1. NAME OF THE MEDICINAL PRODUCT

Maviret 100 mg/40 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg glecaprevir and 40 mg pibrentasvir. Glecaprevir and pibrentasvir are presented as a fixed-dose combination, immediate release bilayer tablet.

Excipient with known effect
Each film-coated tablet contains 7.48 mg lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Pink, oblong, biconvex, film-coated tablet of dimensions 18.8 mm x 10.0 mm, debossed on one side with 'NXT'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Maviret is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults and adolescents 12 years and older (see sections 4.2, 4.4. and 5.1).

4.2 Posology and method of administration

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

Posology

Recommended dosage in adults and adolescents 12 years and older
The recommended dose of Maviret is 300 mg/120 mg (three 100 mg glecaprevir /40 mg pibrentasvir tablets), taken orally, once daily at the same time with food (see section 5.2).

The recommended Maviret treatment durations for HCV genotype 1, 2, 3, 4, 5, or 6 infected patients with compensated liver disease (with or without cirrhosis) are provided in Table 1 and Table 2.

Table 1: Recommended Maviret treatment duration for patients without prior HCV therapy

Genotype	**Recommended treatment duration**	
	No cirrhosis	**Cirrhosis**
GT 1, 2, 3, 4, 5, 6	8 weeks	8 weeks

Table 2: Recommended Maviret treatment duration for patients who failed prior therapy with peg-IFN + ribavirin +/- sofosbuvir, or sofosbuvir + ribavirin

Genotype	**Recommended treatment duration**	
	No cirrhosis	**Cirrhosis**

GT 1, 2, 4, 5, 6	8 weeks	12 weeks
GT 3	16 weeks	16 weeks

For patients who failed prior therapy with an NS3/4A- and/or an NS5A-inhibitor, see section 4.4.

Patients with genotype 3 infection who are treatment-naïve without cirrhosis
A numerically lower SVR12 rate was achieved in genotype 3a-infected patients with NS5A A30K RAV at baseline treated for 8 weeks as compared to those treated for 12 weeks [84% (16/19) vs 93% (13/14)]. Relapse rates were numerically higher in patients treated for 8 weeks as compared to those treated for 12 weeks [15.8 % (3/19) vs 0 % (0/13)]. In patients without NS5A A30K RAV, there was no difference in the SVR12 rates between patients treated for 8 weeks as compared to those treated for 12 weeks [99% (189/191) vs 99% (263/266)] (see section 5.1).

Patients with HIV-1 Co-infection
Follow the dosing recommendations in Tables 1 and 2. For dosing recommendations with HIV antiviral agents, refer to section 4.5.

Paediatric population
No dose adjustment of Maviret is required in adolescents 12 years and older (see sections 5.1 and 5.2). The safety and effectiveness of Maviret in patients less than 12 years of age have not been established.

Elderly
No dose adjustment of Maviret is required in elderly patients (see sections 5.1 and 5.2).

Renal impairment
No dose adjustment of Maviret is required in patients with any degree of renal impairment including patients on dialysis (see sections 5.1 and 5.2).

Hepatic impairment
No dose adjustment of Maviret is required in patients with mild hepatic impairment (Child-Pugh A). Maviret is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C) or those with any history of prior hepatic decompensation (see sections 4.3, 4.4, and 5.2).

Liver or Kidney Transplant Patients
Maviret may be used for 12 weeks in liver or kidney transplant recipients. A 16-week treatment duration should be considered in transplant patients for whom a longer treatment duration is currently indicated for non-transplant patients (see sections 4.2 and 5.1).

Missed dose
In case a dose of Maviret is missed, the prescribed dose can be taken within 18 hours after the time it was supposed to be taken. If more than 18 hours have passed since Maviret is usually taken, the missed dose should **not** be taken and the patient should take the next dose per the usual dosing schedule. Patients should be instructed not to take a double dose.

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

Method of administration

For oral use.

Patients should be instructed to swallow tablets whole or cut in half, with food but not to chew, crush or break the tablets as it may alter the bioavailability of the agents (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Patients with moderate or severe hepatic impairment (Child-Pugh B or C) or those with any history of prior hepatic decompensation (see sections 4.2, 4.4, and 5.2).

Concomitant use with atazanavir containing products, atorvastatin, simvastatin, dabigatran etexilate, ethinyl oestradiol-containing products, strong P-gp and CYP3A inducers (e.g., rifampicin, carbamazepine, St. John's wort (*Hypericum perforatum*), phenobarbital, phenytoin, and primidone) (see section 4.5).

4.4 Special warnings and precautions for use

Hepatitis B Virus reactivation

Cases of hepatitis B virus (HBV) reactivation, some of them fatal, have been reported during or after treatment with direct-acting antiviral agents. HBV screening should be performed in all patients before initiation of treatment. HBV/HCV co-infected patients are at risk of HBV reactivation, and should, therefore, be monitored and managed according to current clinical guidelines.

Potential Effects of HCV Clearance by Direct-Acting Antivirals (DAA)

Patients may experience improvement of liver function with HCV treatment resulting in improved glucose metabolism by the liver. In diabetic patients, this could lead to improved glucose control. Rare cases of symptomatic hypoglycemia have been reported with the use of HCV DAAs. Therefore, close monitoring of blood glucose levels is recommended in diabetic patients to determine if dose adjustment of the anti-diabetes medication is required.

Risk of hepatic decompensation/failure in patients with evidence of advanced liver disease

Postmarketing cases of hepatic decompensation/failure, including those with fatal outcomes, have been reported in 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.

The majority of patients with severe outcomes had evidence of advanced liver disease with moderate or severe liver impairment (Child-Pugh B or C) prior to initiating therapy with Maviret, including some patients reported as having compensated cirrhosis with mild liver impairment (Child-Pugh A) at baseline but with a prior decompensation event (i.e. prior history of ascites, variceal bleeding, encephalopathy). Rare cases of hepatic decompensation/failure were reported in patients without cirrhosis or with compensated cirrhosis (Child-Pugh A); many of these patients had evidence of portal hypertension. Events also occurred in patients taking a concomitant medication not recommended for co-administration, or in patients with confounding factors such as serious liver-related medical or surgical comorbidities. Cases typically occurred within the first 4 weeks of treatment (median of 27 days).

In patients with compensated cirrhosis (Child-Pugh A) or evidence of advanced liver disease such as portal hypertension, perform hepatic laboratory testing as clinically indicated; and monitor for signs and symptoms of hepatic decompensation such as the presence of jaundice, ascites, hepatic encephalopathy, and variceal haemorrhage. Discontinue Maviret in patients who develop evidence of hepatic decompensation/failure.

Hepatic impairment

Maviret is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C) or those with any history of prior hepatic decompensation (see sections 4.2, 4.3, and 5.2).

Patients who failed a prior regimen containing an NS5A- and/or an NS3/4A-inhibitor

Genotype 1-infected (and a very limited number of genotype 4-infected) patients with prior failure on regimens that may confer resistance to glecaprevir/pibrentasvir were studied in the MAGELLAN-1 study (section 5.1). The risk of failure was, as expected, highest for those exposed to both classes. A resistance algorithm predictive of the risk for failure by baseline resistance has not been established. Accumulating double class resistance was a general finding for patients who failed re-treatment with glecaprevir/pibrentasvir in MAGELLAN-1. No re-treatment data is available for patients infected with genotypes 2, 3, 5 or 6. Maviret is not recommended for the re-treatment of patients with prior exposure to NS3/4A- and/or NS5A-inhibitors.

