ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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.

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 (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

The recommended dose of Maviret is 300 mg/120 mg (three 100 mg/40 mg tablets), taken orally, once daily 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**
All HCV genotypes	8 weeks	12 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, 4-6	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.

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.

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 not recommended in patients with moderate hepatic impairment (Child Pugh-B) and is contraindicated in patients with severe hepatic impairment (Child-Pugh C) (see sections 4.3, 4.4, and 5.2).

Liver transplant patients
Maviret may be used for a minimum of 12 weeks in liver transplant recipients (see section 4.4). A 16 week treatment duration should be considered in genotype 3-infected patients who are treatment experienced with peg-IFN + ribavirin +/- sofosbuvir, or sofosbuvir + ribavirin.

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
The safety and efficacy of Maviret in children and adolescents aged less than 18 years have not yet been established. No data are available.

Method of administration

For oral use.

Patients should be instructed to swallow tablets whole with food and 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 severe hepatic impairment (Child-Pugh C) (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.

Liver transplant patients

The safety and efficacy of Maviret in patients who are post-liver transplant have not yet been assessed. Treatment with Maviret in this population in accordance with the recommended posology (see section 4.2) should be guided by an assessment of the potential benefits and risks for the individual patient.

Hepatic impairment

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 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)	1.14 (1.04, 1.25)	--	
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 (Inhibition of OATP1B1/3)	↑ glecaprevir	6.52 (5.06, 8.41)	8.55 (7.01, 10.4)	--	Co-administration is contraindicated (see section 4.3).
	↔ pibrentasvir	↔	↔	--	
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,
	↑ 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)	

					norethidrone or norgestimate as contraceptive progestagen.
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 inhibition by elvitegravir)	↔ 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)	
Lopinavir/ritonavir 400/100 mg once 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 100 mg single dose	↑ glecaprevir[c]	1.30 (0.95, 1.78)	1.37 (1.13, 1.66)	1.34 (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
	↔ glecaprevir	↔	↔	↔	
	↔ pibrentasvir	↔	↔	↔	

					tacrolimus exposure is expected. Therefore, a therapeutic drug monitoring of tacrolimus is recommended and a dose adjustment of tacrolimus made accordingly.
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)	--	Co-administration of Maviret with omeprazole 40 mg once daily may lead to reduced therapeutic effect and is not recommended.
	↔ 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 received ciclosporin dose of 100 mg or less per day had glecaprevir concentrations 4-fold higher than 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 Phase 2 and 3 studies which evaluated approximately 2,300 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 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%).

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 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: not yet assigned

Mechanism of action

Maviret is a fixed-dose combination of 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 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 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 pegylated 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=309), baseline polymorphisms in NS5A (Y93H included) or NS3 did not have a relevant impact on treatment outcomes. All subjects (15/15) with Y93H and 75% (15/20) 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 (1.6%, 2/128) or Y93H (3.9%, 5/128).

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 TE subjects without cirrhosis		
GT1	ENDURANCE-1*	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	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	Maviret for 8 weeks (TN only, n=29) or 12 weeks (n=76) or 16 weeks (TE only, n=22)
GT4, 5, 6	ENDURANCE-4	Maviret for 12 weeks (n=121)
	SURVEYOR-1	Maviret for 12 weeks (n=32)
	SURVEYOR-2	Maviret for 8 weeks (n=58)
TN and TE subjects with cirrhosis		
GT1, 2, 4, 5, 6	EXPEDITION-1	Maviret for 12 weeks (n=146)
GT3	SURVEYOR-2	Maviret for 12 weeks (TN only, n=64) or 16 weeks (TE only, n=51)
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	Maviret for 12 weeks (n=66) or 16 weeks (n=47)

TN=treatment naïve, TE=treatment experienced (includes previous treatment that included pegIFN (or IFN), and/or RBV and/or sofosbuvir), PI=Protease Inhibitor, CKD=chronic kidney disease
*Included 33 subjects co-infected with HIV-1

Serum HCV RNA values were measured during the clinical studies using the Roche COBAS AmpliPrep/COBAS Taqman HCV test (version 2.0) with a lower limit of quantification (LLOQ) of 15 IU/mL (except for SURVEYOR-1 and SURVEYOR-2 which used the Roche COBAS TaqMan real-time reverse transcriptase-PCR (RT-PCR) assay v. 2.0 with an LLOQ of 25 IU/mL). Sustained

virologic response (SVR12), defined as HCV RNA less than LLOQ at 12 weeks after the cessation of treatment, was the primary endpoint in all the studies to determine the HCV cure rate.

