

▼ 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 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 and adolescent patients 12 years and older with chronic hepatitis C virus (HCV) genotype (GT) 1, 2, 3, 4, 5, or 6 infection with or without compensated cirrhosis. This includes patients with HCV GT1 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 5.1 PHARMACODYNAMIC PROPERTIES – 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.

Recommended dosage in adults and adolescents (12 years and older)

The recommended oral dosage of MAVIRET is three tablets (total daily dose: glecaprevir 300 mg and pibrentasvir 120 mg) once daily at the same time 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 coinfecting 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 or SOF + VEL

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

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

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, 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use in Hepatic Impairment 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

No dose adjustment of MAVIRET is required in adolescents 12 years and older (See 5.1 PHARMACOLOGICAL PROPERTIES – Clinical).

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 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 GT1-infected patients who are NS5A inhibitor-experienced without prior treatment with an NS3/4A protease inhibitor or in GT3-infected patients who are PRS treatment experienced (PRS-TE) (see 5.1 PHARMACODYNAMIC PROPERTIES – Clinical Trials).

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, ethinylloestradiol-containing products, rifampicin (see 5.2 PHARMACOKINETIC PROPERTIES – Pharmacokinetics, 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.

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, 4.3 CONTRAINDICATIONS and 5.2 PHARMACOKINETICS PROPERTIES).

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.

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 12 years of age have not been established. Clinical studies in adolescent patients, 12 to < 18 years of age, are ongoing, and long-term data are not currently available.

Effects on laboratory test

Refer to 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) – Serum bilirubin elevations.

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		
Dabigatran etexilate	↑ dabigatran	Coadministration is contraindicated (see 4.3 CONTRAINDICATIONS).
Anticonvulsant		
Carbamazepine	↓ glecaprevir	Coadministration may lead to reduced therapeutic effect of MAVIRET and is not recommended.
	↓ pibrentasvir	
Antimycobacterials		
Rifampicin	↓ glecaprevir	Coadministration is contraindicated because of potential loss of therapeutic effect (see 4.3 CONTRAINDICATIONS).
	↓ pibrentasvir	
Ethinylestradiol-Containing Products		
Ethinylestradiol-containing medications such as combined oral contraceptives	↔ glecaprevir	Coadministration of MAVIRET with ethinylestradiol-containing products may increase the risk of ALT elevations and is contraindicated (see 4.3 CONTRAINDICATIONS).
	↔ pibrentasvir	
Herbal Products		
St. John's Wort (<i>hypericum perforatum</i>)	↓ glecaprevir	Coadministration may lead to reduced therapeutic effect of MAVIRET and is not recommended.
	↓ pibrentasvir	
HIV-Antiviral Agents		
Atazanavir	↑ glecaprevir	Coadministration is contraindicated due to increased risk of ALT elevations (see 4.3 CONTRAINDICATIONS).
	↑ pibrentasvir	
Darunavir Lopinavir Ritonavir	↑ glecaprevir	Coadministration is not recommended.
	↑ pibrentasvir	
Efavirenz	↓ glecaprevir	Coadministration may lead to reduced therapeutic effect of MAVIRET and is not recommended.
	↓ pibrentasvir	
HMG-CoA Reductase Inhibitors		
Atorvastatin Simvastatin	↑ atorvastatin ↑ simvastatin	Coadministration with atorvastatin and simvastatin is contraindicated (see 4.3 CONTRAINDICATIONS).

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comments
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.
Immunosuppressants		
Ciclosporin	↑ glecaprevir	MAVIRET is not recommended for use in patients requiring stable ciclosporin doses > 100 mg per day.
	↑ 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 embryofoetal 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 embryofoetal 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 embryofoetal 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)

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 adult patients infected with GT1, 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 $\geq 5\%$ 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 $\geq 10\%$ of treatment-naïve (TN) 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
² SOF = sofosbuvir
* The 8 week arm was a non-randomised treatment arm

Adverse Reactions in Adult Patients 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 GT1, 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%.

