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

OLYSIO 150 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains simeprevir sodium equivalent to 150 mg of simeprevir.

Excipient with known effect: each capsule contains 78.4 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule)

White gelatin capsule of approximately 22 mm in length, marked with “TMC435 150” in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

OLYSIO is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adult patients (see sections 4.2, 4.4 and 5.1).

For hepatitis C virus (HCV) genotype specific activity, see sections 4.4 and 5.1.

4.2 Posology and method of administration

Treatment with OLYSIO should be initiated and monitored by a physician experienced in the management of CHC.

Posology
The recommended dosage of OLYSIO is one capsule of 150 mg once daily, taken with food.

OLYSIO must be used in combination with other medicinal products for the treatment of CHC (see section 5.1). When considering OLYSIO combination treatment with peginterferon alfa and ribavirin in HCV genotype 1a patients, patients should be tested for the presence of virus with the NS3 Q80K polymorphism before starting treatment (see section 4.4).
Refer also to the Summary of Product Characteristics of the medicinal products that are used in combination with OLYSIO.

The recommended co-administered medicinal product(s) and treatment duration for OLYSIO combination therapy are provided in tables 1 and 2.

Table 1: Recommended treatment duration for OLYSIO combination therapy with sofosbuvir with or without ribavirin in patients with HCV genotype 1 or 4

Patient population	Treatment duration
Patients without cirrhosis	12 weeks OLYSIO + sofosbuvir
Patients with cirrhosis[1]	24 weeks OLYSIO + sofosbuvir or 12 weeks OLYSIO + sofosbuvir + ribavirin[2] 12 weeks OLYSIO + sofosbuvir (without ribavirin) may be considered for patients deemed at low risk for clinical disease progression and who have subsequent retreatment options (see sections 4.4 and 5.1)

1 In HCV genotype 1a infected patients with cirrhosis, testing for the presence of the Q80K polymorphism may be considered prior to initiation of therapy with OLYSIO in combination with sofosbuvir (see section 4.4).

2 The daily dose of ribavirin is weight based (< 75 kg = 1,000 mg and ≥ 75 kg = 1,200 mg) and administered orally in two divided doses with food; also refer to the Summary of Product Characteristics of ribavirin.

Table 2: Recommended treatment duration for OLYSIO combination therapy with peginterferon alfa and ribavirin[1] in HCV genotype 1 or 4

Patient population	Treatment duration
Treatment-naïve and prior relapse patients[2]	
with or without cirrhosis, who are not co-infected with HIV	24 weeks[3] Treatment with OLYSIO must be initiated in combination with peginterferon alfa + ribavirin and administered for 12 weeks and then followed by an additional 12 weeks of peginterferon alfa + ribavirin.
without cirrhosis, who are co-infected with HIV	
with cirrhosis, who are co-infected with HIV	48 weeks[3] Treatment with OLYSIO must be initiated in combination with peginterferon alfa + ribavirin and administered for 12 weeks and then followed by an additional 36 weeks of peginterferon alfa and + ribavirin.
Prior non-responder patients (including partial and null responders)[2]	
with or without cirrhosis, with or without HIV co-infection	48 weeks[3] Treatment with OLYSIO must be initiated in combination with peginterferon alfa + ribavirin and administered for 12 weeks and then followed by an additional 36 weeks of peginterferon alfa + ribavirin.

1 When considering OLYSIO combination treatment with peginterferon alfa and ribavirin in HCV genotype 1a patients, testing for NS3 Q80K polymorphism should be performed before starting treatment (see section 4.4).

2 Following prior treatment with interferon (pegylated or non-pegylated), with or without ribavirin (see section 5.1).

3 Recommended duration of treatment provided that patient does not meet a stopping rule (see table 3).

Refer to table 3 for treatment stopping rules based on HCV RNA levels at weeks 4, 12 and 24 for patients receiving treatment with OLYSIO, peginterferon alfa and ribavirin.

Treatment discontinuation in patients with inadequate on-treatment virologic response
OLYSIO in combination with sofosbuvir
There are no virologic treatment stopping rules that apply to the combination of OLYSIO with sofosbuvir.

OLYSIO in combination with peginterferon alfa and ribavrin
It is unlikely that patients with inadequate on-treatment virologic response will achieve a sustained virologic response (SVR), therefore discontinuation of treatment is recommended in these patients.

The HCV RNA thresholds that trigger discontinuation of treatment (i.e., treatment stopping rules) are presented in table 3.

Table 3: Treatment stopping rules in patients receiving OLYSIO in combination with peginterferon alfa and ribavirin with inadequate on-treatment virologic response

HCV RNA	Action
Treatment week 4: ≥ 25 IU/ml	Discontinue OLYSIO, peginterferon alfa and ribavirin
Treatment week 12: ≥ 25 IU/ml[1]	Discontinue peginterferon alfa and ribavirin (treatment with OLYSIO is complete at week 12)
Treatment week 24: ≥ 25 IU/ml[1]	Discontinue peginterferon alfa and ribavirin

[1] Re-evaluation of HCV RNA is recommended in case of HCV RNA ≥ 25 IU/ml after previous undetectable HCV RNA to confirm HCV RNA levels prior to discontinuing HCV treatment.

Dosage adjustment or interruption of OLYSIO treatment
To prevent treatment failure, the dose of OLYSIO must not be reduced or interrupted. If treatment with OLYSIO is discontinued because of adverse reactions or inadequate on-treatment virologic response, OLYSIO treatment must not be reinitiated.

Dosage adjustment or interruption of medicinal products used in combination with OLYSIO for the treatment of CHC
If adverse reactions, potentially related to the medicinal products that are used in combination with OLYSIO for the treatment of CHC, require dosage adjustment or interruption of the medicinal product(s), refer to the instructions outlined in the respective Summary of Product Characteristics for these medicinal products.
If other medicinal products used in combination with OLYSIO for the treatment of CHC are permanently discontinued for any reason, OLYSIO must also be discontinued. When ribavirin is added to the combination of OLYSIO and sofosbuvir, and ribavirin needs to be discontinued, treatment of OLYSIO with sofosbuvir without ribavirin can be continued (see section 5.1).

Missed dose
If a dose of OLYSIO is missed, and the patient notices within 12 hours of the usual dosing time, the patient should take the missed dose of OLYSIO with food as soon as possible and then take the next dose of OLYSIO at the regularly scheduled time.

If a dose of OLYSIO is missed by more than 12 hours after the usual dosing time, the patient should not take the missed dose of OLYSIO and should resume dosing of OLYSIO with food at the regularly scheduled time.

Special populations
Elderly (over 65 years of age)
There are limited data on the safety and efficacy of OLYSIO in patients older than 65 years. There are no safety and efficacy data of OLYSIO in patients over the age of 75 years. No dose adjustment of OLYSIO is required in elderly patients (see section 5.2).

Renal impairment
No dose adjustment of OLYSIO is required in patients with mild or moderate renal impairment. Increased simeprevir exposures have been observed in individuals with severe renal impairment. OLYSIO has not been studied in HCV infected patients with severe renal impairment (creatinine clearance below 30 ml/min) or end stage renal disease, including patients requiring haemodialysis. As exposure may be increased in HCV infected patients with severe renal impairment, caution is recommended when prescribing OLYSIO to these patients (see section 5.2).
Refer to the respective Summary of Product Characteristics of the medicinal products used in combination with OLYSIO regarding their use in patients with renal impairment.

Hepatic impairment
No dose adjustment of OLYSIO is required in patients with mild hepatic impairment (Child-Pugh A). OLYSIO is not recommended for patients with moderate or severe hepatic impairment (Child-Pugh B or C) (see sections 4.4 and 5.2).

Race
No dose adjustment is necessary based on race (see section 5.2).

Paediatric population
The safety and efficacy of OLYSIO in children aged below 18 years have not yet been established. No data are available.

HCV/Human immunodeficiency virus type 1 (HIV-1) co-infection
No dose adjustment of OLYSIO is required in HCV/HIV-1 co-infected patients (see sections 4.8, 5.1 and 5.2).

OLYSIO in combination with sofosbuvir: HCV/HIV-1 co-infected patients should be treated for the same duration as HCV mono-infected patients.

OLYSIO in combination with peginterferon alfa and ribavirin: HCV/HIV-1 co-infected patients should be treated for the same duration as HCV mono-infected patients, except for co-infected patients with cirrhosis who should receive 36 weeks of treatment with peginterferon alfa and ribavirin after completing 12 weeks of treatment with OLYSIO, peginterferon alfa and ribavirin (total treatment duration of 48 weeks).

Please refer to sections 4.4 and 4.5 for relevant interactions with antiretroviral agents.

Method of administration
OLYSIO must be taken orally once a day with food (see section 5.2). The capsule should be swallowed as a whole.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

General
The efficacy of OLYSIO has not been studied in patients with HCV genotypes 2, 3, 5 or 6; therefore OLYSIO should not be used in these patients (see section 5.1).

OLYSIO must not be administered as monotherapy and must be prescribed in combination with other medicinal products for the treatment of CHC.

Consult the Summary of Product Characteristics of the co-prescribed medicinal products before starting therapy with OLYSIO. Warnings and precautions related to these medicinal products also apply to their use in OLYSIO combination treatment.

There are no clinical data on the use of OLYSIO in re-treating patients who have failed an HCV NS3-4A protease inhibitor-based therapy (see sections 5.1 and 5.3).

Hepatic decompensation and hepatic failure
Hepatic decompensation and hepatic failure, including fatal cases, have been reported post-marketing in patients treated with OLYSIO in combination with peginterferon alfa and ribavirin and in combination with sofosbuvir. Although causality is difficult to establish due to background advanced liver disease, a potential risk cannot be excluded.

Therefore, in patients who are at high risk for hepatic decompensation or hepatic failure, liver function tests should be monitored before and as clinically indicated during OLYSIO combination therapy.

Hepatic impairment
OLYSIO is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C) (see sections 4.2, 4.8 and 5.2).

Severe bradycardia and heart block
Cases of bradycardia have been observed when OLYSIO is used in combination with sofosbuvir and concomitant amiodarone. The mechanism is not established.
Cases are potentially life threatening, therefore amiodarone should only be used in patients on OLYSIO combination treatment with sofosbuvir when other alternative antiarrhythmic treatments are not tolerated or are contraindicated.
Should concomitant use of amiodarone be considered necessary, it is recommended that patients are closely monitored when initiating OLYSIO combination treatment with sofosbuvir. Patients who are identified as being at high risk of bradyarrhythmia should be continuously monitored for 48 hours in an appropriate clinical setting.
Due to the long elimination half-life of amiodarone, appropriate monitoring should also be carried out for patients who have discontinued amiodarone within the past few months and are to be initiated on OLYSIO combination treatment with sofosbuvir.
All patients receiving OLYSIO combination treatment with sofosbuvir in combination with amiodarone with or without other drugs that lower heart rate should also be warned of the symptoms of bradycardia and heart block and should be advised to seek medical advice urgently should they experience them.

Pre-treatment testing for NS3 Q80K polymorphism in patients infected with HCV genotype 1a
OLYSIO in combination with sofosbuvir
In HCV genotype 1a infected patients with cirrhosis, testing for the presence of the NS3 Q80K polymorphism may be considered prior to initiation of therapy with OLYSIO in combination with sofosbuvir (see section 5.1).
In HCV genotype 1a infected patients without cirrhosis, simeprevir efficacy in combination with sofosbuvir at the recommended 12-week treatment duration was not impacted by the presence of the NS3 Q80K polymorphism (see section 5.1).

OLYSIO in combination with peginterferon alfa and ribavirin
Simeprevir efficacy in combination with peginterferon alfa and ribavirin is substantially reduced in patients infected with hepatitis C genotype 1a with the NS3 Q80K polymorphism at baseline compared to patients with hepatitis C genotype 1a without the Q80K polymorphism (see section 5.1). Testing for the presence of the Q80K polymorphism in patients with HCV genotype 1a is strongly recommended when considering therapy with OLYSIO in combination with peginterferon alfa and ribavirin. Alternative therapy should be considered for patients infected with HCV genotype 1a with the Q80K polymorphism or in cases where testing is not accessible.

Co-administration with other direct acting antivirals against HCV
OLYSIO should only be co-administered with other direct acting antiviral medicinal products if the benefits are considered to outweigh the risks based upon available data. There are no data to support the co-administration of OLYSIO and telaprevir or boceprevir. These HCV protease inhibitors are anticipated to be cross-resistant, and co-administration is not recommended (see also section 4.5).

OLYSIO in combination with peginterferon alfa-2b
In the clinical studies, patients randomised to simeprevir in combination with peginterferon alfa-2b and ribavirin obtained numerically lower SVR12 rates and also experienced viral breakthrough and viral relapse more frequently than those treated with simeprevir in combination with peginterferon alfa-2a and ribavirin (see section 5.1).

Pregnancy and contraception
OLYSIO should only be used during pregnancy or in women of childbearing potential if the benefit justifies the risk. Female patients of childbearing potential must use an effective form of contraception (see section 4.6).

The contraindications and warnings regarding pregnancy and contraception requirements applicable to the co-administered medicinal products also apply to their use in OLYSIO combination treatment.

Ribavirin may cause birth defects and/or death of the exposed foetus. Therefore, extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients (see section 4.6).

Photosensitivity
Photosensitivity reactions, some resulting in hospitalisation, have been observed with OLYSIO combination treatment (see section 4.8). Patients should be warned of the risk of photosensitivity reactions and on the importance of applying appropriate sun protective measures, such as wearing protective clothing and using sunscreen, during treatment with OLYSIO. Patients should limit exposure to sun as much as possible and avoid use of tanning devices during treatment with OLYSIO. If photosensitivity reactions occur, discontinuation of OLYSIO should be considered and patients should be monitored until the reaction has resolved.

Rash
Rash has been observed with OLYSIO combination treatment (see section 4.8). Patients with mild to moderate rashes should be monitored for possible progression of rash, including the development of mucosal signs or systemic symptoms. In case of severe rash, OLYSIO and other co-administered medicinal products for the treatment of CHC should be discontinued and the patients should be monitored until the symptoms have resolved.

Laboratory testing during treatment with OLYSIO, peginterferon alfa and ribavirin
HCV RNA levels should be monitored at weeks 4 and 12 and as clinically indicated (see also guidelines for treatment duration and stopping rules; section 4.2). Use of a sensitive quantitative HCV RNA assay for monitoring HCV RNA levels during treatment is recommended.
Refer to the Summary of Product Characteristics of peginterferon alfa and ribavirin for pre-treatment, on-treatment and post-treatment laboratory testing requirements including haematology, biochemistry (including hepatic enzymes and bilirubin), and pregnancy testing requirements.

Interactions with medicinal products
Co-administration of OLYSIO with substances that moderately or strongly induce or inhibit cytochrome P450 3A (CYP3A4) is not recommended as this may lead to significantly lower or higher exposure of simeprevir, respectively.
Please refer to section 4.5 for information on interactions with medicinal products.

Hepatitis B virus (HBV) co-infection
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.

Organ transplant patients
Co-administration of OLYSIO with ciclosporin is not recommended as this leads to significantly higher exposure of simeprevir (see section 4.5).

