PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrMAVIRET®

glecaprevir/pibrentasvir
tablets (100/40 mg)

Antiviral Agent

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RECENT MAJOR LABEL CHANGES

Indication (1)	06/2019
Indication, Pediatrics (1.1)	06/2019
Dosage and Administration, Recommended Dose and Dosage Adjustment (4.1)	06/2019
Warnings and Precautions, Special Populations, Pediatrics (<18 years of age) (7.1.3)	06/2019
Dosage and Administration, Recommended Dose and Dosage Adjustment (4.2)	11/2018
Warnings and Precautions, General	11/2018

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MAVIRET®

glecaprevir/pibrentasvir

PART I: HEALTH PROFESSIONAL INFORMATION

1. INDICATIONS

MAVIRET (glecaprevir/pibrentasvir) is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults and adolescent patients 12 to 18 years of age (see **DOSAGE AND ADMINISTRATION** and **CLINICAL TRIALS**).

1.1. Pediatrics (< 18 years of age)

The safety and efficacy of MAVIRET in patients less than 12 years of age have not been established. MAVIRET exposures in HCV-infected patients 12 to 18 years were comparable to those in HCV-infected adults; however, the safety and efficacy of MAVIRET in patients 12 to 18 years infected with HCV genotype 5 or 6 and/or with compensated cirrhosis and/or previously treated with a regimen containing NS5B inhibitor have not been studied.

1.2. 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.

2. CONTRAINDICATIONS

MAVIRET (glecaprevir/pibrentasvir) is contraindicated:

- 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, STRENGTHS, 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, Pharmacokinetics, 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 INTERACTIONS** section.

3. SERIOUS WARNINGS AND PRECAUTIONS BOX

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 (glecaprevir/pibrentasvir) 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, Hepatic/Biliary/Pancreatic, *Risk of Hepatitis B Virus Reactivation***).

4. DOSAGE AND ADMINISTRATION

4.1. Dosing Considerations

- MAVIRET (glecaprevir/pibrentasvir) treatment should be initiated and monitored by a physician experienced in the management of patients with HCV infection.
- MAVIRET is glecaprevir and pibrentasvir fixed-dose combination tablets.
- MAVIRET tablets should be taken with food; they should be swallowed whole and not chewed, crushed, or broken.
- 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**).

4.2. Recommended Dose and Dosage Adjustment

The recommended daily dose of MAVIRET is three glecaprevir/pibrentasvir 100/40 mg tablets (total dose: glecaprevir 300 mg and pibrentasvir 120 mg) taken orally at the same time with food without regard to fat or calorie content (see **ACTION AND CLINICAL PHARMACOLOGY**).

Table 2 and **Table 3** 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 2. Recommended MAVIRET Treatment Duration for Treatment-Naïve 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 3. 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[d]
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[d]	

(peg)interferon = interferon or pegylated interferon; GT = genotype; PI = protease inhibitor; PR = (peg)interferon/ribavirin; PRS = (peg)interferon/ribavirin + sofosbuvir; SMV = simeprevir; TVR = telaprevir*; BOC = boceprevir*; DCV = daclatasvir; LDV = ledipasvir; SOF = sofosbuvir.

a. Experienced with regimens containing (peg)interferon, 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 TVR + PR.

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

d. See **Liver or Kidney Transplant Patients** for dosing recommendations in patients with a liver or kidney transplant.

* not marketed in Canada

Pediatrics (< 18 years of age)

The recommended oral dose of MAVIRET for adolescent patients from 12 years and older is the same as for adult patients.

No dose adjustment for MAVIRET is required in adolescents 12 years and older (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Population and Conditions, *Pediatrics***).

The safety and efficacy of MAVIRET in patients less than 12 years of age have not been established. MAVIRET exposures in HCV-infected patients 12 to 18 years were comparable to those in HCV-infected adults; however, the safety and efficacy of MAVIRET in patients 12 to 18 years infected with HCV genotype 5 or 6 and/or with compensated cirrhosis and/or previously treated with a regimen containing NS5B inhibitor have not been studied.

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, Pharmacokinetics, Special Populations and Conditions, *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, Pharmacokinetics, Special Populations and Conditions, *Renal Impairment***).

