q This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PI – MAVIRET®

(glecaprevir / pibrentasvir) tablets

1 NAME OF THE MEDICINE

Glecaprevir and pibrentasvir

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

MAVIRET is a fixed-dose combination tablet containing glecaprevir 100 mg and pibrentasvir 40 mg.

The tablets do not contain gluten. The tablets contain lactose. For the full list of excipients, see Section 6.1 List of excipients.

Glecaprevir is a white to off-white crystalline powder with a solubility of less than 0.1 to 0.3 mg/mL across a pH range of 2–7 at 37°C and is practically insoluble in water, but is sparingly soluble in ethanol.

Pibrentasvir is a white to off-white to light yellow crystalline powder with a solubility of less than 0.1 mg/mL across a pH range of 1–7 at 37°C and is practically insoluble in water, but is freely soluble in ethanol.

3 PHARMACEUTICAL FORM

Glecaprevir and pibrentasvir are presented as co-formulated, film-coated, immediate release tablets. The tablet strength is 100 mg glecaprevir (anhydrous) and 40 mg pibrentasvir.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MAVIRET is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection with or without compensated cirrhosis. This includes patients with HCV genotype 1 infection who were previously treated with either a regimen of an NS5A inhibitor or with an NS3/4A protease inhibitor but not both classes of inhibitors (see 4.2 DOSE AND METHOD OF ADMINISTRATION and CLINICAL TRIALS).

4.2 Dose and method of administration

MAVIRET is a fixed-dose combination product containing glecaprevir 100 mg and pibrentasvir 40 mg in each tablet.

The recommended oral dosage of MAVIRET is three tablets (total daily dose: glecaprevir 300 mg and pibrentasvir 120 mg) once daily with food (see 5.1 PHARMACODYNAMIC PROPERTIES). MAVIRET tablets should be swallowed whole and not chewed, crushed, or broken.

Tables 1 and 2 provide the recommended MAVIRET treatment duration based on the patient population in HCV mono-infected and HCV/HIV-1 co-infected patients with compensated liver disease (with or without cirrhosis) and with or without renal impairment (including patients receiving dialysis).

Table 1. Recommended Duration for Treatment-Naïve Patients

Patient Population	Treatment Duration	
	No Cirrhosis	Compensated Cirrhosis (Child Pugh A)
GT 1, 2, 3, 4, 5 or 6	8 weeks	12 weeks

Table 2. Recommended Duration for Treatment-Experienced Patients

Patient Population	Treatment Duration	
	No Cirrhosis	Compensated Cirrhosis (Child Pugh A)
GT 1, 2, 4, 5 or 6 PRS-experienced*	8 weeks	12 weeks
GT 1 NS3/4A PI-experienced[1#] (NS5A inhibitor-naïve)	12 weeks	
GT 1 NS5A inhibitor–experienced[2#] (NS3/4A PI-naïve)	16 weeks	
GT 3 PRS-experienced*		

* PRS = Prior treatment with regimens containing peginterferon (P), ribavirin (R), and/or sofosbuvir (S), but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor

[1] Experienced with regimens containing SMV + SOF or SMV + PR or BOC + PR or TVR + PR

[2] Experienced with regimens containing DCV + SOF or DCV + PR or LDV + SOF

But not both NS3/4A PI and NS5A experienced e.g. EBR + GZR ± RBV or PTV/r + OBV + DSV ± RBV

GT = genotype; PI = protease inhibitor; PR = peginterferon/ribavirin; SMV = simeprevir; TVR = telaprevir; BOC = boceprevir; DCV = daclatasvir; LDV = ledipasvir; SOF = sofosbuvir; EBR = elbasvir; GZR = grazoprevir; PTV/r = paritaprevir/ritonavir; OBV = ombitasvir; DSV = dasabuvir; RBV = ribavirin

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 4.3 CONTRAINDICATIONS and 5.2 PHARMACOKINETIC PROPERTIES – Pharmacokinetics, Specific Populations, Renal Impairment).

Renal Impairment

No dose adjustment of MAVIRET is required in patients with any degree of renal impairment including patients on dialysis (see 5.2 PHARMACOKINETIC PROPERTIES – Pharmacokinetics, Specific Populations, Renal Impairment).

Paediatric Use

The safety and effectiveness of MAVIRET in patients younger than 18 years of age have not been established.

Geriatric Use

No dose adjustment of MAVIRET is required in geriatric patients. In clinical studies of MAVIRET, 328 patients were age 65 years and over and 47 subjects were age 75 years and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the geriatric and younger patients.

Liver Transplant Patients

MAVIRET may be used for a minimum of 12 weeks in liver transplant recipients (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). A longer treatment duration should be considered in patients who are NS5A inhibitor-experienced or genotype 3-infected patients who are treatment experienced.

Missed Dose

In case a dose of MAVIRET is missed and it is:

- Less than 18 hours from the usual time that MAVIRET should have been taken, advise the patient to take the dose as soon as possible and then to take the next dose at the usual time.
- More than 18 hours has passed since MAVIRET should have been taken, advise the patient not to take the missed dose and to take the next dose at the usual time. Patients should be instructed not to take a double dose.

4.3 Contraindications

MAVIRET is contraindicated:

- In patients with severe hepatic impairment (Child-Pugh C) (see 5.2 PHARMACOKINETIC PROPERTIES – Pharmacokinetics, Specific Populations).
- With atazanavir containing products, atorvastatin, simvastatin, dabigatran etexilate, ethinyloestradiol-containing products, rifampicin (see 5.2 PHARMACOKINETIC PROPERTIES – Pharmacokinetics, Special Populations, Drug Interactions).

4.4 Special warnings and precautions for use

Risk of Hepatitis B Virus Reactivation

Cases of Hepatitis B virus (HBV) reactivation, including fatal cases, have been reported during and after treatment of HCV with direct-acting antiviral agents 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 MAVIRET.

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.

MAVIRET has not been studied in patients with HCV/HBV co-infection.

