PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrMAVIRET™

glecaprevir/pibrentasvir
tablets (100/40 mg)

Antiviral Agent

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Table of Contents

MAVIRET™

glecaprevir/pibrentasvir

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Non-medicinal Ingredients
oral	glecaprevir/pibrentasvir tablet 100/40 mg	lactose monohydrate

For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

INDICATIONS AND CLINICAL USE

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

The following point should be considered when initiating treatment with MAVIRET:

MAVIRET treatment should be initiated and monitored by a physician experienced in the management of patients with HCV infection.

Geriatrics (> 65 years of age)

In clinical studies of MAVIRET, 328 patients were age 65 and over and 47 were age 75 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 (see **DOSAGE AND ADMINISTRATION, Special Populations, Geriatrics [> 65 years of age]**).

Pediatrics (< 18 years of age)

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

CONTRAINDICATIONS

- In patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

- In patients with severe hepatic impairment (Child-Pugh C) as the safety and efficacy have not been established (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**, **Hepatic Impairment**).

Table 1. Drugs that Are Contraindicated with MAVIRET

Drug Class/Drug Name	Effect on Concentration	Mechanism of Action	Clinical Comment
ANTICOAGULANTS			
dabigatran etexilate	↑ dabigatran	Inhibition of P-gp by MAVIRET	Coadministration with MAVIRET increased dabigatran concentrations and may increase the risk of bleeding.
ANTIMYCOBACTERIAL			
rifampin	↓ glecaprevir ↓ pibrentasvir	Induction of P-gp, BCRP, and CYP3A by rifampin	Coadministration may significantly decrease concentrations of glecaprevir and pibrentasvir, and lead to loss of therapeutic effect of MAVIRET.
ANTIVIRAL			
atazanavir	↑ glecaprevir ↑ pibrentasvir	Unknown	Risk of ALT elevations when coadministered with MAVIRET.
ETHINYL ESTRADIOL-CONTAINING PRODUCTS			
ethinyl estradiol	↑ ethinyl estradiol	Unknown	Risk of ALT elevations when coadministered with MAVIRET.
HMG-CoA REDUCTASE INHIBITORS			
atorvastatin	↑ atorvastatin	Inhibition of OATP1B1/3, BCRP, P-gp and CYP3A by MAVIRET	Coadministration with MAVIRET increased atorvastatin concentrations and may increase the potential for statin-related myopathy including rhabdomyolysis.
simvastatin	↑ simvastatin	Inhibition of OATP1B1/3 by MAVIRET	Coadministration with MAVIRET increased simvastatin concentrations and may increase the potential for statin-related myopathy including rhabdomyolysis.

See the **DRUG INTERACTION** section.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Potential for Hepatitis B virus (HBV) reactivation: Screen all patients for evidence of current or prior HBV infection before initiating MAVIRET therapy. Cases of HBV reactivation, including those resulting in fulminant hepatitis, hepatic failure, and death, have been reported during HCV treatment and/or post-treatment with regimens containing direct-acting HCV antivirals (DAAs) in patients co-infected with HBV. (See **WARNINGS AND PRECAUTIONS**, **Risk of Hepatitis B Virus Reactivation**)

General

MAVIRET should not be co-administered with other medicinal products containing NS3/4A protease and NS5A inhibitors.

The number of patients infected with GT-5 and GT-6 were limited.

Use with Potent P-gp and CYP3A4 Inducers

Medicinal products that are potent P-glycoprotein (P-gp) and CYP3A4 inducers (e.g. carbamazepine, efavirenz, St. John's Wort, phenobarbital, and phenytoin) significantly decrease the plasma concentration of glecaprevir and pibrentasvir, which may lead to reduced therapeutic effect of MAVIRET or loss of virologic response. These drugs are not recommended with MAVIRET (see **DRUG INTERACTIONS**).

Hepatic/Biliary/Pancreatic

Hepatic Impairment

MAVIRET is not recommended in patients with moderate hepatic impairment (Child-Pugh B). MAVIRET is contraindicated in patients with severe hepatic impairment (Child-Pugh C) (see **CONTRAINDICATIONS**).

Risk of Hepatitis B Virus Reactivation

Cases of hepatitis B virus (HBV) reactivation, including those resulting in fulminant hepatitis, hepatic failure, and death have been reported in HCV/HBV–coinfected patients who were undergoing, or completed treatment with DAA. To decrease the risk of HBV reactivation in patients co-infected with HBV, HBV screening should be performed in all patients prior to initiation of HCV treatment. Patients with positive HBV serology (HBsAg positive) and patients with serologic evidence of resolved HBV infection (i.e. HBsAg negative and anti-HBc positive) should be monitored and treated according to current clinical practice guidelines to manage

potential for HBV reactivation (see **WARNINGS AND PRECAUTIONS**, **Monitoring and Laboratory Tests in Patients Coinfected with HBV**).

Liver Transplant Patients

The safety and efficacy of MAVIRET in post-liver transplant patients have not been established.

Sexual Function/Reproduction

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

Lactose Intolerance

MAVIRET contains lactose. This medicine is not recommended for patients with rare hereditary problems of galactose intolerance (severe lactase deficiency or glucose-galactose malabsorption).

Special Populations

HCV/HBV Co-infection

The safety and efficacy of MAVIRET have not been established in HCV patients co-infected with HBV.

HCV/HIV Co-infection

The safety and efficacy of MAVIRET has not been fully established in HCV patients co-infected with Human Immunodeficiency Virus (HIV) (see **CLINICAL TRIALS**).

Pregnant Women

Pregnancy should be avoided while taking MAVIRET as there are no data on the use of MAVIRET in pregnant women. As a precautionary measure, MAVIRET use is not recommended in pregnancy unless the potential benefit justifies the potential risk to the fetus. Patients should be advised to notify their health care provider immediately in the event of a pregnancy.

In animal reproduction studies, no adverse developmental effects were observed when the components of MAVIRET were administered separately during organogenesis at exposures up to 53 and 0.07 times (rats and rabbits, respectively; glecaprevir) or 51 and 1.5 times (mice and rabbits, respectively; pibrentasvir) higher than the human exposures at the recommended dose of MAVIRET. Maternal toxicity in the rabbit precluded evaluation of glecaprevir at clinical exposures. There were no effects with either compound in rodent peri/postnatal developmental studies in which maternal systemic exposures (AUC) to glecaprevir and pibrentasvir were

approximately 47 and 74 times higher, respectively, than the exposure in humans at the recommended dose.

Nursing Women

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. 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.

Patients Treated with Vitamin K Antagonist

As liver function may change during treatment with MAVIRET, a close monitoring of International Normalised Ratio (INR) is recommended.

Monitoring and Laboratory Tests in Patients Coinfected with HBV

Clearance of HCV may lead to increased replication of HBV in patients who are HCV/HBV coinfected. Co-infected patients with HBV should be monitored for clinical and laboratory signs (e.g. HBsAg, anti-HBc, HBV DNA, serum aminotransferase levels, bilirubin) for hepatitis flare or HBV reactivation during and at post-treatment follow-up as clinically appropriate (see **WARNINGS AND PRECAUTIONS**, **Risk of Hepatitis B Virus Reactivation**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety assessment for MAVIRET in patients with compensated liver disease (with or without cirrhosis) were derived from pooled Phase 2 and 3 studies which evaluated approximately 2,300 patients infected with genotype 1, 2, 3, 4, 5, or 6 HCV who received MAVIRET for 8, 12 or 16 weeks.

MAVIRET was generally well-tolerated and the overall proportion of patients who permanently discontinued treatment due to adverse reactions was 0.1% for patients 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.

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 cirrhosis were comparable to those seen in patients without cirrhosis.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse reactions observed in greater than or equal to 3% of patients receiving 8, 12, or 16 weeks of treatment with MAVIRET are presented in **Table 2**. The most common adverse reactions were headache and fatigue in patients treated with MAVIRET overall. In patients receiving MAVIRET who experienced adverse reactions, 80% had an adverse reaction of mild severity (Grade 1), 19% had an adverse reaction of moderate severity (Grade 2), <1% had an adverse reaction of severe severity (Grade 3), and no subject had a Grade 4 or 5 adverse reaction. In the placebo-controlled study (ENDURANCE-2), 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 for 12 weeks compared to patients treated with MAVIRET for 12 weeks. The rate of discontinuation due to ADRs was similar for MAVIRET (1.3%) and for sofosbuvir and daclatasvir (0.9%).

Table 2. Adverse Reactions (All Grades) Observed in ≥ 3.0% of the Patients in Phase 2, 3 Clinical Studies.

SOC Preferred Term	MAVIRET[a] GT-1, -2, -4, -5 - 6 8, 12 weeks N=1,520 n (%)	MAVIRET[b] GT-3 8, 12, 16 weeks N=632 n (%)	MAVIRET[c] PI or NS5A-I Experienced 12, 16 weeks N=113 n (%)	MAVIRET[d] Overall N=2,265 n (%)
Nervous System Disorders				
Headache	171 (11.3)	106 (16.8)	21 (18.6)	298 (13.2)
General Disorders and Administration Site Conditions				
Fatigue	158 (10.4)	92 (14.6)	9 (8.0)	259 (11.4)
Gastrointestinal Disorders				
Nausea	105 (6.9)	57 (9.0)	10 (8.8)	172 (7.6)
Diarrhea	44 (2.9)	38 (6.0)	4 (3.5)	86 (3.8)
Skin and Subcutaneous Tissue Disorders				
Pruritus	61 (4.0)	12 (3.0)	2 (1.8)	75 (3.3)

a. ADRs observed in registrational clinical studies (M14-867, M14-868, M13-590, M15-464, M15-172, M13-583) for GT-1, -2, -4, -5 or -6 with or without compensated cirrhosis.
b. ADRs observed in registrational studies M14-868 and M13-594 for GT-3 with or without compensated cirrhosis.
c. ADRs observed in registrational study M15-410 for PI and/or NS5A-I experienced patients with or without cirrhosis with GT-1 or -4.
d. Total ADRs observed across all groups TN, TE-PRS or PI and/or NS5A-I experienced and GT1 to 6 with or without cirrhosis.

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

The safety of MAVIRET in patients with chronic kidney disease (Stage 4 or Stage 5 including patients on dialysis) and genotypes 1, 2, 3, 4, 5 or 6 chronic HCV infection with compensated liver disease (with or without 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 3% of patients receiving 12 weeks of treatment with MAVIRET are presented in **Table 3**. In patients treated with MAVIRET who reported an adverse reaction, 55% had adverse reactions of mild severity, 35% had a severity of Grade 2, and 10% had a severity of Grade 3. No patients experienced a serious adverse reaction. The proportion of patients who permanently discontinued treatment due to adverse reactions was 1.9%.