Adverse Reactions in HCV/HIV-1 Coinfected Adult Patients

The overall safety profile in HCV/HIV-1 coinfecting 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 GT1, 2, 3, 4, or 6 chronic HCV infection 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 Adolescent Patients

The safety of MAVIRET in HCV GT 1-6 infected adolescents 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 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.

Post marketing experience

The following adverse reactions have been identified during post approval use of glecaprevir/pibrentasvir. 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 suspected adverse 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.

4.9 Overdose

The highest documented doses administered to healthy volunteers is 1200 mg once daily for seven 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: J05AP57.

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 the 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

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 GT1a, 1b, 2a, 2b, 3a, 4a, 5a, and 6a with IC₅₀ 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 EC₅₀ values of glecaprevir and pibrentasvir against full-length or chimeric replicons encoding NS3 or NS5A from laboratory strains are presented in Table 6. EC₅₀ values are determined in the absence of human plasma.

Table 6. Activity of Glecaprevir and Pibrentasvir Against HCV GT1-6 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 EC₅₀ 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 GT1-6 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
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 GT1 replicon cell culture assays.

Resistance

In Cell Culture

Selection of HCV GT1a, 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 (GT1 to 4) by > 100-fold. Mutations at position 168 had variable effects on glecaprevir susceptibility depending on HCV GT/subtype and specific amino acid change, with the greatest reductions (> 30-fold) observed in GT1a (D168F/Y), 3a (Q168R) and 6a (D168A/G/H/V/Y). Substitutions at position 80 did not reduce susceptibility to glecaprevir except in GT3a, where a Q80R substitution led to a 21-fold increase in EC₅₀. 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 GT1a, 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 GT1a replicons, F28S +

M31I or P29S + K30G in GT2a replicons, and Y93H in GT3a replicons. Single substitutions important for the NS5A inhibitor class at positions 24, 28, 30, 31, 58, 92, or 93 in NS5A in GT1 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 GT1a (244- and 94-fold, respectively), and P32 deletion in GT1b (1036-fold). Some combinations of two or more NS5A inhibitor resistance-associated amino acid substitutions (including A30K + Y93H in GT3a) may result in greater reductions in pibrentasvir susceptibility. In GT3b 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 GT3a replicon.

In Clinical Studies

Studies in TN and PRS-TE Patients with or without Cirrhosis

22 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 GT 1, two with GT2, and 18 with GT3 infection).

Among the two GT1-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 GT2-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 18 GT3-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 11 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 16 patients, and 13 patients had A30K (n=9) or Y93H (n=5) at baseline and post-treatment.

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

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

Among the 10 GT1-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 10 patients had combinations of V36M, Y56H, R155K/T, or D168A/E in NS3 at baseline and post-treatment. All of the GT1-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 TN and PRS-TE 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 GT1, 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 GT1, 2, 3, 4, 5, and 6 infection respectively.

GT1, 2, 4, 5, and 6: Baseline polymorphisms in GT1, 2, 4, 5 and 6 had no impact on treatment outcome.

GT3: Among 309 GT3-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 GT3-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 GT1-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-TE / NS5A TN 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-TE patients (with or without NS3/4A PI-TE) 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) GT1, 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 GT 1, 2, 3, 4, 5 or 6 Infection