Clinical studies in treatment-naïve or treatment-experienced subjects with or without cirrhosis
Of the 2,256 subjects with compensated liver disease (with or without cirrhosis) treated who were treatment-naïve or treatment-experienced to combinations of peginterferon, ribavirin and/or sofosbuvir, the median age was 54 years (range: 19 to 88); 72.7% were treatment-naïve, 27.3% were treatment-experienced to a combination containing either sofosbuvir, ribavirin and/or peginterferon; 38.9% were HCV genotype 1; 21.1% were HCV genotype 2; 28.5% were HCV genotype 3; 7.9% were HCV genotype 4; 3.5% were HCV genotype 5-6; 13.9% were ≥65 years; 54.8% were male; 5.5% were Black; 12.5% had cirrhosis; 4.6% had severe renal impairment or end stage renal disease; 20.3% had a body mass index of at least 30 kg per m^2; median baseline HCV RNA level was 6.2 $\log_{10}$ IU/mL.

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

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

VF=virologic failure
1. Percent of subjects 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 GT5 subjects were TE-PRS, and 3 GT6 subjects were TE-PRS.
2. Includes 15 subjects co-infected with HIV-1 (treated for 8 weeks).
3. Relapse is defined as HCV RNA ≥ LLOQ after end-of-treatment response among those who completed treatment.
4. 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 3 infection
The efficacy of Maviret in subjects who were treatment-naïve or treatment-experienced to combinations of peginterferon, ribavirin and/or sofosbuvir with genotype 3 chronic hepatitis C infection was demonstrated in the ENDURANCE-3 (treatment-naïve without cirrhosis) and SURVEYOR-2 Part 3 (subjects with and without cirrhosis and/or treatment-experienced) clinical studies.

ENDURANCE-3 was a partially-randomized, open-label, active-controlled study in treatment-naïve 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. SURVEYOR-2 Part 3 was an open-label study randomizing non-cirrhotic treatment-experienced subjects to 12- or 16-weeks of treatment; in addition, the study evaluated the efficacy of Maviret in subjects 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 subjects, 46% (42/91) failed a previous regimen containing sofosbuvir.

Table 9: SVR12 in treatment-naïve, genotype 3-infected subjects 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[1]	3.3% (5/150)	1.4% (3/222)	0.9% (1/114)
Other[2]	1.3% (2/157)	3.0% (7/233)	2.6% (3/115)

[1] Relapse is defined as HCV RNA ≥ LLOQ after end-of-treatment response among those who completed treatment.
[2] 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 [78% (14/18) vs 93% (13/14)].

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

	Treatment-naïve with cirrhosis	**Treatment-experienced with or without cirrhosis**
	Maviret 12 weeks (N=40)	**Maviret 16 weeks (N=69)**
SVR	97.5% (39/40)	95.7% (66/69)
Outcome for subjects without SVR12		
On-treatment VF	0% (0/40)	1.4% (1/69)
Relapse[1]	0% (0/39)	2.9% (2/68)
Other[2]	2.5% (1/40)	0% (0/69)
SVR by cirrhosis status		
No Cirrhosis	NA	95.5% (21/22)
Cirrhosis	97.5% (39/40)	95.7% (45/47)

[1] Relapse is defined as HCV RNA ≥ LLOQ after end-of-treatment response among those who completed treatment.
[2] 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.