Excipient of OLYSIO capsules
OLYSIO capsules contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products that affect simeprevir exposure
The primary enzyme involved in the biotransformation of simeprevir is CYP3A4 (see section 5.2) and clinically relevant effects of other medicinal products on simeprevir pharmacokinetics via CYP3A4 may occur. Co-administration of OLYSIO with moderate or strong inhibitors of CYP3A4 may significantly increase the plasma exposure of simeprevir, while co-administration with moderate or strong inducers of CYP3A4 may significantly reduce the plasma exposure of simeprevir and lead to loss of efficacy (see table 4). Therefore, co-administration of OLYSIO with substances that moderately or strongly inhibit or induce CYP3A4 is not recommended.
Hepatic uptake of simeprevir is mediated by OATP1B1/3. Inhibitors of OATP1B1/3 such as eltrombopag or gemfibrozil may result in increases in simeprevir plasma concentrations.

Medicinal products that are affected by the use of simeprevir
Simeprevir mildly inhibits the CYP1A2 activity and intestinal CYP3A4 activity, while it does not affect hepatic CYP3A4 activity. Co-administration of OLYSIO with medicinal products that are primarily metabolised by CYP3A4 may result in increased plasma concentrations of such medicinal products (see table 4). Simeprevir does not affect CYP2C9, CYP2C19 or CYP2D6 *in vivo*.
Simeprevir inhibits OATP1B1/3, P-gp and BCRP transporters. Co-administration of OLYSIO with medicinal products that are substrates for OATP1B1/3, P-gp and BCRP transport may result in increased plasma concentrations of such medicinal products (see table 4).

Patients treated with vitamin K antagonists
As liver function may change during treatment with OLYSIO, close monitoring of International Normalised Ratio (INR) values is recommended.

Interaction table
Established and theoretical interactions between simeprevir and selected medicinal products are listed in table 4 (least square mean ratios with 90% confidence intervals (90% CI) are presented, increase is indicated as "↑", decrease as "↓", no change as "↔"). Interaction studies have been performed in healthy adults with the recommended dose of 150 mg simeprevir once daily unless otherwise noted.

Table 4: Interactions and dose recommendation with other medicinal products

Medicinal products by therapeutic areas	**Effect on drug levels Least Squares Mean Ratio (90%CI)**	**Recommendation for co-administration**
ANALEPTIC		
Caffeine 150 mg	caffeine AUC 1.26 (1.21-1.32) ↑ caffeine C_{max} 1.12 (1.06-1.19) ↔ caffeine C_{min} not studied	No dose adjustment is required.
ANTIARRHYTHMICS		
Digoxin 0.25 mg	digoxin AUC 1.39 (1.16-1.67) ↑ digoxin C_{max} 1.31 (1.14-1.51) ↑ digoxin C_{min} not studied (inhibition of P-gp transporter)	Concentrations of digoxin should be monitored and used for titration of digoxin dose to obtain the desired clinical effect.
Amiodarone	Not studied. Mild increases in concentrations of amiodarone may be expected when amiodarone is administered orally. (intestinal CYP3A4 enzyme inhibition) Mild increases in simeprevir concentrations may occur due to inhibition of CYP3A4 by amiodarone.	*Treatment regimen not containing sofosbuvir:* Caution is warranted and therapeutic drug monitoring for amiodarone and/or clinical monitoring (ECG etc.) when orally administered are recommended. *Treatment regimen with*

		sofosbuvir: Use only if no other alternative is available. Close monitoring is recommended if this medicinal product is administered with OLYSIO in combination with sofosbuvir (see section 4.4).
Disopyramide Flecainide Mexiletine Propafenone Quinidine	Not studied. Mild increases in concentrations of these antiarrhythmics may be expected when these medicinal products are administered orally. (intestinal CYP3A4 enzyme inhibition)	Caution is warranted and therapeutic drug monitoring for these antiarrhythmics and/or clinical monitoring (ECG etc.) when orally administered are recommended.
ANTICOAGULANTS		
Warfarin and other vitamin K antagonists	warfarin 10 mg: S-warfarin AUC 1.04 (1.00-1.07) ↔ S-warfarin C_{max} 1.00 (0.94-1.06) ↔ S-warfarin C_{min} not studied	While no change in the pharmacokinetics of warfarin is expected, close monitoring of INR is recommended with all vitamin K antagonists. This is due to potential liver function changes during treatment with OLYSIO.
ANTICONVULSANTS		
Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	Not studied. Significant decrease in plasma concentrations of simeprevir are expected. (strong CYP3A4 induction)	It is not recommended to co-administer OLYSIO with these anticonvulsants as co-administration may result in loss of therapeutic effect of OLYSIO.
ANTIDEPRESSANTS		
Escitalopram 10 mg once daily	escitalopram AUC 1.00 (0.97-1.03) ↔ escitalopram C_{max} 1.03 (0.99-1.07) ↔ escitalopram C_{min} 1.00 (0.95-1.05) ↔ simeprevir AUC 0.75 (0.68-0.83) ↓ simeprevir C_{max} 0.80 (0.71-0.89) ↓ simeprevir C_{min} 0.68 (0.59-0.79) ↓	No dose adjustment is required.
ANTIHISTAMINES		
Astemizole Terfenadine	Not studied. Astemizole and terfenadine have the potential for cardiac arrhythmias. Mild increases in concentrations of these antihistamines may be expected. (intestinal CYP3A4 enzyme inhibition)	It is not recommended to co-administer OLYSIO with astemizole or terfenadine.
ANTI-INFECTIVES		
Antibiotics – macrolides (systemic administration)		
Azithromycin	Not studied. Based on the elimination pathway of azithromycin, no drug interactions are expected between azithromycin and simeprevir.	No dose adjustment is required.

Erythromycin 500 mg three times a day	erythromycin AUC 1.90 (1.53-2.36) ↑ erythromycin C_{max} 1.59 (1.23-2.05) ↑ erythromycin C_{min} 3.08 (2.54-3.73) ↑ simeprevir AUC 7.47 (6.41-8.70) ↑ simeprevir C_{max} 4.53 (3.91-5.25) ↑ simeprevir C_{min} 12.74 (10.19-15.93) ↑ (inhibition of CYP3A4 enzymes and P-gp transporter by both erythromycin and simeprevir)	It is not recommended to co-administer OLYSIO with systemic erythromycin.
Clarithromycin Telithromycin	Not studied. Increased plasma concentrations of simeprevir are expected. (strong CYP3A4 enzyme inhibition)	It is not recommended to co-administer OLYSIO with clarithromycin or telithromycin.
Antifungals (systemic administration)		
Itraconazole Ketoconazole* Posaconazole	Not studied. Significant increases in plasma concentrations of simeprevir are expected. (strong CYP3A4 enzyme inhibition)	It is not recommended to co-administer OLYSIO with systemic itraconazole, ketoconazole or posaconazole.
Fluconazole Voriconazole	Not studied. Significant increases in plasma concentrations of simeprevir are expected. (mild to moderate CYP3A4 enzyme inhibition)	It is not recommended to co-administer OLYSIO with systemic fluconazole or voriconazole.
Antimycobacterials		
Bedaquiline	Not studied. No clinically relevant drug-drug interaction is expected.	No dose adjustment is required.
Rifampicin[1] 600 mg once daily	rifampicin AUC 1.00 (0.93-1.08) ↔ rifampicin C_{max} 0.92 (0.80-1.07) ↔ rifampicin C_{min} not studied 25-desacetyl-rifampicin AUC 1.24 (1.13-1.36) ↑ 25-desacetyl-rifampicin C_{max} 1.08 (0.98-1.19) ↔ 25-desacetyl-rifampicin C_{min} not studied simeprevir AUC 0.52 (0.41-0.67) ↓ simeprevir C_{max} 1.31 (1.03-1.66) ↑ simeprevir C_{min} 0.08 (0.06-0.11) ↓ (CYP3A4 enzyme induction)	It is not recommended to co-administer OLYSIO with rifampicin as co-administration may result in loss of therapeutic effect of OLYSIO.
Rifabutin Rifapentine	Not studied. Significant decreases in plasma concentrations of simeprevir are expected. (CYP3A4 enzyme induction)	It is not recommended to co-administer OLYSIO with rifabutin or rifapentine as co-administration may result in loss of therapeutic effect of OLYSIO.
ANTITUSSIVE		
Dextromethorphan (DXM) 30 mg	DXM AUC 1.08 (0.87-1.35) ↑ DXM C_{max} 1.21 (0.93-1.57) ↑ DXM C_{min} not studied dextrorphan AUC 1.09 (1.03-1.15) ↔ dextrorphan C_{max} 1.03 (0.93-1.15) ↔ dextrorphan C_{min} not studied	No dose adjustment is required.

CALCIUM CHANNEL BLOCKERS (oral administration)		
Amlodipine Bepridil Diltiazem Felodipine Nicardipine Nifedipine Nisoldipine Verapamil	Not studied. Increased plasma concentrations of orally administered calcium channel blockers may be expeced. (intestinal CYP3A4 enzyme and P-gp transporter inhibition) Increased simeprevir concentrations may occur due to mild inhibition of CYP3A4 by amlodipine and moderate inhibition of CYP3A4 by diltiazem and verapamil.	Caution is warranted and clinical monitoring of patients is recommended when these calcium channel blockers are given orally.
GLUCOCORTICOIDS		
Dexamethasone (systemic)	Not studied. Decreased plasma concentrations of simeprevir are expected. (moderate CYP3A4 enzyme induction)	It is not recommended to co-administer OLYSIO with systemic dexamethasone as co-administration may result in loss of therapeutic effect of OLYSIO.
Budesonide Fluticasone Methylprednisolone Prednisone	Not studied. No clinically relevant drug-drug interaction is expected.	No dose adjustment is required.
GASTROINTESTINAL PRODUCTS		
Antacid		
Aluminium or Magnesium hydroxide Calcium carbonate	Not studied. No clinically relevant drug-drug interaction is expected.	No dose adjustment is required.
H_2-receptor antagonists		
Cimetidine Nizatidine Ranitidine	Not studied. No clinically relevant drug-drug interaction is expected.	No dose adjustment is required.
Propulsive		
Cisapride	Not studied. Cisapride has the potential to cause cardiac arrhythmias. Increased concentrations of cisapride may be possible. (intestinal CYP3A4 enzyme inhibition)	It is not recommended to co-administer OLYSIO with cisapride.
Proton pump inhibitors		
Omeprazole 40 mg	omeprazole AUC 1.21 (1.00-1.46) ↑ omeprazole C_{max} 1.14 (0.93-1.39) ↑ omeprazole C_{min} not studied	No dose adjustment is required.
Dexlansoprazole Esomeprazole Lansoprazole Pantoprazole Rabeprazole	Not studied. No clinically relevant drug-drug interaction is expected.	No dose adjustment is required.

HCV PRODUCTS		
Antiviral		
Daclatasvir 60 mg once daily	daclatasvir AUC 1.96 (1.84-2.10) ↑ daclatasvir C_{max} 1.50 (1.39-1.62) ↑ daclatasvir C_{min} 2.68 (2.42-2.98) ↑ simeprevir AUC 1.44 (1.32-1.56) ↑ simeprevir C_{max} 1.39 (1.27-1.52) ↑ simeprevir C_{min} 1.49 (1.33-1.67) ↑	No dose adjustment of daclatasvir or OLYSIO is required.
Ledipasvir[2] 90 mg once daily	ledipasvir AUC 1.75 (1.56-1.96) ↑ ledipasvir C_{max} 1.64 (1.45-1.86) ↑ ledipasvir C_{min} 1.74 (1.55-1.97) ↑ simeprevir AUC 3.05 (2.43-3.84) ↑ simeprevir C_{max} 2.34 (1.95-2.81) ↑ simeprevir C_{min} 4.69 (3.40-6.47) ↑	It is not recommended to co-administer OLYSIO with a ledipasvir-containing medicinal product.
Sofosbuvir[3] 400 mg once daily	sofosbuvir AUC 3.16 (2.25-4.44) ↑ sofosbuvir C_{max} 1.91 (1.26-2.90) ↑ sofosbuvir C_{min} not studied GS-331007 AUC 1.09 (0.87-1.37) ↔ GS-331007 C_{max} 0.69 (0.52-0.93) ↓ GS-331007 C_{min} not studied simeprevir AUC 0.94 (0.67-1.33) ↔ simeprevir C_{max} 0.96 (0.71-1.30) ↔ simeprevir C_{min} not studied	Increase in sofosbuvir exposure observed in the pharmacokinetic substudy is not clinically relevant.
HERBAL PRODUCTS		
Milk thistle (*Silybum marianum*)	Not studied. Increased plasma concentrations of simeprevir are expected. (CYP3A4 enzyme inhibition)	It is not recommended to co-administer OLYSIO with milk thistle.
St John's wort (*Hypericum perforatum*)	Not studied. Significantly decreased plasma concentrations of simeprevir are expected. (CYP3A4 enzyme induction)	It is not recommended to co-administer OLYSIO with products containing St John's wort as co-administration may result in loss of therapeutic effect of OLYSIO.
HIV PRODUCTS		
Antiretroviral – CCR5 antagonist		
Maraviroc	Not studied. No clinically relevant drug-drug interaction is expected.	No dose adjustment is required for either drug when OLYSIO is co-administered with maraviroc.
Antiretroviral – integrase inhibitor		
Raltegravir 400 mg twice a day	raltegravir AUC 1.08 (0.85-1.38) ↑ raltegravir C_{max} 1.03 (0.78-1.36) ↔ raltegravir C_{min} 1.14 (0.97-1.36) ↑ simeprevir AUC 0.89 (0.81-0.98) ↔ simeprevir C_{max} 0.93 (0.85-1.02) ↔ simeprevir C_{min} 0.86 (0.75-0.98) ↓	No dose adjustment is required.
Dolutegravir	Not studied. No clinically relevant drug-drug interaction is expected.	No dose adjustment is required.