Liver Transplant Patients

The safety and efficacy of MAVIRET in patients who are post-liver transplant have not been assessed. Treatment with MAVIRET in accordance with the recommended posology (see 4.2 DOSE AND METHOD OF ADMINISTRATION) should be guided by an assessment of the potential benefits and risks for the individual patient.

Use in Hepatic Impairment

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 4.2 DOSE AND METHOD OF ADMINISTRATION, 5.1 PHARMACOLOGICAL PROPERTIES and 4.3 CONTRAINDICATIONS).

Drug-drug Interactions

Co-administration is not recommended with several medicinal products (see 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Use in the elderly

No dose adjustment of MAVIRET is required in geriatric patients (see 4.2 DOSE AND METHOD ADMINISTRATION – Geriatric Use).

Paediatric use

The safety and effectiveness of MAVIRET in patients younger than 18 years of age have not been established.

4.5 Interactions with other medicines and other forms of interactions

Potential for MAVIRET to Affect Other Drugs

Glecaprevir and pibrentasvir are inhibitors of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP) 1B1/3 and BSEP. Coadministration with MAVIRET may increase plasma concentration of drugs that are substrates of P-gp, BCRP, OATP1B1, OATP1B3 or BSEP. Glecaprevir and pibrentasvir are weak inhibitors of cytochrome P450 (CYP) 3A, and uridine glucuronosyltransferase (UGT) 1A1. Significant interactions are not expected when MAVIRET is coadministered with substrates of CYP3A, CYP1A2, CYP2C9, CYP2C19, CYP2D6, UGT1A1, or UGT1A4.

If MAVIRET is coadministered with vitamin K antagonist, close monitoring of international normalised ratio (INR) is recommended. This is due to liver function changes during treatment with MAVIRET.

Potential for Other Drugs to Affect MAVIRET

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

Coadministration of MAVIRET with drugs that induce P-gp may decrease glecaprevir and pibrentasvir plasma concentrations.

Established and Other Potential Drug Interactions

Table 3 provides the effect of coadministration of MAVIRET on concentrations of concomitant drugs and the effect of concomitant drugs on glecaprevir and pibrentasvir (see 4.3 CONTRAINDICATIONS for drugs that are contraindicated with MAVIRET).

Table 3. Potentially Significant Drug Interactions Identified in Drug Interaction Studies that May Require Dose Alteration

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comments
Antiarrhythmics		
Digoxin	↑ digoxin	Digoxin dose should be reduced by 50% when coadministered with MAVIRET.
Anticoagulants		

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comments
Dabigatran etexilate	↑ dabigatran	Coadministration is contraindicated (see 4.3 CONTRAINDICATIONS).
Anticonvulsant		
Carbamazepine	↓ glecaprevir ↓ pibrentasvir	Coadministration may lead to reduced therapeutic effect of MAVIRET and is not recommended.
Antimycobacterials		
Rifampicin	↓ glecaprevir ↓ pibrentasvir	Coadministration is contraindicated because of potential loss of therapeutic effect (see 4.3 CONTRAINDICATIONS).
Ethinyloestradiol-Containing Products		
Ethinyloestradiol-containing medications such as combined oral contraceptives	↔ glecaprevir ↔ pibrentasvir	Coadministration of MAVIRET with ethinyloestradiol-containing products may increase the risk of ALT elevations and is contraindicated (see 4.3 CONTRAINDICATIONS).
Herbal Products		
St. John's Wort (*hypericum perforatum*)	↓ glecaprevir ↓ pibrentasvir	Coadministration may lead to reduced therapeutic effect of MAVIRET and is not recommended.
HIV-Antiviral Agents		
Atazanavir	↑ glecaprevir ↑ pibrentasvir	Coadministration is contraindicated due to increased risk of ALT elevations (see 4.3 CONTRAINDICATIONS).
Darunavir Lopinavir Ritonavir	↑ glecaprevir ↑ pibrentasvir	Coadministration is not recommended.
Efavirenz	↓ glecaprevir ↓ pibrentasvir	Coadministration may lead to reduced therapeutic effect of MAVIRET and is not recommended.
HMG-CoA Reductase Inhibitors		
Atorvastatin Simvastatin	↑ atorvastatin ↑ simvastatin	Coadministration with atorvastatin and simvastatin is contraindicated (see 4.3 CONTRAINDICATIONS).
Pravastatin Rosuvastatin	↑ pravastatin ↑ rosuvastatin	Pravastatin dose should be reduced by 50% and rosuvastatin dose should not exceed 10 mg per day when coadministered with MAVIRET.
Lovastatin	↑ lovastatin	Concomitant use is not recommended. Consider alternative therapies, such as pravastatin or rosuvastatin.

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comments
Immunosuppressants		
Ciclosporin	↑ glecaprevir	MAVIRET is not recommended for use in patients requiring stable ciclosporin doses > 100 mg per day. MAVIRET may be initiated in subjects receiving ciclosporin ≤ 100 mg per day and ciclosporin doses may be adjusted up to 400 mg per day following standard therapeutic monitoring practices.
	↑ pibrentasvir	
↑= increase; ↓= decrease; ↔ = no effect See also 5.2 PHARMACOKINETIC PROPERTIES – Pharmacokinetics, Drug Interactions Table 15 and Table 16		

Drugs without Clinically Significant Interactions with MAVIRET

No dose adjustment is required when MAVIRET is coadministered with the following medications: 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

Effects on fertility

No human data on the effect of glecaprevir and/or pibrentasvir on fertility are available. No effects on mating, female or male fertility, or early embryonic development were observed in rats dosed with glecaprevir at up to 120 mg/kg/day PO or in mice dosed with pibrentasvir at up to 100 mg/kg/day PO. Systemic exposures (AUC, Area Under the Curve) to glecaprevir and pibrentasvir were approximately 63 and 102 times higher, respectively, than the exposure in humans at the recommended dose. 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.

Use in pregnancy (Pregnancy Category B1)

There are no or limited data on the use of glecaprevir or pibrentasvir in pregnant women. Animal studies with glecaprevir or pibrentasvir do not indicate direct harmful effects with respect to reproductive toxicity. Maternal toxicity in the rabbit precluded evaluation of glecaprevir at clinical exposures. As a precautionary measure, MAVIRET use is not recommended in pregnancy.