Drug-drug interactions

Co-administration is not recommended with several medicinal products as detailed in section 4.5

Lactose

Maviret contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for Maviret to affect other medicinal products

Glecaprevir and pibrentasvir are inhibitors of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide (OATP) 1B1/3. Co-administration with Maviret may increase plasma concentrations of medicinal products that are substrates of P-gp (e.g. dabigatran etexilate, digoxin), BCRP (e.g. rosuvastatin), or OATP1B1/3 (e.g. atorvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin). See Table 3 for specific recommendations on interactions with sensitive substrates of P-gp, BCRP, and OATP1B1/3. For other P-gp, BCRP, or OATP1B1/3 substrates, dose adjustment may be needed.

Glecaprevir and pibrentasvir are weak inhibitors of cytochrome P450 (CYP) 3A and uridine glucuronosyltransferase (UGT) 1A1 *in vivo.* Clinically significant increases in exposure were not observed for sensitive substrates of CYP3A (midazolam, felodipine) or UGT1A1 (raltegravir) when administered with Maviret.

Both glecaprevir and pibrentasvir inhibit the bile salt export pump (BSEP) *in vitro*.

Significant inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, UGT1A6, UGT1A9, UGT1A4, UGT2B7, OCT1, OCT2, OAT1, OAT3, MATE1 or MATE2K are not expected.

Patients treated with vitamin K antagonists

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

Potential for other medicinal products to affect Maviret

Use with strong P-gp/CYP3A inducers
Medicinal products that are strong P-gp and CYP3A inducers (e.g., rifampicin, carbamazepine, St. John's wort (*Hypericum perforatum*), phenobarbital, phenytoin, and primidone) could significantly decrease glecaprevir or pibrentasvir plasma concentrations and may lead to reduced therapeutic effect of Maviret or loss of virologic response. Co-administration of such medicinal products with Maviret is contraindicated (see section 4.3).

Co-administration of Maviret with medicinal products that are moderate inducers P-gp/CYP3A may decrease glecaprevir and pibrentasvir plasma concentrations (e.g. oxcarbazepine, eslicarbazepine, lumacaftor, crizotinib). Co-administration of moderate inducers is not recommended (see section 4.4).

Glecaprevir and pibrentasvir are substrates of the efflux transporters P-gp and/or BCRP. Glecaprevir is also a substrate of the hepatic uptake transporters OATP1B1/3. Co-administration of Maviret with medicinal products that inhibit P-gp and BCRP (e.g. ciclosporin, cobicistat, dronedarone, itraconazole, ketoconazole, ritonavir) may slow elimination of glecaprevir and pibrentasvir and thereby increase plasma exposure of the antivirals. Medicinal products that inhibit OATP1B1/3 (e.g. elvitegravir, ciclosporin, darunavir, lopinavir) increase systemic concentrations of glecaprevir.

Established and other potential medicinal product interactions

Table 3 provides the least-squares mean Ratio (90% Confidence Interval) effect on concentration of Maviret and some common concomitant medicinal products. The direction of the arrow indicates the direction of the change in exposures (C_{max}, AUC, and C_{min}) in glecaprevir, pibrentasvir, and the co-administered medicinal product (↑ = *increase (more than 25%),* ↓ = *decrease (more than 20%),* ↔ = *no change* (equal to or less than 20% decrease or 25% increase). This is not an exclusive list.

Table 3: Interactions between Maviret and other medicinal products

Medicinal product by therapeutic areas/possible mechanism of interaction	**Effect on medicinal product levels**	**C_{max}**	**AUC**	**C_{min}**	**Clinical comments**
ANGIOTENSIN-II RECEPTOR BLOCKERS					
Losartan 50 mg single dose	↑ losartan	2.51 (2.00, 3.15)	1.56 (1.28, 1.89)	--	No dose adjustment is required.
	↑ losartan carboxylic acid	2.18 (1.88, 2.53)	↔	--	
Valsartan 80 mg single dose (Inhibition of OATP1B1/3)	↑ valsartan	1.36 (1.17, 1.58)	1.31 (1.16, 1.49)	--	No dose adjustment is required.
ANTIARRHYTHMICS					
Digoxin 0.5 mg single dose (Inhibition of P-gp)	↑ digoxin	1.72 (1.45, 2.04)	1.48 (1.40, 1.57)	--	Caution and therapeutic concentration monitoring of digoxin is recommended.
ANTICOAGULANTS					
Dabigatran etexilate 150 mg single dose (Inhibition of P-gp)	↑ dabigatran	2.05 (1.72, 2.44)	2.38 (2.11, 2.70)	--	Co-administration is contraindicated (see section 4.3).
ANTICONVULSANTS					
Carbamazepine 200 mg twice daily (Induction of P-gp/CYP3A)	↓ glecaprevir	0.33 (0.27, 0.41)	0.34 (0.28, 0.40)	--	Co-administration may lead to reduced therapeutic effect of Maviret and is contraindicated (see section 4.3).
	↓ pibrentasvir	0.50 (0.42, 0.59)	0.49 (0.43, 0.55)	--	
Phenytoin, phenobarbital, primidone	Not studied. Expected: ↓ glecaprevir and ↓ pibrentasvir				
ANTIMYCOBACTERIALS					
Rifampicin 600 mg single dose	↑ glecaprevir	6.52 (5.06, 8.41)	8.55 (7.01, 10.4)	--	