Table 3. Adverse Reactions (All Grades) Observed in ≥ 3% of the Patients with Severe Renal Impairment Including Patients on Dialysis (EXPEDITION-4)

SOC Preferred Term	MAVIRET 12 weeks N = 104
Skin and Subcutaneous Tissue Disorders	
Pruritus	17.3%
General Disorders and Administration Site Conditions	
Fatigue	11.5%
Asthenia	6.7%
Gastrointestinal Disorders	
Nausea	8.7%
Diarrhea	3.8%
Gastroesophageal Reflux Disease	3.8%
Nervous System Disorders	
Headache	5.8%
Dizziness	3.8%
Psychiatric Disorders	
Insomnia	3.8%

Abnormal Hematological and Clinical Chemistry Findings

Serum Bilirubin Elevations

Elevations in total bilirubin of at least 2x 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, mostly in patients with pre-existing elevated bilirubin (consistent with Gilbert's Syndrome), and not associated with ALT elevations.

Post-Market Adverse Drug Reactions

The post-marketing adverse drug reactions are not yet available for MAVIRET.

DRUG INTERACTIONS

Drug-Drug Interactions

All drug-drug interaction studies were performed with the glecaprevir and pibrentasvir combination in non-HCV infected subjects.

Potential for MAVIRET to Affect Other Drugs

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

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. Co-administration of MAVIRET with medicinal products that inhibit P-gp and BCRP expressed in the intestine is unlikely to affect glecaprevir or pibrentasvir concentrations, but inhibition of P-gp and BCRP in the liver may slow elimination of glecaprevir and pibrentasvir. Medicinal products that inhibit OATP1B1/3 may increase systemic concentrations of glecaprevir, but total liver exposure of glecaprevir is unaffected.

Coadministration of MAVIRET with drugs that are strong inducers of P-gp/CYP3A may significantly decrease glecaprevir and pibrentasvir plasma concentrations (see **WARNINGS AND PRECAUTIONS**).

Table 4 provides the effect of coadministration of MAVIRET on concentrations of concomitant drugs and the effect of concomitant drugs on glecaprevir and pibrentasvir. Coadministration of MAVIRET with atorvastatin, atazanavir, dabigatran etexilate, ethinyl estradiol-containing products, rifampin and simvastatin are contraindicated (see also **CONTRAINDICATIONS**).

Table 4. Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[a,b]	Clinical Comments
ANTIARRHYTMICS		
digoxin	↑ digoxin	Concomitant administration of MAVIRET with digoxin leads to increases in the concentration of digoxin. Caution is warranted and a 50% dose reduction of digoxin is recommended when coadministered with MAVIRET.
ANTICONVULSANTS		
carbamazepine	↓ glecaprevir ↓ pibrentasvir	Coadministration may lead to reduced therapeutic effect of MAVIRET and is not recommended.
HERBAL PRODUCTS		
St. John's Wort (*Hypericum perforatum*)	↓ glecaprevir ↓ pibrentasvir	It is expected that coadministration may lead to reduced therapeutic effect of MAVIRET and is not recommended.
HCV-ANTIVIRAL AGENTS		
sofosbuvir	↑ sofosbuvir ↔ GS-331007	Coadministration with MAVIRET increases sofosbuvir concentrations, but does not affect GS-331007. No dose adjustment is required.
HIV-ANTIVIRAL AGENTS		
darunavir + ritonavir lopinavir/ritonavir	↑ glecaprevir ↑ pibrentasvir	Coadministration with MAVIRET significantly increased glecaprevir and pibrentasvir concentrations and is not recommended.
efavirenz[c]	↓ glecaprevir ↓ pibrentasvir	Coadministration with efavirenz containing regimens may lead to reduced therapeutic effect of MAVIRET and is not recommended.
rilpivirine	↑ rilpivirine	Coadministration with MAVIRET may lead to increased rilpivirine exposure but no dose adjustment is necessary. Caution should be used when these drugs are coadministered (see rilpivirine Product Monograph).
tenofovir alafenamide[d]	↔tenofovir	No dose adjustment is required.
tenofovir disoproxil fumarate[c]	↑ tenofovir	No dose adjustment is required.
HMG-COA REDUCTASE INHIBITORS		
lovastatin pravastatin rosuvastatin	↑ lovastatin ↑ pravastatin ↑ rosuvastatin	Coadministration with MAVIRET may increase the concentration of HMG-CoA reductase inhibitors which is associated with myopathy, including rhabdomyolysis. Coadministration of lovastatin with the MAVIRET is not recommended. Pravastatin dose should be reduced by 50% when co-

		administered with MAVIRET. Coadministration of rosuvastatin at a dose not exceeding 5 mg may be used with MAVIRET
IMMUNOSUPPRESSANTS		
cyclosporine	↑ glecaprevir ↑ pibrentasvir	MAVIRET is not recommended for use in patients requiring stable cyclosporine doses > 100 mg per day. Cyclosporine concentrations are not affected by MAVIRET.
tacrolimus	↑ tacrolimus	The combination of MAVIRET with tacrolimus should be used with caution. Increase of tacrolimus exposure is expected. Therefore, therapeutic drug monitoring of tacrolimus is recommended and a dose adjustment of tacrolimus made accordingly.
PROTON PUMP INHIBITORS		
omeprazole	↓ glecaprevir ↔ pibrentasvir	Increased gastric pH may reduce absorption of glecaprevir, but is not expected to have a clinically significant effect on the efficacy of MAVIRET. No dose adjustment is required.
VITAMIN K ANTAGONISTS		
vitamin K antagonists	Not studied	Close monitoring of INR is recommended with all vitamin K antagonists. This is due to liver function changes during treatment with MAVIRET.

↑= increase; ↓= decrease; ↔= no effect

See also **DRUG INTERACTIONS Table 5** and **Table 6.**

a. Digoxin, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, lovastatin, pravastatin, rosuvastatin, rilpivirine, sofosbuvir, and tacrolimus did not lead to clinically significant changes in glecaprevir or pibrentasvir concentrations when coadministered with MAVIRET.

b. Coadministration with MAVIRET did not lead to clinically significant changes in carbamazepine, cobicistat, cyclosporine, darunavir, efavirenz, elvitegravir, emtricitabine, lopinavir, omeprazole or ritonavir, concentrations.

c. Interaction studied with the efavirenz/emtricitabine/tenofovir disoproxil fumarate combination.

d. Interaction studied with the elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide combination.

Assessment of Drug Interactions

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, norethindrone or other progestin-only contraceptives, omeprazole, raltegravir, sofosbuvir, tenofovir alafenamide, tenofovir disoproxil fumarate, tolbutamide, and valsartan.

Pharmacokinetic Parameters for Clinically Relevant 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. **Table 5** and **Table 6** summarize the pharmacokinetic effects when glecaprevir/pibrentasvir was coadministered with other drugs which showed potentially clinically relevant changes.

Table 5. Drug Interactions: Changes in Pharmacokinetic Parameters of Glecaprevir (GLE) or Pibrentasvir (PIB) in the Presence of Co-administered Drug

Co-administered Drug	Regimen of Co-administered Drug (mg)	Regimen of GLE/PIB (mg)	N	DAA	Central Value Ratio (90% CI)		
					C_{max}	AUC	C_{min}
ANTICONVULSANTS							
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)	--
ANTIMYCOBACTERIAL							
rifampin	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)	--
				PIB	0.17 (0.14, 0.20)	0.13 (0.11, 0.15)	--
HIV-ANTIVIRAL AGENTS							
atazanavir (ATZ) + ritonavir (rtv)	ATZ 300 + rtv 300 once daily	300/120 once daily[b]	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 (LPV)/rtv	LPV 400 + rtv 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)
IMMUNOSUPPRESSANTS							
cyclosporine	100 single dose	300/120 once daily	12	GLE	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	300/120	11	GLE	4.51	5.08	--

Co-administered Drug	Regimen of Co-administered Drug (mg)	Regimen of GLE/PIB (mg)	N	DAA	Central Value Ratio (90% CI)		
					C_{max}	AUC	C_{min}
	dose	single dose			(3.63, 6.05)	(4.11, 6.29)	
				PIB	↔	1.93 (1.78, 2.09)	--
PROTON PUMP INHIBITORS							
omeprazole	20 once daily	300/120 single dose	9	GLE	0.78 (0.60, 1.00)	0.71 (0.58, 0.86)	--
				PIB	↔	↔	--
	40 once daily	300/120 single dose	12	GLE	0.36 (0.21, 0.59)	0.49 (0.35, 0.68)	--
				PIB	↔	↔	--

DAA=direct acting antiviral

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

a. Effect of rifampin on glecaprevir and pibrentasvir 24 hours after final rifampin dose.

b. Effect of atazanavir and ritonavir on the first dose of glecaprevir and pibrentasvir is reported.

Table 6. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Combination of Glecaprevir/Pibrentasvir (GLE/PIB)

Coadministered Drug	Regimen of Coadministered Drug (mg)	Regimen of GLE/PIB (mg)	N	Central Value Ratio (90% CI)		
				C_{max}	AUC	C_{min}
ANTIARRHYTHMICS						
digoxin	0.5 single dose	400/120 once daily	12	1.72 (1.45, 2.04)	1.48 (1.40, 1.57)	--
ANTICOAGULANTS						
dabigatran etexilate	dabigatran etexilate 150 single dose	300/120 once daily	11	2.05 (1.72, 2.44)	2.38 (2.11, 2.70)	--
CONTRACEPTIVES						
ethinyl estradiol (EE)	EE/norgestimate 35 mcg/ 250 mcg 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)
norgestromin				↔	1.44 (1.34, 1.54)	1.45 (1.33, 1.58)
ethinyl estradiol	EE/levonorgestrel 20 mcg/ 100 mcg 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)
HCV-ANTIVIRAL AGENTS						
sofosbuvir	sofosbuvir 400 once daily	400/120 mg once daily	8	1.66 (1.23, 2.22)	2.25 (1.86, 2.72)	--
GS-331007 (metabolite)			8	↔	↔	1.85 (1.67, 2.04)
HIV-ANTIVIRAL AGENTS						
rilpivirine	25 once daily	300/120 once daily	12	2.05 (1.73, 2.43)	1.84 (1.72, 1.98)	1.77 (1.59, 1.96)
tenofovir alafenamide (TAF)	EVG/COBI/ FTC/TAF 150/150/ 200/10 once daily	300/120 once daily	11	↔	↔	↔
tenofovir disoproxil fumarate (TDF)	EFV/FTC/ TDF 600/200 /300 once	300/120 once daily	12	↔	1.29 (1.23, 1.35)	1.38 (1.31, 1.46)

Coadministered Drug	Regimen of Coadministered Drug (mg)	Regimen of GLE/PIB (mg)	N	Central Value Ratio (90% CI)		
				C_{max}	AUC	C_{min}
	daily					
HMG CoA REDUCTASE INHIBITORS						
atorvastatin	10 once daily	400/120 once daily	11	22.0 (16.4, 29.5)	8.28 (6.06, 11.3)	--
lovastatin	10 once daily	300/120 once daily	12	↔	1.70 (1.40, 2.06)	--
lovastatin acid (metabolite)				5.73 (4.65, 7.07)	4.10 (3.45, 4.87)	--
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)	--
simvastatin	5 once daily	300/120 once daily	12	1.99 (1.60, 2.48)	2.32 (1.93, 2.79)	--
simvastatin acid (metabolite)				10.7 (7.88, 14.6)	4.48 (3.11, 6.46)	--
IMMUNOSUPPRESSANTS						
tacrolimus	1 single dose	300/120 once daily	10	1.50 (1.24, 1.82)	1.45 (1.24, 1.70)	--

↔ = No change (central value ratio 0.80 to 1.25) COBI = cobicistat; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine

Drug-Food Interactions

Food increases the bioavailability of MAVIRET (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment** and **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Drug-Herb Interactions

Coadministration of St. John's Wort *(Hypericum perforatum)*, may lead to reduced therapeutic effect of MAVIRET and is not recommended (see **DRUG INTERACTIONS, Table 4**).

