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 for 12 weeks, taken with food.

OLYSIO must not be administered as monotherapy. 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 table 1.

Table 1: Recommended co-administered medicinal product(s) and treatment duration for OLYSIO combination therapy

Patient population	Treatment	Duration
Treatment-naïve, prior relapse[1] and prior non-responder[2] patients (including partial and null responders) with HCV genotype 1 or 4, with or without cirrhosis, with or without HIV co-infection	OLYSIO + sofosbuvir (+/- ribavirin)[3]	12 weeks[4] (see sections 4.4, 4.8 and 5.1)
Treatment-naïve and prior relapse[1] patients with HCV genotype 1 or 4		
with or without cirrhosis, who are not co-infected with HIV without cirrhosis, who are co-infected with HIV	OLYSIO + peginterferon alfa + ribavirin[5]	24 weeks[6] Treatment with OLYSIO must be initiated in combination with peginterferon alfa and ribavirin and administered for 12 weeks and then followed by an additional 12 weeks of peginterferon alfa and ribavirin.
with cirrhosis, who are co-infected with HIV	OLYSIO + peginterferon alfa + ribavirin[5]	48 weeks[6] Treatment with OLYSIO must be initiated in combination with peginterferon alfa and ribavirin and administered for 12 weeks and then followed by an additional 36 weeks of peginterferon alfa and ribavirin.
Prior non-responder[2] patients (including partial and null responders) with HCV genotype 1 or 4, with or without cirrhosis, with or without HIV co-infection	OLYSIO + peginterferon alfa + ribavirin[5]	48 weeks[6] Treatment with OLYSIO must be initiated in combination with peginterferon alfa and ribavirin and administered for 12 weeks and then followed by an additional 36 weeks of peginterferon alfa and ribavirin.

1 Relapse following prior treatment with interferon (pegylated or non-pegylated), with or without ribavirin (see section 5.1).

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

3 Ribavirin could be added based on a clinical assessment of each individual patient (see sections 4.4, 4.8 and 5.1). The recommended treatment duration is 12 weeks. A longer treatment duration (up to 24 weeks) of OLYSIO with sofosbuvir (with or without ribavirin) could be considered based on an individual basis (see sections 4.4, 4.8 and 5.1).

4 No stopping rules apply to the combination of OLYSIO with sofosbuvir.

5 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).

6 Recommended duration of treatment provided that patient does not meet a stopping rule (see table 2).

Refer to table 2 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
Use with sofosbuvir
There are no virologic treatment stopping rules that apply to the combination of OLYSIO with sofosbuvir.

Use 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 2.

Table 2: 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 the other medicinal products that are used in combination with OLYSIO for the treatment of CHC are permanently discontinued for any reason, OLYSIO must also be discontinued. When ribavirin has been added to the combination of OLYSIO and sofosbuvir, and ribavirin needs to be discontinued, consideration can be given to continue treatment of OLYSIO with sofosbuvir alone (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 class A).
OLYSIO is not recommended for patients with moderate or severe hepatic impairment (Child-Pugh class 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 peginterferon alfa and ribavirin: HCV/HIV-1 co-infected patients, irrespective of prior HCV treatment history, should be treated in the same way 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 class 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.

Use of simeprevir in patients infected with HCV genotype 1a
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.
Data are too limited to evaluate whether the presence of Q80K polymorphism in HCV genotype 1a patients reduces the efficacy of simeprevir when OLYSIO is used in combination with other direct acting antivirals against HCV (see section 5.1). Until confirmatory data becomes available, testing for the presence of the Q80K polymorphism should be considered before initiating OLYSIO in combination with sofosbuvir in patients infected with HCV genotype 1a.

Interferon-free therapy
The optimal regimen and treatment duration for interferon-free regimens have not yet been established.

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 have been observed with OLYSIO combination treatment (see section 4.8). Patients should be informed of the risk of photosensitivity reactions and on the importance of applying appropriate sun protective measures during treatment with OLYSIO. Excess exposure to sun and use of tanning devices during treatment with OLYSIO should be avoided. 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 baseline, 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
The safety and efficacy of OLYSIO for the treatment of HCV infection in patients co-infected with HBV have not been studied.

Organ transplant patients
Co-administration of OLYSIO with ciclosporin is not recommended as this leads to significantly higher exposure of simeprevir based on interim data from an ongoing phase 2 study in HCV infected post-liver transplant patients (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 3). 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 3). 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 3).

Interaction table
Established and theoretical interactions between simeprevir and selected medicinal products are listed in table 3 (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 3: 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 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	No dose adjustment is required. However, it is recommended that the international normalised ratio (INR) be monitored.
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 30 mg once daily	ledipasvir AUC 1.92 (1.77-2.07) ↑ ledipasvir C_{max} 1.81 (1.69-2.94) ↑ ledipasvir C_{min} not studied simeprevir AUC 2.69 (2.44-2.96) ↑ simeprevir C_{max} 2.61 (2.34-2.86) ↑ simeprevir C_{min} not studied	Concentrations of ledipasvir and simeprevir are increased when simeprevir is co-administered with ledipasvir. Co-administration is not recommended.

Sofosbuvir[2] 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[3] 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[4]	ciclosporin AUC 1.19 (1.13-1.26) ↑ ciclosporin C_{max} 1.16 (1.07-1.26) ↑ ciclosporin C_{min} not studied simeprevir AUC 5.81 (3.56-9.48) ↑[5] simeprevir C_{max} 4.74 (3.12-7.18) ↑[5] simeprevir C_{min} not studied[5] (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[4]	tacrolimus AUC 0.83 (0.59-1.16) ↓ tacrolimus C_{max} 0.76 (0.65-0.90) ↓ tacrolimus C_{min} not studied simeprevir AUC 1.85 (1.18-2.91) ↑[6] simeprevir C_{max} 1.79 (1.22-2.62) ↑[6] simeprevir C_{min} not studied[6] (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[7] 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] 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. The safety and efficacy of simeprevir in combination with sofosbuvir have not been established in a phase 3 study.

[3] 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.

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

[5] Comparison based on historic controls. Interim data from a phase 2 study in 9 HCV infected post-liver transplant patients.

[6] Comparison based on historic controls. Interim data from a phase 2 study in 11 HCV infected post-liver transplant patients.

[7] 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

Use with peginterferon alfa and ribavirin
The overall safety profile of simeprevir in combination with peginterferon alfa and ribavirin in patients with HCV genotype 1 infection who were treatment-naïve or who failed prior interferon therapy with or without ribavirin is based on the pooled data from 2 clinical phase 2 studies (studies C205 and C206) and 3 clinical phase 3 studies (studies C208, C216 and HPC3007). The pooled data from these phase 2 and phase 3 studies included 1,486 patients who received simeprevir in combination with peginterferon alfa and ribavirin (of which 924 patients were to receive 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.