(Inhibition of OATP1B1/3)	↔ pibrentasvir	↔	↔	--	Co-administration is contraindicated (see section 4.3).
Rifampicin 600 mg once daily[a] (Induction of P-gp/BCRP/CYP3A)	↓ glecaprevir	0.14 (0.11, 0.19)	0.12 (0.09, 0.15)	--	
	↓ pibrentasvir	0.17 (0.14, 0.20)	0.13 (0.11, 0.15)	--	
ETHINYL-OESTRADIOL-CONTAINING PRODUCTS					
Ethinyloestradiol (EE)/Norgestimate 35 µg/250 µg once daily	↑ EE	1.31 (1.24, 1.38)	1.28 (1.23, 1.32)	1.38 (1.25, 1.52)	Co-administration of Maviret with ethinyloestradiol-containing products is contraindicated due to the risk of ALT elevations (see section 4.3). No dose adjustment is required with levonorgestrel, norethidrone or norgestimate as contraceptive progestagen.
	↑ norelgestromin	↔	1.44 (1.34, 1.54)	1.45 (1.33, 1.58)	
	↑ norgestrel	1.54 (1.34, 1.76)	1.63 (1.50, 1.76)	1.75 (1.62, 1.89)	
EE/Levonorgestrel 20 µg/100 µg once daily	↑ EE	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)	
HERBAL PRODUCTS					
St. John's wort (*Hypericum perforatum*) (Induction of P-gp/CYP3A)	Not studied. Expected: ↓ glecaprevir and ↓ pibrentasvir				Co-administration may lead to reduced therapeutic effect of Maviret and is contraindicated (see section 4.3).
HIV-ANTIVIRAL AGENTS					
Atazanavir + ritonavir 300/100 mg once daily[b]	↑ glecaprevir	≥4.06 (3.15, 5.23)	≥6.53 (5.24, 8.14)	≥14.3 (9.85, 20.7)	Co-administration with atazanavir is contraindicated due to the risk of ALT elevations (see section 4.3).
	↑ pibrentasvir	≥1.29 (1.15, 1.45)	≥1.64 (1.48, 1.82)	≥2.29 (1.95, 2.68)	
Darunavir + ritonavir 800/100 mg once daily	↑ glecaprevir	3.09 (2.26, 4.20)	4.97 (3.62, 6.84)	8.24 (4.40, 15.4)	Co-administration with darunavir is not recommended.
	↔ pibrentasvir	↔	↔	1.66 (1.25, 2.21)	
Efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg once daily	↑ tenofovir	↔	1.29 (1.23, 1.35)	1.38 (1.31, 1.46)	Co-administration with efavirenz may lead to reduced therapeutic effect of Maviret and is not recommended. No clinically significant interactions are expected with tenofovir disoproxil fumarate.
	The effect of efavirenz/emtricitabine/tenofovir disoproxil fumarate on glecaprevir and pibrentasvir was not directly quantified within this study, but glecaprevir and pibrentasvir exposures were significantly lower than historical controls.				
Elvitegravir/cobicistat/emtricitabine/ tenofovir alafenamide (P-gp, BCRP, and OATP inhibition by cobicistat, OATP	↔ tenofovir	↔	↔	↔	No dose adjustment is required.
	↑ glecaprevir	2.50 (2.08, 3.00)	3.05 (2.55, 3.64)	4.58 (3.15, 6.65)	
	↑ pibrentasvir	↔	1.57 (1.39, 1.76)	1.89 (1.63, 2.19)	

inhibition by elvitegravir)					
Lopinavir/ritonavir 400/100 mg twice daily	↑ glecaprevir	2.55 (1.84, 3.52)	4.38 (3.02, 6.36)	18.6 (10.4, 33.5)	Co-administration is not recommended.
	↑ pibrentasvir	1.40 (1.17, 1.67)	2.46 (2.07, 2.92)	5.24 (4.18, 6.58)	
Raltegravir 400 mg twice daily (Inhibition of UGT1A1)	↑ raltegravir	1.34 (0.89, 1.98)	1.47 (1.15, 1.87)	2.64 (1.42, 4.91)	No dose adjustment is required.
HCV-ANTIVIRAL AGENTS					
Sofosbuvir 400 mg single dose (P-gp/BCRP inhibition)	↑ sofosbuvir	1.66 (1.23, 2.22)	2.25 (1.86, 2.72)	--	No dose adjustment is required.
	↑ GS-331007	↔	↔	1.85 (1.67, 2.04)	
	↔ glecaprevir	↔	↔	↔	
	↔ pibrentasvir	↔	↔	↔	
HMG-COA REDUCTASE INHIBITORS					
Atorvastatin 10 mg once daily (Inhibition of OATP1B1/3, P-gp, BCRP, CYP3A)	↑ atorvastatin	22.0 (16.4, 29.5)	8.28 (6.06, 11.3)	--	Co-administration with atorvastatin and simvastatin is contraindicated (see section 4.3).
Simvastatin 5 mg once daily (Inhibition of OATP1B1/3, P-gp, BCRP)	↑ simvastatin	1.99 (1.60, 2.48)	2.32 (1.93, 2.79)	--	
	↑ simvastatin acid	10.7 (7.88, 14.6)	4.48 (3.11, 6.46)	--	
Lovastatin 10 mg once daily (Inhibition of OATP1B1/3, P-gp, BCRP)	↑ lovastatin	↔	1.70 (1.40, 2.06)	--	Co-administration is not recommended. If used, lovastatin should not exceed a dose of 20 mg/day and patients should be monitored.
	↑ lovastatin acid	5.73 (4.65, 7.07)	4.10 (3.45, 4.87)	--	
Pravastatin 10 mg once daily (Inhibition of OATP1B1/3)	↑ pravastatin	2.23 (1.87, 2.65)	2.30 (1.91, 2.76)	--	Caution is recommended. Pravastatin dose should not exceed 20 mg per day and rosuvastatin dose should not exceed 5 mg per day.
Rosuvastatin 5 mg once daily (Inhibition of OATP1B1/3, BCRP)	↑ rosuvastatin	5.62 (4.80, 6.59)	2.15 (1.88, 2.46)	--	
Fluvastatin, Pitavastatin	Not studied. Expected: ↑ fluvastatin and ↑ pitavastatin				Interactions with fluvastatin and pitavastatin are likely and caution is recommended during the combination. A low dose of the statin is recommended at the initiation of the DAA treatment.
IMMUNOSUPPRESSANTS					
Ciclosporin	↑ glecaprevir[c]	1.30	1.37	1.34	

100 mg single dose		(0.95, 1.78)	(1.13, 1.66)	(1.12, 1.60)	Maviret is not recommended for use in patients requiring stable ciclosporin doses > 100 mg per day. If the combination is unavoidable, use can be considered if the benefit outweighs the risk with a close clinical monitoring.
	↑ pibrentasvir	↔	↔	1.26 (1.15, 1.37)	
Ciclosporin 400 mg single dose	↑ glecaprevir	4.51 (3.63, 6.05)	5.08 (4.11, 6.29)	--	
	↑ pibrentasvir	↔	1.93 (1.78, 2.09)	--	
Tacrolimus 1 mg single dose (CYP3A4 and P-gp inhibition)	↑ tacrolimus	1.50 (1.24, 1.82)	1.45 (1.24, 1.70)	--	The combination of Maviret with tacrolimus should be used with caution. Increase of tacrolimus exposure is expected. Therefore, a therapeutic drug monitoring of tacrolimus is recommended and a dose adjustment of tacrolimus made accordingly.
	↔ glecaprevir	↔	↔	↔	
	↔ pibrentasvir	↔	↔	↔	
PROTON PUMP INHIBITORS					
Omeprazole 20 mg once daily (Increase gastric pH value)	↓ glecaprevir	0.78 (0.60, 1.00)	0.71 (0.58, 0.86)	--	No dose adjustment is required.
	↔ pibrentasvir	↔	↔	--	
Omeprazole 40 mg once daily (1 hour before breakfast)	↓ glecaprevir	0.36 (0.21, 0.59)	0.49 (0.35, 0.68)	--	
	↔ pibrentasvir	↔	↔	--	
Omeprazole 40 mg once daily (evening without food)	↓ glecaprevir	0.54 (0.44, 0.65)	0.51 (0.45, 0.59)	--	
	↔ pibrentasvir	↔	↔	--	
VITAMIN K ANTAGONISTS					
Vitamin K antagonists	Not studied.				Close monitoring of INR is recommended with all vitamin K antagonists. This is due to liver function changes during treatment with Maviret.

DAA=direct acting antiviral

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

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

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

Additional drug-drug interaction studies were performed with the following medical products and showed no clinically significant interactions with Maviret: abacavir, amlodipine, buprenorphine, caffeine, dextromethorphan, dolutegravir, emtricitabine, felodipine, lamivudine, lamotrigine, methadone, midazolam, naloxone, norethindrone or other progestin-only contraceptives, rilpivirine, tenofovir alafenamide and tolbutamide.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of glecaprevir or pibrentasvir in pregnant women.

