NEW ZEALAND DATA SHEET

1 PRODUCT NAME

VOSEVI (sofosbuvir/velpatasvir/voxilaprevir 400 mg/100 mg/100 mg) tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

VOSEVI is available as a fixed-dose combination tablet. The active substances in VOSEVI tablets are sofosbuvir, velpatasvir and voxilaprevir.

Each tablet contains 400 mg of sofosbuvir, 100 mg of velpatasvir, and 100 mg of voxilaprevir.

Sofosbuvir is a white to off-white powder with a solubility of ≥ 2 mg/mL across the pH range of 2-7.7 at 37 °C.

Velpatasvir is a white to tan or yellow solid. Velpatasvir is practically insoluble (less than 0.1 mg/mL) above pH 5, slightly soluble (3.6 mg/mL) at pH 2, and soluble (greater than 36 mg/mL) at pH 1.2.

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

For the full list of excipients, see Section 6.1 List of excipients.

Excipient(s) with known effect:
Lactose monohydrate

3 PHARMACEUTICAL FORM

VOSEVI tablets are beige, capsule -shaped, film coated tablets, debossed with “GSI” on one side and “3” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

VOSEVI (sofosbuvir/velpatasvir/voxilaprevir fixed-dose combination) is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults.

4.2 Dose and method of administration

The recommended dose of VOSEVI is one tablet, taken orally, once daily with food.

Table 1 provides the recommended treatment regimen and duration based on patient population.

Table 1 Recommended Treatment Regimen and Duration in Adults Without Cirrhosis or With Compensated Cirrhosis (Child-Pugh A)

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

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

b. Additional benefit of VOSEVI over sofosbuvir/velpatasvir was not shown in adults with genotype 1b, 2, 4, 5, or 6 infection previously treated with sofosbuvir without an NS5A inhibitor.

c. 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).

Children and Adolescents up to 18 Years of Age

No data are available on which to make a dose recommendation for children < 18 years of age.

Elderly

No dose adjustment is warranted for elderly patients.

Renal Impairment

No dose adjustment of VOSEVI is required for patients with mild or moderate renal impairment. The safety and efficacy of VOSEVI have not been established in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) or end stage renal disease (ESRD) requiring haemodialysis (see Section 5.2 Pharmacokinetic properties).

Hepatic Impairment

No dose adjustment of VOSEVI is required for patients with mild hepatic impairment (Child-Pugh A). VOSEVI is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C). (see Section 5.2 Pharmacokinetic properties).

4.3 Contraindications

VOSEVI tablets are contraindicated in patients with known hypersensitivity to the active substance or to any other component of the tablets.

VOSEVI is contraindicated with rifampicin and rosuvastatin.

4.4 Special warnings and precautions for use

Symptomatic Bradycardia When Sofosbuvir Is Coadministered with Amiodarone and Another HCV Direct Acting Antiviral

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 light-headedness, malaise, weakness, excessive tiredness, shortness of breath, chest pains, confusion, or memory problems.

Hepatitis B Virus Reactivation

Cases of HBV reactivation, including fatal cases, have been reported during and after treatment of HCV with direct-acting antiviral agents (DAAs) in HCV/HBV co-infected patients. Screening for current or past HBV infection, including testing for HBV surface antigen (HBsAg) and HBV core antibody (anti-HBc), should be performed in all patients before initiation of treatment with VOSEVI.

Patients with serologic evidence of current or past HBV infection should be monitored and treated according to current clinical practice guidelines to manage potential HBV reactivation. Consider initiation of HBV antiviral therapy, if indicated.

There are no data on the use of VOSEVI in patients with HCV/ HBV co-infection.

Potential for Dysglycaemia in Diabetic Patients

Diabetics may experience dysglycaemia, potentially resulting in symptomatic hypoglycaemia, after initiating HCV direct-acting antiviral treatment. Glucose levels of diabetic patients initiating direct-acting antiviral therapy should be closely monitored, particularly within the first three months, and their diabetic medication modified when necessary. The physician in charge of the diabetic care of the patient should be informed

when direct-acting antiviral therapy is initiated (see also section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

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

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, carbamazepine) may significantly decrease plasma concentrations of sofosbuvir, velpatasvir, and/or voxilaprevir leading to reduced therapeutic effect of VOSEVI. The use of these agents with VOSEVI is not recommended (see Section 4.5 Interactions with other medicines and other forms of interactions).

Use in the elderly

Clinical studies of VOSEVI included 189 patients aged 65 and over (17% of total number of patients in the Phase 2 and 3 clinical trials). The response rates observed for patients ≥ 65 years of age were similar to that of patients < 65 years of age, across treatment groups.

Paediatric use

Safety and effectiveness of VOSEVI in children less than 18 years of age have not been established.

Effects on laboratory tests

No data available.

4.5 Interaction with other medicines and other forms of interaction

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

Potential for VOSEVI to Affect Other Drugs

Velpatasvir and voxilaprevir are inhibitors of drug transporters P-gp, breast cancer resistance protein (BCRP), OATP1B1, and OATP1B3. Velpatasvir is also an inhibitor of OATP2B1. Coadministration of VOSEVI with drugs that are substrates of these transporters may alter the exposure of such drugs. Coadministration of VOSEVI with BCRP substrates is not recommended.

Potential for Other Drugs to Affect VOSEVI

Sofosbuvir, velpatasvir, and voxilaprevir are substrates of drug transporters P-gp and BCRP while GS-331007 is not. Voxilaprevir is also a substrate 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, carbamazepine) may decrease plasma concentrations of sofosbuvir, velpatasvir, or voxilaprevir leading to reduced therapeutic effect of VOSEVI. The use of these agents with VOSEVI is not recommended *(*See Section 4.4 Special warnings and precautions for use*)* Coadministration with drugs that inhibit P-gp and/or BCRP may increase sofosbuvir, velpatasvir, 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 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.