Liver or Kidney Transplant Patients

MAVIRET is recommended for 12 weeks in liver or kidney transplant recipients who are HCV GT-1 to 6 treatment-naïve (TN) or GT-1, -2, -4, -5, -6 PRS- treatment experienced. A 16-week treatment duration should be considered in transplant patients who are GT-1 NS5A inhibitor-experienced (NS3/4A inhibitor-naïve) or GT-3 PRS- treatment experienced (see **Table 2**, **Table** 3 and **CLINICAL TRIALS**).

4.3. Administration

MAVIRET should be administered with food without regard to fat or calorie content (see **ACTION AND CLINICAL PHARMACOLOGY**).

4.4. Reconstitution

Not applicable.

4.5. 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.

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.

5. 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.

6. DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

MAVIRET (glecaprevir/pibrentasvir) 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 100/40 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).

7. WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General

MAVIRET (glecaprevir/pibrentasvir) should not be coadministered 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**).

Endocrine and Metabolism

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).

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–co-infected 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, *Patients Co-infected with HBV***).

Monitoring and Laboratory Tests

Patients Co-infected with HBV

Clearance of HCV may lead to increased replication of HBV in patients who are HCV/HBV co-infected. 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 HCV treatment and at post-treatment follow-up as clinically appropriate (see **WARNINGS AND PRECAUTIONS**, **Hepatic/Biliary/Pancreatic, *Risk of Hepatitis B Virus Reactivation***).

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.

Fertility

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

7.1. Special Populations

7.1.1. 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) 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, respectively, the exposure in humans at the recommended dose.

7.1.2. Breast-feeding

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.

7.1.3. Pediatrics (< 18 years of age)

No dose adjustment for MAVIRET is required in adolescents 12 years and older (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Population and Conditions, *Pediatrics***).

The safety and efficacy of MAVIRET in patients less than 12 years of age have not been established. MAVIRET exposures in HCV-infected patients 12 to 18 years were comparable to those in HCV-infected adults; however, the safety and efficacy of MAVIRET in patients 12 to 18 years infected with HCV genotype 5 or 6 and/or with compensated cirrhosis and/or previously treated with a regimen containing NS5B inhibitor have not been studied.

7.1.4. 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.

7.1.5. HCV/HBV Co-infection

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

8. ADVERSE REACTIONS

8.1. Adverse Drug Reaction Overview

The safety assessment for MAVIRET (glecaprevir/pibrentasvir) in patients with compensated liver disease (with or without cirrhosis) were derived from pooled Phase 2 and 3 studies which evaluated approximately 2,300 adult 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.

8.2. 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 adult patients receiving 8, 12, or 16 weeks of treatment with MAVIRET are presented in **Table 4**. 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 (0.4%) and for sofosbuvir and daclatasvir (0.9%).

Table 4. Adverse Reactions (All Grades) Observed in ≥ 3.0% of the Adult 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 (%)
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)
Nervous System Disorders				
Headache	171 (11.3)	106 (16.8)	21 (18.6)	298 (13.2)
Skin and Subcutaneous Tissue Disorders				
Pruritus	61 (4.0)	12 (1.9)	2 (1.8)	75 (3.3)

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 (%)

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 Adult 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 5**. 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 5. Adverse Reactions (All Grades) Observed in ≥ 3% of the Adult Patients with Severe Renal Impairment Including Patients on Dialysis (EXPEDITION-4)

SOC Preferred Term	MAVIRET 12 weeks N = 104 (%)
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
Metabolism and Nutrition Disorders	
Decreased appetite	4.8
Nervous System Disorders	
Headache	5.8
Dizziness	3.8
Psychiatric Disorders	
Insomnia	3.8
Skin and Subcutaneous Tissue Disorders	
Pruritus	17.3

Adverse Reactions in HCV/HIV-1 Co-infected Adult Patients

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

Adverse Reactions in Adult Patients with Liver or Kidney Transplant

The safety of MAVIRET was assessed in 100 post-liver or -kidney transplant recipients with genotypes 1, 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.

8.3. Less Common Clinical Trial Adverse Drug Reactions (<1%)

Not Applicable

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

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.

8.5. Clinical Trial Adverse Reactions (Pediatrics)

The safety of MAVIRET in HCV GT1-6 infected adolescent patients is based on data from a Phase 2/3 open-label trial in 47 patients aged 12 years to less than 18 years treated with MAVIRET for 8 to 16 weeks (M16-123, DORA-Part 1), The adverse reactions observed were comparable with those observed in clinical studies of MAVIRET in adults.