The safety profile of simeprevir is comparable between patients with HCV genotype 4 infection and genotype 1 infection.

Tabulated list of adverse reactions
Adverse reactions are reported in table 4. 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 4: Adverse reactions of simeprevir in combination with peginterferon alfa and ribavirin reported in adult patients with HCV genotype 1 infection (pooled phase 3 studies C208, C216 and HPC3007; first 12 weeks of treatments; Intent-To-Treat analysis set)

System Organ Class	Frequency category	Simeprevir + peginterferon alfa + ribavirin N=781
Respiratory, thoracic and mediastinal disorders	very common	dyspnoea*
Gastrointestinal disorders	very common common	nausea constipation
Hepatobiliary disorders	common	blood bilirubin increased*
Skin and subcutaneous tissue disorders	very common common	rash*, pruritus* photosensitivity reaction*

* see section below for further details.

Description of selected adverse reactions

Rash and pruritus
During the 12 weeks treatment with simeprevir, rash and pruritus were observed in 21.8% and 21.9% of simeprevir-treated patients, compared to 16.6% and 14.6% in patients treated with placebo, peginterferon alfa and ribavirin, respectively (all grades; pooled phase 3). Most of the rash and pruritus events in simeprevir-treated patients were of mild or moderate severity (grade 1 or grade 2). 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 no patients treated with placebo, peginterferon alfa and ribavirin, respectively.

Blood bilirubin increased
During the 12 weeks treatment with simeprevir, 'blood bilirubin increased' was reported in 7.4% of simeprevir-treated patients, compared to 2.8% in patients treated with placebo, peginterferon alfa and ribavirin (all grades; pooled phase 3). In 2% and 0.3% of the simeprevir-treated patients grade 3 or grade 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). 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.

Photosensitivity reactions
During the 12 weeks treatment with simeprevir, photosensitivity reactions were reported in 4.7% of simeprevir-treated patients compared to 0.8% in patients treated with placebo, peginterferon alfa and ribavirin (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
During the first 12 weeks treatment with simeprevir, dyspnoea was reported in 11.8% of simeprevir-treated patients, compared to 7.6% in patients treated with placebo, peginterferon alfa and ribavirin (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 patients treated with placebo, peginterferon alfa and ribavirin (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
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 5.

Table 5: Treatment-emergent laboratory abnormalities (WHO worst toxicity grades 1 to 4) observed at a higher incidence in patients treated with simeprevir in combination with peginterferon alfa and ribavirin (pooled phase 3 studies C208, C216 and HPC3007; first 12 weeks of treatments; Intent-To-Treat analysis set)

Laboratory parameter	WHO toxicity range	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%)

ULN = Upper Limit of Normal

Use with sofosbuvir with or without ribavirin
In study HPC2002, assessing simeprevir in combination with sofosbuvir with or without ribavirin, no new safety findings were identified other than those observed with simeprevir in combination with peginterferon alfa and ribavirin.
The most common (> 10%) adverse events reported during 12 weeks treatment with simeprevir in combination with sofosbuvir were fatigue (25%), headache (21%), nausea (21%), insomnia (14%) and pruritus (11%).
Other selected adverse events of interest (grouped term) reported during 12 weeks treatment with simeprevir were rash (11% in patients receiving simeprevir in combination with sofosbuvir without ribavirin versus 20% in patients receiving simeprevir in combination with sofosbuvir and ribavirin), anemia (0% versus 13%, respectively), photosensitivity reactions (7% versus 6%, respectively) and increased bilirubin (0% versus 9%, respectively).

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 6).

Table 6: 'Blood bilirubin increased' events observed in Asian patients from the phase 3 study HPC3005 versus the pooled phase 3 studies C208, C216 and HPC3007 treated with 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. A higher incidence of anaemia in patients with advanced fibrosis 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, genotype 3, and genotype 4 baseline isolates tested were 25 (N=4), 1,014 (N=2), and 0.3 (N=8), 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 7.

Table 7: 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 8). 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 8). In patients with HCV genotype 1a with a baseline Q80K amino acid substitution an emerging R155K substitution was observed most frequently at failure.

Table 8: 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 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.

In study HPC2002 in genotype 1 infected patients treated with simeprevir in combination with sofosbuvir with or without ribavirin, 5 out of 6 patients (83%) with relapse had emerging amino acid substitutions R155K or D168E. No emerging amino acid substitutions associated with sofosbuvir resistance were observed.

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 an ongoing, long-term follow-up study (study HPC3002) in patients who did not achieve SVR with a simeprevir-based regimen in a previous phase 2 study showed that in 70% (16/23) of these patients emerging mutations were no longer detected after a median follow-up of 88 weeks (range 47-147 weeks).

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 in the controlled phase 2 and phase 3 studies (n=2,007; studies C208, C216, HPC3007, C206, C205), with exception of the substitution Q80K in HCV genotype 1a patients. The observed prevalence of Q80K polymorphism at baseline in the overall HCV genotype 1 population of the phase 2 and phase 3 studies was 14%, 30% in patients with HCV genotype 1a and 0.5% in patients with HCV genotype 1b. In Europe, the observed prevalence of Q80K polymorphism in genotype 1 overall was 6% (76/1,254), 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 (study HPC3011).

In the pooled analysis of the phase 3 studies C208 and C216, and in study HPC3007, 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 compared to HCV genotype 1a patients treated with simeprevir in combination with peginterferon alfa and ribavirin without Q80K (table 9).

Table 9: SVR12 rates[1] by HCV geno/subtype and presence or absence of baseline Q80K polymorphism in HCV genotype 1 patients treated with simeprevir/placebo in combination with peginterferon alfa and ribavirin (Intent-To-Treat analysis set)

	All patients with HCV genotype 1a[2]	Patients with HCV genotype 1a[2] - presence/absence of Q80K polymorphism at baseline[3]		All patients with HCV genotype 1b
		Presence	Absence	
HCV mono-infected patients (studies C208, C216, HPC3007 and C206)				
Treatment-naïve patients (pooled studies C208 and C216)				
Simeprevir	75% (191/254)	58% (49/84)	84% (138/165)	85% (228/267)
Placebo	47% (62/131)	52% (23/44)	43% (36/83)	53% (70/133)
Prior relapsers (study HPC3007)				
Simeprevir	70% (78/111)	47% (14/30)	79% (62/79)	86% (128/149)
Placebo	28% (15/54)	30% (6/20)	26% (9/34)	43% (34/79)
Prior partial responders (study C206)				
Simeprevir[4]	56% (14/25)	38% (3/8)	65% (11/17)	88% (38/43)
Placebo	13% (1/8)	0% (0/2)	17% (1/6)	7% (1/15)
Prior null responders (study C206)				
Simeprevir[4]	42% (11/26)	75% (3/4)	38% (8/21)	58% (14/24)
Placebo	0% (0/7)	0% (0/0)	0% (0/7)	33% (3/9)
HCV/HIV-1 co-infected patients (study C212)				
Treatment-naïve patients				
Simeprevir	77% (33/43)	86% (12/14)	72% (21/29)	90% (9/10)
Prior relapsers				
Simeprevir	83% (10/12)	33% (1/3)	100% (9/9)	100% (3/3)

