to treat high cholesterol and to help prevent heart attacks and strokes.
- tenofovir disoproxil fumarate (**Atripla**, **Complera**®, **Stribild**®, **Truvada**®, **Viread**®), to treat HIV.
- warfarin (Coumadin®) or other similar medicines called vitamin K antagonists, to thin the

blood. Your doctor may need to test your blood more often to check how well your blood can clot.

*Not sold in Canada.

How to take Vosevi:

- Take this medicine with food.
- If you are taking an antacid, you may need to take **Vosevi** at a different time than the antacid. Talk to your doctor or pharmacist.
- Do NOT stop taking **Vosevi** without first talking with your doctor.

Usual adult dose:

- Take one tablet once daily for 12 weeks.

Overdose:

If you think you have taken too much **Vosevi**, contact your doctor or pharmacist, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:

It is important to take **Vosevi** each day.

- **If you miss a dose** of **Vosevi** and you notice within 18 hours, take a tablet as soon as you can. Then take the next dose at your usual time.
- **If you miss a dose** of **Vosevi** 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).

What to do if you vomit (throw up):

- If you vomit **less than 4 hours** after taking **Vosevi**, take another tablet.
- If you vomit **more than 4 hours** after taking **Vosevi**, wait. Do NOT take another tablet until you are scheduled to take the next tablet.

What are possible side effects from using Vosevi?

These are not all the possible side effects you may feel when taking **Vosevi**. If your side effect is not listed here, contact your doctor or pharmacist.

The most common side effects of **Vosevi** are headache, feeling tired, diarrhea, feeling sick in the stomach, problem with getting to sleep, and less energy or strength.

When sofosbuvir (one of the medicines in **Vosevi**) is used with other hepatitis C medicines (eg, daclatasvir [Daklinza™], simeprevir [Galexos®], or ledipasvir) and amiodarone (a heart drug), side effects may be:

- slow heartbeat leading to a need for a pacemaker or death.

Contact your doctor immediately if you have symptoms of a slow heartbeat such as:

- fainting or near-fainting.
- dizziness or lightheadedness.
- not feeling well.
- feeling weak or very tired.
- shortness of breath.
- chest pains.
- confusion or memory problems.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your doctor.

Reporting side effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:
- Online at MedEffect (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html).

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
- Store **Vosevi** below 30 ^{o}C (86 ^{o}F).
- Keep **Vosevi** in its original container.
- Do NOT use **Vosevi** if the seal over the bottle opening is broken or missing.
- Keep this medication where children cannot reach it or see it.

If you want more information about Vosevi:
- Talk to your doctor or pharmacist.
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-

products/drug-product-database.html); the manufacturer's website (www.gilead.ca), or by calling 1-800-207-4267.

This leaflet was prepared by Gilead Sciences Canada, Inc.

Last Revised: August 16, 2017

Gilead Sciences, Inc.
Foster City, CA 94404
USA

Gilead Sciences Canada, Inc.
Mississauga, ON L5N 2W3

e192340-GS-000