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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OLYSIO® safely and effectively. See full prescribing information for OLYSIO.

OLYSIO (simeprevir) capsules, for oral use
Initial U.S. Approval: 2013

WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV
See full prescribing information for complete boxed warning.

Hepatitis B virus (HBV) reactivation has been reported, in some cases resulting in fulminant hepatitis, hepatic failure, and death. (5.1)

----------RECENT MAJOR CHANGES----------

Boxed warning	02/2017
Dosage and Administration (2.1)	02/2017
Warnings and Precautions (5.1)	02/2017

----------INDICATIONS AND USAGE----------

OLYSIO is a hepatitis C virus (HCV) NS3/4A protease inhibitor indicated for the treatment of adults with chronic hepatitis C virus (HCV) infection:

- in combination with sofosbuvir in patients with HCV genotype 1 without cirrhosis or with compensated cirrhosis
- in combination with peginterferon alfa (Peg-IFN-alfa) and ribavirin (RBV) in patients with HCV genotype 1 or 4 without cirrhosis or with compensated cirrhosis. (1)

Limitations of Use:

- Efficacy of OLYSIO in combination with Peg-IFN-alfa and RBV is substantially reduced in patients infected with HCV genotype 1a with an NS3 Q80K polymorphism. (2.1, 12.4)
- OLYSIO is not recommended in patients who have previously failed therapy with a treatment regimen that included OLYSIO or other HCV protease inhibitors. (1, 12.4)

----------DOSAGE AND ADMINISTRATION----------

- Testing Prior to the Initiation of Therapy:
  - Test all patients for HBV infection by measuring HBsAg and anti-HBc. (2.1)
  - Prior to initiation of treatment with OLYSIO in combination with Peg-IFN-alfa and RBV in patients infected with HCV genotype 1a, screening for the presence of virus with the NS3 Q80K polymorphism is strongly recommended and alternative therapy should be considered if Q80K is detected. (2.1, 12.4)
  - Monitor liver chemistry tests before and during OLYSIO combination therapy. (2.1, 5.3)
- Recommended dosage: One 150 mg capsule taken once daily with food. (2.2)

Treatment Regimens and Duration by Patient Population

Patient population	Treatment regimen	Duration
Genotype 1 without cirrhosis	OLYSIO + sofosbuvir	12 weeks
Genotype 1 with compensated cirrhosis (Child-Pugh A)	OLYSIO + sofosbuvir	24 weeks
Genotype 1 or 4 without cirrhosis or with compensated cirrhosis (Child-Pugh A), with or without HIV-1 co-infection	OLYSIO + Peg-IFN-alfa + RBV	12 weeks†
† followed by 12 or 36 additional weeks of Peg-IFN-alfa + RBV depending on prior response status and presence of HIV-1 co-infection. (2.2)		

- Refer to the Full Prescribing Information for details on stopping rules when discontinuing OLYSIO in combination with Peg-IFN-alfa + RBV and for information on dosing adjustment and interruption. (2.3, 2.4)
- OLYSIO is not recommended in patients with moderate or severe hepatic impairment (Child–Pugh B or C). (2.5)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 150 mg (3)

----------CONTRAINDICATIONS----------

Because OLYSIO is used only in combination with other antiviral drugs (including Peg-IFN-alfa and RBV) for the treatment of chronic HCV infection, the contraindications to other drugs also apply to the combination regimen. (4)

----------WARNINGS AND PRECAUTIONS----------

- Risk of Hepatitis B Virus Reactivation: Test all patients for evidence of current or prior HBV infection before initiation of HCV treatment. Monitor HCV/HBV coinfected patients for HBV reactivation and hepatitis flare during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated. (5.1)
- Serious Symptomatic Bradycardia with Sofosbuvir and Amiodarone coadministration: Serious symptomatic bradycardia may occur in patients taking amiodarone with sofosbuvir in combination with OLYSIO, particularly in patients also receiving beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with OLYSIO in combination with sofosbuvir is not recommended. In patients without alternative treatment options, cardiac monitoring is recommended. (5.2, 6.2, 7.3)
- Hepatic Decompensation and Hepatic Failure: Hepatic decompensation and hepatic failure, including fatal cases have been reported in patients with advanced and/or decompensated cirrhosis. Monitor liver chemistry tests before and during OLYSIO combination therapy. (5.3)
- Photosensitivity: Serious photosensitivity reactions have been observed during OLYSIO combination therapy. Use sun protection measures and limit sun exposure during OLYSIO combination therapy. Consider discontinuation if a photosensitivity reaction occurs. (5.5)
- Rash: Rash has been observed during OLYSIO combination therapy. Discontinue OLYSIO if severe rash occurs. (5.6)

----------ADVERSE REACTIONS----------

- Most common adverse events reported with OLYSIO with sofosbuvir during 12 or 24 weeks of treatment: fatigue, headache and nausea. (6.1)
- Most common adverse reactions reported with OLYSIO with Peg-IFN-alfa and RBV during first 12 weeks of treatment: rash (including photosensitivity), pruritus and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Products, LP at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- Coadministration of amiodarone with sofosbuvir in combination with OLYSIO may result in serious symptomatic bradycardia. (5.2, 7.3)
- Coadministration of OLYSIO with drugs that are moderate or strong inducers or inhibitors of CYP3A may significantly affect the plasma concentrations of simeprevir. The potential for drug-drug interactions must be considered prior to and during treatment. (5.8, 7, 12.3)
- Close monitoring of international normalized ratio (INR) values is recommended in patients receiving warfarin. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2017

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FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV

Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with OLYSIO. HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct-acting antivirals and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV coinfected patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

OLYSIO® is indicated for the treatment of adults with chronic hepatitis C virus (HCV) infection *[see Dosage and Administration (2.2) and Clinical Studies (14)]*:

- in combination with sofosbuvir in patients with HCV genotype 1 without cirrhosis or with compensated cirrhosis
- in combination with peginterferon alfa (Peg-IFN-alfa) and ribavirin (RBV) in patients with HCV genotype 1 or 4 without cirrhosis or with compensated cirrhosis.

Limitations of Use:

- Efficacy of OLYSIO in combination with Peg-IFN-alfa and RBV is substantially reduced in patients infected with HCV genotype 1a with an NS3 Q80K polymorphism at baseline compared to patients infected with hepatitis C virus (HCV) genotype 1a without the Q80K polymorphism *[see Dosage and Administration (2.1) and Microbiology (12.4)]*.
- OLYSIO is not recommended in patients who have previously failed therapy with a treatment regimen that included OLYSIO or other HCV protease inhibitors *[see Microbiology (12.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to the Initiation of Therapy

Testing for HBV infection

Test all patients for evidence of current or prior HBV infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) before initiating HCV treatment with OLYSIO *[see Warnings and Precautions (5.1)]*.

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Q80K Testing in HCV Genotype 1a-Infected Patients

OLYSIO in Combination with Sofosbuvir

In HCV genotype 1a-infected patients with compensated cirrhosis, screening for the presence of virus with the NS3 Q80K polymorphism may be considered prior to initiation of treatment with OLYSIO with sofosbuvir *[see Clinical Studies (14.2)]*.

OLYSIO in Combination with Peg-IFN-alfa and RBV

Prior to initiation of treatment with OLYSIO in combination with Peg-IFN-alfa and RBV, screening patients with HCV genotype 1a infection for the presence of virus with the NS3 Q80K polymorphism is strongly recommended and alternative therapy should be considered for patients infected with HCV genotype 1a containing the Q80K polymorphism *[see Indications and Usage (1) and Microbiology (12.4)]*.

Hepatic Laboratory Testing

Monitor liver chemistry tests before and during OLYSIO combination therapy *[see Warnings and Precautions (5.3)]*.

2.2 OLYSIO Combination Treatment

Administer OLYSIO in combination with other antiviral drugs for the treatment of chronic HCV infection. OLYSIO monotherapy is not recommended. The recommended dosage of OLYSIO is one 150 mg capsule taken orally once daily with food *[see Clinical Pharmacology (12.3)]*. The capsule should be swallowed as a whole. For specific dosing recommendations for the antiviral drugs used in combination with OLYSIO, refer to their respective prescribing information.

OLYSIO can be taken in combination with sofosbuvir or in combination with Peg-IFN-alfa and RBV.

OLYSIO in Combination with Sofosbuvir

Table 1 displays the recommended treatment regimen and duration of OLYSIO in combination with sofosbuvir in patients with chronic HCV genotype 1 infection.

Table 1: Recommended Treatment Regimen and Duration for OLYSIO and Sofosbuvir Combination Therapy in Patients with Chronic HCV Genotype 1 Infection

Patient Population (HCV Genotype 1)	Treatment Regimen and Duration
Treatment-naïve and treatment-experienced* patients:	
without cirrhosis	12 weeks of OLYSIO + sofosbuvir
with compensated cirrhosis (Child-Pugh A)	24 weeks of OLYSIO + sofosbuvir

* Treatment-experienced patients include prior relapsers, prior partial responders and prior null responders who failed prior IFN-based therapy *[see Clinical Studies (14)]*.

OLYSIO in Combination with Peg-IFN-alfa and RBV

Table 2 displays the recommended treatment regimen and duration of OLYSIO in combination with Peg-IFN-alfa and RBV in mono-infected and HCV/HIV-1 co-infected

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patients with HCV genotype 1 or 4 infection. Refer to Table 3 for treatment stopping rules for OLYSIO combination therapy with Peg-IFN-alfa and RBV.

Table 2: Recommended Treatment Regimen and Duration for OLYSIO, Peg-IFN-alfa, and RBV Combination Therapy in Patients with Chronic HCV Genotype 1 or 4 Infection

Patient Population (HCV Genotype 1 or 4)	Treatment Regimen and Duration
Treatment-naïve patients and prior relapsers[*]:	
HCV mono-infected patients without cirrhosis or with compensated cirrhosis (Child-Pugh A)	12 weeks of OLYSIO + Peg-IFN-alfa + RBV followed by additional 12 weeks of Peg-IFN-alfa + RBV (total treatment duration of 24 weeks)[†]
HCV/HIV-1 co-infected patients without cirrhosis	
HCV/HIV-1 co-infected patients with compensated cirrhosis (Child-Pugh A)	12 weeks of OLYSIO + Peg-IFN-alfa + RBV followed by additional 36 weeks of Peg-IFN-alfa + RBV (total treatment duration of 48 weeks)[†]
Prior non-responders (including partial[‡] and null responders[#]):	
HCV/HIV-1 co-infected or HCV mono-infected patients without cirrhosis or with compensated cirrhosis (Child-Pugh A)	12 weeks of OLYSIO + Peg-IFN-alfa + RBV followed by additional 36 weeks of Peg-IFN-alfa + RBV (total treatment duration of 48 weeks)[†]

HIV = human immunodeficiency virus.

[*] Prior relapser: HCV RNA not detected at the end of prior IFN-based therapy and HCV RNA detected during follow-up *[see Clinical Studies (14)]*.

[†] Recommended duration of treatment if patient does not meet stopping rules (see Table 3).

[‡] Prior partial responder: prior on-treatment ≥ 2 $\log_{10}$ IU/mL reduction in HCV RNA from baseline at Week 12 and HCV RNA detected at end of prior IFN-based therapy *[see Clinical Studies (14)]*.

[#] Prior null responder: prior on-treatment < 2 $\log_{10}$ IU/mL reduction in HCV RNA from baseline at Week 12 during prior IFN-based therapy *[see Clinical Studies (14)]*.

2.3 Discontinuation of Dosing

OLYSIO in Combination with Sofosbuvir

No treatment stopping rules apply to the combination of OLYSIO with sofosbuvir *[see Clinical Studies (14.2)]*.

OLYSIO in Combination with Peg-IFN-alfa and RBV

During treatment, HCV RNA levels should be monitored as clinically indicated using a sensitive assay with a lower limit of quantification of at least 25 IU/mL. Because patients with an inadequate on-treatment virologic response (i.e., HCV RNA greater or equal to 25 IU/mL) are not likely to achieve a sustained virologic response (SVR), discontinuation of treatment is recommended in these patients. Table 3 presents treatment stopping rules for patients who experience an inadequate on-treatment virologic response at Weeks 4, 12, and 24.

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Table 3: Treatment Stopping Rules in Patients Receiving OLYSIO in Combination with Peg-IFN-alfa and RBV with Inadequate On-Treatment Virologic Response

Treatment Week	HCV RNA	Action
Week 4	≥ 25 IU/mL	Discontinue OLYSIO, Peg-IFN-alfa, and RBV
Week 12		Discontinue Peg-IFN-alfa, and RBV (treatment with OLYSIO is complete at Week 12)
Week 24		Discontinue Peg-IFN-alfa, and RBV (treatment with OLYSIO is complete at Week 12)

2.4 Dosage Adjustment or Interruption

To prevent treatment failure, avoid reducing the dosage of OLYSIO or interrupting treatment. If treatment with OLYSIO is discontinued because of adverse reactions or inadequate on-treatment virologic response, OLYSIO treatment must not be reinitiated *[see Warnings and Precautions (5.3)]*.

If adverse reactions potentially related to the antiviral drug(s) used in combination with OLYSIO occur, refer to the instructions outlined in their respective prescribing information for recommendations on dosage adjustment or interruption.

If any of the other antiviral drug(s) used in combination with OLYSIO for the treatment of chronic HCV infection are permanently discontinued for any reason, OLYSIO should also be discontinued.

2.5 Not Recommended in Patients with Moderate or Severe Hepatic Impairment

OLYSIO is not recommended for patients with moderate or severe hepatic impairment (Child-Pugh B or C) *[see Warnings and Precautions (5.3), Adverse Reactions (6.1), Use in Specific Populations (8.8), and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

OLYSIO is available as a white gelatin capsule marked with “TMC435 150” in black ink. Each capsule contains 150 mg simeprevir.

4 CONTRAINDICATIONS

Because OLYSIO is used only in combination with other antiviral drugs (including Peg-IFN-alfa and RBV) for the treatment of chronic HCV infection, the contraindications to other drugs also apply to the combination regimen. Refer to the respective prescribing information for a list of contraindications.

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5 WARNINGS AND PRECAUTIONS

5.1 Risk of Hepatitis B Virus Reactivation in Patients Coinfected with HCV and HBV

Hepatitis B virus (HBV) reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct-acting antivirals, and who were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Cases have been reported in patients who are HBsAg positive and also in patients with serologic evidence of resolved HBV infection (i.e., HBsAg negative and anti-HBc positive). HBV reactivation has also been reported in patients receiving certain immunosuppressant or chemotherapeutic agents; the risk of HBV reactivation associated with treatment with HCV direct-acting antivirals may be increased in these patients.

HBV reactivation is characterized as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level. In patients with resolved HBV infection, reappearance of HBsAg can occur. Reactivation of HBV replication may be accompanied by hepatitis, i.e., increases in aminotransferase levels and, in severe cases, increases in bilirubin levels, liver failure, and death can occur.

Test all patients for evidence of current or prior HBV infection by measuring HBsAg and anti-HBc before initiating HCV treatment with OLYSIO. In patients with serologic evidence of HBV infection, monitor for clinical and laboratory signs of hepatitis flare or HBV reactivation during HCV treatment with OLYSIO and during post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.

5.2 Serious Symptomatic Bradycardia When Coadministered with Sofosbuvir and Amiodarone

Postmarketing cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone was coadministered with a sofosbuvir-containing regimen. A fatal cardiac arrest was reported in a patient taking amiodarone who was coadministered a sofosbuvir-containing regimen (ledipasvir/sofosbuvir). Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this effect is unknown.

Coadministration of amiodarone with OLYSIO in combination with sofosbuvir is not recommended. For patients taking amiodarone who have no other alternative treatment options, and who will be coadministered OLYSIO and sofosbuvir:

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- Counsel patients about the risk of serious symptomatic bradycardia.

- Cardiac monitoring in an in-patient setting for the first 48 hours of coadministration is recommended, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment.

Patients who are taking sofosbuvir in combination with OLYSIO who need to start amiodarone therapy due to no other alternative treatment options should undergo similar cardiac monitoring as outlined above.

