

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

Pr MAVIRET®

glecaprevir/pibrentasvir tablets and granules

Tablets, glecaprevir 100 mg / pibrentasvir 40 mg, oral  
Granules, glecaprevir 50 mg / pibrentasvir 20 mg per sachet, oral

Antiviral Agent (ATC Code: J05AP57)

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## RECENT MAJOR LABEL CHANGES

Indication (1)	11/2021
Indication (1), Pediatrics (1.1)	11/2021
Dosage and Administration (4), Recommended Dose and Dosage Adjustment (4.2)	11/2021
Warnings and Precautions (7), Special Populations (7.1), Pediatrics (7.1.3)	11/2021
Warnings and Precautions (7), Monitoring and Laboratory Tests	06/2020
Warnings and Precautions (7), Hepatic Decompensation and Hepatic Failure	03/2021

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## **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 pediatric patients 3 years of age and older and weighing  $\geq 12$  kg (see [4 DOSAGE AND ADMINISTRATION](#) and [14 CLINICAL TRIALS](#)).

#### **1.1 Pediatrics**

Pediatrics (3 to less than 18 years old): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of MAVIRET in pediatric patients 3 to 18 years old has been established. Therefore, Health Canada has authorized an indication for pediatric use (see [4 DOSAGE AND ADMINISTRATION](#) and [14 CLINICAL TRIALS](#)).

MAVIRET has not been authorized for use in pediatric patients less than 3 years of age.

#### **1.2 Geriatrics**

In clinical studies of MAVIRET, 328 patients were age 65 and over and 47 were age 75 and over. No overall difference 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 is contraindicated:

- in patients who are hypersensitive to this drug or to any ingredient in the formulation or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see the [6 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 [10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Impairment](#)).

**Table 1. Drugs that Are Contraindicated with MAVIRET**

<b>Drug Class/Drug Name</b>	<b>Effect on Concentration</b>	<b>Mechanism of Action</b>	<b>Clinical Comment</b>
<b>ANTICOAGULANTS</b>			
dabigatran etexilate	↑ dabigatran	Inhibition of P-gp by MAVIRET	Coadministration with MAVIRET increased dabigatran concentrations and may increase the risk of bleeding.
<b>ANTIMYCOBACTERIAL</b>			
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.
<b>ANTIVIRAL</b>			
atazanavir	↑ glecaprevir ↑ pibrentasvir	Unknown	Risk of alanine aminotransferase (ALT) elevations when coadministered with MAVIRET.
<b>ETHINYL ESTRADIOL-CONTAINING PRODUCTS</b>			
ethinyl estradiol	↑ ethinyl estradiol	Unknown	Risk of ALT elevations when coadministered with MAVIRET.
<b>HMG-CoA REDUCTASE INHIBITORS</b>			
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 <a href="#">9 DRUG INTERACTIONS</a> 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 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 [7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Risk of Hepatitis B Virus Reactivation](#)).

### 4 DOSAGE AND ADMINISTRATION

#### 4.1 Dosing Considerations

- MAVIRET treatment should be initiated and monitored by a physician experienced in the management of patients with HCV infection.
- 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 [7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Risk of Hepatitis B Virus Reactivation](#)).

#### 4.2 Recommended Dose and Dosage Adjustment

**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	

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 <sup>a</sup>	8 Weeks	12 Weeks <sup>d</sup>
GT-1	NS3/4A PI <sup>b</sup> (NS5A inhibitor-naïve)	12 Weeks	

HCV Genotype	Treatment History	Treatment Duration	
		Without Cirrhosis	With Cirrhosis
GT-1	NS5A <sup>c</sup> (NS3/4A inhibitor-naïve)	16 Weeks	
GT-3	PRS <sup>a</sup>	16 Weeks <sup>d</sup>	

(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.

- 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.
- Experienced with regimens containing SMV + SOF or SMV + PR or BOC + PR or TVR + PR.
- Experienced with regimens containing DCV + SOF, DCV + PR, or LDV + SOF.
- See **Liver or Kidney Transplant Patients** for dosing recommendations in patients with a liver or kidney transplant.

\* not marketed in Canada

### **Recommended Dosage of MAVIRET Tablets in Adults, Adolescents 12 Years and Older, or Pediatric Patients Weighing at Least 45 kg**

MAVIRET tablets are a fixed-dosed combination product containing glecaprevir 100 mg and pibrentasvir 40 mg in each tablet.

MAVIRET tablets should be taken with food; they should be swallowed whole and not chewed, crushed or broken.

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 [10 CLINICAL PHARMACOLOGY](#)).

The treatment duration for adults and adolescents are noted in **Table 2** and **Table 3** above.

### **Recommended Dosage of MAVIRET Granules in Sachets in Pediatric Patients 3 Years and Older (Weighing at least 12 kg to less than 45 kg)**

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

MAVIRET granules should be taken with food. The number of sachets and dosage based on body weight for pediatric patients 3 years and older and weighing 12 kg to less than 45 kg are in **Table 4**.

The treatment duration for pediatric patients 3 years and older and weighing 12 kg to less than 45 kg are the same as those for adults and adolescents as noted in **Table 2** and **Table 3** above.

Because the formulations have different pharmacokinetic profiles, the tablets and the granules are not interchangeable.

**Table 4. Recommended Dosage of MAVIRET Granules in Sachets for Pediatric Patients 3 Years to Less than 12 Years Old and Weighing 12 kg to less than 45 kg**

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

The adult and adolescent dose of MAVIRET tablets should be used in children weighing 45 kg or greater (See **Recommended Dosage of MAVIRET Tablets in Adults, Adolescents 12 Years and Older, or Pediatric Patients Weighing at Least 45 kg**). See the **Instructions for Use** for details on the preparation and administration of MAVIRET granules in sachets.

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

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

**Pediatrics (< 18 years of age)**

Pediatric patients from 3 to less than 12 years of age should receive doses based on body weight. See **Recommended Dosage of MAVIRET Granules in Sachets in Pediatric Patients 3 Years and Older (Weighing at least 12 kg to less than 45 kg)**.

No dose adjustment for MAVIRET is required in adolescents 12 years and older (see [10.3 Pharmacokinetics, Special Populations and Conditions, Pediatrics](#)).

The safety and efficacy of MAVIRET in patients less than 3 years of age or weighing less than 12 kg have not been established.

MAVIRET has not been authorized for use in pediatric patients less than 3 years of age.

**Geriatrics (> 65 years of age)**

No dose adjustment of MAVIRET is required in geriatric patients.

**Gender**

No dose adjustment of MAVIRET is necessary based on gender.

**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 [2 CONTRAINDICATIONS](#) and [10.3 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 [10.3 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 genotype 1 to 6 treatment-naïve (TN) or genotype 1, 2, 4, 5, 6 PRS-treatment experienced. A 16-week treatment duration should be considered in transplant patients who are genotype 1 NS5A inhibitor-experienced (NS3/4A inhibitor-naïve) or genotype 3 PRS-treatment experienced (see **Table 2, Table 3** and [14.1 Clinical Trials by Indication, Clinical Study in Liver or Kidney Transplant Recipients](#)).

**4.3 Reconstitution**

Not applicable.

**4.4 Administration**

MAVIRET should be administered with food without regard to fat or calorie content (see [10.3 Pharmacokinetics, Absorption, Effects of Food on Oral Absorption](#)).

**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

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.

For management of a suspected drug overdose, contact your regional poison control centre.

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 5. Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablets 100/40 mg glecaprevir/pibrentasvir	colloidal silicon dioxide, propylene glycol monocaprylate (type II), copovidone (type K 28), croscarmellose sodium, film-coating (hypromellose 2910, lactose monohydrate, titanium dioxide, polyethylene glycol 3350 and iron oxide red), sodium stearyl fumarate and vitamin E polyethylene glycol succinate.
Oral	Granules in Sachet 50/20 mg glecaprevir/pibrentasvir	colloidal silicon dioxide, copovidone (type K 28), croscarmellose sodium (in the glecaprevir granules only), hypromellose 2910, iron oxide red, iron oxide yellow, lactose monohydrate, polyethylene glycol/macrogol 3350, propylene glycol monocaprylate (type II), sodium stearyl fumarate, titanium dioxide, vitamin E (tocopherol) polyethylene glycol succinate.

### Tablets

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

MAVIRET tablets are 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.

MAVIRET tablets are gluten free.

### Granules in sachet

MAVIRET granules are for oral administration, supplied as small pink and yellow granules in unit-dose sachets.

MAVIRET unit-dose sachets are dispensed in a carton. Each carton contains 28 sachets.

Each unit-dose sachet of MAVIRET oral granules contains 50 mg glecaprevir and 20 mg pibrentasvir.

MAVIRET granules are gluten free.

## 7 WARNINGS AND PRECAUTIONS

Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.

### General

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

The number of patients infected with genotype 5 and genotype 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 [9.4 Drug-Drug Interactions, Table 8](#)).

### 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).

### HCV/HBV Co-infection

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

### Hepatic/Biliary/Pancreatic

#### *Hepatic Decompensation and Hepatic Failure*

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 [2 CONTRAINDICATIONS](#)). There have been post-marketing case reports of hepatic decompensation and hepatic failure, including fatal outcomes, mostly in cirrhotic patients treated with HCV NS3/4A protease inhibitor-containing regimens, including MAVIRET. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Hepatic laboratory testing should be performed as clinically indicated in patients with compensated cirrhosis (Child-Pugh A) or evidence of advanced liver disease such as portal hypertension. In patients with cirrhosis, more frequent hepatic laboratory testing may be warranted; and patients should be monitored for signs and symptoms of hepatic decompensation such as the presence of jaundice, ascites, hepatic encephalopathy, and variceal hemorrhage. Discontinue MAVIRET in patients who develop evidence of hepatic decompensation/ failure.

#### *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 [7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Testing, 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 [7 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.

### ***Potential Effects of HCV Clearance by Direct-Acting Antivirals (DAA) (Class Therapeutic Effect)***

Clearance of HCV infection with direct-acting antivirals may lead to changes in hepatic function, which may impact the safe and effective use of concomitant medications. For example, patients may experience improved glucose metabolism by the liver. In diabetic patients, this could lead to improved glucose control. Rare cases of symptomatic hypoglycemia have been reported with the use of HCV DAAs. Close monitoring of relevant laboratory parameters such as blood glucose levels in diabetic patients or International Normalized Ratio [INR] in patients taking vitamin K antagonists is recommended to ensure safe and effective use. Dose adjustments of concomitant medications may be necessary (see [9 DRUG INTERACTIONS](#)).

## **Reproductive Health: Female and Male Potential**

- **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 [16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental 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**

Because the tablet and pediatric granule formulations have different pharmacokinetic profiles, the tablets and the granules are not interchangeable.

No dose adjustment for MAVIRET is required in adolescents 12 years and older (see [10.3 Pharmacokinetics, Special Populations and Conditions, Pediatrics](#)). Pediatric patients aged 3 to less than 12 years of age and weighing 12 kg to less than 45 kg should receive doses based on body weight (see [4 DOSAGE AND ADMINISTRATION](#)).