Studies in rats/mice with glecaprevir or pibrentasvir do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Maternal toxicity associated with embryo-foetal loss has been observed in the rabbit with glecaprevir which precluded evaluation of glecaprevir at clinical exposures in this species (see section 5.3). As a precautionary measure, Maviret use is not recommended in pregnancy.

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 (for details see section 5.3). A risk to the suckling child 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.

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 Section 5.3).

4.7 Effects on ability to drive and use machines

Maviret has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety assessment of Maviret in subjects treated for 8, 12, or 16 weeks with compensated liver disease (with or without cirrhosis) was based on registrational Phase 2 and 3 studies which evaluated approximately 2,300 adult subjects. The most commonly reported adverse reactions (incidence ≥ 10%) were headache and fatigue. Less than 0.1% of subjects treated with Maviret had serious adverse reactions (transient ischaemic attack). The proportion of subjects treated with Maviret who permanently discontinued treatment due to adverse reactions was 0.1%. The type and severity of adverse reactions in subjects with cirrhosis were overall comparable to those seen in subjects without cirrhosis.

Tabulated summary of adverse reactions

The following adverse reactions were identified in patients treated with Maviret. The adverse reactions are listed below by body system organ class and frequency. Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) or very rare (< 1/10,000).

Table 4: Adverse reactions identified with Maviret

Frequency	**Adverse reactions**
Nervous system disorders	
Very common	headache
Gastrointestinal disorders	

Common	diarrhoea, nausea
General disorders and administration site conditions	
Very common	fatigue
Common	asthenia

Description of selected adverse reactions

Adverse reactions in adult subjects with severe renal impairment including subjects on dialysis
The safety of Maviret in subjects with chronic kidney disease (Stage 4 or Stage 5 including subjects 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 subjects (EXPEDITION-4). The most common adverse reactions in subjects with severe renal impairment were pruritus (17%) and fatigue (12%).

Adverse Reactions in HCV/HIV-1 Co-infected Adult Subjects
The overall safety profile in HCV/HIV-1 co-infected subjects (ENDURANCE-1 and EXPEDITION-2) was comparable to that observed in HCV mono-infected subjects.

Adverse Reactions in Adult Subjects 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 subjects in the Phase 2 and 3 studies. Adverse reactions observed in greater than or equal to 5% of subjects receiving Maviret for 12 weeks were headache (17%), fatigue (16%), nausea (8%), and pruritus (7%). In subjects treated with Maviret who reported an adverse reaction, 81% had adverse reactions of mild severity. Two percent of subjects experienced a serious adverse reaction, and no subjects 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 and those on MAT with HCV GT 1- 6 infection is based on data from Phase 2 and 3 trials in which 62 subjects identified as current/recent PWID (defined as self-reported injection drug use within the last 12 months prior to starting Maviret), 959 subjects identified as former PWID (defined as self-reported injection drug use more than 12 months prior to starting Maviret), and 3,282 subjects reported no injection drug use (non-PWID); 225 subjects reported concomitant use of MAT for opioid use disorder, and 4,098 subjects reported no MAT use.

The overall safety of Maviret was similar between subjects who self-identified as current/recent PWID, those who were former PWID, and those who did not report history of injection drug use. The safety of Maviret was also similar between subjects who reported concomitant MAT for opioid use disorder and those who did not report MAT use.

Adverse Reactions in Adolescent Subjects
The safety of Maviret in HCV infected adolescents is based on data from a Phase 2/3 open-label trial in 47 subjects aged 12 years to less than 18 years with HCV GT 1, 2, 3 or 4 infection treated with Maviret for 8 to 16 weeks (DORA-Part 1). The adverse reactions observed were comparable with those observed in clinical studies of Maviret in adults.

Serum bilirubin elevations

Elevations in total bilirubin of at least 2x upper limit normal (ULN) were observed in 1.3% of subjects related to glecaprevir-mediated inhibition of bilirubin transporters and metabolism. Bilirubin elevations were asymptomatic, transient, and typically occurred early during treatment. Bilirubin elevations were predominantly indirect and not associated with ALT elevations. Direct hyperbilirubinemia was reported in 0.3% of subjects.

4.9 Post marketing experience

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

Immune System Disorders: angioedema

Skin and Subcutaneous Tissue Disorders: pruritus

Hepatobiliary Disorders: hepatic decompensation, hepatic failure

4.10 Overdose

The highest documented doses administered to healthy volunteers is 1,200 mg once daily for 7 days for glecaprevir and 600 mg once daily for 10 days for pibrentasvir. Asymptomatic serum ALT elevations (>5x ULN) were observed in 1 out of 70 healthy subjects following multiple doses of glecaprevir (700 mg or 800 mg) once daily for ≥ 7 days. In case of overdose, the patient should be monitored for any signs and symptoms of toxicities (see section 4.8). Appropriate symptomatic treatment should be instituted immediately. Glecaprevir and pibrentasvir are not significantly removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Direct-acting antiviral, ATC code: J05AP57

Mechanism of action

Maviret is a fixed-dose combination tablet containing two pan-genotypic, direct-acting antiviral agents, glecaprevir (NS3/4A protease inhibitor) and pibrentasvir (NS5A inhibitor), targeting multiple steps in the HCV viral lifecycle.

Glecaprevir
Glecaprevir is a pan-genotypic 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.

Pibrentasvir
Pibrentasvir is a pan-genotypic 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.

Antiviral activity

The EC_{50} values of glecaprevir and pibrentasvir against full-length or chimeric replicons encoding NS3 or NS5A from laboratory strains are presented in Table 5.

Table 5. Activity of glecaprevir and pibrentasvir against HCV genotypes 1-6 replicon cell lines

HCV Subtype	Glecaprevir EC_{50}, nM	Pibrentasvir EC_{50}, nM
1a	0.85	0.0018
1b	0.94	0.0043
2a	2.2	0.0023
2b	4.6	0.0019
3a	1.9	0.0021
4a	2.8	0.0019
5a	NA	0.0014
6a	0.86	0.0028

NA = not available

The *in vitro* activity of glecaprevir was also studied in a biochemical assay, with similarly low IC_{50} values across genotypes.

EC_{50} values of glecaprevir and pibrentasvir against chimeric replicons encoding NS3 or NS5A from clinical isolates are presented in Table 6.

