NEW ZEALAND DATA SHEET

1. PRODUCT NAME

MAVIRET 100 mg / 40 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg glecaprevir and 40 mg pibrentasvir.

Excipient with known effect
Each film-coated tablet contains 7.48 mg lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet. Glecaprevir and pibrentasvir are presented as a fixed-dose combination, immediate release bilayer tablet.

Pink, oblong, biconvex, film-coated tablet of dimensions 18.8 mm x 10.0 mm, debossed on one side with 'NXT'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MAVIRET is indicated for the treatment of adults and adolescents 12 years and older with chronic hepatitis C virus (HCV) (see sections 4.2, 4.4 and 5.1).

4.2 Dose and method of administration

Dose
The recommended dose of MAVIRET in adults and adolescents 12 years and older is 300 mg/120 mg (three 100 mg glecaprevir/40 mg pibrentasvir tablets), taken orally, once daily at the same time with food (see section 5.2). Addition of ribavirin is not required.

Tables 1 and 2 provide the recommended MAVIRET treatment duration based on the patient population in HCV genotype (GT) 1, 2, 3, 4, 5 or 6 patients with compensated liver disease (with or without cirrhosis).

Table 1: Recommended duration for treatment-naïve patients

Patient Population	Recommended Treatment Duration	
	No Cirrhosis	Cirrhosis
GT 1-6	8 weeks	8 weeks
Includes patients co-infected with human immunodeficiency virus (HIV).		

Table 2: Recommended duration for treatment-experienced patients

Patient Population	Recommended Treatment Duration	
	No Cirrhosis	Cirrhosis
NS5A inhibitor-naïve* GT 1, 2, 4, 5, 6	8 weeks	12 weeks
NS5A inhibitor-experienced GT 1, 2, 4, 5, 6	16 weeks	16 weeks
GT 3 (any experienced)		
* experienced with PR, SOF + PR, SOF + R, SMV + SOF, SMV + PR, TVR + PR or BOC + PR. PR = (peg)interferon + ribavirin; SOF = Sofosbuvir; R = Ribavirin; SMV = Simeprevir; TVR = Telaprevir; BOC = Boceprevir. Includes patients co-infected with human immunodeficiency virus (HIV).		

Missed doses
In case a dose of MAVIRET is missed, the prescribed dose can be taken within 18 hours. If more than 18 hours have passed since MAVIRET is usually taken, the missed dose should **not** be taken and the patient should take the next dose per the usual dosing schedule. Patients should be instructed not to take a double dose.

Elderly patients
No dose adjustment of MAVIRET is required in elderly patients (see sections 5.1 and 5.2).

Patients with renal impairment
No dose adjustment of MAVIRET is required in patients with any degree of renal impairment, including patients on dialysis (see sections 5.1 and 5.2).

Patients with hepatic impairment
No dose adjustment of MAVIRET is required in patients with mild hepatic impairment (Child-Pugh A) MAVIRET is not recommended in patients with moderate hepatic impairment (Child-Pugh B) and is contraindicated in patients with severe hepatic impairment (Child-Pugh C), (see sections 4.3, 4.4 and 5.2 for contraindications and precautions).

Paediatric population
No dose adjustment of MAVIRET is required in adolescents 12 years and older (see section 5 Pharmacological properties). The safety and efficacy of MAVIRET in children and adolescents aged less than 12 years have not yet been established.

Liver or kidney transplant patients
MAVIRET may be used for 12 weeks in liver or kidney transplant recipients. A 16-week treatment duration should be considered in transplant patients who are NS5A inhibitor-experienced or genotype 3-infected patients who are treatment experienced (see Table 2).

Method of administration
For oral use. Patients should be instructed to swallow tablets whole with food and not to chew, crush, or break the tablets (see section 5.2).

4.3 Contraindications

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

Patients with severe hepatic impairment (Child-Pugh C) (see sections 4.2, 4.4 and 5.2).

Concomitant use with atazanavir and rifampicin (see section 4.5).

4.4 Special warnings and precautions for use

Hepatitis B virus reactivation
Cases of hepatitis B virus (HBV) reactivation, some of them fatal, have been reported during treatment with direct-acting antiviral agents. All patients should be screened for HBV before initiation of treatment. HBV/HCV co-infected patients are at risk of HBV reactivation, and should therefore be monitored and managed according to current clinical guidelines.

Patients with hepatic impairment
MAVIRET is not recommended in patients with moderate hepatic impairment (Child-Pugh B) (see sections 4.2 and 5.2).

Patients with lactose intolerance
MAVIRET contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Potential effects of HCV clearance by Direct-Acting Antivirals (DAA) (class therapeutic effect)
Patients may experience improvement of liver function with HCV treatment resulting in improved glucose metabolism by the liver. In diabetic patients, this could lead to improved glucose control. Rare cases of symptomatic hypoglycaemia have been reported with the use of HCV DAAs. Therefore, close monitoring of blood glucose levels is recommended in diabetic patients to determine if dose adjustment of the anti-diabetes medication is required.

4.5 Interaction with other medicines and other forms of interaction

Potential for MAVIRET to affect other medicines
Glecaprevir and pibrentasvir are inhibitors of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide (OATP) 1B1/3. Therefore, co-administration with MAVIRET may increase plasma concentrations of medicinal products that are substrates of P-gp, BCRP, OATP1B1, or OATP1B3.

Glecaprevir and pibrentasvir are weak inhibitors of cytochrome P450 (CYP) 3A, CYP1A2, and uridine glucuronosyltransferase (UGT) 1A1. Significant interactions are not expected when MAVIRET is co-administered with substrates of CYP3A, CYP1A2, CYP2C9, CYP2C19, CYP2D6, UGT1A1, or UGT1A4.

If MAVIRET is coadministered with a vitamin K antagonist, close monitoring of INR is recommended. This is due to liver function changes during treatment with MAVIRET.

Potential for other medicines to affect MAVIRET

Glecaprevir and pibrentasvir are substrates of P-gp and/or BCRP. Glecaprevir is a substrate of OATP1B1/3. Co-administration of MAVIRET with medicinal products that inhibit hepatic P-gp, BCRP, or OATP1B1/3 may increase the plasma concentrations of glecaprevir and/or pibrentasvir.

Co-administration of MAVIRET with medicinal products that induce P-gp/CYP3A may decrease plasma concentrations of glecaprevir and pibrentasvir.

Interactions with medicinal products

Table 3 shows the effect of co-administration of MAVIRET on concentrations of concomitant drugs, and the effect of concomitant drugs on glecaprevir and pibrentasvir. All interaction studies were performed in adults.

Table 3: Potentially significant interactions between MAVIRET and other medicines

			Central Value Ratio (90% CI)		
Medicines by Class	**Effect on medicine levels*/ Mechanism of interaction**	**Clinical recommendations**	**C_{max}**	**AUC**	**C_{min}**
ANTIARRHYTHMICS					
Digoxin 0.5 mg single dose	↑ digoxin Inhibition of P-gp	Digoxin dose should be reduced by 50% when co-administered with MAVIRET.	1.72 (1.45–2.04)	1.48 (1.40–1.57)	--
ANTICOAGULANTS					
Dabigatran etexilate 150 mg single dose	↑ dabigatran Inhibition of P-gp	Co-administration is not recommended.	2.05 (1.72–2.44)	2.38 (2.11–2.70)	--
ANTICONVULSANTS					
Carbamazepine 200 mg twice daily	↓ glecaprevir Induction of P-gp/CYP3A	Co-administration may lead to reduced therapeutic effect of MAVIRET and is not recommended.	0.33 (0.27–0.41)	0.34 (0.28–0.40)	--
	↓ pibrentasvir Induction of P-gp/CYP3A		0.50 (0.42–0.59)	0.49 (0.43–0.55)	--
ANTIMYCOBACTERIALS					
Rifampicin 600 mg single dose	↑ glecaprevir Inhibition of OATP1B1/3	Co-administration is contraindicated (see section 4.3).	6.52 (5.06–8.41)	8.55 (7.01–10.4)	--
	↔ pibrentasvir Inhibition of OATP1B1/3		↔	↔	--