Glecaprevir

No effects on embryofetal development or maternal toxicity have been observed in rats when dams were administered glecaprevir (oral doses up to 120 mg/kg/day) during organogenesis, associated with systemic exposure to glecaprevir approximately 53 times the exposure in humans at the recommended clinical dose. In rabbits, the highest glecaprevir exposure achieved was 0.07 times the exposure in humans at the recommended clinical dose, and therefore embryofetal development during organogenesis has not been assessed in this species at clinical exposures. There were no effects of glecaprevir in a rat peri/postnatal developmental study in which dams were dosed at up to 120 mg/kg PO during gestation and lactation (from gestation day 6 to lactation 20), with systemic exposures approximately 47 times higher than the exposure in humans at the recommended dose. Glecaprevir was shown to cross the placenta in rats.

Pibrentasvir

No effects on embryofetal development or maternal toxicity have been observed in mice or rabbits when dams were administered pibrentasvir (oral doses up to 100 mg/kg) during organogenesis, associated with systemic exposure to pibrentasvir approximately 51- and 1.4-fold, respectively, the exposure in humans at the recommended clinical dose. There were no effects of pibrentasvir in a mouse peri/postnatal developmental study in which dams were dosed at up to 100 mg/kg PO (systemic exposures approximately 74 times higher than the exposure in humans at the recommended dose). Pibrentasvir was shown to cross the placenta in both species.

Use in lactation.

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 of rats. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from MAVIRET therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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 Adverse effects (Undesirable effects)

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

The safety assessment for MAVIRET in patients without cirrhosis or with compensated cirrhosis were derived from Phase 2 and 3 studies which evaluated approximately 2300 patients infected with genotype 1, 2, 3, 4, 5, or 6 HCV who received MAVIRET for 8, 12 or 16 weeks.

The overall proportion of subjects who permanently discontinued treatment due to adverse reactions was 0.1% for subjects who received MAVIRET.

Across the Phase 2 and 3 clinical studies, the most common (occurring in at least 10% of patients) adverse reactions (adverse events assessed as possibly related by the investigator) were headache and fatigue in patients treated with MAVIRET for 8, 12 or 16 weeks.

Adverse reactions observed in greater than or equal to 5% of patients receiving 8, 12, or 16 weeks of treatment with MAVIRET are presented in Table 4. In patients receiving MAVIRET who experienced adverse reactions, 80% had an adverse reaction of mild severity (Grade 1). In the placebo-controlled study, these adverse reactions occurred at a similar frequency in patients treated with placebo compared to patients 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 (Table 5).

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

Table 4. Adverse reactions observed in ≥ 5% of patients who received MAVIRET in Phase 2 and 3 Clinical Studies

Adverse Reaction	MAVIRET 8, 12 or 16 weeks	Placebo 12 weeks
	N = 2265	N = 100
Headache	13.2%	6.0%
Fatigue	11.4%	8.0%
Nausea	7.6%	2.0%

Table 5. Adverse reactions reported in ≥ 10% of treatment-naïve adults without cirrhosis receiving MAVIRET for 8 or 12 weeks in ENDURANCE-3

Adverse Reaction	MAVIRET* 8 weeks	MAVIRET 12 weeks	DCV[1] + SOF[2] 12 weeks
	N = 157	N = 233	N = 115
Headache	16 %	17 %	15 %
Fatigue	11 %	14 %	12 %
Nausea	9 %	12 %	12 %
[1] DCV = daclatasvir			

Adverse Reaction	MAVIRET* 8 weeks	MAVIRET 12 weeks	DCV[1] + SOF[2] 12 weeks
	N = 157	N = 233	N = 115

[2] SOF = sofosbuvir

* The 8 week arm was a non-randomised treatment arm

Adverse Reactions in Subjects with Severe Renal Impairment Including Subjects on Dialysis

The safety of MAVIRET in patients with chronic kidney disease (Stage 4 or Stage 5 including subjects on dialysis) and genotypes 1, 2, 3, 4, 5 or 6 chronic HCV infection without cirrhosis or with compensated cirrhosis was assessed in 104 patients (EXPEDITION-4). The most common adverse reactions were pruritus and fatigue in patients treated with MAVIRET for 12 weeks. Adverse reactions observed in greater than or equal to 5% of patients receiving 12 weeks of treatment with MAVIRET were pruritus (17.3%), fatigue (11.5%), nausea (8.7%), asthenia (6.7%), and headache (5.8%). In patients treated with MAVIRET who reported an adverse reaction, 55% had adverse reactions of mild severity. No patients experienced a serious adverse reaction. The proportion of patients who permanently discontinued treatment due to adverse reactions was 1.9%.

Serum bilirubin elevations

Elevations in total bilirubin of at least 2x upper limit of 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.

4.9 Overdose

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

For information on the management of overdose in Australia contact the Poisons Information Centre on 131126.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antivirals for systemic use; direct acting antivirals, other antivirals.

ATC code: not yet assigned.

Mechanism of action

MAVIRET is a fixed-dose combination of two pangenotypic direct-acting antiviral agents, glecaprevir (NS3/4A protease inhibitor) and pibrentasvir (NS5A inhibitor), targeting multiple steps in the HCV viral lifecycle (see 5.1 PHARMACODYNAMIC PROPERTIES - Microbiology).

Pharmacodynamics

Effects on Electrocardiogram

The effect of glecaprevir (up to 600 mg) with pibrentasvir (up to 240 mg) on QTc interval was evaluated in an active-controlled (moxifloxacin 400 mg) thorough QT study. At 20-fold of glecaprevir and 5-fold of pibrentasvir therapeutic concentrations, the glecaprevir and pibrentasvir combination does not prolong the QTc interval.

Microbiology

Mechanism of Action

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 6**.** EC_{50} values are determined in the absence of human plasma.

Table 6. Activity of Glecaprevir and Pibrentasvir Against HCV Genotypes 1-6 Replicon Cell Lines

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

NA = not available

The EC_{50} values of glecaprevir and pibrentasvir against chimeric replicons encoding NS3 or NS5A from clinical isolates are presented in Table 7.