Due to amiodarone's long elimination half-life, patients discontinuing amiodarone just prior to starting sofosbuvir in combination with OLYSIO should also undergo similar cardiac monitoring as outlined above.

Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately. Symptoms may include near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pain, confusion or memory problems *[see Adverse Reactions (6.2) and Drug Interactions (7.3)]*.

5.3 Hepatic Decompensation and Hepatic Failure

Hepatic decompensation and hepatic failure, including fatal cases, have been reported postmarketing in patients treated with OLYSIO in combination with Peg-IFN-alfa and RBV or in combination with sofosbuvir. Most cases were reported in patients with advanced and/or decompensated cirrhosis who are at increased risk for hepatic decompensation or hepatic failure. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made; and a causal relationship between treatment with OLYSIO and these events has not been established *[see Adverse Reactions (6.2)]*.

OLYSIO is not recommended for patients with moderate or severe hepatic impairment (Child-Pugh B or C) *[see Dosage and Administration (2.5) and Use in Specific Populations (8.8)]*.

In clinical trials of OLYSIO, modest increases in bilirubin levels were observed without impacting hepatic function *[see Adverse Reactions (6.1)]*. Postmarketing cases of hepatic decompensation with markedly elevated bilirubin levels have been reported. Monitor liver chemistry tests before and as clinically indicated during OLYSIO combination therapy. Patients who experience an increase in total bilirubin to greater than 2.5 times the upper limit of normal should be closely monitored:

- Patients should be instructed to contact their healthcare provider if they have onset of fatigue, weakness, lack of appetite, nausea and vomiting, jaundice or discolored feces.

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- Discontinue OLYSIO if elevation in bilirubin is accompanied by liver transaminase increases or clinical signs and symptoms of hepatic decompensation.

5.4 Risk of Serious Adverse Reactions Associated with Combination Treatment

Because OLYSIO is used in combination with other antiviral drugs for the treatment of chronic HCV infection, consult the prescribing information for these drugs before starting therapy with OLYSIO. Warnings and Precautions related to these drugs also apply to their use in OLYSIO combination treatment.

5.5 Photosensitivity

Photosensitivity reactions have been observed with OLYSIO combination therapy. Serious photosensitivity reactions resulting in hospitalization have been observed with OLYSIO in combination with Peg-IFN-alfa and RBV *[see Adverse Reactions (6.1)]*. Photosensitivity reactions occurred most frequently in the first 4 weeks of treatment, but can occur at any time during treatment. Photosensitivity may present as an exaggerated sunburn reaction, usually affecting areas exposed to light (typically the face, "V" area of the neck, extensor surfaces of the forearms, and dorsa of the hands). Manifestations may include burning, erythema, exudation, blistering, and edema.

Use sun protective measures and limit sun exposure during treatment with OLYSIO. Avoid use of tanning devices during treatment with OLYSIO. Discontinuation of OLYSIO should be considered if a photosensitivity reaction occurs and patients should be monitored until the reaction has resolved. If a decision is made to continue OLYSIO in the setting of a photosensitivity reaction, expert consultation is advised.

5.6 Rash

Rash has been observed with OLYSIO combination therapy *[see Adverse Reactions (6.1)]*. Rash occurred most frequently in the first 4 weeks of treatment, but can occur at any time during treatment. Severe rash and rash requiring discontinuation of OLYSIO have been reported in subjects receiving OLYSIO in combination with Peg-IFN-alfa and RBV. Most of the rash events in OLYSIO-treated patients were of mild or moderate severity *[see Adverse Reactions (6.1)]*. Patients with mild to moderate rashes should be followed for possible progression of rash, including the development of mucosal signs (e.g., oral lesions, conjunctivitis) or systemic symptoms. If the rash becomes severe, OLYSIO should be discontinued. Patients should be monitored until the rash has resolved.

5.7 Sulfa Allergy

OLYSIO contains a sulfonamide moiety. In subjects with a history of sulfa allergy (n=16), no increased incidence of rash or photosensitivity reactions has been observed. However, there are insufficient data to exclude an association between sulfa allergy and the frequency or severity of adverse reactions observed with the use of OLYSIO.

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5.8 Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions

Coadministration of OLYSIO with substances that are moderate or strong inducers or inhibitors of cytochrome P450 3A (CYP3A) is not recommended as this may lead to significantly lower or higher exposure of simeprevir, respectively, which may result in reduced therapeutic effect or adverse reactions *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

Because OLYSIO is administered in combination with other antiviral drugs, refer to the prescribing information of the antiviral drugs used in combination with OLYSIO for a description of adverse reactions associated with their use.

The following serious and otherwise important adverse reactions are described below and in other sections of the labeling:

- Serious Symptomatic Bradycardia When Coadministered with Sofosbuvir and Amiodarone *[see Warnings and Precautions (5.2) and Drug Interactions (7.3)]*
- Hepatic Decompensation and Hepatic Failure *[see Warnings and Precautions (5.3)]*
- Photosensitivity *[see Warnings and Precautions (5.5)]*
- Rash *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

OLYSIO in Combination with Sofosbuvir

The safety profile of OLYSIO in combination with sofosbuvir in patients with HCV genotype 1 infection with compensated cirrhosis (Child-Pugh A) or without cirrhosis is based on pooled data from the Phase 2 COSMOS trial and the Phase 3 OPTIMIST-1 and OPTIMIST-2 trials which included 317 subjects who received OLYSIO with sofosbuvir (without RBV) for 12 or 24 weeks *[see Clinical Studies (14.2)]*.

Table 4 lists adverse events (all grades) that occurred with at least 10% frequency among subjects receiving 12 or 24 weeks of treatment with OLYSIO 150 mg once daily in combination with sofosbuvir 400 mg once daily without RBV. The overall safety profile appeared similar among cirrhotic and non-cirrhotic subjects *[see Dosage and Administration (2.2)]*.

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The majority of the adverse events reported were Grade 1 or 2 in severity. Grade 3 or 4 adverse events were reported in 4% and 13% of subjects receiving 12 or 24 weeks of OLYSIO with sofosbuvir, respectively. Serious adverse events were reported in 2% and 3% of subjects receiving 12 or 24 weeks of OLYSIO with sofosbuvir, respectively. One percent and 6% of subjects receiving 12 or 24 weeks of OLYSIO with sofosbuvir, respectively, discontinued treatment due to adverse events.

Table 4: Adverse Events (all Grades) that Occurred ≥10% Frequency Among Subjects Receiving 12 or 24 Weeks of OLYSIO in Combination with Sofosbuvir[±]

Adverse Events	12 Weeks OLYSIO + Sofosbuvir N=286 % (n)	24 Weeks OLYSIO + Sofosbuvir N=31 % (n)
Headache	17 (49)	23 (7)
Fatigue	16 (47)	32 (10)
Nausea	14 (40)	13 (4)
Rash (including photosensitivity)	12 (34)	16 (5)
Diarrhea	6 (18)	16 (5)
Dizziness	3 (10)	16 (5)

[±] The 12 week group represents subjects pooled from COSMOS, OPTIMIST-1, and OPTIMIST-2 trials. The 24 week group represents subjects from COSMOS trial.

Rash and Photosensitivity

In trials of OLYSIO in combination with sofosbuvir, rash (including photosensitivity reactions) was observed in 12% of OLYSIO-treated subjects receiving 12 weeks of treatment compared to 16% of OLYSIO-treated subjects receiving 24 weeks of treatment.

Most of the rash events in OLYSIO-treated subjects were of mild or moderate severity (Grade 1 or 2). Among 317 subjects, Grade 3 rash was reported in one subject (<1%), leading to treatment discontinuation; none of the subjects experienced Grade 4 rash.

Most photosensitivity reactions were of mild severity (Grade 1); Grade 2 photosensitivity reactions were reported in 2 of 317 subjects (<1%). No Grade 3 or 4 photosensitivity reactions were reported and none of the subjects discontinued treatment due to photosensitivity reactions.

Laboratory Abnormalities

Among subjects who received OLYSIO in combination with sofosbuvir, the most common Grade 3 and 4 laboratory abnormalities were amylase and lipase elevations (Table 5). Most elevations in amylase and lipase were transient and of mild or moderate severity. Amylase and lipase elevations were not associated with pancreatitis.

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Table 5: Laboratory Abnormalities (WHO Worst Toxicity Grades 1 to 4) in Amylase, Hyperbilirubinemia and Lipase in Subjects Receiving 12 or 24 Weeks of OLYSIO in Combination with Sofosbuvir[±]

Laboratory Parameter	WHO Toxicity Range	12 Weeks OLYSIO + Sofosbuvir N=286 %	24 Weeks OLYSIO + Sofosbuvir N=31 %
Chemistry			
Amylase[*]			
Grade 1	≥ 1.1 to ≤ 1.5 x ULN[†]	12	26
Grade 2	> 1.5 to ≤ 2.0 x ULN	5	6
Grade 3	> 2.0 to ≤ 5.0 x ULN	5	10
Hyperbilirubinemia			
Grade 1	≥ 1.1 to ≤ 1.5 x ULN	12	16
Grade 2	> 1.5 to ≤ 3.0 x ULN	3	3
Grade 3	> 3.0 to ≤ 5.0 x ULN	< 1	0
Grade 4	> 5.0 x ULN	0	3
Lipase			
Grade 1	≥ 1.1 to ≤ 1.5 x ULN	5	3
Grade 2	> 1.5 to ≤ 3.0 x ULN	8	10
Grade 3	> 3.0 to ≤ 5.0 x ULN	< 1	3
Grade 4	> 5.0 x ULN	< 1	3

[±] The 12 week group represents subjects pooled from COSMOS, OPTIMIST-1, and OPTIMIST-2 trials. The 24 week group represents subjects from COSMOS trial.
[*] No Grade 4 changes in amylase were observed.
[†] ULN = Upper Limit of Normal

OLYSIO in Combination with Peg-IFN-alfa and RBV

The safety profile of OLYSIO in combination with Peg-IFN-alfa and RBV in patients with HCV genotype 1 infection is based on pooled data from three Phase 3 trials (QUEST-1, QUEST-2 and PROMISE) *[see Clinical Studies (14.3)]*. These trials included a total of 1178 subjects who received OLYSIO or placebo in combination with 24 or 48 weeks of Peg-IFN-alfa and RBV. Of the 1178 subjects, 781 subjects were randomized to receive OLYSIO 150 mg once daily for 12 weeks and 397 subjects were randomized to receive placebo once daily for 12 weeks.

In the pooled Phase 3 safety data, the majority of the adverse reactions reported during 12 weeks treatment with OLYSIO in combination with Peg-IFN-alfa and RBV were Grade 1 to 2 in severity. Grade 3 or 4 adverse reactions were reported in 23% of subjects receiving OLYSIO in combination with Peg-IFN-alfa and RBV versus 25% of subjects receiving placebo in combination with Peg-IFN-alfa and RBV. Serious adverse reactions were reported in 2% of subjects receiving OLYSIO in combination with Peg-IFN-alfa and RBV and in 3% of subjects receiving placebo in combination with Peg-IFN-alfa and RBV. Discontinuation of OLYSIO or placebo due to adverse reactions occurred in 2% and 1% of subjects receiving OLYSIO with Peg-IFN-alfa and RBV and subjects receiving placebo with Peg-IFN-alfa and RBV, respectively.

Table 6 lists adverse reactions (all Grades) that occurred with at least 3% higher frequency among subjects with HCV genotype 1 infection receiving OLYSIO 150 mg once daily in

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combination with Peg-IFN-alfa and RBV, compared to subjects receiving placebo in combination with Peg-IFN-alfa and RBV, during the first 12 weeks of treatment in the pooled Phase 3 trials in subjects who were treatment-naïve or who had previously relapsed after Peg-IFN-alfa and RBV therapy.

Table 6: Adverse Reactions (all Grades) that occurred ≥3% Higher Frequency Among Subjects with HCV Genotype 1 Infection Receiving OLYSIO Combination with Peg-IFN-alfa and RBV Compared to Subjects Receiving Placebo in Combination with Peg-IFN-alfa and RBV During the First 12 Weeks of Treatment in Subjects with Chronic HCV Infection[*] (Pooled Phase 3[†])

Adverse Reaction[‡]	OLYSIO 150 mg + Peg-IFN-alfa+ RBV First 12 Weeks N=781 % (n)	Placebo + Peg-IFN-alfa+ RBV First 12 Weeks N=397 % (n)
Rash (including photosensitivity)	28 (218)	20 (79)
Pruritus	22 (168)	15 (58)
Nausea	22 (173)	18 (70)
Myalgia	16 (126)	13 (53)
Dyspnea	12 (92)	8 (30)

[*] Subjects were treatment-naïve or had previously relapsed after Peg-IFN-alfa and RBV therapy.
[†] Pooled Phase 3 trials: QUEST 1, QUEST 2, PROMISE.
[‡] Adverse reactions that occurred at ≥ 3% higher frequency in the OLYSIO treatment group than in the placebo treatment group.

Rash and Photosensitivity

In the Phase 3 clinical trials of OLYSIO or placebo in combination with Peg-IFN-alfa and RBV, rash (including photosensitivity reactions) was observed in 28% of OLYSIO-treated subjects compared to 20% of placebo-treated subjects during the 12 weeks of treatment with OLYSIO or placebo in combination with Peg-IFN-alfa and RBV. Fifty-six percent (56%) of rash events in the OLYSIO group occurred in the first 4 weeks, with 42% of cases occurring in the first 2 weeks. Most of the rash events in OLYSIO-treated subjects were of mild or moderate severity (Grade 1 or 2). Severe (Grade 3) rash occurred in 1% of OLYSIO-treated subjects and in none of the placebo-treated subjects. There were no reports of life-threatening (Grade 4) rash. Discontinuation of OLYSIO or placebo due to rash occurred in 1% of OLYSIO-treated subjects, compared to less than 1% of placebo-treated subjects. The frequencies of rash and photosensitivity reactions were higher in subjects with higher simeprevir exposures.

All subjects enrolled in the Phase 3 trials were directed to use sun protection measures. In these trials, adverse reactions under the specific category of photosensitivity were reported in 5% of OLYSIO-treated subjects compared to 1% of placebo-treated subjects during the 12 weeks of treatment with OLYSIO or placebo in combination with Peg-IFN-alfa and RBV. Most photosensitivity reactions in OLYSIO-treated subjects were of mild or moderate severity (Grade 1 or 2). Two OLYSIO-treated subjects experienced photosensitivity reactions which resulted in hospitalization. No life-threatening photosensitivity reactions were reported.

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Dyspnea

During the 12 weeks of treatment with OLYSIO or placebo in combination with Peg-IFN-alfa and RBV, dyspnea was reported in 12% of OLYSIO-treated subjects compared to 8% of placebo-treated subjects (all grades; pooled Phase 3 trials). All dyspnea events reported in OLYSIO-treated subjects were of mild or moderate severity (Grade 1 or 2). There were no Grade 3 or 4 dyspnea events reported and no subjects discontinued treatment with OLYSIO due to dyspnea. Sixty-one percent (61%) of dyspnea events occurred in the first 4 weeks of treatment with OLYSIO.

Laboratory Abnormalities

Among subjects who received OLYSIO or placebo plus Peg-IFN-alfa and RBV, there were no differences between treatment groups for the following laboratory parameters: hemoglobin, neutrophils, platelets, aspartate aminotransferase, alanine aminotransferase, amylase, or serum creatinine. Laboratory abnormalities that were observed at a higher incidence in OLYSIO-treated subjects than in placebo-treated subjects are listed in Table 7.