Drug-Laboratory Interactions

Interactions of MAVIRET with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- MAVIRET is glecaprevir and pibrentasvir fixed-dose combination tablets.
- Treatment durations depend on HCV genotype, cirrhosis status, and treatment history.
- Screen all patients for evidence of current or prior HBV infection by measuring HbsAg and anti-HBc before initiating treatment for HCV with MAVIRET (see **WARNINGS AND PRECAUTIONS**).
- MAVIRET tablets should be swallowed whole and not chewed, crushed, or broken.

Recommended Dose and Dosage Adjustment

The recommended oral dose of MAVIRET is three fixed-dose combination glecaprevir/pibrentasvir 100/40 mg tablets administered once daily with food without regard to fat or calorie content (see **ACTION AND CLINICAL PHARMACOLOGY**). No dose adjustment is possible.

Table 7 and **Table 8** provide the recommended MAVIRET treatment duration based on the patient population in HCV mono-infected and HCV/HIV-1 co-infected patients with compensated liver disease (with or without cirrhosis) and with or without renal impairment including patients receiving dialysis.

Table 7. Recommended MAVIRET Treatment Duration for Treatment-Naive Patients Infected by Genotypes 1 to 6

HCV Genotype	Treatment Duration	
	Without Cirrhosis	With Cirrhosis
GT-1, -2, -3, -4, -5 or -6	8 Weeks	12 Weeks

GT= genotype

Table 8. Recommended MAVIRET Treatment Duration for Treatment-Experienced Patients Infected by Genotypes 1 to 6

HCV Genotype	Treatment History	Treatment Duration	
		Without Cirrhosis	With Cirrhosis
GT-1, -2, -4, -5, or -6	PRS[a]	8 Weeks	12 Weeks
GT-1	NS3/4A PI[b] (NS5A inhibitor-naïve)	12 Weeks	
GT-1	NS5A[c] (NS3/4A inhibitor-naïve)	16 Weeks	
GT-3	PRS[a]	16 Weeks	

GT = genotype; PI = protease inhibitor; PR = peginterferon/ribavirin; PRS = peginterferon/ribavirin + sofosbuvir; SMV = simeprevir; TRV = telapevir; BOC = boceprevir; DCV = daclatasvir; LDV = ledipasvir; SOF = sofosbuvir.

a. Experienced with regimens containing interferon, peginterferon, ribavirin, and/or sofosbuvir (PR, SOF + PR, SOF + R), but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor.

b. Experienced with regimens containing SMV + SOF or SMV + PR or BOC + PR or TPV + PR.

c. Experienced with regimens containing DCV + SOF, DCV + PR, or LDV + SOF.

Special Populations

Pediatrics (< 18 years of age)

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

Geriatrics (> 65 years of age)

No dose adjustment of MAVIRET is required in geriatric patients.

Gender/Weight

No dose adjustment of MAVIRET is necessary based on gender or weight.

Race/Ethnicity

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

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 **CONTRAINDICATIONS** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations, Hepatic Impairment**).

Renal Impairment

No dose adjustment of MAVIRET is required in patients with any degree of renal impairment including patients on dialysis (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations, Renal Impairment**).

Missed Dose

Patients should be informed that in case a dose is missed, the prescribed dose can be taken within 18 hours of the scheduled time for the dose that was missed.

If more than 18 hours has passed since the dose is usually taken, the missed dose should NOT be taken and the patient should take the next dose as per the usual dosing schedule.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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

ACTION AND CLINICAL PHARMACOLOGY

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 **MICROBIOLOGY**).

Pharmacodynamics

Effects on Electrocardiogram

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

Pharmacokinetics

Based on the population pharmacokinetic analysis, the median steady-state pharmacokinetic parameters of glecaprevir and pibrentasvir in HCV infected patients and healthy subjects are provided in **Table 9**.

Table 9. Pharmacokinetics of Multiple Doses of Glecaprevir 300 mg Once Daily and Pibrentasvir 120 mg Once Daily in HCV-Infected Patients and Healthy Subjects

Direct Acting Antivirals (DAAs)	Pharmacokinetic Parameters	Healthy Subjects (N=230)[a]	HCV Infected Patients[b]	
			With Cirrhosis (N=280)[c]	Without Cirrhosis (N=1,804)[c]
Glecaprevir	C_{max} (ng/mL)	1,230	1,110	597
	AUC_{24} (ng·h/mL)	4,380	10,500	4,800
Pibrentasvir	C_{max} (ng/mL)	295	111	110
	AUC_{24} (ng·h/mL)	2,170	1,530	1,430

a. Overall geometric mean

b. Pharmacokinetics were similar in treatment-naïve or treatment-experienced patients

c. Geometric mean of individual-estimated AUC24

Absorption

Following single-dose administration of glecaprevir and pibrentasvir in healthy subjects, peak plasma concentrations were observed at 5.0 hours (glecaprevir) and 5.0 hours (pibrentasvir) post-dose.

Effects of Food on Oral Absorption

There were increases in glecaprevir AUC_T and C_{max} when a single 300 mg/120 mg dose of MAVIRET was administered under moderate fat, moderate calorie fed conditions (approximately 142% and 210%, respectively) and high fat, high calorie fed conditions (approximately 67% and 88%, respectively) when compared to administration under fasting conditions.

Similarly, there were increases in pibrentasvir AUC_T and C_{max} when a single 300 mg/120 mg dose of MAVIRET was administered under moderate fat, moderate calorie fed conditions (approximately 27% and 71%, respectively) and high fat, high calorie fed conditions (approximately 42% and 87%, respectively) when compared to administration under fasting conditions.

In Phase 2 and 3 registrational studies, glecaprevir and pibrentasvir were administered with food without regard to fat and calorie content.

Distribution

Glecaprevir and pibrentasvir are highly bound to plasma proteins (97.5% and > 99.9%, respectively). Ex vivo blood to plasma ratios were 0.57 (glecaprevir) and 0.62 (pibrentasvir).

Metabolism

Only unchanged glecaprevir and pibrentasvir were detected in plasma. Several oxidative metabolites (26% of dose) of glecaprevir were identified in feces. Metabolism by CYP3A plays a secondary role in the disposition of glecaprevir. Pibrentasvir was not metabolized and was recovered in feces only as unchanged parent drug.

Elimination

Glecaprevir and pibrentasvir are primarily eliminated through the biliary-fecal route. Mean half-lives of 6 hours (glecaprevir) and 13 hours (pibrentasvir) were observed when coadministered in healthy subjects. Following a single dose of [^{14}C]glecaprevir, 92.1% of the radioactive dose was recovered in feces and 0.7% was recovered in urine. Following a single dose of [^{14}C] pibrentasvir, 96.6% of the radioactive dose was recovered in feces and none was recovered in urine.

Special Populations and Conditions

Pediatrics (< 18 years of age)

The pharmacokinetics of MAVIRET in pediatric patients have not been established (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Pediatrics (< 18 years of age)**).

Geriatrics (≥ 65 years of age)

Within the age range (18 to 88 years) analyzed, age did not have a clinically relevant effect on exposure of glecaprevir or pibrentasvir.

Gender/Weight

Sex and body weight did not have a clinically relevant effect on exposure of glecaprevir or pibrentasvir.

Race/Ethnicity

Race or ethnicity did not have a clinically relevant effect on exposure of glecaprevir or pibrentasvir.

Hepatic Impairment

Hepatic impairment studies were conducted with a single dose of the glecaprevir 300 mg and pibrentasvir 120 mg combination in HCV-negative subjects under non-fasting conditions. Compared to subjects with normal hepatic function, glecaprevir exposures were higher in subjects with Child-Pugh A (↑ 33% AUC), Child-Pugh B (↑ 38% C_{max}, ↑ 2-fold AUC), and Child-Pugh C (↑ 5-fold C_{max}, ↑ 11-fold AUC) hepatic impairment. Pibrentasvir exposures were similar in subjects with Child-Pugh A (≤20% difference in C_{max} or AUC), but higher in subjects

with Child-Pugh B (↑ 26% C_{max} and AUC) and Child-Pugh C (↓ 41% C_{max}, ↑ 2-fold AUC) hepatic impairment.

Population pharmacokinetic analysis demonstrated that following administration of MAVIRET in HCV infected patients with compensated cirrhosis, exposure of glecaprevir was approximately 2-fold and pibrentasvir exposure was similar to non-cirrhotic HCV infected patients (see also **CONTRAINDICATIONS**, **WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION**).

Renal Impairment

Renal impairment studies were conducted with a single dose of the glecaprevir 300 mg and pibrentasvir 120 mg combination in HCV-negative subjects with mild (eGFR 60 to 89 mL/min/1.73 m^2), moderate (eGFR 30 to 59 mL/min/1.73 m^2), severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2), or ESRD not on dialysis (eGFR < 15 mL/min/1.73 m^2). Compared to subjects with normal renal function, glecaprevir AUC values were similar in subjects with mild renal impairment (13% difference), but higher in subjects with moderate renal impairment (↑30%), severe renal impairment (↑ 45%), or ESRD not on dialysis (↑ 56%). Compared to subjects with normal renal function, pibrentasvir AUC values were similar in subjects with mild (11% difference) or moderate (25% difference) renal impairment, but higher in subjects with severe renal impairment (↑ 37%), or ESRD not on dialysis (↑ 46%). C_{max} values were similar across all groups for glecaprevir (≤ 9% difference) and pibrentasvir (≤ 25% difference).