Genotype (GT)	Clinical Study	Summary of Study Design
TN and PRS-TE patients without cirrhosis		
GT 1	ENDURANCE-1 (M13-590) ^a	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) ^b	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) ^c	MAVIRET for 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 (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)
GT 5, 6	ENDURANCE-5, 6 (M16-126)	MAVIRET for 8 weeks (n=75)
GT 1-6	VOYAGE-1 ^f (M15-592)	MAVIRET for 8 weeks (GT1, 2, 4, 5, and 6, and GT3 TN (n=356)) or 16 weeks (GT3 PRS-TE, only (n=6))
TN and PRS-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) ^d	MAVIRET for 12 weeks (TN only) (n=64) or 16 weeks (TE only) (n=51)
GT 5, 6	ENDURANCE-5, 6 (M16-126)	MAVIRET for 12 weeks (n=9)
GT 1-6	VOYAGE-2 ^f (M15-593)	MAVIRET for 12 weeks (GT1, 2, 4, 5, and 6, and GT3 TN (n=157); GT3 PRS-TE, only (n=3))
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) ^e	MAVIRET for 12 (n=66) or 16 weeks (n=47)
HCV/HIV-1 coinfecting patients with or without cirrhosis		
GT 1-6	EXPEDITION-2 (M14-730)	MAVIRET for 8 (n=137) or 12 weeks (n=16)
Liver or Kidney Transplant Recipients		
GT 1-6	MAGELLAN-2 (M13-596)	MAVIRET for 12 weeks (n=100)
Adolescent patients (12 to less than 18 years)		
GT 1-6	DORA – PART 1 (M16-123)	MAVIRET for 8 weeks (n=44) or 16 weeks (n=3)

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

^a. Included 33 subjects co-infected with HIV-1.

^b. GT2 from SURVEYOR-2 Parts 1 and 2 - MAVIRET for 8 weeks (n=54) or 12 weeks (n=25); GT2 from SURVEYOR-2 Part 4 - MAVIRET for 8 weeks (n=145).

^c. GT3 without cirrhosis from SURVEYOR-2 Parts 1 and 2 - MAVIRET for 8 (n=29) or 12 weeks (n=54); GT3 without cirrhosis from SURVEYOR-2 Part 3 - MAVIRET for 12 weeks (n=22) or 16 weeks (n=22).

^d. GT3 with cirrhosis from SURVEYOR-2 Part 2 - MAVIRET for 12 weeks (n=24) or 16 weeks (n=4); GT3 with cirrhosis from SURVEYOR-2 Part 3 - MAVIRET for 12 weeks (n=40) or 16 weeks (n=47).

^e. GT1, 4 from MAGELLAN-1 Part 1 - MAVIRET for 12 (n=22); GT1, 4 from MAGELLAN-1 Part 2 - MAVIRET for 12 (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.

Clinical Studies in TN or PRS-TE Adult Patients with or without Cirrhosis

Of the 2409 patients with compensated liver disease (with or without cirrhosis) treated who were TN or PRS-TE, the median age was 53 years (range: 19 to 88); 73.3% were TN, 26.7% were PRS-TE; 40.3% were HCV GT1; 19.8% were HCV GT2; 27.8% were HCV GT3; 8.1% were HCV GT4; 3.4% were HCV GT5 or 6; 13.1% were ≥ 65 years; 56.6% were male; 6.2% were Black; 12.3% had cirrhosis; 4.3% had severe renal impairment or end stage renal disease; 20.0% had a body mass index of at least 30 kg per m²; 7.7% had HIV-1 coinfection; and the median baseline HCV RNA level was 6.2 log₁₀ IU/mL.

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

The efficacy of MAVIRET in patients who were TN or PRS-TE with GT1, 2, 4, 5 or 6 chronic hepatitis C infection was demonstrated in eight 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, EXPEDITION-2 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 GT1 infection who were either mono-infected with HCV or coinfecting 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 GT2 infection. ENDURANCE-4 was a single-arm, open-label study in non-cirrhotic patients with GT4, 5, or 6 infection. SURVEYOR-2 (Part 4) included a single, open-label arm in non-cirrhotic patients with GT2, 4, 5 or 6 infection treated for 8 weeks.