MAVIRET exposures in HCV-infected patients 12 to less than 18 years were comparable to those in HCV-infected adults. The safety and efficacy of MAVIRET in patients 3 to less than 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. The safety and efficacy of MAVIRET in patients less than 3 years of age or weighing less than 12 kg have not been established.

### **7.1.4 Geriatrics**

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.

## **8 ADVERSE REACTIONS**

### **8.1 Adverse Reaction Overview**

The safety assessment for MAVIRET in patients with compensated liver disease (with or without cirrhosis) were derived from pooled Phase 2 and 3 registrational 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 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 6**. 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 adverse drug reactions (ADRs) was similar for MAVIRET (0.4%) and for sofosbuvir and daclatasvir (0.9%).

**Table 6. Adverse Reactions (All Grades) Observed in  $\geq$  3.0% of the Adult Patients in Phase Registrational 2, 3 Clinical Studies**

System Organ Class (SOC) Preferred Term	MAVIRET <sup>a</sup> GT-1, -2, -4, -5 -6 8, 12 weeks N = 1,520 n (%)	MAVIRET <sup>b</sup> GT-3 8, 12, 16 weeks N = 632 n (%)	MAVIRET <sup>c</sup> PI or NS5A-I Experienced 12, 16 weeks N = 113 n (%)	MAVIRET <sup>d</sup> Overall N = 2,265 n (%)
<b>General Disorders and Administration Site Conditions</b>				
Fatigue	158 (10.4)	92 (14.6)	9 (8.0)	259 (11.4)
<b>Gastrointestinal Disorders</b>				
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)
<b>Nervous System Disorders</b>				
Headache	171 (11.3)	106 (16.8)	21 (18.6)	298 (13.2)

System Organ Class (SOC) Preferred Term	MAVIRET <sup>a</sup> GT-1, -2, -4, -5 -6 8, 12 weeks N = 1,520 n (%)	MAVIRET <sup>b</sup> GT-3 8, 12, 16 weeks N = 632 n (%)	MAVIRET <sup>c</sup> PI or NS5A-I Experienced 12, 16 weeks N = 113 n (%)	MAVIRET <sup>d</sup> Overall N = 2,265 n (%)
<b>Skin and Subcutaneous Tissue Disorders</b>				
Pruritus	61 (4.0)	12 (1.9)	2 (1.8)	75 (3.3)
<p>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.</p> <p>b. ADRs observed in registrational studies M14-868 and M13-594 for GT-3 with or without compensated cirrhosis.</p> <p>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.</p> <p>d. Total ADRs observed across all groups TN, PRS-TE or PI and/or NS5A-I experienced and GT-1 to 6 with or without cirrhosis.</p>				

#### 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 7**. 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 7. 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 (%)
<b>General Disorders and Administration Site Conditions</b>	
Fatigue	11.5
Asthenia	6.7
<b>Gastrointestinal Disorders</b>	
Nausea	8.7
Diarrhea	3.8
Gastroesophageal Reflux Disease	3.8

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

#### **Adverse Reactions in People Who Inject Drugs (PWID) and those on Medication-Assisted Treatment (MAT) for Opioid Use Disorder**

The safety of MAVIRET in PWID with HCV genotype 1, 2, 3, 4, 5 or 6 infection is based on data from Phase 2 and 3 trials of adults and adolescents in which 62 patients identified as current/recent PWID (defined as self-reported injection drug use within the last 12 months prior to starting MAVIRET), and 3,282 patients reported no injection drug use (non-PWID).

Among current/recent PWID, adverse reactions observed in greater than or equal to 5% of patients were fatigue (16%), headache (13%), diarrhea (6%), and nausea (6%). Among non-PWID patients, adverse reactions observed in greater than or equal to 5% of patients were headache (7%) and fatigue (6%). Serious adverse reactions and/or adverse reactions leading to treatment discontinuation occurred in one current/recent PWID patient (2%) as compared to less than 1% in non-PWID patients.

Among 225 patients reporting concomitant use of MAT for opioid use disorder, adverse reactions observed in greater than or equal to 5% of patients were headache (15%), fatigue (12%), nausea (11%), and diarrhea (6%). Among 4,098 patients who were not on MAT, adverse reactions observed in greater

than or equal to 5% of patients were headache (9%), fatigue (8%), and nausea (5%). Serious adverse reactions and/or adverse reactions leading to treatment discontinuation were not observed among patients on MAT and were experienced by less than 1% of patients not on MAT.

### **8.2.1 Clinical Trial Adverse Reactions – Pediatrics**

The safety of MAVIRET in HCV genotype 1 to 6 infected adolescent patients is based on data from a Phase 2 and 3 open-label trial in 47 patients aged 12 years to less than 18 years treated with MAVIRET for 8 to 16 weeks (M16-123, DORA-Part 1). The adverse reactions observed in patients 12 to less than 18 years of age were consistent with those observed in clinical trials of MAVIRET in adults. The only adverse reactions observed in greater than or equal to 3% of patients receiving MAVIRET in DORA-Part 1 were fatigue (occurring at 6%), abdominal pain, and decreased appetite (each occurring at 4%). No patients discontinued or interrupted treatment with MAVIRET due to an adverse reaction.

The safety of MAVIRET in HCV GT 1-6 infected children aged 3 to less than 12 years of age is based on data from a Phase 2 and 3 open-label trial in 80 patients aged 3 to less than 12 years of age treated with weight-based MAVIRET granules in sachets for 8 to 16 weeks (DORA-Part 2).

The adverse reactions observed in patients 3 years to less than 12 years of age were consistent with those observed in clinical trials of MAVIRET in adults with the exception of vomiting (occurring at approximately 8%), rash, and abdominal pain upper (each occurring at approximately 4%) which were observed more frequently in pediatric patients less than 12 years of age compared to adults. Other adverse reactions observed in greater than or equal to 3% of patients receiving MAVIRET in DORA-Part 2 include fatigue and headache, each occurring at approximately 8%, and diarrhoea and nausea, each occurring at approximately 4%.

One patient discontinued treatment due to a Grade 3 adverse reaction of erythematous rash. All other adverse reactions were Grade 1 or 2 and no patients interrupted treatment due to an adverse reaction.

### **8.3 Less Common Clinical Trial Adverse Reactions**

Not applicable

#### **8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics**

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 Post-Market Adverse Reactions**

The following adverse drug reactions have been identified during post approval use of MAVIRET. Given that these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hepatobiliary Disorders: Hepatic decompensation, hepatic failure  
Immune System Disorders: Angioedema

## 9 DRUG INTERACTIONS

### 9.2 Drug Interactions 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 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 [7 WARNINGS AND PRECAUTIONS, General, Use with Potent P-gp and CYP3A4 Inducers](#)).

### 9.4 Drug-Drug Interactions

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

**Table 8** 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 [2 CONTRAINDICATIONS](#)).

**Table 8. Established and Other Potentially Significant Drug Interactions**

Concomitant Drug Class: Drug Name	Effect on Concentration <sup>a,b</sup>	Clinical Comments
<b>ANTIARRHYTHMICS</b>		
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.
<b>ANTICONVULSANTS</b>		
carbamazepine	↓ glecaprevir ↓ pibrentasvir	Coadministration may lead to reduced therapeutic effect of MAVIRET and is not recommended.
<b>HERBAL PRODUCTS</b>		
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.
<b>HCV-ANTIVIRAL AGENTS</b>		
sofosbuvir	↑ sofosbuvir ↔ GS-331007	Coadministration with MAVIRET increases sofosbuvir concentrations, but does not affect GS-331007. No dose adjustment is required.
<b>HIV-ANTIVIRAL AGENTS</b>		
darunavir + ritonavir lopinavir/ritonavir	↑ glecaprevir ↑ pibrentasvir	Coadministration with MAVIRET significantly increased glecaprevir and pibrentasvir concentrations and is not recommended.
Efavirenz <sup>c</sup>	↓ 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 <sup>d</sup>	↔ tenofovir	No dose adjustment is required.
Tenofovir disoproxil fumarate <sup>c</sup>	↑ tenofovir	No dose adjustment is required.

Concomitant Drug Class: Drug Name	Effect on Concentration <sup>a,b</sup>	Clinical Comments
<b>HMG-COA REDUCTASE INHIBITORS</b>		
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.
<b>IMMUNOSUPPRESSANTS</b>		
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.
<b>PROTON PUMP INHIBITORS</b>		
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.
<p>↑= increase; ↓= decrease; ↔ = no effect  See also <a href="#">9 DRUG INTERACTIONS Table 9</a> and <a href="#">Table 10</a></p> <p>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.</p> <p>b. Coadministration with MAVIRET did not lead to clinically significant changes in carbamazepine, cobicistat, cyclosporine, darunavir, efavirenz, elvitegravir, emtricitabine, lopinavir, omeprazole or ritonavir, concentrations.</p> <p>c. Interaction studied with the efavirenz/emtricitabine/tenofovir disoproxil fumarate combination.</p> <p>d. Interaction studied with the elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide combination.</p>		

## Other Forms of Interactions

As liver function may improve due to treatment of HCV with DAAs, it is recommended to closely monitor:

- the International Normalized Ratio [INR] in patients taking vitamin K antagonists,
- blood glucose levels in diabetic patients,

The dose of vitamin K antagonists, anti-diabetic agents or other concomitant medications significantly affected by changes in hepatic function should be modified when necessary.

## 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 9** and **Table 10** summarize the pharmacokinetic effects when glecaprevir/pibrentasvir was coadministered with other drugs which showed potentially clinically relevant changes.