Antiretroviral – non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Efavirenz 600 mg once daily	efavirenz AUC 0.90 (0.85-0.95) ↔ efavirenz C_{max} 0.97 (0.89-1.06) ↔ efavirenz C_{min} 0.87 (0.81-0.93) ↔ simeprevir AUC 0.29 (0.26-0.33) ↓ simeprevir C_{max} 0.49 (0.44-0.54) ↓ simeprevir C_{min} 0.09 (0.08-0.12) ↓ (CYP3A4 enzyme induction)	It is not recommended to co-administer OLYSIO with efavirenz as co-administration may result in loss of therapeutic effect of OLYSIO.
Rilpivirine 25 mg once daily	rilpivirine AUC 1.12 (1.05-1.19) ↔ rilpivirine C_{max} 1.04 (0.95-1.13) ↔ rilpivirine C_{min} 1.25 (1.16-1.35) ↑ simeprevir AUC 1.06 (0.94-1.19) ↔ simeprevir C_{max} 1.10 (0.97-1.26) ↑ simeprevir C_{min} 0.96 (0.83-1.11) ↔	No dose adjustment is required.
Other NNRTIs (Delavirdine, Etravirine, Nevirapine)	Not studied. Altered plasma concentrations of simeprevir are expected. (CYP3A4 enzyme induction [etravirine or nevirapine] or inhibition [delavirdine])	It is not recommended to co-administer OLYSIO with delavirdine, etravirine or nevirapine.
Antiretroviral – nucleoside or nucleotide reverse transcriptase inhibitors (N(t)RTIs)		
Tenofovir disoproxil fumarate 300 mg once daily	tenofovir AUC 1.18 (1.13-1.24) ↔ tenofovir C_{max} 1.19 (1.10-1.30) ↑ tenofovir C_{min} 1.24 (1.15-1.33) ↑ simeprevir AUC 0.86 (0.76-0.98) ↓ simeprevir C_{max} 0.85 (0.73-0.99) ↓ simeprevir C_{min} 0.93 (0.78-1.11) ↓	No dose adjustment is required.
Other NRTIs (Abacavir, Didanosine, Emtricitabine, Lamivudine, Stavudine, Zidovudine)	Not studied. No clinically relevant drug-drug interaction is expected.	No dose adjustment is required.
Antiretroviral – protease inhibitors (PIs)		
Darunavir/ritonavir[4] 800/100 mg once daily	darunavir AUC 1.18 (1.11-1.25) ↑ darunavir C_{max} 1.04 (0.99-1.10) ↔ darunavir C_{min} 1.31 (1.13-1.52) ↑ ritonavir AUC 1.32 (1.25-1.40) ↑ ritonavir C_{max} 1.23 (1.14-1.32) ↑ ritonavir C_{min} 1.44 (1.30-1.61) ↑ simeprevir AUC 2.59 (2.15-3.11) ↑* simeprevir C_{max} 1.79 (1.55-2.06) ↑* simeprevir C_{min} 4.58 (3.54-5.92) ↑* * darunavir/ritonavir + 50 mg simeprevir compared to 150 mg simeprevir alone. (strong CYP3A4 enzyme inhibition)	It is not recommended to co-administer OLYSIO with darunavir/ritonavir.
Ritonavir[1] 100 mg twice daily	simeprevir AUC 7.18 (5.63-9.15) ↑ simeprevir C_{max} 4.70 (3.84-5.76) ↑ simeprevir C_{min} 14.35 (10.29-20.01) ↑ (strong CYP3A4 enzyme inhibition)	It is not recommended to co-administer OLYSIO with ritonavir.

Other ritonavir-boosted or unboosted HIV PIs (Atazanavir, (Fos)amprenavir, Lopinavir, Indinavir, Nelfinavir, Saquinavir, Tipranavir)	Not studied. Altered plasma concentrations of simeprevir are expected. (CYP3A4 enzyme induction or inhibition)	It is not recommended to co-administer OLYSIO with any HIV PI, with or without ritonavir.
Cobicistat-containing medicinal products	Not studied. Significantly increased plasma concentrations of simeprevir are expected. (strong CYP3A4 enzyme inhibition)	It is not recommended to co-administer OLYSIO with cobicistat-containing medicinal products.
HMG CO-A REDUCTASE INHIBITORS		
Rosuvastatin 10 mg	rosuvastatin AUC 2.81 (2.34-3.37) ↑ rosuvastatin C_{max} 3.17 (2.57-3.91) ↑ rosuvastatin C_{min} not studied (OATP1B1/3, BCRP transporter inhibition)	Titrate the rosuvastatin dose carefully and use the lowest necessary dose while monitoring for safety when co-administered with OLYSIO.
Pitavastatin Pravastatin	Not studied. Increased plasma concentrations of pitavastatin and pravastatin are expected. (OATP1B1/3 transporter inhibition)	Titrate the pitavastatin and pravastatin dose carefully and use the lowest necessary dose while monitoring for safety when co-administered with OLYSIO.
Atorvastatin 40 mg	atorvastatin AUC 2.12 (1.72-2.62) ↑ atorvastatin C_{max} 1.70 (1.42-2.04) ↑ atorvastatin C_{min} not studied 2-OH-atorvastatin AUC 2.29 (2.08-2.52) ↑ 2-OH-atorvastatin C_{max} 1.98 (1.70-2.31) ↑ 2-OH-atorvastatin C_{min} not studied (OATP1B1/3 transporter and/or CYP3A4 enzyme inhibition) Increased simeprevir concentrations may occur due to inhibition of OATP1B1 by atorvastatin.	Titrate the atorvastatin dose carefully and use the lowest necessary dose while monitoring for safety when co-administered with OLYSIO.
Simvastatin 40 mg	simvastatin AUC 1.51 (1.32-1.73) ↑ simvastatin C_{max} 1.46 (1.17-1.82) ↑ simvastatin C_{min} not studied simvastatin acid AUC 1.88 (1.63-2.17) ↑ simvastatin acid C_{max} 3.03 (2.49-3.69) ↑ simvastatin acid C_{min} not studied (OATP1B1 transporter and/or CYP3A4 enzyme inhibition)	Titrate the simvastatin dose carefully and use the lowest necessary dose while monitoring for safety when co-administered with OLYSIO.
Lovastatin	Not studied. Increased plasma concentrations of lovastatin are expected. (OATP1B1 transporter and/or CYP3A4 enzyme inhibition)	Titrate the lovastatin dose carefully and use the lowest necessary dose while monitoring for safety when co-administered with OLYSIO.

Fluvastatin	Not studied. No clinically relevant drug-drug interaction is expected.	No dose adjustment is required.
HORMONAL CONTRACEPTIVES		
Ethinylestradiol and norethindrone 0.035 mg once daily/ 1 mg once daily	ethinylestradiol AUC 1.12 (1.05-1.20) ↔ ethinylestradiol C_{max} 1.18 (1.09-1.27) ↑ ethinylestradiol C_{min} 1.00 (0.89-1.13) ↔ norethindrone AUC 1.15 (1.08-1.22) ↔ norethindrone C_{max} 1.06 (0.99-1.14) ↔ norethindrone C_{min} 1.24 (1.13-1.35) ↑	No dose adjustment is required.
IMMUNOSUPPRESSANTS		
Ciclosporin 100 mg patient individualised dose[5]	ciclosporin AUC 1.19 (1.13-1.26) ↑ ciclosporin C_{max} 1.16 (1.07-1.26) ↑ ciclosporin C_{min} not studied simeprevir AUC 5.68 (3.58-9.00) ↑[6] simeprevir C_{max} 4.53 (3.05-6.74) ↑[6] simeprevir C_{min} not studied[6] (OATP1B1/3, P-gp and CYP3A inhibition by ciclosporin)	It is not recommended to co-administer OLYSIO with ciclosporin.
Tacrolimus 2 mg patient individualised dose[5]	tacrolimus AUC 0.83 (0.59-1.16) ↓ tacrolimus C_{max} 0.76 (0.65-0.90) ↓ tacrolimus C_{min} not studied simeprevir AUC 1.90 (1.37-2.63) ↑[7] simeprevir C_{max} 1.85 (1.40-2.46) ↑[7] simeprevir C_{min} not studied[7] (OATP1B1 inhibition by tacrolimus)	No dose adjustment is required for either drug when OLYSIO is co-administered with tacrolimus. Monitoring of blood concentrations of tacrolimus is recommended.
Sirolimus	Not studied. Mild increased or decreased plasma concentrations of sirolimus may occur.	Monitoring of blood concentrations of sirolimus is recommended.
NARCOTIC ANALGESICS		
Methadone[8] 30-150 mg once daily, individualised dose	R(-) methadone AUC 0.99 (0.91-1.09) ↔ R(-) methadone C_{max} 1.03 (0.97-1.09) ↔ R(-) methadone C_{min} 1.02 (0.93-1.12) ↔	No dose adjustment is required.
Buprenorphine Naloxone	Not studied. No clinically relevant drug-drug interaction is expected.	No dose adjustment is required.

PHOSPHODIESTERASE TYPE 5 INHIBITORS		
Sildenafil Tadalafil Vardenafil	Not studied. Mild increases in concentrations of PDE-5 inhibitors may be expected. (intestinal CYP3A4 enzyme inhibition) Mild increases in simeprevir concentrations may occur due to mild inhibition of OATP1B1 by sildenafil.	No dose adjustment is required when OLYSIO is co-administered with doses of sildenafil, vardenafil, or tadalafil indicated for the treatment of erectile dysfunction. Dose adjustment of the PDE-5 inhibitor may be required when OLYSIO is co-administered with sildenafil or tadalafil administered chronically at doses used for the treatment of pulmonary arterial hypertension. Consider starting with the lowest dose of the PDE-5 inhibitor and increase as needed, with clinical monitoring as appropriate.
SEDATIVES/ANXIOLYTICS		
Midazolam *Oral*: 0.075 mg/kg *Intravenous*: 0.025 mg/kg	*Oral:* midazolam AUC 1.45 (1.35-1.57) ↑ midazolam C_{max} 1.31 (1.19-1.45) ↑ midazolam C_{min} not studied *Intravenous:* midazolam AUC 1.10 (0.95-1.26) ↑ midazolam C_{max} 0.78 (0.52-1.17) ↓ midazolam C_{min} not studied (mild intestinal CYP3A4 enzyme inhibition)	Plasma concentrations of midazolam were not affected when administered intravenously as simeprevir does not inhibit hepatic CYP3A4. Caution is warranted when this medicinal product with narrow therapeutic index is co-administered with OLYSIO via the oral route.
Triazolam (oral)	Not studied. Mild increases in concentrations of triazolam may be expected. (intestinal CYP3A4 enzyme inhibition)	Caution is warranted when this medicinal product with narrow therapeutic index is co-administered with OLYSIO via the oral route.
STIMULANTS		
Methylphenidate	Not studied. No clinically relevant drug-drug interaction is expected.	No dose adjustment is required.

The direction of the arrow (↑ = increase, ↓ = decrease, ↔ = no change) for each pharmacokinetic parameter is based on the 90% confidence interval of the geometric mean ratio being within (↔), below (↓) or above (↑) the 0.80 - 1.25 range.

[1] This interaction study has been performed with a dose higher than the recommended dose for simeprevir assessing the maximal effect on the co-administered drug. The dosing recommendation is applicable to the recommended dose of simeprevir 150 mg once daily.

[2] The interaction between simeprevir and the medicinal product was evaluated in a phase 2 pharmacokinetic study in 20 HCV-infected patients.

[3] Comparison based on historic controls. The interaction between simeprevir and the medicinal product was evaluated in a pharmacokinetic substudy within a phase 2 study in 22 HCV infected patients.

[4] The dose of simeprevir in this interaction study was 50 mg when co-administered in combination with darunavir/ritonavir, compared to 150 mg in the simeprevir alone treatment group.

[5] Patient individualised dose at the discretion of the physician, according to local clinical practice.

[6] Comparison based on historic controls. Data from a phase 2 study in 9 HCV infected post-liver transplant patients.
[7] Comparison based on historic controls. Data from a phase 2 study in 11 HCV infected post-liver transplant patients.
[8] The interaction between simeprevir and the medicinal product was evaluated in a pharmacokinetic study in opioid-dependent adults on stable methadone maintenance therapy.
* Ketoconazole: pending further ATC classification.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate and well-controlled studies with simeprevir in pregnant women. Studies in animals have shown reproductive effects (see section 5.3). OLYSIO should only be used during pregnancy or in women of childbearing potential if the benefit justifies the risk. Female patients of childbearing potential must use an effective form of contraception.

Because OLYSIO must be co-administered with other medicinal products, for the treatment of CHC, the contraindications and warnings applicable to those medicinal products also apply to their use in combination treatment with OLYSIO (see section 4.3).

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Female patients of childbearing potential and male patients with female partners of childbearing potential must use an effective form of contraception during treatment with ribavirin and after completion of ribavirin treatment for a duration as specified in the Summary of Product Characteristics for ribavirin.

Breast-feeding
It is not known whether simeprevir or its metabolites are excreted in human milk. When administered to lactating rats, simeprevir was detected in plasma of suckling rats likely due to excretion of simeprevir via milk (see section 5.3). A risk to the newborn/infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from OLYSIO therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

Fertility
There are no data on the effect of simeprevir on human fertility. No effects on fertility were observed in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

OLYSIO has no or negligible influence on the ability to drive and use machines. Combination treatment of OLYSIO with other medicinal products for the treatment of CHC may affect a patient's ability to drive and use machines. Refer to the Summary of Product Characteristics for these co-administered medicinal products regarding their potential effect on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The overall safety profile of simeprevir is based on data from 580 HCV genotype 1 infected patients who received simeprevir in combination with sofosbuvir with or without ribavirin (pooled data from the clinical phase 2 study HPC2002 and the clinical phase 3 studies HPC3017 and HPC3018) and 1,486 HCV genotype 1 infected patients who received simeprevir (or placebo) in combination with peginterferon alfa and ribavirin (pooled data from the clinical phase 2 studies C205 and C206 and the clinical phase 3 studies C208, C216 and HPC3007).

The safety profile of simeprevir is comparable in patients with HCV genotype 4 infection and HCV genotype 1 infection, when given either in combination with sofosbuvir or in combination with peginterferon alfa and ribavirin.

Simeprevir in combination with sofosbuvir
The safety profile of simeprevir in combination with sofosbuvir in patients with HCV genotype 1 infection with or without cirrhosis is based on pooled data from the phase 2 study HPC2002 and the phase 3 studies HPC3017 and HPC3018 which included 472 patients who received simeprevir with sofosbuvir without ribavirin (155, 286 and 31 patients received 8, 12 or 24 weeks of treatment, respectively) and 108 patients who received simeprevir with sofosbuvir and ribavirin (54 patients each received 12 or 24 weeks of treatment).

The majority of the adverse reactions reported were grade 1 in severity. Grade 2 and 3 adverse reactions were reported in 3.5% (n = 10) and 0.3% (n = 1) of patients, respectively, receiving 12 weeks simeprevir with sofosbuvir; no grade 4 adverse reactions were reported. In patients receiving 24 weeks simeprevir with sofosbuvir, no grade 2 or 3 adverse reactions were reported; one patient (3.2%) experienced a grade 4 adverse reaction ('blood bilirubin increased'). No serious adverse reactions were reported.

The most frequently reported adverse reactions (incidence ≥ 5% following 12 or 24 weeks of treatment) were rash, pruritus, constipation and photosensitivity reaction (see section 4.4).

One patient in the 12-week treatment group (0.3%) and none of the patients in the 24-week treatment group discontinued treatment due to adverse reactions.

Simeprevir in combination with peginterferon alfa and ribavirin
The safety profile of simeprevir in combination with peginterferon alfa and ribavirin in patients with HCV genotype 1 infection is based on the pooled data from the phase 2 studies and phase 3 studies C205, C206, C208, C216 and HPC3007 which included 924 patients who received simeprevir 150 mg once daily for 12 weeks and 540 patients who received placebo with peginterferon alfa and ribavirin.

In the pooled phase 3 safety data, the majority of the adverse reactions reported during 12 weeks treatment with simeprevir were grade 1 to 2 in severity. Grade 3 or 4 adverse reactions were reported in 3.1% of patients receiving simeprevir with peginterferon alfa and ribavirin *versus* 0.5% of patients receiving placebo with peginterferon alfa and ribavirin. Serious adverse reactions were reported in 0.3% of simeprevir-treated patients (2 photosensitivity events requiring hospitalisation) and in none of the patients receiving placebo with peginterferon alfa and ribavirin.