EXPEDITION-1 was a single-arm, open-label study in patients with compensated cirrhosis and GT1, 2, 4, 5 or 6 infection. EXPEDITION-2 was an open-label study in HCV GT1-6/HIV-1 coinfecting patients, 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 GT1-6 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^a, -2, -4, SURVEYOR-1, -2, and EXPEDITION-1, -2^a and -4: SVR12 in TN and PRS-TE with GT1, 2, 4, 5 or 6 Infection who Received the Recommended Duration

	GT1	GT2	GT4	GT5	GT6
SVR12 in Patients Without Cirrhosis					
8 weeks	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% (0/60)	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)	10% (1/13)
SVR12 in Patients With Cirrhosis					
12 weeks	97.3% (108/111)	97.2% (35/36)	100% (21/21)	100% (2/2)	100% (7/7)

	GT1	GT2	GT4	GT5	GT6
Outcome for patients without SVR12					
On-treatment VF	0% (0/111)	0% (0/36)	0% (0/21)	0% (0/2)	0% (0/7)
Relapse*	0.9% (1/108)	0% (0/35)	0% (0/20)	0% (0/2)	0% (0/7)
Other**	1.8% (2/111)	2.8% (1/36)	0% (0/21)	0% (0/2)	0% (0/7)

a. Includes a total of 142 patients co-infected with HIV-1 from ENDURANCE-1 or EXPEDITION-2 who received the recommended duration.

b. Relapse is defined as HCV RNA \geq LLOQ after end-of-treatment response among those who completed treatment.

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

Of the GT 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.

Study in Patients with GT5 or GT6 Infection

ENDURANCE-5,6 was an open-label study in 84 HCV GT5- (n=23) or GT6-infected (n=61) TN or PRS-TE 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 HCV GT5, 73% had HCV GT6; 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 GT5-infected patients and 98.4% (60/61) for GT6-infected patients. One TN GT5-infected patient without cirrhosis experienced relapse, and one TN GT6-infected patient with compensated cirrhosis experienced on-treatment virologic failure.

Patients with GT3 Infection

The efficacy of MAVIRET in patients who were TN or PRS-TE with GT3 chronic hepatitis C infection was demonstrated in the ENDURANCE-3 (TN without cirrhosis) and SURVEYOR-2 Part 3 (patients with prior TE and/or compensated cirrhosis) clinical studies. Patients with GT3 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.

Patients with GT3 HCV infection were also included in other studies, such as the two Asian regional studies, VOYAGE-1 and VOYAGE-2.

ENDURANCE-3 was a partially-randomised, open-label, active-controlled study in TN 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 PRS-TE patients without cirrhosis to 12- or 16-weeks of treatment; in addition, the study evaluated the efficacy of MAVIRET in subjects with compensated cirrhosis and GT3 infection in two dedicated treatment arms using 12-week (TN only) and 16-week (PRS-TE only) durations. Among PRS-TE patients, 46% (42/91) failed a previous regimen containing sofosbuvir.

Table 10. ENDURANCE-3: SVR12 in TN, GT3-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 ^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)

^a. Relapse is defined as HCV RNA \geq LLOQ after end-of-treatment response among those who completed treatment.

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

Table 11. SURVEYOR-2 Part 3: SVR12 in GT3-Infected Patients with or without Cirrhosis who Received the Recommended Duration

	TN with Cirrhosis	PRS-TE with Cirrhosis	PRS-TE 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 ^a	0% (0/39)	2.2% (1/46)	4.5% (1/22)
Other ^b	2.5% (1/40)	0% (0/47)	0% (0/22)

-
- ^a Relapse is defined as HCV RNA \geq LLOQ after end-of-treatment response among those who completed treatment.
- ^b Includes patients who discontinued due to adverse event, lost to follow-up, or subject withdrawal.

Of the GT3-infected patients with end stage renal disease enrolled in EXPEDITION-4, 100% (11/11) achieved SVR12.