**Table 9. 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 <sub>max</sub>	AUC	C <sub>min</sub>
<b>ANTICONVULSANTS</b>							
carbamazepine	200 twice daily	300/120 single dose	10	GLE	0.33 (0.27, 0.41)	0.34 (0.28, 0.40)	--
				PIB	0.50 (0.42, 0.59)	0.49 (0.43, 0.55)	--

Co-administered Drug	Regimen of Co-administered Drug (mg)	Regimen of GLE/PIB (mg)	N	DAA	Central Value Ratio (90% CI)		
					C <sub>max</sub>	AUC	C <sub>min</sub>
<b>ANTIMYCOBACTERIAL</b>							
rifampin	600 (first dose)	300/120 single dose	12	GLE	6.52 (5.06, 8.41)	8.55 (7.01, 10.4)	--
				PIB	↔	↔	--
	600 once daily	300/120 single dose <sup>a</sup>	12	GLE	0.14 (0.11, 0.19)	0.12 (0.09, 0.15)	--
				PIB	0.17 (0.14, 0.20)	0.13 (0.11, 0.15)	--
<b>HIV-ANTIVIRAL AGENTS</b>							
atazanavir (ATZ) + ritonavir (rtv)	ATZ 300 + rtv 100 once daily	300/120 once daily <sup>b</sup>	12	GLE	≥ 4.06 (3.15, 5.23)	≥ 6.53 (5.24, 8.14)	≥ 14.3 (9.85, 20.7)
				PIB	≥ 1.29 (1.15, 1.45)	≥ 1.64 (1.48, 1.82)	≥ 2.29 (1.95, 2.68)
darunavir (DRV) + rtv	DRV 800 + rtv 100 once daily	300/120 once daily	8	GLE	3.09 (2.26, 4.20)	4.97 (3.62, 6.84)	8.24 (4.40, 15.4)
				PIB	↔	↔	1.66 (1.25, 2.21)
lopinavir (LPV)/rtv	LPV 400 + rtv 100 twice daily	300/120 once daily	9	GLE	2.55 (1.84, 3.52)	4.38 (3.02, 6.36)	18.6 (10.4, 33.5)
				PIB	1.40 (1.17, 1.67)	2.46 (2.07, 2.92)	5.24 (4.18, 6.58)

Co-administered Drug	Regimen of Co-administered Drug (mg)	Regimen of GLE/PIB (mg)	N	DAA	Central Value Ratio (90% CI)		
					C <sub>max</sub>	AUC	C <sub>min</sub>
<b>IMMUNOSUPPRESSANTS</b>							
cyclosporine	100 single dose	300/120 once daily	12 <sup>c</sup>	GLE	1.30 (0.95, 1.78)	1.37 (1.13, 1.66)	1.34 (1.12, 1.60)
				PIB	↔	↔	1.26 (1.15, 1.37)
	400 single dose	300/120 single dose	11	GLE	4.51 (3.63, 6.05)	5.08 (4.11, 6.29)	--
				PIB	↔	1.93 (1.78, 2.09)	--
<b>PROTON PUMP INHIBITORS</b>							
omeprazole	20 once daily	300/120 single dose	9	GLE	0.78 (0.60, 1.00)	0.71 (0.58, 0.86)	--
				PIB	↔	↔	--
	40 once daily	300/120 single dose	12	GLE	0.36 (0.21, 0.59)	0.49 (0.35, 0.68)	--
				PIB	↔	↔	--
DAA = direct acting antiviral ↔ = No change (central value ratio 0.80 to 1.25) a. Effect of rifampin on glecaprevir and pibrentasvir 24 hours after final rifampin dose. b. Effect of atazanavir and ritonavir on the first dose of glecaprevir and pibrentasvir is reported. 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 10. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Combination of Glecaprevir/Pibrentasvir (GLE/PIB)**

Co-administered Drug	Regimen of Co-administered Drug (mg)	Regimen of GLE/PIB (mg)	N	Central Value Ratio (90% CI)		
				C <sub>max</sub>	AUC	C <sub>min</sub>
<b>ANTIARRHYTHMICS</b>						
digoxin	0.5 single dose	400/120 once daily	12	1.72 (1.45, 2.04)	1.48 (1.40, 1.57)	--
<b>ANTICOAGULANTS</b>						
dabigatran etexilate	150 single dose	300/120 once daily	11	2.05 (1.72, 2.44)	2.38 (2.11, 2.70)	--
<b>CONTRACEPTIVES</b>						
ethinyl estradiol (EE)	EE/norgestimate 35 mcg/ 250 mcg once daily	300/120 once daily	11	1.31 (1.24, 1.38)	1.28 (1.23, 1.32)	1.38 (1.25, 1.52)
norgestrel				1.54 (1.34, 1.76)	1.63 (1.50, 1.76)	1.75 (1.62, 1.89)
norelgestromin				↔	1.44 (1.34, 1.54)	1.45 (1.33, 1.58)
ethinyl estradiol	EE/levonorgestrel 20 mcg/ 100 mcg once daily	300/120 once daily	12	1.30 (1.18, 1.44)	1.40 (1.33, 1.48)	1.56 (1.41, 1.72)
norgestrel				1.37 (1.23, 1.52)	1.68 (1.57, 1.80)	1.77 (1.58, 1.98)
<b>HCV-ANTIVIRAL AGENTS</b>						
sofosbuvir	sofosbuvir 400 once daily	400/120 mg once daily	8	1.66 (1.23, 2.22)	2.25 (1.86, 2.72)	--
GS-331007 (metabolite)			8	↔	↔	1.85 (1.67, 2.04)

Co-administered Drug	Regimen of Co-administered Drug (mg)	Regimen of GLE/PIB (mg)	N	Central Value Ratio (90% CI)		
				C <sub>max</sub>	AUC	C <sub>min</sub>
<b>HIV-ANTIVIRAL AGENTS</b>						
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)
<b>HMG CoA REDUCTASE INHIBITORS</b>						
atorvastatin	10 once daily	400/120 once daily	11	22.0 (16.4, 29.5)	8.28 (6.06, 11.3)	--
lovastatin	10 once daily	300/120 once daily	12	↔	1.70 (1.40, 2.06)	--
lovastatin acid (metabolite)				5.73 (4.65, 7.07)	4.10 (3.45, 4.87)	--
pravastatin	10 once daily	400/120 once daily	12	2.23 (1.87, 2.65)	2.30 (1.91, 2.76)	--
rosuvastatin	5 once daily	400/120 once daily	11	5.62 (4.80, 6.59)	2.15 (1.88, 2.46)	--
simvastatin	5 once daily	300/120 once daily	12	1.99 (1.60, 2.48)	2.32 (1.93, 2.79)	--
simvastatin acid (metabolite)				10.7 (7.88, 14.6)	4.48 (3.11, 6.46)	--

Co-administered Drug	Regimen of Co-administered Drug (mg)	Regimen of GLE/PIB (mg)	N	Central Value Ratio (90% CI)		
				C <sub>max</sub>	AUC	C <sub>min</sub>
<b>IMMUNOSUPPRESSANTS</b>						
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)						

## 9.5 Drug-Food Interactions

Food increases the bioavailability of MAVIRET (see [4.2 Recommended Dose and Dosage Adjustment](#) and [10.3 Pharmacokinetics, Absorption, Effects of Food on Oral Absorption](#)).

## 9.6 Drug-Herb Interactions

Coadministration of St. John's Wort (*Hypericum perforatum*), may lead to reduced therapeutic effect of MAVIRET and is not recommended (see **Table 8**).

## 9.7 Drug-Laboratory Test Interactions

Interactions of MAVIRET with laboratory tests have not been established.

# 10 CLINICAL PHARMACOLOGY

## 10.1 Mechanism of Action

MAVIRET is a fixed-dose combination of two pangenotypic, direct-acting antiviral agents, glecaprevir (NS3/4A protease inhibitor) and pibrentasvir (NS5A inhibitor), targeting multiple steps in the HCV viral lifecycle (see [15 MICROBIOLOGY](#)).

## 10.2 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.

## 10.3 Pharmacokinetics

Based on the population pharmacokinetic analysis, the median steady-state pharmacokinetic parameters of glecaprevir and pibrentasvir tablets in HCV-infected patients and healthy subjects are provided in **Table 11**.

**Table 11. 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) <sup>a</sup>	HCV Infected Patients <sup>b</sup>	
			With Cirrhosis (N = 280) <sup>c</sup>	Without Cirrhosis (N = 1,804) <sup>c</sup>
Glecaprevir	C <sub>max</sub> (ng/mL)	1,230	1,110	597
	AUC <sub>24</sub> (ng·h/mL)	4,380	10,500	4,800
Pibrentasvir	C <sub>max</sub> (ng/mL)	295	111	110
	AUC <sub>24</sub> (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 AUC<sub>24</sub>

## Absorption

### Tablets

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

### Granules

Following single-dose administration of glecaprevir and pibrentasvir granules in healthy subjects, peak plasma concentrations were observed at 3.0 hours (glecaprevir) and 5.0 hours (pibrentasvir) post-dose.

## Effects of Food on Oral Absorption

### Tablets

There were increases in glecaprevir AUC<sub>T</sub> and C<sub>max</sub> when a single 300 mg/120 mg dose of MAVIRET tablets were 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<sub>T</sub> and C<sub>max</sub> 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.

## Granules

There were increases in glecaprevir AUC<sub>T</sub> and C<sub>max</sub> when a single dose of GLE 300 mg + PIB 120 mg granules (pediatric formulation) were administered under low fat fed conditions (approximately 168% and 189% respectively) and high fat fed conditions (approximately 131% and 112%, respectively) when compared to administration under fasting conditions.

Similarly, there were increases in pibrentasvir AUC<sub>T</sub> and C<sub>max</sub> when a single dose of GLE 300 mg + PIB 120 mg granules (pediatric formulation) were administered under low fat fed conditions (approximately 57% and 83% respectively) and high fat fed conditions (approximately 115% and 130%, respectively) when compared to administration under fasting conditions.

### **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 [<sup>14</sup>C] glecaprevir, 92.1% of the radioactive dose was recovered in feces and 0.7% was recovered in urine. Following a single dose of [<sup>14</sup>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 or pediatric patients weighing at least 45 kg. Pediatric patients aged 3 to less than 12 years of age and weighing 12 kg to less than 45 kg should receive doses of MAVIRET granules in sachets based on body weight (See [4.2 Recommended Dose and Dosage Adjustment](#)). At the recommended doses, exposures of glecaprevir and pibrentasvir in patients aged 3 to less than 18 years were comparable to those in adults from Phase 2 and 3 studies.

The pharmacokinetics of glecaprevir and pibrentasvir have not been established for children less than 3 years of age or weighing less than 12 kg.

The pharmacokinetics of glecaprevir and pibrentasvir were determined in HCV-infected pediatric patients 3 years of age and older receiving a daily dose of MAVIRET as described below in **Table 12**. All pediatric glecaprevir and pibrentasvir PK parameter values fell within the safe and efficacious range observed in adult patients. These differences were not considered clinically significant.

**Table 12. Pharmacokinetic Parameters of Glecaprevir (GLE) and Pibrentasvir (PIB) in HCV Infected Pediatric Patients**

Age and Weight (kg)	N	Total Daily Dose of GLE/PIB (mg)	PK Parameter	Geometric Mean (%CV)	
				GLE	PIB
12 to < 18 years, ≥ 45 kg	14	300/120	AUC <sub>24</sub> (ng•h/mL)	4790 (72)	1380 (40)
			C <sub>max</sub> (ng/mL)	1040 (86)	174 (36)
			C <sub>trough</sub> (ng/mL)	3.79 (82)	15.0 (61)
9 to < 12 years, 30 to < 45 kg	13	250/100	AUC <sub>24</sub> (ng•h/mL)	7870 (209)	2200 (99)
			C <sub>max</sub> (ng/mL)	1370 (169)	225 (72)
			C <sub>trough</sub> (ng/mL)	12.4 (856)	36.5 (164)
6 to < 9 years, 20 to < 30 kg	13	200/80	AUC <sub>24</sub> (ng•h/mL)	6860 (142)	1640 (63)
			C <sub>max</sub> (ng/mL)	1600 (155)	197 (52)
			C <sub>trough</sub> (ng/mL)	7.44 (383)	19.4 (103)
3 to < 6 years, 12 to < 20 kg	12	150/60	AUC <sub>24</sub> (ng•h/mL)	7520 (205)	1790 (58)
			C <sub>max</sub> (ng/mL)	1530 (280)	233 (48)
			C <sub>trough</sub> (ng/mL)	6.58 (318)	17.9 (119)

- **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 [7.1.1 Pregnant Women](#) and [7.1.2 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 [2 CONTRAINDICATIONS](#), [4.2 Recommended Dose and Dosage Adjustment, Hepatic Impairment](#) and [7 WARNINGS AND PRECAUTION, Hepatic/Biliary/Pancreatic, Hepatic Decompensation and Hepatic Failure](#)).