8.6. Post-Market Adverse Drug Reactions

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

9. DRUG INTERACTIONS

9.1. Serious Drug Interactions Box

Not applicable.

9.2. Overview

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 (glecaprevir/pibrentasvir) 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. Coadministration 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**).

9.3. Drug-Drug Interactions

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

Table 6 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 6. 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.

Concomitant Drug Class: Drug Name	Effect on Concentration[a,b]	Clinical Comments
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 coadministered 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.

Concomitant Drug Class: Drug Name	Effect on Concentration[a,b]	Clinical Comments
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 7** and **Table 8**

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 with No Observed 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

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 7** and **Table 8** summarize the pharmacokinetic effects when glecaprevir/pibrentasvir was coadministered with other drugs which showed potentially clinically relevant changes.

Table 7. Drug Interactions: Changes in Pharmacokinetic Parameters of Glecaprevir (GLE) or Pibrentasvir (PIB) in the Presence of Coadministered 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							
				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							
				GLE	6.52 (5.06, 8.41)	8.55 (7.01, 10.4)	--
				PIB	↔	↔	--
				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							
				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)
				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)
				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							
				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)
				GLE	4.51 (3.63, 6.05)	5.08 (4.11, 6.29)	--
				PIB	↔	1.93 (1.78, 2.09)	--

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}
PROTON PUMP INHIBITORS							
				GLE	0.78 (0.60, 1.00)	0.71 (0.58, 0.86)	--
				PIB	↔	↔	--
				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.

c. HCV-infected transplant recipients who received cyclosporine doses of 100 mg or less per day had glecaprevir exposures 2.4-fold of those not receiving cyclosporine.

Table 8. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Combination of Glecaprevir/Pibrentasvir (GLE/PIB)

Co-administered 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)				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)
ethinyl estradiol				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)

Co-administered Drug	Regimen of Coadministered Drug (mg)	Regimen of GLE/PIB (mg)	N	Central Value Ratio (90% CI)		
				C_{max}	AUC	C_{min}
HCV-ANTIVIRAL AGENTS						
sofosbuvir			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 daily	300/120 once daily	12	↔	1.29 (1.23, 1.35)	1.38 (1.31, 1.46)
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				↔	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				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)	--

COBI = cobicistat; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine

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

9.4. Drug-Food Interactions

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

9.5. 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 6**).

9.6. Drug-Laboratory Test Interactions

Interactions of MAVIRET with laboratory tests have not been established.

10. ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

MAVIRET (glecaprevir/pibrentasvir) 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 **Clinical** Study in Adolescent Patients

Trial Design and Study Demographics

DORA (Part 1) was an open-label trial to evaluate safety and efficacy in 47 adolescent patients (age range: 12-17 years old; weight range: 32 to 109 kg) without cirrhosis who received MAVIRET for 8 weeks (44 patients) or 16 weeks (3 patients), as summarized in **Table 27.**

The demographic and disease characteristic of the patient population in DORA Part 1 are summarized in **Table 27.**

Table 27. Demographic and Other Baseline Characteristics of the Adolescent Patient Population (DORA Part 1)

Characteristics	MAVIRET N=47 n (%)
Gender	
Male	21 (44.7)
Female	26 (55.3)
Race	
White	35 (74.5)
Black	5 (10.6)
Asian	6 (12.8)

Characteristics	MAVIRET N=47 n (%)
Other	1 (2.1)
Viral Load	
HCV RNA (Log10 IU/mL), mean (SD)	6.11 (0.60)
HCV Genotype/Subtype	
1	37 (78.7)
2	3 (6.4)
3	4 (8.5)
4	3 (6.4)
Prior Treatment History	
TN	36 (76.6)
TE-PR	11 (23.4)
Stages of Fibrosis	
F0-F2	46 (97.9)
F3	1 (2.1)
HCV/HIV Co-infection	
Yes	2 (4.3)
No	45 (95.7)

SD = standard deviation; GT = genotype; TN = treatment-naïve; TE-PR = treatment experienced to regimens containing interferon, (peg)interferon and/or ribavirin

Study Results

The response rates in adolescent patients with chronic HCV infection are presented in **Table** 28. No patients experienced virologic failure.