The glecaprevir 300 mg and pibrentasvir 120 mg combination was also administered to subjects requiring dialysis 3 hours before the start of hemodialysis and on a non-dialysis day. Exposures were similar for glecaprevir (≤ 7% difference in C_{max} or AUC) and pibrentasvir (≤ 18% difference in C_{max} or AUC) when dosed before dialysis compared to the non-dialysis day.

Overall, the changes in exposures of MAVIRET in HCV-infected patients with renal impairment with or without dialysis were not considered clinically significant (see **DOSAGE AND ADMINISTRATION**).

STORAGE AND STABILITY

Store between 2 and 30°C.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

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

MAVIRET is dispensed in a monthly carton. Each monthly carton contains four weekly cartons. Each weekly carton contains seven daily dose packs.

Each daily dose pack contains three 100 mg/40 mg glecaprevir/pibrentasvir tablets.

Listing of Non-Medicinal Ingredients

Each glecaprevir/pibrentasvir co-formulated immediate release tablet contains 100 mg glecaprevir /40 mg pibrentasvir with the following non-medicinal ingredients: copovidone (type K 28), vitamin E polyethylene glycol succinate, colloidal silicon dioxide, propylene glycol monocaprylate (type II), croscarmellose sodium, sodium stearyl fumarate, and film-coating (hypromellose 2910, lactose monohydrate, titanium dioxide, polyethylene glycol 3350 and iron oxide red).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

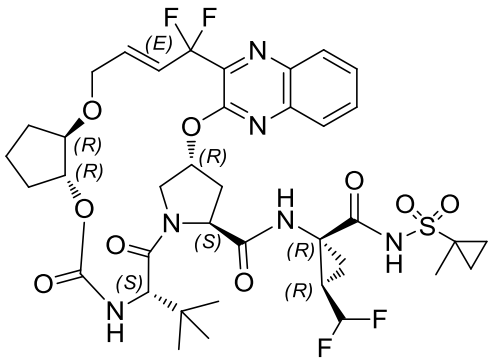
Glecaprevir

Common name: glecaprevir

Chemical name: (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

Molecular formula and molecular mass: $C_{38}H_{46}F_4N_6O_9S$ (anhydrate) 838.87 g/mol (anhydrate)

Structural formula:



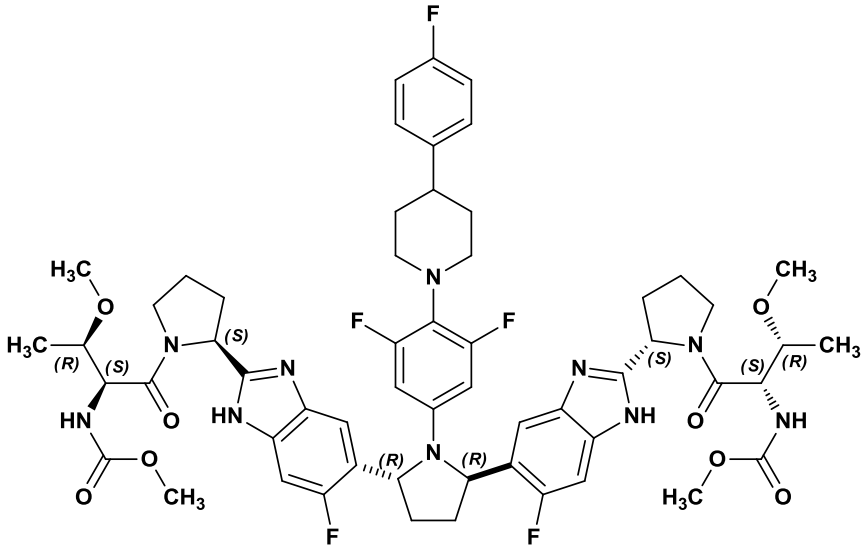
• X H_2O

Physicochemical properties:

Appearance: Glecaprevir is a white to off-white powder.

Solubility: Glecaprevir has a solubility of less than 0.1 to 0.3 mg/mL across a pH range of 2–7 at 37ºC and is practically insoluble in water, but is sparingly soluble in ethanol.

Pibrentasvir

Common name:	pibrentasvir
Chemical name:	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
Molecular formula and molecular mass:	$C_{57}H_{65}F_5N_{10}O_8$ 1113.18 g/mol
Structural formula:	

Physicochemical properties:

Appearance	Pibrentasvir is a white to off-white to light yellow powder.
Solubility	Pibrentasvir has 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.

CLINICAL TRIALS

Trial Design

The efficacy and safety of MAVIRET was evaluated in nine Phase 2-3 clinical trials, in over 2,300 patients with genotype 1, 2, 3, 4, 5 or 6 HCV infection and with compensated liver disease (with or without cirrhosis), as summarized in **Table 10**.

Table 10. Clinical Studies Conducted with MAVIRET in Patients with HCV Genotype 1, 2, 3, 4, 5 or 6 Infection

HCV Genotype (GT)	Study #	Number of Patients Treated N (regimen)	Trial Design	Dosage, Route of Administration and Duration
TN and TE patients without cirrhosis				
GT-1	ENDURANCE-1 (M13-590)	351 (8 weeks) 352 (12 weeks)	Randomized (1:1) and open-label study	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 8 or 12 weeks
	SURVEYOR-1 (M14-867)	34	Open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 8 weeks
GT-2	ENDURANCE-2 (M15-464)	202 (12 weeks) 100 (Placebo)	Randomized (2:1), placebo-controlled	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 12 weeks
	SURVEYOR-2 (M14-868)	199 (8 weeks) 25 (12 weeks)	Open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 8 or 12 weeks
GT-3	ENDURANCE-3 (M13-594)	157 (8 weeks) 233 (12 weeks) 115 (Sofosbuvir + daclatasvir 12 weeks)	Partially-randomized, open-label, active-controlled (all TN patients)	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 8 or 12 weeks
	SURVEYOR-2 (M14-868)	29 TN only (8 weeks) 76 (12 weeks) 22 TE only (16 weeks)	Partially Randomized, Open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 8 or 12 or 16 weeks
GT-4, -5, -6	ENDURANCE-4 (M13-583)	121	Single-arm, open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 12 weeks
	SURVEYOR-1 (M14-867)	32	Open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 12 weeks

	SURVEYOR-2 (M14-868)	58	Open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 8 weeks
TN and TE patients with cirrhosis				
GT-1, -2, -4, -5, -6	EXPEDITION-1 (M14-172)	146	Single-arm, open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 12 weeks
GT-3	SURVEYOR-2 (M14-868)	64 TN only (12 weeks) 51 TE only (16 weeks)	Open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 12 or 16 weeks
Patients with CKD stage 4 and 5 with or without cirrhosis				
GT-1to -6	EXPEDITION-4 (M15-462)	104	Single-arm, open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 12 weeks
NS5A and/or PI-experienced patients with or without cirrhosis				
GT-1, -4	MAGELLAN-1 (M15-410)	66 (12 weeks) 47 (16 weeks)	Randomized, multipart, open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 12 or 16 weeks

TN = treatment-naïve, TE = treatment-experienced (includes previous treatment that included pegylated interferon (or interferon), and/or ribavirin and/or sofosbuvir), PI = Protease Inhibitor, CKD = chronic kidney disease, QD = once daily

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-2which 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.

Among patients in Phase 2 and 3 clinical trials who received the recommended regimen (N=1190), 97% achieved SVR (97% with cirrhosis and 97% without cirrhosis), while 0.6% experienced on treatment virologic failure and 0.9% experienced post-treatment relapse. Among the treatment naïve patients without cirrhosis (all genotypes) who received MAVIRET for 8 weeks, the SVR12 rate was 97% (639/657) with <1% (6/657) virologic failure rate.

Clinical Studies in Treatment-Naive or Treatment-Experienced-PRS Patients with or without Cirrhosis Infected with Genotypes 1, 2, 4, 5 or 6.

Demographic and Other Baseline Characteristics

Demographic and baseline characteristics for treatment-naïve or PRS-treatment-experienced patients with or without cirrhosis with genotype 1, 2, 4, 5, or 6 infection in ENDURANCE-1, -2, -4, SURVEYOR-1 , -2, and EXPEDITION-1 are provided in **Table 11**.

Table 11. Demographic and Other Baseline Disease Characteristics of the Population for the Treatment of HCV Genotypes 1, 2, 4, 5 or 6 (Phase 2, 3 Studies[a])

Characteristics	Genotype					Total N=1,520 n (%)
	GT-1 N=834 n (%)	GT-2 N=450 n (%)	GT-4 N=158 n (%)	GT-5 N=31 n (%)	GT-6 N=47 n (%)	
Age (years)						
< 65	724 (86.8)	345 (76.7)	141 (89.2)	19 (61.3)	42 (89.4)	1,271 (83.6)
≥ 65	110 (13.2)	105 (23.3)	17 (10.8)	12 (38.7)	5 (10.6)	249 (16.4)
Gender						
Male	420 (50.4)	226 (50.2)	101 (63.9)	17 (54.8)	26 (55.3)	790 (52.0)
Female	414 (49.6)	224 (49.8)	57 (36.1)	14 (45.2)	21 (44.7)	730 (48.0)
Race						
White	708 (84.9)	338 (75.1)	124 (78.5)	20 (64.5)	5 (10.6)	1,195 (78.6)
Black	36 (4.3)	21 (4.7)	24 (15.2)	4 (12.9)	NA	85 (5.6)
Asian	81 (9.7)	80 (17.8)	10 (6.3)	2 (6.5)	41 (87.2)	214 (14.1)
Other	9 (1.1)	11 (2.4)	NA	5 (16.1)	1 (2.1)	26 (1.7)
BMI						
< 30 kg/m^2	674 (80.8)	344 (76.4)	128 (81.0)	21 (67.7)	44 (93.6)	1,211 (79.7)
≥ 30 kg/m^2	160 (19.2)	106 (23.6)	30 (19.0)	10 (32.3)	3 (6.4)	309 (20.3)
Genotype/Subtype						
1a	377 (45.2)	NA	NA	NA	NA	377 (24.8)
1b	454 (54.4)	NA	NA	NA	NA	454 (29.9)
2	NA	450 (100)	NA	NA	NA	450 (29.6)
4	NA	NA	158 (100)	NA	NA	158 (10.4)
5 and 6	NA	NA	NA	31 (100)	47 (100)	78 (5.1)
HCV RNA Viral Load (Log_{10} IU/mL), mean (SD)	6.1 (0.68)	6.2 (0.94)	5.9 (0.67)	6.1 (0.56)	6.6 (0.83)	6.1 (0.78)
Fibrosis Stage						
F0-F2	676 (81.1)	371 (82.4)	130(82.3)	27 (87.1)	33 (70.2)	1,237 (81.4)
F3	64 (7.7)	48 (10.7)	12 (7.6)	2 (6.5)	7 (14.9)	133 (8.8)
F4	90 (10.8)	31 (6.9)	16 (10.1)	2 (6.5)	7 (14.9)	146 (9.6)
Cirrhosis						
Yes	90 (10.8)	31 (6.9)	16 (10.1)	2 (6.5)	7 (14.9)	146 (9.6)
No	744 (89.2)	419 (93.1)	142 (89.9)	29 (93.5)	40 (85.1)	1,374 (90.4)
Prior HCV Therapy						
TN	533 (63.9)	359 (79.8)	112 (70.9)	25 (80.6)	41 (87.2)	1,070 (70.4)
TE-PRS	301 (36.1)	91 (20.2)	46 (29.1)	6 (19.4)	6 (12.8)	450 (29.6)
P/R-experienced	293 (35.1)	74 (16.4)	45 (28.5)	6 (19.4)	6 (12.8)	424 (27.9)
SOF-experienced	8 (1.0)	17 (3.8)	1 (0.6)	NA	NA	26 (1.7)

a. Population includes TN or TE-PRS patients and excludes patients with severe renal impairment (Study M15-462).