During the first 12 weeks of treatment, the most frequently reported adverse reactions (incidence ≥ 5%) were nausea, rash, pruritus, dyspnoea, blood bilirubin increase and photosensitivity reaction (see section 4.4).

Discontinuation of simeprevir due to adverse reactions occurred in 0.9% of patients receiving simeprevir with peginterferon alfa and ribavirin.

Tabulated list of adverse reactions
Adverse reactions of simeprevir in combination with sofosbuvir or in combination with peginterferon alfa and ribavirin reported in adult patients with HCV genotype 1 infection are listed in table 5. The adverse reactions are listed by system organ class (SOC) and frequency: 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), very rare (< 1/10,000).

Table 5: Adverse reactions identified with simeprevir in combination with sofosbuvir or simeprevir in combination with peginterferon alfa and ribavirin[1]

SOC Frequency Category	simeprevir + sofosbuvir		simeprevir + peginterferon alfa + ribavirin N = 781
	12 weeks N = 286	24 weeks N = 31	
Respiratory, thoracic and mediastinal disorders:			
very common			dyspnoea*
Gastrointestinal disorders:			
very common			nausea
common	constipation	constipation	constipation
Hepatobiliary disorders:			
common	blood bilirubin increased*	blood bilirubin increased*	blood bilirubin increased*
Skin and subcutaneous tissue disorders:			
very common		rash*	rash*, pruritus*
common	rash*, pruritus*, photosensitivity reaction*	pruritus*, photosensitivity reaction*	photosensitivity reaction*

[1] Simeprevir in combination with sofosbuvir: pooled studies HPC2002, HPC3017 and HPC3018 (12 weeks) or study HPC2002 (24 weeks); simeprevir in combination with peginterferon alfa and ribavirin: pooled phase 3 studies C208, C216 and HPC3007 (first 12 weeks of treatments).

* see section below for further details.

Description of selected adverse reactions

Rash and pruritus

Most of the rash and pruritus events in simeprevir-treated patients were of mild or moderate severity (grade 1 or 2).

Simeprevir in combination with sofosbuvir: Rash and pruritus were reported in 8.0% and 8.4%, respectively, of patients receiving 12 weeks of treatment compared to 12.9% and 3.2%, respectively, of patients receiving 24 weeks of treatment (all grades). Grade 3 rash was reported in one patient (0.3%; 12-week treatment group) which led to treatment discontinuation; none of the patients experienced grade 4 rash. None of the patients experienced grade 3 or 4 pruritus; none of the patients discontinued treatment due to pruritus.

In study HPC2002, rash (grouped term) was reported in 10.7% of patients receiving 12 weeks of simeprevir and sofosbuvir without ribavirin versus 20.4% of patients receiving 12 weeks of simeprevir and sofosbuvir with ribavirin.

Simeprevir in combination with peginterferon alfa and ribavirin: During the 12 weeks treatment with simeprevir, rash and pruritus were reported in 21.8% and 21.9% of simeprevir-treated patients, compared to 16.6% and 14.6% in placebo-treated patients, respectively (all grades; pooled phase 3). Grade 3 rash or pruritus occurred in 0.5% and 0.1% of simeprevir-treated patients, respectively. Discontinuation of simeprevir due to rash or pruritus occurred in 0.8% and 0.1% of simeprevir-treated patients, compared to 0.3% and 0% of placebo-treated patients, respectively.

Blood bilirubin increased

Elevations in direct and indirect bilirubin have been reported in patients treated with simeprevir and were mostly of mild or moderate severity. Bilirubin elevations were generally not associated with elevations in liver transaminases and bilirubin levels normalised after end of treatment.

Simeprevir in combination with sofosbuvir: 'Blood bilirubin increased' was reported in 1.0% of patients receiving 12 weeks of treatment compared to 3.2% in patients receiving 24 weeks of treatment (all grades). Grade 2 'blood bilirubin increased' was reported in one patient (0.3%) receiving 12 weeks of treatment. There were no grade 3 events reported. One patient (3.2%) receiving 24 weeks of treatment experienced a grade 4 'blood bilirubin increased' event. None of the patients discontinued treatment due to 'blood bilirubin increased'.

In study HPC2002, increased bilirubin was reported in 0% of patients receiving 12 weeks of simeprevir and sofosbuvir without ribavirin versus 9.3% of patients receiving 12 weeks of simeprevir and sofosbuvir with ribavirin.

Simeprevir in combination with peginterferon alfa and ribavirin: During the 12 weeks treatment with simeprevir, 'blood bilirubin increased' was reported in 7.4% of simeprevir-treated patients, compared to 2.8% in placebo-treated patients (all grades; pooled phase 3). In 2% and 0.3% of the simeprevir-treated patients grade 3 or 4 'blood bilirubin increased' was reported, respectively (pooled phase 3 studies). Discontinuation of simeprevir due to 'blood bilirubin increased' was rare (0.1%; n = 1).

Photosensitivity reactions
Photosensitivity reactions, some resulting in hospitalisation, have been reported in the post-marketing setting with OLYSIO combination treatment.

Simeprevir in combination with sofosbuvir: In clinical trials, photosensitivity reactions were reported in 3.1% of simeprevir-treated patients receiving 12 weeks of treatment compared to 6.5% in patients receiving 24 weeks of treatment (all grades). Most of the photosensitivity reactions were of mild severity (grade 1); grade 2 photosensitivity reactions were reported in two patients (0.7%) receiving 12 weeks of treatment. There were no grade 3 or 4 photosensitivity reactions reported and none of the patients discontinued treatment due to photosensitivity reactions.

In study HPC2002, photosensitivity reactions (grouped term) was reported in 7.1% of patients receiving 12 weeks of simeprevir and sofosbuvir without ribavirin versus 5.6% of patients receiving 12 weeks of simeprevir and sofosbuvir with ribavirin.

Simeprevir in combination with peginterferon alfa and ribavirin: In clinical trials during the 12 weeks treatment with simeprevir, photosensitivity reactions were reported in 4.7% of simeprevir-treated patients compared to 0.8% in placebo-treated patients (all grades; pooled phase 3). Most photosensitivity reactions in simeprevir-treated patients were of mild or moderate severity (grade 1 or 2); 0.3% of the simeprevir-treated patients experienced serious reactions leading to hospitalisation (see section 4.4).

Dyspnoea
Simeprevir in combination with peginterferon alfa and ribavirin: During the first 12 weeks treatment with simeprevir, dyspnoea was reported in 11.8% of simeprevir-treated patients, compared to 7.6% in placebo-treated patients (all grades; pooled phase 3). Only grade 1 and 2 events were reported and there were no events leading to discontinuation of any of the study drugs. In patients aged > 45 years, dyspnoea was reported in 16.4% of simeprevir-treated patients compared to 9.1% in placebo-treated patients (all grades; pooled phase 3).

Cardiac arrhythmias
Cases of bradycardia have been observed when OLYSIO is used in combination with sofosbuvir and concomitant amiodarone (see sections 4.4 and 4.5).

Laboratory abnormalities
Simeprevir in combination with sofosbuvir
Treatment-emergent laboratory abnormalities in amylase and lipase have been observed in patients treated with simeprevir in combination with sofosbuvir (table 6). Elevations in amylase and lipase were transient and mostly of mild or moderate severity. Amylase and lipase elevations were not associated with pancreatitis.

Table 6: Treatment-emergent laboratory abnormalities in amylase and lipase in patients receiving 12 or 24 weeks of simeprevir in combination with sofosbuvir (12 weeks: pooled studies HPC2002, HPC3017 and HPC3018; 24 weeks: study HPC2002)

Laboratory parameter	WHO toxicity range[1]	12 weeks simeprevir + sofosbuvir N = 286 n (%)	24 weeks simeprevir + sofosbuvir N = 31 n (%)
Chemistry			
Amylase			
Grade 1	≥ 1.1 to ≤ 1.5 x ULN	34 (11.9%)	8 (25.8%)
Grade 2	> 1.5 to ≤ 2.0 x ULN	15 (5.2%)	2 (6.5%)
Grade 3	> 2.0 to ≤ 5.0 x ULN	13 (4.5%)	3 (9.7%)
Lipase			
Grade 1	≥ 1.1 to ≤ 1.5 x ULN	13 (4.5%)	1 (3.2%)
Grade 2	> 1.5 to ≤ 3.0 x ULN	22 (7.7%)	3 (9.7%)
Grade 3	> 3.0 to ≤ 5.0 x ULN	1 (0.3%)	1 (3.2%)
Grade 4	> 5.0 x ULN	1 (0.3%)	1 (3.2%)

[1] WHO worst toxicity grades 1 to 4.
ULN = Upper Limit of Normal.

Simeprevir in combination with peginterferon alfa and ribavirin
There were no differences in haemoglobin, neutrophils or platelets between both treatment groups. Treatment-emergent laboratory abnormalities that were observed at a higher incidence in simeprevir-treated patients than in patients treated with placebo, peginterferon alfa and ribavirin are given in table 7.

Table 7: Treatment-emergent laboratory abnormalities observed at a higher incidence in patients receiving simeprevir in combination with peginterferon alfa and ribavirin (pooled phase 3 studies C208, C216 and HPC3007; first 12 weeks of treatments)

Laboratory parameter	WHO toxicity range[1]	simeprevir + peginterferon alfa + ribavirin N = 781 n (%)
Chemistry		
Alkaline phosphatase		
Grade 1	≥ 1.25 to ≤ 2.50 x ULN	26 (3.3%)
Grade 2	> 2.50 to ≤ 5.00 x ULN	1 (0.1%)
Hyperbilirubinemia		
Grade 1	≥ 1.1 to ≤ 1.5 x ULN	208 (26.7%)
Grade 2	> 1.5 to ≤ 2.5 x ULN	143 (18.3%)
Grade 3	> 2.5 to ≤ 5.0 x ULN	32 (4.1%)
Grade 4	> 5.0 x ULN	3 (0.4%)

[1] WHO worst toxicity grades 1 to 4.
ULN = Upper Limit of Normal.

Other special populations
Patients co-infected with HIV-1
The safety profile of simeprevir in combination with peginterferon alfa and ribavirin is comparable between HCV genotype 1 infected patients with and without HIV-1 co-infection.

Asian patients
The safety profile of OLYSIO 150 mg in combination with peginterferon alfa and ribavirin in a phase 3 study conducted in Asian patients in China and South-Korea is comparable to non-Asian patients from a pooled phase 3 population from global studies, except for higher frequencies for 'blood bilirubin increased' events (see table 8).

Table 8: 'Blood bilirubin increased' events observed in Asian patients from the phase 3 study HPC3005 versus the pooled phase 3 studies C208, C216 and HPC3007 receiving simeprevir or placebo in combination with peginterferon alfa and ribavirin (first 12 weeks of treatment)

Blood bilirubin increased	Phase 3 study in Asian patients		Pooled phase 3 studies	
	simeprevir + peginterferon alfa + ribavirin N = 152 n (%)	placebo + peginterferon alfa + ribavirin N = 152 n (%)	simeprevir + peginterferon alfa + ribavirin N = 781 n (%)	placebo + peginterferon alfa + ribavirin N = 397 n (%)
All grades	67 (44.1%)	28 (18.4%)	58 (7.4%)	11 (2.8%)
Grade 3	10 (6.6%)	2 (1.3%)	16 (2.0%)	2 (0.5%)
Grade 4	0 (0%)	0 (0%)	2 (0.3%)	0 (0%)
Related discontinuations	1 (0.7%)	0 (0%)	1 (0.1%)	0 (0%)

During administration of simeprevir with peginterferon alfa and ribavirin, the elevations in direct and indirect bilirubin were generally not associated with elevations in liver transaminases and normalised after end of treatment.

Hepatic impairment
Simeprevir exposure is significantly increased in patients with severe hepatic impairment (see section 5.2). A trend for a higher incidence of increased bilirubin levels with increasing simeprevir plasma exposure was observed. These increases in bilirubin levels were not associated with any adverse liver safety finding. However, reports of hepatic decompensation and hepatic failure during OLYSIO combination therapy have been received in the post marketing setting (see section 4.4).
A higher incidence of anaemia in patients with advanced fibrosis receiving simeprevir in combination with peginterferon alfa and ribavirin has been reported.

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

Human experience of overdose with simeprevir is limited. In healthy adult subjects receiving single doses up to 600 mg or once daily doses up to 400 mg for 5 days, and in HCV infected adult patients receiving 200 mg once daily for 4 weeks, adverse reactions were consistent with those observed in clinical studies at the recommended dose (see section 4.8).

There is no specific antidote for overdose with OLYSIO. In the event of an overdose with OLYSIO, it is recommended to employ the usual supportive measures and observe the patient's clinical status.

Simeprevir is highly protein bound, therefore dialysis is unlikely to result in significant removal of simeprevir (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, direct acting antivirals, ATC code: J05AE14.

Mechanism of action
Simeprevir is a specific inhibitor of the HCV NS3/4A serine protease, which is essential for viral replication. In a biochemical assay, simeprevir inhibited the proteolytic activity of recombinant genotype 1a and 1b HCV NS3/4A proteases, with median K_i values of 0.5 nM and 1.4 nM, respectively.

Antiviral activity *in vitro*
The median simeprevir EC_{50} and EC_{90} values against a HCV genotype 1b replicon were 9.4 nM (7.05 ng/ml) and 19 nM (14.25 ng/ml), respectively. Chimeric replicons carrying NS3 sequences derived from HCV PI treatment-naïve genotype 1a and genotype 1b patients displayed median fold change (FC) in simeprevir EC_{50} values of 1.4 (N = 78) and 0.4 (N = 59) compared to reference genotype 1b replicon, respectively. Genotype 1a and 1b isolates with a baseline Q80K polymorphism resulted in median FC in simeprevir EC_{50} of 11 (N = 33) and 8.4 (N = 2), respectively. Median simeprevir FC values against genotype 2 and genotype 3 baseline isolates tested were 25 (N = 4) and 1,014 (N = 2), respectively. Median simeprevir FC values against baseline isolates of genotype 4a, genotype 4d and genotype 4other were 0.5 (N = 38), 0.4 (N = 24), and 0.8 (N = 29), respectively. The presence of 50% human serum reduced simeprevir replicon activity by 2.4-fold. *In vitro* combination of simeprevir with interferon, ribavirin, NS5A or NS5B inhibitors resulted in additive or synergistic effects.

Antiviral activity *in vivo*
Short term monotherapy data of simeprevir from studies C201 (genotype 1) and C202 (genotype 2, 3, 4, 5 and 6) in patients receiving 200 mg once daily simeprevir for 7 days is presented in table 9.