Rifampicin 600 mg once daily[a]	↓ glecaprevir Induction of P-gp/CYP3A		0.14 (0.11–0.19)	0.12 (0.09–0.15)	--
	↓ pibrentasvir Induction of P-gp/CYP3A		0.17 (0.14–0.20)	0.13 (0.11–0.15)	--
HERBAL PRODUCTS					
St. John's wort (*Hypericum perforatum*)	Not studied. Expected: ↓ glecaprevir ↓ pibrentasvir Induction of P-gp/CYP3A	Co-administration may lead to reduced therapeutic effect of MAVIRET and is not recommended.	Not studied.		
HIV-ANTIVIRAL AGENTS					
Atazanavir + ritonavir 300/100 mg once daily[b]	↑ glecaprevir	Co-administration is contraindicated (see section 4.3).	≥4.06 (3.15–5.23)	≥6.53 (5.24–8.14)	≥14.3 (9.85–20.7)
	↑ pibrentasvir		≥1.29 (1.15–1.45)	≥1.64 (1.48–1.82)	≥2.29 (1.95–2.68)
Darunavir + ritonavir 800/100 mg once daily	↑ glecaprevir	Co-administration is not recommended.	3.09 (2.26–4.20)	4.97 (3.62–6.84)	8.24 (4.40–15.4)
	↔ pibrentasvir		↔	↔	1.66 (1.25–2.21)
Efavirenz/ emtricitabine/ tenofovir disoproxil fumarate (TDF)	The effect of efavirenz/ emtricitabine/ TDF on glecaprevir and pibrentasvir was not evaluated, but glecaprevir and pibrentasvir exposures were significantly lower than in other studies of similar doses.	Co-administration with efavirenz may lead to reduced therapeutic effect of MAVIRET and is not recommended.	Not studied		
Lopinavir/ ritonavir 400/100 mg once daily	↑ glecaprevir	Co-administration is not recommended.	2.55 (1.84–3.52)	4.38 (3.02–6.36)	18.6 (10.4–33.5)
	↑ pibrentasvir		1.40 (1.17–1.67)	2.46 (2.07–2.92)	5.24 (4.18–6.58)

HMG-COA REDUCTASE INHIBITORS					
Pravastatin 10 mg once daily	↑ pravastatin Inhibition of OATP1B1/3	Pravastatin dose should be reduced by 50% and rosuvastatin dose should not exceed 10 mg per day when co-administered with MAVIRET.	2.23 (1.87–2.65)	2.30 (1.91–2.76)	--
Rosuvastatin 5 mg once daily	↑ rosuvastatin Inhibition of OATP1B1/3, BCRP		5.62 (4.80–6.59)	2.15 (1.88–2.46)	--
Atorvastatin 10 mg once daily	↑ atorvastatin Inhibition of OATP1B1/3, CYP3A	Co-administration is not recommended. Consider alternative therapies, such as pravastatin or rosuvastatin.	22.0 (16.4–29.5)	8.28 (6.06–11.3)	--
Lovastatin 10 mg once daily	↑ lovastatin		↔	1.70 (1.40–2.06)	--
	↑ lovastatin acid		5.73 (4.65–7.07)	4.10 (3.45–4.87)	--
Simvastatin 5 mg once daily	↑ simvastatin		1.99 (1.60–2.48)	2.32 (1.93–2.79)	--
	↑ simvastatin acid		10.7 (7.88–14.6)	4.48 (3.11–6.46)	--
IMMUNOSUPPRESSANTS					
Ciclosporin 100 mg single dose	↑ glecaprevir[c]	MAVIRET is not recommended for use in patients requiring stable ciclosporin doses >100 mg per day.	1.30 (0.95–1.78)	1.37 (1.13–1.66)	1.34 (1.12–1.60)
	↑ pibrentasvir		↔	↔	1.26 (1.15–1.37)
Ciclosporin 400 mg single dose	↑ glecaprevir		4.51 (3.63–6.05)	5.08 (4.11–6.29)	--
	↑ pibrentasvir		↔	1.93 (1.78–2.09)	--
ETHINYLOESTRADIOL-CONTAINING PRODUCTS					
Ethinyloestradiol/ Norgestimate 35 µg/250 µg once daily	↑ ethinyloestradiol	Co-administration of MAVIRET with ethinyloestradiol-containing products may increase the risk of ALT elevations and is not recommended.	1.31 (1.24–1.38)	1.28 (1.23–1.32)	1.38 (1.25–1.52)
	↑ norelgestromin		↔	1.44 (1.34–1.54)	1.45 (1.33–1.58)
	↑ norgestrel		1.54 (1.34–1.76)	1.63 (1.50–1.76)	1.75 (1.62–1.89)
Ethinyloestradiol / Levonorgestrel 20 µg/100 µg once daily	↑ ethinyloestradiol		1.30 (1.18–1.44)	1.40 (1.33–1.48)	1.56 (1.41–1.72)
	↑ norgestrel		1.37 (1.23–1.52)	1.68 (1.57–1.80)	1.77 (1.58–1.98)

* The directions of the arrows indicate the direction of the change in exposures (C_{max} and AUC) in glecaprevir, pibrentasvir, and the coadministered medicine (↑ = increase by more than 25%, ↓ = decrease by more than 20%, and ↔ = no change, less than 20% decrease, or less than 25% increase).

a. Effect of rifampicin on glecaprevir and pibrentasvir 24 hours after final rifampicin dose.
b. Effect of atazanavir and ritonavir on the first dose of glecaprevir and pibrentasvir.
c. HCV-infected transplant recipients who received ciclosporin doses of 100 mg or less per day had glecaprevir exposures 2.4-fold of those not receiving ciclosporin.

Medicines without clinically significant interactions with MAVIRET
No dose adjustment is required when MAVIRET is co-administered with the following medicines: abacavir, amlodipine, buprenorphine, caffeine, dextromethorphan, dolutegravir, elvitegravir/ cobicistat, emtricitabine, felodipine, lamivudine, lamotrigine, losartan, methadone, midazolam, naloxone, norethisterone or other progestin-only contraceptives, omeprazole, raltegravir, rilpivirine, sofosbuvir, tacrolimus, tenofovir alafenamide, tenofovir disoproxil fumarate, tolbutamide, and valsartan.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited data from the use of glecaprevir or pibrentasvir in pregnant women.

Animal studies with glecaprevir or pibrentasvir do not indicate direct harmful effects on reproductive toxicity. Maternal toxicity in the rabbit precluded evaluation of glecaprevir at clinical exposures (see section 5.3). As a precautionary measure, MAVIRET use is not recommended in pregnancy.

Breastfeeding
It is unknown whether glecaprevir or pibrentasvir are excreted in human milk. Available pharmacokinetic data in animals have shown excretion of glecaprevir and pibrentasvir in milk, and a risk to newborns or infants cannot be excluded. Therefore, a decision must be made whether to discontinue breastfeeding or to discontinue/abstain from MAVIRET therapy, taking into account the benefits of breastfeeding for the child and the benefit of therapy for the woman.

Fertility
No human data on the effect of glecaprevir and/or pibrentasvir on fertility are available. Animal studies do not indicate harmful effects of glecaprevir or pibrentasvir on fertility at exposures higher than the exposures in humans at the recommended dose (see Section 5.3).

4.7 Effects on ability to drive and use machines

MAVIRET has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The safety assessment for MAVIRET in patients with compensated liver disease (with or without cirrhosis) was derived from registration Phase 2 and 3 studies, which evaluated approximately 2,300 adult patients with chronic HCV genotype 1, 2, 3, 4, 5 or 6 who received MAVIRET for 8, 12, or 16 weeks.

The overall proportion of patients who permanently discontinued treatment with MAVIRET due to adverse reactions was 0.1%.

Across the Phase 2 and 3 clinical studies in patients treated with MAVIRET, adverse reactions with a frequency of very common (incidence ≥10%) were headache (13.2%) and fatigue (11.4%). Nausea (7.6%) was observed with a frequency of common (incidence ≥5% and <10%).

Most patients (80%) who experienced adverse reactions with MAVIRET had reactions of mild severity (Grade 1). In the placebo-controlled study (ENDURANCE-2), these adverse reactions occurred at a similar frequency in patients given placebo and those treated with MAVIRET.

In the active-controlled study (ENDURANCE-3), adverse reactions occurred at a similar frequency in patients treated with sofosbuvir and daclatasvir compared to patients treated with MAVIRET.