Patients with GT3b infection

GT3b is a subtype reported in a relatively small number of HCV infected patients in China and 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 HCV GT1-6 subjects 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 GT3 PRS-TE patients 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 GT3b patients 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 GT3a patients without cirrhosis (92.9% (13/14)). Three GT3b TN patients experienced relapse and 2 GT3b PRS-TE patients experienced on-treatment virologic failure. Among patients with compensated cirrhosis, the overall SVR12 rate for GT3b infected patients 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 GT3a infected patients. One GT3b TN patient experienced relapse.

Overall SVR12 Rate from the Clinical Studies in TN or TE Adult Patients with or without Cirrhosis

Among all patients, regardless of renal function, cirrhosis status or presence of HIV-1 coinfection, who were TN or PRS-TE who received the recommended duration, 97.5% (1252/1284) achieved SVR overall, while 0.3% (4/1284) experienced on-treatment virologic failure and 0.9% (11/1262) experienced post-treatment relapse.

In TN 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 relapses.

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 TN or PRS-TE subjects with compensated cirrhosis who received the recommended duration, 97.0% (288/297) achieved SVR12 (among which 98.0% [192/196] of TN subjects achieved SVR12), while 0.7% (2/297) experienced on-treatment virologic failure and 1.0% (3/289) experienced post-treatment relapse.

The presence of HIV-1 coinfection did not impact efficacy. In a dedicated HIV-1 coinfection study (EXPEDITION-2), the SVR12 rate in HCV/HIV-1 coinfecting 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) (99.1% (110/111) for TN subjects and 100% (26/26) for PRS-TE subjects. Among HCV/HIV-1 coinfecting patients from ENDURANCE-1 and EXPEDITION-2 combined who were TN 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 subjects relapsed.

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

MAGELLAN-1 was a randomised, multipart, open-label study in 141 GT1 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 GT1- or GT4-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 GT1 and 4.4% had HCV GT4 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 m²; 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^a	94.4% (17/18)
On-treatment VF	5.6% (1/18)
Relapse ^b	0% (0/17)
SVR NS5A-Inhibitor and PI-experienced	81.3% (13/16)
On-treatment VF	18.8% (3/16)
Relapse ^b	0% (0/13)

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

^b. Relapse is defined as HCV RNA \geq 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 GT3 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 GT3 who have failed therapy on an NS5A inhibitor-containing regimen and who are deemed at high risk for clinical disease progression.

Clinical Study in Adult Liver or Kidney Transplant Recipients

MAGELLAN-2 was a single-arm, open-label study in 100 post-liver or -kidney transplant HCV GT1 – 6 infected patients without cirrhosis who received MAVIRET for 12 weeks. The study included patients who were HCV TN or PRS-TE, with the exception of GT3-infected subjects who were all TN.

Of the 100 patients treated, the median age was 60 years (range: 39 to 78); 57% had HCV GT1, 13% had HCV GT2, 24% had HCV GT3, 4% had HCV GT4, 2% had HCV GT6; 75% were male; 8% were Black; 80% of patients were post-liver transplant and 20% were post-kidney transplant. Immunosuppressants allowed for co-administration were ciclosporin \leq 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.

Clinical Study in Adolescent Patients

DORA (Part 1) was an open-label trial to evaluate safety and efficacy in adolescents aged 12 to less than 18 years who received MAVIRET for 8 or 16 weeks. Treatment duration was chosen to match approved adult durations based on HCV genotype and prior treatment experience.

47 subjects 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; 11% were Black; 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 subject experienced virologic failure.

The DORA open-label trial is ongoing, and long-term data are not currently available.

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 [¹⁴C]glecaprevir or [¹⁴C]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

No dose adjustment of MAVIRET is required in adolescents 12 years and older. Using pharmacokinetic results from 47 adolescent patients (DORA – PART 1 (M16-123)), 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.