Table 9: Antiviral activity of simeprevir 200 mg monotherapy (studies C201 and C202)

Genotype	**Mean (SE) change in HCV RNA at day 7/8 (log_{10} IU/mL)**
Genotype 1 (N = 9)	-4.18 (0.158)
Genotype 2 (N = 6)	-2.73 (0.71)
Genotype 3 (N = 8)	-0.04 (0.23)
Genotype 4 (N = 8)	-3.52 (0.43)
Genotype 5 (N = 7)	-2.19 (0.39)
Genotype 6 (N = 8)	-4.35 (0.29)

Resistance
Resistance in cell culture
Resistance to simeprevir was characterised in HCV genotype 1a and 1b replicon-containing cells. Ninety-six percent of simeprevir-selected genotype 1 replicons carried one or multiple amino acid substitutions at NS3 protease positions 43, 80, 155, 156, and/or 168, with substitutions at NS3 position D168 being most frequently observed (78%). Additionally, resistance to simeprevir was evaluated in HCV genotype 1a and 1b replicon assays using site-directed mutants and chimeric replicons carrying NS3 sequences derived from clinical isolates. Amino acid substitutions at NS3 positions 43, 80, 122, 155, 156, and 168 reduced *in vitro* simeprevir activity. Substitutions such as D168V or A, and R155K were usually associated with large reductions in susceptibility to simeprevir *in vitro* (FC in $EC_{50} > 50$), whereas other substitutions such as Q80K or R, S122R, and D168E displayed *in vitro* low level resistance (FC in EC_{50} between 2 and 50). Other substitutions such as Q80G or L, S122G, N or T did not reduce simeprevir activity (FC in $EC_{50} \leq 2$). Amino acid substitutions at NS3 positions 80, 122, 155, and/or 168, associated with *in vitro* low level resistance to simeprevir when occurring alone, reduced simeprevir activity by more than 50-fold when present in combination.

Resistance in clinical studies
In a pooled analysis of patients treated with 150 mg simeprevir in combination with peginterferon alfa and ribavirin who did not achieve SVR in the controlled phase 2 and phase 3 clinical studies (studies C205, C206, C208, C216, HPC3007), emerging amino acid substitutions at NS3 positions 80, 122, 155 and/or 168 were observed in 180 out of 197 (91%) patients. Substitutions D168V and R155K alone or in combinations with other mutations at these positions emerged most frequently (table 10).

Most of these emerging substitutions have been shown to reduce simeprevir anti-HCV activity in cell culture replicon assays.

HCV genotype 1 subtype-specific patterns of simeprevir treatment-emergent amino acid substitutions were observed in patients not achieving SVR. Patients with HCV genotype 1a predominantly had emerging R155K alone or in combination with amino acid substitutions at NS3 positions 80, 122 and/or 168, while patients with HCV genotype 1b had most often an emerging D168V substitution (table 10). In patients with HCV genotype 1a with a baseline Q80K amino acid substitution an emerging R155K substitution was observed most frequently at failure.

Table 10: Treatment-emergent amino-acid substitutions in pooled phase 2 and phase 3 studies: patients who did not achieve SVR with 150 mg simeprevir in combination with peginterferon alfa and ribavirin

Emerging amino-acid substitutions in NS3	**All HCV genotypes N = 197 % (n)**	**Genotype 1a[1] N = 116 % (n)**	**Genotype 1b N = 81 % (n)**
Any substitution at NS3 position 43, 80, 122, 155, 156, or 168[2]	91.4% (180)	94.8% (110)	86.4% (70)
D168E	15.7% (31)	14.7% (17)	17.3% (14)
D168V	31.0% (61)	10.3% (12)	60.5% (49)
Q80R[3]	7.6% (15)	4.3% (5)	12.3% (10)
R155K	45.2% (89)	76.7% (89)	0% (0)
Q80X+D168X[4]	8.1% (16)	4.3% (5)	13.6% (11)
R155X+ D168X[4]	9.1% (18)	12.9% (15)	3.7% (3)
Q80K[3], S122A/G/I/T[3], S122R, R155Q[3], D168A, D168F[3], D168H, D168T, I170T[5]	Less than 10%	Less than 10%	Less than 10%

1 May include few patients with HCV non-genotype 1a/1b.

2 Alone or in combination with other substitutions (includes mixtures).

3 Substitutions only observed in combinations with other emerging substitutions at one or more of the NS3 positions 80, 122, 155 and/or 168.

4 Patients with these combinations are also included in other rows describing the individual substitutions. X represents multiple amino acids. Other double or triple mutations were observed with lower frequencies.

5 Two patients had emerging single substitution I170T.

Note, substitutions at NS3 position 43 and 156 associated with reduced simeprevir activity *in vitro* were not observed at time of failure.

In study HPC3011 in HCV genotype 4 infected patients, 28 of 32 (88%) patients who did not achieve SVR had emerging amino acid substitutions at NS3 positions 80, 122, 155, 156 and/or 168 (mainly substitutions at position 168; 24 out of 32 [75%] patients), similar to the emerging amino acid substitutions observed in genotype 1 infected patients.

The majority of HCV genotype 1 infected patients treated with simeprevir in combination with sofosbuvir (with or without ribavirin) for 12 or 24 weeks who did not achieve SVR due to virologic reasons and with sequencing data available had emerging NS3 amino acid substitutions at position 168 and/or emerging R155K: 5 out of 6 patients in study HPC2002, 1 out of 3 patients in study HPC3017 and 11 out of 13 patients in study HPC3018. The emerging NS3 amino acid substitutions were similar to those observed in patients who did not achieve SVR following treatment with simeprevir in combination with peginterferon alfa and ribavirin. No emerging NS5B amino acid substitutions associated with sofosbuvir resistance were observed in patients who did not achieve SVR following treatment of simeprevir in combination with sofosbuvir (with or without ribavirin) for 12 or 24 weeks.

Persistence of resistance–associated substitutions

The persistence of simeprevir-resistant NS3 amino acid substitutions was assessed following treatment failure.

In the pooled analysis of patients receiving 150 mg simeprevir in combination with peginterferon alfa and ribavirin in the controlled phase 2 and phase 3 studies, treatment-emergent simeprevir-resistance variants were no longer detectable in 90 out of 180 patients (50%) at the end of the studies after a median follow-up of 28 weeks (range 0-70 weeks). In 32 out of 48 patients (67%) with emerging single D168V and in 34 out of 66 (52%) patients with emerging single R155K, the respective emerging variants were no longer detected at end of the studies.

Data from a 3-year follow-up study in patients who did not achieve SVR with simeprevir in combination with peginterferon alfa and ribavirin in a previous phase 2 or phase 3 study showed that in 86% (37/43) of these patients the emerging mutations at time of failure in the previous study were no longer detected after a median follow-up of 180 weeks (range 47-230 weeks) (study HPC3002).

The long-term clinical impact of the emergence or persistence of simeprevir-resistance-associated substitutions is unknown.

Effect of baseline HCV polymorphisms on treatment response
Analyses were conducted to explore the association between naturally-occurring baseline NS3/4A amino acid substitutions (polymorphisms) and treatment outcome.

Baseline polymorphisms at NS3 positions 43, 80, 122, 155, 156, and/or 168, associated with reduced simeprevir activity *in vitro* were generally uncommon (1.3%) in patients with HCV genotype 1 infection (n = 2,007; pooled phase 2 and phase 3 studies with simeprevir in combination with peginterferon alfa and ribavirin), with exception of the substitution Q80K in HCV genotype 1a patients which was seen in 30% of patients with HCV genotype 1a and in 0.5% of patients with HCV genotype 1b. In Europe, the prevalence was lower, 19% (73/377) in patients with HCV genotype 1a and 0.3% (3/877) in genotype 1b.

The Q80K polymorphism was not observed in patients with genotype 4 infection.

The presence of Q80K at baseline was associated with lower SVR rates in HCV genotype 1a patients treated with simeprevir in combination with peginterferon alfa and ribavirin (tables 19, 21, 22).

Cross-resistance
Some of the treatment-emergent NS3 amino acid substitutions detected in simeprevir-treated patients who did not achieve SVR in clinical studies (e.g., R155K) have been shown to reduce anti-HCV activity of telaprevir, boceprevir, and other NS3/4A PIs. The impact of prior exposure to simeprevir in patients not achieving SVR on the efficacy of subsequent HCV NS3/4A PI-based treatment regimens has not been established. There are no clinical data on the efficacy of simeprevir in patients with a history of exposure to the NS3/4A PIs telaprevir or boceprevir.

Cross-resistance is not expected between direct-acting antiviral agents with different mechanisms of action. Simeprevir-resistant variants studied remained susceptible to representative HCV nucleoside and non-nucleoside polymerase inhibitors, and NS5A inhibitors. Variants carrying amino-acid substitutions conferring reduced susceptibility to NS5A inhibitors (L31F/V, Y93C/H), nucleoside polymerase inhibitors (S282T) and non-nucleoside polymerase inhibitors (C316N, M414I/L, P495A) remained susceptible to simeprevir *in vitro*.

Clinical efficacy and safety
Sustained virologic response (SVR) was the primary endpoint in all studies and was defined as HCV RNA less than the lower limit of quantification (LLOQ) detectable or undetectable 12 weeks (SVR12) or 24 weeks (SVR24) after the planned end of treatment (studies C206, C208, C212, C216, HPC2002, HPC3007 and HPC3011) or after the actual end of treatment (studies HPC2014, HPC3017, HPC3018 and HPC3021) (LLOQ of 25 IU/ml and limit of detection of 15 IU/ml, except in studies HPC2014 and HPC3021 where LLOQ and limit of detection were 15 IU/ml).

Patients had compensated liver disease (including cirrhosis), HCV RNA of at least 10,000 IU/ml, and liver histopathology consistent with CHC (if available).

Simeprevir in combination with sofosbuvir

The efficacy of simeprevir (150 mg once daily) as part of an interferon-free regimen (sofosbuvir, 400 mg once daily) was evaluated in patients with HCV genotype 1 or 4 infection, who were treatment-naïve or treatment-experienced patients (following prior interferon-based therapy) (table 11).

Table 11: Studies conducted with simeprevir + sofosbuvir: population and summary of study design

Study[1]	**Population**	**Number of patients enrolled**	**Summary of study design**
HPC3017 (OPTIMIST-1; Phase 3)	Genotype 1, treatment-naïve or treatment-experienced[2], without cirrhosis	310	8 or 12 weeks SMV + sofosbuvir
HPC3018 (OPTIMIST-2; Phase 3)	Genotype 1, treatment-naïve or treatment-experienced[2], with compensated cirrhosis	103	12 weeks SMV + sofosbuvir
HPC2002 (COSMOS; Phase 2)	Genotype 1, treatment-naïve or null responders[3], with compensated cirrhosis or without cirrhosis	167	12 or 24 weeks SMV + sofosbuvir, with or without ribavirin[4]
HPC2014 (OSIRIS; Phase 2)	Genotype 4, treatment-naïve or treatment-experienced[2], with compensated cirrhosis or without cirrhosis	63	patients without cirrhosis: 8 or 12 weeks SMV + sofosbuvir; patients with cirrhosis: 12 weeks SMV + sofosbuvir
HPC3021 (PLUTO; Phase 3)	Genotype 4, treatment-naïve or treatment-experienced[2], with compensated cirrhosis or without cirrhosis	40	12 weeks SMV + sofosbuvir

SMV = simeprevir.

1 Open-label, randomised, except for studies HPC3018 and HPC3021 which were single arm, and study HPC2014 which was partly randomised.

2 Includes relapsers, partial and null reponders to prior treatment with interferon (pegylated or non-pegylated), with or without ribavirin.

3 To prior treatment with peginterferon alfa and ribavirin.

4 Body-weight based twice daily ribavirin dosing, according to the Summary of Product Characteristics of ribavirin.

Efficacy in patients with HCV genotype 1

OPTIMIST-1 and OPTIMIST-2

In studies HPC3017 (OPTIMIST-1) and HPC3018 (OPTIMIST-2), patients received simeprevir + sofosbuvir for 8 weeks (HPC3017 only) or 12 weeks (HPC3017 and HPC3018) (see table 11). In study HPC3017, patients without cirrhosis were enrolled; in study HPC3018, patients with cirrhosis were enrolled (table 12).

Table 12: Demographics and baseline characteristics (studies HPC3017 and HPC3018)

	HPC3017 N = 310	**HPC3018 N = 103**
Age (years)		
median (range)	56 (19-70)	58 (29-69)
% above 65 yrs	6%	6%
Male gender	55%	81%
Race		
White	80%	81%
Black/African American	18%	19%
Hispanic	16%	16%
BMI $\geq$ 30 kg/m^2	34%	40%

Median baseline HCV RNA levels (log_{10} IU/ml)	6.8	6.8
Presence of cirrhosis		
no cirrhosis	100%	0%
with cirrhosis	0%	100%
Prior treatment history		
treatment-naïve	70%	49%
treatment-experienced[1]	30%	51%
IL28B genotype		
CC	27%	28%
non-CC	73%	72%
HCV geno/subtype and presence of baseline Q80K polymorphism in HCV genotype 1a		
HCV genotype 1a	75%	70%
with Q80K	41%	47%
HCV genotype 1b	25%	30%

[1] Includes relapsers, partial and null reponders to prior treatment with interferon (pegylated or non-pegylated), with or without ribavirin, and interferon-intolerant patients.

The overall SVR12 rate for patients without cirrhosis receiving 8 weeks of simeprevir + sofosbuvir was 83% (128/155); all patients not achieving SVR12 had viral relapse (17%; 27/155). The response rates for patients with or without cirrhosis receiving 12 weeks of simeprevir + sofosbuvir are shown in table 13.

Table 13: Treatment outcome in HCV genotype 1 infected patients receiving 12 weeks simeprevir + sofosbuvir (studies HPC3017 and HPC3018)

Treatment outcome	**Patients without cirrhosis N = 155 % (n/N)**	**Patients with cirrhosis N = 103 % (n/N)**
SVR12	97% (150/155)[1]	83% (86/103)[1]
Outcome for patients without SVR12		
On-treatment failure[2]	0% (0/155)	3% (3/103)
Viral relapse[3]	3% (4/154)	13% (13/99)
SVR12 rates for selected subgroups		
Prior treatment history		
treatment-naïve	97% (112/115)	88% (44/50)
treatment-experienced[4]	95% (38/40)	79% (42/53)
HCV geno/subtype and presence of baseline Q80K polymorphism in HCV genotype 1a		
Genotype 1a	97% (112/116)	83% (60/72)
with Q80K	96% (44/46)	74% (25/34)
without Q80K	97% (68/70)	92% (35/38)
Genotype 1b	97% (38/39)	84% (26/31)

[1] Superior versus historical control rate (historical SVR rates of approved combination treatments of direct acting antivirals with peginterferon alfa and ribavirin).

[2] Out of the 3 patients with on-treatment failure, 2 patients experienced viral breakthrough and one patient discontinued treatment early due to an adverse event.

[3] Viral relapse rates are calculated with a denominator of patients with undetectable (or unconfirmed detectable) HCV RNA at EOT.

[4] Includes relapsers, partial and null reponders to prior treatment with interferon (pegylated or non-pegylated), with or without ribavirin.

COSMOS

In study HPC2002 (COSMOS), prior null responders with METAVIR fibrosis score F0-F2, or treatment-naïve and prior null responder patients with METAVIR fibrosis score F3-F4 and compensated liver disease received simeprevir + sofosbuvir, with or without ribavirin, for 12 or 24 weeks (see table 11). The 167 enrolled patients had a median age of 57 years (range 27 to 70 years; with 5% above 65 years); 64% were male; 81% were White, 19% Black or African American, and 21% Hispanic; 37% had a BMI ≥ 30 kg/m^2; the median baseline HCV RNA level was 6.7 log_{10} IU/ml;

75% had no cirrhosis (METAVIR fibrosis score F0-3) and 25% had cirrhosis (METAVIR fibrosis score F4); 78% had HCV genotype 1a of which 45% carried Q80K at baseline, and 22% had HCV genotype 1b; 86% had non-CC *IL28B* alleles (CT or TT); 76% were prior null responders to peginterferon alfa and ribavirin, and 24% were treatment-naïve.