There were no differences in the overall safety for patients receiving MAVIRET for 8, 12, or 16 weeks. The types and severity of adverse reactions in patients with compensated cirrhosis were comparable to those seen in patients without cirrhosis.

Adverse reactions in adult patients with severe renal impairment, including patients on dialysis

The safety of MAVIRET was assessed in 104 patients with chronic kidney disease (stage 4 or Stage 5, including patients on dialysis) and chronic HCV genotypes 1, 2, 3, 4, 5 or 6 with compensated liver disease (with or without cirrhosis) (EXPEDITION-4). Pruritus and fatigue had a frequency of very common, occurring with an incidence of 17.3% and 11.5%, respectively, in these patients. Nausea, asthenia, and headache were observed with a frequency of common (incidence 8.7%, 6.7%, and 5.8%, respectively, in patients receiving 12 weeks of treatment with MAVIRET. In patients treated with MAVIRET who reported an adverse reaction, 55% had adverse reactions of mild severity (Grade 1). No patients experienced a serious adverse reaction. The proportion of patients who permanently discontinued treatment due to adverse reactions was 1.9%.

Adverse reactions in HCV/HIV-1 co-infected adult patients

The overall safety profile in HCV/HIV-1 co-infected patients (ENDURANCE-1 and EXPEDITION-2) was comparable to that observed in HCV mono-infected patients.

Adverse reactions in adult patients with liver or kidney transplant

The safety of MAVIRET was assessed in 100 post-liver or -kidney transplant recipients with chronic HCV genotypes 1, 2, 3, 4, or 6 without cirrhosis (MAGELLAN-2). The overall safety profile in transplant recipients was comparable to that observed in patients in the Phase 2 and 3 studies. Adverse reactions observed in greater than or equal to 5% of patients receiving MAVIRET for 12 weeks were headache (17%), fatigue (16%), nausea (8%), and pruritus (7%). In patients treated with MAVIRET who reported an adverse reaction, 81% had adverse reactions of mild severity. Two percent of patients experienced a serious adverse reaction, and no patients permanently discontinued treatment due to adverse reactions.

Adverse Reactions in People Who Inject Drugs (PWID) and those on Medication-Assisted Treatment (MAT) for Opioid Use Disorder

The safety of MAVIRET in PWID and those on MAT with HCV genotype 1-6 is based on data from Phase 2 and 3 trials in which 62 patients identified as current/recent PWID (defined as self-reported injection drug use within the last 12 months prior to starting MAVIRET), 959 patients identified as former PWID (defined as self-reported injection drug use more than 12 months prior to starting MAVIRET), and 3,282 patients who reported no injection drug use (non-PWID); 225 patients reported concomitant use of MAT for opioid use disorder, and 4,098 patients reported no MAT use.

The overall safety of MAVIRET was similar between patients who self-identified as current/recent PWID, those who were former PWID, and those who did not report history of injection drug use. The safety of MAVIRET was also similar between patients who reported concomitant MAT for opioid use disorder and those who did not report MAT use.

Adverse Reactions in Adolescent Patients

The safety of MAVIRET in adolescents with chronic HCV genotype 1-6 is based on data from a Phase 2/3 open-label trial in 47 patients aged 12 years to less than 18 years treated with MAVIRET for 8 to 16 weeks (DORA-Part 1). The adverse reactions observed were comparable with those observed in clinical studies of MAVIRET in adults.

Serum bilirubin elevations
Elevations in total bilirubin of at least 2 x upper limit normal (ULN) were observed in 1% of subjects related to glecaprevir-mediated inhibition of bilirubin transporters and metabolism. Bilirubin elevations were asymptomatic, transient, and typically occurred early during treatment. Bilirubin elevations were predominantly indirect and not associated with ALT elevations.

Adverse reactions in the paediatric population
No data are available.

Post marketing experience
The following adverse reactions have been identified during post approval use of MAVIRET. Because these 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.
Immune System Disorders: angioedema
Skin and Subcutaneous Tissue Disorders: pruritus

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 via https://nzphvc.otago.ac.nz/reporting/ .

4.9 Overdose

The highest documented doses administered to healthy volunteers were 1200 mg once daily for 7 days for glecaprevir, and 600 mg once daily for 10 days for pibrentasvir. In the case of overdose, the patient should be monitored for any signs and symptoms of toxicities, and appropriate symptomatic treatment should be implemented immediately. Glecaprevir and pibrentasvir are not significantly removed by haemodialysis.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Direct-acting antiviral, ATC code: J05AX.

Mechanism of action
MAVIRET is a fixed-dose combination tablet containing two pangenotypic, direct-acting antiviral agents, glecaprevir (HCV NS3/4A protease inhibitor) and pibrentasvir (HCV NS5A inhibitor), targeting multiple steps in the HCV viral lifecycle.

Glecaprevir
Glecaprevir is a pangenotypic inhibitor of the HCV NS3/4A protease, which is necessary for the proteolytic cleavage of the HCV-encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication. In a biochemical assay, glecaprevir inhibited the proteolytic activity of recombinant NS3/4A enzymes from clinical isolates of HCV genotypes 1a, 1b, 2a, 2b, 3a, 4a, 5a and 6a, with IC_{50} values ranging from 3.5 to 11.3 nM.

Pibrentasvir

Pibrentasvir is a pangenotypic inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly. The mechanism of action of pibrentasvir has been characterised based on cell-culture antiviral activity and drug-resistance mapping studies.

Antiviral Activity

The EC_{50} values of glecaprevir and pibrentasvir against full-length or chimeric replicons encoding NS3 or NS5A from laboratory strains are presented in Table 4.

Table 4: Activity of glecaprevir and pibrentasvir against replicon cell lines of HCV genotypes 1−6

HCV subgenotype	Glecaprevir EC_{50}, nM	Pibrentasvir EC_{50}, nM
GT 1a	0.85	0.0018
GT 1b	0.94	0.0043
GT 2a	2.2	0.0023
GT 2b	4.6	0.0019
GT 3a	1.9	0.0021
GT 4a	2.8	0.0019
GT 5a	NA	0.0014
GT 6a	0.86	0.0028

NA = not available.
GT = genotype/subgenotype.

The EC_{50} values of glecaprevir and pibrentasvir against chimeric replicons encoding NS3 or NS5A from clinical isolates are presented in Table 5.

Table 5: Activity of glecaprevir and pibrentasvir against transient replicons containing NS3 or NS5A from HCV genotypes 1−6 clinical isolates

HCV Subgenotype	Glecaprevir		Pibrentasvir	
	Number of clinical isolates	Median EC_{50}, nM (range)	Number of clinical isolates	Median EC_{50}, nM (range)
GT 1a	11	0.08 (0.05–0.12)	11	0.0009 (0.0006–0.0017)
GT 1b	9	0.29 (0.20–0.68)	8	0.0027 (0.0014–0.0035)
GT 2a	4	1.6 (0.66–1.9)	6	0.0009 (0.0005–0.0019)
GT 2b	4	2.2 (1.4–3.2)	11	0.0013 (0.0011–0.0019)
GT 3a	2	2.3 (0.71–3.8)	14	0.0007 (0.0005–0.0017)
GT 4a	6	0.41 (0.31–0.55)	8	0.0005 (0.0003–0.0013)
GT 4b	NA	NA	3	0.0012 (0.0005 – 0.0018)
GT 4d	3	0.17 (0.13–0.25)	7	0.0014 (0.0010–0.0018)
GT 5a	1	0.12	1	0.0011
GT 6a	NA	NA	3	0.0007 (0.0006–0.0010)
GT 6e	NA	NA	1	0.0008
GT 6p	NA	NA	1	0.0005

NA = not available.
GT = genotype/subgenotype.

Combination Activity *in vitro*

No antiviral antagonism between glecaprevir and pibrentasvir was detected when their combined activity was evaluated in HCV genotype 1 replicon cell-culture assays.

Resistance-associated substitutions

Studies in cell culture

Amino acid substitutions in NS3 or NS5A selected in cell culture or important for the inhibitor class were characterised phenotypically in replicons.