Established and Other Potentially Significant Drug Interactions

Table 2 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/or voxilaprevir), or are predicted drug interactions that may occur with VOSEVI. This table is not all inclusive.

Table 2 Established and Other Potentially Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
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 Section 4.4 Special warnings and precautions for use).
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 Comment
Anticoagulants: dabigatran etexilate[c]	↑ dabigatran	Coadministration of VOSEVI with dabigatran etexilate may increase the concentration of dabigatran. Caution is warranted and clinical monitoring of dabigatran is recommended when coadministered with VOSEVI.
Anticonvulsants: carbamazepine phenytoin phenobarbital oxcarbazepine	↓ sofosbuvir ↓ velpatasvir ↓ voxilaprevir	Coadministration is not recommended.
Antimycobacterials: rifampicin[c]	↓ sofosbuvir ↓ velpatasvir ↑voxilaprevir (single dose) ↓voxilaprevir (multiple dose)	Coadministration with rifampicin is contraindicated.
rifabutin rifapentine	↓ sofosbuvir ↓ velpatasvir ↓ voxilaprevir	Coadministration is not recommended.
Antiretrovirals: atazanavir[c] lopinavir	↑ voxilaprevir	Coadministration of VOSEVI with atazanavir- or lopinavir-containing regimens is not recommended.
efavirenz[c]	↓ velpatasvir ↓ voxilaprevir	Coadministration of VOSEVI with efavirenz containing regimens is not recommended.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
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 prescribing information of the tenofovir DF-containing product for recommendations on renal monitoring.
Herbal Supplements: St. John's wort	↓ sofosbuvir ↓ velpatasvir ↓ voxilaprevir	Coadministration is not recommended.
HMG-CoA Reductase Inhibitors: atorvastatin[c]	↑ 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 20 mg.
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.
rosuvastatin[c]	↑ rosuvastatin	Coadministration with rosuvastatin is contraindicated.
fluvastatin lovastatin simvastatin	↑ fluvastatin ↑ lovastatin ↑ simvastatin	Coadministration with VOSEVI may increase the concentrations of fluvastatin, lovastatin, and simvastatin. Increased statin concentrations may increase the 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.
Immunosuppressants: cyclosporine[c]	↑ voxilaprevir	Coadministration of voxilaprevir with cyclosporine has been shown to substantially increase the plasma concentration of voxilaprevir, the safety of which has not been established. Coadministration of VOSEVI with cyclosporine is not recommended.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
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.

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, or voxilaprevir) or VOSEVI, no clinically significant drug interactions have been either observed or are expected when VOSEVI is combined with the following drugs (seeSection 5.2): cobicistat, darunavir, dolutegravir, elvitegravir, emtricitabine, gemfibrozil, ketoconazole, methadone, oral contraceptives, raltegravir, rilpivirine, ritonavir, tacrolimus (see 4.5 Interactions with Other Medicinal Products and Other Forms of Interaction: Other Forms of Interaction), tenofovir alafenamide, or voriconazole.

Other Forms of Interaction

Improvement in hepatic function as a result of treatment of HCV with DAAs may require monitoring of relevant laboratory parameters in susceptible patients (e.g., International Normalized Ratio [INR] in patients taking vitamin K antagonists, blood glucose levels in diabetic patients [see also section 4.4 Special warnings and precautions for use - Potential for Dysglycaemia in Diabetic Patients]). Concomitant medications significantly affected by changes in hepatic function (e.g., calcineurin inhibitors) may require monitoring or dose modification to ensure continued efficacy.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Sofosbuvir: Sofosbuvir had no effects on embryo-fetal viability or on fertility when evaluated in rats. At the highest dose tested, AUC exposure to the predominant circulating metabolite GS-331007 was approximately 4-fold the exposure in humans at the recommended clinical dose.

Velpatasvir: Velpatasvir had no effects on embryo-fetal viability or on fertility when evaluated in rats. At the highest dose tested, velpatasvir exposure was approximately 4-fold the exposure in humans at the recommended clinical dose.

Voxilaprevir: Voxilaprevir had no effects on embryo-fetal viability or on fertility when evaluated in rats. At the highest dose tested, voxilaprevir exposure was approximately 149–fold the exposure in humans at the recommended clinical dose.

Use in pregnancy – Pregnancy Category B1

There are no adequate and well-controlled studies with VOSEVI in pregnant women.

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with the administration of sofosbuvir, velpatasvir or voxilaprevir.

Sofosbuvir: No effect on fetal development has been observed in rats and rabbits at the highest doses tested. In the rat and rabbit, exposure to the predominant circulating metabolite GS-331007 was approximately 6-fold and 16-fold the exposure in humans at the recommended clinical dose, respectively. Sofosbuvir had no adverse effects on behaviour, reproduction, or development of the offspring in the rat pre- and post-natal development study at AUC exposures approximately 7-fold higher than the human exposure at the recommended clinical dose.

Velpatasvir: No effects on fetal development have been observed in mice, rats and rabbits at the highest doses tested. In the mouse, rat and rabbit, AUC exposure to velpatasvir was approximately 23-, 4-, and 0.5-fold, respectively, the exposure in humans at the recommended clinical dose. Velpatasvir had no adverse effects on behaviour, reproduction, or development of the offspring in the rat pre- and post-natal development study at AUC exposures approximately 3-fold higher, respectively than the human exposure at the recommended clinical dose.

Voxilaprevir: No effects on fetal development have been observed in rats and rabbits at the highest doses tested. In the rat and rabbit AUC exposures to voxilaprevir were approximately 141- and 4-fold higher, respectively than the human exposure at the recommended clinical dose. Voxilaprevir had no adverse effects on behavior, reproduction, or development of the offspring in the rat pre- and post-natal development study at AUC exposures approximately 238-fold higher than the human exposure at the recommended clinical dose.

Because animal reproduction studies are not always predictive of human response, VOSEVI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in lactation

It is not known whether sofosbuvir, velpatasvir or voxilaprevir or their metabolites are present in human breast milk.