Table 6. Activity of glecaprevir and pibrentasvir against transient replicons containing NS3 or NS5A from HCV genotypes 1-6 clinical isolates

HCV subtype	Glecaprevir		Pibrentasvir	
	Number of clinical isolates	Median EC_{50}, nM (range)	Number of clinical isolates	Median EC_{50}, nM (range)
1a	11	0.08 (0.05 – 0.12)	11	0.0009 (0.0006 – 0.0017)
1b	9	0.29 (0.20 – 0.68)	8	0.0027 (0.0014 – 0.0035)
2a	4	1.6 (0.66 – 1.9)	6	0.0009 (0.0005 – 0.0019)
2b	4	2.2 (1.4 – 3.2)	11	0.0013 (0.0011 – 0.0019)
3a	2	2.3 (0.71 – 3.8)	14	0.0007 (0.0005 – 0.0017)
4a	6	0.41 (0.31 – 0.55)	8	0.0005 (0.0003 – 0.0013)
4b	NA	NA	3	0.0012 (0.0005 – 0.0018)
4d	3	0.17 (0.13 – 0.25)	7	0.0014 (0.0010 – 0.0018)
5a	1	0.12	1	0.0011
6a	NA	NA	3	0.0007 (0.0006 – 0.0010)
6e	NA	NA	1	0.0008
6p	NA	NA	1	0.0005

NA = not available

Resistance

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

Substitutions important for the HCV protease inhibitor class at positions 36, 43, 54, 55, 56, 155, 166, or 170 in NS3 had no impact on glecaprevir activity. Substitutions at amino acid position 168 in NS3 had no impact in genotype 2, while some substitutions at position 168 reduced glecaprevir susceptibility by up to 55-fold (genotypes 1, 3, 4), or reduced susceptibility by > 100-fold (genotype 6). Some substitutions at position 156 reduced susceptibility to glecaprevir (genotypes 1 to 4) by

> 100-fold. Substitutions at amino acid position 80 did not reduce susceptibility to glecaprevir except for Q80R in genotype 3a, which reduced susceptibility to glecaprevir by 21-fold.

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. 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 peginterferon (pegIFN), ribavirin (RBV) and/or sofosbuvir treatment-experienced subjects with or without cirrhosis
Twenty-two of the approximately 2,300 subjects 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).

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

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

Among the 18 genotype 3-infected subjects 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 subjects. A166S or Q168R were present at baseline and post-treatment in 5 subjects. Treatment-emergent NS5A substitutions M28G, A30G/K, L31F, P58T, or Y93H were observed in 16 subjects, and 13 subjects had A30K (n=9) or Y93H (n=5) at baseline and post-treatment.

Studies in subjects with or without compensated cirrhosis who were treatment-experienced to NS3/4A protease and/or NS5A inhibitors
Ten of 113 subjects treated with Maviret in the MAGELLAN-1 study for 12 or 16 weeks experienced virologic failure.

Among the 10 genotype 1-infected subjects with virologic failure, treatment-emergent NS3 substitutions V36A/M, R155K/T, A156G/T/V, or D168A/T were observed in 7 subjects. 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 subjects 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 subjects at the time of failure.

Effect of baseline HCV amino acid polymorphisms on treatment response
A pooled analysis of treatment-naïve and (peg)interferon, ribavirin and/or sofosbuvir treatment-experienced subjects receiving Maviret in the Phase 2 and Phase 3 clinical studies was conducted to explore the association between baseline polymorphisms and treatment outcome and to describe substitutions seen upon virologic failure. Baseline polymorphisms relative to a subtype-specific reference sequence at amino acid positions 155, 156, and 168 in NS3, and 24, 28, 30, 31, 58, 92, and 93 in NS5A were evaluated at a 15% detection threshold by next-generation sequencing. Baseline polymorphisms in NS3 were detected in 1.1% (9/845), 0.8% (3/398), 1.6% (10/613), 1.2% (2/164), 41.9% (13/31), and 2.9% (1/34) of subjects with HCV genotype 1, 2, 3, 4, 5, and 6 infection, respectively. Baseline polymorphisms in NS5A were detected in 26.8% (225/841), 79.8% (331/415),

22.1% (136/615), 49.7% (80/161), 12.9% (4/31), and 54.1% (20/37) of subjects with HCV genotype 1, 2, 3, 4, 5, and 6 infection, respectively.

Genotype 1, 2, 4, 5, and 6: Baseline polymorphisms in genotypes 1, 2, 4, 5 and 6 had no impact on treatment outcome.

Genotype 3: For subjects who received the recommended regimen (n=313), baseline polymorphisms in NS5A (Y93H included) or NS3 did not have a relevant impact on treatment outcomes. All subjects (15/15) with Y93H and 77% (17/22) with A30K in NS5A at baseline achieved SVR12. The overall prevalence of A30K and Y93H at baseline was 6.5% and 4.9%, respectively. The ability to assess the impact of baseline polymorphisms in NS5A was limited among treatment-naïve subjects with cirrhosis and treatment-experienced subjects due to low prevalence of A30K (3.0%, 4/132) or Y93H (3.8%, 5/132).

Cross-resistance

In vitro data indicate that the majority of the resistance-associated substitutions in NS5A at amino acid positions 24, 28, 30, 31, 58, 92, or 93 that confer resistance to ombitasvir, daclatasvir, ledipasvir, elbasvir, or velpatasvir remained susceptible to pibrentasvir. Some combinations of NS5A substitutions at these positions showed reductions in susceptibility to pibrentasvir. Glecaprevir was fully active against resistance-associated substitutions in NS5A, while pibrentasvir was fully active against resistance-associated substitutions in NS3. Both glecaprevir and pibrentasvir were fully active against substitutions associated with resistance to NS5B nucleotide and non-nucleotide inhibitors.

Clinical efficacy and safety

Table 7 summarizes clinical studies conducted with Maviret in subjects with HCV genotype 1, 2, 3, 4, 5 or 6 infection.

Table 7: Clinical studies conducted with Maviret in subjects with HCV genotype 1, 2, 3, 4, 5 or 6 Infection

Genotype (GT)	Clinical study	Summary of study design
TN and PRS-TE subjects without cirrhosis		
GT1	ENDURANCE-1[a]	Maviret for 8 weeks (n=351) or 12 weeks (n=352)
	SURVEYOR-1	Maviret for 8 weeks (n=34)
GT2	ENDURANCE-2	Maviret (n=202) or Placebo (n=100) for 12 weeks
	SURVEYOR-2[b]	Maviret for 8 weeks (n=199) or 12 weeks (n=25)
GT3	ENDURANCE-3	Maviret for 8 weeks (n=157) or 12 weeks (n=233) Sofosbuvir + daclatasvir for 12 weeks (n=115)
	SURVEYOR-2[c]	Maviret for 8 weeks (TN only, n=29) or 12 weeks (n=76) or 16 weeks (PRS-TE only, n=22)
GT4, 5, 6	ENDURANCE-4	Maviret for 12 weeks (n=121)
	ENDURANCE-5,6	Maviret for 8 weeks (n=75)
	SURVEYOR-1	Maviret for 12 weeks (n=32)
	SURVEYOR-2	Maviret for 8 weeks (n=58)
GT1-6	VOYAGE-1[f]	Maviret for 8 weeks (GT1, 2, 4, 5, and 6 and GT3 TN) (n=356) or 16 weeks (GT3 PRS-TE only) (n=6)
TN and PRS-TE subjects with cirrhosis		
GT1, 2, 4, 5, 6	EXPEDITION-1	Maviret for 12 weeks (n=146)
GT3	SURVEYOR-2[d]	Maviret for 12 weeks (TN only, n=64) or 16 weeks (PRS-TE only, n=51)
GT1, 2, 3, 4, 5, 6	EXPEDITION-8	Maviret for 8 weeks (n=343) (TN only)
GT5, 6	ENDURANCE-5,6	Maviret for 12 weeks (n=9)
GT1-6	VOYAGE-2[f]	Maviret for 12 weeks (GT1, 2, 4, 5, and 6 and GT3 TN) (n=157) or 16 weeks (GT3 PRS-TE only) (n=3)
Subjects with CKD stage 4 and 5 with or without cirrhosis		
GT1-6	EXPEDITION-4	Maviret for 12 weeks (n=104)
NS5A inhibitor and/or PI-experienced subjects with or without cirrhosis		
GT1, 4	MAGELLAN-1[e]	Maviret for 12 weeks (n=66) or 16 weeks (n=47)
HCV/HIV-1 Co-Infected Subjects with or without Cirrhosis		
GT1-6	EXPEDITION-2	Maviret for 8 (n=137) or 12 weeks (n=16)
Liver or Kidney Transplant Recipients		
GT1-6	MAGELLAN-2	Maviret for 12 weeks (n=100)
Adolescent subjects (12 years to less than 18 years)		
GT1-6	DORA (Part 1)	Maviret for 8 weeks (n=44) or 16 weeks (n=3)