In subjects who are treatment-naïve or treatment-experienced to combinations of peginterferon, ribavirin and/or sofosbuvir who received the recommended duration, 97.4% (1102/1131) achieved SVR12 overall (among which 97.5% (274/281) subjects with compensated cirrhosis achieved SVR), while 0.3% (3/1131) experienced on-treatment virologic failure and 1.0% (11/1111) experienced post-treatment relapse.

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.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with glecaprevir/pibrentasvir in one or more subsets of the paediatric population from 3 years to less than 18 years in the treatment of chronic hepatitis C (see section 4.2 for information on paediatric use).

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 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.

Elderly
No dose adjustment of Maviret is required in elderly patients. Population pharmacokinetic analysis in HCV-infected subjects showed that within the age range (18 to 88 years) analysed, age did not have a clinically relevant effect on the exposure to glecaprevir or pibrentasvir.

Renal impairment
Glecaprevir and pibrentasvir AUC were increased ≤ 56% in non-HCV infected subjects with mild, 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) higher than 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 higher, respectively, than 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)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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. MARKETING AUTHORISATION HOLDER

AbbVie Ltd

Maidenhead
SL6 4UB
United Kingdom

8. MARKETING AUTHORISATION NUMBER

EU/1/17/1213/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
GERMANY

AbbVie Logistics B.V
Zuiderzeelaan 53
8017 JV Zwolle
NETHERLANDS

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Non-interventional post-authorisation safety study (PASS): In order to evaluate the recurrence of hepatocellular carcinoma associated with Maviret, the MAH shall conduct and submit the results of a prospective safety study using data deriving from a cohort of a well-defined group of patients, based on an agreed protocol. The final study report shall be submitted by:	Q2 2021

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Maviret 100 mg/40 mg film-coated tablets
glecaprevir/pibrentasvir

2. STATEMENT OF ACTIVE SUBSTANCE

Each film-coated tablet contains 100 mg of glecaprevir and 40 mg of pibrentasvir.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablets

84 (4 x 21) film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1213/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

maviret

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Maviret 100 mg/40 mg film-coated tablets
glecaprevir/pibrentasvir

2. STATEMENT OF ACTIVE SUBSTANCE

Each film-coated tablet contains 100 mg of glecaprevir and 40 mg of pibrentasvir.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablets

21 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Take all 3 tablets in 1 blister once daily with food

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1213/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

maviret

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Maviret 100 mg/40 mg tablets
glecaprevir/pibrentasvir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Maviret 100 mg/40 mg film-coated tablets
glecaprevir/pibrentasvir

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Maviret is and what it is used for

Maviret is an antiviral medicine used to treat adults with long-term (‘chronic’) hepatitis C (an infectious disease that affects the liver, caused by the hepatitis C virus). It contains the active substances glecaprevir and pibrentasvir.

Maviret works by stopping the hepatitis C virus from multiplying and infecting new cells. This allows the infection to be eliminated from the body.

2. What you need to know before you take Maviret

Do not take Maviret if:
- you are allergic to glecaprevir, pibrentasvir or any of the other ingredients of this medicine (listed in section 6 of this leaflet).
- you have severe liver problems other than from hepatitis C.
- you are taking the following medicines:
    - atazanavir (for HIV infection)
    - atorvastatin or simvastatin (to lower blood cholesterol)
    - carbamazepine, phenobarbital, phenytoin, primidone (normally used for epilepsy)
    - dabigatran etexilate (to prevent blood clots)
    - ethinyl oestradiol-containing medicines (such as contraception medicines, including vaginal rings and tablets)
    - rifampicin (for infections)
    - St. John’s wort (*Hypericum perforatum*), (herbal remedy used for mild depression).

Do not take Maviret if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Maviret.

Warnings and precautions
Talk to your doctor if you have the following because your doctor may want to check you more closely:

- liver problems other than hepatitis C
    - current or previous infection with the hepatitis B virus
- had a liver transplant.

Blood tests
Your doctor will test your blood before, during and after your treatment with Maviret. This is so that your doctor can decide if:

- you should take Maviret and for how long
- your treatment has worked and you are free of the hepatitis C virus.