Prior partial responders				
Simeprevir	67% (6/9)	100% (1/1)	63% (5/8)	100% (1/1)
Prior null responders				
Simeprevir	54% (13/24)	50% (6/12)	58% (7/12)	75% (3/4)

[1] SVR24 for study C206.
[2] May include few patients with HCV non-genotype 1a/1b.
[3] Number of patients in the simeprevir treatment group: only patients with sequence data available.
[4] Pooled 150 mg simeprevir treatment group.
Note: In studies C208, C216, HPC3007 and C206, three HCV genotype 1b infected patients had baseline Q80K polymorphism. All three patients had SVR12.
SVR12/24: sustained virologic response 12/24 weeks after planned end of treatment (EOT).

In the pooled analysis of studies C208 and C216, 69% (58/84) of the HCV genotype 1a infected patients treated with simeprevir in combination with peginterferon alfa and ribavirin with Q80K polymorphism at baseline were eligible for a total treatment duration of 24 weeks by meeting the protocol-defined RGT criteria (HCV RNA < 25 IU/ml detectable or undetectable at week 4 and undetectable HCV RNA at week 12); in these patients the SVR12 rate was 78%. Sixty-five percent (53/81) of HCV genotype 1a infected patients treated with simeprevir in combination with peginterferon alfa and ribavirin with Q80K polymorphism had undetectable HCV RNA at week 4 (Rapid Virologic Response; RVR); in these patients the SVR12 rate was 79%. Twenty-one percent (17/81) of HCV genotype 1a infected patients treated with simeprevir in combination with peginterferon alfa and ribavirin with Q80K polymorphism had HCV RNA ≥ 25 IU/ml at week 4; in these patients the SVR12 rate was 12%.

In study HPC3007, 80% (24/30) of the HCV genotype 1a infected patients treated with simeprevir in combination with peginterferon alfa and ribavirin with Q80K polymorphism at baseline were eligible for a total treatment duration of 24 weeks by meeting the protocol-defined RGT criteria (HCV RNA < 25 IU/ml detectable or undetectable at week 4 and undetectable HCV RNA at week 12); in these patients the SVR12 rate was 58%. Forty-three percent (13/30) of HCV genotype 1a infected patients treated with simeprevir in combination with peginterferon alfa and ribavirin with Q80K polymorphism at baseline had undetectable HCV RNA at week 4 (RVR); in these patients the SVR12 rate was 77%. Thirteen percent (4/30) of HCV genotype 1a infected patients treated with simeprevir in combination with peginterferon alfa and ribavirin with Q80K polymorphism had HCV RNA ≥ 25 IU/ml at week 4; none of these patients achieved a SVR12.

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. 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 inhibitors (S96T, S282T) and non-nucleoside inhibitors (C316N, M414I/L, P495A) remained susceptible to simeprevir *in vitro*.

Clinical efficacy and safety

The efficacy of simeprevir in combination with peginterferon alfa and ribavirin in patients with HCV genotype 1 infection was evaluated in two phase 3 studies in treatment-naïve patients (studies C208 and C216), one phase 3 study in patients who relapsed after prior interferon-based therapy (study HPC3007), one phase 2 study in patients who failed prior therapy with peginterferon and ribavirin (including prior relapsers, partial and null responders) (study C206), and one phase 3 study in patients with HCV genotype 1 and HIV-1 co-infection who were HCV treatment-naïve or failed previous HCV therapy with peginterferon and ribavirin (study C212). The efficacy of simeprevir in combination with peginterferon alfa and ribavirin in patients with HCV genotype 4 infection was evaluated in one phase 3 study in treatment-naïve patients or patients who failed previous therapy with

peginterferon and ribavirin (study HPC3011). The efficacy of simeprevir as part of an interferon-free regimen with or without ribavirin was evaluated in a phase 2a study in HCV genotype 1 infected 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 (study HPC2002).

Prior relapsers were patients who had undetectable HCV RNA at the end of prior interferon-based therapy and detectable HCV RNA during follow-up; prior partial responders were patients with prior on-treatment ≥ 2 $\log_{10}$ reduction in HCV RNA from baseline at week 12 and detectable HCV RNA at the end of prior therapy with peginterferon and ribavirin; and null responders were patients with prior on-treatment < 2 $\log_{10}$ reduction in HCV RNA from baseline at week 12 during prior therapy with peginterferon and ribavirin. Patients in these studies had compensated liver disease (including cirrhosis), HCV RNA of at least 10,000 IU/ml, and liver histopathology consistent with CHC.

In treatment-naïve and prior relapser patients, the overall duration of treatment with peginterferon alfa and ribavirin in the phase 3 studies was response-guided. In these patients, the planned total duration of HCV treatment was 24 weeks if the following on-treatment protocol-defined response-guided therapy (RGT) criteria were met: HCV RNA < 25 IU/ml detectable or undetectable at week 4 AND undetectable HCV RNA at week 12. Plasma HCV RNA levels were measured using the COBAS TaqMan HCV test (version 2.0), for use with the High Pure System (25 IU/ml LLOQ and 15 IU/ml limit of detection). Treatment stopping rules for HCV therapy were used to ensure that patients with inadequate on-treatment virologic response discontinued treatment in a timely manner. In the phase 3 study C212 in HCV/HIV-1 co-infected patients, the overall duration of treatment with peginterferon alfa and ribavirin in treatment-naïve and prior relapser patients with cirrhosis was not response-guided; these patients received a fixed total duration of HCV treatment of 48 weeks. The total duration of treatment with peginterferon alfa and ribavirin in non-cirrhotic HCV/HIV-1 co-infected treatment-naïve or prior relapser patients was response-guided using the same criteria.

SVR (virologic cure) was defined as undetectable HCV RNA 24 weeks after planned end of treatment in the C206 study and was defined as HCV RNA < 25 IU/ml detectable or undetectable 12 weeks after the planned end of treatment in the HPC2002 study and phase 3 studies.