The predominant circulating metabolite of sofosbuvir (GS-331007) was the primary component observed in the milk of lactating rats, without effect on nursing pups. Velpatasvir was present in the milk of lactating rats, without clear effects on nursing pups. When administered to lactating rats, voxilaprevir was detected in the plasma of nursing pups. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for VOSEVI and any potential adverse effects on the breastfed infant from VOSEVI or from the underlying maternal condition

4.7 Effects on ability to drive and use machines

No studies on the effects of VOSEVI on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/}

Clinical Trials

The safety assessment of VOSEVI was based on Phase 3 clinical trial data from DAA-experienced patients (POLARIS-1 and POLARIS-4) and DAA-naïve patients (POLARIS-2 and POLARIS-3) with genotype 1, 2, 3, 4, 5 or 6 HCV infection (without cirrhosis or with compensated cirrhosis) including:

- 611 patients who received VOSEVI for 8 weeks,
- 445 patients who received VOSEVI for 12 weeks,
- 700 patients who received sofosbuvir/velpatasvir for 12 weeks,
- 152 patients who received placebo for 12 weeks.

The proportion of patients who permanently discontinued treatment due to adverse events was 0.2% for patients receiving VOSEVI for 12 weeks. There were no patients receiving VOSEVI for 8 weeks who permanently discontinued treatment due to adverse events.

Table 3 lists adverse events (all grades and without regard to causality) observed in at least 5% of patients receiving 8 or 12 weeks treatment with VOSEVI in clinical trials compared to 12 weeks of treatment with SOF/VEL or placebo.

Table 4 lists adverse events observed in at least 5% of DAA-experienced patients receiving 12 weeks treatment with VOSEVI in POLARIS-1 and POLARIS-4.

Table 3 Adverse Events (All Grades and without Regard to Causality) Reported in ≥5% of Patients Receiving 8 or 12 Weeks of Treatment with VOSEVI Compared to 12 Weeks of Treatment with SOF/VEL or Placebo (POLARIS-1, POLARIS-2, POLARIS-3 and POLARIS-4)

VOSEVI 8 Weeks (N=611)	VOSEVI 12 Weeks (N=445)	SOF/VEL 12 Weeks (N=700)	Placebo 12 Weeks (N=152)	
Headache	26%	26%	25%	17%
Fatigue	22%	22%	23%	20%
Diarrhoea	17%	19%	6%	13%
Nausea	17%	13%	9%	8%
Asthenia	6%	7%	6%	6%
Insomnia	5%	7%	4%	5%
Abdominal pain	5%	2%	3%	2%
Back pain	1%	5%	4%	5%

Table 4 Adverse Events (All Grades and without Regard to Causality) Reported in ≥5% of Patients with HCV without Cirrhosis or With Compensated Cirrhosis Receiving VOSEVI in POLARIS-1 and 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	25%	17%	27%	28%
Fatigue	21%	20%	24%	28%
Diarrhoea	18%	13%	20%	5%
Nausea	14%	8%	12%	8%
Asthenia	8%	6%	5%	6%
Insomnia	7%	5%	7%	2%
Back pain	4%	5%	7%	5%

In POLARIS-1, of the patients receiving VOSEVI who experienced these adverse events, >99% of patients had an adverse event of mild or moderate (Grade 1 or 2) severity. Each of these adverse events occurred at a similar frequency or more frequently than in patients treated with placebo.

Laboratory Abnormalities:

Lipase Elevations: In the POLARIS-1 and POLARIS-4 Phase 3 trials, isolated, asymptomatic lipase elevations of greater than 3×ULN were observed in 2%, 3% and 1% of patients treated with VOSEVI, placebo and SOF/VEL for 12 weeks, respectively.

Creatine Kinase: In the POLARIS-1 and POLARIS-4 Phase 3 trials, isolated, asymptomatic creatine kinase elevations greater than or equal to 10×ULN were reported in less than 1%, 1%, and less than 1% of patients treated with VOSEVI, placebo and SOF/VEL for 12 weeks, respectively.

Total bilirubin: In the POLARIS-1 and POLARIS-4 Phase 3 trials, increases in total bilirubin less than or equal to 1.5×ULN were observed in 5% of patients without cirrhosis and 9% of patients with compensated cirrhosis, due to inhibition of OATP1B1 and OATP1B3 by voxilaprevir. No patients experienced jaundice and total bilirubin levels decreased after completing VOSEVI treatment.

Post marketing Surveillance

The following possible adverse reactions were identified during postapproval use of sofosbuvir or VOSEVI. Because these reactions were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Cardiac Disorders

Symptomatic bradycardia (when amiodarone is coadministered with sofosbuvir in combination with another HCV direct acting antiviral) (see Section 4.4 [Special warnings and precautions for use]).

Skin and Subcutaneous Tissue Disorders

Angioedema, rash, Stevens-Johnson syndrome

4.9 Overdose

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 patients receiving voxilaprevir 900 mg were diarrhoea (34%), vomiting (19%), and nausea (17%). The effects of higher doses/exposures are not known.

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. Haemodialysis can efficiently remove the predominant circulating metabolite of sofosbuvir, GS-331007, with an extraction ratio of 53%. Haemodialysis is unlikely to result in significant removal of velpatasvir or voxilaprevir since velpatasvir and voxilaprevir are highly bound to plasma proteins.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia) and 0800 764 766 (New Zealand).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use; direct acting antivirals, other antivirals, ATC code: J05AP56.

Mechanism of action

Sofosbuvir is a pan-genotypic inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated by HCV NS5B and acts as a chain terminator. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a and 4a with an IC_{50} value ranging from 0.36 to 3.3 μM. GS-461203 is neither an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

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

Antiviral activity *in vitro*

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 5. The EC_{50} values of sofosbuvir, velpatasvir, and voxilaprevir against clinical isolates are presented in Table 6.

Table 5 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]
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 in Huh-7-Lunet or Huh7-1C cells.