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

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

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

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

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

e. GT1, 4 from MAGELLAN-1 Part 1 - Maviret for 12 (n=22); GT1, 4 from MAGELLAN-1 Part 2 - Maviret for 12 (n=44) or 16 weeks (n=47).

f. VOYAGE-1 and VOYAGE-2 were Asian regional studies.

Serum HCV RNA values were measured during the clinical studies using the Roche COBAS AmpliPrep/COBAS TaqMan HCV test (version 2.0) with a lower limit of quantification (LLOQ) of 15 IU/mL (except for SURVEYOR-1 and SURVEYOR-2 which used the Roche COBAS TaqMan real-time reverse transcriptase-PCR (RT-PCR) assay v. 2.0 with an LLOQ of 25 IU/mL). Sustained virologic response (SVR12), defined as HCV RNA less than LLOQ at 12 weeks after the cessation of treatment, was the primary endpoint in all the studies to determine the HCV cure rate.

Clinical studies in TN or PRS-TE adult subjects with or without cirrhosis

Of the 2,409 subjects with compensated liver disease (with or without cirrhosis) treated who were treatment-naïve (TN) or treatment-experienced to combinations of (peg)interferon, ribavirin and/or sofosbuvir (PRS-TE), the median age was 53 years (range: 19 to 88); 73.3% were TN, 26.7% were PRS-TE; 40.3% were HCV genotype 1; 19.8% were HCV genotype 2; 27.8% were HCV genotype 3; 8.1% were HCV genotype 4; 3.4% were HCV genotype 5-6; 13.1% were ≥65 years; 56.6% were male; 6.2% were Black; 12.3% had cirrhosis; 4.3% had severe renal impairment or end stage renal disease; 20.2% had a body mass index of at least 30 kg per m^2; 7.7% had HIV-1 co-infection; and the median baseline HCV RNA level was 6.2 $\log_{10}$ IU/mL.

Table 8: SVR12 in treatment-naïve and treatment-experienced[a] adults to (Peg)interferon, ribavirin and/or sofosbuvir with genotype 1, 2, 4, 5 and 6 infection who received the recommended duration (pooled data from ENDURANCE-1[b], -2, -4, SURVEYOR-1, -2, and EXPEDITION-1, 2[b], -4 and -8)

	Genotype 1	Genotype 2	Genotype 4	Genotype 5	Genotype 6
SVR12 in subjects without cirrhosis					
8 weeks	99.2% (470/474)	98.1% (202/206)	95.2% (59/62)	100% (2/2)	92.3% (12/13)
Outcome for subjects without SVR12					
On-treatment VF	0.2% (1/474)	0% (0/206)	0% (0/62)	0% (0/2)	0% (0/13)
Relapse[c]	0% (0/471)	1.0% (2/204)	0% (0/61)	0% (0/2)	0% (0/13)
Other[d]	0.6% (3/474)	1.0% (2/206)	4.8% (3/62)	0% (0/2)	7.7% (1/13)
SVR12 in subjects with cirrhosis					
8 weeks	97.8% (226/231)	100% (26/26)	100% (13/13)	100% (1/1)	100% (9/9)
12 weeks	96.8% (30/31)	90.0% (9/10)	100% (8/8)	-	100% (1/1)
Outcome for subjects without SVR12					
On-treatment VF	0% (0/262)	0% (0/36)	0% (0/21)	0% (0/1)	0% (0/10)
Relapse[c]	0.4% (1/256)	0% (0/35)	0% (0/20)	0% (0/1)	0% (0/10)
Other[d]	1.9% (5/262)	2.8% (1/36)	0% (0/21)	0% (0/1)	0% (0/10)

VF=virologic failure

a. Percent of subjects with prior treatment experience to PRS is 26%, 14%, 24%, 0%, and 13% for genotypes 1, 2, 4, 5, and 6, respectively. None of the GT5 subjects were TE-PRS, and 3 GT6 subjects were TE-PRS.

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

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

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

Of the genotype 1-, 2-, 4-, 5-, or 6-infected subjects with end stage renal disease enrolled in EXPEDITION-4, 97.8% (91/93) achieved SVR12 with no virologic failures.

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

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

The overall SVR12 rate was 98.2% (275/280). There were no virologic failures.

Study in Subjects with Genotype 5 or 6 Infection
ENDURANCE-5,6 was an open-label study in 84 HCV GT5 (N=23) or 6-infected (N=61) TN or PRS-TE adult subjects. Subjects without cirrhosis received Maviret for 8 weeks, and subjects with compensated cirrhosis received Maviret for 12 weeks.

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

The overall SVR12 rate was 97.6% (82/84). The SVR12 rate was 95.7% (22/23) for GT5-infected subjects and 98.4% (60/61) for GT6-infected subjects. One TN GT5-infected subject without cirrhosis experienced relapse, and one TN GT6-infected subject with compensated cirrhosis experienced on-treatment virologic failure.

Subjects with genotype 3 infection
The efficacy of Maviret in adult subjects with genotype 3 chronic hepatitis C infection was demonstrated in the ENDURANCE-3 (TN without cirrhosis), EXPEDITION-8 (TN with compensated cirrhosis), and SURVEYOR-2 Part 3 (subjects with and without cirrhosis and/or PRS-TE) clinical studies.

Subjects 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 TN genotype 3-infected subjects. Subjects 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. EXPEDITION-8 was a single-arm, open-label study in TN subjects with compensated cirrhosis and genotype 1, 2, 3, 4, 5 or 6 infection who received Maviret for 8 weeks. SURVEYOR-2 Part 3 was an open-label study that evaluated the efficacy of Maviret in PRS-TE genotype 3-infected subjects without cirrhosis and with compensated cirrhosis for 16-weeks. Among PRS-TE subjects, 46% (42/91) failed a previous regimen containing sofosbuvir.