Table 7: Laboratory Abnormalities (WHO Worst Toxicity Grades 1 to 4) Observed at a Higher Incidence in OLYSIO-Treated Subjects (Pooled Phase 3[*]; First 12 Weeks of Treatment)

Laboratory Parameter	WHO Toxicity Range	OLYSIO 150 mg + Peg-IFN-alfa + RBV N=781 %	Placebo + Peg-IFN-alfa + RBV N=397 %
Chemistry			
Alkaline phosphatase[†]			
Grade 1	> 1.25 to ≤ 2.50 x ULN[‡]	3	1
Grade 2	> 2.50 to ≤ 5.00 x ULN	< 1	0
Hyperbilirubinemia			
Grade 1	> 1.1 to ≤ 1.5 x ULN	27	15
Grade 2	> 1.5 to ≤ 2.5 x ULN	18	9
Grade 3	> 2.5 to ≤ 5.0 x ULN	4	2
Grade 4	> 5.0 x ULN	< 1	0

[*] Pooled Phase 3 trials: QUEST 1, QUEST 2, PROMISE.
[†] No Grade 3 or 4 changes in alkaline phosphatase were observed.
[‡] ULN = Upper Limit of Normal

Elevations in bilirubin were predominately mild to moderate (Grade 1 or 2) in severity, and included elevation of both direct and indirect bilirubin. Elevations in bilirubin occurred early after treatment initiation, peaking by study Week 2, and were rapidly reversible upon cessation of OLYSIO. Bilirubin elevations were generally not associated with elevations in liver transaminases. The frequency of elevated bilirubin was higher in subjects with higher simeprevir exposures.

Adverse Reactions in HCV/HIV-1 Co-infection

OLYSIO in combination with Peg-IFN-alfa and RBV was studied in 106 subjects with HCV genotype 1/HIV-1 co-infection (C212). The safety profile in HCV/HIV co-infected subjects was generally comparable to HCV mono-infected subjects.

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Adverse Reactions in HCV Genotype 4 Infection

OLYSIO in combination with Peg-IFN-alfa and RBV was studied in 107 subjects with HCV genotype 4 infection (RESTORE). The safety profile of OLYSIO in subjects with HCV genotype 4 infection was comparable to subjects with HCV genotype 1 infection.

Adverse Reactions in East Asian Subjects

OLYSIO in combination with Peg-IFN-alfa and RBV was studied in a Phase 3 trial conducted in China and South Korea in treatment-naïve subjects with chronic HCV genotype 1 infection (TIGER). The safety profile of OLYSIO in East Asian subjects was similar to that of the pooled Phase 3 population from global trials; however, a higher incidence of the laboratory abnormality hyperbilirubinemia was observed in patients receiving 150 mg OLYSIO plus Peg-IFN-alfa and RBV compared to patients receiving placebo plus Peg-IFN-alfa and RBV. Elevation of total bilirubin (all grades) was observed in 66% (99/151) of subjects treated with 150 mg OLYSIO plus Peg-IFN-alfa and RBV and in 26% (40/152) of subjects treated with placebo plus Peg-IFN-alfa and RBV. Bilirubin elevations were mainly Grade 1 or Grade 2. Grade 3 elevations in bilirubin were observed in 9% (13/151) of subjects treated with 150 mg OLYSIO plus Peg-IFN-alfa and RBV and in 1% (2/152) of subjects treated with placebo plus Peg-IFN-alfa and RBV. There were no Grade 4 elevations in bilirubin. The bilirubin elevations were not associated with increases in liver transaminases and were reversible after the end of treatment *[see Use in Specific Populations (8.6) and Clinical Studies (14.3)]*.

6.2 Postmarketing Experience

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

Cardiac Disorders: Serious symptomatic bradycardia has been reported in patients taking amiodarone who initiated treatment with a sofosbuvir-containing regimen *[see Warnings and Precautions (5.2) and Drug Interactions (7.3)]*.

Hepatobiliary Disorders: hepatic decompensation, hepatic failure *[see Warnings and Precautions (5.3)]*.

7 DRUG INTERACTIONS

7.1 Potential for OLYSIO to Affect Other Drugs

Simeprevir mildly inhibits CYP1A2 activity and intestinal CYP3A4 activity, but does not affect hepatic CYP3A4 activity. Coadministration of OLYSIO with drugs that are primarily metabolized by CYP3A4 may result in increased plasma concentrations of such drugs (see Table 8).

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Simeprevir inhibits OATP1B1/3, P-glycoprotein (P-gp) and BCRP transporters, and does not inhibit OCT2 *in vitro*. Coadministration of OLYSIO with drugs that are substrates for OATP1B1/3, and P-gp and BCRP transport may result in increased plasma concentrations of such drugs (see Table 8).

Fluctuations in INR values may occur in patients receiving warfarin concomitant with HCV treatment, including treatment with OLYSIO. Close monitoring of INR values is recommended during treatment and post-treatment follow-up.

7.2 Potential for Other Drugs to Affect OLYSIO

The primary enzyme involved in the biotransformation of simeprevir is CYP3A *[see Clinical Pharmacology (12.3)]*. Clinically relevant effects of other drugs on simeprevir pharmacokinetics via CYP3A may occur. Coadministration of OLYSIO with moderate or strong inhibitors of CYP3A may significantly increase the plasma exposure of simeprevir. Coadministration with moderate or strong inducers of CYP3A may significantly reduce the plasma exposure of simeprevir and lead to loss of efficacy (see Table 8). Therefore, coadministration of OLYSIO with substances that are moderate or strong inducers or inhibitors of CYP3A is not recommended *[see Warnings and Precautions (5.8) and Clinical Pharmacology (12.3)]*.

7.3 Established and Other Potentially Significant Drug Interactions

Table 8 shows the established and other potentially significant drug interactions based on which alterations in dose or regimen of OLYSIO and/or coadministered drug may be recommended. Drugs that are not recommended for coadministration with OLYSIO are also included in Table 8. For information regarding the magnitude of interaction, see Tables 9 and 10 *[see Clinical Pharmacology (12.3)]*.

Table 8: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class Drug Name	**Effect on Concentration of Simeprevir or Concomitant Drug**	**Clinical Comment**
Antiarrhythmics		
Amiodarone	Effect on amiodarone, simeprevir, and sofosbuvir concentrations unknown	Coadministration of amiodarone with OLYSIO in combination with sofosbuvir is not recommended because it may result in serious symptomatic bradycardia. If coadministration is required, cardiac monitoring is recommended *[see Warnings and Precautions (5.2), Adverse Reactions (6.2)]*.

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	↑ amiodarone	Caution is warranted and therapeutic drug monitoring of amiodarone, if available, is recommended for concomitant use of amiodarone with an OLYSIO-containing regimen that does not contain sofosbuvir.
Digoxin*	↑ digoxin	Routine therapeutic drug monitoring of digoxin concentrations is recommended.
Oral administration Disopyramide, Flecainide, Mexiletine, Propafenone, Quinidine	↑ antiarrhythmics	Therapeutic drug monitoring for these antiarrhythmics, if available, is recommended when coadministered with OLYSIO.
Anticonvulsants		
Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin	↓ simeprevir	Coadministration is not recommended.
Anti-infectives		
Antibiotics (systemic administration): Erythromycin*	↑ simeprevir ↑ erythromycin	Coadministration is not recommended.
Antibiotics (systemic administration): Clarithromycin, Telithromycin	↑ simeprevir	Coadministration is not recommended.
Antifungals (systemic administration): Itraconazole, Ketoconazole, Posaconazole	↑ simeprevir	Coadministration is not recommended.
Antifungals (systemic administration): Fluconazole, Voriconazole	↑ simeprevir	Coadministration is not recommended.
Antimycobacterials: Rifampin*†, Rifabutin, Rifapentine	↓ simeprevir ↔ rifampin, rifabutin, rifapentine	Coadministration is not recommended.
Calcium Channel Blockers (oral administration)		
Amlodipine, Diltiazem, Felodipine, Nicardipine, Nifedipine, Nisoldipine, Verapamil	↑ calcium channel blockers	Clinical monitoring of patients is recommended when OLYSIO is coadministered with calcium channel blockers.
Corticosteroids		
Systemic Dexamethasone	↓ simeprevir	Coadministration is not recommended.
Gastrointestinal Products		
Propulsive: Cisapride	↑ cisapride	Coadministration is not recommended.
HCV Products		
Antiviral: Ledipasvir‡	↑ ledipasvir ↑ simeprevir	Coadministration of OLYSIO with products containing ledipasvir is not recommended.
Herbal Products		

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Milk thistle (*Silybum marianum*)	↑ simeprevir	Coadministration is not recommended.
St. John's wort (*Hypericum perforatum*)	↓ simeprevir	Coadministration of OLYSIO with products containing St. John's wort is not recommended.
HIV Products		
Cobicistat-containing products	↑ simeprevir	Coadministration is not recommended.
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs): Efavirenz*	↓ simeprevir ↔ efavirenz	Coadministration is not recommended.
Other NNRTIs Delavirdine Etravirine, Nevirapine	 ↑ simeprevir ↓ simeprevir	Coadministration is not recommended.
Protease Inhibitors (PIs): Darunavir/ritonavir*,#	↑ simeprevir ↑ darunavir	Coadministration is not recommended.
Protease Inhibitors (PIs): Ritonavir*,§	↑ simeprevir	Coadministration is not recommended.
Other ritonavir-boosted or unboosted HIV PIs (Atazanavir, Fosamprenavir, Lopinavir, Indinavir, Nelfinavir, Saquinavir, Tipranavir)	↑ or ↓ simeprevir	Coadministration of OLYSIO with any HIV PI, with or without ritonavir is not recommended.
HMG CO-A Reductase Inhibitors		
Atorvastatin, Rosuvastatin, Simvastatin*	↑ statin	Coadministration of OLYSIO with statins is expected to increase statin concentrations, which is associated with increased risk of myopathy, including rhabdomyolysis. Use the lowest necessary statin dose, titrate the statin dose carefully, and monitor closely for statin-associated adverse reactions, such as myopathy or rhabdomyolysis.
Pitavastatin, Pravastatin, Lovastatin, Fluvastatin	↑statin	
Immunosuppressants		
Cyclosporine*	↑ cyclosporine ↑ simeprevir¶	Coadministration is not recommended.
Sirolimus	↑ or ↓ sirolimus	Routine monitoring of blood concentrations of sirolimus is recommended.
Phosphodiesterase Type 5 (PDE-5) Inhibitors		

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Sildenafil, Tadalafil, Vardenafil	↑ PDE-5 inhibitors	Dose adjustment of the PDE-5 inhibitor may be required when OLYSIO is coadministered 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. No dose adjustment is required when OLYSIO is coadministered with doses of sildenafil, tadalafil or vardenafil indicated for the treatment of erectile dysfunction.
Sedatives/Anxiolytics		
Midazolam* (oral administration)	↑ midazolam	Caution is warranted when midazolam, which has a narrow therapeutic index, is coadministered with OLYSIO.
Triazolam (oral administration)	↑ triazolam	Caution is warranted when triazolam, which has a narrow therapeutic index, is coadministered with OLYSIO.

The direction of the arrow (↑ = increase, ↓ = decrease, ↔ = no change) indicates the direction of the change in PK.

* These interactions have been studied in healthy adults with the recommended dose of 150 mg simeprevir once daily unless otherwise noted *[see Clinical Pharmacology (12.3), Tables 9* and *10]*.

† The dose of OLYSIO in this interaction study was 200 mg once daily both when given alone and when coadministered with rifampin 600 mg once daily.

‡ The interaction between simeprevir and ledipasvir was evaluated in a pharmacokinetic study in HCV-infected patients by comparing simeprevir exposure following simeprevir + 90/400 mg ledipasvir/sofosbuvir dosing versus simeprevir + 400 mg sofosbuvir dosing and by comparing ledipasvir exposure following simeprevir + 90/400 mg ledipasvir/sofosbuvir dosing versus 90/400 mg ledipasvir/sofosbuvir dosing.

The dose of OLYSIO in this interaction study was 50 mg when coadministered in combination with darunavir/ritonavir, compared to 150 mg in the OLYSIO alone treatment group.

§ The dose of OLYSIO in this interaction study was 200 mg once daily both when given alone and when coadministered in combination with ritonavir 100 mg given twice daily.

¶ Studied in combination with daclatasvir and RBV in a Phase 2 trial in HCV-infected post-liver transplant patients.

7.4 Drugs Without Clinically Significant Interactions with OLYSIO

In addition to the drugs included in Table 8, the interaction between OLYSIO and the following drugs were evaluated in clinical studies and no dose adjustments are needed for either drug *[see Clinical Pharmacology (12.3)]*: caffeine, daclatasvir, dextromethorphan, escitalopram, ethinyl estradiol/norethindrone, methadone, midazolam (intravenous administration), omeprazole, raltegravir, rilpivirine, sofosbuvir, tacrolimus, and tenofovir disoproxil fumarate.

No clinically relevant drug-drug interaction is expected when OLYSIO is coadministered with antacids, azithromycin, bedaquiline, corticosteroids (budesonide, fluticasone, methylprednisolone, and prednisone), dolutegravir, H_2-receptor antagonists, the narcotic analgesics buprenorphine and naloxone, NRTIs (such as abacavir, didanosine, emtricitabine, lamivudine, stavudine, zidovudine), maraviroc, methylphenidate, and proton pump inhibitors.

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8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

If OLYSIO is administered with RBV, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. Refer to prescribing information for RBV and for other drugs used in combination with OLYSIO for information on use in pregnancy.

No adequate human data are available to establish whether or not OLYSIO poses a risk to pregnancy outcomes. In animal reproduction studies with simeprevir, embryofetal developmental toxicity (including fetal loss) was observed in mice at simeprevir exposures greater than or equal to 1.9 times higher than exposure in humans at the recommended clinical dose while no adverse embryofetal developmental outcomes were observed in mice and rats at exposures similar to the exposure in humans at the recommended clinical dose *[see Data]*. Given these findings, pregnant women should be advised of potential risk to the fetus. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In embryofetal development studies in rats and mice, pregnant animals were administered simeprevir at doses up to 500 mg/kg/day (rats) and at 150, 500 and 1000 mg/kg/day (mice) on gestation days 6 to 17 (rats) and gestation days 6 to 15 (mice), resulting in late *in utero* fetal losses in mice at an exposure greater than or equal to 1.9 times higher than the exposure in humans at the recommended clinical dose. In addition, decreased fetal weights and an increase in fetal skeletal variations were observed in mice at exposures greater than or equal to 1.2 times higher than the exposure in humans at the recommended clinical dose. No adverse embryofetal developmental effects were observed in mice (at the lowest dose tested) or in rats (at up to the highest dose tested) at exposures similar to the exposure in humans at the recommended clinical dose.

In a rat pre- and post-natal development study, maternal animals were exposed to simeprevir from gestation day 6 to lactation/post-partum day 20 at doses up to 1000 mg/kg/day. At maternally toxic doses, the developing rat offspring exhibited significantly decreased body weight and negative effects on physical growth (delay and small size) and development (decreased motor activity) following simeprevir exposure *in utero* (via maternal dosing) and during lactation (via maternal milk to nursing pups) at maternal exposures similar to the exposure in humans at the recommended clinical dose. Subsequent survival, behavior and reproductive capacity of the offspring were not affected.

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8.2 Lactation

Risk Summary

It is not known whether OLYSIO and its metabolites are present in human breast milk, affect human milk production, or have effects on the breastfed infant. When administered to lactating rats, simeprevir was detected in plasma of nursing pups, likely due to the presence of simeprevir in milk *[see Data]*.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OLYSIO and any potential adverse effects on the breastfed child from OLYSIO or from the underlying maternal condition.

If OLYSIO is administered with RBV, the nursing mother's information for RBV also applies to this combination regimen. Refer to prescribing information for RBV and for other drugs used in combination with OLYSIO for more information on use during lactation.

Data

Animal Data

Although not measured directly, simeprevir was likely present in the milk of lactating rats in the pre- and post-natal development study, because systemic exposures (AUC) of simeprevir were observed in nursing pups on lactation/post-partum day 6 at concentrations approximately 10% of maternal simeprevir exposures *[see Use in Specific Populations (8.1)]*.

8.3 Females and Males of Reproductive Potential

If OLYSIO is administered with RBV, follow the recommendations for pregnancy testing and contraception within RBV's prescribing information. Refer to prescribing information for other drugs used in combination with OLYSIO for additional information on use in females and males of reproductive potential.