Table 14 shows the response rates for patients without cirrhosis (METAVIR scores F0-3) receiving 12 weeks of simeprevir +sofosbuvir with or without ribavirin; extending treatment to 24 weeks did not increase response rates in comparison with 12 weeks treatment. Ribavirin use and prior treatment status (treatment-naïve and prior null responders) did not impact treatment outcome. The overall SVR12 rate was similar in patients receiving simeprevir + sofosbuvir with or without ribavirin. The response rates for patients with cirrhosis (METAVIR score F4) receiving 12 or 24 weeks of simeprevir + sofosbuvir are shown in table 15.

Table 14: Treatment outcome in HCV genotype 1 infected patients without cirrhosis receiving 12 weeks simeprevir + sofosbuvir, with or without ribavirin (study HPC2002)

Treatment outcome	**simeprevir + sofosbuvir N = 21 % (n/N)**	**simeprevir + sofosbuvir + ribavirin N = 43 % (n/N)**
SVR12	95% (20/21)	95% (41/43)
Outcome for patients without SVR12		
On-treatment failure	0% (0/21)	0% (0/43)
Viral relapse[1]	5% (1/21)	5%(2/43)

[1] Viral relapse rates are calculated with a denominator of patients with undetectable HCV RNA at EOT and with at least one follow-up HCV RNA assessment.

Table 15: Treatment outcome in HCV genotype 1 infected patients with cirrhosis receiving 12 or 24 weeks simeprevir + sofosbuvir, with or without ribavirin (study HPC2002)

Treatment outcome	**12 weeks**		**24 weeks**	
	simeprevir + sofosbuvir N = 7 % (n/N)	**simeprevir + sofosbuvir + ribavirin N = 11 % (n/N)**	**simeprevir + sofosbuvir N = 10 % (n/N)**	**simeprevir + sofosbuvir + ribavirin N = 13 % (n/N)**
SVR12	86% (6/7)	91% (10/11)	100% (10/10)	92% (12/13)
Outcome for patients without SVR12				
On-treatment failure[1]	0% (0/7)	0% (0/11)	0% (0/10)	8% (1/13)
Viral relapse[2]	14% (1/7)	9% (1/11)	0% (0/10)	0% (0/12)

[1] The one patient with on-treatment failure discontinued treatment early due to an adverse event.

[2] Viral relapse rates are calculated with a denominator of patients with undetectable HCV RNA at EOT and with at least one follow-up HCV RNA assessment.

Efficacy in adults with HCV genotype 4

In study HPC2014 (OSIRIS), patients received simeprevir + sofosbuvir for 8 weeks (patients without cirrhosis) or 12 weeks (patients with or without cirrhosis) (see table 11). The 63 enrolled patients had a median age of 51 years (range 24 to 68 years; with 2% above 65 years); 54% were male; 43% had a BMI $\geq$ 30 kg/m^2; the median baseline HCV RNA level was 6.01 $\log_{10}$ IU/ml; 37% had cirrhosis; 30% had HCV genotype 4a, and 56% HCV genotype 4c or 4d; 79% had non-CC *IL28B* alleles (CT or TT); 52% were treatment-naïve, and 48% were treatment-experienced.

In study HPC3021 (PLUTO), patients received simeprevir + sofosbuvir for 12 weeks (see table 11). The 40 enrolled patients had a median age of 51 years (range 29 to 69 years; with 5% above 65 years); 73% were male; 18% had a BMI $\geq$ 30 kg/m^2; the median baseline HCV RNA level was 6.35 $\log_{10}$ IU/ml; 18% had cirrhosis; 25% had HCV genotype 4a, and 73% HCV genotype 4d; 85%

had non-CC *IL28B* alleles (CT or TT); 33% were treatment-naïve, and 68% were treatment-experienced.

The overall SVR12 rate for patients without cirrhosis receiving 8 weeks of simeprevir + sofosbuvir was 75% (15/20); all patients not achieving SVR12 had viral relapse (25%; 5/20). All patients with or without cirrhosis receiving 12 weeks of simeprevir + sofosbuvir achieved SVR12 (table 16).

Table 16: Treatment outcome in HCV genotype 4 infected patients receiving 12 weeks simeprevir + sofosbuvir (studies HPC2014 and HPC3021)

Treatment outcome	Study HPC2014 N = 43 % (n/N)	Study HPC3021 N = 40 % (n/N)
SVR12	100% (43/43)	100% (40/40)
without cirrhosis	100% (20/20)	100% (33/33)
with cirrhosis	100% (23/23)	100% (7/7)

Simeprevir in combination with peginterferon alfa and ribavirin

The efficacy of simeprevir in combination with peginterferon alfa and ribavirin was evaluated in patients with HCV genotype 1 or 4 infection, with or without HIV-1 co-infection, who were treatment-naïve or treatment-experienced (following prior interferon-based therapy) (tables 17 and 18).

Table 17: Studies conducted with simeprevir + peginterferon alfa + ribavirin: population and summary of study design

Study[1]	Population	Number of patients enrolled	Summary of study design
C208 - C216 (QUEST-1 and QUEST-2; Phase 3)	Genotype 1, treatment-naïve patients, with compensated cirrhosis or without cirrhosis	785	12 weeks SMV + peg-IFN-alfa + RBV, followed by 12 or 36 weeks peg-IFN-alfa + RBV[3]; control group: 48 weeks placebo + peg-IFN-alfa + RBV
HPC3007 (PROMISE; Phase 3)	Genotype 1, prior relapsers[2], with compensated cirrhosis or without cirrhosis	393	
C206 (ASPIRE; Phase 2)	Genotype 1, treatment-experienced[4] patients, with compensated cirrhosis or without cirrhosis	462	12, 24 or 48 weeks SMV in combination with 48 weeks peg-IFN-alfa + RBV; control group: 48 weeks placebo + peg-IFN-alfa + RBV
C212 (Phase 3)	Genotype 1, treatment-naïve or treatment-experienced[4], HCV/HIV-1 co-infected patients, with compensated cirrhosis or without cirrhosis	106	treatment-naïve patients or prior relapsers without cirrhosis: 12 weeks SMV + peg-IFN-alfa + RBV, followed by 12 or 36 weeks peg-IFN-alfa + RBV[3]; prior non-responder patients (partial and null responders) without cirrhosis and all treatment-naïve and treatment-experienced patients with cirrhosis: 12 weeks SMV + peg-IFN-alfa + RBV, followed by 36 weeks peg-IFN-alfa + RBV
HPC3011 (RESTORE; Phase 3)	Genotype 4, treatment-naïve or treatment-experienced[4] patients, with compensated cirrhosis or without cirrhosis	107	treatment-naïve patients or prior relapsers: 12 weeks SMV + peg-IFN-alfa + RBV, followed by 12 or 36 weeks peg-IFN-alfa + RBV[3]; prior non-responder patients (partial

			and null responders): 12 weeks SMV + peg-IFN-alfa + RBV, followed by 36 weeks peg-IFN-alfa + RBV

peg-IFN-alfa = peginterferon alfa; RBV = ribavirin (body-weight based twice daily ribavirin dosing, according to the Summary of Product Characteristics of ribavirin); SMV = simeprevir.

[1] Double-blind, randomised, placebo-controlled, except for studies C212 and HPC3011 which were open-label, single arm.

[2] Relapsers after prior interferon-based therapy.

[3] Overall treatment duration with peg-IFN-alfa and RBV was response-guided. The planned total duration of HCV treatment was 24 weeks if the following on-treatment protocol-defined response-guided therapy criteria were met: HCV RNA < 25 IU/ml detectable or undetectable at week 4 AND undetectable HCV RNA at week 12. Treatment stopping rules for HCV therapy were used to ensure that patients with inadequate on-treatment virologic response discontinued treatment in a timely manner.

[4] Includes relapsers, partial and null responders to prior treatment with peginterferon and ribavirin.

Table 18: Studies conducted with simeprevir + peginterferon alfa + ribavirin: demographics and baseline characteristics

	Pooled C208 and C216 N = 785	**HPC3007 N = 393**	**C206 N = 462**	**C212[1] N = 106**	**HPC3011 N = 107**
Age (years)					
median (range)	47 (18-73)	52 (20-71)	50 (20-69)	48 (27-67)	49 (27-69)
% above 65 yrs	2%	3%	3%	2%	5%
Male gender	56%	66%	67%	85%	79%
Race					
White	91%	94%	93%	82%	72%
Black/African American	7%	3%	5%	14%	28%
Asian	1%	2%	2%	1%	-
Hispanic	17%	7%	-	6%	7%
BMI ≥ 30 kg/m^2	23%	26%	25%	12%	14%
Baseline HCV RNA levels > 800,000 IU/ml	78%	84%	86%	86%	60%
METAVIR fibrosis score					
F0-2	74%	69%	63%	67%	57%
F3	16%	15%	19%	19%	14%
F4	10%	15%	18%	13%	29%
IL28B genotype					
CC	29%	24%	18%	27%	8%
CT	56%	64%	65%	56%	58%
TT	15%	12%	18%	17%	35%
HCV geno/subtype and presence of baseline Q80K polymorphism in HCV genotype 1a					
HCV genotype 1a	48%	42%	41%	82%	-
with Q80K	34%	31%	27%	34%	-
HCV genotype 1b	51%	58%	58%	17%	-
HCV genotype 4a - 4d	-	-	-	-	42% - 24%
Prior treatment history					
treatment-naïve	100%	-	-	50%	33%
treatment-experienced[2]	-				
prior relapser		100%	40%	14%	21%
prior partial responder		-	35%	9%	9%
prior null responder		-	25%	26%	37%

[1] HCV/HIV-1 co-infected patients.

[2] Treatment-experienced to prior treatment with peginterferon and ribavirin.

Efficacy in treatment-naïve patients with HCV genotype 1 infection

In studies C208 (QUEST-1) and C216 (QUEST-2), treatment-naïve patients received simeprevir (150 mg once daily) + peginterferon alfa + ribavirin for 12 weeks, followed by 12 or 36 additional

weeks of peginterferon alfa + ribavirin (see tables 17 and 18). In study C208, all patients received peginterferon alfa-2a; in study C216, 69% of the patients received peginterferon alfa-2a and 31% received peginterferon alfa-2b.

Table 19 shows the response rates in HCV genotype 1 infected treatment-naïve patients.

Table 19: Treatment outcome in treatment-naïve HCV genotype 1 infected patients (pooled data studies C208 and C216)

Treatment Outcome	**simeprevir + peginterferon + ribavirin N = 521 % (n/N)**	**placebo + peginterferon + ribavirin N = 264 % (n/N)**
Overall SVR12	80% (419/521)[1]	50% (132/264)
Outcome for patients without SVR12		
On-treatment failure	8% (42/521)	33% (87/264)
Viral relapse[2]	11% (51/470)	23% (39/172)
SVR12 rates for selected subgroups		
METAVIR fibrosis score		
F0-2	84% (317/378)	55% (106/192)
F3-4	68% (89/130)	36% (26/72)
F4	60% (29/48)	34% (11/32)
IL28B genotype		
CC	95% (144/152)	80% (63/79)
CT	78% (228/292)	41% (61/147)
TT	61% (47/77)	21% (8/38)
HCV geno/subtype and presence of Q80K polymorphism in HCV genotype 1a		
Genotype 1a	75% (191/254)	47% (62/131)
with Q80K	58% (49/84)	52% (23/44)
without Q80K	84% (138/165)	43% (36/83)
Genotype 1b	85% (228/267)	53% (70/133)

[1] $p < 0.001$.

[2] Viral relapse rates are calculated with a denominator of patients with undetectable HCV RNA at actual EOT. Includes 4 simeprevir-treated patients who experienced relapse after SVR12.

Eighty-eight percent (459/521) of the simeprevir-treated patients were eligible for a total treatment duration of 24 weeks; in these patients the SVR12 rate was 88%. Seventy-nine percent (404/509) of simeprevir-treated patients had undetectable HCV RNA at week 4; in these patients the SVR12 rate was 90%. The proportion of simeprevir-treated patients with HCV RNA < 25 IU/ml detectable at week 4 was 14% (70/509); 67% achieved SVR12.

In the pooled analysis of studies C208 and C216, 69% (58/84) of the simeprevir-treated HCV genotype 1a infected patients with Q80K polymorphism at baseline were eligible for a total treatment duration of 24 weeks; in these patients the SVR12 rate was 78%. Sixty-five percent (53/81) of the simeprevir-treated HCV genotype 1a infected patients with Q80K polymorphism had undetectable HCV RNA at week 4; in these patients the SVR12 rate was 79%.

SVR12 rates were statistically significantly higher for patients receiving simeprevir with peginterferon alfa-2a or peginterferon alfa-2b and ribavirin (88% and 78%, respectively) compared to patients receiving placebo with peginterferon alfa-2a or peginterferon alfa-2b and ribavirin (62% and 42%, respectively) (study C216).

Efficacy in treatment-experienced patients with HCV genotype 1 infection
In study HPC3007 (PROMISE), patients who relapsed after prior IFN-based therapy received simeprevir (150 mg once daily) + peginterferon alfa-2a + ribavirin for 12 weeks, followed by 12 or 36 additional weeks of peginterferon alfa-2a + ribavirin (see tables 17 and 18).

In study C206 (ASPIRE), patients who failed prior peg-IFN/RBV therapy received 12, 24 or 48 weeks simeprevir (100 mg or 150 mg once daily) in combination with 48 weeks of peginterferon alfa-2a + ribavirin (see tables 17 and 18).

Table 20 shows the response rates in treatment-experienced patients with HCV genotype 1 infection. Table 21 shows the SVR rates for selected subgroups for study HPC3007.

Table 20: Treatment outcome in treatment-experienced[1] HCV genotype 1 infected patients (studies HPC3007 and C206)

Treatment Outcome	Study HPC3007		Study C206	
	simeprevir % (n/N)	placebo % (n/N)	150 mg simeprevir 12 weeks % (n/N)	placebo % (n/N)
SVR[2]				
Prior relapsers	79% (206/260)[3]	37% (49/133)	77% (20/26)	37% (10/27)
Prior partial responders	-	-	65% (15/23)	9% (2/23)
Prior null responders	-	-	53% (9/17)	19% (3/16)
Outcome for patients without SVR				
On-treatment failure				
Prior relapsers	3% (8/260)	27% (36/133)	8% (2/26)	22% (6/27)
Prior partial responders	-	-	22% (5/23)	78% (18/23)
Prior null responders	-	-	35% (6/17)	75% (12/16)
Viral relapse[4]				
Prior relapsers	19% (46/249)	48% (45/93)	13% (3/23)	47% (9/19)
Prior partial responders	-	-	6% (1/17)	50% (2/4)
Prior null responders	-	-	18% (2/11)	25% (1/4)

1 Treatment-experienced to prior treatment with peginterferon and ribavirin.

2 SVR: SVR12 for study HPC3007 and SVR24 for study C206.

3 $p < 0.001$.