Efficacy in treatment-naïve adults with HCV genotype 1 infection
Study C208 (QUEST 1) and study C216 (QUEST 2)
The efficacy of simeprevir in treatment-naïve patients with HCV genotype 1 infection was demonstrated in two randomised, double-blind, placebo-controlled, 2-arm, multicenter, phase 3 studies (study C208 and study C216). The design of both studies was similar. Patients received 12 weeks of once daily treatment with 150 mg simeprevir or placebo, plus peginterferon alfa-2a (studies C208 and C216) or peginterferon alfa-2b (study C216) and ribavirin, followed by 12 or 36 weeks of therapy with peginterferon alfa and ribavirin in accordance with the on-treatment protocol-defined RGT criteria. Patients in the control groups received 48 weeks of peginterferon alfa-2a or -2b and ribavirin.

In the pooled analysis of studies C208 and C216, the 785 enrolled patients had a median age of 47 years (range: 18 to 73 years; with 2% above 65 years); 56% were male; 91% were White, 7% Black or African American, 1% Asian, and 17% Hispanic; 23% had a body mass index (BMI) ≥ 30 kg/m^2; 78% had baseline HCV RNA levels > 800,000 IU/ml; 74% had METAVIR fibrosis score F0, F1 or F2, 16% METAVIR fibrosis score F3, and 10% METAVIR fibrosis score F4 (cirrhosis); 48% had HCV genotype 1a, and 51% HCV genotype 1b; 17% of the overall population and 34% of the patients with genotype 1a had Q80K polymorphism at baseline; 29% had *IL28B* CC genotype, 56% *IL28B* CT genotype, and 15% *IL28B* TT genotype. 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.

The proportion of patients who discontinued all treatment due to an adverse event was 2% in the simeprevir with peginterferon alfa and ribavirin treatment group compared to 1% in the placebo with peginterferon alfa and ribavirin treatment group. Discontinuation of simeprevir or placebo alone due to an adverse event was 1% in both treatments groups. Table 10 shows the response rates in treatment-naïve adult patients with HCV genotype 1 infection.

Table 10: Treatment outcome in treatment-naïve adult patients with HCV genotype 1 infection (pooled data studies C208 and C216; week 60 analysis; Intent-To-Treat analysis set)

Treatment Outcome	Simeprevir N=521 % (n/N)	Placebo N=264 % (n/N)
Overall SVR12	80% (419/521)[1]	50% (132/264)
Outcome for patients without SVR12		
On-treatment failure[2]	8% (42/521)	33% (87/264)
Viral relapse[3]	11% (51/470)	23% (39/172)
Missing SVR12[4]	3% (13/521)	2% (6/264)

Simeprevir: 150 mg simeprevir for 12 weeks with peginterferon alfa-2a or -2b and ribavirin for 24 or 48 weeks; Placebo: placebo for 12 weeks with peginterferon alfa-2a or -2b and ribavirin for 48 weeks. SVR12: sustained virologic response 12 weeks after planned EOT.

1 $p < 0.001$.

2 On-treatment failure was defined as the proportion of patients with confirmed detectable HCV RNA EOT (including but not limited to patients who met the protocol-specified treatment stopping rules and/or experienced viral breakthrough).

3 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.

4 Patients with missing data at the SVR assessment time point.

Eighty-eight percent (459/521) of the simeprevir-treated patients were eligible for a total treatment duration of 24 weeks by meeting the protocol-defined RGT criteria (HCV RNA < 25 IU/ml detectable or undetectable at week 4 and undetectable HCV RNA at week 12); in these patients the SVR12 rate was 88%.

Seventy-eight percent (404/521) of simeprevir-treated patients had undetectable HCV RNA at week 4 (RVR); 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 13% (70/521); 67% achieved SVR12.

Seven percent (35/521) of simeprevir-treated patients had HCV RNA ≥ 25 IU/ml at week 4; in these patients the SVR12 rate was 20%.

In both C208 and C216 studies, addition of simeprevir to peginterferon alfa and ribavirin did not increase severity of patient-reported fatigue, depressive symptoms or impairments in work and daily activities beyond what was observed in patients treated with peginterferon alfa and ribavirin alone. Additionally, simeprevir-treated patients had significantly reduced time (weeks) with fatigue and impairments in work and daily activity as compared to peginterferon alfa and ribavirin alone.

SVR12 rates were statistically significantly higher for the simeprevir treatment group compared to the placebo treatment group by sex, age, race, BMI, HCV genotype subtype, baseline HCV RNA (less than or equal to 800,000 IU/ml, greater than 800,000 IU/ml), METAVIR fibrosis score, and *IL28B* genotype. Table 11 shows the SVR rates by METAVIR fibrosis score and *IL28B* genotype.

Table 11: SVR12 rates by METAVIR fibrosis score and IL28B genotype in treatment-naïve adult patients with HCV genotype 1 infection (pooled data studies C208 and C216; week 60 analysis; Intent-To-Treat analysis set)

Subgroup	Simeprevir % (n/N)	Placebo % (n/N)
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)

Simeprevir: 150 mg simeprevir for 12 weeks with peginterferon alfa-2a or -2b and ribavirin for 24 or 48 weeks; Placebo: placebo for 12 weeks with peginterferon alfa-2a or -2b and ribavirin for 48 weeks. SVR12: sustained virologic response 12 weeks after planned EOT.

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 adults with HCV genotype 1 infection who failed previous therapy
Study HPC3007 (PROMISE)
This was a randomised, double-blind, placebo-controlled, 2-arm, multicenter, phase 3 study in patients with HCV genotype 1 infection who relapsed after prior interferon-based therapy. Patients received 12 weeks of once daily treatment with 150 mg simeprevir or placebo, plus peginterferon alfa-2a and ribavirin, followed by 12 or 36 weeks of therapy with peginterferon alfa-2a and ribavirin in accordance with the protocol-defined RGT criteria. Patients in the control group received 48 weeks of peginterferon alfa-2a and ribavirin.

The 393 enrolled patients in study HPC3007 had a median age of 52 years (range: 20 to 71 years; with 3% above 65 years); 66% were male; 94% were White, 3% Black or African American, 2% Asian, and 7% Hispanic; 26% had a BMI ≥ 30 kg/m^2; 84% had baseline HCV RNA levels > 800,000 IU/ml; 69% had METAVIR fibrosis score F0, F1 or F2, 15% METAVIR fibrosis score F3, and 15% METAVIR fibrosis score F4 (cirrhosis); 42% had HCV genotype 1a, and 58% HCV genotype 1b; 13% of the overall population and 31% of the patients with genotype 1a had Q80K polymorphism at baseline; 24% had *IL28B* CC genotype, 64% *IL28B* CT genotype, and 12% *IL28B* TT genotype. The prior interferon-based HCV therapy was peginterferon alfa-2a/ribavirin (68%) or peginterferon alfa-2b/ribavirin (27%).