Infertility

There are no data on the effect of simeprevir on human fertility. Limited effects on male fertility were observed in animal studies *[see Nonclinical Toxicology (13.1)]*. If OLYSIO is administered with RBV, the information for RBV with regard to infertility also applies to this combination regimen. In addition, refer to prescribing information for other drugs used in combination with OLYSIO for information on effects on fertility.

8.4 Pediatric Use

The safety and efficacy of OLYSIO in pediatric patients have not been established.

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8.5 Geriatric Use

Clinical studies of OLYSIO did not include sufficient numbers of patients older than 65 years to determine whether they respond differently from younger patients. No dosage adjustment of OLYSIO is required in geriatric patients *[see Clinical Pharmacology (12.3)]*.

8.6 Race

Patients of East Asian ancestry exhibit higher simeprevir plasma exposures, but no dosage adjustment is required based on race *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.3)]*.

8.7 Renal Impairment

No dosage adjustment of OLYSIO is required in patients with mild, moderate or severe renal impairment *[see Clinical Pharmacology (12.3)]*. The safety and efficacy of OLYSIO have 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 dialysis. Simeprevir is highly protein-bound; therefore, dialysis is unlikely to result in significant removal of simeprevir *[see Clinical Pharmacology (12.3)]*.

Refer to the prescribing information for the other antiviral drug(s) used in combination with OLYSIO regarding their use in patients with renal impairment.

8.8 Hepatic Impairment

No dosage adjustment of OLYSIO is required in patients with mild hepatic impairment (Child-Pugh A) *[see Clinical Pharmacology (12.3)]*.

OLYSIO is not recommended for patients with moderate or severe hepatic impairment (Child-Pugh B or C). Simeprevir exposures are increased in patients with moderate or severe hepatic impairment (Child-Pugh B or C). In clinical trials of OLYSIO in combination with Peg-IFN-alfa and RBV, higher simeprevir exposures were associated with increased frequency of adverse reactions, including increased bilirubin, rash and photosensitivity. There have been postmarketing reports of hepatic decompensation, hepatic failure, and death in patients with advanced or decompensated cirrhosis receiving OLYSIO combination therapy *[see Dosage and Administration (2.5), Warnings and Precautions (5.3), Adverse Reactions (6.1, 6.2), and Clinical Pharmacology (12.3)]*.

The safety and efficacy of OLYSIO have not been established in liver transplant patients.

See the Peg-IFN-alfa prescribing information regarding its contraindication in patients with hepatic decompensation.

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10 OVERDOSAGE

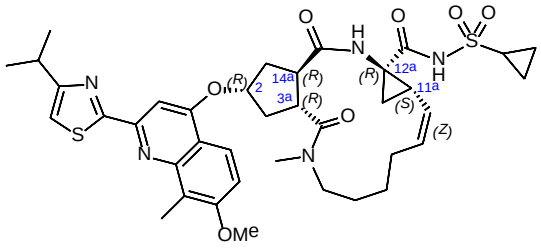
Human experience of overdose with OLYSIO is limited. There is no specific antidote for overdose with OLYSIO. In the event of an overdose, the patient's clinical status should be observed and the usual supportive measures employed.

Simeprevir is highly protein-bound; therefore, dialysis is unlikely to result in significant removal of simeprevir *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

OLYSIO (simeprevir) is an inhibitor of the HCV NS3/4A protease.

The chemical name for simeprevir is (2*R*,3a*R*,10*Z*,11a*S*,12a*R*,14a*R*)-*N*-(cyclopropylsulfonyl)-2-[[2-(4-isopropyl-1,3-thiazol-2-yl)-7-methoxy-8-methyl-4-quinolinyl]oxy]-5-methyl-4,14-dioxo-2,3,3a,4,5,6,7,8,9,11a,12,13,14,14a-tetradecahydrocyclopenta[*c*]cyclopropa[*g*][1,6]diazacyclotetradecine-12a(1*H*)-carboxamide. Its molecular formula is $C_{38}H_{47}N_5O_7S_2$ and its molecular weight is 749.94. Simeprevir has the following structural formula:



Simeprevir drug substance is a white to almost white powder. Simeprevir is practically insoluble in water over a wide pH range. It is practically insoluble in propylene glycol, very slightly soluble in ethanol, and slightly soluble in acetone. It is soluble in dichloromethane and freely soluble in some organic solvents (e.g., tetrahydrofuran and N,N-dimethylformamide).

OLYSIO (simeprevir) for oral administration is available as 150 mg strength hard gelatin capsules. Each capsule contains 154.4 mg of simeprevir sodium salt, which is equivalent to 150 mg of simeprevir. OLYSIO (simeprevir) capsules contain the following inactive ingredients: colloidal anhydrous silica, croscarmellose sodium, lactose monohydrate, magnesium stearate and sodium lauryl sulphate. The white capsule contains gelatin and titanium dioxide (E171) and is printed with ink containing iron oxide black (E172) and shellac (E904).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Simeprevir is a direct-acting antiviral (DAA) agent against the hepatitis C virus *[see Microbiology (12.4)]*.

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12.2 Pharmacodynamics

Cardiac Electrophysiology

In a thorough QT/QTc study in 60 healthy subjects, simeprevir 150 mg (recommended dose) and 350 mg (2.3 times the recommended dose) did not affect the QT/QTc interval.

12.3 Pharmacokinetics

The pharmacokinetic properties of simeprevir have been evaluated in healthy adult subjects and in adult HCV-infected subjects. Plasma C_{max} and AUC increased more than dose-proportionally 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. Plasma exposure (AUC) of simeprevir in HCV-infected subjects was about 2- to 3-fold higher compared to that observed in HCV-uninfected subjects. Plasma C_{max} and AUC of simeprevir were similar during coadministration of simeprevir with Peg-IFN-alfa and RBV compared with administration of simeprevir alone. In Phase 3 trials with Peg-IFN-alfa and RBV in HCV-infected subjects, the geometric mean steady-state pre-dose plasma concentration was 1009 ng/mL (geometric coefficient of variation [gCV] = 162%) and the geometric mean steady-state AUC_{24} was 39140 ng.h/mL (gCV = 98%).

Absorption

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

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

Effects of Food on Oral 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 breakfast (928 kcal) and by 69% after a normal-caloric breakfast (533 kcal), and delayed the absorption by 1 hour and 1.5 hours, respectively.

Distribution

Simeprevir is extensively bound to plasma proteins (greater than 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.

In animals, simeprevir is extensively distributed to gut and liver (liver:blood ratio of 29:1 in rat) tissues. *In vitro* data and physiologically-based pharmacokinetic modeling and simulations indicate that hepatic uptake in humans is mediated by OATP1B1/3.

Metabolism

Simeprevir is metabolized in the liver. *In vitro* experiments with human liver microsomes indicated that simeprevir primarily undergoes oxidative metabolism by the hepatic CYP3A

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system. Involvement of CYP2C8 and CYP2C19 cannot be excluded. Coadministration of OLYSIO with moderate or strong inhibitors of CYP3A may significantly increase the plasma exposure of simeprevir, and coadministration with moderate or strong inducers of CYP3A may significantly reduce the plasma exposure of simeprevir *[see Drug Interactions (7)]*.

Following a single oral administration of 200 mg (1.3 times the recommended dosage) ^{14}C-simeprevir to healthy subjects, the majority of the radioactivity in plasma (mean: 83%) 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 feces 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 feces. Less than 1% of the administered dose was recovered in urine. Unchanged simeprevir in feces accounted for on average 31% of the administered dose.

The terminal elimination half-life of simeprevir was 10 to 13 hours in HCV-uninfected subjects and 41 hours in HCV-infected subjects receiving 200 mg (1.3 times the recommended dosage) of simeprevir.

Specific Populations

Geriatric Use

There is limited data on the use of OLYSIO in patients aged 65 years and older. Age (18-73 years) had no clinically meaningful effect on the pharmacokinetics of simeprevir based on a population pharmacokinetic analysis of HCV-infected subjects treated with OLYSIO *[see Use in Specific Populations (8.5)]*.

Renal Impairment

Compared to HCV-uninfected subjects with normal renal function (classified using the Modification of Diet in Renal Disease [MDRD] eGFR formula; eGFR greater than or equal to 80 mL/min) the mean steady-state AUC of simeprevir was 62% higher in HCV-uninfected subjects with severe renal impairment (eGFR below 30 mL/min).

In a population pharmacokinetic analysis of mild or moderate renally impaired HCV-infected subjects treated with OLYSIO 150 mg once daily, creatinine clearance was not found to influence the pharmacokinetic parameters of simeprevir. It is therefore not expected that renal impairment will have a clinically relevant effect on the exposure to simeprevir *[see Use in Specific Populations (8.7)]*.

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

Hepatic Impairment

Compared to HCV-uninfected subjects with normal hepatic function, the mean steady-state AUC of simeprevir was 2.4-fold higher in HCV-uninfected subjects with moderate hepatic impairment (Child-Pugh B) and 5.2-fold higher in HCV-uninfected subjects with severe hepatic impairment (Child-Pugh C) *[see Use in Specific Populations (8.8)]*.

Based on a population pharmacokinetic analysis of HCV-infected subjects with mild hepatic impairment (Child-Pugh A) treated with OLYSIO, liver fibrosis stage did not have a clinically relevant effect on the pharmacokinetics of simeprevir.

Gender, Body Weight, Body Mass Index

Gender, body weight or body mass index have no clinically meaningful relevant effect on the pharmacokinetics of simeprevir based on a population pharmacokinetic analysis of HCV-infected subjects treated with OLYSIO.

Race

Population pharmacokinetic estimates of exposure of simeprevir were comparable between Caucasian and Black/African American HCV-infected subjects.

In a Phase 3 trial conducted in China and South Korea, the mean plasma exposure of simeprevir in East Asian HCV-infected subjects was 2.1-fold higher compared to non-Asian HCV-infected subjects in a pooled Phase 3 population from global trials *[see Use in Specific Populations (8.6)]*.

Patients co-infected with HIV-1

Simeprevir exposures were slightly lower in subjects with HCV genotype 1 infection with HIV-1 co-infection compared to subjects with HCV genotype 1 mono-infection. This difference is not considered to be clinically meaningful.

Drug Interactions

[See also Warnings and Precautions (5.8) and Drug Interactions (7)]

In vitro studies indicated that simeprevir is a substrate and mild inhibitor of CYP3A. Simeprevir does not affect CYP2C9, CYP2C19 or CYP2D6 *in vivo*. Simeprevir does not induce CYP1A2 or CYP3A4 *in vitro*. *In vivo*, simeprevir mildly inhibits the CYP1A2 activity and intestinal CYP3A4 activity, while it does not affect hepatic CYP3A4 activity. Simeprevir is not a clinically relevant inhibitor of cathepsin A enzyme activity.

In vitro, simeprevir is a substrate for P-gp, MRP2, BCRP, OATP1B1/3 and OATP2B1; simeprevir inhibits the uptake transporters OATP1B1/3 and NTCP and the efflux transporters P-gp/MDR1, MRP2, BCRP and BSEP and does not inhibit OCT2. The

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inhibitory effects of simeprevir on the bilirubin transporters OATP1B1/3 and MRP2 likely contribute to clinical observations of elevated bilirubin *[see Adverse Reactions (6.1)]*.

Simeprevir is transported into the liver by OATP1B1/3 where it undergoes metabolism by CYP3A. Based on results from *in vivo* studies, coadministration of OLYSIO with moderate or strong inhibitors of CYP3A may significantly increase the plasma exposure of simeprevir and coadministration with moderate or strong inducers of CYP3A may significantly reduce the plasma exposure of simeprevir, which may lead to loss of efficacy.

Drug interaction studies were performed in healthy adults with simeprevir (at the recommended dose of 150 mg once daily unless otherwise noted) and drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interactions. The effects of coadministration of other drugs on the C_{max}, AUC, and C_{min} values of simeprevir are summarized in Table 9 (effect of other drugs on OLYSIO). The effect of coadministration of OLYSIO on the C_{max}, AUC, and C_{min} values of other drugs are summarized in Table 10 (effect of OLYSIO on other drugs). For information regarding clinical recommendations, *see Drug Interactions (7)*.

Table 9: Drug Interactions: Pharmacokinetic Parameters for Simeprevir in the Presence of Coadministered Drugs

Coadministered Drug	Dose (mg) and Schedule		N	Effect on PK*	LS Mean Ratio (90% CI) of Simeprevir PK Parameters with/without Drug		
	Drug	Simeprevir			C_{max}	AUC	C_{min}
Cyclosporine†	individualized dose‡	150 mg q.d. for 14 days	10	↑	4.53 (3.05-6.74)	5.68 (3.58-9.00)	NA
Erythromycin	500 mg t.i.d. for 7 days	150 mg q.d. for 7 days	24	↑	4.53 (3.91-5.25)	7.47 (6.41-8.70)	12.74 (10.19-15.93)
Escitalopram	10 mg q.d. for 7 days	150 mg q.d. for 7 days	18	↓	0.80 (0.71-0.89)	0.75 (0.68-0.83)	0.68 (0.59-0.79)
Rifampin	600 mg q.d. for 7 days	200 mg q.d. for 7 days	18	↓	1.31 (1.03-1.66)	0.52 (0.41-0.67)	0.08 (0.06-0.11)
Tacrolimus†	individualized dose‡	150 mg q.d. for 14 days	25	↑	1.85 (1.40-2.46)	1.90 (1.37-2.63)	NA
Anti-HCV Drug							
Daclatasvir	60 mg q.d. for 7 days	150 mg q.d. for 7 days	24	↑	1.39 (1.27-1.52)	1.44 (1.32-1.56)	1.49 (1.33-1.67)
Ledipasvir#	90 mg q.d. for 14 days	150 mg q.d. for 14 days	20	↑	2.34 (1.95-2.81)	3.05 (2.34-3.84)	4.69 (3.40-6.47)
Sofosbuvir§	400 mg q.d.	150 mg q.d.	21	↔	0.96 (0.71-1.30)	0.94 (0.67-1.33)	NA
Anti-HIV Drugs							
Darunavir/Ritonavir¶	800/100 mg q.d. for 7 days	50 mg and 150 mg q.d. for 7 days	25	↑	1.79 (1.55-2.06)	2.59 (2.15-3.11)	4.58 (3.54-5.92)
Efavirenz	600 mg q.d. for 14 days	150 mg q.d. for 14 days	23	↓	0.49 (0.44-0.54)	0.29 (0.26-0.33)	0.09 (0.08-0.12)
Raltegravir	400 mg b.i.d. for 7 days	150 mg q.d. for 7 days	24	↔	0.93 (0.85-1.02)	0.89 (0.81-0.98)	0.86 (0.75-0.98)

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Rilpivirine	25 mg q.d. for 11 days	150 mg q.d. for 11 days	21	↔	1.10 (0.97-1.26)	1.06 (0.94-1.19)	0.96 (0.83-1.11)
Ritonavir	100 mg b.i.d. for 15 days	200 mg q.d. for 7 days	12	↑	4.70 (3.84-5.76)	7.18 (5.63-9.15)	14.35 (10.29-20.01)
Tenofovir disoproxil fumarate	300 mg q.d. for 7 days	150 mg q.d. for 7 days	24	↓	0.85 (0.73-0.99)	0.86 (0.76-0.98)	0.93 (0.78-1.11)

CI = Confidence Interval; N = number of subjects with data; NA = not available; PK = pharmacokinetics; LS = least square; q.d. = once daily; b.i.d. = twice daily; t.i.d. = three times a day

* The direction of the arrow (↑ = increase, ↓ = decrease, ↔ = no change) indicates the direction of the change in PK (i.e., AUC).

† Comparison based on historic controls. Data from a Phase 2 trial in combination with daclatasvir and RBV in HCV-infected post-liver transplant patients.

‡ Individualized dose at the discretion of the physician, according to local clinical practice.

The interaction between simeprevir and ledipasvir was evaluated in a pharmacokinetic study in HCV-infected patients, by comparing simeprevir exposure following simeprevir + 90/400 mg ledipasvir/sofosbuvir dosing versus simeprevir + 400 mg sofosbuvir dosing.