Table 7. Activity of Glecaprevir and Pibrentasvir Against Transient Replicons Containing NS3 or NS5A from HCV Genotypes 1-6 Clinical Isolates

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

HCV Subtype	Glecaprevir		Pibrentasvir	
	Number of clinical isolates	Median EC_{50}, nM (range)	Number of clinical isolates	Median EC_{50}, nM (range)
6p	NA	NA	1	0.0005

NA = not available

Combination Activity in vitro

Evaluation of the combination of glecaprevir and pibrentasvir showed no antagonism in antiviral activity in HCV genotype 1 replicon cell culture assays.

Resistance

In Cell Culture

Selection of HCV genotype 1a, 1b, 2a, 3a, 4a or 6a replicons for reduced susceptibility to glecaprevir resulted in the emergence of amino acid substitutions most commonly at NS3 positions A156 or D/Q168. Single amino acid substitutions introduced at NS3/4A position 156 reduced susceptibility to glecaprevir (genotypes 1 to 4) by > 100-fold. Mutations at position 168 had variable effects on glecaprevir susceptibility depending on HCV genotype/subtype and specific amino acid change, with the greatest reductions (> 30-fold) observed in genotypes 1a (D168F/Y), 3a (Q168R) and 6a (D168A/G/H/V/Y). Substitutions at position 80 did not reduce susceptibility to glecaprevir except in genotype 3a, where a Q80R substitution led to a 21-fold increase in EC_{50}. 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 activity.

Selection of HCV genotype 1a, 2a or 3a replicons for reduced susceptibility to pibrentasvir resulted in the emergence of amino acid substitutions at known NS5A inhibitor resistance-associated positions, including Q30D/deletion, Y93D/H/N or H58D + Y93H in genotype 1a replicons, F28S + M31I or P29S + K30G in genotype 2a replicons, and Y93H in genotype 3a replicons. 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. Individual NS5A amino acid substitutions that reduced susceptibility to pibrentasvir include M28G or Q30D in genotype 1a (244- and 94-fold, respectively), and P32 deletion in genotype 1b (1036-fold). Some combinations of two or more NS5A inhibitor resistance-associated amino acid substitutions (including A30K + Y93H in genotype 3a) may result in greater reductions in pibrentasvir susceptibility.

In Clinical Studies

Studies in Treatment-Naïve and Peginterferon, Ribavirin and/or Sofosbuvir Treatment-Experienced Patients with or without Cirrhosis

Twenty two of the approximately 2300 patients treated with MAVIRET for 8, 12, or 16 weeks in Phase 2 and 3 clinical studies experienced virologic failure (two with genotype 1, two with genotype 2, and eighteen with genotype 3 infection).

Among the two genotype 1-infected patients 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.

Among the two genotype 2-infected patients, no treatment-emergent substitutions were observed in NS3 or NS5A (the M31 polymorphism in NS5A was present at baseline and post-treatment in both subjects).

Among the eighteen genotype 3-infected patients treated with MAVIRET for 8, 12, or 16 weeks who experienced virologic failure, treatment-emergent NS3 substitutions Y56H/N, Q80K/R, A156G, or Q168L/R were observed in eleven patients. A166S or Q168R were present at baseline and post-treatment in five patients. Treatment-emergent NS5A substitutions M28G, A30G/K, L31F, P58T, or Y93H were observed in sixteen patients, and thirteen patients had A30K (n=9) or Y93H (n=5) at baseline and post-treatment.

Studies in Patients with or without Cirrhosis who were Treatment-Experienced to NS3/4A Protease and/or NS5A Inhibitors

Ten of 113 patients treated with MAVIRET in the MAGELLAN-1 study for 12 or 16 weeks experienced virologic failure.

Among the ten genotype 1-infected patients with virologic failure, treatment-emergent NS3 substitutions V36A/M, R155K/T, A156G/T/V, or D168A/T were observed in seven patients. Five of the ten patients had combinations of V36M, Y56H, R155K/T, or D168A/E in NS3 at baseline and post-treatment. All of the genotype 1-infected virologic failure 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 treatment-naïve and pegylated interferon, ribavirin and/or sofosbuvir treatment-experienced patients receiving MAVIRET in the Phase 2 and Phase 3 clinical studies was conducted to explore the association between baseline polymorphisms and treatment outcome and to describe substitutions seen upon 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 infection, 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 subjects with HCV genotype 1, 2, 3, 4, 5, and 6 infection 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 309 genotype 3-infected patients receiving the recommended regimen, baseline NS3 polymorphisms had no impact on treatment outcome. All patients (100%, 15/15) with Y93H in NS5A at baseline achieved SVR12. Among patients receiving the recommended regimen, 75% (15/20) with A30K in NS5A at baseline achieved SVR12. Among genotype 3-infected patients with compensated cirrhosis receiving the recommended regimen, 100% (18/18) 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. Some combinations of NS5A substitutions at these positions showed reductions in susceptibility 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.

Based on resistance patterns observed in cell culture replicon studies, cross-resistance is possible between glecaprevir and other HCV NS3/4A protease inhibitors, and between pibrentasvir and other HCV NS5A polymerase 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 genotype 1 infection: 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 genotype 1-infected patients: 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 NS3/4A PI-experienced / NS5A inhibitor-naïve patients receiving 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 NS5A inhibitor-experienced patients (with or without NS3/4A PI-experience) receiving 16 weeks of treatment, 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 polymorphisms in NS3 or NS5A, respectively.

Clinical trials

Description of Clinical Studies

Table 8 summarises clinical studies conducted with MAVIRET in patients with chronic hepatitis C (HCV) genotype 1, 2, 3, 4, 5 or 6 infection. For the recommended treatment duration see 4.2 DOSE AND METHOD OF ADMINISTRATION.