Children and adolescents
Do not give this medicine to children and adolescents under 18 years of age. The use of Maviret in children and adolescents has not yet been studied.

Other medicines and Maviret
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Tell your doctor or pharmacist before taking Maviret, if you are taking any of the medicines in the table below. The doctor may need to change your dose of these medicines.

Medicines you must tell your doctor about before taking Maviret	
Medicine	**Purpose of the medicine**
ciclosporin, tacrolimus	to suppress the immune system
darunavir, efavirenz, lopinavir, ritonavir	for HIV infection
digoxin	for heart problems
fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin	to lower blood cholesterol
omeprazole	for stomach ulcers and other stomach problems
warfarin and other similar medicines*	to prevent blood clots

*Your doctor may need to increase the frequency of your blood tests to check how well your blood can clot.

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

Pregnancy and contraception
The effects of Maviret during pregnancy are not known. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine, as the use of Maviret in pregnancy is not recommended. Contraceptive medicines that contain ethinylestradiol must not be used in combination with Maviret.

Breast-feeding
Talk to your doctor before taking Maviret if you are breast-feeding**.** It is not known whether the two medicines in Maviret pass into breast milk.

Driving and using machines
Maviret should not affect your ability to drive or use any tools or machines.

Maviret contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.

3. How to take Maviret

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. Your doctor will tell you how long you need to take Maviret for.

How much to take
The recommended dose is three tablets of Maviret 100mg/40mg taken together, once a day.
Three tablets in one blister is the daily dose.

How to take
- Take the tablets with food.
- Swallow the tablets whole.
- Do not chew, crush or break the tablets as it may affect the amount of Maviret in your blood.

If you are sick (vomit) after taking Maviret it may affect the amount of Maviret in your blood. This may make Maviret work less well.
- If you vomit **less than 3 hours** after taking Maviret, take another dose.
- If you vomit **more than 3 hours** after taking Maviret, you do not need to take another dose until your next scheduled dose.

If you take more Maviret than you should
If you accidentally take more than the recommended dose, contact your doctor or go to the nearest hospital straight away. Take the medicine pack with you so that you can show the doctor what you have taken.

If you forget to take Maviret
It is important not to miss a dose of this medicine.

If you do miss a dose, work out how long it is since you should have last taken Maviret:
- If you notice **within 18 hours** of the time you usually take Maviret take the dose as soon as possible. Then take the next dose at your usual time.
- If you notice **18 hours or more** after the time you usually take Maviret, wait and take the next dose at your usual time. Do not take a double dose (two doses too close together).

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor or pharmacist if you notice any of the following side effects:

Very common: may affect more than 1 in 10 people
- feeling very tired (fatigue)
- headache

Common: may affect up to 1 in 10 people
- feeling sick (nausea)
- diarrhoea
- feeling weak or lack of energy (asthenia)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Maviret

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after 'EXP'.

This medicine does not require any special storage.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Maviret contains
- The active substances are glecaprevir and pibrentasvir. Each tablet contains 100 mg of glecaprevir and 40 mg of pibrentasvir.
- The other ingredients are:
  - Tablet core: copovidone (Type K 28), vitamin E polyethylene glycol succinate, silica, anhydrous colloidal, propylene glycol monocaprylate (type II), croscarmellose sodium, sodium stearyl fumarate.
  - Tablet film-coating: hypromellose (E464), lactose monohydrate, titanium dioxide, macrogol 3350, iron oxide red (E172).

What Maviret looks like and contents of the pack
Maviret tablets are pink, oblong, curved on both sides (biconvex), film-coated tablets with dimensions of 18.8 mm x 10.0 mm and debossed on one side with 'NXT'.

Maviret tablets are packed into foil blisters, each containing 3 tablets. Maviret is available in a pack of 84 tablets as 4 cartons, each containing 21 film-coated tablets.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

To listen to or request a copy of this leaflet in <Braille>, <large print> or <audio>, please contact the local representative of the Marketing Authorisation Holder.