Substitutions important for the HCV protease inhibitor class at positions 36, 43, 54, 55, 56, 155, 166, or 170 in NS3 had no impact on glecaprevir's activity. Substitutions at amino-acid position 168 in NS3 had no impact in genotype 2, while some substitutions at position 168 reduced glecaprevir susceptibility by up to 55-fold (genotypes 1, 3, and 4), or reduced susceptibility by >100-fold (genotype 6). Some substitutions at position 156 reduced susceptibility to glecaprevir (genotypes 1 to 4) by >100-fold. Substitutions at amino-acid position 80 did not reduce susceptibility to glecaprevir except for Q80R in genotype 3a, which reduced susceptibility to glecaprevir by 21-fold.

Single substitutions important for the NS5A inhibitor class at positions 24, 28, 30, 31, 58, 92, or 93 in NS5A in genotypes 1 to 6 had no impact on the activity of pibrentasvir. Specifically, in genotype 3a, A30K or Y93H had no impact on pibrentasvir activity. Some combinations of substitutions in genotypes 1a and 3a (including A30K+Y93H in genotype 3a) showed reductions in susceptibility to pibrentasvir. In genotype 3b replicon, the presence of naturally-occurring polymorphisms K30 and M31 in NS5A reduced susceptibility to pibrentasvir by 24-fold relative to the activity of pibrentasvir in genotype 3a replicon.

Phase 2 and 3 clinical studies

Treatment-naïve patients and those previously treated with (peg)interferon, ribavirin, and/or sofosbuvir

Of approximately 2,300 patients given MAVIRET for 8, 12, or 16 weeks in the registration Phase 2 and 3 studies, 22 experienced virologic failure (two patients with genotype 1, two patients with genotype 2, and 18 patients with genotype 3 infection).

Among the two patients with genotype 1 who experienced virologic failure, one had treatment-emergent substitutions (A156V in NS3 and Q30R/L31M/H58D in NS5A), and one had Q30R/H58D (while Y93N was present at baseline and post-treatment) in NS5A.

Neither of the patients with genotype 2 had treatment-emergent substitutions in NS3 or NS5A (both patients had the M31 polymorphism in NS5A at baseline and post-treatment).

Among the 18 patients with genotype 3 who experienced virologic failure, 11 had treatment-emergent NS3 substitutions Y56H/N, Q80K/R, A156G, or Q168L/R. A166S or Q168R were present at baseline and post-treatment in five patients. 16 Patients had treatment-emergent NS5A substitutions M28G, A30G/K, L31F, P58T, or Y93H, and 13 patients had A30K (n=9) or Y93H (n=5) at baseline and post-treatment.

Patients previously treated with NS3/4A protease and/or NS5A inhibitors

In the MAGELLAN-1 study, 113 patients who were previously treated with NS3/4A protease and/or NS5A inhibitors were given MAVIRET for 12 or 16 weeks.

Among the ten patients with genotype 1 who experienced virologic failure, seven had treatment-emergent NS3 substitutions V36A/M, R155K/T, A156G/T/V, or D168A/T. Five of the ten had combinations of V36M, Y56H, R155K/T, or D168A/E in NS3 at baseline and post-treatment. All of these patients had one or more NS5A substitutions L/M28M/T/V, Q30E/G/H/K/L/R, L31M, P32 deletion, H58C/D, or Y93H at baseline, with additional treatment-emergent NS5A substitutions M28A/G, P29Q/R, Q30K, H58D, or Y93H observed in seven of the patients at the time of failure.

Effect of baseline HCV amino-acid polymorphisms on treatment response

A pooled analysis of all patients who were either treatment-naïve or had previous experience with (peg)interferon, ribavirin, and/or sofosbuvir was conducted to assess whether there was an association between baseline polymorphisms and treatment outcome, and to describe substitutions seen in patients with virologic failure. Baseline polymorphisms relative to a subtype-specific reference sequence at amino-acid positions 155, 156, and 168 in NS3, and 24, 28, 30, 31, 58, 92, and 93 in NS5A were evaluated at a 15% detection threshold by next-generation sequencing. Baseline polymorphisms in NS3 were detected in 1.1% (9/845), 0.8% (3/398), 1.6% (10/613), 1.2% (2/164), 41.9% (13/31), and 2.9% (1/34) of patients with HCV genotype 1, 2, 3, 4, 5 and 6, respectively. Baseline polymorphisms in NS5A were detected in 26.8% (225/841), 79.8% (331/415), 22.1% (136/615), 49.7% (80/161), 12.9 % (4/31), and 54.1% (20/37) of patients with HCV genotype 1, 2, 3, 4, 5 and 6, respectively.

- *Genotype 1, 2, 4, 5 and 6:* Baseline polymorphisms in genotypes 1, 2, 4, 5 and 6 had no impact on treatment outcome.
- *Genotype 3*: Among 313 patients with genotype 3 who received the recommended regimen, baseline NS3 polymorphisms had no impact on treatment outcome. All 15 patients (100%) with Y93H in NS5A at baseline achieved a sustained virologic response (SVR12). Among patients receiving the recommended regimen, 77% (17/22) with A30K in NS5A at baseline achieved SVR12. Among 21 patients with genotype 3 and compensated cirrhosis who received the recommended regimen, 100% (21/21) who had polymorphisms in NS5A at baseline achieved SVR12.

Cross-resistance

In vitro data indicate that the majority of the resistance-associated substitutions in NS5A at amino acid positions 24, 28, 30, 31, 58, 92, or 93 that confer resistance to ombitasvir, daclatasvir, ledipasvir, elbasvir, or velpatasvir remained susceptible to pibrentasvir. Glecaprevir was fully active against resistance-associated substitutions in NS5A, while pibrentasvir was fully active against resistance-associated substitutions in NS3. Both glecaprevir and pibrentasvir were fully active against substitutions associated with resistance to NS5B nucleotide and non-nucleotide inhibitors.

In the MAGELLAN 1 study, patients who had failed prior treatment with NS3/4A protease and/or NS5A inhibitors were treated with MAVIRET for 12 or 16 weeks. Baseline sequences were analysed by next-generation sequencing at 15% detection threshold. One or more of the following NS3 polymorphisms were detected at baseline in 16% (17/105) of patients with HCV genotype 1: R155K/T (n=8) or D168A/E/N/T/V (n=10). One or more of the following NS5A substitutions were detected in 60% (63/105) of the patients with genotype 1: K24Q/R (n=4), L/M28A/M/T/V (n=11), Q/R30E/G/H/K/L/Q/R (n=29), L31I/M/V (n=14), H/P58C/D/P/Q/S/T/Y (n=17), A92E/T (n=2), or Y93H/N/S (n=23).

Among 23 patients who had been treated with a protease inhibitor but not with an NS5A inhibitor and who receive 12 weeks of treatment, two patients each had baseline polymorphisms in NS3-only, NS5A-only, or NS3+NS5A; all 23 patients achieved SVR12. Among 32 patients who had been treated with an NS5A inhibitor (with or without PI-experience) and who received 16 weeks of treatment, the SVR12 rate was 100% (1/1), 95.0% (19/20), 25.0% (1/4), and 100% (7/7) in patients with baseline polymorphisms in NS3-only, NS5A-only, NS3+NS5A, or without any polymorphisms in NS3 or NS5A, respectively.

Clinical efficacy and safety

Table 6 summarises clinical studies conducted with MAVIRET in patients with HCV genotype 1, 2, 3, 4, 5 or 6.