Table 9: SVR12 in TN, genotype 3-infected adults without cirrhosis (ENDURANCE-3)

SVR	**Maviret 8 weeks N=157**	**Maviret 12 weeks N=233**	**SOF+DCV 12 weeks N=115**
	94.9% (149/157)	95.3% (222/233)	96.5% (111/115)
		Treatment difference -1.2%; 95% confidence interval (-5.6% to 3.1%)	
	Treatment difference -0.4%; 97.5% confidence interval (-5.4% to 4.6%)		
Outcome for subjects without SVR12			
On-treatment VF	0.6% (1/157)	0.4% (1/233)	0% (0/115)
Relapse[a]	3.3% (5/150)	1.4% (3/222)	0.9% (1/114)
Other[b]	1.3% (2/157)	3.0% (7/233)	2.6% (3/115)

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

In a pooled analysis of treatment naïve patients without cirrhosis (including Phase 2 and 3 data) where SVR12 was assessed according to the presence of baseline A30K, a numerically lower SVR12 rate was achieved in patients with A30K treated for 8 weeks as compared to those treated for 12 weeks [84% (16/19) vs 93% (13/14)]. In patients without A30K, there was no difference in the SVR12 rates between patients treated for 8 weeks as compared to those treated for 12 weeks [99% (189/191) vs 99% (263/266)].

Table 10: SVR12 in genotype 3-infected adults with or without cirrhosis who received the recommended duration (SURVEYOR-2 Part 3 and EXPEDITION-8)

	TN with cirrhosis	**PRS-TE with or without cirrhosis**
	Maviret 8 weeks (N=63)	**Maviret 16 weeks (N=69)**
SVR	95.2% (60/63)	95.7% (66/69)
Outcome for subjects without SVR12		
On-treatment VF	0% (0/63)	1.4% (1/69)
Relapse[a]	1.6% (1/62)	2.9% (2/68)
Other[b]	3.2% (2/63)	0% (0/69)
SVR by cirrhosis status		

No Cirrhosis	NA	95.5% (21/22)
Cirrhosis	95.2% (60/63)	95.7% (45/47)

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

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

Subjects with genotype 3b infection
GT3b is a subtype reported in a relatively small number of HCV infected patients in China and a few countries in South and Southeast Asia, but rarely outside of this region. Studies VOYAGE-1 and VOYAGE-2 were conducted in China, Singapore, and South Korea in HCV genotype 1-6 adults without cirrhosis (VOYAGE-1) or with compensated cirrhosis (VOYAGE-2) that were TN or PRS-TE. All subjects without cirrhosis or with compensated cirrhosis received 8 or 12 weeks of Maviret, respectively, except GT3 PRS-TE subjects who received 16 weeks of Maviret. The overall SVR12 rates were 97.2% (352/362) and 99.4% (159/160) in VOYAGE-1 and VOYAGE-2, respectively.

Among GT3b subjects without cirrhosis, a numerically lower SVR12 rate of 58.3% (7/12) [62.5% (5/8) for TN subjects and 50% (2/4) for PRS-TE subjects] was observed compared to GT3a subjects without cirrhosis (92.9% (13/14)). Three GT3b TN subjects experienced relapse and 2 GT3b PRS-TE subjects experienced on-treatment virologic failure. Among subjects with compensated cirrhosis, the overall SVR12 rate for GT3b infected subjects was 87.5% (7/8) [85.7% (6/7) for TN subjects and 100% (1/1) for PRS-TE subjects] and 100% (6/6) for GT3a infected subjects. One GT3b TN subject experienced relapse.

Overall SVR12 Rate from the Clinical Studies in Treatment-Naïve or Treatment-Experienced Adults with or without Cirrhosis
Among all subjects, regardless of renal function, cirrhosis status, or presence of HIV-1 co-infection, who were TN or PRS-TE who received the recommended duration, 97.5% (1395/1431) achieved SVR12 overall, while 0.2% (3/1431) experienced on-treatment virologic failure and 0.9% (12/1407) experienced post-treatment relapse.

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

In TN or PRS-TE subjects with compensated cirrhosis who received the recommended duration, 97.1% (431/444) achieved SVR12 (among which 97.7% [335/343] of TN subjects achieved SVR12), while 0.2% (1/444) experienced on-treatment virologic failure and 0.9% (4/434) experienced post-treatment relapse.

The presence of HIV-1 co-infection did not impact efficacy. In a dedicated HIV-1 co-infection study (EXPEDITION-2), the SVR12 rate in HCV/HIV-1 co-infected subjects was 98% (150/153) with one virologic failure. Among subjects without cirrhosis that received 8 weeks of Maviret the overall SVR12 rate was 99.3% (136/137) (99.1% (110/111) for TN subjects and 100% (26/26) for PRS-TE subjects). Among HCV/HIV-1 co-infected subjects from ENDURANCE-1 and EXPEDITION-2 combined who were TN or PRS-TE treated with the recommended duration, the SVR12 rate was 98.2% (165/168). One subject experienced on-treatment virologic failure and no subjects relapsed.

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

Of the 100 subjects treated, the median age was 60 years (range: 39 to 78); 57% had HCV genotype 1, 13% had HCV genotype 2, 24% had HCV genotype 3, 4% had HCV genotype 4, 2% had HCV genotype 6; 75% were male; 8% were Black; 80% of subjects were post-liver transplant and 20% were post-kidney transplant. Immunosuppressants allowed for co-administration were cyclosporine ⩽100 mg, tacrolimus, sirolimus, everolimus, azathioprine, mycophenolic acid, prednisone, and prednisolone.

The overall SVR12 rate in post-transplant subjects was 98.0% (98/100). There was one relapse, and no on-treatment virologic failure.

Elderly
Clinical studies of Maviret included 328 patients aged 65 and over (13.8% of the total number of subjects). The response rates observed for patients ≥ 65 years of age were similar to that of patients < 65 years of age, across treatment groups.

People Who Inject Drugs (PWID) and those on Medication-Assisted Treatment (MAT) for Opioid Use Disorder
The efficacy of Maviret in PWID and those on MAT with HCV GT 1-6 infection is based on data from Phase 2 and 3 trials of adults and adolescents in which 62 subjects identified as current/recent PWID (defined as self-reported injection drug use within the last 12 months prior to starting Maviret), 959 subjects identified as former PWID (defined as self-reported injection drug use more than 12 months prior to starting Maviret), and 3,282 subjects reported no injection drug use (non-PWID); 225 subjects reported concomitant use of MAT for opioid use disorder, and 4,098 subjects reported no MAT use.

Compared to former/non-PWID subjects (n=4,241), the current/recent PWID subjects 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%). Compared to those not on MAT, subjects 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%). Of subjects on MAT, 74% were non-cirrhotic, and 7% were co-infected with HIV, similar to those not on MAT. There were a limited number of subjects with genotype 4, 5 or 6 infection in the PWID- and MAT-analyzed population.

The overall SVR12 rate was 97.8% (4,147/4,241) in former/non-PWID subjects and 88.7% (55/62) in current/recent PWID subjects; 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 subjects and 1.2% (50/4,241) in former/non-PWID subjects.

The SVR12 rates were also similar between subjects 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).

Clinical study in adolescent subjects
DORA (Part 1) was an open-label trial to evaluate safety and efficacy in adolescents aged 12 years to less than 18 years who received Maviret for 8, 12, or 16 weeks.

47 subjects were enrolled in DORA (Part 1). The median age was 14 years (range: 12 to 17); 79% had HCV genotype 1, 6% had HCV genotype 2, 9% had HCV genotype 3, 6% had HCV genotype 4; 55% were female; 11% were Black; 77% were HCV treatment-naïve; 23% were treatment-experienced to interferon; 4% had HIV-coinfection; none had cirrhosis; the mean weight was 59 kg (range: 32 to 109 kg).