The proportion of patients who discontinued all treatment due to an adverse event was 0.4% in the simeprevir with peginterferon alfa and ribavirin treatment group compared to none in the placebo with peginterferon alfa and ribavirin treatment group. None of the patients discontinued simeprevir alone due to an adverse event. Table 12 shows the response rates for the simeprevir and placebo treatment groups in adult patients with HCV genotype 1 infection who relapsed after prior interferon-based therapy.

Table 12: Treatment outcome in adult patients with HCV genotype 1 infection who relapsed after prior interferon-based therapy (study HPC3007; week 60 analysis; Intent-To-Treat analysis set)

Treatment outcome	**Simeprevir N=260 % (n/N)**	**Placebo N=133 % (n/N)**
Overall SVR12	79% (206/260)[1]	37% (49/133)
Outcome for patients without SVR12		
On-treatment failure[2]	3% (8/260)	27% (36/133)
Viral relapse[3]	19% (46/249)	48% (45/93)
Missing SVR12[4]	2% (5/260)	4% (5/133)

Simeprevir: 150 mg simeprevir for 12 weeks with peginterferon alfa-2a and ribavirin for 24 or 48 weeks; Placebo: placebo for 12 weeks with peginterferon alfa-2a and ribavirin for 48 weeks. SVR12: sustained virologic response 12 weeks after planned EOT.

[1] $p < 0.001$.

[2] On-treatment failure was defined as the proportion of patients with confirmed detectable HCV RNA at EOT (including but not limited to patients who met the protocol-specified treatment stopping rules and/or experienced viral breakthrough).

[3] 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 5 simeprevir-treated patients who experienced relapse after SVR12.

[4] Patients with missing data at the SVR assessment time point.

Ninety-three percent (241/260) of the simeprevir-treated patients were eligible for a total treatment duration of 24 weeks by meeting the protocol-defined RGT criteria (HCV RNA < 25 IU/ml detectable or undetectable at week 4 and undetectable HCV RNA at week 12); in these patients the SVR12 rate was 83%.

Seventy-seven percent (200/260) of simeprevir-treated patients had undetectable HCV RNA at week 4 (RVR); 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% (47/260); 60% achieved SVR12.

Five percent (12/260) of simeprevir-treated patients had HCV RNA ≥ 25 IU/ml at week 4; in these patients the SVR12 rate was 42%.

In study HPC3007, the increases in severity of patient-reported fatigue, depressive symptoms and impairments in work and daily activities were comparable in both treatment groups. The increases lasted longer in patients treated with peginterferon alfa and ribavirin alone.

SVR12 rates were statistically significantly higher for the simeprevir treatment group compared to the placebo treatment group by sex, age, race, BMI, HCV genotype subtype, baseline HCV RNA (less than or equal to 800,000 IU/ml, greater than 800,000 IU/ml), prior HCV therapy, METAVIR fibrosis score, and *IL28B* genotype. Table 13 shows the SVR rates by METAVIR fibrosis score and *IL28B* genotype.

Table 13: SVR12 rates by METAVIR fibrosis score and IL28B genotype in adult patients with HCV genotype 1 infection who relapsed after prior interferon-based therapy (study HPC3007; week 60 analysis; Intent-To-Treat analysis set)

Subgroup	**Simeprevir % (n/N)**	**Placebo % (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)

Simeprevir: 150 mg simeprevir for 12 weeks with peginterferon alfa-2a and ribavirin for 24 or 48 weeks; Placebo: placebo for 12 weeks with peginterferon alfa-2a and ribavirin for 48 weeks. SVR12: sustained virologic response 12 weeks after planned EOT.

Study C206 (ASPIRE)

This was a randomised, double-blind, placebo-controlled, 7-arm, phase 2 study in patients with HCV genotype 1 infection, who failed prior therapy with peginterferon alfa and ribavirin (including prior relapsers, partial responders or null responders*)*. Patients received 12, 24 or 48 weeks of 100 mg or 150 mg simeprevir in combination with 48 weeks of peginterferon alfa-2a and ribavirin, or 48 weeks of placebo in combination with 48 weeks of peginterferon alfa-2a and ribavirin.

The 462 enrolled patients in study C206 had a median age of 50 years (range: 20 to 69 years; with 3% above 65 years); 67% were male; 93% were White, 5% Black or African American, and 2% Asian; 25% had a BMI ≥ 30 kg/m^2; 86% had baseline HCV RNA levels > 800,000 IU/ml; 63% had METAVIR fibrosis score F0, F1 or F2, 19% METAVIR fibrosis score F3, and 18% METAVIR fibrosis score F4 (cirrhosis); 41% had HCV genotype 1a, and 58% HCV genotype 1b; 12% of the overall population and 27% of the patients with genotype 1a had Q80K polymorphism at baseline; 18% had *IL28B* CC genotype, 65% *IL28B* CT genotype, and 18% *IL28B* TT genotype (information available for 328 patients). Forty percent of patients were prior relapsers, 35% prior partial responders, and 25% prior null responders following prior therapy with peginterferon alfa and ribavirin. One hundred ninety-nine patients received simeprevir 150 mg once daily (pooled analysis) of which 66 patients received simeprevir for 12 weeks, and 66 patients received placebo in combination with peginterferon alfa and ribavirin.

The proportion of patients who discontinued all treatment due to an adverse event was 5% in both the 150 mg simeprevir for 12 weeks and the placebo treatment groups; none of the patients discontinued simeprevir or placebo alone. Table 14 shows the response rates for the simeprevir and placebo treatment groups in prior partial responders and null responders.

Table 14: Treatment outcome in adult patients with HCV genotype 1 infection who failed prior peginterferon alfa and ribavirin therapy (study C206; prior partial and null responders; Intent-To-Treat analysis set)

Treatment Outcome	150 mg simeprevir 12 weeks % (n/N)	Pooled 150 mg simeprevir % (n/N)	Placebo % (n/N)
SVR24			
Prior partial responders	65% (15/23)	75% (52/69)[1]	9% (2/23)
Prior null responders	53% (9/17)	51% (26/51)[2]	19% (3/16)
Outcome for patients without SVR24			
On-treatment virologic failure[3]			
Prior partial responders	22% (5/23)	16% (11/69)	78% (18/23)
Prior null responders	35% (6/17)	29% (15/51)	75% (12/16)
Viral relapse[4]			
Prior partial responders	6% (1/17)	5% (3/56)	50% (2/4)
Prior null responders	18% (2/11)	28% (10/36)	25% (1/4)

150 mg simeprevir: 150 mg simeprevir for 12 weeks with peginterferon alfa-2a and ribavirin for 48 weeks; pooled 150 mg simeprevir: 150 mg simeprevir for 12, 24 or 48 weeks with peginterferon alfa-2a and ribavirin for 48 weeks; Placebo: placebo with peginterferon alfa-2a and ribavirin for 48 weeks. SVR24: sustained virologic response 24 weeks after planned EOT.