4 Viral relapse rates are calculated with a denominator of patients with undetectable HCV RNA at EOT and with at least one follow-up HCV RNA assessment. Study HPC3007: includes 5 simeprevir-treated patients who experienced relapse after SVR12.

Table 21: SVR12 rates for selected subgroups (study HPC3007)

Subgroup	simeprevir + peginterferon + ribavirin % (n/N)	placebo + peginterferon + ribavirin % (n/N)
METAVIR fibrosis score		
F0-2	82% (137/167)	41% (40/98)
F3-4	73% (61/83)	24% (8/34)
F4	74% (29/39)	26% (5/19)
IL28B genotype		
CC	89% (55/62)	53% (18/34)
CT	78% (131/167)	34% (28/83)
TT	65% (20/31)	19% (3/16)
HCV geno/subtype and presence of Q80K polymorphism in HCV genotype 1a		
Genotype 1a	70% (78/111)	28% (15/54)
with Q80K	47% (14/30)	30% (6/20)
without Q80K	79% (62/79)	26% (9/34)
Genotype 1b	86% (128/149)	43% (34/79)

In study HPC3007, 93% (241/260) of the simeprevir-treated patients were eligible for a total treatment duration of 24 weeks; in these patients the SVR12 rate was 83%. Seventy-seven percent (200/259) of simeprevir-treated patients had undetectable HCV RNA at week 4; in these patients the SVR12 rate

was 87%. The proportion of simeprevir-treated patients with HCV RNA < 25 IU/ml detectable at week 4 was 18% (47/259); 60% achieved SVR12.

In study HPC3007, 80% (24/30) of the simeprevir-treated HCV genotype 1a infected patients with Q80K polymorphism at baseline were eligible for a total treatment duration of 24 weeks; in these patients the SVR12 rate was 58%. Forty-five percent (13/29) of the simeprevir-treated HCV genotype 1a infected patients with Q80K polymorphism had undetectable HCV RNA at week 4; in these patients the SVR12 rate was 77%.

Efficacy in patients with HCV genotype 1 and HIV-1 co-infection
In study C212, patients with HIV-1 co-infection who were treatment-naïve or failed prior peg-IFN/RBV therapy received simeprevir (150 mg once daily) + peginterferon alfa-2a + ribavirin for 12 weeks, followed by 12 or 36 additional weeks of peginterferon alfa-2a + ribavirin (see tables 17 and 18). Eighty-eight percent (n = 93) of the patients were on HIV therapy, most commonly with 2 NRTIs + raltegravir. The median baseline CD4+ cell count in patients on highly active antiretroviral therapy (HAART) was 561 x 10^6 cells/ml (range: 275-1,407 x 10^6 cells/ml).

Table 22 shows the response rates in HCV genotype 1 infected patients with HIV-1 co-infection.

Table 22: Treatment outcome in HCV genotype 1 infected patients with HIV-1 co-infection (study C212)

Treatment outcome	**Treatment-naïve patients N = 53 % (n/N)**	**Prior relapsers N = 15 % (n/N)**	**Prior partial responders N = 10 % (n/N)**	**Prior null responders N = 28 % (n/N)**
SVR12	79% (42/53)[1]	87% (13/15)	70% (7/10)	57% (16/28)[1]
Outcome for patients without SVR12				
On-treatment failure	9% (5/53)	0% (0/15)	20% (2/10)	39% (11/28)
Viral relapse[2]	10% (5/48)	13% (2/15)	0% (0/7)	12% (2/17)
SVR12 rates for selected subgroups				
METAVIR fibrosis score				
F0-2	89% (24/27)	78% (7/9)	50% (1/2)	57% (4/7)
F3-4	57% (4/7)	100% (2/2)	67% (2/3)	60% (6/10)
F4	100% (2/2)	100% (1/1)	100% (1/1)	60% (3/5)
IL28B genotype				
CC	100% (15/15)	100% (7/7)	100% (1/1)	80% (4/5)
CT	70% (19/27)	100% (6/6)	71% (5/7)	53% (10/19)
TT	80% (8/10)	0% (0/2)	50% (1/2)	50% (2/4)
HCV geno/subtype and presence of Q80K polymorphism in HCV genotype 1a				
Genotype 1a	77% (33/43)	83% (10/12)	67% (6/9)	54% (13/24)
with Q80K	86% (12/14)	33% (1/3)	100% (1/1)	50% (6/12)
without Q80K	72% (21/29)	100% (9/9)	63% (5/8)	58% (7/12)
Genotype 1b	90% (9/10)	100% (3/3)	100% (1/1)	75% (3/4)

[1] $p < 0.001$ compared to historical control of peginterferon alfa and ribavirin.

[2] Viral relapse rates are calculated with a denominator of patients with undetectable HCV RNA at actual EOT and with at least one follow-up HCV RNA assessment. Includes one prior null responder who experienced relapse after SVR12, who was considered to have an HCV re-infection (based on phylogenetic analyses).

Eighty-nine percent (54/61) of the simeprevir-treated treatment-naïve patients and prior relapsers without cirrhosis were eligible for 24 weeks of treatment; in these patients the SVR12 rate was 87%. Seventy-one percent (37/52), 93% (14/15), 80% (8/10) and 36% (10/28) of simeprevir-treated treatment-naïve patients, prior relapsers, prior partial responders and prior null responders had undetectable HCV RNA at week 4. In these patients the SVR12 rates were 89%, 93%, 75% and 90%, respectively.

Two patients had HIV virologic failure defined as confirmed HIV-1 RNA ≥ 200 copies/ml after previous < 50 copies/ml; these failures occurred 36 and 48 weeks after end of simeprevir treatment.

Efficacy in patients with HCV genotype 4 infection
In study HPC3011 (RESTORE), patients who were treatment-naïve or failed prior peg-IFN/RBV therapy received simeprevir (150 mg once daily) + peginterferon alfa-2a + ribavirin for 12 weeks, followed by 12 or 36 additional weeks of peginterferon alfa-2a + ribavirin (see tables 17 and 18).

Table 23 shows the response rates in HCV genotype 4 infected patients.

Table 23: Treatment outcome in HCV genotype 4 infected patients (study HPC3011)

Treatment outcome	**Treatment-naïve patients N = 35 % (n/N)**	**Prior relapsers N = 22 % (n/N)**	**Prior partial responders N = 10 % (n/N)**	**Prior null responders N = 40 % (n/N)**
SVR12	83% (29/35)	86% (19/22)	60% (6/10)	40% (16/40)
Outcome for patients without SVR12				
On-treatment failure	9% (3/35)	9% (2/22)	20% (2/10)	45% (18/40)
Viral relapse[1]	9% (3/35)	5% (1/22)	20% (2/10)	15% (6/40)
SVR12 rates for selected subgroups				
METAVIR fibrosis score				
F0-2	85% (22/26)	91% (10/11)	100% (5/5)	47% (8/17)
F3-4	78% (7/9)	82% (9/11)	20% (1/5)	35% (7/20)
F4	50% (1/2)	78% (7/9)	20% (1/5)	36% (5/14)
IL28B genotype				
CC	100% (7/7)	100% (1/1)	-	-
CT	82% (14/17)	82% (14/17)	60% (3/5)	41% (9/22)
TT	80% (8/10)	100% (4/4)	60% (3/5)	39% (7/18)

[1] Viral relapse rates are calculated with a denominator of patients with undetectable (or unconfirmed detectable) HCV RNA at actual EOT.

Eighty-nine percent (51/57) of the simeprevir-treated treatment-naïve patients and prior relapsers were eligible for a total treatment duration of 24 weeks; in these patients the SVR12 rate was 94%. Eighty percent (28/35), 90% (18/20), 40% (4/10) and 49% (19/39) of simeprevir-treated treatment-naïve patients, prior relapsers, prior partial responders and prior null responders, respectively, had undetectable HCV RNA at week 4. In these patients the SVR12 rates were 96%, 94%, 100% and 68%, respectively.

Viral breakthrough rates were 24% (11/45), 20% (5/25) and 11% (4/36) in patients with genotype 4a, 4d and 4/other, respectively. The clinical relevance of this difference in viral breakthrough rates is unknown.

Clinical study examining QT interval
The effect of simeprevir 150 mg once daily and 350 mg once daily for 7 days on the QT interval was evaluated in a randomised, double-blind, placebo- and positive-controlled (moxifloxacin 400 mg once daily), 4-way cross-over study in 60 healthy subjects. No meaningful changes in QTc interval were observed with either the recommended dose of 150 mg once daily or the supratherapeutic dose of 350 mg once daily.

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

5.2 Pharmacokinetic properties

The pharmacokinetic properties of simeprevir have been evaluated in healthy adult subjects and in adult HCV infected patients. Plasma exposure of simeprevir (AUC) in HCV infected patients was about 2- to 3-fold higher compared to that observed in healthy subjects. Plasma C_{max} and AUC of simeprevir were similar during co-administration of simeprevir with peginterferon alfa and ribavirin compared with administration of simeprevir alone.

Absorption
The mean absolute bioavailability of simeprevir following a single oral 150 mg dose of simeprevir in fed conditions is 62%. Maximum plasma concentrations (C_{max}) are typically achieved between 4 to 6 hours post dose.

In vitro experiments with human Caco-2 cells indicated that simeprevir is a substrate of P-gp.

Effect of food on absorption
Compared to intake without food, administration of simeprevir with food to healthy subjects increased the AUC by 61% after a high-fat, high-caloric (928 kcal) and 69% after a normal caloric (533 kcal) breakfast, and delayed the absorption by 1 hour and 1.5 hours, respectively.

Simeprevir must be taken with food (see section 4.2). The type of food does not affect exposure to simeprevir.

Distribution
Simeprevir is extensively bound to plasma proteins (> 99.9%), primarily to albumin and, to a lesser extent, alfa-1-acid glycoprotein. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment.

Biotransformation
Simeprevir is metabolised in the liver. *In vitro* experiments with human liver microsomes indicated that simeprevir primarily undergoes oxidative metabolism by the hepatic CYP3A4 system. Involvement of CYP2C8 and CYP2C19 cannot be excluded. Moderate or strong inhibitors of CYP3A4 significantly increase the plasma exposure of simeprevir, and moderate or strong inducers of CYP3A4 significantly reduce plasma exposure of simeprevir. Simeprevir does not induce CYP1A2 or CYP3A4 *in vitro*. Simeprevir is not a clinically relevant inhibitor of cathepsin A enzyme activity.

In vitro experiments show that simeprevir is a substrate for the drug transporters P-glycoprotein (P-gp), MRP2, OATP1B1/3 and OATP2B1. Simeprevir inhibits the uptake transporters OATP1B1/3 and NTCP and the efflux transporters P-gp/MDR1, MRP2, BCRP and BSEP. OATP1B1/3 and MRP2 are involved in the transport of bilirubin into and out of hepatocytes. Simeprevir does not inhibit OCT2 *in vitro*.

Following a single oral administration of 200 mg ^{14}C-simeprevir to healthy subjects, the majority of the radioactivity in plasma (up to 98%) was accounted for by unchanged drug and a small part of the radioactivity in plasma was related to metabolites (none being major metabolites). Metabolites identified in faeces were formed via oxidation at the macrocyclic moiety or aromatic moiety or both and by O-demethylation followed by oxidation.

Elimination
Elimination of simeprevir occurs via biliary excretion. Renal clearance plays an insignificant role in its elimination. Following a single oral administration of 200 mg ^{14}C-simeprevir to healthy subjects, on average 91% of the total radioactivity was recovered in faeces. Less than 1% of the administered dose was recovered in urine. Unchanged simeprevir in faeces accounted for on average 31% of the administered dose.

The terminal elimination half-life of simeprevir was 10 to 13 hours in healthy subjects and 41 hours in HCV infected patients receiving 200 mg simeprevir.

Linearity/non-linearity
Plasma C_{max} and the area under the plasma concentration time curve (AUC) increased more than dose proportional after multiple doses between 75 mg and 200 mg once daily, with accumulation occurring following repeated dosing. Steady-state was reached after 7 days of once daily dosing.

Special populations
Elderly (above 65 years of age)
There is limited data on the use of simeprevir in patients older than 65 years. Age (18-73 years) had no clinically meaningful effect on the pharmacokinetics of simeprevir based on a population pharmacokinetic analysis (n = 21, age above 65 years) of HCV infected patients treated with simeprevir. No dose adjustment of simeprevir is required in elderly patients (see section 4.2).

Renal impairment
Renal elimination of simeprevir is negligible. Therefore, it is not expected that renal impairment will have a clinically relevant effect on the exposure to simeprevir.

Compared to healthy subjects with normal renal function (classified using the Modification of Diet in Renal Disease [MDRD] eGFR formula; eGFR ≥ 80 ml/min), the mean steady-state AUC of simeprevir was 1.62-fold higher (90% confidence interval: 0.73-3.6) in subjects with severe renal impairment (eGFR below 30 ml/min). As exposure may be increased in HCV infected patients with severe renal impairment, caution is recommended when prescribing simeprevir to these patients (see section 4.2).

As simeprevir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

Refer to the respective Summary of Product Characteristics of the medicinal products used in combination with simeprevir regarding their use in patients with renal impairment.

Hepatic impairment
Simeprevir is primarily metabolised by the liver.
Plasma exposure of simeprevir in HCV infected patients was about 2- to 3-fold higher compared to that observed in healthy subjects.

Compared to healthy subjects with normal hepatic function, the mean steady-state AUC of simeprevir was 2.4-fold higher in non-HCV infected subjects with moderate hepatic impairment (Child-Pugh B) and 5.2-fold higher in non-HCV infected subjects with severe hepatic impairment (Child-Pugh C).

No dose adjustment of simeprevir is necessary in patients with mild hepatic impairment. The safety and efficacy of simeprevir have not been established in HCV infected patients with moderate or severe hepatic impairment (Child-Pugh B or C). OLYSIO is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C) (see sections 4.2 and 4.4).

Refer to the respective Summary of Product Characteristics of the medicinal products used in combination with simeprevir regarding their use in patients with hepatic impairment.

Gender
No dose adjustment is necessary based on gender. Gender had no clinically relevant effect on the pharmacokinetics of simeprevir based on a population pharmacokinetic analysis of HCV infected patients treated with simeprevir in combination with peginterferon alfa and ribavirin.

Body weight
No dose adjustment is necessary based on body weight or body mass index. These characteristics have no clinically relevant effect on the pharmacokinetics of simeprevir based on a population pharmacokinetic analysis of HCV infected patients treated with simeprevir in combination with peginterferon alfa and ribavirin.

Race
Population pharmacokinetic estimates of exposure of simeprevir were comparable between Caucasian and Black/African American HCV infected patients treated with simeprevir in combination with peginterferon alfa and ribavirin.

In a phase 3 study conducted in China and South-Korea, the mean plasma exposure of simeprevir in Asian HCV infected patients was 2.1-fold higher compared to non-Asian HCV infected patients in a pooled phase 3 population from global studies.

No dose adjustment is necessary based on race.

Patients co-infected with HIV-1
Pharmacokinetic parameters of simeprevir were comparable between patients with HCV genotype 1 infection with or without HIV-1 co-infection.

Paediatric population
The pharmacokinetics of simeprevir in children aged below 18 years have not been investigated.