BMI = body mass index; GT = genotype; P/R = peginterferon/ribavirin; PRS = regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir; SD = standard deviation; TN = treatment-naïve; TE = treatment-experienced; SOF = sofosbuvir

Study Results

The response rates for MAVIRET in genotype 1, 2, 4, 5 or 6 infected patients who were treatment-naïve or those who previously failed regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir (PRS) treated for 8 weeks (without cirrhosis) and 12 weeks (with cirrhosis) are shown in **Table 12**.

Table 12. Sustained Virologic Response (SVR12) in Treatment-Naive Patients and Patients Experienced[a] to Peginterferon, Ribavirin, and/or Sofosbuvir with or without Cirrhosis after 8 or 12 Weeks of Treatment with MAVIRET (pooled data from ENDURANCE-1, -2, -4, SURVEYOR-1, -2, and EXPEDITION-1, and -4)

	GT-1[b] % (n/N)	GT-2 % (n/N)	GT-4 % (n/N)	GT-5 % (n/N)	GT-6 % (n/N)
SVR12 in subjects without cirrhosis					
8 weeks	99.0 (383/387)	98.0 (193/197)	93.5 (43/46)	100 (2/2)	90.0 (9/10)
Outcome for subjects without SVR12					
On-treatment VF	0.3 (1/387)	0 (0/197)	0 (0/46)	0 (0/2)	0 (0/10)
Relapse[c]	0 (0/384)	1.0 (2/195)	0 (0/45)	0 (0/2)	0 (0/10)
Other[d]	0.8 (3/387)	1.0 (2/197)	6.5 (3/46)	0 (0/2)	10 (1/10)
SVR12 in subjects with cirrhosis					
12 weeks	97.0 (98/101)	100 (35/35)	100 (20/20)	100 (2/2)	100 (7/7)
Outcome for subjects without SVR12					
On-treatment VF	0 (0/101)	0 (0/35)	0 (0/20)	0 (0/2)	0 (0/7)
Relapse[c]	1.0 (1/98)	0 (0/35)	0 (0/19)	0 (0/2)	0 (0/7)
Other[d]	2.0 (2/101)	0 (0/35)	0 (0/20)	0 (0/2)	0 (0/7)

GT = genotype; VF = virologic failure

a. Percent of patients with prior treatment experience to PRS is 35%, 14%, 23%, 0%, and 18% for genotypes 1, 2, 4, 5, and 6, respectively. None of the GT-5 patients were TE-PRS, and 3 GT-6 patients were TE-PRS.

b. Includes 15 patients co-infected with HIV-1 (treated for 8 weeks).

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

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

Subgroup analyses were performed for the primary efficacy endpoint (SVR12) for selected subgroups of patients treated with MAVIRET for the recommended duration as summarized in **Table 13.**

Table 13. Sustained Virologic Response (SVR12) in Selected Subgroups of Treatment-Naive Patients and Patients Experienced to Peginterferon, Ribavirin, and/or Sofosbuvir , Infected with HCV Genotypes 1, 2, 4, 5 or 6 without Cirrhosis Treated for 8 weeks and with Cirrhosis Treated for 12 weeks (Phase 2, 3 Studies[a])

SVR12	Genotype				Total N=788 % (n/N)
	GT-1 N=477 % (n/N)	GT-2 N=228 % (n/N)	GT-4 N=62 % (n/N)	GT-5, -6 N=21 % (n/N)	
HCV Genotype/ Subtype					
1a	97.8 (223/228)	NA	NA	NA	97.8 (223/228)
1b	100 (247/247)	NA	NA	NA	100 (247/247)
Prior Treatment History					
TN	99.0 (311/314)	99.0 (196/198)	94.1 (48/51)	94.4 (17/18)	98.5 (572/581)
Cirrhotic	100 (66/66)	100 (24/24)	100 (12/12)	100 (8/8)	100 (110/110)
Non-cirrhotic	98.8 (245/248)	98.9 (172/174)	92.3 (36/39)	90 (9/10)	98.1 (462/471)
TE-PRS	98.8 (161/163)	93.3 (28/30)	100 (11/11)	100 (3/3)	98.1 (203/207)
P/R-experienced	98.7 (156/158)	94.4 (17/18)	100 (10/10)	100 (3/3)	98.4 (186/189)
SOF-experienced	100 (5/5)	91.7 (11/12)	100 (1/1)	NA	94.4 (17/18)
HCV/HIV Coinfection[b]					
Yes	100 (15/15)	NA	NA	NA	100 (15/15)
No	98.9 (457/462)	98.2 (224/228)	95.2 (59/62)	95.2% (20/21)	98.3 (760/773)

GT = genotype; P/R = peginterferon/ribavirin; TN = treatment-naïve; TE = treatment-experienced; PRS = regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir; SOF = sofosbuvir.
a. Population excludes patients with severe renal impairment (Study M15-462), including only patients administered the recommended duration of MAVIRET: 8 weeks for non-cirrhotics patients and 12 weeks for cirrhotic patients.
b. Baseline HIV antiretroviral combination regimens used: dolutegravir/abacavir/lamuvidine (n = 4), raltegravir plus emtricitabine/tenofovir disoproxil fumarate (n = 6), rilpivirine/emtricitabine/tenofovir disoproxil fumarate (n = 3), dolutegravir plus emtricitabine/tenofovir disoproxil fumarate (n = 1), raltegravir plus abacavir/lamuvidine (n = 1)

High SVR12 rates were achieved across all HCV genotypes in all subgroups including by age, gender, race, ethnicity, BMI, HCV RNA level, cirrhosis status, HIV coinfection, prior treatment history and IL28B genotype. The SVR12 rate of MAVIRET across all treatment-naïve patients without cirrhosis with genotype 1, 2, 4, 5, 6 chronic HCV infection treated for 8 weeks was 98.1% (462/471) with no virologic failures.

Clinical Studies in Genotype 3 Infected Patients

Demographic and Other Baseline Characteristics

The efficacy of MAVIRET in patients who were treatment-naïve or treatment-experienced to combinations of peginterferon, ribavirin and/or sofosbuvir with genotype 3 chronic hepatitis C infection was demonstrated in the ENDURANCE-3 (treatment-naïve without cirrhosis) and SURVEYOR-2 Parts 1-3 (patients with and without cirrhosis and treatment-naïve and/or treatment-experienced) clinical studies.

ENDURANCE-3 was a partially-randomized, open-label, active-controlled study in treatment-naïve patients. Patients were randomized (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-randomized) with MAVIRET for 8 weeks. SURVEYOR-2 Part 3 was an open-label study randomizing non-cirrhotic treatment-experienced patients to 12- or 16-weeks of treatment; in addition, the study evaluated the efficacy of MAVIRET in patients with compensated cirrhosis and genotype 3 infection in two dedicated treatment arms using 12-week (treatment-naïve only) and 16-week (treatment-experienced only) durations. Among treatment-experienced patients, 46% (42/91) failed a previous regimen containing sofosbuvir.

The demographic and disease characteristics of the population with HCV genotype 3 infection in ENDURANCE-3 and SURVEYOR-2 are summarized in **Table 14**.

Table 14. Demographic and Other Baseline Characteristics of the Patient Population Infected with HCV Genotypes 3 (ENDURANCE-3, SURVEYOR-2)

Characteristics	MAVIRET 8, 12 or 16 Weeks N=632 n (%)
Age (years)	
< 65	596 (94.3)
≥65	36 (5.7)
Gender	
Male	367 (58.1)
Female	265 (41.9)
Race	
White	558 (88.3)
Black	9 (1.4)
Asian	47 (7.4)
Other	18 (2.8)
Viral Load	
HCV RNA (Log_{10} IU/mL) mean (SD)	6.2 (0.79)
BMI	
< 30 kg/m^2	509 (80.5)
≥ 30 kg/m^2	123 (19.5)
HCV Genotype/Subtype	
3a	587 (92.9)
3-other	45 (7.1)
Prior Treatment History	
TN	510 (80.7)
TE-PRS	122 (19.3)
P/R-experienced	80 (12.7)
SOF-experienced	42 (6.6)
Stages of Fibrosis	
F0-F2	440 (69.6)
F3	78 (12.3)
F4	114 (18.0)
Cirrhosis	
Yes	115 (18.2)
No	517 (81.8)

P/R = peginterferon/ribavirin; PRS = regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir; SD = standard deviation; TE = treatment-experienced; TN = treatment-naïve

Study Results

The response rates of the treatment-naïve genotype 3-infected patients without cirrhosis treated with MAVIRET for 8 and 12 weeks and patients treated with sofosbuvir and daclatasvir for 12 weeks are presented in **Table 15**.