Table 8. Clinical Studies Conducted with MAVIRET in Patients with HCV Genotype 1, 2, 3, 4, 5 or 6 Infection

Genotype (GT)	Clinical Study	Summary of Study Design
TN and TE patients without cirrhosis		
GT 1	ENDURANCE-1 (M13-590)	MAVIRET for 8 (n=351) or 12 weeks (n=352)
	SURVEYOR-1 (M14-867)	MAVIRET for 8 weeks (n=34)
GT 2	ENDURANCE-2 (M15-464)	MAVIRET (n=202) or Placebo (n=100) for 12 weeks
	SURVEYOR-2 (M14-868)	MAVIRET for 8 weeks (n=199) or 12 weeks (n=25)
GT 3	ENDURANCE-3 (M13-594)	MAVIRET for 8 (n=157) or 12 weeks (n=233) Sofosbuvir + daclatasvir for 12 weeks (n=115)
	SURVEYOR-2 (M14-868)	MAVIRET for for 8 (TN only) (n=29) or 12 weeks (n=76) or 16 (TE only) weeks (n=22)
GT 4, 5, 6	ENDURANCE-4 (M13-583)	MAVIRET for 12 weeks (n=121)
	SURVEYOR-1 (M14-867)	MAVIRET for 12 weeks (n=32)
	SURVEYOR-2 (M14-868)	MAVIRET for 8 weeks (n=58)
TN and TE patients with cirrhosis		
GT 1, 2, 4, 5, 6	EXPEDITION-1 (M14-172)	MAVIRET for 12 weeks (n=146)
GT 3	SURVEYOR-2 (M14-868)	MAVIRET for 12 weeks (TN only) (n=64) or 16 weeks (TE only) (n=51)
Patients with CKD stage 4 and 5 with or without cirrhosis		
GT 1-6	EXPEDITION-4 (M15-462)	MAVIRET for 12 weeks (n=104)
NS5A inhibitor and/or NS3/4A PI-experienced patients with or without cirrhosis		
GT 1, 4	MAGELLAN-1 (M15-410)	MAVIRET for 12 (n=66) or 16 weeks (n=47)

TN = treatment-naïve, TE = treatment-experienced (includes previous treatment that included pegIFN or IFN, and/or RBV and/or sofosbuvir), PI = Protease Inhibitor, CKD = chronic kidney disease

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.

Clinical Studies in Treatment-Naïve or Treatment-Experienced Patients with or without Cirrhosis

Of the 2256 patients with compensated liver disease (with or without cirrhosis) treated who were treatment-naïve or treatment-experienced to combinations of peginterferon, ribavirin and/or sofosbuvir, the median age was 54 years (range: 19 to 88); 72.7% were treatment-naïve, 27.3% were treatment-experienced to a combination containing either sofosbuvir, ribavirin and/or peginterferon; 38.9% were HCV genotype 1; 21.1% were HCV genotype 2; 28.5% were HCV genotype 3; 7.9% were HCV genotype 4; 3.5% were HCV genotype 5 or 6; 13.9% were ≥ 65 years; 54.8% were male; 5.5% were Black; 12.5% had cirrhosis; 4.6% had severe renal impairment or end stage renal disease; 20.3% had a body mass index of at least 30 kg per m^2; median baseline HCV RNA level was 6.2 $\log_{10}$ IU/mL.

Patients with Genotype 1, 2, 4, 5, or 6 Infection

The efficacy of MAVIRET in patients who were treatment-naïve or treatment-experienced to combinations of peginterferon, ribavirin and/or sofosbuvir with genotype 1, 2, 4, 5 or 6 chronic hepatitis C infection was demonstrated in seven studies using 8- or 12-week durations: ENDURANCE-1, ENDURANCE-2, ENDURANCE-4, SURVEYOR-1 (Part 1), SURVEYOR-2 (Part 1, Part 2, Part 4), EXPEDITION-1, and EXPEDITION-4.

ENDURANCE-1 was a randomised (1:1) and open-label study comparing the efficacy of 8 weeks of treatment with MAVIRET versus 12 weeks of treatment in non-cirrhotic patients with genotype 1 infection who were either mono-infected with HCV or coinfected with HCV/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 genotype 2 infection. ENDURANCE-4 was a single-arm, open-label study in non-cirrhotic patients with genotype 4, 5, or 6 infection. SURVEYOR-2 (Part 4) included a single, open-label arm in non-cirrhotic patients with genotype 2, 4, 5 or 6 infection treated for 8 weeks.

EXPEDITION-1 was a single-arm, open-label study in patients with compensated cirrhosis and genotype 1, 2, 4, 5 or 6 infection. EXPEDITION-4 was a single-arm, open-label study in genotype 1-6 infected patients with chronic kidney disease stage 4 and 5. In addition, treatment arms in Phase 2 studies investigating MAVIRET using glecaprevir 300 mg plus pibrentasvir 120 mg once daily were included (SURVEYOR-1 Part 2 and SURVEYOR-2 Parts 1-2).

Table 9. ENDURANCE-1, -2, -4, SURVEYOR-1, -2, and EXPEDITION-1 and -4: SVR12 in Treatment-Naïve and Treatment-Experienced Patients to Peginterferon, Ribavirin and/or Sofosbuvir with Genotype 1, 2, 4, 5 or 6 Infection who Received the Recommended Duration

	Genotype 1^	Genotype 2	Genotype 4	Genotype 5	Genotype 6
SVR12 in Patients Without Cirrhosis					
8 weeks	99.0% (383/387)	98.0% (193/197)	93.5% (43/46)	100% (2/2)	90.0% (9/10)
Outcome for patients without SVR12					
On-treatment VF	0.3% (1/387)	0% (0/197)	0% (0/46)	0% (0/2)	0% (0/10)
Relapse*	0% (0/384)	1.0% (2/195)	0% (0/45)	0% (0/2)	0% (0/10)
Other**	0.8% (3/387)	1.0% (2/197)	6.5% (3/46)	0% (0/2)	10% (1/10)
SVR12 in Patients With Cirrhosis					
12 weeks	97.0% (98/101)	100% (35/35)	100% (20/20)	100% (2/2)	100% (7/7)
Outcome for patients without SVR12					
On-treatment VF	0% (0/101)	0% (0/35)	0% (0/20)	0% (0/2)	0% (0/7)
Relapse*	1.0% (1/98)	0% (0/35)	0% (0/19)	0% (0/2)	0% (0/7)
Other**	2.0% (2/101)	0% (0/35)	0% (0/20)	0% (0/2)	0% (0/7)

^ Includes 33 patients co-infected with HIV-1.

