▼ 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 and granules

1 NAME OF THE MEDICINE

Glecaprevir and pibrentasvir

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

Tablets

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

Granules

MAVIRET granules in sachets are a fixed-dose combination product containing glecaprevir 50 mg and pibrentasvir 20 mg.

Both MAVIRET tablets and granules do not contain gluten. Both MAVIRET tablets and granules contain lactose.

For the full list of excipients, see 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Tablets

MAVIRET immediate release tablets are pink-coloured, film-coated, oblong biconvex shaped, and debossed with “NXT” on one side.

Granules

MAVIRET granules are available as pink granules (glecaprevir) and yellow granules (pibrentasvir). Both granules are round and biconvex.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MAVIRET is indicated for the treatment of adult and paediatric patients 3 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

Tables 1 and 2 provide the recommended MAVIRET treatment duration based on the patient population in HCV mono-infected and HCV/HIV-1 coinfected 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*	

***** A treatment duration of 12 weeks may be considered for patients with compensated cirrhosis at the discretion of the prescriber.

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

Patient Population	Treatment Duration	
	No Cirrhosis	Compensated Cirrhosis (Child Pugh A)
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

Recommended dosage of MAVIRET tablets in adults and adolescents 12 years and older or weighing at least 45 kg

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 at the same time with food (see 5.1 PHARMACODYNAMIC PROPERTIES). MAVIRET tablets should be swallowed whole and not chewed, crushed, or broken.

The treatment durations for adults and adolescents are noted in Tables 1 and 2.

Recommended dosage of MAVIRET granules in sachets in paediatric patients 3 years to less than 12 years (weighing 12 kg to less than 45 kg)

MAVIRET granules in sachets are a fixed-dose combination product containing glecaprevir 50 mg and pibrentasvir 20 mg in each sachet. The number of sachets and dosage based on body weight for paediatric patients 3 years to less than 12 years old and weighing 12 kg to less than 45 kg are shown in Table 3. The treatment durations for paediatric patients 3 years to less than 12 years old and weighing 12 kg to less than 45 kg are the same as those for adults and adolescents as noted in Tables 1 and 2 above.

Since the formulations have different pharmacokinetic profiles, the tablets and the granules are **not interchangeable**. A full course of treatment with the same formulation is therefore required.

Table 3. Recommended Dosage for Paediatric Patients 3 Years and Older Weighing Less Than 45 kg

Weight of child (kg)	Number of sachets once daily
≥ 12 to < 20 kg	3 sachets (150 mg/60 mg)
≥ 20 to < 30 kg	4 sachets (200 mg/80 mg)
≥ 30 to < 45 kg	5 sachets (250 mg/100 mg)

The adult and adolescent dose of MAVIRET tablets should be used in children weighing 45 kg or greater (see 'Recommended Dosage of MAVIRET Tablets in adults and adolescents 12 years and older or weighing at least 45 kg').

Preparation and Administration of Oral Granules in Sachets

- The sachets should be taken together, with food, once daily. In addition, the total daily dose of the granules should be sprinkled on a small amount of soft food with a low water content that will stick to a spoon and can be swallowed without chewing (e.g., peanut butter, chocolate hazelnut spread, cream cheese, thick jam, or Greek yogurt). Liquids or foods that would drip or slide off the spoon should not be used as the drug may dissolve quickly and become less effective.
- The mixture of food and granules should be swallowed immediately (within 15 minutes of preparation); the granules should not be crushed or chewed.

Note: Opened sachets with granules should be used immediately and not stored.

Refer to 'Instructions for Use' in the Consumer Medicine Information and Package Insert for further details on the preparation and administration of granules.

<u>Dosing in Special Populations</u>

Hepatic Impairment

No dose adjustment of MAVIRET is required in patients with mild hepatic impairment (Child-Pugh A). MAVIRET is contraindicated in patients with moderate and severe hepatic impairment (Child-Pugh B and C) (see 4.3 CONTRAINDICATIONS, 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Hepatic Decompensation and Hepatic Failure 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 (less than 3 years old)

The safety and effectiveness of MAVIRET in patients less than 3 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 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:

- 18 hours or less 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.

If vomiting occurs within 3 hours of dosing, an additional dose of MAVIRET should be taken. If vomiting occurs more than 3 hours after dosing, an additional dose of MAVIRET is not needed.

4.3 Contraindications

MAVIRET is contraindicated:

- In patients with moderate and severe hepatic impairment (Child-Pugh B and C) (see 5.2 PHARMACOKINETIC PROPERTIES – Pharmacokinetics, Specific Populations).
- With atazanavir-containing products, atorvastatin, simvastatin, dabigatran etexilate, ethinyloestradiol-containing products, and rifampicin (see 5.2 PHARMACOKINETIC PROPERTIES – Pharmacokinetics, Drug Interactions).
- In patients with hypersensitivity to the active substances or to any of the excipients.