Table 15. Sustained Virologic Response (SVR12) in Treatment-Naïve Patients Infected with HCV Genotype 3 without Cirrhosis (ENDURANCE-3)

	MAVIRET 8 weeks N=157 % (n/N)	**MAVIRET 12 weeks N=233 % (n/N)**	**SOF+DCV 12 weeks N=115 % (n/N)**
SVR	94.9 (149/157)	95.3 (222/233)[a]	96.5 (111/115)[b]
Outcome for patients without SVR			
On-treatment VF	0.6 (1/157)	0.4 (1/233)	0 (0/115)
Relapse[c]	3.3 (5/150)	1.4 (3/222)	0.9 (1/114)
Other[d]	1.3 (2/157)	3.0(7/233)	2.6 (3/115)
Outcome by HCV genotype/subtype			
3a	94.9 (148/156)	95.7 (220/230)	96.5 (111/115)
3-other	100 (1/1)	66.7 (2/3)	NA

VF = virologic failure; SOF = sofosbuvir; DCV = daclatasvir; NA = not applicable.

a. Treatment difference between MAVIRET for 8 weeks and MAVIRET for 12 weeks was -0.4%; 97.5% confidence interval (-5.4% to 4.6%).

b. Treatment difference between MAVIRET for 12 weeks and SOF+DCV was -1.2%; 95% confidence interval (-5.6% to 3.1%).

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

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

The response rates in genotype 3-infected treatment-naive patients with cirrhosis treated with MAVIRET for 12 weeks and PRS treatment-experienced patients with or without cirrhosis treated with MAVIRET for 16 weeks in SURVEYOR-2 Part 3 are presented in **Table 16**.

Table 16. Sustained Virologic Response (SVR12) in Treatment-Naive Patients and Patients Experienced to Peginterferon, Ribavirin, and/or Sofosbuvir, Infected with HCV Genotype 3 with or without Cirrhosis (SURVEYOR-2 Part 3)

	Treatment-Naïve with Cirrhosis	Treatment-Experienced with or without Cirrhosis
	MAVIRET 12 weeks (N=40) % (n/N)	**MAVIRET 16 weeks (N=69) % (n/N)**
SVR	97.5 (39/40)	95.7 (66/69)
Outcome for patients without SVR		
On-treatment VF	0 (0/40)	1.4 (1/69)
Relapse[a]	0 (0/39)	2.9 (2/68)
Other[b]	2.5 (1/40)	0 (0/69)
Outcome in selected subgroups		
HCV Genotype/Subtype		
3a	97.4 (38/39)	95.5 (64/67)
3-other	100 (1/1)	100 (2/2)
Prior Treatment History		
TN	97.5 (39/40)	NA
TE-PRS	NA	95.7 (66/69)
P/R-experienced	NA	94.3 (33/35)
SOF-experienced	NA	97.1 (33/34)

VF = virologic failure; TN = treatment-naïve; TE = treatment-experienced; PRS = regimens containing interferon, pegylated interferon, ribavirin and/or sofosbuvir; P/R = peginterferon/ribavirin; SOF = sofosbuvir.

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 patient withdrawal.

The SVR12 rate of MAVIRET across all treatment-naïve patients without cirrhosis with genotype 3 chronic HCV infection treated in Phase 2 and 3 studies (ENDURANCE-3 or SURVEYOR-2 Parts 1 and 2) was 95.2% (177/186) with 2.8% relapse (5/178) for patients treated for 8 weeks, and 95.4% (248/260) with 1.2% relapse (3/248) for patients treated for 12 weeks.

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

Among treatment-experienced patients treated for 16 weeks, SVR12 rates were 95% (n=22) in patients without cirrhosis and 96% (n=47) in patients with cirrhosis.

High SVR12 rates were achieved across all subgroups including by age, gender, race, ethnicity, BMI, HCV RNA level, cirrhosis status, prior treatment history and IL28B genotype.

SVR12 rate in all GT-3 patients irrespective of cirrhosis status or prior treatment history treated with MAVIRET for the recommended durations was 95.7% (n=324) with 3.0% virologic failures.

Clinical Study in Chronic Kidney Disease (CKD) Patients

Demographic and Other Baseline Characteristics

The demographic and disease characteristics of the population with stages 4 and 5 chronic kidney disease are summarized in **Table 17**.

Table 17. Demographic and Other Baseline Characteristics of the Patient Population with and without Cirrhosis with Chronic Kidney Disease (Stages 4, 5) Infected with HCV Genotypes 1 to 6 (EXPEDITION-4)

Characteristics	MAVIRET 12 Weeks N=104 n (%)
Age	
< 65	76 (73.1)
≥ 65	28 (26.9)
Gender	
Male	79 (76.0)
Female	25 (24.0)
Race	
White	64 (61.5)
Black	25 (24.0)
Asian	9 (8.7)
Other	6 (5.8)
Viral Load	
HCV RNA (Log_{10} IU/mL), mean (SD)	5.85 (0.74)
BMI	
< 30 kg/m^2	79 (76.0)
≥ 30 kg/m^2	25 (24.0)
HCV Genotype/Subtype	
1a	23 (22.1)
1b	29 (27.9)
2	17 (16.3)
3	11 (10.6)
4	20 (19.2)
5 and 6	2 (2.0)
Prior Treatment History	
TN	60 (57.7)
TE-PRS	44 (42.3)
P/R-experienced	42 (40.4)
SOF-experienced	2 (1.9)
Stages of Fibrosis	
F0-F2	69 (66.3)
F3	17 (16.3)
F4	17 (16.3)

Cirrhosis	
Yes	20 (19.2)
Child Pugh Score 5 cirrhosis	15 (14.4)
Child Pugh Score 6 cirrhosis	4 (3.8)
Child Pugh Score > 6 cirrhosis[a]	1 (1.0)
No	84 (80.8)
Stages of Chronic Kidney Disease	
Stage 4 without dialysis[b]	13 (12.5)
Stage 5 without dialysis[c]	6 (5.8)
Stage 5 requiring dialysis[d]	85 (81.7)

P/R = peginterferon/ribavirin; BMI = body mass index; GT = genotype; PRS = regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir; SD = standard deviation; TE = treatment-experienced; TN = treatment-naïve.

a. one patient had Child Pugh Score 7 at baseline.

b. Stage 4, defined as patients with eGFR 15 to 30 mL/min/1.73 m^2.

c. Stage 5 defined as eGFR < 15 mL/min/1.73 m^2

d. Stage 5, requiring routine dialysis. 19% (16/85) of the patients requiring dialysis had cirrhosis, mostly of Child-Pugh 5 and 6.

Study Results

The response rates in patients with CKD (stages 4 and 5) infected with HCV genotypes 1 to 6 are presented in **Table 18**.

Table 18. Sustained Virologic Response (SVR12) in Chronic Kidney Disease (Stages 4 and 5), HCV Genotypes 1to 6 Infected Patients with or without Cirrhosis (EXPEDITION-4)

Assessment	MAVIRET 12 Weeks N=104 % (n/N)
SVR12	98.1 (102/104)
95% CI	(95.4, 100)
Outcomes in Patients Without SVR	
On Treatment VF	0 (0/104)
Relapse[a]	0 (0/104)
Other[b]	1.9 (2/104)

VF = virologic failure; P/R = peginterferon/ribavirin; GT = genotype; PRS = regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir; TE = treatment-experienced; TN = treatment-naïve

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 patient withdrawal.

Subgroup analyses were performed for the primary efficacy endpoint (SVR12) for selected subgroups as summarized in **Table 19**.

Table 19. Sustained Virologic Response (SVR12) in Selected Subgroups of Chronic Kidney Disease (Stages 4 and 5 Patients Infected with HCV Genotypes 1 to 6 (EXPEDITION-4)

Subgroups	MAVIRET 12 Weeks N=104 % (n/N)
Genotypes	
1	96.4 (53/55)
2	100 (16/16)
3	100 (11/11)
4	100 (20/20)
5 and 6	100 (2/2)
Cirrhosis	
Yes	90 (18/ 20)
No	100 (84/84)
Child-Pugh Score	
5	86.7 (13/ 15)
6	100 (4/4)
≥ 6	100 (1/1)
Baseline CKD Stage	
Stage 4 without dialysis[a]	100 (13/13)
Stage 5 without dialysis[b]	100 (6/6)
Stage 5 requiring dialysis[c]	97.6 (83/85)
Prior Treatment History	
TN	96.7 (58/60)
TE-PRS	100 (44/44)
P/R-experienced	100 (42/42)
SOF-experienced	100 (2/2)

P/R = peginterferon/ribavirin; GT = genotype; PRS = regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir; TE = treatment-experienced; TN = treatment-naïve.

a. Stage 4, defined as patients with eGFR 15 to 30 mL/min/1.73 m^2.

b. Stage 5, defined as eGFR < 15 mL/min/1.73 m^2.

c. Stage 5, requiring routine dialysis.

Among patients with advanced renal disease, high SVR12 rates were achieved across all subgroups including by age, gender, race, ethnicity, BMI, HCV RNA level, cirrhosis status, prior treatment history, CKD stage and IL28B genotype.

Among all patients, regardless of renal function or cirrhosis status, who were treatment-naïve or treatment-experienced to combinations of peginterferon, ribavirin, and/or sofosbuvir and infected

with any HCV genotype who received the recommended treatment duration, 97.4% (1102/1131) achieved SVR12, 0.3% (3/1131) experienced on-treatment virologic failure, and 1.0% (11/1111) experienced post-treatment relapse. For the subset of patients with compensated cirrhosis, 97.5% (274/281) achieved SVR12.

Clinical Studies in NS5A Inhibitor and/or Protease Inhibitor (NS3/4A) Treatment-Experienced Patients with or without Cirrhosis

Demographic and Other Baseline Characteristics

Demographic and baseline characteristics for NS5A inhibitor and/or NS3/4A protease inhibitor (PI) treatment-experienced patients with or without cirrhosis with genotype 1 HCV infection in MAGELLAN-1 Part 2 are provided in **Table 20Error! Reference source not found.**.