Table 6 Activity of Sofosbuvir, Velpatasvir and Voxilaprevir Against Transient Replicons Containing NS5A, NS5B, or NS3 protease from Clinical Isolates

Replicon Genotype	Replicons containing NS5B from clinical isolates		Replicons containing NS5A from clinical isolates		Replicons containing NS3 protease from clinical isolates	
	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.

Drug 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 was reduced compared to its ability to inhibit wild-type recombinant NS5B polymerase, as indicated by a 8.5- to 24-fold increase in IC50.

HCV genotype 1a, 1b, 2a, 3a, 4a, 5a and 6a replicon variants with reduced susceptibility to velpatasvir were selected in cell culture. 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. Site directed mutagenesis of known NS5A RAVs showed that substitutions conferring a > 100-fold reduction in velpatasvir susceptibility are M28G, A92K and Y93H/N/R/W in genotype 1a, A92K in genotype 1b, C92T and Y93H/N in genotype 2b, Y93H in genotype 3, and L31V and P32A/L/Q/R in genotype 6. 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.

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. Site directed mutagenesis of NS3 RAVs showed that substitutions conferring a > 100-fold reduction in voxilaprevir susceptibility are A156L/T in genotype 1a, A156T/V in genotype 1b, A156L/V in genotype 2a, A156T/V in genotype 3a, and A156L/T/V in genotype 4. No individual substitutions tested in genotypes 2b, 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.

In Clinical Trials:

Studies in DAA-Experienced Patients

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 inhibitor (NI) RAVs emerged in the other 5 patients who relapsed.

Of the 182 DAA inhibitor-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.

Studies in DAA-Naïve Patients

In the POLARIS-2 VOSEVI 8-week treatment group, a total of 21 of 501 (4%) patients (16 with genotype 1, 2 with genotype 2, 2 with genotype 4, and 1 with genotype 5) qualified for resistance analysis due to relapse. Of these 21 patients, 1 patient had virus with emergent NS5A RAVs Q30R and L31M at failure. No NS3 and NS5B NI RAVs emerged in any of these 21 patients at failure.

In the POLARIS-3 VOSEVI 8-week treatment group, 2 of 110 (2%) patients (genotype 3) qualified for resistance analysis due to relapse. No NS3, NS5A, or NS5B NI RAVs emerged in either of these patients.

Effect of Baseline HCV Resistance Associated Variants on Treatment Outcome

Studies in DAA-Experienced Patients

Analyses were conducted to explore the association between pre-existing baseline NS3 and NS5A RAVs and treatment outcome for patients that had previously 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 RAV 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 7.

Table 7 SVR12 in DAA-Experienced Patients With or Without Baseline NS3 or NS5A RAVs by Study

	POLARIS-1	POLARIS-4	
	VOSEVI 12 Weeks (N=260)	VOSEVI 12 Weeks (N=179)	SOF/VEL 12 Weeks (N = 151)
No NS3 or NS5A RAVs	98% (42/43)	99% (85/86)	89% (67/75)
Any NS3 or NS5A RAV	97% (199/205)	100% (83/83)	90% (63/70)
NS3 Only	100% (9/9)	100% (39/39)	91% (29/32)
NS5A Only	97% (120/124)	100% (40/40)	94% (32/34)
NS3 and NS5A	97% (70/72)	100% (4/4)	50% (2/4)
RAVs Not Determined for Both NS3 and NS5A[a]	100% (12/12)	100% (10/10)	100% (6/6)

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.

Studies in DAA-Naïve Patients

Analyses were conducted to explore the association between pre-existing baseline NS3 and NS5A RAVs and treatment outcome for patients that had not previously been treated with DAA regimens in POLARIS-2 and POLARIS-3. Patients were included in the analysis if they had a known virologic outcome. Of the patients treated with VOSEVI for 8 weeks, 498 of 501 in POLARIS-2 and 108 of 110 in POLARIS-3 were included in the analysis of NS3 and NS5A RAVs. Overall, 250 of 498 (50%) patients from POLARIS-2 and 23 of 108 (21%) patients from POLARIS-3 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-2 and POLARIS-3 trials are shown in Table 8.

Table 8 SVR12 in DAA-Naïve Patients With or Without Baseline NS3 or NS5A RAVs by Study

	POLARIS-2		**POLARIS-3**	
	VOSEVI8 Weeks (N=498)	**SOF/VEL 12 Weeks N=435**	**VOSEVI 8 Weeks (N=108)**	**SOF/VEL 12 Weeks (N= 107)**
No NS3 or NS5A RAVs	98% (224/229)	99% (206/208)	98% (80/82)	97% (76/78)
Any NS3 or NS5A RAV	94% (234/250)	99% (217/218)	100% (23/23)	100% (23/23)
NS3 Only	91% (100/110)	100% (97/97)	100% (2/2)	100% (4/4)
NS5A Only	95% (114/120)	99% (90/91)	100% (20/20)	100% (19/19)
NS3 and NS5A	100% (20/20)	100% (30/30)	100% (1/1)	0
RAVs Not Determined for Both NS3 and NS5A[a]	100% (19/19)	100% (9/9)	100% (3/3)	100% (6/6)

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

SVR12 was achieved in all 39 patients who had baseline NS5B NI RAVs in POLARIS-2 and 2 of 3 (67%) patients in POLARIS-3. The NS5B NI RAV S282T was not detected in any patient in POLARIS-2 and POLARIS-3 trials.

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.

Clinical trials

The efficacy of VOSEVI was evaluated in two Phase 3 trials in DAA-experienced patients and two Phase 3 trials in DAA-naïve patients with genotype 1 to 6 HCV infection without cirrhosis or with compensated cirrhosis, as summarized in Table 9.