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.

Hepatic Decompensation and Hepatic Failure

MAVIRET is contraindicated in patients with moderate and severe hepatic impairment (Child-Pugh B and C). There have been post-marketing case reports of hepatic decompensation and hepatic failure, including fatal outcomes, mostly in cirrhotic patients treated with HCV NS3/4A protease inhibitor-containing regimens, including MAVIRET. Because these events 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. In patients with compensated cirrhosis (Child-Pugh A) or evidence of advanced liver disease such as portal hypertension, perform laboratory testing as clinically indicated and monitor for signs and symptoms of hepatic decompensation such as the presence of jaundice, ascites, hepatic encephalopathy, and variceal haemorrhage. Discontinue MAVIRET in patients who develop evidence of hepatic decompensation/failure.

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

Coadministration 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 3 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 4 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). All interaction studies were performed in adults.

Table 4. 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 ↓ 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).

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 16 and Table 17		

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 registrational 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 5. 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 6).

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 5. 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 6. Adverse reactions reported in ≥ 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 coinfected 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 Paediatric Patients (3 years to less than 18 years old)

The safety of MAVIRET in HCV GT 1-6 infected adolescents is based on data from a Phase 2 and 3 open-label trial in 47 patients aged 12 years to less than 18 years treated with MAVIRET tablets for 8 to 16 weeks (DORA-Part 1).

The safety of MAVIRET in HCV GT1-6 infected children aged 3 years to less than 12 years is based on data from a Phase 2 and 3 open-label trial in 80 patients aged 3 years to less than 12 years treated with weight-based MAVIRET granules in sachets for 8 to 16 weeks (DORA-Part 2).

The adverse reactions observed in patients 3 years to less than 18 years old 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 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 7**.** EC_{50} values are determined in the absence of human plasma.

Table 7. 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 EC_{50} values of glecaprevir and pibrentasvir against chimeric replicons encoding NS3 or NS5A from clinical isolates are presented in Table 8**.**

Table 8. 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 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 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 the registrational Phase 2 and 3 clinical studies experienced virologic failure (two with GT1, 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 the 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 313 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, 77% (17/22) with A30K in NS5A at baseline achieved SVR12. Among GT3-infected patients with compensated cirrhosis receiving the recommended regimen, 100% (21/21) who had polymorphisms in NS5A at baseline achieved SVR12.

Cross-resistance

In vitro data indicate that the majority of the resistance-associated substitutions in NS5A at amino acid positions 24, 28, 30, 31, 58, 92, or 93 that confer resistance to ombitasvir, daclatasvir, ledipasvir, elbasvir, or velpatasvir remained susceptible to pibrentasvir. 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 9 summarises clinical studies conducted with MAVIRET in patients with HCV GT1, 2, 3, 4, 5 or 6 infection. For the recommended treatment duration see 4.2 DOSE AND METHOD OF ADMINISTRATION.

Table 9. Clinical Studies Conducted with MAVIRET in Patients with HCV GT1, 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	EXPEDITION-8 (M16-135)	MAVIRET for 8 weeks (n=343) (TN only)
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 coinfected 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 years to less than 18 years)		
GT 1-6	DORA – PART 1 (M16-123)	MAVIRET for 8 weeks (n=44) or 16 weeks (n=3)
Paediatric patients (3 years to less than 12 years)		
GT 1-6	DORA – PART 2 (M16-123)	MAVIRET for 8 (n=78), 12 (n=1), or 16 weeks (n=1)

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

* Treatment durations for some trial arms shown in this table do not reflect recommended dosing for the respective genotypes, prior treatment history, and/or cirrhosis status. Refer to Section 4.2 Dose and method of administration for recommended dosing in adults, adolescents and paediatric patients 3 years and older (weighing at least 12 kg)

[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 m^2; 7.7% had HIV-1 coinfection; and the median baseline HCV RNA level was 6.2 $\log_{10}$ IU/mL.

Patients with GT1, 2, 4, 5, or 6 Infection

The efficacy of MAVIRET in adult patients who were TN or PRS TE with GT1, 2, 4, 5 or 6 chronic hepatitis C infection was demonstrated in nine 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, EXPEDITION-4 and EXPEDITION-8.