- **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<sup>2</sup>), moderate (eGFR 30 to 59 mL/min/1.73 m<sup>2</sup>), severe renal impairment (eGFR 15 to 29 mL/min/1.73 m<sup>2</sup>), or ESRD not on dialysis (eGFR < 15 mL/min/1.73 m<sup>2</sup>). 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 [4.2 Recommended Dose and Dosage Adjustment, Renal Impairment](#)).

- **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

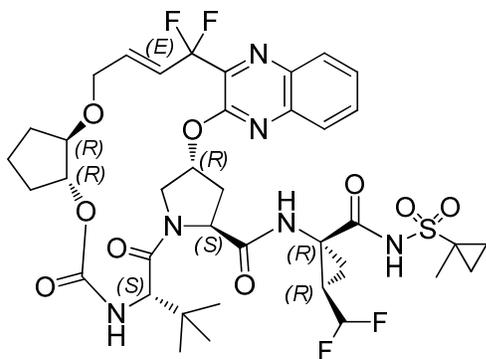
### 13 PHARMACEUTICAL INFORMATION

#### Drug Substance

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<sub>38</sub>H<sub>46</sub>F<sub>4</sub>N<sub>6</sub>O<sub>9</sub>S (anhydrate) and 838.87 g/mol (anhydrate)



Structural formula:

• X H<sub>2</sub>O

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 37°C and is practically insoluble in water, but is sparingly soluble in ethanol.

## Drug Substance

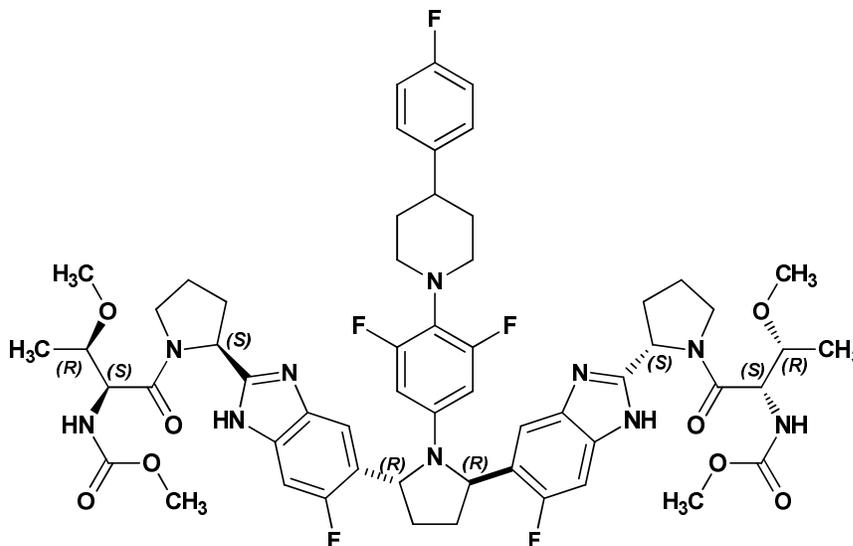
Proper name:

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-1*H*-benzimidazol-2-yl]pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate

Molecular formula and molecular mass: C<sub>57</sub>H<sub>65</sub>F<sub>5</sub>N<sub>10</sub>O<sub>8</sub> and 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

### 14.1 Clinical Trials by Indication

The efficacy and safety of MAVIRET (glecaprevir/pibrentasvir) was evaluated in twelve 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 13**.

**Table 13. Clinical Studies Conducted with MAVIRET in Patients with HCV Genotype 1, 2, 3, 4, 5 or 6 Infection**

HCV Genotype (GT)	Study #	Number of Patients Treated N (regimen)	Trial Design*	Dosage, Route of Administration and Duration
<b>TN and PRS-TE patients without cirrhosis</b>				
GT-1	ENDURANCE-1 <sup>a</sup> (M13-590)	351 (8 weeks) 352 (12 weeks)	Randomized (1:1) and open-label study	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 8 or 12 weeks
	SURVEYOR-1 (M14-867)	34	Open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 8 weeks
GT-2	ENDURANCE-2 (M15-464)	202 (12 weeks) 100 (Placebo)	Randomized (2:1), placebo-controlled	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 12 weeks
	SURVEYOR-2 (M14-868)	199 (8 weeks) 25 (12 weeks)	Open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 8 or 12 weeks
GT-3	ENDURANCE-3 (M13-594)	157 (8 weeks) 233 (12 weeks) 115 (Sofosbuvir + daclatasvir 12 weeks)	Partially-randomized, open-label, active-controlled (all TN patients)	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 8 or 12 weeks

HCV Genotype (GT)	Study #	Number of Patients Treated N (regimen)	Trial Design*	Dosage, Route of Administration and Duration
	SURVEYOR-2 (M14-868)	29 TN only (8 weeks), 76 (12 weeks) 22 PRS-TE only (16 weeks)	Partially Randomized, Open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 8 or 12 or 16 weeks
GT-4, -5, -6	ENDURANCE-4 (M13-583)	121	Single-arm, open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 12 weeks
	ENDURANCE-5,6 (M16-126)	75	Open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 8 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
GT-1 to -6	VOYAGE-1 <sup>b</sup> (M15-592)	356 (GT-1, -2, -4, -5, -6 and -3 TN; 8 weeks) 6 (GT-3 PRS-TE only; 16 weeks)	Randomized, double-blind	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 8 or 16 weeks
<b>TN and PRS-TE patients with cirrhosis</b>				
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

HCV Genotype (GT)	Study #	Number of Patients Treated N (regimen)	Trial Design*	Dosage, Route of Administration and Duration
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
GT-1, -2, -3, -4, -5, -6	EXPEDITION-8 (M16-135)	343 (TN only)	Single-arm, open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD  Oral  8 weeks
GT-5, -6	ENDURANCE-5,6 (M16-126)	9	Open-label	glecaprevir/pibrentasvir tablet : 300/120 mg QD  Oral  12 weeks
GT-1 to -6	VOYAGE-2 <sup>b</sup> (M15-593)	157 (GT-1, -2, -4, -5, -6 and -3 TN; 12 weeks) 3 (GT-3 PRS-TE only; 16 weeks)	Open-label	glecaprevir/pibrentasvir tablet : 300/120 mg QD  Oral  12 or 16 weeks
<b>Patients with CKD stage 4 and 5 with or without cirrhosis</b>				
GT-1 to -6	EXPEDITION-4 (M15-462)	104	Single-arm, open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD  Oral  12 weeks
<b>NS5A and/or PI-experienced patients with or without cirrhosis</b>				
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 Genotype (GT)	Study #	Number of Patients Treated N (regimen)	Trial Design*	Dosage, Route of Administration and Duration
<b>HCV/HIV-1 co-infected patients with or without cirrhosis</b>				
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
<b>Liver or kidney transplant recipients</b>				
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
<b>Adolescent Subjects (12 to less than 18 years)</b>				
GT-1 to -6	DORA (Part 1) M16-123	44 (8 weeks) 3 (16 weeks)	Open-label	glecaprevir/pibrentasvir tablet : 300/120 mg QD Oral 8 or 16 weeks
<b>Children (3 to less than 12 years)</b>				
GT-1 to -6	DORA (Part 2) M16-123	78 (8 weeks) 1 (12 weeks) 1 (16 weeks)	Open-label	glecaprevir/pibrentasvir granules in sachets: QD dosing based on body weight Oral 8, 12, or 16 weeks
<p>(peg)interferon = interferon or pegylated interferon; TN = treatment-naïve, PRS-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</p> <p>* Treatment durations for some trial arms shown in this table do not reflect recommended dosing for the respective genotypes, prior treatment history, and/or cirrhosis status. Refer to the Dosage and Administration section for recommended dosing in adults and pediatric patients 3 years and older (weighing at least 12 kg).</p> <p>a. ENDURANCE-1 included 33 patients co-infected with HIV-1. DORA included patients co-infected with HIV-1.</p> <p>b. VOYAGE-1 and VOYAGE-2 were Asian regional studies.</p>				

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

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

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 14**.

**Table 14. 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<sup>a</sup>)**

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 (%)	
<b>Age (years)</b>						
< 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)
<b>Gender</b>						
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)
<b>Race</b>						
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)
<b>BMI</b>						
< 30 kg/m <sup>2</sup>	674 (80.8)	344 (76.4)	128 (81.0)	21 (67.7)	44 (93.6)	1,211 (79.7)
≥ 30 kg/m <sup>2</sup>	160 (19.2)	106 (23.6)	30 (19.0)	10 (32.3)	3 (6.4)	309 (20.3)
<b>Genotype/Subtype</b>						
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)
<b>HCV RNA Viral Load (Log<sub>10</sub> IU/mL), mean (SD)</b>	6.1 (0.68)	6.2 (0.94)	5.9 (0.67)	6.1 (0.56)	6.6 (0.83)	6.1 (0.78)

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 (%)	
<b>Fibrosis Stage</b>						
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)
<b>Cirrhosis</b>						
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)
<b>Prior HCV Therapy</b>						
TN	533 (63.9)	359 (79.8)	112 (70.9)	25 (80.6)	41 (87.2)	1,070 (70.4)
PRS-TE	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 PRS-TE patients and excludes patients with severe renal impairment (Study M15-462).						

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 15**.

**Table 15. Sustained Virologic Response (SVR12) in Treatment-Naïve Patients and Patients Experienced<sup>a</sup> 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 <sup>b</sup> % (n/N)	GT-2 % (n/N)	GT-4 % (n/N)	GT-5 % (n/N)	GT-6 % (n/N)
<b>SVR12 in patients without cirrhosis</b>					
8 weeks	99.0 (383/387)	98.0 (193/197)	93.5 (43/46)	100 (2/2)	90.0 (9/10)
<b>Outcome for patients without SVR12</b>					
On-treatment VF	0.3 (1/387)	0 (0/197)	0 (0/46)	0 (0/2)	0 (0/10)
Relapse <sup>c</sup>	0 (0/384)	1.0 (2/195)	0 (0/45)	0 (0/2)	0 (0/10)
Other <sup>d</sup>	0.8 (3/387)	1.0 (2/197)	6.5 (3/46)	0 (0/2)	10 (1/10)

	GT-1 <sup>b</sup> % (n/N)	GT-2 % (n/N)	GT-4 % (n/N)	GT-5 % (n/N)	GT-6 % (n/N)
<b>SVR12 in patients with cirrhosis</b>					
12 weeks	97.0 (98/101)	100 (35/35)	100 (20/20)	100 (2/2)	100 (7/7)
<b>Outcome for patients without SVR12</b>					
On-treatment VF	0 (0/101)	0 (0/35)	0 (0/20)	0 (0/2)	0 (0/7)
Relapse <sup>c</sup>	1.0 (1/98)	0 (0/35)	0 (0/19)	0 (0/2)	0 (0/7)
Other <sup>d</sup>	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 PRS-TE, and 3 GT-6 patients were PRS-TE.					
b. Includes 15 patients co-infected with HIV-1 (treated for 8 weeks).					
c. Relapse is defined as HCV RNA $\geq$ 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 16**.