Table 9 Trials Conducted with VOSEVI in DAA-Experienced and DAA-Naïve Patients with Genotype 1, 2, 3, 4, 5 or 6 HCV Infection

Trial	Population	Study Arms (Number of Patients Treated)
POLARIS-1	NS5A inhibitor-experienced patients, without cirrhosis or with compensated cirrhosis	VOSEVI 12 weeks (263) Placebo 12 weeks (152)
POLARIS-4	DAA-experienced patients who have not received an NS5A inhibitor, without cirrhosis or with compensated cirrhosis	VOSEVI 12 weeks (182) SOF/VEL 12 weeks (151)
POLARIS-2	DAA-naïve patients, genotype 1, 2, 3, 4, 5, or 6 HCV infection, without cirrhosis or with compensated cirrhosis	VOSEVI 8 weeks (501) SOF/VEL 12 weeks (440)
POLARIS-3	DAA-naïve patients with genotype 3 HCV infection and compensated cirrhosis	VOSEVI 8 weeks (110) SOF/VEL 12 weeks (109)

DAA: direct acting-antiviral; SOF: sofosbuvir; VEL: velpatasvir

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

Clinical Studies in DAA-Experienced Patients

NS5A Inhibitor-Experienced Adults (POLARIS-1)

POLARIS-1 was a randomised, double-blind, placebo-controlled trial that evaluated 12 weeks of treatment with VOSEVI compared with 12 weeks of placebo in DAA-experienced patients with genotype 1, 2, 3, 4, 5, or 6 HCV infection without cirrhosis or with compensated cirrhosis who previously failed a regimen containing an NS5A inhibitor. Patients with genotype 1 HCV infection were randomised 1:1 to each group. Randomisation was stratified by the presence or absence of cirrhosis.

Demographics and baseline characteristics were generally balanced across treatment groups. Of the 415 treated patients, the median age was 59 years (range: 27 to 84); 77% of the patients were male; 81% were White; 14% were Black; 6% were Hispanic or Latino; 33% had a baseline body mass index at least 30 kg/m^2; the majority of patients had genotype 1 (72%) or genotype 3 (19%) HCV infection; 82% had a non-CC IL28B genotype (CT or TT); 74% had baseline HCV RNA levels at least 800,000 IU/mL; and 41% had compensated cirrhosis. Of the 263 patients treated with VOSEVI in POLARIS-1, the most common prior NS5A inhibitors were ledipasvir (LDV) (51%), daclatasvir (27%), and ombitasvir (11%).

Table 10 presents the SVR12 by HCV genotype for the POLARIS-1 trial. No patients in the placebo group achieved SVR4.

Table 10 SVR12 by HCV Genotype in Study 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	<1% (1/263)	1% (1/101)	0/45	1% (1/150)	0/5	0/78	0/22	0/1	0/6
Relapse[c]	2% (6/261)	1% (1/100)	0/45	1% (1/149)	0/5	5% (4/78)	5% (1/21)	0/1	0/6
Other[d]	1% (3/263)	2% (2/101)	0/45	1% (2/150)	0/5	0/78	5% (1/22)	0/1	0/6

GT: genotype

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

d. Other includes patients with missing data and those who discontinued treatment prior to virologic suppression.

Treatment with VOSEVI for 12 weeks in POLARIS-1 was statistically superior relative to the prespecified performance goal of 85% ($p < 0.001$).

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

POLARIS-4 was a randomised, open-label trial that evaluated 12 weeks of treatment with VOSEVI and 12 weeks of treatment with SOF/VEL in patients with genotype 1, 2, 3, or 4 HCV infection without cirrhosis or with compensated cirrhosis who had previously failed a DAA-containing regimen that did not include an NS5A inhibitor. Patients whose only DAA exposure was an NS3/4A protease inhibitor were excluded, given the availability of approved regimens to treat these individuals. Patients with genotype 1, 2, or 3 HCV infection were randomised 1:1 to each group. Randomisation 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.

Demographics and baseline characteristics were generally balanced across treatment groups. Of the 333 treated patients, the median age was 58 years (range: 24 to 85); 77% of the patients were male; 87% were White, 9% were Black; 8% were Hispanic or Latino; 35% had a baseline body mass index at least 30 kg/m^2; the majority of patients had genotype 1 (43%) or genotype 3 (32%) HCV infection; 81% had non-CC IL28B genotypes (CT or TT); 75% had baseline HCV RNA levels at least 800,000 IU/mL; and 46% had compensated cirrhosis. The majority (85%) of patients previously failed a regimen containing sofosbuvir.

Table 11 presents the SVR12 by HCV genotype and virologic outcome for the POLARIS-4 trial.

Table 11 SVR12 by HCV Genotype and Virologic Outcome in Study 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	96% (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

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.

Treatment with VOSEVI for 12 weeks resulted in numerically higher SVR12 rates than treatment with sofosbuvir/velpatasvir for 12 weeks in patients with HCV genotype 1a and 3 infection. Comparable SVR12 rates were observed in patients with HCV genotype 1b and 2 infection treated with VOSEVI for 12 weeks or with sofosbuvir/velpatasvir for 12 weeks. No comparison data are available for HCV genotypes 4, 5, and 6. Given these data, the additional benefit of VOSEVI has not been shown over sofosbuvir/velpatasvir in adults with genotype 1b, 2, 4, 5 or 6 infection previously treated with sofosbuvir without an NS5A inhibitor and VOSEVI is only indicated for the treatment of HCV genotypes 1a or 3 infection in adults who previously received sofosbuvir without an NS5A inhibitor.

Clinical Studies in DAA-Naïve Patients

DAA-Naïve Adults with Genotype 1, 2, 3, 4, 5, or 6 HCV Infection (POLARIS-2)

POLARIS-2 was a randomised, open-label trial that evaluated 8 weeks of treatment with VOSEVI and 12 weeks of treatment with SOF/VEL in DAA-naïve patients with genotype 1, 2, 4, 5, or 6 HCV infection without cirrhosis or with compensated cirrhosis or genotype 3 HCV infection without cirrhosis. Patients with genotype 3 HCV infection and cirrhosis were excluded from enrollment in this trial; they were enrolled in the POLARIS-3 trial (see below). Patients with genotype 1, 2, 3, or 4 HCV infection were randomised 1:1 to each group. Randomisation was stratified by HCV genotype, by treatment history (treatment naïve or treatment experienced with an interferon-based regimen), and by the presence or absence of cirrhosis. Patients with other HCV genotypes were enrolled in the VOSEVI 8-week group.