* Relapse is defined as HCV RNA ≥ LLOQ after end-of-treatment response among those who completed treatment.

** Includes patients who discontinued due to adverse event, lost to follow-up, or subject withdrawal.

Of the genotype 1, 2, 4, 5 or 6-infected patients with end stage renal disease enrolled in EXPEDITION-4, 97.8% (91/93) achieved SVR12 with no virologic failures.

Patients with Genotype 3 Infection

The efficacy of MAVIRET in patients who were treatment-naïve or treatment-experienced to combinations of peginterferon, ribavirin and/or sofosbuvir with genotype 3 chronic hepatitis C infection was demonstrated in the ENDURANCE-3 (treatment-naïve without cirrhosis) and

SURVEYOR-2 Part 3 (patients with prior treatment experience and/or compensated cirrhosis) clinical studies. Patients with genotype 3 chronic hepatitis infection were excluded from the MAGELLAN-1 study of patients who failed a previous regimen containing NS5A and/or NS3/4A protease inhibitors.

ENDURANCE-3 was a partially-randomised, open-label, active-controlled study in treatment-naïve patients. 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. SURVEYOR-2 Part 3 was an open-label study randomising non-cirrhotic treatment-experienced patients to 12- or 16-weeks of treatment; in addition, the study evaluated the efficacy of MAVIRET in subjects with compensated cirrhosis and genotype 3 infection in two dedicated treatment arms using 12-week (treatment-naïve only) and 16-week (treatment-experienced only) durations. Among treatment-experienced patients, 46% (42/91) failed a previous regimen containing sofosbuvir.

Table 10. ENDURANCE-3: SVR12 in Treatment-naïve, Genotype 3-Infected Patients without Cirrhosis

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

* Relapse is defined as HCV RNA ≥ LLOQ after end-of-treatment response among those who completed treatment.

** Includes patients who discontinued due to adverse event, lost to follow-up, or subject withdrawal.

Table 11. SURVEYOR-2 Part 3: SVR12 in Genotype 3-Infected Patients with or without Cirrhosis who Received the Recommended Duration

	Treatment-Naïve with Cirrhosis	**Treatment-Experienced with Cirrhosis**	**Treatment-Experienced without Cirrhosis**

	MAVIRET 12 weeks (N=40)	**MAVIRET 16 weeks (N=47)**	**MAVIRET 16 weeks (N=22)**
SVR	97.5% (39/40)	95.7% (45/47)	95.5% (21/22)
Outcome for patients without SVR12			
On-treatment VF	0% (0/40)	2.1% (1/47)	0% (0/22)
Relapse*	0% (0/39)	2.2% (1/46)	4.5% (1/22)
Other**	2.5% (1/40)	0% (0/47)	0% (0/22)

* Relapse is defined as HCV RNA ≥ LLOQ after end-of-treatment response among those who completed treatment.

** Includes patients who discontinued due to adverse event, lost to follow-up, or subject withdrawal.

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

In patients who are treatment-naïve or treatment-experienced to combinations of peginterferon, ribavirin and/or sofosbuvir who received the recommended duration, 97.4% (1102/1131) achieved SVR overall (among which 97.5% (274/281) patients with compensated cirrhosis achieved SVR), while 0.3% (3/1131) experienced on-treatment virologic failure and 1.0% (11/1111) experienced post-treatment relapse.

Clinical Study in NS5A and/or Protease Inhibitor-Experienced Patients with or without Cirrhosis

MAGELLAN-1 was a randomised, multipart, open-label study in 141 genotype 1 or 4-infected patients 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 (glecaprevir 300 mg plus pibrentasvir 120 mg without ribavirin only included in the analysis). Part 2 (n=91) randomised genotype 1 or 4-infected patients 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); 37.4%, 29.7%, and 33.0% had treatment-experience to NS5A only, protease inhibitors only, or both NS5A inhibitors and protease inhibitors; 95.6% had HCV genotype 1 and 4.4% had HCV genotype 4 infection; 12.1% were ≥65 years; 70.3% were male; 22.0% were Black; 38.5% had a body mass index of at least 30 kg per m^2; 62.6% had baseline HCV RNA levels of at least 1,000,000 IU per mL.

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 were experienced to NS5A inhibitors (alone or with a protease inhibitor) is presented in Table 12.

Table 12. MAGELLAN-1 Part 2: SVR12 in NS5A Inhibitor-Experienced Patients with or without Cirrhosis who Received the Recommended Duration

	MAVIRET 16 weeks (N=34)
SVR NS5A-Inhibitor Experienced Only*	94.4% (17/18)
On-treatment VF	5.6% (1/18)
Relapse**	0% (0/17)
SVR NS5A-Inhibitor and PI-experienced	81.3% (13/16)
On-treatment VF	18.8% (3/16)
Relapse**	0% (0/13)

* Includes patients who previously failed LDV / SOF or DCV containing regimens.

** Relapse is defined as HCV RNA ≥ LLOQ after end-of-treatment response among those who completed treatment.

Lower SVR rates were observed in GT1a-infected patients who were retreated with MAVIRET within 12 months of failing a regimen containing both NS3/4A protease inhibitors and NS5A inhibitors.

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 inhibitor containing regimens, and the favourable outcomes of MAVIRET treatment in NS5A inhibitor-naïve patients 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.

Geriatric Patients

Clinical studies of MAVIRET included 328 patients aged 65 and over (13.8% of total number of patients in the Phase 2 and 3 clinical studies). The response rates observed for patients ≥ 65 years of age (97.9%) were similar to that of patients < 65 years of age (97.3%), across treatment groups.