[1] $p < 0.001$.

[2] $p = 0.001$.

[3] On-treatment virologic failure was defined as the proportion of patients who met the protocol-specified treatment stopping rules (including stopping rule due to viral breakthrough) or who had detectable HCV RNA at EOT (for patients who completed therapy).

[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.

Thirteen percent (9/69) and 26% (13/51) of simeprevir-treated prior partial responders and null responders, respectively, had HCV RNA ≥ 25 IU/ml at week 4; in these patients, the SVR24 rates were 11% and 8%, respectively (pooled 150 mg simeprevir).

In study C206, no treatment related differences in patient reported fatigue severity were observed. Fatigue increased to similar extent and returned to baseline levels after week 48 in all treatment arms.

SVR24 rates were higher in the simeprevir-treated patients compared to patients receiving placebo in combination with peginterferon alfa and ribavirin, regardless of HCV geno/subtype, METAVIR fibrosis score and *IL28B* genotype. Table 15 shows the SVR rates by METAVIR fibrosis scores.

Table 15: SVR24 rates by METAVIR fibrosis score in adult patients with HCV genotype 1 infection who failed prior peginterferon alfa and ribavirin therapy (study C206; prior partial and null responders; Intent-To-Treat analysis set)

METAVIR fibrosis score	Prior partial responders		Prior null responders	
	Pooled 150 mg simeprevir % (n/N)	Placebo % (n/N)	Pooled 150 mg simeprevir % (n/N)	Placebo % (n/N)
F0-2	79% (38/48)	8% (1/12)	66% (19/29)	23% (3/13)
F3-4	67% (14/21)	10% (1/10)	33% (7/21)	0% (0/3)
F4	82% (9/11)	0% (0/2)	31% (4/13)	0% (0/2)

Pooled 150 mg simeprevir: 150 mg simeprevir for 12, 24 or 48 weeks with peginterferon alfa-2a and ribavirin for 48 weeks; Placebo: placebo for 12 weeks with peginterferon alfa-2a and ribavirin for 48 weeks. SVR24: sustained virologic response 24 weeks after planned EOT.

Long-term efficacy in adults with HCV genotype 1 infection
Study HPC3002
Interim data from an ongoing 3-year follow-up study (study HPC3002) in patients who achieved SVR with a simeprevir-based regimen in previous phase 2 studies showed that all patients (n=166) maintained undetectable HCV RNA during a median follow-up time of 16 months.

Efficacy in adults with HCV genotype 1 and HIV-1 co-infection
Study C212
This is an open label, single arm phase 3 study in HIV-1 patients co-infected with HCV genotype 1 who are treatment-naïve or failed prior HCV therapy with peginterferon alfa and ribavirin (including prior relapsers, partial responders or null responders). Non-cirrhotic treatment-naïve patients or prior relapsers received 12 weeks of once daily treatment with 150 mg simeprevir plus peginterferon alfa-2a and ribavirin, followed by 12 or 36 weeks of therapy with peginterferon alfa-2a and ribavirin in accordance with the protocol-defined RGT criteria. Prior non-responder patients (partial and null response) and all cirrhotic patients (METAVIR fibrosis score F4) received 36 weeks of peginterferon alfa-2a and ribavirin after the initial 12 weeks of simeprevir in combination with peginterferon alfa-2a and ribavirin.

The 106 enrolled patients in study C212 had a median age of 48 years (range: 27 to 67 years; with 2% above 65 years); 85% were male; 82% were White, 14% Black or African American, 1% Asian, and 6% Hispanic; 12% had a BMI ≥ 30 kg/m^2; 86% had baseline HCV RNA levels > 800,000 IU/ml; 68% had METAVIR fibrosis score F0, F1 or F2, 19% METAVIR fibrosis score F3, and 13% METAVIR fibrosis score F4; 82% had HCV genotype 1a, and 17% HCV genotype 1b; 28% of the overall population and 34% of the patients with genotype 1a had Q80K polymorphism at baseline; 27% had *IL28B* CC genotype, 56% *IL28B* CT genotype, and 17% *IL28B* TT genotype; 50% (n=53) were HCV treatment-naïve patients, 14% (n=15) prior relapsers, 9% (n=10) prior partial responders, and 26% (n=28) prior null responders. Eighty-eight percent (n=93) of the patients were on highly active antiretroviral therapy (HAART), with nucleoside reverse transcriptase inhibitors and the integrase inhibitor raltegravir being the most commonly used HIV antiretroviral. The median baseline HIV-1 RNA levels and CD4+ cell count in patients not on HAART were 4.18 $\log_{10}$ copies/ml (range: 1.3-4.9 $\log_{10}$ copies/ml) and 677 x 10^6 cells/l (range: 489-1,076 x 10^6 cells/l), respectively. The median baseline CD4+ cell count in patients on HAART was 561 x 10^6 cells/ml (range: 275-1,407 x 10^6 cells/ml).

The proportion of patients who discontinued all treatment due to an adverse event was 3%. The proportion of patients who discontinued simeprevir alone due to an adverse event was 1%. Table 16 shows the response rates in treatment-naïve, prior relapsers, prior partial responders and null responders.

Table 16: Treatment outcome in adult patients with HCV genotype 1 infection and HIV-1 co-infection (study C212; treatment-naïve patients, prior relapsers, prior partial and null responders; final analysis; Intent-To-Treat analysis set)

Treatment outcome[1]	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)[2]	87% (13/15)	70% (7/10)	57% (16/28)[2]
Outcome for patients without SVR12				
On-treatment failure[3]	9% (5/53)	0% (0/15)	20% (2/10)	39% (11/28)
Viral relapse[4]	10% (5/48)	13% (2/15)	0% (0/7)	12% (2/17)
Missing SVR12[5]	2% (1/53)	0% (0/15)	10% (1/10)	0% (0/28)

1 150 mg simeprevir for 12 weeks with peginterferon alfa-2a and ribavirin for 24 or 48 weeks.

2 $p < 0.001$ compared to historical control of peginterferon alfa and ribavirin.

3 On-treatment failure was defined as the proportion of patients with confirmed detectable HCV RNA at EOT (including but not limited to patients who met the protocol-specified treatment stopping rules and/or experienced viral breakthrough).

4 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).