Demographics and baseline characteristics were generally balanced across treatment groups. Of the 941 treated patients, the median age was 55 years (range: 18 to 82); 52% of the patients were male; 80% were White, 10% were Black; 9% were Hispanic or Latino; 24% had a baseline body mass index at least 30 kg/m^2; the majority of patients had genotype 1 (49%) or genotype 3 (19%) HCV infection; 68% had non-CC IL28B genotypes (CT or TT); 69% had baseline HCV RNA levels at least 800,000 IU/mL; 18% had compensated cirrhosis; and 23% were treatment experienced with an interferon-based regimen.

Table 12 presents the SVR12 by HCV genotype and virologic outcome for the POLARIS trial.

Table 12 SVR12 by HCV genotype and virologic outcome in Study POLARIS-2

	VOSEVI 8 weeks (N = 501)	**SOF/VEL 12 weeks (N = 440)**
Overall SVR12[a]	**95% (477/501)**	**98% (432/440)**
Genotype 1[b]	93% (217/233)	98% (228/232)
Genotype 1a	92% (155/169)	99% (170/172)
Genotype 1b	97% (61/63)	97% (57/59)
Genotype 2	97% (61/63)	100% (53/53)
Genotype 3	99% (91/92)	97% (86/89)
Genotype 4	94% (59/63)	98% (56/57)
Genotype 5	94% (17/18)	0/0
Genotype 6	100% (30/30)	100% (9/9)
Outcome for patients without SVR		
On-treatment virologic failure	0/501	0/440
Relapse[c]	4% (21/498)	1% (3/439)
Other[d]	1% (3/501)	1% (5/440)

a Two patients with undetermined genotype in the VOSEVI group achieved SVR12.

b Two patients had genotype 1 subtypes other than genotype 1a or genotype 1b; both patients achieved SVR12.

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

d Other includes patients with missing data and those who discontinued treatment prior to virologic suppression.

Treatment with VOSEVI for 8 weeks in POLARIS-2 did not demonstrate noninferiority to treatment with SOF/VEL for 12 weeks with a prespecified margin of -5%.

DAA-Naïve Adults with Genotype 3 HCV Infection and Compensated Cirrhosis (POLARIS-3)

POLARIS-3 was a randomised, open-label trial that evaluated 8 weeks of treatment with VOSEVI and 12 weeks of treatment with SOF/VEL in DAA-naïve patients with genotype 3 HCV infection with compensated cirrhosis. Patients were randomised 1:1 to each group. Randomisation was stratified by treatment history (treatment naïve or treatment experienced with an interferon-based regimen).

Demographics and baseline characteristics were generally balanced across treatment groups. Of the 219 treated patients, all patients had genotype 3 HCV infection and compensated cirrhosis; the median age was 56 years (range: 25 to 75); 72% of the patients were male; 90% were White, 8% were Asian, 8% were Hispanic or Latino; 26% had a baseline body mass index at least 30 kg/m^2; 58% had non-CC IL28B genotypes (CT or TT); 69% had baseline HCV RNA levels at least 800,000 IU/mL; and 31% were treatment experienced with an interferon-based regimen.

Table 13 presents the SVR12 and virologic outcome for the POLARIS-3 trial.

Table 13 SVR12 and virologic outcome in Study POLARIS-3 (HCV genotype 3)

	VOSEVI 8 weeks (N = 110)	**SOF/VEL 12 weeks[a] (N = 109)**
SVR12	96% (106/110)	96% (105/109)
Outcome for patients without SVR		
On-treatment virologic failure	0/110	1% (1/109)
Relapse[a]	2% (2/108)	1% (1/107)
Other[b]	2% (2/110)	2% (2/109)

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.

The SVR12 rate for each treatment group was statistically superior relative to the prespecified SVR12 performance goal of 83% ($p < 0.001$ for both groups).

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetic properties of sofosbuvir, GS-331007, velpatasvir and voxilaprevir have been evaluated in healthy adult patients and in patients with chronic hepatitis C. Following oral administration of VOSEVI, sofosbuvir was absorbed quickly and the peak median plasma concentration was observed 2 hours post-dose. Median peak plasma concentration of GS-331007 was observed 4 hours post-dose. Velpatasvir median peak concentrations were observed at 4 hours post-dose. Voxilaprevir median peak concentrations were observed 4 hours post-dose.

Based on the population pharmacokinetic analysis in HCV-infected patients, mean steady-state AUC_{0-24} and C_{max} for sofosbuvir (n = 1038) were 1665 ng•hr/mL and 678 ng/mL, respectively; mean steady-state AUC_{0-24} and C_{max} for GS-331007 (n = 1593) were

12834 ng•hr/mL and 744 ng/mL, respectively; mean steady-state AUC_{0-24} and C_{max} for velpatasvir (n = 1595) were 4041 ng•hr/mL and 311 ng/mL, respectively; mean steady-state AUC_{0-24} and C_{max} for voxilaprevir (n = 1591) were 2577 ng•hr/mL and 192 ng/mL, respectively. Sofosbuvir and GS-331007 AUC_{0-24} and C_{max} were similar in healthy adult patients and in patients with HCV infection. Relative to healthy patients (n = 137), velpatasvir AUC_{0-24} and C_{max} were 41% lower and 39% lower, respectively, in HCV-infected patients. Relative to healthy patients (n = 63), voxilaprevir AUC_{0-24} and C_{max} were both 260% higher in HCV-infected patients.

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 patients, 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 patients, 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 patients, the blood to plasma ratio of [^{14}C]-radioactivity ranged between 0.5 and 0.8.

Metabolism

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

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

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. Unchanged voxilaprevir is the major species present in faeces.