The overall SVR12 rate was 100% (47/47). No subject experienced virologic failure.

Durability of Sustained Virologic Response

In a long-term follow-up study (M13-576), 99.5% (374/376) of adult subjects who had achieved SVR12 in prior clinical studies of Maviret maintained SVR up to their last follow-up visit (median duration of follow-up: 35.5 months), including all 87 subjects who had been treated with an 8-week regimen of Maviret. Among the 2 subjects who did not maintain SVR, 1 subject who had been infected by a contaminated needle or intravenous drug use experienced a late relapse 390 days after 12 weeks of Maviret therapy, and the other subject experienced re-infection with a different HCV genotype 191 days after 16 weeks of Maviret therapy.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of the components of Maviret are provided in Table 11.

Table 11: Pharmacokinetic properties of the components of Maviret in healthy adult subjects

	Glecaprevir	**Pibrentasvir**
Absorption		
T_{max} (h)[a]	5.0	5.0
Effect of meal (relative to fasting)[b]	↑ 83-163%	↑ 40-53%
Distribution		
% Bound to human plasma proteins	97.5	>99.9
Blood-to-plasma ratio	0.57	0.62
Biotransformation		
Metabolism	secondary	none
Elimination		
Major route of elimination	Biliary excretion	Biliary excretion
$t_{1/2}$ (h) at steady-state	6 - 9	23 - 29
% of dose excreted in urine[c]	0.7	0
% of dose excreted in faeces[c]	92.1[d]	96.6
Transport		
Substrate of transporter	P-gp, BCRP, and OATP1B1/3	P-gp and not excluded BCRP

a. Median T_{max} following single doses of glecaprevir and pibrentasvir in healthy subjects.
b. Mean systemic exposure with moderate to high fat meals.
c. Single dose administration of [^{14}C]glecaprevir or [^{14}C]pibrentasvir in mass balance studies.
d. Oxidative metabolites or their byproducts accounted for 26% of radioactive dose. No glecaprevir metabolites were observed in plasma.

In patients with chronic hepatitis C infection without cirrhosis, following 3 days of monotherapy with either glecaprevir 300 mg per day (N=6) or pibrentasvir 120 mg per day (N=8) alone, geometric mean AUC_{24} values were 13600 ng·h/mL for glecaprevir and 459 ng·h/mL for pibrentasvir. Estimation of the pharmacokinetic parameters using population pharmacokinetic models has inherent uncertainty due to dose non-linearity and cross interaction between glecaprevir and pibrentasvir. Based on population pharmacokinetic models for Maviret in chronic hepatitis C patients, steady-state AUC_{24} values for glecaprevir and pibrentasvir were 4800 and 1430 ng·h/mL in subjects without cirrhosis (N=1804), and 10500 and 1530 ng·h/mL in subjects with cirrhosis (N=280), respectively. Relative to healthy subjects (N=230), population estimates of $AUC_{24,ss}$ were similar (10% difference) for glecaprevir and 34% lower for pibrentasvir in HCV-infected patients without cirrhosis.

Linearity/non-linearity

Glecaprevir AUC increased in a greater than dose-proportional manner (1200 mg QD had 60-fold higher exposure than 200 mg QD) which may be related to saturation of uptake and efflux transporters.

Pibrentasvir AUC increased in a greater than dose-proportional manner at doses up to 120 mg, (over 10-fold exposure increase at 120 mg QD compared to 30 mg QD), but exhibited linear

pharmacokinetics at doses ≥ 120 mg. The non-linear exposure increase <120 mg may be related to saturation of efflux transporters.

Pibrentasvir bioavailability when coadministered with glecaprevir is 3-fold of pibrentasvir alone. Glecaprevir is affected to a lower extent by coadministration with pibrentasvir.

Pharmacokinetics in special populations

Race/ethnicity
No dose adjustment of Maviret is required based on race or ethnicity.

Gender/weight
No dose adjustment of Maviret is required based on gender or body weight.

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

Elderly
No dose adjustment of Maviret is required in elderly patients. Population pharmacokinetic analysis in HCV-infected subjects showed that within the age range (12 to 88 years) analysed, age did not have a clinically relevant effect on the exposure to glecaprevir or pibrentasvir.

Renal impairment
Glecaprevir and pibrentasvir AUC were increased ≤ 56% in non-HCV infected subjects with mild, moderate, severe, or end-stage renal impairment not on dialysis compared to subjects with normal renal function. Glecaprevir and pibrentasvir AUC were similar with and without dialysis (≤ 18% difference) in dialysis-dependent non-HCV infected subjects. In population pharmacokinetic analysis of HCV-infected subjects, 86% higher glecaprevir and 54% higher pibrentasvir AUC were observed for subjects with end stage renal disease, with or without dialysis, compared to subjects with normal renal function. Larger increases may be expected when unbound concentration is considered.

Overall, the changes in exposures of Maviret in HCV-infected subjects with renal impairment with or without dialysis were not clinically significant.

Hepatic impairment
At the clinical dose, compared to non-HCV infected subjects with normal hepatic function, glecaprevir AUC was 33% higher in Child-Pugh A subjects, 100% higher in Child-Pugh B subjects, and increased to 11-fold in Child-Pugh C subjects. Pibrentasvir AUC was similar in Child-Pugh A subjects, 26% higher in Child-Pugh B subjects, and 114% higher in Child-Pugh C subjects. Larger increases may be expected when unbound concentration is considered.

Population pharmacokinetic analysis demonstrated that following administration of Maviret in HCV-infected subjects with compensated cirrhosis, exposure of glecaprevir was approximately 2-fold and pibrentasvir exposure was similar to non-cirrhotic HCV-infected subjects. The mechanism for the differences between glecaprevir exposure in chronic Hepatitis C patients with or without cirrhosis is unknown.

5.3 Preclinical safety data

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.

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, than the exposure in humans at the recommended dose.

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 times (rats; glecaprevir) or 51 and 1.5 times (mice and rabbits, respectively; pibrentasvir) the human exposures at the recommended dose of Maviret. Maternal toxicity (anorexia, lower body weight, and lower body weight gain) with some embryofoetal toxicity (increase in post-implantation loss and number of resorptions and a decrease in mean fetal body weight), precluded the ability to evaluate glecaprevir in the rabbit at clinical exposures. There were no developmental 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. Unchanged glecaprevir was the main component observed in the milk of lactating rats without effect on nursing pups. Pibrentasvir was the only component observed in the milk of lactating rats without effect on nursing pups.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Copovidone (Type K 28)
Vitamin E (tocopherol) polyethylene glycol succinate
Silica, colloidal anhydrous
Propylene glycol monocaprylate (Type II)
Croscarmellose sodium
Sodium stearyl fumarate

Film coating

Hypromellose 2910 (E464)
Lactose monohydrate
Titanium dioxide
Macrogol 3350
Iron oxide red (E172)

The tablets do not contain gluten.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Refer to expiry date printed on the packaging.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

PVC/PE/PCTFE aluminium foil blister packs.
Pack containing 84 (4 x 21) film-coated tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT OWNER

AbbVie Inc., North Chicago, IL 60064, USA

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