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 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 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 who received MAVIRET for 12 weeks. EXPEDITION-8 was a single-arm, open-label study in TN subjects with compensated cirrhosis and genotype 1, 2, 3, 4, 5 or 6 infection who received MAVIRET for 8 weeks. EXPEDITION-2 was an open-label study in HCV GT1-6/HIV-1 coinfected 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 10. ENDURANCE-1[a], -2, -4, SURVEYOR-1, -2, and EXPEDITION-1, -2[a], -4 and -8: SVR12 in TN and PRS-TE Adults 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% (0/62)	0% (0/2)	0% (0/13)
Relapse[b]	0% (0/471)	1.0% (2/204)	0% (0/61)	0% (0/2)	0% (0/13)
Other[c]	0.6% (3/474)	1.0% (2/206)	4.8% (3/62)	0% (0/2)	10% (1/13)
SVR12 in Patients With Compensated Cirrhosis					
8 weeks[*]	97.8% (226/231)	100% (26/26)	100% (13/13)	100% (1/1)	100% (9/9)
12 weeks[**]	96.8% (30/31)	90.0% (9/10)	100% (8/8)	-	100% (1/1)
Outcome for patients without SVR12					
On-treatment VF	0% (0/262)	0% (0/36)	0% (0/21)	0% (0/1)	0% (0/10)
Relapse[b]	0.4% (1/256)	0% (0/35)	0% (0/20)	0% (0/1)	0% (0/10)
Other[c]	1.9% (5/262)	2.8% (1/36)	0% (0/21)	0% (0/1)	0% (0/10)

[a.] Includes a total of 132 patients co-infected with HIV-1 from ENDURANCE-1 or EXPEDITION-2 who received the recommended duration.

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

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

[*] In TN patients

[**] In PRS-TE patients

Of the GT1, 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 GT1, 2, 4, 5, or 6 Infection with compensated cirrhosis who received 8 weeks of MAVIRET

The safety and efficacy of MAVIRET given for 8 weeks in GT 1, 2, 4, 5 or 6 TN subjects with compensated cirrhosis was evaluated in a single-arm, open-label study (EXPEDITION-8).

Of the 280 subjects treated, the median age was 60 years (range: 34 to 88); 81.8% had HCV genotype 1, 10% had HCV genotype 2, 4.6% had HCV genotype 4, 0.4% had HCV genotype 5; 3.2% had HCV genotype 6; 60% were male; 9.6% were Black.

The overall SVR12 rate was 98.2% (275/280). There were 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 adults 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 adult patients with GT3 chronic hepatitis C infection was demonstrated in the ENDURANCE-3 (TN without cirrhosis), EXPEDITION-8 (TN with compensated cirrhosis) and SURVEYOR-2 Part 3 (PRS-TE patients 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 GT3-infected 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. EXPEDITION-8 was a single-arm, open-label study in TN subjects with compensated cirrhosis and GT1, 2, 3, 4, 5 or 6 infection who received MAVIRET for 8 weeks. SURVEYOR-2 Part 3 was an open-label study that evaluated the efficacy of MAVIRET in PRS-TE GT3-infected patients without cirrhosis and with compensated cirrhosis for 16-weeks. Among PRS-TE patients, 46% (42/91) failed a previous regimen containing sofosbuvir.

Table 11. ENDURANCE-3: SVR12 in TN, GT3-Infected Adult 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 ≥ 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 12. SURVEYOR-2 Part 3 and EXPEDITION-8: SVR12 in GT3-Infected Adult Patients with or without Compensated Cirrhosis who Received the Recommended Duration

	TN with Cirrhosis	**PRS-TE with Cirrhosis**	**PRS-TE without Cirrhosis**
	MAVIRET	**MAVIRET**	**MAVIRET**

	8 weeks (n=63)	16 weeks (n=47)	16 weeks (n=22)
SVR	95.2% (60/63)	95.7% (45/47)	95.5% (21/22)
Outcome for patients without SVR12			
On-treatment VF	0% (0/63)	2.1% (1/47)	0% (0/22)
Relapse[a]	1.6% (1/62)	2.2% (1/46)	4.5% (1/22)
Other[b]	3.2% (2/63)	0% (0/47)	0% (0/22)

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

b. Includes patients who discontinued due to adverse 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 a few countries in South and Southeast Asia, but rarely outside of this region. Studies VOYAGE-1 and VOYAGE-2 were conducted in China, Singapore, and South Korea in HCV GT1-6 adult 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 Compensated 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% (1395/1431) achieved SVR12 overall, while 0.2% (3/1431) experienced on-treatment virologic failure and 0.9% (12/1407) 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 patients with compensated cirrhosis who received the recommended duration, 97.1% (431/444) achieved SVR12 (among which 97.7% [335/343] of TN patients achieved SVR12), while 0.2% (1/444) experienced on-treatment virologic failure and 0.9% (4/434) experienced post-treatment relapse.