Table 28. Sustained Virologic Response (SVR12) in HCV-Infected Adolescent Patients (DORA Part 1)

Assessment	MAVIRET N = 47
SVR12, % (n/N)	100 (47/47)
95% CI, (%)	(92.4, 100.0)

SVR12 = sustained virologic response 12 weeks post-treatment; CI = confidence interval

MICROBIOLOGY).

10.1. 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.

10.2. 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]
	C_{max} (ng/mL)	1,230	1,110	597
	AUC_{24} (ng·h/mL)	4,380	10,500	4,800
	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

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

Geriatrics

Within the age range (12 to 88 years) analyzed, age did not have a clinically relevant effect on exposure of glecaprevir or pibrentasvir.

Sex

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

Pregnancy and Breast-feeding

There are no data on the use of MAVIRET in pregnant women, and it is unknown whether glecaprevir or pibrentasvir are excreted in human milk (see **WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women** and **Breast-feeding**).

Genetic Polymorphism

Genetic polymorphism such as SLCO1B1 phenotype for OATP1B1 showed no clinically significant impact on glecaprevir exposure.

Ethnic origin

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** and **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).**

Obesity

Body weight did not have a clinically relevant effect on exposure of glecaprevir or pibrentasvir.

11. STORAGE, STABILITY AND DISPOSAL

Temperature:

Store between 2 and 30°C.

Others:

Keep out of reach and sight of children.

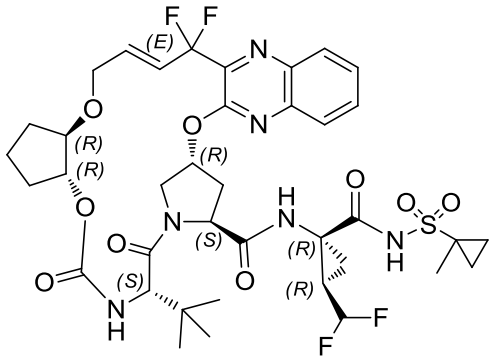
12. SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13. PHARMACEUTICAL INFORMATION

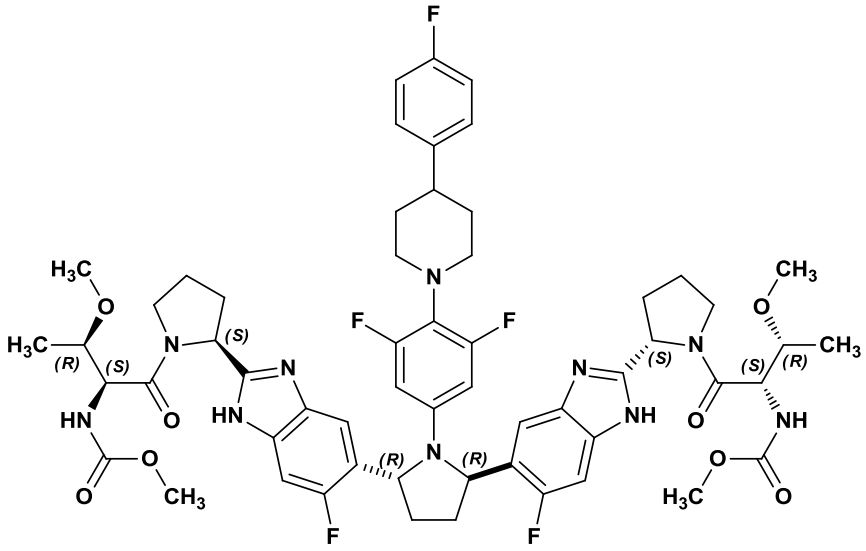
Glecaprevir

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

Pibrentasvir

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

14. CLINICAL TRIALS

The efficacy and safety of MAVIRET (glecaprevir/pibrentasvir) was evaluated in nine Phase 2-3 clinical trials, in over 2,300 adult 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 Adult 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				
	ENDURANCE-1[a] (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
	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
	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

HCV Genotype (GT)	Study #	Number of Patients Treated N (regimen)	Trial Design	Dosage, Route of Administration and Duration
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-1 to -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
HCV/HIV-1 co-infected patients with or without cirrhosis				
GT-1 to -4, -6	EXPEDITION-2 (M14-730)	137 (8 weeks) 16 (12 weeks)	Open-label	glecaprevir/pibrentasvir tablet : 300/120 mg QD Oral 8 or 12 weeks

HCV Genotype (GT)	Study #	Number of Patients Treated N (regimen)	Trial Design	Dosage, Route of Administration and Duration
Liver or kidney transplant recipients				
GT-1 to -4, -6	MAGELLAN-2 (M13-596)	100 (12 weeks)	Single-arm, open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 12 weeks

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

a. ENDURANCE-1 included 33 patients co-infected with HIV-1.