§ Comparison based on historic controls. The interaction between simeprevir and sofosbuvir was evaluated in a pharmacokinetic substudy within a Phase 2 trial in HCV-infected patients.

¶ The dose of OLYSIO in this interaction study was 50 mg when coadministered in combination with darunavir/ritonavir compared to 150 mg once daily in the OLYSIO alone treatment group.

Table 10: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of OLYSIO

Coadministered Drug	**Dose (mg) and Schedule**		**N**	**Effect on PK***	**LS Mean Ratio (90% CI) of Coadministered Drug PK Parameters with/without OLYSIO**		
	Drug	**Simeprevir**			**C_{max}**	**AUC**	**C_{min}**
Atorvastatin	40 mg single dose	150 mg q.d. for 10 days	18	↑	1.70 (1.42-2.04)	2.12 (1.72-2.62)	NA
2-hydroxy-atorvastatin				↑	1.98 (1.70-2.31)	2.29 (2.08-2.52)	NA
Caffeine	150 mg	150 mg q.d. for 11 days	16	↑	1.12 (1.06-1.19)	1.26 (1.21-1.32)	NA
Cyclosporine	100 mg single dose	150 mg q.d. for 7 days	14	↑	1.16 (1.07-1.26)	1.19 (1.13-1.26)	NA
Dextromethorphan	30 mg	150 mg q.d. for 11 days	16	↑	1.21 (0.93-1.57)	1.08 (0.87-1.35)	NA
Dextrorphan				↔	1.03 (0.93-1.15)	1.09 (1.03-1.15)	NA
Digoxin	0.25 mg single dose	150 mg q.d. for 7 days	16	↑	1.31 (1.14-1.51)	1.39 (1.16-1.67)	NA
Erythromycin	500 mg t.i.d. for 7 days	150 mg q.d. for 7 days	24	↑	1.59 (1.23-2.05)	1.90 (1.53-2.36)	3.08 (2.54-3.73)
Escitalopram	10 mg q.d. for 7 days	150 mg q.d. for 7 days	17	↔	1.03 (0.99-1.07)	1.00 (0.97-1.03)	1.00 (0.95-1.05)
Ethinyl estradiol (EE), coadministered with norethindrone (NE)	0.035 mg q.d. EE + 1 mg q.d. NE for 21 days	150 mg q.d. for 10 days	18	↔	1.18 (1.09-1.27)	1.12 (1.05-1.20)	1.00 (0.89-1.13)
Midazolam (oral)	0.075 mg/kg	150 mg q.d. for 10 days	16	↑	1.31 (1.19-1.45)	1.45 (1.35-1.57)	NA
Midazolam (i.v.)	0.025 mg/kg	150 mg q.d. for 11 days	16	↑	0.78 (0.52-1.17)	1.10 (0.95-1.26)	NA
R(-) methadone†	30-150 mg q.d., individualized dose	150 mg q.d. for 7 days	12	↔	1.03 (0.97-1.09)	0.99 (0.91-1.09)	1.02 (0.93-1.12)

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Norethindrone (NE), coadministered with EE	0.035 mg q.d. EE + 1 mg q.d. NE for 21 days	150 mg q.d. for 10 days	18	↔	1.06 (0.99-1.14)	1.15 (1.08-1.22)	1.24 (1.13-1.35)
Omeprazole	40 mg single dose	150 mg q.d. for 11 days	16	↑	1.14 (0.93-1.39)	1.21 (1.00-1.46)	NA
Rifampin	600 mg q.d. for 7 days	200 mg q.d. for 7 days	18	↔	0.92 (0.80-1.07)	1.00 (0.93-1.08)	NA
25-desacetyl-rifampin			17	↑	1.08 (0.98-1.19)	1.24 (1.13-1.36)	NA
Rosuvastatin	10 mg single dose	150 mg q.d. for 7 days	16	↑	3.17 (2.57-3.91)	2.81 (2.34-3.37)	NA
Simvastatin	40 mg single dose	150 mg q.d. for 10 days	18	↑	1.46 (1.17-1.82)	1.51 (1.32-1.73)	NA
Simvastatin acid				↑	3.03 (2.49-3.69)	1.88 (1.63-2.17)	NA
Tacrolimus	2 mg single dose	150 mg q.d. for 7 days	14	↓	0.76 (0.65-0.90)	0.83 (0.59-1.16)	NA
S-Warfarin	10 mg single dose	150 mg q.d. for 11 days	16	↔	1.00 (0.94-1.06)	1.04 (1.00-1.07)	NA
Anti-HCV Drug							
Daclatasvir	60 mg q.d. for 7 days	150 mg q.d. for 7 days	24	↑	1.50 (1.39-1.62)	1.96 (1.84-2.10)	2.68 (2.42-2.98)
Ledipasvir‡	90 mg q.d. for 14 days	150 mg q.d. for 14 days	20	↑	1.64 (1.45-1.86)	1.75 (1.56-1.96)	1.74 (1.55-1.97)
Sofosbuvir#	400 mg q.d.	150 mg q.d.	22	↑	1.91 (1.26-2.90)	3.16 (2.25-4.44)	NA
GS-331007§				↔	0.69 (0.52-0.93)	1.09 (0.87-1.37)	NA
Anti-HIV Drugs							
Darunavir¶	800 mg q.d. for 7 days	50 mg q.d. for 7 days	25	↑	1.04 (0.99-1.10)	1.18 (1.11-1.25)	1.31 (1.13-1.52)
Ritonavir¶	100 mg q.d. for 7 days			↑	1.23 (1.14-1.32)	1.32 (1.25-1.40)	1.44 (1.30-1.61)
Efavirenz	600 mg q.d. for 14 days	150 mg q.d. for 14 days	23	↔	0.97 (0.89-1.06)	0.90 (0.85-0.95)	0.87 (0.81-0.93)
Raltegravir	400 mg b.i.d. for 7 days	150 mg q.d. for 7 days	24	↑	1.03 (0.78-1.36)	1.08 (0.85-1.38)	1.14 (0.97-1.36)
Rilpivirine	25 mg q.d. for 11 days	150 mg q.d. for 11 days	23	↔	1.04 (0.95-1.13)	1.12 (1.05-1.19)	1.25 (1.16-1.35)
Tenofovir disoproxil fumarate	300 mg q.d. for 7 days	150 mg q.d. for 7 days	24	↔	1.19 (1.10-1.30)	1.18 (1.13-1.24)	1.24 (1.15-1.33)

CI = Confidence Interval; i.v.= intravenous; N = number of subjects with data; NA = not available; PK = pharmacokinetics; LS = least square; q.d. = once daily; b.i.d. = twice daily; t.i.d. = three times a day

* The direction of the arrow (↑ = increase, ↓ = decrease, ↔ = no change) indicates the direction of the change in PK (i.e., AUC).

† The interaction between simeprevir and the drug was evaluated in a pharmacokinetic study in opioid-dependent adults on stable methadone maintenance therapy.

‡ The interaction between simeprevir and ledipasvir was evaluated in a pharmacokinetic study in HCV-infected patients by comparing ledipasvir exposure following simeprevir + 90/400 mg ledipasvir/sofosbuvir dosing versus 90/400 mg ledipasvir/sofosbuvir dosing.

Comparison based on historic controls. The interaction between simeprevir and sofosbuvir was evaluated in a pharmacokinetic substudy within a Phase 2 trial in HCV-infected patients.

§ Primary circulating metabolite of sofosbuvir.

¶ The dose of OLYSIO in this interaction study was 50 mg when coadministered in combination with darunavir/ritonavir which is lower than the recommended 150 mg dose.

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12.4 Microbiology

Mechanism of Action

Simeprevir is an inhibitor of the HCV NS3/4A 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

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 protease inhibitor treatment-naïve genotype 1a- or genotype 1b-infected patients displayed median fold change (FC) in EC_{50} values of 1.4 (interquartile range, IQR: 0.8 to 11; N=78) and 0.4 (IQR: 0.3 to 0.7; N=59) compared to reference genotype 1b replicon, respectively. Genotype 1a (N=33) and 1b (N=2) isolates with a baseline Q80K polymorphism resulted in median FC in simeprevir EC_{50} value of 11 (IQR: 7.4 to 13) and 8.4, respectively. Chimeric replicons carrying NS3 sequences derived from HCV protease inhibitor treatment-naïve genotype 4a-, 4d-, or 4r-infected patients displayed median FC in EC_{50} values of 0.5 (IQR: 0.4 to 0.6; N=38), 0.4 (IQR: 0.2 to 0.5; N=24), and 1.6 (IQR: 0.7 to 4.5; N=8), compared to reference genotype 1b replicon, respectively. A pooled analysis of chimeric replicons carrying the NS3 sequences from HCV protease inhibitor-naïve patients infected with other HCV genotype 4 subtypes, including 4c (N=1), 4e (N=2), 4f (N=3), 4h (N=3), 4k (N=1), 4o (N=2), 4q (N=2), or unidentified subtype (N=7) displayed a median FC in EC_{50} value of 0.7 (IQR: 0.5 to 1.1; N=21) compared to reference genotype 1b replicon. The presence of 50% human serum reduced simeprevir replicon activity by 2.4-fold. Combination of simeprevir with IFN, RBV, NS5A inhibitors, nucleoside analog NS5B polymerase inhibitors or non-nucleoside analog NS5B polymerase inhibitors, including NS5B thumb 1-, thumb 2-, and palm-domain targeting drugs, was not antagonistic.

Resistance in Cell Culture

Resistance to simeprevir was characterized in HCV genotype 1a and 1b replicon-containing cells. Ninety-six percent (96%) of simeprevir-selected genotype 1 replicons carried one or multiple amino acid substitutions at NS3 protease positions F43, Q80, R155, A156, and/or D168, 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 F43, Q80, S122, R155, A156, and D168 reduced susceptibility to simeprevir. Replicons with D168V or A, and R155K substitutions displayed large reductions in susceptibility to simeprevir (FC in EC_{50} value greater than 50), whereas other substitutions such as Q80K or R, S122R, and D168E displayed lower reductions in susceptibility (FC in EC_{50} value between 2 and 50). Other substitutions such as Q80G or L, S122G, N or T did

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not reduce susceptibility to simeprevir in the replicon assay (FC in EC_{50} value lower than 2). Amino acid substitutions at NS3 positions Q80, S122, R155, and/or D168 that were associated with lower reductions in susceptibility to simeprevir when occurring alone, reduced susceptibility to simeprevir by more than 50-fold when present in combination.

Resistance in Clinical Studies

In a pooled analysis of subjects treated with 150 mg OLYSIO in combination with Peg-IFN-alfa and RBV who did not achieve SVR in the controlled Phase 2 and Phase 3 clinical trials (PILLAR, ASPIRE, QUEST 1 and QUEST 2, PROMISE), emerging virus with amino acid substitutions at NS3 positions Q80, S122, R155 and/or D168 were observed in 180 out of 197 (91%) subjects. Substitutions D168V and R155K alone or in combination with other substitutions at these positions emerged most frequently (Table 11). Most of these emerging substitutions have been shown to reduce susceptibility to simeprevir in cell culture replicon assays.

HCV genotype 1 subtype-specific patterns of simeprevir treatment-emergent amino acid substitutions were observed. HCV genotype 1a predominately had emerging R155K alone or in combination with amino acid substitutions at NS3 positions Q80, S122 and/or D168, while HCV genotype 1b had most often an emerging D168V substitution (Table 11). In HCV genotype 1a with a baseline Q80K amino acid polymorphism, an emerging R155K substitution was observed most frequently at failure.

Table 11: Emergent Amino Acid Substitutions in Controlled Phase 2 and Phase 3 Trials: Subjects who did not Achieve SVR with 150 mg OLYSIO in Combination with Peg-IFN-alfa and RBV

Emerging Amino Acid Substitutions in NS3	Genotype 1a* N=116 % (n)	Genotype 1b N=81 % (n)
Any substitution at NS3 position F43, Q80, S122, R155, A156, or D168†	95 (110)	86 (70)
D168E	15 (17)	17 (14)
D168V	10 (12)	60 (49)
Q80R‡	4 (5)	12 (10)
R155K	77 (89)	0 (0)
Q80X+D168X#	4 (5)	14 (11)
R155X+D168X#	13 (15)	4 (3)
Q80K‡, S122A/G/I/T‡, S122R, R155Q‡, D168A, D168F‡, D168H, D168T, I170T§	Less than 10%	Less than 10%

* May include few subjects infected with HCV genotype 1 viruses of non-1a/1b subtypes.
† Alone or in combination with other substitutions (includes mixtures).
‡ Substitutions only observed in combinations with other emerging substitutions at one or more of the NS3 positions Q80, S122, R155 and/or D168.
# Subjects with virus carrying these combinations are also included in other rows describing the individual substitutions. X represents multiple amino acids. Other double or triple substitutions were observed with lower frequencies.
§ Emerged alone (n=2) or in combination with R155K (n=3).
Note: substitutions at NS3 position F43 and A156 were selected in cell culture and associated with reduced simeprevir activity in the replicon assay but were not observed at time of failure.

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The majority of HCV genotype 1-infected subjects treated with OLYSIO in combination with sofosbuvir (with or without RBV) for 12 or 24 weeks who did not achieve SVR due to virologic reasons and with sequencing data available had emerging NS3 amino acid substitutions at position 168 and/or R155K: 5 out of 6 subjects in COSMOS and 1 out of 3 subjects in OPTIMIST-1. The emerging NS3 amino acid substitutions were similar to those observed in subjects who did not achieve SVR following treatment with OLYSIO in combination with Peg-IFN-alfa and RBV. No emerging NS5B amino acid substitutions associated with sofosbuvir resistance were observed in subjects who did not achieve SVR following treatment of OLYSIO in combination with sofosbuvir (with or without RBV) for 12 or 24 weeks.

In the RESTORE trial in genotype 4-infected subjects, 30 out of 34 (88%) subjects who did not achieve SVR had emerging amino acid substitutions at NS3 positions Q80, T122, R155, A156 and/or D168 (mainly substitutions at position D168; 26 out of 34 [76%] subjects), similar to the emerging amino acid substitutions observed in genotype 1-infected subjects.

Persistence of Resistance–Associated Substitutions

The persistence of simeprevir-resistant virus was assessed following treatment failure in the pooled analysis of subjects receiving 150 mg OLYSIO in combination with Peg-IFN-alfa and RBV in the controlled Phase 2 and Phase 3 trials. The proportion of subjects with detectable levels of treatment-emergent, resistance-associated variants was followed post-treatment for a median time of 28 weeks (range 0 to 70 weeks). Resistant variants remained at detectable levels in 32 out of 66 subjects (48%) with single emerging R155K and in 16 out of 48 subjects (33%) with single emerging D168V.

The lack of detection of virus containing a resistance-associated substitution does not necessarily indicate that the resistant virus is no longer present at clinically significant levels. The long-term clinical impact of the emergence or persistence of virus containing OLYSIO-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. In the pooled analysis of the Phase 3 trials QUEST 1 and QUEST 2, and in the PROMISE trial, the efficacy of OLYSIO in combination with Peg-IFN-alfa and RBV was substantially reduced in subjects infected with HCV genotype 1a virus with the NS3 Q80K polymorphism at baseline *[see Clinical Studies (14.3)]*.

The observed prevalence of NS3 Q80K polymorphic variants at baseline in the overall population of the Phase 2 and Phase 3 trials (PILLAR, ASPIRE, PROMISE, QUEST 1 and QUEST 2) was 14%; while the observed prevalence of the Q80K polymorphism was 30% in subjects infected with HCV genotype 1a and 0.5% in subjects infected with HCV

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genotype 1b. The observed prevalence of Q80K polymorphic variants at baseline in the U.S. population of these Phase 2 and Phase 3 trials was 35% overall, 48% in subjects infected with HCV genotype 1a and 0% in subjects infected with HCV genotype 1b. With the exception of the NS3 Q80K polymorphism, baseline HCV variants with polymorphisms at NS3 positions F43, Q80, S122, R155, A156, and/or D168 that were associated with reduced simeprevir activity in replicon assays were generally uncommon (1.3%) in subjects with HCV genotype 1 infection in these Phase 2 and Phase 3 trials (n=2007).