The presence of HIV-1 coinfection did not impact efficacy. In a dedicated HIV-1 coinfection study (EXPEDITION-2), the SVR12 rate in HCV/HIV-1 coinfected 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 coinfected 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 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 13.

Table 13. MAGELLAN-1 Part 2: SVR12 in NS5A Inhibitor-Experienced Adult 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 ≥ LLOQ after end-of-treatment response among those who completed treatment.

Lower SVR12 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 adult 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 coadministration were ciclosporin ≤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 Paediatric Patients (3 years to less than 18 years old and weighing at least 12 kg)

DORA (Part 1 and Part 2) was an open-label study to evaluate the safety and efficacy of MAVIRET in paediatric patients aged 3 years to less than 18 years old.

DORA Part 1 evaluated the safety and efficacy in 47 adolescent patients aged 12 to less than 18 years who received MAVIRET tablets for 8 or 16 weeks. Treatment duration was chosen to match approved adult durations based on HCV genotype and prior treatment experience.

The median age was 14 years (range: 12 to 17); the mean weight was 59 kg (range: 32 to 109 kg); 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 overall SVR12 rate was 100% (47/47). No subject experienced virologic failure.

DORA Part 2 evaluated the safety and efficacy in 80 paediatric patients aged 3 years to less than 12 years who received weight-based MAVIRET granules in sachets for 8, 12 or 16 weeks. 18 patients received the initial lower dose, and 62 patients received the final recommended dose. The median age was 7 years (range: 3 to 11); the mean weight was 26 kg (range: 13 to 44); 73% had HCV genotype 1, 3% had genotype 2, 23% had HCV genotype 3, 3% had HCV genotype 4; 55% were female; 6% were Black; 97.5% were HCV TN; 3% were treatment-experienced to interferon; 1% had HIV-coinfection; none had cirrhosis.

The overall SVR12 rate for the patients who received the final recommended dose ratio was 98.4% (61/62). No patient taking the final recommended dose ratio experienced virologic failure.

Durability of Sustained Virologic Response

In a long-term follow-up study (M13-576), 99.5% (374/376) of adult subjects who had achieved SVR12 in prior clinical studies of MAVIRET maintained SVR up to their last follow-up visit (median duration of follow-up: 35.5 months), including all 87 subjects who had been treated with an 8-week regimen of MAVIRET. Two subjects who previously achieved SVR12 in a prior study, did not maintain SVR: 1 subject experienced a late relapse 390 days after 12 weeks of MAVIRET therapy, while the other subject experienced reinfection with a different HCV genotype 191 days after 16 weeks of MAVIRET therapy.

SVR4 and SVR12 Concordance

The concordance of SVR4 (defined as HCV RNA less than LLOQ at 4 weeks after the cessation of treatment) and SVR12 is based on data from Phase 2 and 3 trials of 2855 adults and adolescents who were assigned to receive the label-recommended dose and duration of MAVIRET, in which 2549, 216, and 90 subjects received MAVIRET for 8, 12, and 16 weeks, respectively. The median age was 54 years (range: 12 to 88); 1.6% were 12 to less than 18 years of age; 54.9% were male; 5.3% were Black; 78.2% were HCV TN; 17.8%

had compensated cirrhosis; 5.4% had HIV coinfection; 26.9% had a history of injection drug use; and 92.2% were compliant with MAVIRET treatment.

A high concordance of SVR4 and SVR12 was demonstrated. The SVR4 and SVR12 rates were 99.0% (2827/2855) and 98.8% (2821/2855), respectively.

The data demonstrated a positive predictive value of 99.8% i.e., 99.8% (2821/2827) of subjects who achieved SVR4, also achieved SVR12; and a negative predictive value of 100% i.e., 100% (28/28) of subjects who did not achieve SVR4 did not achieve SVR12.

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 14. The steady-state pharmacokinetic parameters of glecaprevir and pibrentasvir in HCV-infected patients without cirrhosis are provided in Table 15**.**

Table 14. Pharmacokinetic Properties of the Components of MAVIRET in Healthy Subjects

	Glecaprevir	**Pibrentasvir**
Absorption		
T_{max} (h)[a] of tablets	5.0	5.0
T_{max} (h)[a] of granules	3.0	5.0
Effect of meal (relative to fasting)[b] on tablets	↑ 83-163%	↑ 40-53%
Effect of meal (relative to fasting)[b] on granules	↑ 131-167%	↑ 56-114%
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 15. 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

No dose adjustment of MAVIRET is recommended based on gender.