Table 20. Demographic and Other Baseline Characteristics of NS5A Inhibitor and/or NS3/4A Protease Inhibitor Treatment-Experienced Patients Infected with HCV Genotypes 1 (MAGELLAN-1 Part 2)

Characteristics	MAVIRET 12 Weeks N=43 % (n/N)	MAVIRET 16 Weeks N=44 % (n/N)
Age		
< 65	93.0 (40/43)	81.8 (36/44)
≥ 65	7.0 (3/43)	18.2 (8/44)
Gender		
Male	69.8 (30/43)	72.7 (32/44)
Female	30.2 (13/43)	27.3 (12/44)
Race		
White	79.1(34/43)	79.5 (35/44)
Black	18.6 (8/43)	18.2 (8/44)
Asian	2.3 (1/43)	2.3 (1/44)
BMI		
< 30 kg/m^2	67.4 (29/43)	56.8 (25/44)
≥ 30 kg/m^2	32.6 (14/43)	43.2 (19/44)
HCV Genotypes		
1	100 (43/43)	97.7 (43/44)
1a	81.4 (35/43)	72.7 (32/44)
1b	18.6 (8/43)	25.0 (11/44)
HCV RNA Viral Load (Log_{10} IU/mL), mean (SD)	6.02 (0.67)	6.24 (0.57)
Fibrosis Stage		
F0-F2	51.2 (22/43)	70.5 (31/44)
F3	16.3 (7/43)	6.8 (3/44)
F4	32.6 (14/43)	22.7 (10/44)
Cirrhosis		
Yes	34.9 (15/43)	22.7 (10/44)
No	65.1 (28/43)	77.3 (34/44)

Previous DAA Experience[a]		
PI experienced only	32.6 (14/43)	27.3 (12/44)
With Cirrhosis	16.3 (7/43)	9.1 (4/44)
Without Cirrhosis	16.3 (7/43)	18.2 (8/44)
NS5A experienced only	37.2 (16/43)	38.6 (17/44)
With Cirrhosis	16.3 (7/43)	6.8 (3/44)
Without Cirrhosis	20.9 (9/43)	31.8 (14/44)
NS5A and PI experienced	30.2 (13/43)	34.1 (15/44)
With Cirrhosis	2.3 (1/43)	6.8 (3/44)
Without Cirrhosis	27.9 (12/43)	27.3 (12/44)

NS5A = nonstructural viral protein 5A; PI = protease inhibitor

a. DAA experience was considered additive, i.e., a subject treated in the past with PI-containing regimen (e.g., TVR + PR) and subsequently with an NS5A-containing regimen (e.g., LDV + SOF) was considered NS5A- and PI-experienced.

Study Results

The response rates in patients with NS5A inhibitor and/or NS3/4A PI treatment experience with or without cirrhosis in MAGELLAN-1 Part 2 are presented in **Table 21**. The SVR12 rate in patients in MAGELLAN-1 Part 1 and Part 2 with prior PI or NS5A inhibitor treatment experience treated with MAVIRET for the recommended duration was 92.9% (n=42) with 2.4% virologic failure.

Table 21. Sustained Virologic Response (SVR12) in NS5A Inhibitor and/or NS3/4A Protease Inhibitor Treatment-Experienced Patients Infected with HCV Genotypes 1 with or without Cirrhosis (MAGELLAN-1 Part 2)

Assessment	MAVIRET 12 Weeks N=43 % (n/N)	MAVIRET 16 Weeks N=44 % (n/N)
SVR12	88.4 (38/43)	90.9 (40/44)
95% CI	(75.5, 94.9)	(78.8, 96.4)
Outcome in Patients Without SVR		
Virologic Failure	11.6 (5/43)	9.1 (4/44)
On treatment VF	2.3 (1/43)	9.1 (4/44)
Relapse[a]	9.5 (4/42)	0 (0/40)

VF = virologic failure

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

Subgroup analyses were performed for the primary efficacy endpoint (SVR12) for selected subgroups as summarized in **Table 22**.

Table 22. Sustained Virologic Response (SVR12) in Selected Subgroups of NS5A Inhibitor and/or NS3/4A Protease Inhibitor Treatment-Experienced Patients Infected with HCV Genotypes 1 (MAGELLAN-1 Part-2)

Subgroups	MAVIRET 12 Weeks N=43 % (n/N)	MAVIRET 16 Weeks N=44 % (n/N)
Cirrhosis		
Yes	93.3 (14/15)	70.0 (7/10)
No	85.7 (24/28)	97.1 (33/34)
Previous DAA Regimen class		
PI only	100 (14/14)	100 (12/12)
NS5A Inhibitors only[a]	87.5 (14/16)	94.1 (16/17)
NS5A Inhibitors and PI	76.9 (10/13)	80 (12/15)
Presence of Key Baseline Substitutions[b]		
None	100 (13/13)	100 (13/13)
NS3 only	100 (2/2)	100 (4/4)
NS5A only	83.3 (20/24)	95.2 (20/21)
Both NS3 and NS5A[c]	75.0 (3/4)	25.0 (1/4)

NS5A = nonstructural viral protein 5A; PI = protease inhibitor

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

b. Detected by next generation sequencing using 15% detection threshold at amino acid positions 155, 156, and 168 in NS3, and 24, 28, 30, 31, 58, 92, and 93 in NS5A in patients who had baseline sequences available.

c. In a limited number of patients significantly lower SVR12 rates were observed at the studied treatment durations of 12 and 16 weeks

High SVR12 rates were achieved in patients who failed a prior treatment containing NS5A inhibitors (ledipasvir or daclatasvir) and in patients with pre-existing NS5A substitutions (while PI-naïve and without pre-existing treatment emergent NS3 substitutions in positions 155, 156 and 168) treated with MAVIRET for the recommended duration (16 weeks). High SVR12 rates were achieved in patients with prior failure to a protease inhibitor only (while NS5A-inhibitor naïve) treated for the recommended duration (12 weeks). Lower efficacy was observed in patients who previously failed both NS5A inhibitors and NS3/4A PIs and had pre-existing treatment emergent substitutions in both NS5A and NS3.

MICROBIOLOGY

Description

MAVIRET is a fixed-dose bilayer tablet (3X) combination regimen of glecaprevir and pibrentasvir.

Antiviral Activity *in vitro*

Glecaprevir

Glecaprevir is a pangenotypic inhibitor of the HCV NS3/4A protease, which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication. In a biochemical assay, glecaprevir inhibited the proteolytic activity of recombinant NS3/4A enzymes from clinical isolates of HCV genotypes 1a, 1b, 2a, 2b, 3a, 4a, 5a, and 6a with IC50 value 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 characterized based on cell culture antiviral activity and drug resistance mapping studies.

Combination Activity

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

Antiviral Activity in Cell Culture

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 23**.

Table 23. Activity of Glecaprevir and Pibrentasvir Against HCV Genotypes 1 to 6 Replicon Cell Lines

HCV Subtype	Glecaprevir EC_{50}, nM[a]	Pibrentasvir EC_{50}, nM[b]
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

a. Stable replicon cell lines containing full-length NS3-5B from genotypes 1a, 1b, or 2a; or chimeric replicons containing NS3 from genotype 2b, 3a, 4a, or 6a.

b. Stable replicon cell lines containing full-length NS3-5B from genotype 1a or 1b; or chimeric replicons containing NS5A from genotype 2a, 2b, 3a, 4a, 5a, or 6a.

The EC_{50} values of glecaprevir and pibrentasvir against chimeric replicons encoding NS3 or NS5A from clinical isolates are presented in **Table 24**.

Table 24. Activity of Glecaprevir and Pibrentasvir against Transient Replicons Containing NS3 or NS5A from HCV Genotypes 1 to 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

Resistance

In Cell Culture

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

Substitutions important for the HCV protease inhibitor class at positions 36, 43, 54, 55, 56, 155, 166, or 170 in NS3 had no impact on glecaprevir activity. Individual substitutions at NS3 amino acid position A156 introduced into HCV replicons by site-directed mutagenesis generally caused the greatest reductions (>100-fold) in susceptibility to glecaprevir. Individual substitutions at NS3 position D/Q168 had varying effects on glecaprevir susceptibility depending on HCV genotype/subtype and specific amino acid change, with the greatest reductions (>30-fold) observed in genotypes 1a (D168F/Y), 3a (Q168R) and 6a (D168A/G/H/V/Y). Combinations of NS3 Y56H plus D/Q168 substitutions resulted in greater reductions in glecaprevir susceptibility. An NS3 Q80R substitution in genotype 3a caused a 21-fold reduction in glecaprevir susceptibility, while Q80 substitutions in genotypes 1a and 1b (including genotype 1a Q80K) did not reduce glecaprevir susceptibility.

Single substitutions important for the NS5A inhibitor class at positions 24, 28, 30, 31, 58, 92, or 93 in NS5A in genotypes 1 to 6 had no impact on the activity of pibrentasvir. Amino acid substitutions resulting from multiple nucleotide changes reduced susceptibility to pibrentasvir in a genotype 1a replicon (M28G or Q30D, 244- and 94-fold, respectively), and in a genotype 1b replicon (P32-deletion, 1,036-fold). Some combinations of two or more NS5A inhibitor resistance-associated amino acid substitutions may result in greater reductions in pibrentasvir susceptibility. Specifically in genotype 3a, A30K or Y93H had no impact on pibrentasvir activity. Some combinations of substitutions in genotypes 1a and 3a (including A30K+Y93H in genotype 3a) showed reductions in susceptibility to pibrentasvir.

In Clinical Studies

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

Twenty two of the approximately 2,300 patients treated with MAVIRET for 8, 12, or 16 weeks in Phase 2 and 3 clinical studies experienced virologic failure (2 with genotype 1, 2 with genotype 2, 18 with genotype 3 infection). In addition, 1 GT-3-infected patient experiencing virologic failure was determined to be reinfected with a GT-3 virus distinct from the one present at baseline. Among the 22 patients experiencing virologic failure, treatment-emergent substitutions were detected in 54.5% (12/22) of patients in NS3 and 81.8% (18/22) of patients in NS5A.

Among the 2 genotype 1-infected patients who experienced virologic failure, one had treatment-emergent substitutions A156V in NS3 and Q30R/L31M/H58D in NS5A, and 1 had Q30R/H58D (while Y93N was present at baseline and post-treatment) in NS5A.

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

Among the 18 genotype 3-infected patients treated with MAVIRET for 8, 12, or 16 weeks who experienced virologic failure, treatment-emergent NS3 substitutions Y56H/N, Q80K/R, A156G, or Q168L/R were observed in 11 patients. A166S or Q168R were present at baseline and post-treatment in 5 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 Treatment-Experienced to NS3/4A Protease and/or NS5A Inhibitors

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

Among the 10 genotype 1-infected patients with virologic failure, treatment-emergent NS3 substitutions V36A/M, R155K/T, A156G/T/V, or D168A/T were observed in 7 patients. Five of the 10 had combinations of V36M, Y56H, R155K/T, or D168A/E in NS3 at baseline and post-treatment. All of the genotype 1-infected virologic failure patients had one or more NS5A substitutions L/M28M/T/V, Q30E/G/H/K/L/R, L31M, P32deletion, H58C/D, or Y93H at baseline, with additional treatment-emergent NS5A substitutions M28A/G, P29Q/R, Q30K, H58D, or Y93H observed in 7 of the patients at the time of failure.