The Q80K polymorphic variant was not observed in subjects infected with HCV genotype 4.

Cross-Resistance

Based on resistance patterns observed in cell culture replicon studies and HCV-infected subjects, cross-resistance between OLYSIO and other NS3/4A protease inhibitors is expected. No cross-resistance is expected between direct-acting antiviral agents with different mechanisms of action. OLYSIO remained fully active against substitutions associated with resistance to NS5A inhibitors, NS5B nucleoside and non-nucleoside polymerase inhibitors.

12.5 Pharmacogenomics

A genetic variant near the gene encoding interferon-lambda-3 (*IL28B* rs12979860, a C [cytosine] to T [thymine] substitution) is a strong predictor of response to Peg-IFN-alfa and RBV (PR). In the Phase 3 trials, *IL28B* genotype was a stratification factor.

Overall, SVR rates were lower in subjects with the CT and TT genotypes compared to those with the CC genotype (Tables 12 and 13). Among both treatment-naïve subjects and those who experienced previous treatment failures, subjects of all *IL28B* genotypes had the highest SVR rates with OLYSIO-containing regimens (Table 12).

Table 12: SVR12 Rates by *IL28B* rs12979860 Genotype in Adult Subjects with HCV Genotype 1 Infection Receiving OLYSIO 150 mg Once Daily with Peg-IFN-alfa and RBV Compared to Subjects Receiving Placebo with Peg-IFN-alfa and RBV (QUEST 1, QUEST 2, PROMISE)

Trial (Population)	*IL28B* rs12979860 Genotype	OLYSIO + PR % (n/N)	Placebo + PR % (n/N)
QUEST 1 and QUEST 2 (treatment-naïve subjects)	C/C	95 (144/152)	80 (63/79)
	C/T	78 (228/292)	41 (61/147)
	T/T	61 (47/77)	21 (8/38)
PROMISE (prior relapsers)	C/C	89 (55/62)	53 (18/34)
	C/T	78 (131/167)	34 (28/83)
	T/T	65 (20/31)	19 (3/16)

SVR12: sustained virologic response 12 weeks after planned end of treatment (EOT).

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Table 13: SVR12 Rates by *IL28B* rs12979860 Genotype in Adult Patients Receiving OLYSIO 150 mg Once Daily in Combination with Peg-IFN-alfa and RBV (C212 and RESTORE)

Trial (Population)	*IL28B* rs12979860 Genotype	Treatment-Naïve Subjects % (n/N)	Prior Relapsers % (n/N)	Prior Partial Responders % (n/N)	Prior Null Responders % (n/N)
C212 (HIV-1 co-infection)	C/C	100 (15/15)	100 (7/7)	100 (1/1)	80 (4/5)
	C/T	70 (19/27)	100 (6/6)	71 (5/7)	53 (10/19)
	T/T	80 (8/10)	0 (0/2)	50 (1/2)	50 (2/4)
RESTORE (HCV genotype 4)	C/C	100 (7/7)	100 (1/1)	-	-
	C/T	82 (14/17)	82 (14/17)	60 (3/5)	41 (9/22)
	T/T	80 (8/10)	100 (4/4)	60 (3/5)	39 (7/18)

SVR12: sustained virologic response 12 weeks after planned EOT.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Simeprevir was not genotoxic in a series of *in vitro* and *in vivo* tests including the Ames test, the mammalian forward mutation assay in mouse lymphoma cells or the *in vivo* mammalian micronucleus test. Carcinogenicity studies with simeprevir have not been conducted.

If OLYSIO is administered in a combination regimen containing RBV, refer to the prescribing information for RBV for information on carcinogenesis and mutagenesis.

Impairment of Fertility

In a rat fertility study at doses up to 500 mg/kg/day, 3 male rats treated with simeprevir (2/24 rats at 50 mg/kg/day and 1/24 rats at 500 mg/kg/day) showed no motile sperm, small testes and epididymides, and resulted in infertility in 2 out of 3 of the male rats at exposures less than the exposure in humans at the recommended clinical dose.

If OLYSIO is administered with Peg-IFN-alfa and RBV, refer to the prescribing information for Peg-IFN-alfa and RBV for information on impairment of fertility.

13.2 Animal Toxicology and/or Pharmacology

Cardiovascular toxicity consisting of acute endocardial and myocardial necrosis restricted to the left ventricular subendocardial area was seen in 2 out of 6 animals in a 2-week oral dog toxicity study at an exposure approximately 28 times the mean AUC in humans at the recommended daily dose of 150 mg. No cardiac findings were observed in a 6-month and a 9-month oral toxicity study at exposures, respectively, of 11 and 4 times the mean AUC in humans at the recommended daily dose of 150 mg.

If OLYSIO is administered with Peg-IFN-alfa and RBV, refer to the prescribing information for Peg-IFN-alfa and RBV for information on animal toxicology.

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14 CLINICAL STUDIES

14.1 Overview of Clinical Trials

The efficacy of OLYSIO in combination with sofosbuvir in subjects with HCV genotype 1 infection was evaluated in one Phase 2 trial (COSMOS) in prior null responders and treatment-naïve subjects with compensated cirrhosis (Child-Pugh A) or without cirrhosis, and in two Phase 3 trials in subjects with compensated cirrhosis (Child-Pugh A) or without cirrhosis (OPTIMIST-2 and OPTIMIST-1, respectively) who were HCV treatment-naïve or treatment-experienced (following prior treatment with IFN [pegylated or non-pegylated], with or without RBV) (see Table 14). Efficacy data from OPTIMIST-2, which evaluated OLYSIO in combination with sofosbuvir in subjects with compensated cirrhosis, are not shown because subjects in this trial received a shorter than recommended duration of therapy.

Table 14: Trials Conducted with OLYSIO in Combination with Sofosbuvir

Trial	Population	Relevant Study Arms (Number of Subjects Treated)
COSMOS (open-label)	GT 1, TN or TE*, with compensated cirrhosis or without cirrhosis	• OLYSIO + sofosbuvir (12 weeks) (28) • OLYSIO + sofosbuvir (24 weeks) (31)
OPTIMIST-1 (open-label)	GT 1, TN or TE†, without cirrhosis	• OLYSIO + sofosbuvir (12 weeks) (155)
OPTIMIST-2 (open-label)	GT 1, TN or TE†, with compensated cirrhosis	• OLYSIO + sofosbuvir (12 weeks) (103)

GT: genotype; TN: treatment-naïve; TE: treatment-experienced.
* Includes only null responders to prior Peg-IFN/RBV therapy.
† Includes relapsers and non-responders to prior Peg-IFN-based therapy (with or without RBV), and IFN-intolerant subjects.

The efficacy of OLYSIO in combination with Peg-IFN-alfa and RBV in patients with HCV genotype 1 infection was evaluated in three Phase 3 trials in treatment-naïve subjects (QUEST 1, QUEST 2 and TIGER), one Phase 3 trial in subjects who relapsed after prior interferon-based therapy (PROMISE), one Phase 2 trial in subjects who failed prior therapy with Peg-IFN and RBV (including prior relapsers, partial and null responders) (ASPIRE), and one Phase 3 trial in subjects with HCV genotype 1 and HIV-1 co-infection who were HCV treatment-naïve or failed previous HCV therapy with Peg-IFN and RBV (C212), as summarized in Table 15.

The efficacy of OLYSIO in combination with Peg-IFN-alfa and RBV in patients with HCV genotype 4 infection was evaluated in one Phase 3 trial in treatment-naïve subjects or subjects who failed previous therapy with Peg-IFN and RBV (RESTORE) (see Table 15).

Table 15: Trials Conducted with OLYSIO in Combination with Peg-IFN-alfa and RBV

Trial	Population	Relevant Study Arms (Number of Subjects Treated)
QUEST-1 (double-blind)	GT 1, TN, with compensated cirrhosis or without cirrhosis	• OLYSIO + Peg-IFN-alfa + RBV (264) • Placebo (130)
QUEST-2 (double-blind)	GT 1, TN, with compensated cirrhosis or without cirrhosis	• OLYSIO + Peg-IFN-alfa + RBV (257) • Placebo (134)

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TIGER (double-blind)	GT 1, TN, with compensated cirrhosis or without cirrhosis	• OLYSIO + Peg-IFN-alfa + RBV (152) • Placebo (152)
PROMISE (double-blind)	GT 1, TE*, with compensated cirrhosis or without cirrhosis	• OLYSIO + Peg-IFN-alfa + RBV (260) • Placebo (133)
ASPIRE (double-blind)	GT 1, TE, with compensated cirrhosis or without cirrhosis	• OLYSIO + Peg-IFN-alfa + RBV (66) • Placebo (66)
C212 (open-label)	GT 1, TN or TE, with compensated cirrhosis or without cirrhosis, HCV/HIV-1 co-infected	• OLYSIO + Peg-IFN-alfa + RBV (106)
RESTORE (open-label)	GT 4, TN or TE, with compensated cirrhosis or without cirrhosis	• OLYSIO + Peg-IFN-alfa + RBV (107)

GT: genotype; TN: treatment-naïve; TE: treatment-experienced, includes prior relapsers, partial responders and null responders following prior treatment with Peg-IFN and RBV.

* Includes only relapsers after prior IFN-based therapy.

Prior relapsers were subjects who had HCV RNA not detected at the end of prior IFN-based therapy and HCV RNA detected during follow-up; prior partial responders were subjects with prior on-treatment greater than or equal to 2 $\log_{10}$ reduction in HCV RNA from baseline at Week 12 and HCV RNA detected at the end of prior therapy with Peg-IFN and RBV; and null responders were subjects with prior on-treatment less than 2 $\log_{10}$ reduction in HCV RNA from baseline at Week 12 during prior therapy with Peg-IFN and RBV. These trials included subjects with compensated cirrhosis (Child-Pugh A) or without cirrhosis, HCV RNA of at least 10000 IU/mL, and liver histopathology consistent with chronic HCV infection. In subjects who were treatment-naïve and prior relapsers, the overall duration of treatment with Peg-IFN-alfa and RBV in the Phase 3 trials was response-guided. In these subjects, 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 lower than 25 IU/mL (detected or not detected) at Week 4 AND HCV RNA not detected at Week 12. Plasma HCV RNA levels were measured using the Roche COBAS® TaqMan® HCV test (version 2.0), for use with the High Pure System (25 IU/mL lower limit of quantification and 15 IU/mL limit of detection). Treatment stopping rules for HCV therapy were used to ensure that subjects with inadequate on-treatment virologic response discontinued treatment in a timely manner. In the Phase 3 trial C212 in HCV/HIV-1 co-infected subjects, the total duration of treatment with Peg-IFN-alfa and RBV in treatment-naïve and prior relapser subjects with compensated cirrhosis was not response-guided; these subjects received a fixed total duration of HCV treatment of 48 weeks. The total duration of treatment with Peg-IFN-alfa and RBV in non-cirrhotic HCV/HIV-1 co-infected treatment-naïve or prior relapser subjects was response-guided using the same criteria.

14.2 OLYSIO in Combination with Sofosbuvir

Adult Subjects with HCV Genotype 1 Infection

The efficacy of OLYSIO (150 mg once daily) in combination with sofosbuvir (400 mg once daily) in HCV genotype 1-infected treatment-naïve or treatment-experienced subjects with compensated cirrhosis (Child-Pugh A) or without cirrhosis was demonstrated in one Phase 2 trial (COSMOS) and one Phase 3 trial (OPTIMIST-1).

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The COSMOS trial was an open-label, randomized Phase 2 trial to investigate the efficacy and safety of 12 or 24 weeks of OLYSIO (150 mg once daily) in combination with sofosbuvir (400 mg once daily) without or with RBV in HCV genotype 1-infected prior null responders with METAVIR fibrosis score F0-F2, or treatment-naïve subjects and prior null responders with METAVIR fibrosis score F3-F4 and compensated liver disease. Results from treatment arms containing RBV in addition to OLYSIO and sofosbuvir in the COSMOS trial are not shown because efficacy was similar with or without RBV, and thus addition of RBV to OLYSIO and sofosbuvir is not recommended. In this trial, 28 subjects received 12 weeks of OLYSIO in combination with sofosbuvir and 31 subjects received 24 weeks of OLYSIO in combination with sofosbuvir. These 59 subjects had a median age of 57 years (range 27 to 68 years; with 2% above 65 years); 53% were male; 76% were White, and 24% Black or African American; 46% had a BMI greater than or equal to 30 kg/m^2; the median baseline HCV RNA level was 6.75 log_{10} IU/mL; 19%, 31% and 22% had METAVIR fibrosis scores F0-F1, F2 and F3, respectively, and 29% had METAVIR fibrosis score F4 (cirrhosis); 75% had HCV genotype 1a of which 41% carried Q80K at baseline, and 25% had HCV genotype 1b; 14% had *IL28B* CC genotype, 64% *IL28B* CT genotype, and 22% *IL28B* TT genotype; 75% were prior null responders to Peg-IFN-alfa and RBV, and 25% were treatment-naïve.

OPTIMIST-1 was an open-label, randomized Phase 3 trial in HCV genotype 1-infected subjects without cirrhosis who were treatment-naïve or treatment-experienced (including prior relapsers, non-responders and IFN-intolerant subjects). Subjects were randomized to treatment arms of different durations. One hundred fifty-five subjects received 12 weeks of OLYSIO with sofosbuvir. The 155 subjects without cirrhosis receiving 12 weeks of OLYSIO with sofosbuvir had a median age of 56 years (range 19 to 70 years; with 7% above 65 years); 53% were male; 78% were White, 20% Black or African American, and 16% Hispanic; 37% had a BMI $\geq$ 30 kg/m^2; the median baseline HCV RNA level was 6.83 log_{10} IU/mL; 75% had HCV genotype 1a of which 40% had Q80K polymorphism at baseline, and 25% had HCV genotype 1b; 28% had *IL28B* CC genotype, 55% *IL28B* CT genotype, and 17% *IL28B* TT genotype; 74% were treatment-naïve and 26% were treatment-experienced.

In the COSMOS and OPTIMIST-1 trials, SVR12 was achieved in 170/176 (97%) subjects without cirrhosis treated with 12 weeks OLYSIO in combination with sofosbuvir, as shown in Table 16. In the COSMOS trial, 10/10 (100%) subjects with compensated cirrhosis (Child-Pugh A) who received 24 weeks of OLYSIO with sofosbuvir achieved SVR12.

Table 16: Virologic Outcomes in Adults without Cirrhosis Receiving 12 Weeks of OLYSIO with Sofosbuvir (Pooled data from OPTIMIST-1 and COSMOS Trials)

Response Rates	**OLYSIO+sofosbuvir* 12 weeks N=176 % (n/N)**
Overall SVR12	97 (170/176)

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Outcome for subjects without SVR12	
Viral relapse†	3 (5/175)

SVR12: sustained virologic response 12 weeks after actual (OPTIMIST-1) or planned (COSMOS) EOT.
* 150 mg once daily OLYSIO for 12 weeks with 400 mg once daily sofosbuvir.
† Viral relapse rates are calculated with a denominator of subjects with undetectable (or unconfirmed detectable) HCV RNA at EOT. In addition to five subjects with viral relapse, one subject failed to achieve SVR12 due to missing SVR12 data. No subjects experienced on-treatment virologic failure.

Among subjects without cirrhosis in OPTIMIST-1 who received 12 weeks of OLYSIO in combination with sofosbuvir, similar SVR12 rates were observed among subgroups, including: treatment-naïve and treatment-experienced subjects (112/115 [97%] and 38/40 [95%] respectively), subjects with HCV genotype 1a with and without NS3 Q80K polymorphism (44/46 [96%] and 68/70 [97%], respectively), genotype 1b (38/39 [97%]), and subjects with *IL28B* CC and non-CC genotypes (43/43 [100%] and 107/112 [96%], respectively).