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.

Among adult 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.

14.1. Clinical Studies in Treatment-Naïve or Treatment-Experienced-PRS Adult 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)

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 (%)	
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)

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

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

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 (peg) 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-Naïve Patients and Patients Experienced[a] to (Peg)interferon, 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 patients without cirrhosis					
8 weeks	99.0 (383/387)	98.0 (193/197)	93.5 (43/46)	100 (2/2)	90.0 (9/10)
Outcome for patient 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 patients with cirrhosis					
12 weeks	97.0 (98/101)	100 (35/35)	100 (20/20)	100 (2/2)	100 (7/7)

	GT-1[b] % (n/N)	GT-2 % (n/N)	GT-4 % (n/N)	GT-5 % (n/N)	GT-6 % (n/N)
Outcome for patients 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-Naïve Patients and Patients Experienced to (Peg)interferon, 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)

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/HIV Co-infection[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 = (peg)interferon/ribavirin; TN = treatment-naïve; TE = treatment-experienced; PRS = regimens containing (peg)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 co-infection, 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.

14.2. Clinical Studies in Genotype 3 Infected Adult 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 Genotype 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 = (peg)interferon/ribavirin; PRS = regimens containing (peg)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-naïve 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-Naïve Patients and Patients Experienced to (Peg)interferon, 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 (peg)interferon, ribavirin and/or sofosbuvir; P/R = (peg)interferon/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.

14.3. Clinical Study in Chronic Kidney Disease (CKD) Adult 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)

Characteristics	MAVIRET 12 Weeks N=104 n (%)
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 = (peg)interferon/ribavirin; BMI = body mass index; GT = genotype; PRS = regimens containing (peg)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 m2.

c. Stage 5 defined as eGFR < 15 mL/min/1.73 m2

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 1 to 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 = (peg)interferon/ribavirin; GT = genotype; PRS = regimens containing (peg)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 = (peg)interferon/ribavirin; GT = genotype; PRS = regimens containing (peg)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 m2.

b. Stage 5, defined as eGFR < 15 mL/min/1.73 m2.

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.

14.4. Clinical Study in Treatment-Naïve or Treatment-Experienced-PRS Adult Patients with HCV/HIV-1 Co-infection with or without Cirrhosis

EXPEDITION-2 was an open-label study in HCV/HIV-1 co-infected patients, in which patients without cirrhosis received MAVIRET for 8 weeks, and patients with cirrhosis received MAVIRET for 12 weeks.

The demographic and disease characteristics of the patient population in EXPEDITION-2 are summarized in **Table 20**.

Table 20. Demographic and Other Baseline Characteristics of the HCV/HIV-1 Co-Infected Patient Population with or without cirrhosis (EXPEDITION-2)

Characteristics	MAVIRET 8 or 12 Weeks N=153 n (%)
Age	
< 65	151 (98.7)
≥ 65	2 (1.3)
Gender	
Male	128 (83.7)
Female	25 (16.3)
Race	
White	121 (79.1)
Black	25 (16.3)
Asian	6 (3.9)
Other	1 (0.7)
Viral Load	
HCV RNA (Log_{10} IU/mL), mean (SD)	6.09 (0.70)
BMI	
< 30 kg/m^2	128 (83.7)
≥ 30 kg/m^2	25 (16.3)
HCV Genotype/Subtype	
1	94 (61.4)
2	13 (8.5)
3	26 (17.0)
4	17 (11.1)
6	3 (2.0)
Prior Treatment History	
TN	125 (81.7)
TE-PRS	28 (18.3)

Characteristics	MAVIRET 8 or 12 Weeks N=153 n (%)
Stages of Fibrosis	
F0-F2	122 (79.7)
F3	15 (9.8)
F4	16 (10.5)
Cirrhosis	
Yes	16 (10.5)
Child-Pugh Score 5 cirrhosis	15 (9.8)
Child-Pugh Score 6 cirrhosis	0
Child-Pugh Score > 6 cirrhosis	1 (0.7)
No	137 (89.5)