**Table 16. 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<sup>a</sup>)**

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)	
<b>HCV Genotype/ Subtype</b>					
1a	97.8 (223/228)	NA	NA	NA	97.8 (223/228)
1b	100 (247/247)	NA	NA	NA	100 (247/247)
<b>Prior Treatment History</b>					
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)

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)	
PRS-TE	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)
<b>HCV/HIV Co-infection<sup>b</sup></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/lamivudine (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/lamivudine (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.

#### Clinical Studies in Patients with Genotypes 5 or 6 Infection

ENDURANCE-5,6 was an open-label study in 84 HCV genotype 5- (N = 23) or genotype 6-infected (N = 61) treatment-naïve or PRS-treatment-experienced patients. Patients without cirrhosis received MAVIRET for 8 weeks, and patients with compensated cirrhosis received MAVIRET for 12 weeks.

Of the 84 patients treated, the median age was 59 years (range 24 to 79); 27% had HCV genotype 5, 73% had HCV genotype 6; 54% were female, 30% were White, 68% were Asian; 90% were HCV treatment-naïve; 11% had compensated cirrhosis.

The overall SVR12 rate in study ENDURANCE-5,6 was 97.6% (82/84). The SVR12 rate was 95.7% (22/23) for genotype 5-infected patients and 98.4% (60/61) for genotype 6-infected patients. One treatment-naïve genotype 5-infected patient without cirrhosis experienced relapse, and one treatment-naïve genotype 6-infected patient with compensated cirrhosis experienced on-treatment virologic failure.

**Clinical Study in Treatment-Naïve Patients with Cirrhosis Infected with Genotypes 1, 2, 4, 5, or 6 who received 8 Weeks of MAVIRET**

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

Of the 280 patients treated, the median age was 60 years (range: 34 to 99); 81.8% had HCV genotype 1, 10% had HCV genotype 2, 4.6% had HCV genotype 4, 0.4% had HCV genotype 5; 3.2% had HCV genotype 6; 60% were male; 9.6% were Black.

The response rates in patients with compensated cirrhosis and genotype 1, 2, 4, 5, or 6 given MAVIRET for 8 weeks are presented in **Table 17**.

The overall SVR12 rate was 97.9% (274/280). There were no virologic failures.

**Table 17. Sustained Virologic Response (SVR12) in Treatment-Naïve Patients Infected with HCV Genotypes 1, 2, 4, 5, or 6 Infection with Compensated Cirrhosis (EXPEDITION-8)**

Assessment	MAVIRET 8 Weeks (N = 280)					
	Total N = 280 % (n/N)	GT-1 N = 231 % (n/N)	GT-2 N = 26 % (n/N)	GT-4 N = 13 % (n/N)	GT-5 N = 1 % (n/N)	GT-6 N = 9 % (n/N)
<b>SVR12</b>	98 (274/280)	97 (225/231)	100 (26/26)	100 (13/13)	100 (1/1)	100 (9/9)
<b>Outcome for patients without SVR12</b>						
On-treatment VF	0 (0/280)	0 (0/231)	0 (0/26)	0 (0/13)	0 (0/1)	0 (0/9)
Relapse	0 (0/274)	0 (0/225)	0 (0/26)	0 (0/13)	0 (0/1)	0 (0/9)
Other <sup>a</sup>	2 (6/280)	3 (6/231)	0 (0/26)	0 (0/13)	0 (0/1)	0 (0/9)
GT = genotype; VF = virologic failure						
a. Includes patients who discontinued due to lost to follow-up or subject withdrawal.						

**Clinical Studies in Genotype 3 Infected Adult Patients**

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), EXPEDITION-8 and SURVEYOR-2 Parts 1-3 (patients with and without cirrhosis and treatment-naïve and/or treatment-experienced) clinical studies.

Patients with genotype 3 HCV infection were also included in other studies, such as the two Asian regional studies, VOYAGE-1 and VOYAGE-2.

ENDURANCE-3 was a partially-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 18**.

**Table 18. 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 (%)
<b>Age (years)</b>	
< 65	596 (94.3)
≥ 65	36 (5.7)
<b>Gender</b>	
Male	367 (58.1)
Female	265 (41.9)
<b>Race</b>	
White	558 (88.3)
Black	9 (1.4)
Asian	47 (7.4)
Other	18 (2.8)
<b>Viral Load</b>	
HCV RNA (Log <sub>10</sub> IU/mL) mean (SD)	6.2 (0.79)
<b>BMI</b>	
< 30 kg/m <sup>2</sup>	509 (80.5)
≥ 30 kg/m <sup>2</sup>	123 (19.5)
<b>HCV Genotype/Subtype</b>	
3a	587 (92.9)
3-other	45 (7.1)
<b>Prior Treatment History</b>	
TN	510 (80.7)
PRS-TE	122 (19.3)
P/R-experienced	80 (12.7)
SOF-experienced	42 (6.6)

Characteristics	MAVIRET 8, 12 or 16 Weeks N = 632 n (%)
<b>Stages of Fibrosis</b>	
F0-F2	440 (69.6)
F3	78 (12.3)
F4	114 (18.0)
<b>Cirrhosis</b>	
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	

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 19**.

**Table 19. 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)
<b>SVR</b>	94.9 (149/157)	95.3 (222/233) <sup>a</sup>	96.5 (111/115) <sup>b</sup>
<b>Outcome for patients without SVR</b>			
On-treatment VF	0.6 (1/157)	0.4 (1/233)	0 (0/115)
Relapse <sup>c</sup>	3.3 (5/150)	1.4 (3/222)	0.9 (1/114)
Other <sup>d</sup>	1.3 (2/157)	3.0(7/233)	2.6 (3/115)
<b>Outcome by HCV genotype/subtype</b>			
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 20**.

**Table 20. 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)
<b>SVR</b>	97.5 (39/40)	95.7 (66/69)
<b>Outcome for patients without SVR</b>		
On-treatment VF	0 (0/40)	1.4 (1/69)
Relapse <sup>a</sup>	0 (0/39)	2.9 (2/68)
Other <sup>b</sup>	2.5 (1/40)	0 (0/69)
<b>Outcome in selected subgroups</b>		
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
PRS-TE	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 genotype 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.

### Patients with Genotype 3b Infection

Genotype 3b is a subtype that is uncommon in Canada but has been reported in China and other South and Southeast Asian countries. Studies VOYAGE-1 and VOYAGE-2 were conducted in China, Singapore, and South Korea in HCV genotype 1 to 6 patients without cirrhosis (VOYAGE-1) or with compensated cirrhosis (VOYAGE-2) who were treatment-naïve or treatment-experienced with PRS. Patients without cirrhosis or with compensated cirrhosis received 8 or 12 weeks of MAVIRET, respectively, except genotype 3 PRS-treatment-experienced patients who received 16 weeks of MAVIRET.

The overall SVR12 rates were 97.2% (352/362) and 99.4% (159/160) in VOYAGE-1 and VOYAGE-2, respectively.

Across both trials, subjects with HCV genotype 3b infection had a numerically lower SVR12 rate of 70% (14/20) [58% (7/12) for non-cirrhotic subjects and 88% (7/8) for subjects with compensated cirrhosis] compared to subjects infected with genotype 3a or other HCV genotypes. All six genotype 3b subjects without SVR12 experienced virologic failure (2 on-treatment virologic failure, 4 relapse). SVR12 results in subjects with genotype 3a or other HCV genotypes were comparable with other trials.

### Clinical Study in Treatment-Naïve Patients with Cirrhosis Infected with Genotype 3 who received 8 Weeks of MAVIRET

The safety and efficacy of MAVIRET given for 8 weeks in genotype 3 treatment-naïve patients with compensated cirrhosis was evaluated in a single-arm, open-label study (EXPEDITION-8).

Of the 63 genotype 3 treatment-naïve patients with compensated cirrhosis treated, the median age was 52 years (range: 32 to 83); 77.8% were male; 1.6% were Black.

The response rate in patients with compensated cirrhosis and genotype 3 given MAVIRET for 8 weeks is presented in **Table 21**. There was 1 virologic relapse.

**Table 21. Sustained Virologic Response (SVR12) in Treatment-Naïve Patients Infected with HCV Genotype 3 Infection with Compensated Cirrhosis (EXPEDITION-8)**

Assessment	MAVIRET 8 Weeks (N = 63)
	GT-3 N = 63 % (n/N)
SVR12	95.2 (60/63)
<b>Outcome for patients without SVR12</b>	
On-treatment VF	0 (0/63)
Relapse	2 (1/62)
Other <sup>a</sup>	3 (2/63)
GT = genotype; VF = virologic failure	
a. Includes patients who discontinued due to lost to follow-up or subject withdrawal.	

### **Clinical Study in Chronic Kidney Disease (CKD) Adult Patients**

The demographic and disease characteristics of the population with stages 4 and 5 chronic kidney disease are summarized in **Table 22**.

**Table 22. 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 (%)
<b>Age</b>	
< 65	76 (73.1)
≥ 65	28 (26.9)
<b>Gender</b>	
Male	79 (76.0)
Female	25 (24.0)
<b>Race</b>	
White	64 (61.5)
Black	25 (24.0)
Asian	9 (8.7)
Other	6 (5.8)
<b>Viral Load</b>	
HCV RNA (Log <sub>10</sub> IU/mL), mean (SD)	5.85 (0.74)
<b>BMI</b>	
< 30 kg/m <sup>2</sup>	79 (76.0)
≥ 30 kg/m <sup>2</sup>	25 (24.0)
<b>HCV Genotype/Subtype</b>	
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)
<b>Prior Treatment History</b>	
TN	60 (57.7)
PRS-TE	44 (42.3)
P/R-experienced	42 (40.4)
SOF-experienced	2 (1.9)

Characteristics	MAVIRET 12 Weeks N = 104 n (%)
<b>Stages of Fibrosis</b>	
F0-F2	69 (66.3)
F3	17 (16.3)
F4	17 (16.3)
<b>Cirrhosis</b>	
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 <sup>a</sup>	1 (1.0)
No	84 (80.8)
<b>Stages of Chronic Kidney Disease</b>	
Stage 4 without dialysis <sup>b</sup>	13 (12.5)
Stage 5 without dialysis <sup>c</sup>	6 (5.8)
Stage 5 requiring dialysis <sup>d</sup>	85 (81.7)
<p>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.</p> <p>a. One patient had Child Pugh Score 7 at baseline.</p> <p>b. Stage 4, defined as patients with eGFR 15 to 30 mL/min/1.73 m<sup>2</sup>.</p> <p>c. Stage 5 defined as eGFR &lt; 15 mL/min/1.73 m<sup>2</sup></p> <p>d. Stage 5, requiring routine dialysis. 19% (16/85) of the patients requiring dialysis had cirrhosis, mostly of Child-Pugh 5 and 6.</p>	

The response rates in patients with CKD (stages 4 and 5) infected with HCV genotypes 1 to 6 are presented in **Table 23**.