Table 6: Clinical studies with MAVIRET in patients with HCV genotypes 1, 2, 3, 4, 5 or 6

Genotype (GT)	Clinical study	Summary of study design*
TN and PRS-TE patients without cirrhosis		
GT 1	ENDURANCE-1[a]	MAVIRET for 8 (n=351) or 12 weeks (n=352)
	SURVEYOR-1	MAVIRET for 8 weeks (n=34)
GT 2	ENDURANCE-2	MAVIRET (n=202) or Placebo (n=100) for 12 weeks
	SURVEYOR-2[b]	MAVIRET for 8 weeks (n=199) or 12 weeks (n=25)
GT 3	ENDURANCE-3	MAVIRET for 8 (n=157) or 12 weeks (n=233) Sofosbuvir + daclatasvir for 12 weeks (n=115)
	SURVEYOR-2[c]	MAVIRET for 8 (TN only) (n=29) or 12 weeks (n=76) or 16 (PRS-TE only) weeks (n=22)
GT 4, 5, 6	ENDURANCE-4	MAVIRET for 12 weeks (n=121)
	ENDURANCE-5,6	MAVIRET for 8 weeks (n=75)
	SURVEYOR-1	MAVIRET for 12 weeks (n=32)
	SURVEYOR-2	MAVIRET for 8 weeks (n=58)
GT 1-6	VOYAGE-1[f]	MAVIRET for 8 weeks (GT 1, 2, 4, 5, 6 and GT 3 TN) (n=356) or 16 weeks (GT 3 PRS -TE only) (n=6)
TN and PRS-TE patients with cirrhosis		
GT 1, 2, 4, 5, 6	EXPEDITION-1	MAVIRET for 12 weeks (n=146)
GT 3	SURVEYOR-2[d]	MAVIRET for 12 (TN only) weeks (n=64) or 16 weeks (PRS-TE only) (n=51)
GT 5, 6	ENDURANCE-5,6	MAVIRET for 12 weeks (n=9)
GT 1-6	VOYAGE-2[f]	MAVIRET for 12 weeks (GT 1, 2, 4, 5, 6 and GT 3 TN) (n=157) or 16 weeks (GT 3 PRS -TE only) (n=3)
GT 1-6	EXPEDITION-8	MAVIRET for 8 weeks (n=343) (TN only)
Patients with CKD stage 4 and 5 with or without cirrhosis		
GT 1-6	EXPEDITION-4	MAVIRET for 12 weeks (n=104)
NS5A inhibitor and/or PI-experienced patients with or without cirrhosis		
GT 1, 4	MAGELLAN-1[e]	MAVIRET for 12 (n=66) or 16 weeks (n=47)
HCV/HIV-1 co-infected patients with or without cirrhosis		
GT 1-6	EXPEDITION-2	MAVIRET for 8 (n=137) or 12 weeks (n=16)
Liver or kidney transplant recipients		
GT 1-6	MAGELLAN-2	MAVIRET for 12 weeks (n=100)
Adolescent patients (12 years to less than 18 years)		
GT 1-6	DORA (Part 1)	MAVIRET for 8 weeks (n=44) or 16 weeks (n=3)

TN = treatment naïve, PRS-TE = treatment experienced (includes previous treatment that included (peg)interferon, and/or ribavirin, and/or sofosbuvir), PI = Protease Inhibitor, CKD=chronic kidney disease.

* Treatment durations for some trial arms shown in this table do not reflect recommended dosing for the respective genotypes, prior treatment history, and/or cirrhosis status. Refer to section 4.2 Dose and method of administration for recommended dosing.

a. Included 33 patients co-infected with HIV-1.
b. GT 2 from SURVEYOR-2 Parts 1 and 2 – MAVIRET for 8 weeks (n=54) or 12 weeks (n=25); GT 2 from SURVEYOR-2 Part 4 – MAVIRET for 8 weeks (n=145).
c. GT 3 without cirrhosis from SURVEYOR-2 Parts 1 and 2 – MAVIRET for 8 weeks (n=29) or 12 weeks (n=54); GT 3 without cirrhosis from SURVEYOR-2 Part 3 – MAVIRET for 12 weeks (n=22) or 16 weeks (n=22).
d. GT 3 with cirrhosis from SURVEYOR-2 Part 2 – MAVIRET for 12 weeks (n=24) or 16 weeks (n=4); GT 3 with cirrhosis from SURVEYOR-2 Part 3 – MAVIRET for 12 weeks (n=40) or 16 weeks (n=47).
e. GT 1, 4 from MAGELLAN-1 Part 1 – MAVIRET for 12 weeks (n=22); GT 1, 4 from MAGELLAN-1 Part 2 – MAVIRET for 12 weeks (n=44) or 16 weeks (n=47).
f. VOYAGE-1 and VOYAGE-2 were Asian regional studies.

Serum HCV RNA values were measured during the clinical studies using the Roche COBAS AmpliPrep/COBAS TaqMan HCV test (version 2.0), with a lower limit of quantification (LLOQ) of 15 IU/mL (except for SURVEYOR-1 and SURVEYOR-2, which used the Roche COBAS TaqMan real-time reverse transcriptase-PCR (RT-PCR) assay v. 2.0 with an LLOQ of 25 IU/mL). Sustained virologic response (SVR12), defined as HCV RNA less than LLOQ at 12 weeks after the cessation of treatment, was the primary endpoint in all the studies to determine the HCV cure rate.

Treatment-naïve or treatment-experienced adult patients with or without cirrhosis
Baseline characteristics of 2,409 patients with or without compensated cirrhosis, who were treated with MAVIRET in clinical trials, are shown in Table 7. Their median age was 53 years (range: 19 to 88). The median baseline HCV RNA level in these patients was 6.2 $\log_{10}$ IU/mL.

Table 7: Baseline characteristics of patients in clinical trials

		Number of patients (%)
		N=2,409
Treatment history	Treatment-naïve	73.3
	Treatment-experienced*	26.7
Genotype	GT 1	40.3
	GT 2	19.8
	GT 3	27.8
	GT 4	8.1
	GT 5, 6	3.4
Age	≥65 years	13.1
Sex	Male	56.6
Liver disease	Cirrhosis	12.3
Kidney disease	Severe renal impairment or end-stage renal disease	4.3
Body-mass index	≥30 kg per m^2	20.0
Co-infection	HIV-1 co-infection	7.7

* Defined as previous treatment with a combination containing either sofosbuvir, ribavirin, and/or (peg)interferon (PRS-TE).

Patients with chronic HCV genotype 1, 2, 4, 5 or 6
Nine studies assessed the efficacy of 8- or 12-week durations of MAVIRET in adult patients with HCV genotype 1, 2, 4, 5 or 6 who were TN or PRS-TE:

- ENDURANCE-1 was a randomised (1:1) and open-label study comparing the efficacy of 8 weeks versus 12 weeks of treatment with MAVIRET in non-cirrhotic patients with HCV genotype 1, including those co-infected with HCV and HIV-1.
- ENDURANCE-2 was a randomised (2:1), placebo-controlled study comparing the safety of MAVIRET for 12 weeks versus matching placebo for 12 weeks in non-cirrhotic patients with HCV genotype 2.
- ENDURANCE-4 was a single-arm, open-label study in non-cirrhotic patients with HCV genotype 4, 5 or 6.
- SURVEYOR-2 (Part 4) included a single, open-label arm in non-cirrhotic patients with HCV genotype 2, 4, 5 or 6 treated for 8 weeks.
- EXPEDITION-1 was a single-arm, open-label study in TN or PRS-TE patients with compensated cirrhosis and HCV genotype 1, 2, 4, 5 or 6 who received MAVIRET for 12 weeks.
- EXPEDITION-2 was an open-label study in patients with HCV genotype 1–6/HIV-1 co-infection, in which patients without cirrhosis received MAVIRET for 8 weeks, and patients with cirrhosis received MAVIRET for 12 weeks.
- EXPEDITION-4 was a single-arm, open-label study in patients with HCV genotype 1–6 and chronic kidney disease (stage 4 or 5).

- EXPEDITION-8 was a single-arm, open-label study in TN patients with compensated cirrhosis and HCV genotype 1-6 for 8 weeks.

In addition to these Phase 3 studies, treatment arms in Phase 2 studies investigating the recommended duration of glecaprevir 300 mg plus pibrentasvir 120 mg once daily were included (SURVEYOR-1 Part 2 and SURVEYOR-2 Parts 1–2).