5 Patients with missing data at the SVR assessment time point.

Eighty-nine percent (54/61) of the simeprevir-treated treatment-naïve patients and prior relapsers without cirrhosis were eligible for 24 weeks of treatment by meeting the protocol-defined RGT criteria (HCV RNA < 25 IU/ml detectable or undetectable at week 4 and undetectable HCV RNA at week 12); 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 (RVR). In these patients the SVR12 rates were 89%, 93%, 75% and 90%, respectively.

Six percent (3/52), 0% (0/15), 20% (2/10) and 25% (7/28) of simeprevir-treated treatment-naïve patients, prior relapsers, prior partial responders and prior null responders, respectively, had HCV RNA ≥ 25 IU/ml at week 4. The SVR12 rates were 0% in treatment-naïve patients, prior relapsers and prior null responders and 50% (1/2) in prior partial responders.

Table 17 shows the SVR rates by METAVIR fibrosis scores and *IL28B* genotype.

Table 17: SVR12 rates by METAVIR fibrosis score and IL28B genotype in adult patients with HCV genotype 1 infection and HIV-1 co-infection (study C212; treatment-naïve patients, prior relapsers, prior partial and null responders; final analysis; Intent-To-Treat analysis set)

Subgroup	Treatment-naïve patients % (n/N)	Prior relapsers % (n/N)	Prior partial responders % (n/N)	Prior null responders % (n/N)
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)

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 adults with HCV genotype 4 infection
Study HPC3011 (RESTORE)
This is an open label, single arm phase 3 study in patients with HCV genotype 4 infection who are treatment-naïve or failed prior therapy with peginterferon alfa and ribavirin (including prior relapsers, partial responders or null responders). Treatment-naïve patients or prior relapsers received once daily treatment with 150 mg simeprevir plus peginterferon alfa-2a and ribavirin for 12 weeks, followed by 12 or 36 weeks of therapy with peginterferon alfa-2a and ribavirin in accordance with the protocol-defined RGT criteria. Prior non-responder patients (partial and null response) received once daily treatment with 150 mg simeprevir plus peginterferon alfa-2a and ribavirin for 12 weeks, followed by 36 weeks of peginterferon alfa-2a and ribavirin.

The 107 enrolled patients in study HPC3011 with HCV genotype 4 had a median age of 49 years (range: 27 to 69 years; with 5% above 65 years); 79% were male; 72% were White, 28% Black or African American, and 7% Hispanic; 14% had a BMI ≥ 30 kg/m^2; 60% had baseline HCV RNA levels > 800,000 IU/ml; 57% had METAVIR fibrosis score F0, F1, or F2, 14% METAVIR fibrosis score F3, and 29% METAVIR fibrosis score F4; 8% had *IL28B* CC genotype, 58% *IL28B* CT genotype, and 35% *IL28B* TT genotype; 42% had HCV genotype 4a, and 24% had HCV genotype 4d; none of the patients had Q80K polymorphism at baseline; 33% (n=35) were treatment-naïve HCV patients, 21% (n=22) prior relapsers, 9% (n=10) prior partial responders, and 37% (n=40) prior null responders.

The proportion of patients who discontinued simeprevir due to an adverse event was 1%. Table 18 shows the response rates in treatment-naïve, prior relapsers, prior partial responders and prior null responders.

Table 18: Treatment outcome in adult patients with HCV genotype 4 infection (Study HPC3011; final analysis; Intent-To-Treat analysis set)

Treatment outcome[1]	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[2]	9% (3/35)	9% (2/22)	20% (2/10)	45% (18/40)
Viral relapse[3]	9% (3/35)	5% (1/22)	20% (2/10)	15% (6/40)
Missing SVR12[4]	0% (0/35)	0% (0/22)	0% (0/10)	0% (0/40)

1 150 mg simeprevir for 12 weeks with peginterferon alfa-2a and ribavirin for 24 or 48 weeks.
2 On-treatment failure was defined as the proportion of patients with confirmed detectable HCV RNA at EOT (including but not limited to patients who met the protocol-specified treatment stopping rules and/or experienced viral breakthrough).
3 Viral relapse rates are calculated with a denominator of patients with undetectable (or unconfirmed detectable) HCV RNA at actual EOT.
4 Patients with missing data at the SVR assessment time point.

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 by meeting the protocol-defined RGT criteria; in these patients the SVR12 rate was 94%.

Eighty percent (28/35), 82% (18/22), 40% (4/10) and 48% (19/40) of simeprevir-treated treatment-naïve patients, prior relapsers, prior partial responders and prior null responders, respectively, had undetectable HCV RNA at week 4 (RVR). In these patients the SVR12 rates were 96%, 94%, 100% and 68%, respectively.

Eleven percent (4/35), 5% (1/22), 10% (1/10) and 23% (9/40) of simeprevir-treated treatment-naïve patients, prior relapsers, prior partial responders and prior null responders, respectively, had HCV RNA ≥ 25 IU/ml at week 4; none achieved SVR12.

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.

Table 19 shows the SVR rates by METAVIR fibrosis scores and *IL28B* genotype.

Table 19: SVR12 rates by METAVIR fibrosis score and IL28B genotype in adult patients with HCV genotype 4 infection (Study HPC3011; final analysis; Intent-To-Treat analysis set)

Subgroup	Treatment-naïve patients % (n/N)	Prior relapsers % (n/N)	Prior partial responders % (n/N)	Prior null responders % (n/N)
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)

Efficacy in adults with HCV genotype 1 treated with an interferon-free regimen
Study HPC2002 (COSMOS)
This is an open-label, randomised phase 2a study to investigate the efficacy and safety of 12 or 24 weeks of simeprevir (150 mg once daily) in combination with sofosbuvir (400 mg once daily) with or without ribavirin in HCV genotype 1 infected prior null responders with METAVIR fibrosis score F0-F2 (Cohort 1), or treatment-naïve and prior null responder patients with METAVIR fibrosis score F3-F4 and compensated liver disease (Cohort 2).