**Table 23. 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)
<b>SVR12</b>	98.1 (102/104)
95% CI	(95.4, 100)
<b>Outcomes in Patients Without SVR</b>	
On Treatment VF	0 (0/104)
Relapse <sup>a</sup>	0 (0/104)
Other <sup>b</sup>	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 $\geq$ LLOQ after end-of-treatment response among those who completed treatment. b. Includes patients who discontinued due to adverse event, lost to follow-up, or patient withdrawal.	

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 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)
<b>Genotypes</b>	
1	96.4 (53/55)
2	100 (16/16)
3	100 (11/11)
4	100 (20/20)
5 and 6	100 (2/2)
<b>Cirrhosis</b>	
Yes	90 (18/20)
No	100 (84/84)
<b>Child-Pugh Score</b>	
5	86.7 (13/15)
6	100 (4/4)
$\geq 6$	100 (1/1)

Subgroups	MAVIRET 12 Weeks N = 104 % (n/N)
<b>Baseline CKD Stage</b>	
Stage 4 without dialysis <sup>a</sup>	100 (13/13)
Stage 5 without dialysis <sup>b</sup>	100 (6/6)
Stage 5 requiring dialysis <sup>c</sup>	97.6 (83/85)
<b>Prior Treatment History</b>	
TN	96.7 (58/60)
PRS-TE	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 m <sup>2</sup> .	
b. Stage 5, defined as eGFR < 15 mL/min/1.73 m <sup>2</sup> .	
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.

**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 25**.

**Table 25. 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 (%)
<b>Age</b>	
< 65	151 (98.7)
≥ 65	2 (1.3)
<b>Gender</b>	
Male	128 (83.7)
Female	25 (16.3)

Characteristics	MAVIRET 8 or 12 Weeks N = 153 n (%)
<b>Race</b>	
White	121 (79.1)
Black	25 (16.3)
Asian	6 (3.9)
Other	1 (0.7)
<b>Viral Load</b>	
HCV RNA (Log <sub>10</sub> IU/mL), mean (SD)	6.09 (0.70)
<b>BMI</b>	
< 30 kg/m <sup>2</sup>	128 (83.7)
≥ 30 kg/m <sup>2</sup>	25 (16.3)
<b>HCV Genotype/Subtype</b>	
1	94 (61.4)
2	13 (8.5)
3	26 (17.0)
4	17 (11.1)
6	3 (2.0)
<b>Prior Treatment History</b>	
TN	125 (81.7)
PRS-TE	28 (18.3)
<b>Stages of Fibrosis</b>	
F0-F2	122 (79.7)
F3	15 (9.8)
F4	16 (10.5)
<b>Cirrhosis</b>	
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; PRS-TE = treatment experienced to regimens containing interferon, (peg)interferon, ribavirin, and/or sofosbuvir	

The response rates in HCV/HIV-1 co-infected patients are presented in **Table 26**.

**Table 26. Sustained Virologic Response (SVR12) in HCV/HIV-1 Co-Infected Patients (EXPEDITION-2)**

Assessment	MAVIRET N = 153 % (n/N)
<b>SVR12</b>	98.0% (150/153)
95% CI	(95.8, 100.0)
<b>Outcomes in Patients Without SVR</b>	
On Treatment VF	0.7 (1/153)
Relapse <sup>a</sup>	0 (0/151)
Other <sup>b</sup>	1.3 (2/153)
VF = virologic failure	
a. Relapse is defined as HCV RNA $\geq$ LLOQ after end-of-treatment response among those who completed treatment	
b. Includes patients who discontinued due to adverse event, lost to follow-up, or 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).

#### **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% (1,401/1,437) achieved SVR12, 0.3% (4/1,284) experienced on-treatment virologic failure, and 0.8% (11/1,413) 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, 97.1% (437/450) achieved SVR12 (among which 97.7% [341/349] of treatment-naïve patients achieved SVR12), while 0.4% (2/450) experienced on-treatment virologic failure and 0.7% (3/440) 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.

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

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 27**.

**Table 27. 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)
<b>Age</b>		
< 65	93.0 (40/43)	81.8 (36/44)
≥ 65	7.0 (3/43)	18.2 (8/44)
<b>Gender</b>		
Male	69.8 (30/43)	72.7 (32/44)
Female	30.2 (13/43)	27.3 (12/44)
<b>Race</b>		
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)
<b>BMI</b>		
< 30 kg/m <sup>2</sup>	67.4 (29/43)	56.8 (25/44)
≥ 30 kg/m <sup>2</sup>	32.6 (14/43)	43.2 (19/44)
<b>HCV Genotype/Subtype</b>		
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)
<b>HCV RNA Viral Load (Log<sub>10</sub> IU/mL), mean (SD)</b>		
	6.02 (0.67)	6.24 (0.57)
<b>Fibrosis Stage</b>		
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)
<b>Cirrhosis</b>		
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)
<b>Previous DAA Experience<sup>a</sup></b>		
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.		

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 28**. 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 28. 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)
<b>SVR12</b>	88.4 (38/43)	90.9 (40/44)
95% CI	(75.5, 94.9)	(78.8, 96.4)
<b>Outcomes in Patients Without SVR</b>		
Virologic Failure	11.6 (5/43)	9.1 (4/44)
On Treatment VF	2.3 (1/43)	9.1 (4/44)
Relapse <sup>a</sup>	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 29**.

**Table 29. 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)
<b>Cirrhosis</b>		
Yes	93.3 (14/15)	70.0 (7/10)
No	85.7 (24/28)	97.1 (33/34)
<b>Previous DAA Regimen class</b>		
PI only	100 (14/14)	100 (12/12)
NS5A Inhibitors only <sup>a</sup>	87.5 (14/16)	94.1 (16/17)
NS5A Inhibitors and PI	76.9 (10/13)	80 (12/15)
<b>Presence of Key Baseline Substitutions<sup>b</sup></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 <sup>c</sup>	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.

#### **Clinical Study in Liver or Kidney Transplant Recipients**

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 30**.

**Table 30. 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 (%)
<b>Age</b>	
< 65	74 (74.0)
≥ 65	26 (26.0)
<b>Gender</b>	
Male	75 (75.0)
Female	25 (25.0)
<b>Race</b>	
White	78 (78.0)
Black	8 (8.0)
Asian	10 (10.0)
Other	4 (4.0)
<b>Viral Load</b>	
HCV RNA (Log <sub>10</sub> IU/mL), mean (SD)	6.42 (0.72)
<b>BMI</b>	
< 30 kg/m <sup>2</sup>	73 (73.0)
≥ 30 kg/m <sup>2</sup>	27 (27.0)
<b>HCV Genotype/Subtype</b>	
1	57 (57.0)
2	13 (13.0)
3	24 (24.0)
4	4 (4.0)
6	2 (2.0)
<b>Prior Treatment History</b>	
TN	66 (66.0)
PRS-TE	34 (34.0) <sup>a</sup>
<b>Stages of Fibrosis</b>	
F0-F2	86 (86.0)
F3	14 (14.0)

Characteristics	MAVIRET 12 Weeks N = 100 n (%)
<b>Transplant type</b>	
Liver	80 (80.0)
Kidney	20 (20.0)
SD = standard deviation; BMI = body mass index; GT = genotype; TN = treatment-naïve; PRS-TE = 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.	

The response rates in post-liver or kidney transplant patients are presented in **Table 31**.

**Table 31. Sustained Virologic Response (SVR12) in Post-Liver or Kidney Transplant Recipient Patients (MAGELLAN-2)**

Assessment	MAVIRET 12 Weeks N = 100 % (n/N)
<b>SVR12</b>	98.0 (98/100)
95% CI	(95.3, 100.0)
<b>Outcomes in Patients Without SVR</b>	
On Treatment VF	0 (0/100)
Relapse <sup>a</sup>	1 (1/99)
Other <sup>b</sup>	1 (1/100)
VF = virologic failure	
a. Relapse is defined as HCV RNA $\geq$ LLOQ after end-of-treatment response among those who completed treatment.	
b. Includes patients who discontinued due to adverse event, lost to follow-up, or patient withdrawal.	

### **People Who Inject Drugs (PWID) and those on Medication-Assisted Treatment (MAT) for Opioid Use Disorder**

The efficacy of MAVIRET in PWID and patients on MAT with HCV genotype 1, 2, 3, 4, 5 or 6 infection is based on data from Phase 2 and 3 trials in 4,655 adults and adolescents who received MAVIRET; 1,373 patients were identified as PWID based on self-reported history of injection drug use at trial enrollment, 3,282 patients did not report injection drug use (non-PWID), 225 patients reported concomitant use of MAT for opioid use disorder, and 4,098 patients reported no use of MAT (332 patients were not included in the analysis due to missing assessment of MAT).

In the PWID population, 62 patients were considered current/recent PWID (defined as self-reported injection drug use within the last 12 months prior to starting MAVIRET), 959 patients were considered former PWID (defined as self-reported injection drug use more than 12 months prior to starting MAVIRET), and 352 patients did not specify current/recent PWID versus former PWID and were not

included in the analysis. Compared to former/non-PWID patients (n = 4,241), the current/recent PWID patients were more frequently male (79%), White (73%), younger (median age [range]: 40 years [19 to 64]), treatment-naïve (94%), and had higher proportions of HCV genotype 3 infection (44%) and HIV co-infection (24%). Similar to the former/non-PWID patients, the majority of current/recent PWID patients were non-cirrhotic (73%).

The overall SVR12 rate was 97.8% (4,147/4,241) in former/non-PWID patients and 88.7% (55/62) in current/recent PWID patients; the difference between the two groups was primarily due to missing data at the time of the SVR12 measurement window in the current/recent PWID group. Virologic failure rates, however, were similar in both groups: 1.6% (1/62) in the current/recent PWID patients and 1.2% (50/4,241) in former/non-PWID patients.

Patients on MAT were more frequently male (70%), White (92%), younger (median age [range]: 47 years [23 to 76]), treatment-naïve (89%), and had a higher proportion of HCV genotype 3 infection (50%) as compared to patients not on MAT. Among the patients on MAT, 74% were non-cirrhotic, and 7% were co-infected with HIV, similar to those not on MAT.