Table 8: SVR12 and outcome in patients with genotype 1, 2, 4, 5 or 6 who received the recommended duration of MAVIRET

	Genotype 1[a]	Genotype 2	Genotype 4	Genotype 5	Genotype 6
Patients without cirrhosis					
SVR12 after 8 weeks of treatment					
	99.2% (470/474)	98.1% (202/206)	95.2% (59/62)	100% (2/2)	92.3% (12/13)
Outcome for patients without SVR12					
On-treatment VF	0.2% (1/474)	0% (0/206)	0% (0/62)	0% (0/2)	0% (0/13)
Relapse[b]	0% (0/471)	1.0% (2/204)	0% (0/61)	0% (0/2)	0% (0/13)
Other[c]	0.6% (3/474)	1.0% (2/206)	4.8% (3/62)	0% (0/2)	7.7% (1/13)
SVR12 in patients with compensated cirrhosis					
12 weeks	96.8% (30/31)	90.0% (9/10)	100% (8/8)	---	100% (1/1)
8 weeks	97.8% (226/231)	100% (26/26)	100% (13/13)	100% (1/1)	100% (9/9)
Outcome for patients without SVR12					
On-treatment VF	0% (0/262)	0% (0/36)	0% (0/21)	0% (0/1)	0% (0/10)
Relapse [b]	0.4% (1/256)	0% (0/35)	0% (0/20)	0% (0/1)	0% (0/10)
Other [c]	1.9% (5/262)	2.8% (1/36)	0% (0/21)	0% (0/1)	0% (0/10)

These data are from ENDURANCE-1, -2, -4, SURVEYOR-1, -2, and EXPEDITION-1, -2, -4 and -8. Patients were either treatment-naïve (TN) or had previous treatment with (peg)interferon, ribavirin, and/or sofosbuvir (PRS-TE).
VF = virologic failure.

a. Includes a total of 132 patients co-infected with HIV-1 from ENDURANCE-1 or EXPEDITION-2 who received the recommended duration.
b. Relapse is defined as HCV RNA ≥LLOQ after end-of-treatment response among those who completed treatment.
c. Includes patients who discontinued due to adverse events, were lost to follow-up, or withdrew.

Of patients with genotypes 1, 2, 4, 5 or 6 who had end-stage renal disease and were enrolled in EXPEDITION-4, 97.8% (91/93) achieved SVR12, with no virologic failures.

Patients with chronic HCV genotype 1, 2, 4, 5 or 6 with cirrhosis who received 8 weeks of MAVIRET

The safety and efficacy of MAVIRET given for 8 weeks in HCV genotype 1, 2, 4, 5 or 6 treatment-naïve adult patients with compensated cirrhosis was evaluated in a single-arm, open-label study (EXPEDITION-8).

Of the 280 patients treated, the median age was 60 years (range: 34 to 88); 81.8% had HCV genotype 1, 10% had HCV genotype 2, 4.6% had HCV genotype 4, 0.4% had HCV genotype 5; 3.2% had HCV genotype 6; 60% were male.

The overall SVR12 rate was 98.2% (275/280). There were no virologic failures.

Study in subjects with HCV genotype 5 or 6 infection

ENDURANCE-5,6 was an open-label study in 84 patients with genotype 5 (n=23) or genotype 6 (n=61) TN or PRS-TE adult patients. Patients without cirrhosis received MAVIRET for 8 weeks, and patients with compensated cirrhosis received MAVIRET for 12 weeks.

Of the 84 patients treated, the median age was 59 years (range 24-79); 27% had genotype 5, 73% had genotype 6; 54% were female, 30% were White, 68% were Asian; 90% were HCV TN; 11% had compensated cirrhosis.

The overall SVR12 rate was 97.6% (82/84). The SVR12 rate was 95.7% (22/23) for patients with genotype 5 and 98.4% (60/61) for patients with genotype 6. One TN patient with genotype 5 without cirrhosis experienced relapse, and one TN patient with genotype 6 with compensated cirrhosis experienced on-treatment virologic failure.

Patients with chronic HCV genotype 3

The efficacy of MAVIRET in adult patients with HCV genotype 3 who were treatment-naïve or had previous treatment with combinations of (peg)interferon, ribavirin, and/or sofosbuvir, was demonstrated in the following clinical studies:

- ENDURANCE-3 was a partially-randomised, open-label, active-controlled study in treatment-naïve patients without cirrhosis. Patients were randomised (2:1) to either MAVIRET for 12 weeks or the combination of sofosbuvir and daclatasvir for 12 weeks; subsequently the study included a third arm (which was non-randomised) with MAVIRET for 8 weeks.
- EXPEDITION-8 was a single-arm, open-label study in TN patients with compensated cirrhosis and genotype 1, 2, 3, 4, 5, or 6 infection with MAVIRET for 8 weeks.
- SURVEYOR-2 Part 3 was an open-label study that evaluated the efficacy of MAVIRET in treatment-experienced genotype 3-infected patients with or without compensated cirrhosis for 16 weeks. Among treatment-experienced patients, 46% (42/91) had failed a previous regimen containing sofosbuvir.

Patients with HCV genotype 3 were also included in other studies, such as the two Asian regional studies, VOYAGE-1 and VOYAGE-2.

Table 9: SVR12 in treatment-naïve adult patients with HCV genotype 3 and no cirrhosis

	MAVIRET, 8 weeks N=157	**MAVIRET, 12 weeks N=233**	**SOF+DCV, 12 weeks N=115**
SVR12	94.9% (149/157)	95.3% (222/233)	96.5% (111/115)
		Treatment difference -1.2% 95% confidence interval (-5.6–3.1%)	
	Treatment difference -0.4% 97.5% confidence interval (-5.4–4.6%)		
Outcome for patients without SVR12			
On-treatment VF	0.6% (1/157)	0.4% (1/233)	0% (0/115)
Relapse [a]	3.3% (5/150)	1.4% (3/222)	0.9% (1/114)
Other [b]	1.3% (2/157)	3.0% (7/233)	2.6% (3/115)

These data are from the ENDURANCE-3 study.
VF = virologic failure.
SOF+DCV = Sofosbuvir + Daclatasvir.

a. Relapse is defined as HCV RNA ≥LLOQ after end-of-treatment response among those who completed treatment.
b. Includes patients who discontinued due to adverse events, were lost to follow-up, or withdrew.

Table 10: SVR12 in adult patients with genotype 3 with or without cirrhosis who received the recommended duration

	Treatment-naïve (TN) with cirrhosis	Treatment-experienced (PRS-TE) with or without cirrhosis
	MAVIRET 8 weeks (N=63)	**MAVIRET 16 weeks (N=69)**
SVR12	95.2% (60/63)	95.7% (66/69)
Outcome for patients without SVR12		
On-treatment VF	0% (0/63)	1.4% (1/69)
Relapse [a]	1.6% (1/62)	2.9% (2/68)
Other [b]	3.2% (2/63)	0% (0/69)
SVR by cirrhosis status		
No Cirrhosis	NA	95.5% (21/22)
Compensated cirrhosis	95.2% (60/63)	95.7% (45/47)

These data are from EXPEDITION-8 and SURVEYOR-2 Part 3 studies.
VF = virologic failure.

a. Relapse is defined as HCV RNA ≥LLOQ after end-of-treatment response among those who completed treatment.
b. Includes patients who discontinued due to adverse events, were lost to follow-up, or withdrew.

Of the 11 patients with genotype 3 who had end-stage renal disease in EXPEDITION-4, 100% (11/11) achieved SVR12.

Patients with HCV genotype 3b

Genotype 3b is a subtype reported in a relatively small number of HCV patients in China and a few countries in South and Southeast Asia, but rarely outside of this region. Studies VOYAGE-1 and VOYAGE-2 were conducted in China, Singapore and South Korea in adult patients with genotype 1-6 without cirrhosis (VOYAGE-1) or with compensated cirrhosis (VOYAGE-2) that were TN or PRS-TE. All patients without cirrhosis or with compensated cirrhosis received 8 or 12 weeks of MAVIRET, respectively, except patients with genotype 3 PRS-TE who received 16 weeks of MAVIRET. The overall SVR12 rates were 97.2% (352/362) and 99.4% (159/160) in VOYAGE-1 and VOYAGE-2, respectively.

Among patients with genotype 3b without cirrhosis, a numerically lower SVR12 rate of 58.3% (7/12) [62.5% (5/8) for TN patients and 50% (2/4) for PRS-TE patients] was observed compared to patients with genotype 3a without cirrhosis (92.9% (13/14)). Three TN patients with genotype 3b experienced relapse and two PRS-TE patients with genotype 3b experienced on-treatment virologic failure. Among patients with compensated cirrhosis, the overall SVR12 rate for patients with genotype 3b was 87.5% (7/8) [85.7% (6/7) for TN patients and 100% (1/1) for PRS-TE patients] and 100% (6/6) for patients with genotype 3a. One TN patient with genotype 3b experienced relapse.