5.3 Preclinical safety data

In rodents, simeprevir elicited toxic effects in the liver, pancreas and gastrointestinal systems. Dosing of animals resulted in similar (dogs) or lower (rats) exposures than those observed in humans at the recommended dose of 150 mg once daily. In dogs, simeprevir was associated with a reversible multifocal hepatocellular necrosis with associated increases in ALT, AST, alkaline phosphatase and/or bilirubin. This effect was observed at higher systemic exposures (11-fold) than those in humans at the recommended dose of 150 mg once daily.

Simeprevir *in vitro* was very mildly irritating to the eyes. *In vitro*, simeprevir induced a phototoxic response on BALB/c 3T3 fibroblasts after UVA exposure, in the absence and presence of protein supplements. Simeprevir was not irritating to rabbit skin, and is not likely to cause skin sensitisation.

There were no adverse effects of simeprevir on vital functions (cardiac, respiratory and central nervous system) in animal studies.

Carcinogenicity and mutagenicity
Simeprevir was not genotoxic in a series of *in vitro* and *in vivo* tests. Carcinogenicity studies with simeprevir have not been conducted.

Reproductive toxicology
Studies carried out in rats did not reveal significant findings on fertility, embryo-fetal development or pre- and post-natal development at any of the tested doses (corresponding to a systemic exposure in rats similar or lower than that observed in humans at the recommended dose of 150 mg once daily). Supernumerary ribs and delayed ossification were reported in mice at 4-fold higher exposures than those observed in humans at the recommended dose of 150 mg once daily.

In pregnant rats, simeprevir concentrations in placenta, fetal liver and foetus were lower compared to those observed in blood. When administered to lactating rats, simeprevir was detected in plasma of suckling rats likely due to excretion of simeprevir via milk.

Environmental Risk Assessment (ERA)
Simeprevir is classified as a PBT (persistent, bioaccumulative and toxic) substance (see section 6.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Sodium lauryl sulfate
Magnesium stearate
Colloidal anhydrous silica
Croscarmellose sodium
Lactose monohydrate

Capsule shell
Gelatin
Titanium dioxide (E171)

Black printing ink
Shellac (E904)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Opaque polyvinylchloride/polyethylene/polyvinylidenechloride (PVC/PE/PVDC) aluminium push-through blister strips of 7 capsules.

Pack sizes of 7 or 28 capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment (see section 5.3). Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/924/001 (7 capsules)

EU/1/14/924/002 (28 capsules)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 May 2014

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER 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. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Janssen-Cilag SpA
Via C. Janssen
Borgo San Michele
04100 Latina
Italy

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.

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
In order to evaluate the recurrence of hepatocellular carcinoma associated with OLYSIO, 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

OLYSIO 150 mg hard capsules
simeprevir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains simeprevir sodium equivalent to 150 mg simeprevir.

3. LIST OF EXCIPIENTS

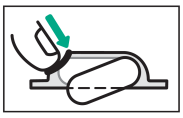
Contains lactose monohydrate

4. PHARMACEUTICAL FORM AND CONTENTS

7 hard capsules
28 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use



Press edge of pocket

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(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

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

Disposal: Read the package leaflet.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/924/001 (7 capsules)
EU/1/14/924/002 (28 capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

olysio 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

OLYSIO 150 mg capsules
simeprevir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon
Tue
Wed
Thu
Fri
Sat
Sun

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

OLYSIO 150 mg hard capsules
simeprevir

▼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 OLYSIO is and what it is used for

What OLYSIO is
- OLYSIO contains the active substance ‘simeprevir’. It acts against the virus that causes hepatitis C infection, called ‘hepatitis C virus’ (HCV).
- OLYSIO must not be used by itself. OLYSIO must always be used as part of a course of treatment with other medicines for treating chronic hepatitis C infection. It is therefore important that you also read the package leaflets that are provided with these other medicines before you start taking OLYSIO. If you have any further questions about any of these medicines, ask your doctor or pharmacist.

What OLYSIO is used for
OLYSIO is used with other medicines to treat chronic (long-term) hepatitis C infection in adults.

How OLYSIO works
OLYSIO helps to fight against hepatitis C infection by preventing HCV from multiplying. When used together with other medicines to treat chronic hepatitis C infection, OLYSIO helps to clear HCV from your body.

2. What you need to know before you take OLYSIO

Do not take OLYSIO if you are allergic to simeprevir or any of the other ingredients of this medicine (listed in section 6). Do not take OLYSIO if this applies to you. If you are not sure, talk to your doctor or pharmacist before taking OLYSIO.

Warnings and precautions
Talk to your doctor or pharmacist about all your medical conditions before taking OLYSIO in particular if:
- you have hepatitis C that is not ‘genotype 1’ or ‘genotype 4’;

- you have ever taken any medicines to treat hepatitis C;
- you have any other liver problems in addition to hepatitis C;
- you have a current or previous infection with the hepatitis B virus, since your doctor may want to monitor you more closely;
- you have had or are going to have an organ transplant.

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

When taking OLYSIO combination treatment, tell your doctor if you have the following symptoms as they may be a sign of worsening liver problems:
- notice yellowing of your skin or eyes
- your urine is darker than normal
- notice swelling of your stomach area.

This is particularly significant if these are accompanied by either of the following symptoms:
- feel sick (nauseous), are sick (vomit) or lose your appetite
- confusion.

OLYSIO combination treatment with sofosbuvir may result in slowing of the heart rate (pulse) along with other symptoms when taken with amiodarone, a medicine used to treat irregular heart beat.
Tell your doctor if any of the following applies:
- you currently take, or have taken in the last few months, the medicine amiodarone (your doctor may consider alternative treatments if you have taken this medicine)
- you take other medicines to treat irregular heart beat or high blood pressure.

Tell your doctor immediately if you are taking OLYSIO with sofosbuvir and any medicines for heart problems, and during treatment you experience:
- shortness of breath
- light-headedness
- palpitations
- fainting.

Sensitivity to sunlight
You may be more sensitive to sunlight (photosensitivity) when taking OLYSIO (see section 4 for information about side effects).
During your treatment with OLYSIO, use appropriate sun protection (such as a sun hat, sunglasses and sunscreen). Especially avoid intense or prolonged exposure to sunlight (including tanning devices).
If you develop a photosensitivity reaction during treatment, contact your doctor immediately.

Rash
You may experience a rash during treatment with OLYSIO. Rash may become severe.
If you develop a rash during treatment, contact your doctor immediately.

Blood tests
Your doctor will test your blood before you start your treatment and regularly during your treatment. These blood tests help your doctor to
- check if the treatment is working for you
- check your liver function.

Children and adolescents
OLYSIO must not be used in children and adolescents (under 18 years of age) because it has not been studied in this age group.

Other medicines and OLYSIO
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because OLYSIO and other medicines may interact with each other.

In particular tell your doctor or pharmacist if you take any of the following medicines:

- digoxin, disopyramide, flecainide, mexiletine, propafenone or quinidine (when taken by mouth) or amiodarone to treat irregular heart beat
- clarithromycin, erythromycin (when taken by mouth or given by injection) or telithromycin to treat bacterial infections
- warfarin and other similar medicines called vitamin K antagonists used to thin the blood. Your doctor may need to increase the frequency of your blood tests to check how well your blood can clot.
- carbamazepine, oxcarbazepine, phenobarbital or phenytoin to prevent seizures
- astemizole or terfenadine to treat allergies
- itraconazole, fluconazole, ketoconazole, posaconazole or voriconazole (when taken by mouth or given by injection) to treat fungal infections
- rifabutin, rifampicin or rifapentine to treat infections like tuberculosis
- amlodipine, bepridil, diltiazem, felodipine, nicardipine, nifedipine, nisoldipine or verapamil (when taken by mouth) to decrease blood pressure
- dexamethasone (when given by injection or taken by mouth) to treat asthma or inflammation and auto-immune diseases
- cisapride to treat stomach problems
- milk thistle (a herbal medicine) for liver problems
- St John's wort (*Hypericum perforatum*, a herbal medicine) for anxiety or depression
- ledipasvir to treat hepatitis C infection
- cobicistat to increase levels of some medicines used to treat HIV infection
- atazanavir, darunavir, delavirdine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir or tipranavir to treat HIV infection
- atorvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin or simvastatin to lower cholesterol levels
- ciclosporin, sirolimus or tacrolimus to lower immune response or prevent organ transplant failures
- sildenafil or tadalafil to treat 'pulmonary arterial hypertension'
- midazolam or triazolam (when taken by mouth) to help you sleep or for anxiety

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

In addition, tell your doctor if you take any medicines used to treat irregular heart beat or high blood pressure.

Pregnancy, contraception and breast-feeding

Pregnancy

If you are pregnant, think you might be pregnant or are planning to become pregnant, ask your doctor or pharmacist for advice before taking this medicine.
Pregnant women should not take OLYSIO unless specifically directed by the doctor.
When OLYSIO is used with ribavirin, please read the package leaflet for ribavirin for information regarding pregnancy. Ribavirin can affect your unborn baby.
- If you are a woman, you **must not become pregnant during treatment and for several months afterwards**.
- If you are a man, your female partner **must not become pregnant during your treatment and for several months afterwards.**

If pregnancy occurs during this period, you must contact your doctor straight away.

Contraception

Women must use an effective method of contraception during treatment with OLYSIO.
When OLYSIO is used with ribavirin, read the package leaflet for ribavirin for information regarding contraception requirements. You and your partner must use an effective method of contraception during treatment and for several months afterwards.

Breast-feeding
Talk to your doctor if you are breast-feeding before taking OLYSIO. This is important because it is not known whether simeprevir can pass into breast milk. The doctor will advise you to stop breast-feeding or to stop taking OLYSIO while breast-feeding.

Driving and using machines
Combination treatment of OLYSIO with other medicines used for treating your chronic hepatitis C infection may affect your ability to drive and use machines. Do not drive or use machines if you feel faint or have problems with your vision. Read the package leaflets for these other medicines for information regarding driving and using machines.

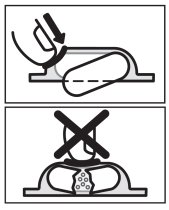
OLYSIO contains lactose
OLYSIO contains lactose (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.

3. How to take OLYSIO

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.
You must take OLYSIO as part of a course of treatment with other medicines for treating your chronic hepatitis C infection. A course of OLYSIO lasts for either 12 or 24 weeks but you may need to take the other medicines for longer, according to your doctor's instructions. Read the package leaflets for these medicines for their dosage and directions on 'how to take' them.

How to take
- The recommended dose of OLYSIO is one capsule (150 milligrams) once a day.
- The days of the week are printed on the blister strip - this will help you remember to take your capsule.
- Try to take OLYSIO at the same time each day.
- Always take OLYSIO with food. The type of food is not important.
- Take this medicine by mouth.
- Swallow the capsule whole.

How to remove capsule
Press either **edge** of the pocket to push the capsule through the foil, as shown.
Do not press the capsule from the center of the pocket. This can damage or break open the capsule.



If the capsule shell has been broken or opened, some medicine may be lost and you should take a new capsule. If the capsule shell is indented or bent - without being broken or opened - the capsule can still be used.

If you take more OLYSIO than you should
If you take more OLYSIO than you should, talk to your doctor or pharmacist immediately.

If you forget to take OLYSIO
- If it is more than 12 hours until your next dose, take the missed dose as soon as possible with food. Then continue taking OLYSIO at the usual scheduled time.
- If it is less than 12 hours until your next dose, skip the missed dose. Then take the next dose of OLYSIO at the usual scheduled time.
- Do not take a double dose to make up for a forgotten dose.

If you are not sure what to do, contact your doctor or pharmacist.

Do not stop taking OLYSIO
Do not stop taking OLYSIO unless your doctor tells you to. If you do, your medicine may not work properly.

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

4. Possible side effects

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

The following side effects may happen with **OLYSIO** when used **in combination with sofosbuvir**:
Common: may affect up to 1 in 10 people:
- itching of the skin
- skin rash*
- constipation
- being sensitive to sunlight (photosensitivity)
- increased 'bilirubin' levels in your blood (bilirubin is a pigment made by the liver).

* Skin rash may affect more than 1 in 10 people (very common) when OLYSIO is used in combination with sofosbuvir for 24 weeks.

The following side effects may happen with **OLYSIO** when used **in combination with peginterferon alfa and ribavirin**:
Very common: may affect more than 1 in 10 people:
- feeling sick (nausea)
- itching of the skin
- skin rash
- being short of breath.

Common: may affect up to 1 in 10 people:
- increased 'bilirubin' levels in your blood (bilirubin is a pigment made by the liver)*
- being sensitive to sunlight (photosensitivity)
- constipation.

* In a clinical study in Asian patients from China and South-Korea, increased blood 'bilirubin' levels were reported in more than 1 in 10 people (very common).

Read the package leaflets for the other medicines used for treating your hepatitis C infection for side effects reported with these medicines.

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 OLYSIO

- 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 packaging after EXP. The expiry date refers to the last day of that month.
- This medicine does not require any special temperature storage conditions.
- Store in the original package in order to protect from light.
- This medicine may pose a risk to the environment. 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 OLYSIO contains
- The active substance is simeprevir. Each capsule contains simeprevir sodium equivalent to 150 milligrams of simeprevir.
- The other ingredients are sodium lauryl sulfate, magnesium stearate, colloidal anhydrous silica, croscarmellose sodium, lactose monohydrate, gelatin, titanium dioxide (E171), iron oxide black (E172) and shellac (E904).

What OLYSIO looks like and contents of the pack
The hard capsules are white, with 'TMC435 150' printed in black ink.
OLYSIO is supplied in push-through blister strips of 7 capsules. The days of the week are printed on the blister strip.
OLYSIO is available in packs containing 7 capsules (1 blister) or 28 capsules (4 blisters).
Not all pack sizes may be marketed.

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This leaflet was last revised in {month YYYY}.

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

ANNEX IV
SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions
Taking into account the PRAC Assessment Report on the PSUR(s) for simeprevir, the scientific conclusions of CHMP are as follows:
The SmPC currently includes the information on photosensitivity reactions that were observed in the clinical trials, following treatment with simeprevir in combination with sofosbuvir there were no grade 3 or 4 photosensitivity reactions reported and none of the patients discontinued treatment due to photosensitivity reactions. Additionally, the SmPC states that following treatment with simeprevir in combination with peginterferon alfa and ribavirin, most photosensitivity reactions in simeprevir-treated patients were of mild or moderate severity (grade 1 or 2) and 0.3% of the simeprevir-treated patients experienced serious reactions leading to hospitalisation.
The cumulative data from the post-marketing setting indicates higher percentage of cases (5.8%) of photosensitivity reactions reported permanent disability or hospitalisation. The percentage of simeprevir-treated patients experiencing serious photosensitivity reactions leading to hospitalisation is therefore higher in the post-marketing setting than in clinical trials.
Based on the cumulative data, the wording in the SmPC is updated to inform prescribers of the risk of serious photosensitivity reactions in the context of the post-marketing experience and additionally to strengthen the wording on sun protective measures to be considered during treatment with Olysio. The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)
On the basis of the scientific conclusions for simeprevir the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing simeprevir is unchanged subject to the proposed changes to the product information
The CHMP recommends that the terms of the marketing authorisation should be varied.