SD = standard deviation; BMI = body mass index; GT = genotype; TN = treatment-naïve; TE-PRS = treatment experienced to regimens containing interferon, (peg)interferon, ribavirin, and/or sofosbuvir

Study Results

The response rates in HCV/HIV-1 co-infected patients are presented in **Table 21.**

Table 21. Sustained Virologic Response (SVR12) in HCV/HIV-1 Co-Infected Patients (EXPEDITION-2)

Assessment	MAVIRET N=153 % (n/N)
SVR12	98.0% (150/153)
95% CI	(95.8, 100.0)
Outcome in Patients Without SVR	
On treatment VF	0.7 (1/153)
Relapse[a]	0 (0/151)
Other[b]	1.3 (2/153)

VF = virologic failure

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

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

Among patients without cirrhosis that received 8 weeks of MAVIRET, the overall SVR12 rate was 99.3% (136/137) (99.1% [110/111] for treatment-naïve patients and 100% [26/26] for PRS-treatment-experienced patients).

14.5. Overall SVR12 Rate from the Clinical Studies in Treatment-Naïve or Treatment-Experienced-PRS Adult Patients with or without Cirrhosis

Among all patients, regardless of renal function, cirrhosis status, or presence of HIV-1 co-infection, who were treatment-naïve or treatment-experienced to combinations of (peg)interferon, ribavirin, and/or sofosbuvir and infected with any HCV genotype who received the recommended treatment duration, 97.5% (1252/1284) achieved SVR12, 0.3% (4/1284) experienced on-treatment virologic failure, and 0.9% (11/1262) experienced post-treatment relapse.

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

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

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

The presence of HIV-1 co-infection did not impact efficacy. Among HCV/HIV-1 co-infected patients from ENDURANCE-1 and EXPEDITION-2 combined who were treatment-naïve or PRS-treatment-experienced treated with the recommended duration, the SVR12 rate was 98.2% (165/168). One (1/168; 0.6%) patient experienced on-treatment virologic failure and no patients relapsed.

14.6. Clinical Studies in NS5A Inhibitor and/or Protease Inhibitor (NS3/4A) Treatment-Experienced Adult 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 22**.

Table 22. 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 (years)		
< 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 Genotype/Subtype		
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)

Characteristics	MAVIRET 12 Weeks N=43 % (n/N)	MAVIRET 16 Weeks N=44 % (n/N)
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 23**. 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 23. 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 24**.

Table 24. 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.

14.7. Clinical Study in Liver or Kidney Transplant Recipients

Demographic and Other Baseline Characteristics

MAGELLAN-2 was a single-arm, open-label study in post-liver or -kidney transplant HCV infected patients without cirrhosis.

In this study, the immunosuppressants allowed for co-administration were cyclosporine ≤100 mg, tacrolimus, sirolimus, everolimus, azathioprine, mycophenolic acid, prednisone, and prednisolone.

The demographic and disease characteristics of the patient population in MAGELLAN-2 are summarized in **Table 25**.

Table 25. Demographic and Other Baseline Characteristics of the Liver or Kidney Transplant Recipient Patient Population with or without Cirrhosis (MAGELLAN-2)

Characteristics	MAVIRET 12 Weeks N=100 n (%)
Age	
< 65	74 (74.0)
≥ 65	26 (26.0)
Gender	
Male	75 (75.0)
Female	25 (25.0)
Race	
White	78 (78.0)
Black	8 (8.0)
Asian	10 (10.0)
Other	4 (4.0)
Viral Load	
HCV RNA (Log_{10} IU/mL), mean (SD)	6.42 (0.72)
BMI	
< 30 kg/m^2	73 (73.0)
≥ 30 kg/m^2	27 (27.0)
HCV Genotype/Subtype	
1	57 (57.0)
2	13 (13.0)
3	24 (24.0)
4	4 (4.0)
6	2 (2.0)

Characteristics	MAVIRET 12 Weeks N=100 n (%)
Prior Treatment History	
TN	66 (66.0)
TE-PRS	34 (34.0)[a]
Stages of Fibrosis	
F0-F2	86 (86.0)
F3	14 (14.0)
Transplant type	
Liver	80 (80.0)
Kidney	20 (20.0)

SD = standard deviation; BMI = body mass index; GT = genotype; TN = treatment-naïve; TE-PRS = treatment experienced to regimens containing interferon, (peg)interferon, ribavirin, and/or sofosbuvir;

a. One patient previously received boceprevir + pegIFN/RBV. No other patients with prior treatment experience with NS5A inhibitors or NS3/4A protease inhibitors were included in the study.