Excretion

Following a single 400 mg oral dose of [^{14}C]-sofosbuvir, mean total recovery of the [^{14}C]-radioactivity was greater than 92%, consisting of approximately 80%, 14%, and 2.5% recovered in urine, faeces, and expired air, respectively. The majority of the sofosbuvir dose

recovered in urine was GS-331007 (78%) while 3.5% was recovered as sofosbuvir. These data indicate that renal clearance is the major elimination pathway for GS-331007. The median terminal half-lives of sofosbuvir and GS-331007 following administration of VOSEVI were 0.5 and 29 hours, respectively.

Following a single 100 mg oral dose of [^{14}C]-velpatasvir, mean total recovery of the [^{14}C]-radioactivity was 95%, consisting of approximately 94% and 0.4% recovered from the faeces and urine, respectively. Unchanged velpatasvir was the major species in faeces accounting for a mean of 77% of the administered dose, followed by monohydroxylated velpatasvir (5.9%) and desmethylated velpatasvir (3.0%). These data indicate that 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.

Following a single 100 mg oral dose of [^{14}C]-voxilaprevir, mean total recovery of the [^{14}C]-radioactivity was 94%, with all radioactivity measured in the faeces and none in the urine. Unchanged voxilaprevir was the major species in faeces accounting for a mean of 40% of the administered dose. Voxilaprevir metabolites also identified in faeces included des-[methylcyclopropylsulphonamide]-voxilaprevir (22.1%), which is formed intestinally, dehydro-voxilaprevir (7.5%), and two des-[methylcyclopropylsulphonamide]-oxy-voxilaprevir metabolites (5.4% and 3.9%). 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.

Effect of Food

When VOSEVI or its components taken together were administered with food, sofosbuvir $AUC_{0\text{-}inf}$ and C_{max} were 64% to 144% and 9% to 76% higher, respectively; velpatasvir $AUC_{0\text{-}inf}$ and C_{max} were 40% to 166% and 37% to 187% higher, respectively; and voxilaprevir $AUC_{0\text{-}inf}$ and C_{max} were 112% to 435% and 147% to 680% higher, respectively. GS-331007 $AUC_{0\text{-}inf}$ did not change and C_{max} was 19% to 35% lower when VOSEVI or its components together were administered with food. VOSEVI should be administered with food.

Special Populations

Race and Gender

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

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

Elderly Patients

Population pharmacokinetic analysis in HCV-infected patients showed that within the age range (18 to 85 years) analyzed, age did not have a clinically relevant effect on the exposure to sofosbuvir, GS-331007, velpatasvir, or voxilaprevir.

Paediatric Patients

The pharmacokinetics of VOSEVI, in paediatric patients have not been established.

Patients with Impaired Renal Function

The pharmacokinetics of sofosbuvir were studied in HCV negative patients 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 patients with end stage renal disease (ESRD) requiring haemodialysis following a single 400 mg dose of sofosbuvir. Relative to patients with normal renal function (eGFR > 80 mL/min/1.73m^2), the sofosbuvir $AUC_{0\text{-}inf}$ was 61%, 107% and 171% higher in mild, moderate, and severe renal impairment, while the GS-331007 $AUC_{0\text{-}inf}$ was 55%, 88%, and 451% higher, respectively. In patients with ESRD, sofosbuvir $AUC_{0\text{-}inf}$ was 28% higher when sofosbuvir was dosed 1 hour before haemodialysis compared with 60% higher when dosed 1 hour after haemodialysis, respectively. The $AUC_{0\text{-}inf}$ of GS-331007 in patients with ESRD administered with sofosbuvir 1 hour before or 1 hour after haemodialysis was at least 10-fold and 20-fold higher, respectively. GS-331007 is efficiently removed by haemodialysis with an extraction coefficient of approximately 53%. Following a single 400 mg dose of sofosbuvir, a 4 hour haemodialysis removed 18% of administered dose. No dose adjustment is required for patients with mild or moderate renal impairment. The safety and efficacy of sofosbuvir have not been established in patients with severe renal impairment or ESRD.

The pharmacokinetics of velpatasvir were studied with a single dose of 100 mg velpatasvir in HCV negative patients with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault). No clinically relevant differences in velpatasvir pharmacokinetics were observed between healthy patients and patients with severe renal impairment. No dose adjustment of velpatasvir is required for patients with mild, moderate, or severe renal impairment.

The pharmacokinetics of voxilaprevir were studied with a single dose of 100 mg voxilaprevir in HCV negative patients with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault). No clinically relevant differences in voxilaprevir pharmacokinetics were observed between healthy patients and patients with severe renal impairment. No dose adjustment of voxilaprevir is required for patients with mild, moderate, or severe renal impairment.

Patients with Hepatic Impairment

The pharmacokinetics of sofosbuvir were studied following 7-day dosing of 400 mg sofosbuvir in HCV-infected patients with moderate and severe hepatic impairment (Child-Pugh B and C). Relative to patients with normal hepatic function, the sofosbuvir $AUC_{0\text{-}24}$ was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 $AUC_{0\text{-}24}$ was 18% and 9% higher, respectively. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure of sofosbuvir and GS-331007. No dose adjustment of sofosbuvir is recommended for patients with mild, moderate, and severe hepatic impairment.

The pharmacokinetics of velpatasvir were studied with a single dose of 100 mg velpatasvir in HCV negative patients with moderate and severe hepatic impairment (Child-Pugh B and C). Velpatasvir plasma exposure (AUC_{inf}) was similar in patients with moderate hepatic impairment, severe hepatic impairment, and control patients 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. No dose adjustment of velpatasvir is required for patients with mild, moderate, or severe hepatic impairment.

The pharmacokinetics of voxilaprevir were studied with a single dose of 100 mg voxilaprevir in HCV negative patients with moderate and severe hepatic impairment (Child-Pugh B and C). Relative to patients with normal hepatic function, the voxilaprevir AUC_{inf} was 299% and 500% higher in patients 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. No dose adjustment of voxilaprevir is required for patients with cirrhosis (Child-Pugh A).