Effect of Baseline HCV Substitutions/Polymorphisms on Treatment Response

A pooled analysis of treatment-naïve and pegylated interferon, ribavirin and/or sofosbuvir treatment-experienced patients receiving MAVIRET in the Phase 2 and Phase 3 clinical studies was conducted to explore the association between baseline polymorphisms and treatment outcome and to describe substitutions seen upon virologic failure. Baseline polymorphisms relative to a subtype-specific reference sequence at amino acid positions 155, 156, and 168 in NS3, and 24, 28, 30, 31, 58, 92, and 93 in NS5A were evaluated at a 15% detection threshold by next-generation sequencing. Baseline polymorphisms in NS3 at any of the above-listed amino acid positions were detected in 1.1% (9/845), 0.8% (3/398), 1.6% (10/613), 1.2% (2/164), 41.9% (13/31), and 2.9% (1/34) of patients with HCV genotype 1, 2, 3, 4, 5, and 6 infection, respectively. Baseline polymorphisms in NS5A at any of the above-listed amino acid positions were detected in 26.8% (225/841), 79.8% (331/415), 22.1% (136/615), 49.7% (80/161), 12.9 % (4/31), and 54.1% (20/37) of subjects with HCV genotype 1, 2, 3, 4, 5, and 6 infection, respectively. The prevalence of baseline polymorphisms in NS3 was higher in GT-5 as compared to other genotypes; the high prevalence in GT-5 was due to the common D168E polymorphism, which remains susceptible to glecaprevir. In general, with the exception of GT-5, the prevalence of baseline polymorphisms was higher in NS5A than in NS3.

Genotype 1, 2, 4, 5, and 6: The presence of baseline polymorphism in NS3 and NS5A did not have an impact on SVR12 rates for GT-1, -2, -4, -5 and -6.

Genotype 3: Among 309 genotype 3-infected patients receiving the recommended duration, 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 duration, 75% (15/20) with A30K in NS5A at baseline achieved SVR12. Among genotype 3-infected patients without cirrhosis receiving the recommended regimen, 91.4% (53/58) who had polymorphisms in NS5A at baseline achieved SVR12. Among genotype 3-infected patients with compensated cirrhosis receiving the recommended regimen, 100% (18/18) who had polymorphisms in NS5A at baseline achieved SVR12.

Cross-resistance

In vitro

In vitro data indicate that the majority of the resistance-associated substitutions in NS5A at amino acid positions 24, 28, 30, 31, 58, 92, or 93 that confer resistance to ombitasvir, daclatasvir,

ledipasvir, elbasvir, or velpatasvir remained susceptible to pibrentasvir. Glecaprevir was fully active against resistance-associated substitutions in NS5A, while pibrentasvir was fully active against resistance-associated substitutions in NS3. Both glecaprevir and pibrentasvir were fully active against substitutions associated with resistance to NS5B nucleotide and non-nucleotide inhibitors.

Clinical Studies

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 analyzed by next generation sequencing at 15% detection threshold. One or more of the following NS3 polymorphisms were detected at baseline in 16% (17/105) of patients with genotype 1 infection: R155K/T (n=8) or D168A/E/N/T/V (n=10). One or more of the following NS5A substitutions were detected in 60% (63/105) of the genotype 1-infected patients: K24Q/R (n=4), L/M28A/M/T/V (n=11), Q/R30E/G/H/K/L/Q/R (n=29), L31I/M/V (n=14), H/P58C/D/P/Q/S/T/Y (n=17), A92E/T (n=2), or Y93H/N/S (n=23). The number of GT-4-infected patients enrolled in the study was small, and did not allow for analysis of resistance.

Among 23 PI-experienced/NS5A inhibitor-naïve patients receiving 12 weeks of treatment, 2 patients each had baseline polymorphisms in NS3-only, NS5A-only, or NS3+NS5A; all 23 patients achieved SVR12. Among 32 NS5A inhibitor-experienced patients (with or without PI-experience) receiving 16 weeks of treatment, SVR12 rate was 100% (1/1), 95.0% (19/20), 25.0% (1/4), and 100% (7/7) in patients with baseline polymorphisms in NS3-only, NS5A-only, NS3+NS5A, or without any polymorphisms in NS3 or NS5A, respectively.

NON-CLINICAL TOXICOLOGY

Repeat-Dose Toxicity

Glecaprevir

Glecaprevir was well tolerated without adverse effects in studies for up to 1-month (mouse), 6-months (rat) and 9-months (dog). Maximum achieved glecaprevir plasma exposures in the longest duration studies were approximately 70 times (mice and rats) and 137 times (dog) higher when compared to human exposure at the recommended dose.

Pibrentasvir

Pibrentasvir was well tolerated without adverse effects in studies for up to 6-months (rat), 3-months (mouse) and 9-months (dog). Maximum achieved pibrentasvir plasma exposures in the longest duration studies were approximately 85 times (mice), 6 times (rat) and 17 times (dog) higher when compared to human exposure at the recommended dose.

Mutagenicity and Carcinogenicity

Glecaprevir and pibrentasvir were not genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and in vivo rodent micronucleus assays.

Carcinogenicity studies with glecaprevir and pibrentasvir have not been conducted.

Fertility

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

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICATION INFORMATION

MAVIRET

glecaprevir/pibrentasvir tablets

Read this carefully before you start taking MAVIRET and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about MAVIRET.

Serious Warnings and Precautions

Hepatitis B activity (e.g., inflamed liver) may increase when taking antiviral drugs like MAVIRET, sometimes leading to liver failure and death. (See the "**To help avoid side effects…**" section, *Hepatitis B Reactivation.*)

What is MAVIRET used for?

- MAVIRET treats people with chronic (long-lasting) hepatitis C in adults. Hepatitis C is caused by an infection with the hepatitis C virus (HCV).
- There are 2 medicines in MAVIRET. They are called glecaprevir and pibrentasvir.
- It is not known if taking MAVIRET is safe and effective in children under 18 years of age.

How does MAVIRET work?

MAVIRET works by stopping the hepatitis C virus from multiplying. This will help remove the virus from your blood over time.

What are the ingredients in MAVIRET?

Each tablet contains the following medicinal ingredients: glecaprevir, pibrentasvir.

Each tablet has the following ingredients that are not medicines: copovidone (type K 28), vitamin E polyethylene glycol succinate, colloidal silicon dioxide, propylene glycol monocaprylate (type II), croscarmellose sodium, sodium stearyl fumarate, hypromellose 2910, lactose monohydrate, titanium dioxide, polyethylene glycol 3350 and iron oxide red.

What does MAVIRET look like?

MAVIRET tablets are pink, oblong, film-coated tablets that are curved on both sides, and debossed on one side with 'NXT'.

MAVIRET comes in the following dosage forms:

Each tablet has 100 mg of glecaprevir and 40 mg of pibrentasvir.

Do not use MAVIRET if:

- you are allergic to any of the ingredients in MAVIRET. (See the section "**What are the ingredients in MAVIRET?**" to see all the ingredients.)
- your doctor has told you that you have severe loss of liver function.
- you are taking any of the following medicines:
    - atazanavir (Evotaz®, Reyataz®)
    - atorvastatin (Lipitor®)
    - dabigatran etexilate (Pradaxa®)
    - ethinyl estradiol-containing medicines such as tablets or vaginal rings used to prevent pregnancy
    - rifampin (Rifadin®, Rofact®)
    - simvastatin (Zocor®)

To help avoid side effects and make sure you are using your medicines correctly, talk to your doctor before you take MAVIRET. Talk about any health problems you may have, including if you:

- have liver problems other than hepatitis C infection.
- are taking other drugs for viral infections.
- are pregnant or plan to become pregnant. The effects of MAVIRET during pregnancy are not known. Avoid pregnancy while taking MAVIRET. Tell your doctor if you become pregnant while taking MAVIRET.
- are breastfeeding or plan to breastfeed. It is not known if MAVIRET passes into your breast milk. Talk to your doctor about the best way to feed your baby if you take MAVIRET.
- have galactose intolerance (e.g., lactase deficiency or glucose-galactose malabsorption) as this product contains lactose.

Hepatitis B Reactivation

Taking antiviral drugs such as MAVIRET may increase hepatitis B activity. This can lead to liver problems such as liver failure and death. Talk to your doctor if:

- you have never been tested for hepatitis B.
- you know you have a current hepatitis B infection.
- you have had a previous hepatitis B infection.

Your doctor may order blood tests to see if you need hepatitis B treatment.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking MAVIRET.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

If you are taking any of the medicines in the table below, your doctor may need to change your dose of these medicines.

Medicines you must tell your doctor about before taking MAVIRET

Medicine	Purpose of the medicine
lovastatin pravastatin (Pravachol®) rosuvastatin (Crestor®)	to lower blood cholesterol
carbamazepine (Tegretol®) phenobarbital phenytoin (Dilantin®)	normally used for seizures
cyclosporine (Neoral®, Sandimmune®) tacrolimus (Prograf®)	to suppress the immune system
darunavir (Prezista®) efavirenz (Sustiva®, Atripla®) lopinavir/ritonavir (Kaletra®) rilpivirine (Edurant®, Complera®) ritonavir (Norvir®)	for HIV infection
digoxin (Lanoxin®)	for heart problems or high blood pressure
St John's Wort (*Hypericum perforatum*)	for mild depression
vitamin K antagonists (e.g., warfarin [Coumadin®])	to help reduce clots from forming in the blood

How to take MAVIRET:

- Take MAVIRET exactly as your doctor tells you. Do not change your dose or stop unless your doctor tells you to. If you reduce or miss a dose, the medicines may not be as effective against the virus.
- It is important that you do not miss or skip doses of MAVIRET during treatment.
- Swallow MAVIRET tablets whole. Do not chew, break, or crush MAVIRET tablets.

Usual adult dose:

- Take 3 MAVIRET tablets all at once each day with food. The type of food is not important.
- MAVIRET is taken for either 8, 12 or 16 weeks. Your doctor will tell you exactly how long you need to take MAVIRET.

Overdose:

If you think you have taken too much MAVIRET, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed dose:

If you do miss a dose and it is:

- less than 18 hours from the time you usually take MAVIRET - take the missed dose with food as soon as possible. Then take your next dose at your usual time.
- more than 18 hours from the time you usually take MAVIRET - do not take the missed dose. Take your next dose as usual with food.

Do not take a double dose to make up for a forgotten dose.

What are possible side effects from using MAVIRET?

These are not all the possible side effects you may feel when taking MAVIRET. If you experience any side effects not listed here, contact your healthcare professional.

The most common side effects of MAVIRET are tiredness and headache. You could also have nausea (feeling sick in the stomach).

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store between 2 and 30°C.
- Keep MAVIRET out of the reach and sight of children and adolescents under 18 years of age.

If you want more information about MAVIRET:

- Talk to your doctor.
- Find the most recent version of the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (www.canada.ca/en/health-canada), the manufacturer's website www.abbvie.ca, or by calling 1-888-704-8271.

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