Overall SVR12 rate from the clinical studies in treatment-naïve or treatment-experienced adult patients with or without cirrhosis

In 1,284 patients, regardless of renal function, cirrhosis status or presence of HIV-1 co-infection, who were either TN or PRS-TE, and who received the recommended duration of treatment with MAVIRET, 97.5% (1,395/1,431) achieved SVR12 overall. On-treatment virologic failure was seen in 0.2% (3/1,431) of patients, and 0.9% (12/1,407) experienced post-treatment relapse.

In treatment-naïve patients without cirrhosis who received the recommended duration of 8 weeks, 97.5% (749/768) achieved SVR12, while 0.1% (1/768) experienced on-treatment virologic failure, and 0.7% (5/755) experienced post-treatment relapse.

In PRS-TE patients without cirrhosis who received the recommended duration, 98.2% (215/219) achieved SVR12, while 0.5% (1/219) experienced on-treatment virologic failure, and 1.4% (3/218) experienced post-treatment relapse.

In treatment-naïve or PRS-TE patients with compensated cirrhosis who received the recommended duration, 97.1% (431/444) achieved SVR12 (among which 97.7% (335/343) of treatment-naïve patients achieved SVR12), while 0.2% (1/444) experienced on-treatment virologic failure, and 0.9% (4/434) experienced post-treatment relapse.

The presence of HIV-1 co-infection did not impact efficacy. In a dedicated HIV-1 co-infection study (EXPEDITION-2), the SVR12 rate in HCV/HIV-1 co-infected patients was 98% (150/153) with one virologic failure. Among patients without cirrhosis that received 8 weeks of MAVIRET, the overall SVR12 rate was 99.3% (136/137) with (99.1% (110/111) for treatment-naïve patients and 100% (26/26) for PRS-TE patients). Among HCV/HIV-1 co-infected patients from ENDURANCE-1 and EXPEDITION-2 combined, who were treatment-naïve or PRS-TE treated with the recommended duration, the SVR12 rate was 98.2% (165/168). One patient experienced on-treatment virologic failure and no patients relapsed.

Adult patients who had previous treatment with an NS5A inhibitor and/or a protease inhibitor
MAGELLAN-1 was a randomised, multipart, open-label study in 141 patients with HCV genotype 1 or 4, with or without cirrhosis, who failed a previous regimen containing NS5A and/or protease inhibitors. Part 1 (n=50) was a randomised study exploring 12 weeks of glecaprevir (300 mg or 200 mg) and pibrentasvir (120 mg or 80 mg), with and without ribavirin. Only glecaprevir 300 mg plus pibrentasvir 120 mg without ribavirin are included in this analysis. Part 2 (n=91) randomised 91 patients with genotype 1 or 4 with or without cirrhosis to 12 or 16 weeks of treatment with MAVIRET.

Of the 91 patients treated in Part 2, the median age was 57 years (range: 22 to 70), and other baseline characteristics are shown in Table 11.

Table 11: Baseline characteristics of patients in MAGELLAN-1

		Number of patients N (%)
		N=91
Treatment history	Treatment-experience with protease inhibitors only	27 (29.7)
	Treatment-experience with NS5A inhibitors only	34 (37.4)
	Treatment-experience with both NS5A and protease inhibitors	30 (33.0)
Genotype	GT 1	87 (95.6)
	GT 4	4 (4.4)
Age	≥65 years	11 (12.1)
Sex	Male	64 (70.3)
Liver disease	Cirrhosis	27 (29.7)
Body-mass index	≥30 kg per m^2	35 (38.5)
HCV RNA levels	≥1,000,000 IU per mL	57 (62.6)

The SVR12 in protease inhibitor-experienced (NS5A-inhibitor naïve) patients, with or without cirrhosis, who received 12 weeks of treatment with MAVIRET, was 100% (14/14).

The SVR12 in patients who had experience with NS5A inhibitors (alone or with a protease inhibitor) is shown in Table 12.

Table 12: SVR12 in NS5A inhibitor-experienced adult patients with or without cirrhosis who received the recommended duration

Treatment history		MAVIRET 16 weeks N=34
Treatment-experience with NS5A inhibitors only[a]	**SVR12**	94.4% (17/18)
	On-treatment VF	5.6% (1/18)
	Relapse [b]	0% (0/17)
Treatment-experience with both NS5A and protease inhibitors	**SVR12**	81.3% (13/16)
	On-treatment VF	18.8% (3/16)
	Relapse [b]	0% (0/13)

These data are from MAGELLAN-1 Part 2.

a. Includes patients who previously failed with regimens containing ledipasvir/sofosbuvir, or daclatasvir.
b. Relapse is defined as HCV RNA ≥LLOQ after end-of-treatment response among those who completed treatment.

On the basis of the *in vitro* pharmacology of pibrentasvir, demonstrating that it retains antiviral activity against NS5A substitutions typically seen in genotype 3 patients who have failed therapy with other NS5A inhibitors, and the favourable clinical outcomes for patients with no previous treatment with NS5A inhibitors but with baseline NS5A polymorphisms such as Y93H, enrolled into the Phase 2 and 3 studies, treatment with MAVIRET for 16 weeks can be considered for patients with genotype 3 who have failed therapy on an NS5A inhibitor-containing regimen and who are deemed at high risk for clinical disease progression.

Clinical study in liver or kidney transplant recipients

MAGELLAN-2 was a single-arm, open-label study in 100 post-liver or -kidney transplant HCV GT 1-6 infected adult patients without cirrhosis who received MAVIRET for 12 weeks. The study included patients who were HCV treatment-naïve or treatment-experienced to combinations of (peg)interferon, ribavirin, and/or sofosbuvir, with the exception of GT 3-infected patients who were all treatment-naïve.

Of the 100 patients treated, the median age was 60 years (range: 39 to 78), and other baseline characteristics are shown in Table 13.

Table 13: Baseline characteristics of patients in MAGELLAN-2

		Number of patients N (%)
		N=100
Genotype	GT 1	57 (57)
	GT 2	13 (13)
	GT 3	24 (24)
	GT 4	4 (4)
	GT 6	2 (2)
Sex	Male	75 (75)
Transplant	Post-liver transplant	80 (80)
	Post-kidney transplant	20 (20)

Immunosuppressants allowed for co-administration were cyclosporine ⩽100 mg, tacrolimus, sirolimus, everolimus, azathioprine, mycophenolic acid, prednisone, and prednisolone.

The overall SVR12 rate in post-transplant patients was 98.0% (98/100). There was one relapse, and no on-treatment virologic failure.

Paediatric population
The safety and efficacy of MAVIRET in children aged less than 12 years have not yet been established.

Elderly patients
Clinical studies of MAVIRET included 328 patients aged 65 years and older (13.8% of the total number of patients). The response rates observed for patients aged 65 years and older were similar to those of patients younger than 65 years of age, across treatment groups.

People Who Inject Drugs (PWID) and those on Medication-Assisted Treatment (MAT) for Opioid Use Disorder
The efficacy of MAVIRET in PWID and those on MAT with HCV genotype 1-6 is based on data from Phase 2 and 3 trials of adults and adolescents in which 62 patients identified as current/recent PWID (defined as self-reported injection drug use within the last 12 months prior to starting MAVIRET), 959 patients identified as former PWID (defined as self-reported injection drug use more than 12 months prior to starting MAVIRET), and 3,282 patients who reported no injection drug use (non-PWID); 225 patients reported concomitant use of MAT for opioid use disorder, and 4,098 patients reported no MAT use.

The overall SVR12 rate was 97.8% (4,147/4,241) in former/non-PWID patients and 88.7% (55/62) in current/recent PWID patients; the difference between the two groups was primarily due to missing data at the time of the SVR12 measurement window in the current/recent PWID group. Virologic failure rates, however, were similar in both groups: 1.6% (1/62) in the current/recent PWID patients and 1.2% (50/4,241) in former/non-PWID patients.

The SVR12 rates were also similar between patients on MAT (95.6% [215/225]) and those not on MAT (97.7% [4,002/4,098]), with low rates of virologic failure in both groups: 0.4% (1/225) and 1.3% (52/4,098), respectively.

Clinical Study in Adolescent Patients
DORA (Part 1) was an open-label trial to evaluate safety and efficacy in adolescents aged 12 years to less than 18 years who received MAVIRET for 8, 12, or 16 weeks.