The 80 enrolled patients without advanced hepatic fibrosis in Cohort 1 had a median age of 56 years (range 27 to 70 years; with 8% above 65 years); 61% were male; 71% were White, 29% Black or African American; and 25% Hispanic, 30% had a BMI ≥ 30 kg/m^2; 98% had baseline HCV RNA levels > 800,000 IU/ml; 41% had METAVIR fibrosis score F0 or F1 and 59% had METAVIR fibrosis score F2; 78% had HCV genotype 1a, and the remaining patients had HCV genotype 1b; 39% of the overall population and 50% of the patients with genotype 1a had Q80K polymorphism at baseline; 6% had *IL28B* CC genotype, 70% *IL28B* CT genotype, and 24% *IL28B* TT genotype. All patients were prior null responders to peginterferon alfa and ribavirin.
The 87 enrolled patients with advanced hepatic fibrosis in Cohort 2 had a median age of 58 years (range 28 to 70 years; with 3% above 65 years); 67% were male; 91% were White, 9% Black or African American; and 17% Hispanic 44% had a BMI ≥ 30 kg/m^2; 84% had baseline HCV RNA levels > 800,000 IU/ml; 53% had METAVIR fibrosis score F3 and 47% had METAVIR fibrosis score F4 (cirrhosis); 78% had HCV genotype 1a, and 22% HCV genotype 1b; 31% of the overall population and 40% of the patients with genotype 1a had Q80K polymorphism at baseline; 21% had *IL28B* CC genotype, 56% *IL28B* CT genotype, and 23% *IL28B* TT genotype. Fifty four percent of patients were prior null responders to peginterferon alfa and ribavirin and 46% were treatment-naïve.

In both cohorts, none of the patients from the 12-week treatment groups discontinued treatment due to an adverse event. In the 24-week treatment groups, the proportion of patients who discontinued treatment due to an adverse event was 3% and 2% in Cohort 1 and 2, respectively.

Table 20 shows the response rates for prior null responders in Cohort 1 and for treatment-naïve and prior null responder patients in Cohort 2.

Table 20: Treatment outcome in adult patients with HCV genotype 1 infection who were null responders to prior peginterferon alfa and ribavirin therapy or treatment-naïve receiving 12 weeks of simeprevir combination treatment with sofosbuvir with or without ribavirin (study HPC2002; final analysis; Intent-to-Treat analysis set)

Treatment outcome	Cohort 1 (Prior null responders; METAVIR fibrosis score F0-F2)		Cohort 2 (Treatment-naïve and prior null responders; METAVIR fibrosis score F3-F4)	
	Simeprevir + sofosbuvir + ribavirin 12 weeks % (n/N)	Simeprevir + sofosbuvir 12 weeks % (n/N)	Simeprevir + sofosbuvir + ribavirin 12 weeks % (n/N)	Simeprevir + sofosbuvir 12 weeks % (n/N)
SVR12	96% (26/27)	93% (13/14)	93% (25/27)	93% (13/14)
Outcome for patients without SVR12				
On-treatment failure[1]	0% (0/27)	0% (0/14)	0% (0/27)	0% (0/14)
Viral Relapse[2]	4% (1/27)	7% (1/14)	7% (2/27)	7% (1/14)
Missing SVR12[3]	0% (0/27)	0% (0/14)	0% (0/27)	0% (0/14)

150 mg once daily simeprevir for 12 weeks with 400 mg once daily sofosbuvir with or without ribavirin. SVR12: sustained virologic response 12 weeks after planned EOT.

[1] On-treatment failure was defined as the proportion of patients with confirmed detectable HCV RNA at EOT (including but not limited to patients who met the protocol-specified treatment stopping rules.

[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.

[3] Patients with missing data at the SVR assessment time point.

The overall SVR12 rate was 93% (26/28) in patients receiving 12 weeks treatment of simeprevir in combination with sofosbuvir without ribavirin when pooling both cohorts.

The overall SVR12 rates in patients receiving 12 weeks of simeprevir in combination with sofosbuvir with or without ribavirin were 95% (39/41) and 93% (38/41) in Cohort 1 and Cohort 2, respectively, and 94% (77/82) across both cohorts. Ribavirin use and prior treatment status (treatment-naïve and prior null responders) did not impact treatment outcome.

In Cohort 1, the SVR12 rates in the 24-week treatment groups were 79% (19/24) for the simeprevir with sofosbuvir with ribavirin treatment group and 93% (14/15) in the simeprevir with sofosbuvir without ribavirin treatment group. In Cohort 2, the SVR12 rates in the 24-week treatment groups were 93% (28/30) for the simeprevir with sofosbuvir with ribavirin treatment group and 100% (16/16) in the simeprevir with sofosbuvir without ribavirin treatment group. A total of 6 patients with viral relapse were reported (6/162, 4%): 4 occurred in HCV genotype 1a patients with baseline Q80K polymorphism (3 in Cohort 1 and 1 in Cohort 2) and 2 occurred in HCV genotype 1a patients without Q80K polymorphism.

Table 21 shows the SVR12 rates by HCV geno/subtype and Q80K baseline polymorphism.

Table 21: SVR12 rates in adult patients with HCV genotype 1 infection who were null responders to prior peginterferon alfa and ribavirin therapy or treatment-naïve by geno/subtype and Q80K baseline polymorphism (study HPC2002; final analysis; Intent-To-Treat analysis set)

Subgroup	Cohort 1 (Prior null responders; METAVIR fibrosis score F0-F2)		Cohort 2 (Treatment-naïve and prior null responders; METAVIR fibrosis score F3-F4)	
	Simeprevir + sofosbuvir + ribavirin 12 weeks % (n/N)	Simeprevir + sofosbuvir 12 weeks % (n/N)	Simeprevir + sofosbuvir + ribavirin 12 weeks % (n/N)	Simeprevir + sofosbuvir 12 weeks % (n/N)
Genotype 1a	95% (20/21)	90% (9/10)	91% (20/22)	91% (10/11)
Q80K	89% (8/9)	83% (5/6)	88% (7/8)	100% (3/3)
No Q80K	100% (12/12)	100% (4/4)	93% (13/14)	88% (7/8)
Genotype 1b	100% (6/6)	100% (4/4)	100% (5/5)	100% (3/3)

150 mg once daily simeprevir for 12 weeks with 400 mg once daily sofosbuvir with or without ribavirin. SVR12: sustained virologic response 12 weeks after planned EOT.

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 62% higher with a 90% confidence interval of 27% lower to 3.6-fold higher 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 class B) and 5.2-fold higher in non-HCV infected subjects with severe hepatic impairment (Child-Pugh class 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 class B or C). OLYSIO is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh class 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

2 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.

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

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

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
2. What you need to know before you take OLYSIO
3. How to take OLYSIO
4. Possible side effects
5. How to store OLYSIO
6. Contents of the pack and other information

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 hepatitis B infection
- 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.

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:

Medicine (active substance)	**Purpose of the medicine**
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	to prevent blood clots
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 12 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.

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 this medicine 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).

In clinical studies, the following side effects were reported in more than 1 in 10 patients taking this medicine in combination with sofosbuvir: feeling very tired, headache, nausea, difficulty sleeping and itching of the skin.

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.

Marketing Authorisation Holder
Janssen-Cilag International NV, Turnhoutseweg 30, B-2340 Beerse, Belgium

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

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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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.