The SVR12 rates were also similar between patients on MAT (95.6% [215/225]) and those not on MAT (97.7% [4,002/4,098]), with low rates of virologic failure in both groups (0.4% [1/225] and 1.3% [52/4,098], respectively).

#### **Durability of Sustained Virologic Response**

In a long-term follow-up study (M13-576), 99.5% (374/376) of adult patients who had achieved SVR12 in prior clinical studies of MAVIRET maintained SVR up to their last follow-up visit (median duration of follow-up: 35.5 months): 100%, 99.6%, and 95.8% of patients who had received 8, 12, and 16 weeks of MAVIRET therapy, respectively. Among the 2 patients who did not maintain SVR, 1 experienced a late relapse 390 days after MAVIRET therapy, and the other patient experienced re-infection with a different HCV genotype.

#### **Clinical Study in Pediatric Patients (3 to less than 18 years of age and weighing at least 12 kg)**

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

DORA Part 1 evaluated the safety and efficacy in 47 adolescent patients (age range: 12 to 17 years old; weight range: 32 to 109 kg) without cirrhosis who received MAVIRET tablets for 8 weeks (44 patients) or 16 weeks (3 patients).

The demographic and disease characteristic of the patient population in DORA Part 1 are summarized in **Table 32**.

**Table 32. Demographic and Other Baseline Characteristics of the Adolescent Patient Population (DORA Part 1)**

Characteristics	MAVIRET N = 47 n (%)
<b>Gender</b>	
Male	21 (44.7)
Female	26 (55.3)
<b>Race</b>	
White	35 (74.5)
Black	4 (8.5)
Asian	6 (12.8)
Other	2 (4.3)
<b>Viral Load</b>	
HCV RNA (Log <sub>10</sub> IU/mL), mean (SD)	6.11 (0.60)
<b>HCV Genotype/Subtype</b>	
1	37 (78.7)
2	3 (6.4)
3	4 (8.5)
4	3 (6.4)
<b>Prior Treatment History</b>	
TN	36 (76.6)
TE-PR	11 (23.4)
<b>Stages of Fibrosis</b>	
F0-F2	46 (97.9)
F3	1 (2.1)
<b>HCV/HIV Co-infection</b>	
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	

DORA Part 2 evaluated the safety and efficacy in 80 pediatric patients aged 3 years to less than 12 years who received weight based MAVIRET granules in sachets for 8, 12 or 16 weeks. 18 patients received the initial lower dose, and 62 patients received the final recommended dose. The median age was 7 years (range: 3 to 11).

The demographic and disease characteristics of the patient population in DORA Part 2 are summarized in **Table 33**.

**Table 33. Demographic and Other Baseline Characteristics of the Pediatric Patient Population (DORA Part 2)**

Characteristics	MAVIRET N = 80 n (%)
<b>Gender</b>	
Male	36 (45.0)
Female	44 (55.0)
<b>Race</b>	
White	55 (68.8)
Black	3 (3.8)
Asian	14 (17.5)
Other	8 (10.0)
<b>Viral Load</b>	
HCV RNA (Log <sub>10</sub> IU/mL), mean (SD)	5.95 (0.79)
<b>HCV Genotype/Subtype</b>	
1	58 (72.5)
2	2 (2.5)
3	18 (22.5)
4	2 (2.5)
<b>Prior Treatment History</b>	
TN	78 (97.5)
TE-PR	2 (2.5)
<b>Stages of Fibrosis</b>	
F0-F2	80 (100.0)
F3	0 (0.0)
<b>HCV/HIV Co-infection</b>	
Yes	1 (1.3)
No	79 (98.8)
SD = standard deviation; GT = genotype; TN = treatment-naïve; TE-PR = treatment experienced to regimens containing interferon, (peg)interferon and/or ribavirin	

The response rates in adolescent patients with chronic HCV infection are presented in **Table 34**. No patients experienced virologic failure.

**Table 34. Sustained Virologic Response (SVR12) in HCV-Infected Adolescent Patients (DORA Part 1)**

Assessment	MAVIRET N = 47 % (n/N)
SVR12, % (n/N)	100 (47/47)
95% CI, (%)	(92.4, 100.0)
SVR12 = sustained virologic response 12 weeks post-treatment; CI = confidence interval	

The response rates in pediatric patients with chronic HCV infection are presented in **Table 35**. The overall SVR12 rate for the patients who received the final recommended dose ratio was 98.4% (61/62). No patients taking the final recommended dose ratio experienced virologic failure.

**Table 35. Sustained Virologic Response (SVR12) in HCV-Infected Pediatric Patients (DORA Part 2)**

Assessment	MAVIRET N = 80
SVR12, % (n/N)	96.3 (77/80)
95% CI, (%)	(89.5, 98.7)
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 IC<sub>50</sub> 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<sub>50</sub> values of glecaprevir and pibrentasvir against full-length or chimeric replicons encoding NS3 or NS5A from laboratory strains are presented in **Table 36**.

**Table 36. Activity of Glecaprevir and Pibrentasvir Against HCV Genotypes 1 to 6 Replicon Cell Lines**

HCV Subtype	Glecaprevir EC <sub>50</sub> , nM <sup>a</sup>	Pibrentasvir EC <sub>50</sub> , nM <sup>b</sup>
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<sub>50</sub> values of glecaprevir and pibrentasvir against chimeric replicons encoding NS3 or NS5A from clinical isolates are presented in **Table 37**.

**Table 37. 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 <sub>50</sub> , nM (range)	Number of clinical isolates	Median EC <sub>50</sub> , 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 genotype 3b replicon, the presence of naturally occurring polymorphisms K30 and M31 in NS5A reduced susceptibility to pibrentasvir by 24-fold relative to the activity of pibrentasvir in genotype 3a replicon.

### *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 the registrational 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 genotype 3-infected patient experiencing virologic failure was determined to be reinfected with a genotype 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 genotype 5 as compared to other genotypes; the high prevalence in genotype 5 was due to the common D168E polymorphism, which remains susceptible to glecaprevir. In general, with the exception of genotype 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 genotype 1, 2, 4, 5 and 6.

*Genotype 3:* Among 313 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, 77% (17/22) 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% (21/21) 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 genotype 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:

#### *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.

## PATIENT MEDICATION INFORMATION

### READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

#### 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**.

If your child is taking MAVIRET, all of the information in this PATIENT MEDICATION INFORMATION applies to them. As their caregiver, please read this information before they start taking MAVIRET. Talk with your child's healthcare professional if you need any additional information on their condition and treatment.

#### 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 [Hepatitis B Reactivation](#) subsection.)

#### What is MAVIRET used for?

- MAVIRET treats adults and children (3 years and older and weighing 12 kg or more) 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 3 years of age or weighing less than 12 kg.

#### How does MAVIRET work?

There are 2 medicines in MAVIRET: 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 Tablets?

Medicinal ingredients: glecaprevir, pibrentasvir.

Non-medicinal ingredients: colloidal silicon dioxide, copovidone (type K 28), croscarmellose sodium, hypromellose 2910, iron oxide red, lactose monohydrate, polyethylene glycol 3350, propylene glycol monocaprylate (type II), sodium stearyl fumarate, titanium dioxide and vitamin E polyethylene glycol succinate.

#### What do MAVIRET Tablets 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:

Tablet containing 100 milligrams of glecaprevir and 40 milligrams of pibrentasvir.

Granules in sachets containing 50 milligrams of glecaprevir and 20 milligrams of pibrentasvir. See the PATIENT MEDICATION INFORMATION for MAVIRET granules for further information about MAVIRET granules.

**Do not use MAVIRET if:**

- you are allergic to any of the ingredients in MAVIRET. (See the section "**What are the ingredients in MAVIRET Tablets?**" 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<sup>®</sup>, Reyataz<sup>®</sup>)
  - atorvastatin (Lipitor<sup>®</sup>)
  - dabigatran etexilate (Pradaxa<sup>®</sup>)
  - ethinyl estradiol-containing medicines such as tablets or vaginal rings used to prevent pregnancy
  - rifampin (Rifadin<sup>®</sup>, Rofact<sup>®</sup>)
  - simvastatin (Zocor<sup>®</sup>)

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MAVIRET. Talk about any health conditions or problems you may have, including if you:**

- are taking other drugs for viral infections.
- have had a liver or a kidney transplant.
- have diabetes.
- 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.

Liver Issues

Talk to your doctor if you had or have liver problems other than hepatitis C infection. Your doctor may order medical tests to determine how your liver is functioning. Tell your doctor right away if you experience symptoms of liver failure such as:

- abdominal pain or pressure, fluid in your abdomen

- bleeding or bruising more easily than normal
- confusion, difficulty concentrating, loss of consciousness, tiredness
- nausea, vomiting, diarrhea
- dark or bloody stools, dark or brown (tea coloured) urine
- yellowing of the skin and eyes

**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.**

**The following may interact with MAVIRET:**

<b>Medicine</b>	<b>Purpose of the medicine</b>
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 ( <i>Hypericum perforatum</i> )	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.
- MAVIRET tablets and MAVIRET granules are not interchangeable.

**Usual dose for adult, adolescent (12 to less than 18 years of age) or children weighing at least 45 kg:**

- 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, or a person you are caring for, have taken too much MAVIRET, contact a 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 have when taking MAVIRET. If you experience any side effects not listed here, tell your healthcare professional.

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

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>FREQUENCY UNKNOWN</b>			
<b>Angioedema:</b> swelling of the face, hands, feet, genitals, tongue or throat, difficulty swallowing or breathing; swelling of the digestive tract which may cause diarrhea, nausea or vomiting			✓
<b>Hepatic decompensation and hepatic failure (liver failure):</b> abdominal pain or pressure, fluid in your abdomen, bleeding or bruising more easily than normal,		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
confusion, difficulty concentrating, loss of consciousness, tiredness, nausea, vomiting, diarrhea, dark or bloody stools, dark or brown (tea coloured) urine, yellowing of the skin and eyes			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

### 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 (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) 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 out of reach and sight of children.

### If you want more information about MAVIRET:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website ([www.abbvie.ca](http://www.abbvie.ca)), or by calling 1-800-704-8271.

This leaflet was prepared by AbbVie Corporation.

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Atripla, Complera, Coumadin, Crestor, Dilantin, Edurant, Evotaz, Lanoxin, Lipitor, Neoral, Pradaxa, Pravachol, Prezista, Prograf, Reyataz, Rifadin, Rofact, Sandimmune, Sustiva and Tegretol are trademarks of their respective owners and are not trademarks of AbbVie Corporation. The makers of these brands are not affiliated with and do not endorse AbbVie or its products.

## PATIENT MEDICATION INFORMATION

### READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

#### MAVIRET®

#### glecaprevir/pibrentasvir granules

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**.

If your child is taking MAVIRET, all of the information in this PATIENT MEDICATION INFORMATION applies to them. As their caregiver, please read this information before they start taking MAVIRET. Talk with your child's healthcare professional if you need any additional information on their condition and treatment.