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 \leq 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 (\leq 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 (GLE) or Pibrentasvir (PIB) in the Presence of Coadministered Drug

Coadministered Drug	Regimen of Coadministered 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	GLE	0.33 (0.27, 0.41)	0.34 (0.28, 0.40)	--
				PIB	0.50 (0.42, 0.59)	0.49 (0.43, 0.55)	--
Rifampicin	600 (first dose)	300/120 single dose	12	GLE	6.52 (5.06, 8.41)	8.55 (7.01, 10.4)	--
				PIB	↔	↔	--
	600 once daily	300/120 single dose ^a	12	GLE	0.14 (0.11, 0.19)	0.12 (0.09, 0.15)	--

Coadministered Drug	Regimen of Coadministered Drug (mg)	Regimen of glecaprevir/pibrentasvir (mg)	N	DAA	Central Value Ratio (90% CI)		
					C _{max}	AUC	C _{min}
				PIB	0.17 (0.14, 0.20)	0.13 (0.11, 0.15)	--
Ciclosporin	100 single dose	300/120 once daily	12	GLE ^b	1.30 (0.95, 1.78)	1.37 (1.13, 1.66)	1.34 (1.12, 1.60)
				PIB	↔	↔	1.26 (1.15, 1.37)
	400 single dose	300/120 single dose	11	GLE	4.51 (3.63, 6.05)	5.08 (4.11, 6.29)	--
				PIB	↔	1.93 (1.78, 2.09)	--
Atazanavir (ATZ) + ritonavir (RTV)	ATZ 300 + RTV 100 once daily	300/120 once daily ^c	12	GLE	≥ 4.06 (3.15, 5.23)	≥ 6.53 (5.24, 8.14)	≥ 14.3 (9.85, 20.7)
				PIB	≥ 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	GLE	3.09 (2.26, 4.20)	4.97 (3.62, 6.84)	8.24 (4.40, 15.4)
				PIB	↔	↔	1.66 (1.25, 2.21)
Lopinavir / ritonavir	400/100 twice daily	300/120 once daily	9	GLE	2.55 (1.84, 3.52)	4.38 (3.02, 6.36)	18.6 (10.4, 33.5)
				PIB	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. 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.

^c. 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)	--
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)	--
Ethinylestradiol (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)
Ethinylestradiol	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, tocopherol, colloidal anhydrous silica, propylene glycol monocaprylate, croscarmellose sodium, sodium stearyl fumarate 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 containing a total of 84 film-coated tablets. 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.

MAVIRET is also available in a High Density Polyethylene (HDPE) bottle containing 84 film-tablets and a silica-gel desiccant enclosed with a child resistant closure.

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

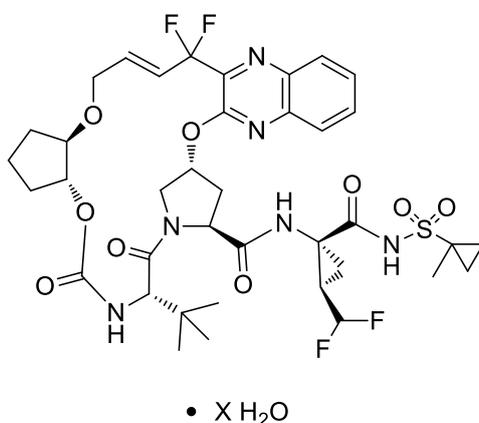
Chemical structure and CAS numbers

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 C₃₈H₄₆F₄N₆O₉S (anhydrate) and the molecular weight for the drug substance is 838.87 g/mol (anhydrate).