5.2 Pharmacokinetic properties

Absorption, Distribution, Metabolism and Excretion

The pharmacokinetic properties of the components of MAVIRET in healthy subjects are provided in Table 13. The steady-state pharmacokinetic parameters of glecaprevir and pibrentasvir in HCV-infected patients without cirrhosis are provided in Table 14**.**

Table 13. 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		
% Bound to human plasma proteins	97.5	> 99.9
Blood-to-plasma ratio	0.57	0.62
Metabolism		
Metabolism	secondary, CYP3A	none
Elimination		
Major route of elimination	biliary-faecal	biliary-faecal
$t_{1/2}$ (h)	6	13
% of dose excreted in urine[c]	0.7	0
% 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 14. Steady-State Pharmacokinetic Parameters of Glecaprevir and Pibrentasvir Following Administration of MAVIRET in Non-Cirrhotic HCV-Infected Patients

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 HCV-infected patients without cirrhosis; pibrentasvir C_{max} and $AUC_{24,ss}$ were 63% and 34% lower, respectively.

Specific Populations

Race/ethnicity

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

Gender/weight

No dose adjustment of MAVIRET is recommended based on sex or body weight.

Paediatric Patients

The pharmacokinetics of MAVIRET in paediatric patients has not been established.

Geriatric Patients

No dose adjustment of MAVIRET is recommended in geriatric patients. Population pharmacokinetic analysis in HCV-infected patients showed that within the age range (18 to 88 years) analysed, age did not have a clinically relevant effect on the exposure to glecaprevir or pibrentasvir.

Renal Impairment

Glecaprevir and pibrentasvir AUC were increased ≤ 56% in non-HCV infected subjects with mild (n=8), moderate (n=8), severe (n=8), or end-stage renal impairment who were not on dialysis (n=6) compared to subjects with normal renal function (n=8). Glecaprevir and pibrentasvir AUC were similar with and without dialysis (≤ 18% difference) in dialysis-dependent non-HCV infected subjects. In population pharmacokinetic analysis of HCV-infected patients, 86% higher glecaprevir 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 HCV-infected patients with renal impairment with or without dialysis were not clinically significant.

Hepatic Impairment

At the clinical dose, compared to non-HCV infected subjects with normal hepatic function (n=6), glecaprevir AUC was 33% higher in Child-Pugh A patients (n=6), 100% higher in Child-Pugh B patients (n=6), and increased to 11-fold in Child-Pugh C patients (n=6). Pibrentasvir AUC was similar in Child-Pugh A patients, 26% higher in Child-Pugh B patients, and 114% higher in Child-Pugh C patients.

Following administration of MAVIRET in HCV infected patients with compensated (Child-Pugh A) cirrhosis, exposure of glecaprevir was approximately 2-fold and pibrentasvir exposure was similar to non-cirrhotic HCV infected patients, however there was significant

overlap in exposures. Therefore, recommendations for drug-drug interactions are not different for cirrhotic (Child-Pugh A) and non-cirrhotic subjects.

Drug Interactions

Drug interaction studies were performed with glecaprevir / pibrentasvir and other drugs that are likely to be coadministered and with drugs commonly used as probes for pharmacokinetic interactions. Tables 15 and 16 summarise the pharmacokinetic effects when glecaprevir / pibrentasvir was coadministered with other drugs which showed potentially clinically relevant changes.

Table 15. Drug Interactions: Changes in Pharmacokinetic Parameters of Glecaprevir or Pibrentasvir in the Presence of Coadministered Drug

Co-administered Drug	Regimen of Co-administered Drug (mg)	Regimen of glecaprevir / pibrentasvir (mg)	N	DAA	Central Value Ratio (90% CI)		
					C_{max}	AUC	C_{min}
Carbamazepine	200 twice daily	300/120 single dose	10	glecaprevir	0.33 (0.27, 0.41)	0.34 (0.28, 0.40)	--
				pibrentasvir	0.50 (0.42, 0.59)	0.49 (0.43, 0.55)	--
Rifampicin	600 (first dose)	300/120 single dose	12	glecaprevir	6.52 (5.06, 8.41)	8.55 (7.01, 10.4)	--
				pibrentasvir	↔	↔	--
	600 once daily	300/120 single dose[a]	12	glecaprevir	0.14 (0.11, 0.19)	0.12 (0.09, 0.15)	--
				pibrentasvir	0.17 (0.14, 0.20)	0.13 (0.11, 0.15)	--
Ciclosporin	100 single dose	300/120 once daily	12	glecaprevir	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)
	400 single	300/120	11	glecaprevir	4.51 (3.63,	5.08 (4.11,	--

Co-administered Drug	Regimen of Co-administered Drug (mg)	Regimen of glecaprevir / pibrentasvir (mg)	N	DAA	Central Value Ratio (90% CI)		
					C_{max}	AUC	C_{min}
	dose	single dose			6.05)	6.29)	
				pibrentasvir	↔	1.93 (1.78, 2.09)	--
Atazanavir (ATZ) + ritonavir (RTV)	ATZ 300 + RTV 100 once daily	300/120 once daily[b]	12	glecaprevir	≥ 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 (DRV) + RTV	DRV 800 + RTV 100 once daily	300/120 once daily	8	glecaprevir	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)
Lopinavir / ritonavir	400/100 twice daily	300/120 once daily	9	glecaprevir	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)

↔ = No change (central value ratio 0.80 to 1.25).

[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 is reported.