47 patients were enrolled in DORA (Part 1). The median age was 14 years (range: 12 to 17); 79% had HCV genotype 1, 6% had HCV genotype 2, 9% had HCV genotype 3, 6% had HCV genotype 4; 55% were female; 77% were HCV treatment-naïve; 23% were treatment-experienced to interferon; 4% had HIV-coinfection; none had cirrhosis; the mean weight was 59 kg (range: 32 to 109 kg).

The overall SVR12 rate was 100% (47/47). No patient experienced virologic failure.

Durability of Sustained Virologic response
In a long-term follow-up study (M13-576), 99.5% (374/376) of adult patients who had achieved SVR12 in prior clinical studies of MAVIRET maintained SVR up to their last follow-up visit (median duration of follow-up: 35.5 months), including all 87 patients who had been treated with an 8-week regimen of MAVIRET. Among the two patients who did not maintain SVR, one patient who had been infected by a contaminated needle or intravenous drug use experienced a late relapse 390 days after 12 weeks of MAVIRET therapy, and the other patient experienced re-infection with a different HCV genotype 191 days after 16 weeks of MAVIRET therapy.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of the components of MAVIRET are provided in Table 14. Based on the population pharmacokinetic analysis, the median steady-state pharmacokinetic parameters of glecaprevir and pibrentasvir in patients with HCV are provided in Table 15.

Table 14: Pharmacokinetic properties of the components of MAVIRET in healthy subjects

	Glecaprevir	Pibrentasvir
Absorption		
T_{max} (h)[a]	5.0	5.0
Effect of meal (relative to fasting)[b]	↑ 83-163%	↑ 40-53%
Distribution		
Proportion bound to human plasma proteins	97.5%	>99.9%
Blood-to-plasma ratio	0.57	0.62
Biotransformation		
Metabolism	secondary, CYP3A	none
Elimination		
Major route of elimination	biliary-faecal	biliary-faecal
$t_{1/2}$ (h)	6	13
Proportion of dose excreted in urine[c]	0.7%	0%
Proportion of dose excreted in faeces[c]	92.1%	96.6%

a. Median T_{max} following single doses of glecaprevir and pibrentasvir in healthy subjects.
b. Mean systemic exposure with moderate- to high-fat meals.
c. Single-dose administration of [^{14}C]glecaprevir or [^{14}C]pibrentasvir in mass-balance studies.

Table 15: Steady-state pharmacokinetic parameters of glecaprevir and pibrentasvir following administration of MAVIRET in non-cirrhotic patients with HCV

Pharmacokinetic Parameter	Glecaprevir	Pibrentasvir
C_{max} (ng/mL)[a]	597 (150)	110 (49)
$AUC_{24,ss}$ (ng h/mL)[a]	4800 (198)	1430 (63)

a. Geometric mean (%CV) of individual-estimated C_{max} and $AUC_{24,ss}$ values.

Relative to healthy subjects (N=230), glecaprevir C_{max} was 51% lower and $AUC_{24,ss}$ was similar (10% difference) in non-cirrhotic patients with HCV; pibrentasvir C_{max} and $AUC_{24,ss}$ were 63% and 34% lower, respectively.

Pharmacokinetics in special populations

Race/ethnicity

No dose adjustment of MAVIRET is required based on race or ethnicity.

Gender/weight

No dose adjustment of MAVIRET is required based on gender or bodyweight.

Elderly patients

No dose adjustment of MAVIRET is required in elderly patients. Population pharmacokinetic analysis in patients with HCV showed that within the age range assessed (12 to 88 years), age did not have a clinically relevant effect on the exposure to glecaprevir or pibrentasvir.

Patients with renal impairment

Glecaprevir and pibrentasvir AUC were increased by ≤56% in non-HCV patients with mild, moderate, severe, or end-stage renal impairment (not on dialysis) compared to those with normal renal function. Glecaprevir and pibrentasvir AUC were similar with and without dialysis (≤ 18% difference) in dialysis-dependent non-HCV patients. In population pharmacokinetic analysis of patients with HCV,

86% higher glecaprevir AUC and 54% higher pibrentasvir AUC were observed for patients with end stage renal disease, with or without dialysis, compared to patients with normal renal function.

Overall, the changes in exposures of MAVIRET in patients with HCV with renal impairment, with or without dialysis, were not clinically significant.

Patients with hepatic impairment
At the clinical dose, compared to study participants without HCV and with normal hepatic function, glecaprevir AUC was 33% higher in patients with Child-Pugh A cirrhosis, 100% higher in patients with Child-Pugh B, and 11-fold higher in patients with Child-Pugh C. Pibrentasvir AUC was similar in Child-Pugh A patients, 26% higher in Child-Pugh B patients, and 114% higher in Child-Pugh C patients.

Population pharmacokinetic analysis demonstrated that after administration of MAVIRET in patients with HCV and compensated cirrhosis, exposure of glecaprevir was approximately two-fold and pibrentasvir exposure was similar to patients with HCV and no cirrhosis.

Paediatric patients
No dose adjustment of MAVIRET is required in adolescents 12 years and older. Exposures of glecaprevir and pibrentasvir in adolescents were comparable to those in adults from Phase 2/3 studies. The pharmacokinetics of glecaprevir and pibrentasvir have not been established in children less than 12 years of age.

5.3 Preclinical safety data

Glecaprevir and pibrentasvir were 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* rodent micronucleus assays. Carcinogenicity studies with glecaprevir and pibrentasvir have not been conducted.

No effects on mating, female or male fertility, or early embryonic development were observed in rodents at up to the highest dose tested. Systemic exposures (AUC) to glecaprevir and pibrentasvir were approximately 63- and 102- times higher, respectively, than the exposure in humans at the recommended dose.

In animal reproduction studies, no adverse developmental effects were observed when the components of MAVIRET were administered separately during organogenesis at glecaprevir exposures up to 53- and 0.07- times (rats and rabbits, respectively) or pibrentasvir exposures 51- and 1.5- times (mice and rabbits, respectively) the human exposures at the recommended dose of MAVIRET. Maternal toxicity (anorexia, lower bodyweight, and lower bodyweight gain) precluded the ability to evaluate glecaprevir in the rabbit at clinical exposures. There were no effects with either compound in rodent peri/postnatal developmental studies in which maternal systemic exposures (AUC) to glecaprevir and pibrentasvir were approximately 47- and 74- times, respectively, the exposure in humans at the recommended dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:
Copovidone (Type K 28)
Tocofersolan
Colloidal silicon dioxide
Propylene Glycol Monocaprylate (Type II)
Croscarmellose Sodium
Sodium Stearyl Fumarate

Film Coating:
Hypromellose 2910 (E464)
Lactose Monohydrate
Titanium Dioxide
Macrogol 3350
Iron Oxide Red (E172)

The tablets do not contain gluten.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PE/PCTFE aluminium foil blister-packs –
Multipack containing 84 (four packs of 21) film-coated tablets.

HDPE bottle with a child-resistant closure and a silica gel desiccant. Pack size of 84 film-coated tablets.

Not all presentations may be marketed.

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

AbbVie Limited
6th Floor, 156-158 Victoria St
Wellington, 6011
New Zealand

Telephone: 0800 900 030

9. DATE OF FIRST APPROVAL

20 June 2018

10. DATE OF REVISION OF THE TEXT

27 January 2021

Version 10

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.5 Interaction with other medicines and other forms of interaction	Comment added that all interaction studies were performed in adults.
4.8 Undesirable effects	New section added: *Adverse Reactions in People Who Inject Drugs (PWID) and those on Medication-Assisted Treatment (MAT) for Opioid Use Disorder*
5.1 Pharmacodynamic properties	Footnote added to Table 6 (*Clinical studies with MAVIRET in patients with HCV genotypes 1, 2, 3, 4, 5 or 6*) indicating that treatment durations for some trial arms shown in the table do not reflect recommended dosing for the respective genotypes, prior treatment history, and/or cirrhosis status, plus a reference to the Dose and Method of Administration section. Additional information provided where clinical studies specifically included adult patients. Two new sections added: *People Who Inject Drugs (PWID) and those on Medication-Assisted Treatment (MAT) for Opioid Use Disorder* *Durability of Sustained Virologic response*
6.1 List of excipients	Editorial change to how excipients are stated.