Study Results

The response rates in post-liver or kidney transplant patients are presented in **Table 26**.

Table 26. Sustained Virologic Response (SVR12) in Post-Liver or Kidney Transplant Recipient Patients (MAGELLAN-2)

Assessment	MAVIRET 12 Weeks N=100 % (n/N)
SVR12	98.0 (98/100)
95% CI	(95.3, 100.0)
Outcomes in Patients Without SVR	
On Treatment VF	0 (0/100)
Relapse[a]	1 (1/99)
Other[b]	1 (1/100)

VF = virologic failure

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

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

14.8. Clinical Study in Adolescent Patients

Trial Design and Study Demographics

DORA (Part 1) was an open-label trial to evaluate safety and efficacy in 47 adolescent patients (age range: 12-17 years old; weight range: 32 to 109 kg) without cirrhosis who received MAVIRET for 8 weeks (44 patients) or 16 weeks (3 patients), as summarized in **Table 27**.

The demographic and disease characteristic of the patient population in DORA Part 1 are summarized in **Table 27**.

Table 27. Demographic and Other Baseline Characteristics of the Adolescent Patient Population (DORA Part 1)

Characteristics	MAVIRET N=47 n (%)
Gender	
Male	21 (44.7)
Female	26 (55.3)
Race	
White	35 (74.5)
Black	5 (10.6)
Asian	6 (12.8)
Other	1 (2.1)
Viral Load	
HCV RNA (Log_{10} IU/mL), mean (SD)	6.11 (0.60)
HCV Genotype/Subtype	
1	37 (78.7)
2	3 (6.4)
3	4 (8.5)
4	3 (6.4)
Prior Treatment History	
TN	36 (76.6)
TE-PR	11 (23.4)
Stages of Fibrosis	
F0-F2	46 (97.9)
F3	1 (2.1)

Characteristics	MAVIRET N=47 n (%)
HCV/HIV Co-infection	
Yes	2 (4.3)
No	45 (95.7)

SD = standard deviation; GT = genotype; TN = treatment-naïve; TE-PR = treatment experienced to regimens containing interferon, (peg)interferon and/or ribavirin

Study Results

The response rates in adolescent patients with chronic HCV infection are presented in **Table 28.** No patients experienced virologic failure.

Table 28. Sustained Virologic Response (SVR12) in HCV-Infected Adolescent Patients (DORA Part 1)

Assessment	MAVIRET N = 47
SVR12, % (n/N)	100 (47/47)
95% CI, (%)	(92.4, 100.0)

SVR12 = sustained virologic response 12 weeks post-treatment; CI = confidence interval

15. MICROBIOLOGY

MAVIRET (glecaprevir/pibrentasvir) 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 29**.

Table 29. 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 30**.

Table 30. 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 (Peg)interferon, 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, P32 deletion, 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 (peg)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 patients 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.

16. NON-CLINICAL TOXICOLOGY

General Toxicology (repeat-dose studies)

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.

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.

Reproductive and Developmental Toxicology

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

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 adults and adolescents 12 years and older with chronic (long-lasting) hepatitis C. Hepatitis C is caused by an infection with the hepatitis C virus (HCV).
- It is not known if taking MAVIRET is safe and effective in children under 12 years of age.

How does MAVIRET work?

There are 2 medicines in each MAVIRET pill: glecaprevir and pibrentasvir. These medicines work together to stop hepatitis C virus from multiplying and to remove the virus from your blood over time. MAVIRET can cure HCV infection in most patients. Cure means HCV remains cleared from your blood 3 months after finishing the medicine.

Talk with your doctor about ways to avoid getting infected again with HCV.

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 milligrams of glecaprevir and 40 milligrams 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 liver problems.
- 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.
- have had a liver or a kidney transplant.
- 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 and adolescent (12 to less than 18 years of age) dose:

- Take 3 MAVIRET tablets all at once each day (once daily) 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.

If you vomit (throw up) and it has been less than 3 hours after taking MAVIRET, you should take another dose. If you vomit and it has been more than 3 hours after taking MAVIRET, do not take another 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.

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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