Table 16. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Combination of Glecaprevir / Pibrentasvir

Coadministered Drug	Regimen of Coadministered Drug (mg)	Regimen of glecaprevir / pibrentasvir (mg)	N	Central Value Ratio (90% CI)		
				C_{max}	AUC	C_{min}
Digoxin	0.5 single dose	400/120 once daily	12	1.72 (1.45, 2.04)	1.48 (1.40, 1.57)	--

Coadministered Drug	Regimen of Coadministered Drug (mg)	Regimen of glecaprevir / pibrentasvir (mg)	N	Central Value Ratio (90% CI)		
				C_{max}	AUC	C_{min}
Dabigatran	Dabigatran etexilate 150 single dose	300/120 once daily	12	2.05 (1.72, 2.44)	2.38 (2.11, 2.70)	--
Pravastatin	10 once daily	400/120 once daily	12	2.23 (1.87, 2.65)	2.30 (1.91, 2.76)	--
Rosuvastatin	5 once daily	400/120 once daily	12	5.62 (4.80, 6.59)	2.15 (1.88, 2.46)	--
Atorvastatin	10 once daily	400/120 once daily	11	22.0 (16.4, 29.6)	8.28 (6.06, 11.3)	--
Lovastatin	Lovastatin 10 once daily	300/120 once daily	12	↔	1.70 (1.40, 2.06)	--
Lovastatin metabolite, lovastatin acid				5.73 (4.65, 7.07)	4.10 (3.45, 4.87)	--
Simvastatin	Simvastatin 5 once daily	300/120 once daily	12	1.99 (1.60, 2.48)	2.32 (1.93, 2.79)	--
Simvastatin metabolite, simvastatin acid				10.7 (7.88, 14.6)	4.48 (3.11, 6.46)	--
Ethinyloestradiol (EE)	EE / Norgestimate 35 µg / 250 µg once daily	300/120 once daily	11	1.31 (1.24, 1.38)	1.28 (1.23, 1.32)	1.38 (1.25, 1.52)
Norgestrel				1.54 (1.34, 1.76)	1.63 (1.50, 1.76)	1.75 (1.62, 1.89)
Norelgestromin				↔	1.44 (1.34, 1.54)	1.45 (1.33, 1.58)
Ethinyloestradiol	EE / Levonorgestrel 20 µg/ 100 µg once daily	300/120 once daily	12	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)

↔ = No change (central value ratio 0.80 to 1.25)

5.3 Preclinical safety data

Genotoxicity

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

Carcinogenicity studies with glecaprevir and pibrentasvir have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The tablets also contain copovidone, tocofersolan, colloidal anhydrous silica, propylene glycol monocaprylate, croscarmellose sodium, sodium stearylfumarate and Opadry II 32F240023 pink (hypromellose 2910, lactose monohydrate, titanium dioxide, macrogol 3350 and iron oxide red).

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

MAVIRET 100 mg / 40 mg tablets are pink-coloured, film-coated, oblong biconvex shaped, and debossed with “NXT” on one side.

MAVIRET is dispensed in a monthly carton. Each monthly carton contains four weekly cartons. Each weekly carton contains seven daily blister packs. Each daily dose contains three 100 mg / 40 mg glecaprevir / pibrentasvir tablets in PVC/PE/PCTFE(Aclar)/Al blisters.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy

6.7 Physicochemical properties

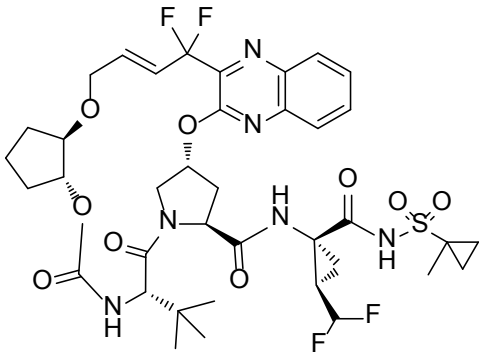
Chemical structure and CAS numbers

Glecaprevir

The chemical name of glecaprevir is (3a*R*,7*S*,10*S*,12*R*,21*E*,24a*R*)-7-*tert*-butyl-*N*-{(1*R*,2*R*)-2-(difluoromethyl)-1-[(1-methylcyclopropane-1-sulfonyl)carbamoyl]cyclopropyl}-20,20-difluoro-5,8-dioxo-2,3,3a,5,6,7,8,11,12,20,23,24a-dodecahydro-1*H*,10*H*-9,12-methanocyclopenta[18,19][1,10,17,3,6]trioxadiazacyclononadecino[11,12-b]quinoxaline-10-carboxamide hydrate.

The molecular formula is $C_{38}H_{46}F_4N_6O_9S$ (anhydrate) and the molecular weight for the drug substance is 838.87 g/mol (anhydrate).

Glecaprevir has the following molecular structure:



- X H_2O

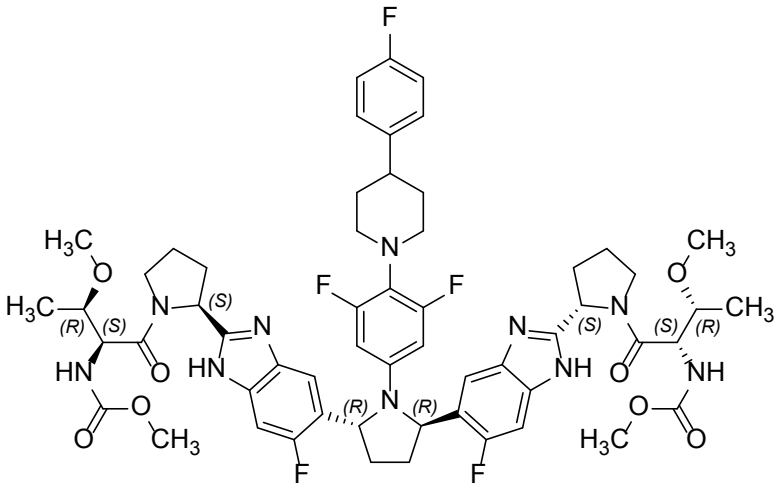
CAS Number: 1838571-99-5 (anhydrate)

Pibrentasvir

The chemical name of pibrentasvir is methyl {(2*S*,3*R*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{3,5-difluoro-4-[4-(4-fluorophenyl)piperidin-1-yl]phenyl}-5-(6-fluoro-2-{(2*S*)-1-[*N*-(methoxycarbonyl)-*O*-methyl-L-threonyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl)pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate.

The molecular formula is $C_{57}H_{65}F_5N_{10}O_8$ and the molecular weight for the drug substance is 1113.18 g/mol.

Pibrentasvir has the following molecular structure:



CAS Number: 1353900-92-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8 SPONSOR

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AUSTRALIA

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NEW ZEALAND

9 DATE OF FIRST APPROVAL

2 January 2018

10 DATE OF REVISION

Not applicable