Assessment of Drug Interactions

After oral administration of VOSEVI sofosbuvir is rapidly absorbed and subject to extensive first-pass hepatic extraction. Hydrolytic prodrug cleavage and sequential phosphorylation steps results in formation of the pharmacologically active uridine nucleoside analog triphosphate. Dephosphorylation of nucleotide metabolites results in conversion to the predominant circulating metabolite GS-331007 that accounts for the majority of total systemic exposure. In clinical pharmacology studies, both sofosbuvir and GS-331007 were monitored for purposes of pharmacokinetic analyses.

Sofosbuvir, velpatasvir, and voxilaprevir are substrates of drug transporters P-gp and BCRP, while GS-331007 is not. 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.

Sofosbuvir and GS-331007 are not inhibitors of drug transporters P-gp, BCRP, OATP1B1, OATP1B3, and OCT1, and GS-331007 is not an inhibitor of OAT1, OAT3, OCT2, and MATE1. Sofosbuvir and GS-331007 are not inhibitors or inducers of CYP or UGT1A1 enzymes.

Velpatasvir is an inhibitor of drug transporters P-gp, 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 concentration, 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 drug interactions with these transporters is primarily limited to the process of absorption. At clinically relevant concentrations, voxilaprevir is not an inhibitor of hepatic transporters OCT1, renal transporters OCT2, OAT1, OAT3 or MATE1, or CYP or UGT1A1 enzymes.

The effects of coadministered drugs on the exposure of sofosbuvir, GS-331007, velpatasvir and voxilaprevir are shown in Table 14. The effects of sofosbuvir, velpatasvir or voxilaprevir on the exposure of coadministered drugs are shown in Table 15.

Table 14 Drug Interactions: Changes in Pharmacokinetic Parameters for Sofosbuvir, its 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)			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)	N	Component	C_{max}	AUC	C_{min}
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
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
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/	150/150/200/ 10 once daily			29	sofosbuvir	1.27 (1.09, 1.48)	1.22 (1.12, 1.32)	NA

emtricitabine/ tenofovir alafenamide[c]		SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily		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)
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
Gemfibrozil	600 twice daily	VOX	100 single dose	24	voxilaprevir	0.98 (0.85, 1.13)	1.11 (1.01, 1.23)	NA
Ketoconazole	200 twice daily	VEL	100 single dose	12	velpatasvir	1.29 (1.02, 1.64)	1.71 (1.35, 2.18)	NA
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

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
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)
Rifampicin	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
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
Voriconazole	200 twice daily	VOX	100 single dose	24	voxilaprevir	1.13 (0.98, 1.31)	1.84 (1.66, 2.03)	NA

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

a. All interaction studies conducted in healthy volunteers.

b. Administered as ATRIPLA (efavirenz, emtricitabine and tenofovir DF fixed-dose combination).

c. Administered as GENVOYA (elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide fixed-dose combination).

d. Administered as ODEFSEY (emtricitabine, rilpivirine, and tenofovir alafenamide fixed-dose combination).

Table 15 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}
Atorvastatin	40 single dose	SOF/VEL	400/100 once daily	26	1.68 (1.49, 1.89)	1.54 (1.45, 1.64)	N/A
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
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
Darunavir + ritonavir + emtricitabine/ tenofovir DFb	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)
Digoxin	0.25 single dose	VEL	100 once daily	21	1.88 (1.71, 2.08)	1.34 (1.13, 1.60)	NA
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	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

Co-administered Drug		Sofosbuvir (SOF)/ Velpatasvir (VEL)/ Voxilaprevir (VOX)			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)	N	C_{max}	AUC	C_{min}
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)
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)
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	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
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)
Tacrolimus	5 single dose	SOF	400 once daily	16	0.73 (0.59, 0.90)	1.09 (0.84, 1.40)	NA

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, and tenofovir DF fixed-dose combination).
d. Administered as GENVOYA (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide fixed-dose combination).
e. Administered as ODEFSEY (emtricitabine, rilpivirine, and tenofovir alafenamide fixed-dose combination).

5.3 Preclinical safety data

Genotoxicity

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

Velapatasvir 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.

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

Carcinogenicity studies in mice and rats do not indicate any carcinogenicity potential of sofosbuvir administered at doses up to 200 mg/kg/day in male mice and 600 mg/kg/day in female mice, and 750 mg/kg/day in rats. Exposure to GS-331007 in these studies in mice was up to 4 times (male) and 17 times (female), and in rats up to 8 times (male) and 10 times (female) higher than the clinical exposure at 400 mg sofosbuvir.

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

Carcinogenicity studies for voxilaprevir have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: silicon dioxide, copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose.

Film-coating: ferrosoferric oxide, iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, purified talc, and titanium dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

VOSEVI should be stored below 30 °C.

6.5 Nature and contents of container

VOSEVI tablets are supplied in high-density polyethylene (HDPE) bottle and a child-resistant closure containing 28 film-coated tablets with polyester coil.

Each VOSEVI tablet is film-coated and beige in colour. The tablets are capsule shaped debossed with “GSI” on one side and “3” on the other side. The tablets are supplied in bottles with a polyester coil, silica gel desiccant, and are closed with a child-resistant closure.

6.6 Special precautions for disposal

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

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Gilead Sciences (NZ)
c/- Grant Thornton New Zealand Limited,
L4, 152 Fanshawe Street
Auckland 1010
New Zealand

Tel: 0800 443 933

9 DATE OF FIRST APPROVAL

31 January 2019

10 DATE OF REVISION OF THE TEXT

24 May 2022

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4, 4.5	New subheading and text in section 4.4: Potential for Dysglycaemia in Diabetic patients; Section 4.5 addition of new subsequent cross-reference.
4.8	Addition of Stevens-Johnson syndrome under Post marketing surveillance.