Glecaprevir has the following molecular structure:



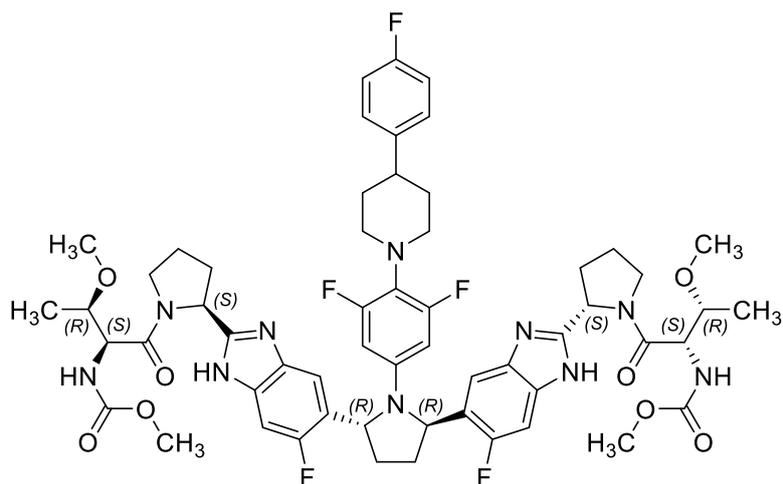
CAS Number: 1838571-99-5 (anhydrate)

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 C₅₇H₆₅F₅N₁₀O₈ 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

AbbVie Pty Ltd
241 O'Riordan Street
Mascot NSW 2020
AUSTRALIA
Tel: 1800 043 460

AbbVie Limited
6th Floor, 156-158 Victoria St
Wellington 6011
NEW ZEALAND

9 DATE OF FIRST APPROVAL

2 January 2018

10 DATE OF REVISION

19 March 2020

Section Changed	Summary of new information
4.1 Therapeutic indications	Addition of adolescent population following TGA approval on 18 December 2019 (Ref: PM-2018-05597-1-2).
4.2 Dose and method of administration	Addition of adolescent dosage following TGA approval on 18 December 2019 (Ref: PM-2018-05597-1-2).
	Update to information on paediatric use following TGA approval on 18 December 2019 (Ref: PM-2018-05597-1-2).
4.4 Special warnings and precautions for use	Addition of text regarding glucose metabolism under the heading "Potential Effects of HCV Clearance by Direct-Acting Antivirals (DAA) (Class Therapeutic Effect)" following approval by TGA 5 July 2019 (Ref: PM-2019-01630-1-2)
	Update to section regarding paediatric use following approval by TGA on 18 December 2019 (Ref: PM-2018-05597-1-2)
4.8 Adverse effects (Undesirable effects)	Update to headings to distinguish between adult and adolescent populations referenced in clinical studies
	Addition of data from studies conducted in the adolescent population following approval by TGA on 18 December 2019 (Ref: PM-2018-05597-1-2).
	Addition of post-marketing experience following approval by TGA on 18 December 2019 (Ref: PM-2018-05597-1-2).
5.1 Pharmacodynamic properties	Minor editorial change/correction under the heading "Studies in Patients with or without Cirrhosis who were TE to NS3/4A Protease and/or NS5A Inhibitors".
5.1 Pharmacodynamic properties; Clinical Studies	Additional summary detail on the percentage of female study participants in the information captured under the heading "Study in Patients with GT5 or GT6 Infection". This has been cross-referenced in the annotation to Modules 2.5, 2.7.3, and 5 (Study M16-126).
	Additional information on new clinical data from the trial in adolescents, and associated update to Table 8: <ul style="list-style-type: none"> DORA under the heading "Adolescent patients (12 to less than 18 years)" following approval by TGA on 18 December 2019 (Ref: PM-2018-05597-1-2).
	Update to headings to distinguish between adult and adolescent populations referenced in clinical studies following approval by TGA on 18 December 2019 (Ref: PM-2018-05597-1-2).
	Update to information on experience in paediatric patients following approval by TGA on 18 December 2019 (Ref: PM-2018-05597-1-2).
6.5 Nature and contents of container	Inclusion of the explanation of the total number of dosage units (84) in the monthly blister pack following approval by TGA on 13 January 2020 (Ref: PM-2019-04988-1-2).
	Addition of reference to a new DDPE bottle presentation following approval by TGA on 13 January 2020 (Ref: PM-2019-04988-1-2).