Paediatric Patients

No dose adjustment of MAVIRET is required in adolescents 12 years and older.

Paediatric patients aged 3 years to less than 12 years of age should receive doses based on body weight (see 4.2 Dose and method of administration - Recommended Dosage of MAVIRET Granules in Sachets in Paediatric Patients 3 Years and Older (Weighing 12 kg to less than 45 kg)). At the recommended doses according to body weight, exposures of glecaprevir and pibrentasvir in children aged 3 to < 12 years fell within the observed efficacious exposure range in adults from Phase 2 and 3 studies.

The pharmacokinetics of glecaprevir and pibrentasvir have not been established in children less than 3 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 ≤ 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 16 and 17 summarise the pharmacokinetic effects when glecaprevir / pibrentasvir was coadministered with other drugs which showed potentially clinically relevant changes.

Table 16. 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	↔	↔	--
Rifampicin	600 once daily	300/120 single dose[a]	12	GLE	0.14 (0.11, 0.19)	0.12 (0.09, 0.15)	--
				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)

Coadministered Drug	Regimen of Coadministered Drug (mg)	Regimen of glecaprevir / pibrentasvir (mg)	N	DAA	Central Value Ratio (90% CI)		
					C_{max}	AUC	C_{min}
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 17. 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	11	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	11	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)	--

Coadministered Drug	Regimen of Coadministered Drug (mg)	Regimen of glecaprevir / pibrentasvir (mg)	N	Central Value Ratio (90% CI)		
				C_{max}	AUC	C_{min}
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

Tablets

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).

Granules

Both granules also contain copovidone, tocofersolan, colloidal anhydrous silica and sodium stearylfumarate. Glecaprevir granules also contains croscarmellose sodium and Opadry II 32F240023 pink (hypromellose 2910, lactose monohydrate, titanium dioxide, macrogol 3350, iron oxide red). Pibrentasvir granules also contains propylene glycol monocaprylate and Opadry II 32F220006 yellow (hypromellose 2910, lactose monohydrate, titanium dioxide, macrogol 3350, iron oxide yellow).

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

Tablets

Store below 30°C.

Granules

Store below 30°C.

Note: Opened sachets with granules should be used immediately and not stored.

6.5 Nature and contents of container

Tablets

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-coated tablets and a silica-gel desiccant enclosed with a child resistant closure.

Granules

MAVIRET granules are available in PET/Al/PE sachets inside cartons. Each carton containing a total of 28 sachets.

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

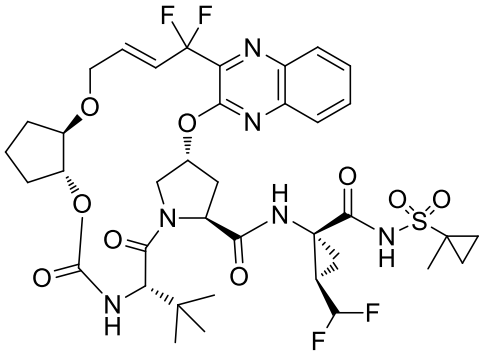
Chemical structure and CAS numbers

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

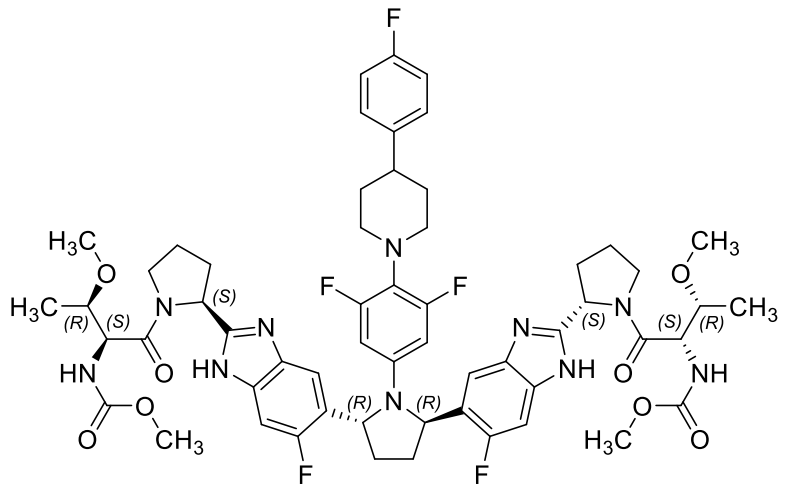
CAS Number: 1838571-99-5 (anhydrate)

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

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

9 November 2023

Section Changed	Summary of new information
5.1	Addition of SVR4 and SVR12 concordance data.