#### 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 [Hepatitis B Reactivation](#) subsection.)

#### What is MAVIRET used for?

- MAVIRET treats adults and children (3 years and older and weighing 12 kg or more) 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 3 years of age or weighing less than 12 kg.

#### How does MAVIRET work?

There are 2 medicines in MAVIRET: 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 Granules?

Medicinal ingredients: glecaprevir, pibrentasvir.

Non-medicinal ingredients: colloidal silicon dioxide, copovidone (type K 28), croscarmellose sodium (in the glecaprevir granules only), hypromellose 2910, iron oxide red, iron oxide yellow, lactose monohydrate, polyethylene glycol/macrogol 3350, propylene glycol monocaprylate (type II), sodium stearyl fumarate, titanium dioxide and vitamin E (tocopherol) polyethylene glycol succinate.

#### What do MAVIRET Granules look like?

MAVIRET granules are pink and yellow, round, biconvex and approximately 2 millimeters in diameters.

#### MAVIRET comes in the following dosage forms:

Granules in sachets containing 50 milligrams of glecaprevir and 20 milligrams of pibrentasvir.

Tablets containing 100 milligrams of glecaprevir and 40 milligrams of pibrentasvir. See the PATIENT MEDICATION INFORMATION for MAVIRET tablets for further information about MAVIRET tablets.

**Do not use MAVIRET if:**

- you are allergic to any of the ingredients in MAVIRET. (See the section " **What are the ingredients in MAVIRET Granules in Sachets**" 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<sup>®</sup>, Reyataz<sup>®</sup>)
  - atorvastatin (Lipitor<sup>®</sup>)
  - dabigatran etexilate (Pradaxa<sup>®</sup>)
  - ethinyl estradiol-containing medicines such as tablets or vaginal rings used to prevent pregnancy
  - rifampin (Rifadin<sup>®</sup>, Rofact<sup>®</sup>)
  - simvastatin (Zocor<sup>®</sup>)

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MAVIRET. Talk about any health conditions or problems you may have, including if you:**

- are taking other drugs for viral infections.
- have had a liver or a kidney transplant.
- have diabetes.
- 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.

Liver Issues

Talk to your doctor if you or the person you are caring for had or have liver problems other than hepatitis C infection. Your doctor may order medical tests to determine how your liver is functioning. Tell your doctor right away if you or the person you are caring for experience symptoms of liver failure such as:

- abdominal pain or pressure, fluid in your abdomen

- bleeding or bruising more easily than normal
- confusion, difficulty concentrating, loss of consciousness, tiredness
- nausea, vomiting, diarrhea
- dark or bloody stools, dark or brown (tea coloured) urine
- yellowing of the skin and eyes

**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.**

**The following may interact with MAVIRET:**

<b>Medicine</b>	<b>Purpose of the medicine</b>
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 ( <i>Hypericum perforatum</i> )	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.
- MAVIRET tablets and MAVIRET granules are not interchangeable.

- **How to take a dose of MAVIRET oral granules or give it to your child. See detailed Instructions for Use for information.**
  - Give MAVIRET once a day at the same time or after a snack or meal.
  - Do not open the sachet until ready for use.
  - Hold the MAVIRET granules sachet with the cut line on top.
  - Tap the MAVIRET granules sachet gently to settle the granules.
  - Cut the MAVIRET sachet along the cut line.
  - Pour the granules into a bowl and check the sachet to make sure no granules remain.
  - Mix the granules with a small amount of recommended food and swallow (See Instructions for Use for list of recommended food).
  - Do not store any leftover MAVIRET mixture (oral granules mixed with food) for use at a later time.

**Usual dose for children (3 to less than 12 years of age weighing at least 12 to less than 45 kg) :**

- The usual dose for children 3 to less than 12 years of age will be based on a child's body weight. The child's doctor will decide what dose a child should receive.
- 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, or a person you are caring for, have taken too much MAVIRET, contact a 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 have when taking MAVIRET. If you experience any side effects not listed here, tell your healthcare professional.

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

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>FREQUENCY UNKNOWN</b>			
<b>Angioedema:</b> swelling of the face, hands, feet, genitals, tongue or throat, difficulty swallowing or breathing; swelling of the digestive tract which may cause diarrhea, nausea or vomiting			✓
<b>Hepatic decompensation and hepatic failure (liver failure):</b> abdominal pain or pressure, fluid in your abdomen, bleeding or bruising more easily than normal, confusion, difficulty concentrating, loss of consciousness, tiredness, nausea, vomiting, diarrhea, dark or bloody stools, dark or brown (tea coloured) urine, yellowing of the skin and eyes		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

### 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 (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) 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.

**If you want more information about MAVIRET:**

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website ([www.abbvie.ca](http://www.abbvie.ca)), or by calling 1-800-704-8271.

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## Instructions for Use

### MAVIRET®

glecaprevir/pibrentasvir granules

#### Step 1. Get the number of sachets as advised by your child's doctor

Weight of child (kg)	Number of sachets once daily	Food Amount (approximate)
From 12 to less than 20 kg	3 sachets	About 1-2 teaspoons (5-10 ml) of recommended food listed in step 2
From 20 to less than 30 kg	4 sachets	
From 30 to less than 45 kg	5 sachets	

For children weighing 45 kg or more, talk to your child's doctor about giving MAVIRET tablets.

Do not give more than 5 sachets.



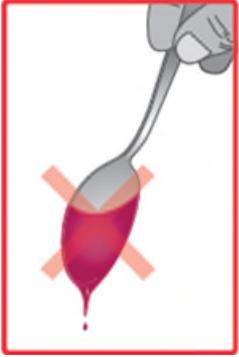
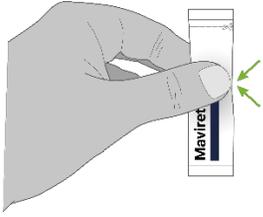
#### Step 2. Choose suitable food to mix with MAVIRET granules

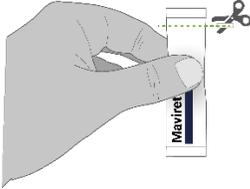
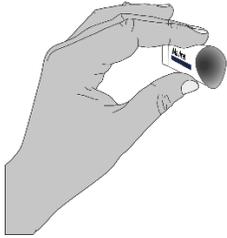
Suitable food should stick to the spoon. It must be soft, low in water content and can be swallowed without chewing.

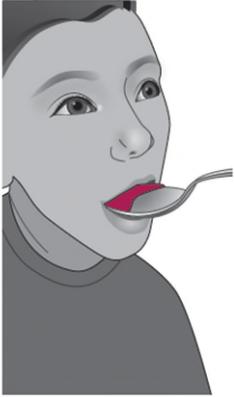
Examples of recommended foods:

- Greek yogurt
- Cream cheese
- Peanut butter
- Chocolate hazelnut spread
- Thick jam
- Other food that sticks to the spoon

Note: in addition to the food used to mix the granules, MAVIRET should also be taken at the same time or straight after a meal or snack. The food used to mix the granules does not replace the meal or snack to take with MAVIRET.

	<p><b>Do not</b> use food if it drips off a spoon as the medicine may dissolve quickly, taste bitter, and become less effective. <b>Do not</b> use food that your child is allergic to.</p> <p>Examples of foods not to use:</p> <ul style="list-style-type: none"> <li>✗ Liquids or watery food</li> <li>✗ Apple sauce</li> <li>✗ Food or liquid that is heated or frozen</li> <li>✗ Bread or other food that requires chewing</li> <li>✗ Non-Greek yogurt</li> <li>✗ Baby food</li> <li>✗ Food that drips off the spoon</li> </ul> <p>For more information about suitable foods, contact your child’s doctor or pharmacist.</p>
	<p><b>Step 3. Gather materials</b></p> <p>Place the following on a clean surface:</p> <ul style="list-style-type: none"> <li>● Box with sachets in it</li> <li>● Soft food</li> <li>● Bowl to use for mixing</li> <li>● Teaspoon</li> <li>● Scissors</li> </ul>
	<p><b>Step 4. Measure food</b></p> <ul style="list-style-type: none"> <li>● Place a small amount (1-2 teaspoons or 5-10 ml) of soft food into a bowl.</li> <li>● The granules inside the sachets are very small, so placing food in the bowl first will help contain them.</li> </ul>
	<p><b>Step 5. Prepare sachet</b></p> <ul style="list-style-type: none"> <li>● Look for the dotted line on the sachet to find the top end.</li> <li>● Hold the sachet upright and tap the top of the sachet. Keep tapping until all the granules inside fall to the bottom.</li> <li>● Feel top area of sachet thoroughly to make sure all granules are at the bottom.</li> </ul>

	<p><b>Step 6. Cut top of sachet</b></p> <ul style="list-style-type: none"> <li>● Pinch the sachet in the center, above the granules inside.</li> <li>● Use scissors to cut the top of the sachet completely off.</li> </ul> <p>Be Careful: Granules are very small and can fall out easily.</p> <p>Use opened sachet immediately and do not store opened sachet.</p>
	<p><b>Step 7. Pour sachet</b></p> <ul style="list-style-type: none"> <li>● Make sure the sachet is fully open.</li> <li>● Carefully pour all granules out of the sachet into the bowl of food. Granules are pink and yellow.</li> <li>● Tap sachet to get all the granules out.</li> <li>● Repeat for each sachet for your child's daily dose.</li> </ul>
	<p><b>Step 8. Check sachet</b></p> <p>Look inside each sachet to make sure there are no granules left inside.</p> <p><b>Do not leave any granules behind as the medicine will not work as well if the full dose is not taken.</b></p>
	<p><b>Step 9. Mix</b></p> <ul style="list-style-type: none"> <li>● Use the teaspoon to gently stir the granules into the food.</li> <li>● <b>Do not</b> crush the granules. If the granules are crushed, they will taste bitter.</li> <li>● <b>Do not</b> store the mixture, give it to your child immediately.</li> </ul> <p>If not given within 5 minutes, the mixture may taste bitter.</p> <p><b>If not given immediately (within 15 minutes), the medicine may be less effective. Throw away and start again.</b></p>

	<p><b>Step 10. Give the medicine</b></p> <ul style="list-style-type: none"> <li>● Scoop a small amount of mixture onto the teaspoon.</li> <li>● Make sure your child swallows the mixture without chewing.</li> <li>● Repeat until your child has taken all the mixture.</li> <li>● If any granules are left, add more food and mix. Then finish the dose.</li> <li>● Make sure your child takes the full dose of the medicine.</li> </ul> <p>⚠ If your child misses a dose, see “<b>Missed Dose</b>” in the Patient Mediation Information for further information.</p>
	<p><b>Step 11. Confirm dose for tomorrow</b></p> <p>Check to make sure there are enough sachets for your child’s next dose of MAVIRET.</p> <p><b>For replacement sachets or to refill your prescription, contact your child’s doctor or pharmacist.</b></p>

This leaflet was prepared by AbbVie Corporation.

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