14.3 OLYSIO in Combination with Peg-IFN-alfa and RBV

Treatment-Naïve Adult Subjects with HCV Genotype 1 Infection

The efficacy of OLYSIO in treatment-naïve patients with HCV genotype 1 infection was demonstrated in two randomized, double-blind, placebo-controlled, 2-arm, multicenter, Phase 3 trials (QUEST 1 and QUEST 2). The designs of both trials were similar. All subjects received 12 weeks of once daily treatment with 150 mg OLYSIO or placebo, plus Peg-IFN-alfa-2a (QUEST 1 and QUEST 2) or Peg-IFN-alfa-2b (QUEST 2) and RBV, followed by 12 or 36 weeks of therapy with Peg-IFN-alfa and RBV in accordance with the on-treatment protocol-defined RGT criteria. Subjects in the control groups received 48 weeks of Peg-IFN-alfa-2a or -2b and RBV.

In the pooled analysis for QUEST 1 and QUEST 2, demographics and baseline characteristics were balanced between both trials and between the OLYSIO and placebo treatment groups. In the pooled analysis of trials (QUEST 1 and QUEST 2), the 785 enrolled subjects 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) greater than or equal to 30 kg/m^2; 78% had baseline HCV RNA levels greater than 800000 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; 29% had *IL28B* CC genotype, 56% *IL28B* CT genotype, and 15% *IL28B* TT genotype; 17% of the overall population and 34% of the subjects with genotype 1a virus had the NS3 Q80K polymorphism at baseline. In QUEST 1, all subjects received Peg-IFN-alfa-2a; in QUEST 2, 69% of the subjects received Peg-IFN-alfa-2a and 31% received Peg-IFN-alfa-2b.

Table 17 shows the response rates in treatment-naïve adult subjects with HCV genotype 1 infection. In the OLYSIO treatment group, SVR12 rates were lower in subjects with

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genotype 1a virus with the NS3 Q80K polymorphism at baseline compared to subjects infected with genotype 1a virus without the Q80K polymorphism.

Table 17: Virologic Outcomes in Treatment-Naïve Adult Subjects with HCV Genotype 1 Infection (Pooled Data QUEST 1 and QUEST 2 Trials)

Response Rate	OLYSIO + PR N=521 % (n/N)	Placebo + PR N=264 % (n/N)
Overall SVR12 (genotype 1a and 1b)	80 (419/521)	50 (132/264)
Genotype 1a	75 (191/254)	47 (62/131)
Without Q80K	84 (138/165)	43 (36/83)
With Q80K	58 (49/84)	52 (23/44)
Genotype 1b	85 (228/267)	53 (70/133)
Outcome for subjects without SVR12		
On-treatment failure*	8 (42/521)	33 (87/264)
Viral relapse†	11 (51/470)	23 (39/172)

OLYSIO: 150 mg OLYSIO for 12 weeks with Peg-IFN-alfa-2a or -2b and RBV for 24 or 48 weeks; Placebo: placebo for 12 weeks with Peg-IFN-alfa-2a or -2b and RBV for 48 weeks.
SVR12: sustained virologic response 12 weeks after planned EOT.
* On-treatment failure was defined as the proportion of subjects with confirmed HCV RNA detected at EOT (including but not limited to subjects who met the protocol-specified treatment stopping rules and/or experienced viral breakthrough).
† Viral relapse rates are calculated with a denominator of subjects with HCV RNA not detected at actual EOT. Includes 4 OLYSIO-treated subjects who experienced relapse after SVR12.

In the pooled analysis of QUEST 1 and QUEST 2, 88% (459/521) of OLYSIO-treated subjects were eligible for a total treatment duration of 24 weeks. In these subjects, the SVR12 rate was 88% (405/459).

Seventy-nine percent (79%; 404/509) of OLYSIO-treated subjects had HCV RNA not detected at Week 4 (RVR); in these subjects the SVR12 rate was 90% (362/404).

SVR12 rates were higher for the OLYSIO treatment group compared to the placebo treatment group by sex, age, race, BMI, HCV genotype/subtype, baseline HCV RNA load (less than or equal to 800000 IU/mL, greater than 800000 IU/mL), METAVIR fibrosis score, and *IL28B* genotype. Table 18 shows the SVR rates by METAVIR fibrosis score.

Table 18: SVR12 Rates by METAVIR Fibrosis Score in Treatment-Naïve Adult Subjects with HCV Genotype 1 Infection (Pooled Data QUEST 1 and QUEST 2 Trials)

Subgroup	OLYSIO + PR % (n/N)	Placebo + PR % (n/N)
F0-2	84 (317/378)	55 (106/192)
F3-4	68 (89/130)	36 (26/72)

OLYSIO: 150 mg OLYSIO for 12 weeks with Peg-IFN-alfa-2a or -2b and RBV for 24 or 48 weeks; Placebo: placebo for 12 weeks with Peg-IFN-alfa-2a or -2b and RBV for 48 weeks.
SVR12: sustained virologic response 12 weeks after planned EOT.

SVR12 rates were higher for subjects receiving OLYSIO with Peg-IFN-alfa-2a or Peg-IFN-alfa-2b and RBV (88% and 78%, respectively) compared to subjects receiving placebo with Peg-IFN-alfa-2a or Peg-IFN-alfa-2b and RBV (62% and 42%, respectively) (QUEST 2).

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Treatment-Naïve East Asian Subjects with HCV Genotype 1 Infection

TIGER was a Phase 3, randomized, double-blind, placebo-controlled trial in HCV genotype 1-infected treatment-naïve adult subjects from China and South Korea.

In this trial, 152 subjects received 12 weeks of once-daily treatment with 150 mg OLYSIO plus Peg-IFN-alfa-2a and RBV, followed by 12 or 36 weeks of therapy with Peg-IFN-alfa-2a and RBV in accordance with protocol-defined RGT criteria; and 152 subjects received 12 weeks of placebo plus Peg-IFN-alfa-2a and RBV, followed by 36 weeks therapy with Peg-IFN-alfa-2a and RBV. These 304 subjects had a median age of 45 years (range: 18 to 68 years; with 2% above 65 years); 49% were male; all were East Asians (81% were enrolled in China, and 19% in South Korea); 3% had a body mass index (BMI) greater or equal to 30 kg/m^2; 84% had baseline HCV RNA levels greater than 800000 IU/mL; 82% had METAVIR fibrosis score F0, F1 or F2, 12% METAVIR fibrosis score F3, and 6% METAVIR fibrosis score F4 (cirrhosis); 1% had HCV genotype 1a, and 99% HCV genotype 1b; less than 1% of the overall population had Q80K polymorphism at baseline; 79% had *IL28B* CC genotype, 20% *IL28B* CT genotype, and 1% *IL28B* TT genotype. Demographics and baseline characteristics were balanced across the OLYSIO 150 mg and placebo treatment groups.

SVR12 rates were 91% (138/152) in the OLYSIO 150 mg treatment group and 76% (115/152) in the placebo treatment group *[see Adverse Reactions (6.1), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

Adult Subjects with HCV Genotype 1 Infection who Failed Prior Peg-IFN-alfa and RBV Therapy

The PROMISE trial was a randomized, double-blind, placebo-controlled, 2-arm, multicenter, Phase 3 trial in subjects with HCV genotype 1 infection who relapsed after prior IFN-based therapy. All subjects received 12 weeks of once daily treatment with 150 mg OLYSIO or placebo, plus Peg-IFN-alfa-2a and RBV, followed by 12 or 36 weeks of therapy with Peg-IFN-alfa-2a and RBV in accordance with the protocol-defined RGT criteria. Subjects in the control group received 48 weeks of Peg-IFN-alfa-2a and RBV.

Demographics and baseline characteristics were balanced between the OLYSIO and placebo treatment groups. The 393 subjects enrolled in the PROMISE trial 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 greater than or equal to 30 kg/m^2; 84% had baseline HCV RNA levels greater than 800000 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; 24% had *IL28B* CC genotype, 64% *IL28B* CT genotype, and 12% *IL28B* TT genotype; 13% of the overall population and 31% of the subjects with genotype 1a virus had the NS3 Q80K polymorphism at baseline. The prior IFN-based HCV therapy was Peg-IFN-alfa-2a/RBV (68%) or Peg-IFN-alfa-2b/RBV (27%).

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Table 19 shows the response rates for the OLYSIO and placebo treatment groups in adult subjects with HCV genotype 1 infection who relapsed after prior interferon-based therapy. In the OLYSIO treatment group, SVR12 rates were lower in subjects infected with genotype 1a virus with the NS3 Q80K polymorphism at baseline compared to subjects infected with genotype 1a virus without the Q80K polymorphism.

Table 19: Virologic Outcomes in Adult Subjects with HCV Genotype 1 Infection who Relapsed after Prior IFN-Based Therapy (PROMISE Trial)

Response Rates	**OLYSIO + PR N=260 % (n/N)**	**Placebo + PR N=133 % (n/N)**
Overall SVR12 (genotype 1a and 1b)	79 (206/260)	37 (49/133)
Genotype 1a	70 (78/111)	28 (15/54)
Without Q80K	78 (62/79)	26 (9/34)
With Q80K	47 (14/30)	30 (6/20)
Genotype 1b	86 (128/149)	43 (34/79)
Outcome for subjects without SVR12		
On-treatment failure*	3 (8/260)	27 (36/133)
Viral relapse†	18 (46/249)	48 (45/93)

OLYSIO: 150 mg OLYSIO for 12 weeks with Peg-IFN-alfa-2a and RBV for 24 or 48 weeks; Placebo: placebo for 12 weeks with Peg-IFN-alfa-2a and RBV for 48 weeks.
SVR12: sustained virologic response 12 weeks after planned EOT.
* On-treatment failure was defined as the proportion of subjects with confirmed HCV RNA detected at EOT (including but not limited to subjects who met the protocol-specified treatment stopping rules and/or experienced viral breakthrough).
† Viral relapse rates are calculated with a denominator of subjects with HCV RNA not detected at actual EOT and with at least one follow-up HCV RNA assessment. Includes 5 OLYSIO-treated subjects who experienced relapse after SVR12.

In PROMISE, 93% (241/260) of OLYSIO-treated subjects were eligible for a total treatment duration of 24 weeks. In these subjects, the SVR12 rate was 83% (200/241).

Seventy-seven percent (77%; 200/259) of OLYSIO-treated subjects had HCV RNA not detected at Week 4 (RVR); in these subjects the SVR12 rate was 87% (173/200).

SVR12 rates were higher for the OLYSIO treatment group compared to the placebo treatment group by sex, age, race, BMI, HCV genotype/subtype, baseline HCV RNA load (less than or equal to 800000 IU/mL, greater than 800000 IU/mL), prior HCV therapy, METAVIR fibrosis score, and *IL28B* genotype. Table 20 shows the SVR rates by METAVIR fibrosis score.

Table 20: SVR12 Rates by METAVIR Fibrosis Score in Adult Subjects with HCV Genotype 1 Infection who Relapsed after Prior IFN-Based Therapy (PROMISE Trial)

Subgroup	**OLYSIO + PR % (n/N)**	**Placebo + PR % (n/N)**
F0-2	82 (137/167)	41 (40/98)
F3-4	73 (61/83)	24 (8/34)

OLYSIO: 150 mg OLYSIO for 12 weeks with Peg-IFN-alfa-2a and RBV for 24 or 48 weeks; Placebo: placebo for 12 weeks with Peg-IFN-alfa-2a and RBV for 48 weeks.
SVR12: sustained virologic response 12 weeks after planned EOT.

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The ASPIRE trial was a randomized, double-blind, placebo-controlled, Phase 2 trial in subjects with HCV genotype 1 infection, who failed prior therapy with Peg-IFN-alfa and RBV (including prior relapsers, partial responders or null responders).

In this trial, 66 subjects received 12 weeks of 150 mg OLYSIO in combination with Peg-IFN-alfa-2a and RBV for 48 weeks, and 66 subjects received placebo in combination with Peg-IFN-alfa-2a and RBV for 48 weeks. These 132 subjects had a median age of 49 years (range: 20 to 66 years; with 1% above 65 years); 66% were male; 93% were White, 3% Black or African American, and 2% Asian; 27% had a BMI greater than or equal to 30 kg/m^2; 85% had baseline HCV RNA levels greater than 800000 IU/mL; 64% had METAVIR fibrosis score F0, F1, or F2, 18% METAVIR fibrosis score F3, and 18% METAVIR fibrosis score F4 (cirrhosis); 43% had HCV genotype 1a, and 57% HCV genotype 1b; 17% had *IL28B* CC genotype, 67% *IL28B* CT genotype, and 16% *IL28B* TT genotype (information available for 93 subjects); 27% of the overall population and 23% of the subjects with genotype 1a virus had the NS3 Q80K polymorphism at baseline. Forty percent (40%) of subjects were prior relapsers, 35% prior partial responders, and 25% prior null responders following prior therapy with Peg-IFN-alfa and RBV. Demographics and baseline characteristics were balanced between the 12 weeks 150 mg OLYSIO and placebo treatment groups.

Table 21 shows the response rates for the 12 weeks of 150 mg OLYSIO and placebo treatment groups in prior relapsers, prior partial responders and prior null responders.

Table 21: Virologic Outcomes in Prior Partial and Null Responders with HCV Genotype 1 Infection who Failed Prior Peg-IFN-alfa and RBV Therapy (ASPIRE Trial)

Response Rates	**OLYSIO + PR N=66 % (n/N)**	**Placebo + PR N=66 % (n/N)**
SVR24		
Prior relapsers	77 (20/26)	37 (10/27)
Prior partial responders	65 (15/23)	9 (2/23)
Prior null responders	53 (9/17)	19 (3/16)
Outcome for subjects without SVR24		
On-treatment virologic failure*		
Prior relapsers	8 (2/26)	22 (6/27)
Prior partial responders	22 (5/23)	78 (18/23)
Prior null responders	35 (6/17)	75 (12/16)
Viral relapse†		
Prior relapsers	13 (3/23)	47 (9/19)
Prior partial responders	6 (1/17)	50 (2/4)
Prior null responders	18 (2/11)	25 (1/4)

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150 mg OLYSIO: 150 mg OLYSIO for 12 weeks with Peg-IFN-alfa-2a and RBV for 48 weeks; Placebo: placebo with Peg-IFN-alfa-2a and RBV for 48 weeks.
SVR24: sustained virologic response defined as undetectable HCV RNA 24 weeks after planned EOT.

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

† Viral relapse rates are calculated with a denominator of subjects with HCV RNA not detected at EOT and with at least one follow-up HCV RNA assessment.

SVR24 rates were higher in the OLYSIO-treated subjects compared to subjects receiving placebo in combination with Peg-IFN-alfa and RBV, regardless of HCV geno/subtype, METAVIR fibrosis score, and *IL28B* genotype.

Subjects with HCV/HIV-1 Co-Infection

C212 was an open-label, single-arm Phase 3 trial in HIV-1 subjects co-infected with HCV genotype 1 who were treatment-naïve or failed prior HCV therapy with Peg-IFN-alfa and RBV (including prior relapsers, partial responders or null responders). Non-cirrhotic treatment-naïve subjects or prior relapsers received 12 weeks of once-daily treatment with 150 mg OLYSIO plus Peg-IFN-alfa-2a and RBV, followed by 12 or 36 weeks of therapy with Peg-IFN-alfa-2a and RBV in accordance with the protocol-defined RGT criteria. Prior non-responder subjects (partial and null response) and all cirrhotic subjects (METAVIR fibrosis score F4) received 36 weeks of Peg-IFN-alfa-2a and RBV after the initial 12 weeks of OLYSIO in combination with Peg-IFN-alfa-2a and RBV.

The 106 enrolled subjects in the C212 trial 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 greater than or equal to 30 kg/m^2; 86% had baseline HCV RNA levels greater than 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 subjects 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 subjects, 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 subjects were on highly active antiretroviral therapy (HAART), with nucleoside reverse transcriptase inhibitors and the integrase inhibitor raltegravir being the most commonly used HIV antiretroviral. HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors (except rilpivirine) were prohibited from use in this study.

The median baseline HIV-1 RNA levels and CD4+ cell count in subjects not on HAART were 4.18 $\log_{10}$ copies/mL (range: 1.3-4.9 $\log_{10}$ copies/mL) and 677 × 10^6 cells/L (range: 489-1076 × 10^6 cells/L), respectively. The median baseline CD4+ cell count in subjects on HAART was 561 × 10^6 cells/mL (range: 275-1407 × 10^6 cells/mL).

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Table 22 shows the response rates in treatment-naïve, prior relapsers, prior partial responders and null responders.

Table 22: Virologic Outcomes in Adult Subjects with HCV Genotype 1 Infection and HIV-1 Co-Infection (C212 Trial)

Response Rates	Treatment-Naïve Subjects N=53 % (n/N)	Prior Relapsers N=15 % (n/N)	Prior Partial Responders N=10 % (n/N)	Prior Null Responders N=28 % (n/N)
Overall SVR12 (genotype 1a and 1b)	79 (42/53)	87 (13/15)	70 (7/10)	57 (16/28)
Genotype 1a	77 (33/43)	83 (10/12)	67 (6/9)	54 (13/24)
Genotype 1b	90 (9/10)	100 (3/3)	100 (1/1)	75 (3/4)
Outcome for subjects without SVR12				
On-treatment failure*	9 (5/53)	0 (0/15)	20 (2/10)	39 (11/28)
Viral relapse†	10 (5/48)	13 (2/15)	0 (0/7)	12 (2/17)

150 mg OLYSIO for 12 weeks with Peg-IFN-alfa-2a and RBV for 24 or 48 weeks.

SVR12: sustained virologic response 12 weeks after planned EOT.

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

† Viral relapse rates are calculated with a denominator of subjects 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.

Eighty-nine percent (n=54/61) of the OLYSIO-treated treatment-naïve subjects and prior relapsers without cirrhosis were eligible for a total treatment duration of 24 weeks. In these subjects, the SVR12 rate was 87%.

Seventy-one percent (n=37/52), 93% (n=14/15), 80% (n=8/10) and 36% (n=10/28) of OLYSIO-treated treatment-naïve subjects, prior relapsers, prior partial responders and prior null responders had undetectable HCV RNA at week 4 (RVR). In these subjects the SVR12 rates were 89%, 93%, 75% and 90%, respectively.

Table 23 shows the SVR rates by METAVIR fibrosis scores.

Table 23: SVR12 Rates by METAVIR Fibrosis Score in Adult Subjects with HCV Genotype 1 Infection and HIV-1 Co-Infection (C212 Trial)

Subgroup	Treatment-Naïve Subjects % (n/N)	Prior Relapsers % (n/N)	Prior Partial Responders % (n/N)	Prior Null Responders % (n/N)
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)

150 mg OLYSIO for 12 weeks with Peg-IFN-alfa-2a and RBV for 24 or 48 weeks.
SVR12: sustained virologic response 12 weeks after planned EOT.

Two subjects had HIV virologic failure defined as confirmed HIV-1 RNA at least 200 copies/mL after previous less than 50 copies/mL; these failures occurred 36 and 48 weeks after end of OLYSIO treatment.

Adult Subjects with HCV Genotype 4 Infection

RESTORE was an open-label, single-arm Phase 3 trial in subjects with HCV genotype 4 infection who were treatment-naïve or failed prior therapy with Peg-IFN-alfa and RBV

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(including prior relapsers, partial responders or null responders). Treatment-naïve subjects or prior relapsers received once-daily treatment with 150 mg OLYSIO plus Peg-IFN-alfa-2a and RBV for 12 weeks, followed by 12 or 36 weeks of therapy with Peg-IFN-alfa-2a and RBV in accordance with the protocol-defined RGT criteria. Prior non-responder subjects (partial and null response) received once-daily treatment with 150 mg OLYSIO plus Peg-IFN-alfa-2a and RBV for 12 weeks, followed by 36 weeks of Peg-IFN-alfa-2a and RBV.

The 107 enrolled subjects in the RESTORE trial 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 greater than or equal to 30 kg/m^2; 60% had baseline HCV RNA levels greater than 800,000 IU/mL; 57% had METAVIR fibrosis score F0, F1 or F2, 14% METAVIR fibrosis score F3, and 29% METAVIR fibrosis score F4; 42% had HCV genotype 4a, and 24% had HCV genotype 4d; 8% had *IL28B* CC genotype, 58% *IL28B* CT genotype, and 35% *IL28B* TT genotype; 33% (n=35) were treatment-naïve HCV subjects, 21% (n=22) prior relapsers, 9% (n=10) prior partial responders, and 37% (n=40) prior null responders.

Table 24 shows the response rates in treatment-naïve, prior relapsers, prior partial responders and null responders. Table 25 shows the SVR rates by METAVIR fibrosis scores.

Table 24: Virologic Outcomes in Adult Subjects with HCV Genotype 4 Infection (RESTORE Trial)

Response Rates	Treatment-Naïve Subjects N=35 % (n/N)	Prior Relapsers N=22 % (n/N)	Prior Partial Responders N=10 % (n/N)	Prior Null Responders N=40 % (n/N)
Overall SVR12	83 (29/35)	86 (19/22)	60 (6/10)	40 (16/40)
Outcome for subjects without SVR12				
On-treatment failure*	9 (3/35)	9 (2/22)	20 (2/10)	45 (18/40)
Viral relapse†	9 (3/35)	5 (1/22)	20 (2/10)	15 (6/40)

150 mg OLYSIO for 12 weeks with Peg-IFN-alfa-2a and RBV for 24 or 48 weeks.

SVR12: sustained virologic response 12 weeks after planned EOT.

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

† Viral relapse rates are calculated with a denominator of subjects with undetectable (or unconfirmed detectable) HCV RNA at actual EOT.

Table 25: SVR12 Rates by METAVIR Fibrosis Score in Adult Subjects with HCV Genotype 4 Infection (RESTORE Trial)

Subgroup	Treatment-Naïve Subjects % (n/N)	Prior Relapsers % (n/N)	Prior Partial Responders % (n/N)	Prior Null Responders % (n/N)
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)

150 mg OLYSIO for 12 weeks with Peg-IFN-alfa-2a and RBV for 24 or 48 weeks.
SVR12: sustained virologic response 12 weeks after planned EOT.

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16 HOW SUPPLIED/STORAGE AND HANDLING

OLYSIO 150 mg capsules are white, marked with "TMC435 150" in black ink. The capsules are packaged into a bottle containing 28 capsules (NDC 59676-225-28).

Store OLYSIO capsules in the original bottle in order to protect from light at room temperature below 30°C (86°F).

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Patient Information).

Risk of Hepatitis B Virus Reactivation in Patients Coinfected with HCV and HBV

Inform patients that HBV reactivation can occur in patients coinfected with HBV during or after treatment of HCV infection. Advise patients to tell their healthcare provider if they have a history of HBV infection *[see Warnings and Precautions (5.1)]*.

Symptomatic Bradycardia When Used in Combination with Sofosbuvir and Amiodarone

Advise patients to seek medical evaluation immediately for symptoms of bradycardia such as near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pain, confusion or memory problems *[see Warnings and Precautions (5.2), Adverse Reactions (6.2) and Drug Interactions (7.3)]*.

Pregnancy

Advise patients taking OLYSIO of the potential risk to the fetus. In addition, when OLYSIO is taken with RBV, advise patients to avoid pregnancy during treatment and within 6 months of stopping RBV and to notify their healthcare provider immediately in the event of a pregnancy *[see Use in Specific Populations (8.1)]*.

Hepatic Decompensation and Failure

Inform patients to watch for early warning signs of liver inflammation, such as fatigue, weakness, lack of appetite, nausea and vomiting, as well as later signs such as jaundice and discolored feces, and to contact their healthcare provider immediately if such symptoms occur *[see Warnings and Precautions (5.3)]*.

Photosensitivity

Advise patients of the risk of photosensitivity reactions related to OLYSIO combination treatment and that these reactions may be severe. Instruct patients to use effective sun protection measures to limit exposure to natural sunlight and to avoid artificial sunlight (tanning beds or phototherapy) during treatment with OLYSIO.

Advise patients to contact their healthcare provider immediately if they develop a photosensitivity reaction. Inform patients not to stop OLYSIO due to photosensitivity

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reactions unless instructed by their healthcare provider *[see Warnings and Precautions (5.5)]*.

Rash

Advise patients of the risk of rash related to OLYSIO combination treatment and that rash may become severe. Advise patients to contact their healthcare provider immediately if they develop a rash. Inform patients not to stop OLYSIO due to rash unless instructed by their healthcare provider *[see Warnings and Precautions (5.6)]*.

Administration

Advise patients to use OLYSIO only in combination with other antiviral drugs for the treatment of chronic HCV infection. Advise patients to discontinue OLYSIO if any of the other antiviral drugs used in combination with OLYSIO are permanently discontinued for any reason. Advise patients that the dose of OLYSIO must not be reduced or interrupted, as it may increase the possibility of treatment failure *[see Dosage and Administration (2.1)]*.

Advise patients to take OLYSIO every day at the regularly scheduled time with food. Inform patients that it is important not to miss or skip doses and to take OLYSIO for the duration that is recommended by the healthcare provider. Inform patients not to take more or less than the prescribed dose of OLYSIO at any one time.

Product of Belgium

Manufactured by:
Janssen-Cilag SpA, Latina, Italy

Manufactured for:
Janssen Therapeutics, Division of Janssen Products, LP
Titusville NJ 08560

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PATIENT INFORMATION
OLYSIO® (oh li see oh)
(simeprevir)
capsules

Read this Patient Information before you start taking OLYSIO and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

Important: You should not take OLYSIO alone. OLYSIO should be used together with other antiviral medicines to treat chronic hepatitis C virus infection. **When taking OLYSIO in combination with peginterferon alfa and ribavirin you should also read those Medication Guides.** When taking OLYSIO in combination with sofosbuvir, you should also read its Patient Information leaflet.

What is the most important information I should know about OLYSIO?

OLYSIO can cause serious side effects, including:

Hepatitis B virus reactivation: Before starting treatment with OLYSIO, your healthcare provider will do blood tests to check for hepatitis B virus infection. If you have ever had hepatitis B virus infection, the hepatitis B virus could become active again during or after treatment of hepatitis C virus with OLYSIO. Hepatitis B virus becoming active again (called reactivation) may cause serious liver problems including liver failure and death. Your healthcare provider will monitor you if you are at risk for hepatitis B virus reactivation during treatment and after you stop taking OLYSIO.

OLYSIO combination treatment with sofosbuvir (Sovaldi®) may result in slowing of the heart rate (pulse) along with other symptoms when taken with amiodarone (Cordarone®, Nexterone®, Pacerone®), a medicine used to treat certain heart problems.

- If you are taking OLYSIO with sofosbuvir and amiodarone and you get any of the following symptoms, or if you have a slow heart rate call your healthcare provider right away:
  - o fainting or near-fainting
  - o dizziness or lightheadedness
  - o weakness, extreme tiredness
  - o chest pain, shortness of breath
  - o confusion or memory problems

OLYSIO may cause severe liver problems in some people. These severe liver problems may lead to liver failure or death.

- Your healthcare provider may do blood tests to check your liver function during treatment with OLYSIO.
- Your healthcare provider may tell you to stop taking OLYSIO if you develop signs and symptoms of liver problems.
- Tell your healthcare provider right away if you develop any of the following symptoms, or if they worsen during treatment with OLYSIO:
  - o tiredness
  - o weakness
  - o loss of appetite
  - o nausea and vomiting
  - o yellowing of your skin or eyes
  - o color changes in your stools

OLYSIO combination treatment may cause rashes and skin reactions to sunlight. These rashes and skin reactions to sunlight can be severe and you may need to be treated in a hospital. Rashes and skin reactions to sunlight are most common during the first 4 weeks of treatment, but can happen at any time during combination treatment with OLYSIO.

- Limit sunlight exposure during treatment with OLYSIO.
- Use sunscreen and wear a hat, sunglasses, and protective clothing during treatment with OLYSIO.
- Avoid use of tanning beds, sunlamps, or other types of light therapy during treatment with OLYSIO.
- Call your healthcare provider right away if you get any of the following symptoms:
  - o burning, redness, swelling or blisters on your skin
  - o mouth sores or ulcers
  - o red or inflamed eyes, like “pink eye” (conjunctivitis)

For more information about side effects, see the section “What are the possible side effects of OLYSIO?”

What is OLYSIO?

- OLYSIO is a prescription medicine used with other antiviral medicines to treat chronic (lasting a long time) hepatitis C virus genotype 1 or 4 infection. **OLYSIO should not be taken alone.**
- **OLYSIO is not for people with certain types of liver problems.**

It is not known if OLYSIO is safe and effective in children under 18 years of age.

What should I tell my healthcare provider before taking OLYSIO?

Before taking OLYSIO, tell your healthcare provider about all of your medical conditions, including if you:

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- have ever had hepatitis B virus infection
- have liver problems other than hepatitis C virus infection
- have ever taken any medicine to treat hepatitis C virus infection
- had a liver transplant
- are receiving phototherapy
- have any other medical condition
- are pregnant or plan to become pregnant. It is not known if OLYSIO will harm your unborn baby. Do not take OLYSIO in combination with ribavirin if you are pregnant, or your sexual partner is pregnant.
  - **Females who take OLYSIO in combination with ribavirin should avoid becoming pregnant during treatment and for 6 months after stopping ribavirin. Call your healthcare provider right away if you think you may be pregnant or become pregnant during treatment with OLYSIO in combination with ribavirin.**
  - **Males and females who take OLYSIO with ribavirin should read the ribavirin Medication Guide for important pregnancy, contraception, and infertility information.**
- are breastfeeding. It is not known if OLYSIO passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with OLYSIO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some medicines may interact with OLYSIO. This can cause you to have too much or not enough OLYSIO or other medicines in your body, which may affect the way OLYSIO or your other medicines work, or may cause side effects. **Keep a list of your medicines and show it to your healthcare provider and pharmacist**.

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with OLYSIO.
- **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take OLYSIO with other medicines.

How should I take OLYSIO?

- Take OLYSIO exactly as your healthcare provider tells you to take it. Do not change your dose unless your healthcare provider tells you to.
- Do not stop taking OLYSIO unless your healthcare provider tells you to. If you think there is a reason to stop taking OLYSIO, talk to your healthcare provider before doing so.
- Take 1 OLYSIO capsule each day with food.
- Swallow OLYSIO capsules whole.
- It is important that you do not miss or skip doses of OLYSIO during treatment.
- Do not take two doses of OLYSIO at the same time to make up for a missed dose.
- If you take too much OLYSIO, call your healthcare provider right away or go to the nearest hospital emergency room.

What are the possible side effects of OLYSIO?

OLYSIO can cause serious side effects, including:

- Hepatitis B virus reactivation. See “What is the most important information I should know about OLYSIO?”

The most common side effects of OLYSIO when used in combination with sofosbuvir include:

- tiredness
- headache
- nausea

The most common side effects of OLYSIO when used in combination with peginterferon alfa and ribavirin include:

- skin rash
- itching
- nausea

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of OLYSIO. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store OLYSIO?

- Store OLYSIO at room temperature below 86°F (30°C).
- Store OLYSIO in the original bottle to protect it from light.

Keep OLYSIO and all medicines out of the reach of children.

General information about the safe and effective use of OLYSIO

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use OLYSIO for a condition for which it was not prescribed. Do not give your OLYSIO to other people, even if they have the same symptoms that you have. It may harm them.

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If you would like more information about OLYSIO, talk with your pharmacist or healthcare provider. You can ask your pharmacist or healthcare provider for information about OLYSIO that is written for health professionals.

For more information about OLYSIO, go to www.OLYSIO.com or call 1-800-526-7736.

What are the ingredients in OLYSIO?

Active ingredient: simeprevir

Inactive ingredients: colloidal anhydrous silica, croscarmellose sodium, lactose monohydrate, magnesium stearate, sodium lauryl sulphate. The white capsule contains gelatin and titanium dioxide (E171) and is printed with ink containing iron oxide black (E172) and shellac (E904).

Product of Belgium

Manufactured by: Janssen-Cilag SpA, Latina, Italy

Manufactured for: Janssen Therapeutics, Division of Janssen Products, LP, Titusville NJ 08560

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